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Review Article

The Impact of Cognitive Training in Mild Cognitive Impairment and Early Stage Alzheimer's Disease. A Selective Review

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Abstract

Importance: Patients with Alzheimer's disease (AD) and a substantial portion of patients with Mild Cognitive Impairment (MCI) present prominent language deficits that usually appear earlier than other cognitive deficits. The aim of this selective review is to summarize the characteristics of the cognitive training programs (i.e., cognitive domains targeted, number of sessions, and method of training) administered in patients with MCI and early stage AD, and evaluate the evidence for the effectiveness of these approaches.

Methods: A selective review of English language peer-reviewed journal articles was conducted using PubMed. The selected studies reported pre and post cognitive training neuropsychological performances and included both training and control/no-training MCI and early stage AD groups. The studies reported also the effect of the training.

Results: In total ten studies fulfilled the criteria for inclusion. In six studies, a computer-based training program for memory was administered. One study used multi-domain training with an emphasis on episodic memory, attention, processing speed, executive function and one study did not report the characteristics of the training exercises used. In only one study language training exercises were included, however used without any information about the type of language strategies used. Overall, outcome measures suggested that cognitive training improved attention, naming, working memory and spatial abilities in both clinical groups.

Conclusion: The present selective review revealed that the different kinds of cognitive training had positive impact on only one cognitive domain after training (i.e. attention, naming, working memory, spatial abilities) while there were domains in which both patients with AD and MCI did not show any improvement (i.e. episodic memory, attention, language, executive function). Possibly, the multi-component cognitive training (computer-based cognitive training, language exercises with pen and paper, and extra home practice) with an emphasis on language deficits are expected to have concurrently improvement in more than one domain.

Keywords: *Early AD; Mild Cognitive Impairment; Cognitive Training; Computer-Based Cognitive Training*

Introduction

Mild cognitive impairment (MCI, now termed Mild Neurocognitive Disorder, MCD, in Diagnostic and Statistical Manual of Mental Disorders, DSM V, 5th Edition) [1] is a heterogeneous clinical entity. Although some people with MCI never get worse and a few eventually revert

to "normal" cognitive status, a large portion progress to dementia. It is, thus, often considered the precursor period between normal aging and dementia [2,3]. MCI can be divided into amnestic MCI (a-MCI) and non-amnestic MCI (na-MCI) depending on whether or not memory is impaired [4], and into single (sd-MCI) and multiple domain MCI (md-MCI) depending on whether impairments are present on one or multiple cognitive domains. Thus, the proposed subtypes of MCI are a) amnestic single domain (as-MCI), b) amnestic multiple domain (am-MCI), c) non-amnestic single domain (nas-MCI), d) non-amnestic multiple domain (nam-MCI) [5,6]. The most common subtype is am-MCI (42,8%), followed by nam-MCI (26,7%) (Rapp et al.). Patients with nam-MCI are more likely to progress to a non-AD dementia [7]. When MCI individuals demonstrate impairments in domains other than memory, including language, they are more likely to develop dementia than are those with pure memory impairment [8]. Thus, understanding the nature of language impairment and possibly identifying sensitive measures of linguistic impairment constitutes a vital tool in early detection of dementia [3].

Alzheimer's disease (AD, DSM V, 5th Edition) is a progressive, neurocognitive disease characterized by memory loss (episodic and semantic), and possible impairments in language, attention, executive function, processing speed, ability to mentally manipulate visual information, executive function, activities of daily living (ADL), and judgment [9]. AD is the most common cause for dementia. These difficulties can have a major impact on self-confidence, anxiety and mood [10,11]. One of the most prominent domains of impairment in patients with AD and a substantial portion of patients with MCI is language. Language deficits may constitute early biomarkers and possible diagnostic criteria of importance for AD and MCI, and they are apparent earlier than other cognitive deficits [11].

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Specifically, language deficits manifest in several language functions, such as verbal fluency and especially in category fluency [11,12]. In fact, category fluency that imposes only minimal demands upon effortful retrieval is significantly more impaired than phonemic fluency [12,13]. Furthermore, naming [14,15], semantic knowledge, semantic processing [16], and syntactic and phonological difficulties are reported in a substantial portion of MCI and AD patients [11].

Pharmacological treatments have proven ineffective to decelerate the progression of MCI to dementia [6]. Non-pharmacological interventions have, therefore, been proposed as an alternative intervention method to decelerate cognitive impairment, and are often preferable due to the lack of side effects [17]. Among the non-pharmacological therapies in MCI, and AD, cognitive rehabilitation (CR) has been highlighted [5]. Several cognitive training programs are currently available as a means to improve cognitive symptoms or slow down their progression in patients with MCI and AD [1,2,5,18]. Most research studies in MCI and AD report a positive impact on cognition and mood with various rehabilitation approaches [17]. The terms "rehabilitation", "training" and "stimulation" are applied somewhat interchangeably.

In the present selective review, we summarized the characteristics of the cognitive training programs administered to AD patients and persons with MCI and evaluated the evidence of their effectiveness on the cognitive and specifically language abilities of patients with MCI and early stage AD. In addition, the present review aimed to evaluate whether cognitive rehabilitation improves neuropsychological performances, in specific cognitive domains or cognition overall.

Methods

Search strategy

A selective review of peer-reviewed journal articles was conducted using PubMed. Last literature search was performed on December 1st, 2017. Combinations of the following terms: "cognitive training"; "cognitive intervention"; "memory training"; "memory rehabilitation"; "language training"; "mild cognitive impairment"; "early stage AD" were used.

Inclusion criteria

We selected studies: 1) in which participants with MCI and early stage AD met Petersen's diagnostic criteria for MCI and NINCDS-ADRAA criteria for probable AD, respectively; 2) which stated clearly their aims, objectives and methods; 3) which reported quantitative and mixed-method results and 4) in which early stage AD was indicated by score of 1 and MCI by a score of 0.5 in the Clinical Dementia Rating (CDR) [19-21].

Exclusion criteria

We did not consider studies which included participants with other neurological conditions, visual and hearing impairments, writing/reading disabilities sufficient to interfere with training, or moderate and severe depression as determined by a score > 11 (moderate depression) on the Geriatric Depression Scale [22]. We further excluded studies that did not include a control group.

Results

Study selection

The electronic searches retrieved a combined total 395 studies published until December 31 2017. After preliminary screening, 91 records (44 for MCI patients and 47 for early stage AD patients) forwarded to the review authors for further evaluation. Subsequently to the title and abstract 23 studies (11 for patients with MCI and 12 for patients with early stage AD) were selected for closer assessment. Eventually, 10 studies met out criteria for cognitive training. Specifically, six articles reported computer based [2,18,23,24] and pen and paper [25] interventions with an emphasis on memory [2,18,23,24,25] and executive function [5] in patients with MCI. Three studies assessed the effects of computer-based cognitive interventions on memory [26], on processing speed [27], and attention, memory, executive function, language [1] in patients with early stage AD. One study had two groups (one with MCI and one group with AD), and used homework multi-component cognitive training with an emphasis in memory. A summary of each study groups' characteristics is presented in table 1.

Citation	Type of training	MCI- early stage AD sample size	Age (yrs)	Gender (%male)	MMSE	Criteria for diagnosis of MCI and AD	Exclusion of co-morbidities
1. Hwang., *et al*. 2012	Multicomponent cognitive training with emphasis on memory	Total MCI n = 10 Treatment n = 5 Control n = 5 Total AD n = 7 Treatment n = 4 Control n = 3	**MCI** TG: 63.4 (9.4) CG: 67.2 (8.8) **Mild AD:** TG: 70.5 (3.5) CG: 75.3 (4.7)	 20% 40% 25% 0%	 26.2 (3.6) 25.0 (3.1) 18.8 (0.5) 19.3 (4.7)	Petersen (2001) NINCDS-ADRDA 4thedition	Primary neurodegenerative or psychiatric disorders, severe medical disease, hearing or visual impairment
2. Greenaway., *et al*. 2013	Memory training	Total MCI n = 40 Treatment n = 20 Control n = 20	TG: 72.7 (6.9) CG: 72.3 (7.9)	40% 38%	26.4 (2.2) 27.2 (2.4)	Petersen (2001)	Dementia diagnosis, visual/hearing or reading disabilities, depression or psychiatric illness
3. Shomaly., *et al*. 2013	Working memory	Total MCI n = 30 Treatment n = 15 Control n = 15	70-79 10% 80-89 25 %	No reported	No reported	MMSE score lower than 25	Neurological, psychiatric disorders, movement –sensory dysfunctions according to the mood
4. Barekatan., *et al*. 2016	Cognitive training in all domains, except memory	Total MCI n = 36 Treatment n = 17 Control n = 19	TG: 66.2 (5.5) CG: 65.7 (4.7)	5% 10%	27.67 (1.49) 27.53 (1.99)	Petersen (2001)	Major psychiatric and neurological disorders
5. Cavallo., *et al*. 2016	Cognitive training	Total mild AD n = 80 Treatment n = 40 Control n = 40	TG 76.50 (2.9) CG 76.33 (3.8)	48% 66%	22.65 (1.74) 23.05 (2.44)	NINCDS-ADRDA	Neurological or psychiatric disorders Sensorial impairment
6. Gooding., *et al*. 2015	Cognitive training	Total MCI and mild AD n = 72	TG 76 (8.7) CG: not reported	58% male Not reported	50.58 (2.72) Not reported	NINCDS-ADRDA	Not reported
7. Rojas., *et al*. 2013	Cognitive training	Total MCI n = 48 Treatment n = 24 Control n = 24	TG 72 (14.29) CG 77 (7.05)	37% 33%	27.53 (2.33) 27.13 (2.10)	Petersen (2001)	No reported
8. Herrera., *et al*. 2012	Memory-attention strategy	Total MCI n = 22 Treatment n = 11 Control n = 11	TG 75.09 (2.0) CG 78.18 (1.4)	54% 45%	1.73 (0.20) 1.82 (0.24)	Petersen (2001)	depression, hearing, motor, vision or language deficits
9. Viola., *et al*. 2011	Memory training	Total mild AD n = 42 Treatment n = 25 Control n = 16	Average 75 years	36% 38%	22.6 (2.9) 23.3 (3.9)	NINCDS-ADRDA	Not reported
10. Barnes., *et al*. 2009	Cognitive exercise	Total mild AD n = 47 Treatment n = 22 Control n = 25	TG 74.1 (8.7) CG 74.8 (7.2)	59% 60%	Not reported	Winbald (2004)	Cerebrovascular disease, starting treatment with ChEIs

Table 1: *Participant characteristics of the selective reviews of cognitive training intervention in mild cognitive impairment and early stage AD.*

TG: Training Group; CG: Control Group; MCI: Mild Cognitive Impairment; AD: Alzheimer disease; MMSE: Mini Mental Stage Examination; NINCDS-ADRDA: National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association

Patient's characteristics

Sample

The sample sizes in the selected studies ranged from 5 to 86 participants. In total, 505 participants were studied, 354 of whom were mild AD (205 participants constituted "the training group") and 151 MCI (77 participants constituted "the training group"). Recruitment sources were variable, with referrals from geriatric, psychiatric, memory clinics or neurology units being the most common. However, frequently no recruitment information was provided. Participants were predominantly female. In one study, the characteristics of the treatment and control group at baseline differed with respect to gender ratio and overall cognition, as indicated by Mini Mental State Examination (MMSE) [28] scores [1]. One study did not report the demographic characteristics of the treatment and control group [18]. Three studies [23,25,26] did not describe exclusion criteria. On the other hand, all studies reported inclusion criteria. Limited information was provided regarding brain imaging (CT or MRI) of the participants and only six studies [1,2,23, 24,25,29] reported that the participants underwent brain imaging. In four of the ten studies, participants in the intervention group were receiving pharmacological treatment [1,23,26,29]. In one study, participants did not receive treatment [25] and five studies did not provide information regarding pharmacological treatment [2,5,18,24,27].

MCI and AD diagnosis

Seven trials applied formal diagnostic criteria to determine the MCI and AD status of the participants. Petersen's MCI criteria were most commonly used for MCI [2,5,24,25,29] and NINCDS-ADRDA for AD [1,23,26,29]. All, but one study [18], provided MMSE scores as a measure of baseline cognitive function, with inclusion criterion a score lower than 25.

Outcome measures

There was considerable variability in the type and quality of outcome measures used to assess the efficacy of the cognitive training in persons with MCI and early stage AD in each study, limiting the extent to which a totally efficacy can be evaluated. The types of outcome measures employed can be broadly classified into domain-specific cognitive measures (memory, attention, executive function and speed) and global/overall cognition measures.

Participants in all studies underwent neuropsychological assessments before training, after training and sometimes after 3, 4, 6 or 12 months. In all studies, initially, participants were assessed with the MMSE and the CDR. Both measures were also used as primary outcome measures in all studies [1,2,5,18,23-27,29].

All studies used neuropsychological measures before and after treatment to evaluate specific cognitive domains (executive function, memory, language, visuospatial ability). Executive function was assessed with the Trail Making Test part B [25,27], the Brixton Test [1], and the Behavioral Rating Inventory of Executive Function in Adults (BriEF-A) [5].

Episodic memory was evaluated with Signoret's Memory Battery [25], Rivermead Behavioural Memory Test (RBMT) [1,24], Selective Reminding Test [23], and episodic memory subtests of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [27].

Working memory was assessed with the N-Back test [18], the Trail Making Test part A [25,27], the Digit Span Forward and Backward Test from the Wechsler Adult Intelligence Scale III [1,24,29], California Verbal Learning Test [27], Seoul Verbal Learning Test [29]. Furthermore, recall was assessed with BEM word list recall test [24].

In the domain of language, naming was assessed with the Boston Naming Test [25,27,29] and the Token Test (Cavallo., *et al*. 2016). Verbal fluency was evaluated with the Graded Verbal Fluency test [1,25,27,29].

Finally, visuospatial abilities were assessed with the Block Design [25], Visual object and Space Perception Battery (VOSP) [1,23], and the Stroop Color Test [29].

Cognitive training

Training format and delivery

Computerized exercises were the most common form of training. The computer program Memory Support System (MSM) [2] was used to train memory. Brainer 1 [1] and Brain Fitness [23] were used to train global cognition whilst the POSIT Science corporation program was used for training on auditory processing [27]. Barekatain., *et al.* (2016), Shomaly., *et al*. 2013, Herrera., *et al.* (2012) and Viola., *et al.* (2011) did not report the computer program they used [3,18,24,26].

Four of the studies used group sessions [1,18,25-27], and the other five studies used individual sessions [2,23,24,29]. The study of Barnes., *et al.* (2009) does not mention the type of sessions they used. One elementary domain of cognition exercise exclusively used printed materials [25] and one cognitive strategy included homework exercises [29]. One cognitive program exclusively involved individual home training [27]. Neuropsychologists or speech therapists supervised training [1,5,25,26,29]. Training characteristics are presented in table 2.

Citation	Cognitive training	Control condition	No. of session (months)	Session length (hrs/week)	Follow up	Cognitive outcome measures
1. Hwang., *et al*. 2012	Multicomponent cognitive training program, targeted largely at memory training with homework. Individual format	Wait list control group	4,5 months	50 minutes	3 months	MMSE BNT ROCF DSFT DSBT VF SCT SVLT SAC
2. Greenaway., *et al*. 2013	Memory support system. Individual format	Controls with training or without training	2 months	2 hours	6 months	MMSE E-Cog SE GOL-AD
3. Shomaly., *et al*. 2013	Computer based memory exercise. Group format	No reported	3 months	2 hours	No reported	MMSE WMS N-Back 1 N-Back 2
4. Barekatan., *et al*. 2016	No mention	No reported	2 months	2 hours	6 months	MMSE BriEF-A CTT VF SF
5. Cavallo., *et al*. 2016	Computer- assisted memory, attention, language, executive function training. Group format	Control underwent a control intervention	3 months	1,5 hour	6 months	MMSE GNT VOSP VF RBMT DSFT DSBT GNT BT TT
6. Gooding., *et al*. 2015	Computer cognitive memory. Brain Fitness software. Individual format	No reported	4 months	2 hours	4 months	RSS BDI-II MMSE BSRT VR LM
7. Rojas., *et al*. 2013	Cognitive exercises with multi-domain pen and paper cognitive exercises. Group format	No reported	6 months	4 hours	12 months	MMSE MEM-REC BN SF PF CDR
8. Herrera., *et al*. 2012	Computer-based memory –attention training program based on recognition. Individual format	Control group trained in cognitively stimulating activities	3 months	2 hours	6 months	MMSE ROCF MEM 12 DPMTB DSFT DSBT
9. Viola., *et al*. 2011	Computer-assisted cognitive stimulation, expressive activities, physical training. Group format		1,5 months	6,5 hours	No reported	MMSE Memory Attention GDS GOL-AD
10. Barnes., *et al*. 2009	Cognitive exercises computer-based training of 7 exercises to improve information processing and accuracy of auditory cortex developed by POSIT. Individual home-based format.	3 types of computer activities	1,5 months	9 hours	No reported	MMSE RBANS delay VF BNT TMT SS

Table 2: *Cognitive training intervention characteristics and cognitive outcomes in mild cognitive impairment and early stage AD.*

MMSE: Mini Mental Stage Test; BNT: Boston Naming Test; RT: Rey test; DSFT: Digit Span forward Test; DSBT: Digit Span Backward Test; VF: Verbal fluency; SF: Semantic Fluency; PF; Phonemic Fluency; SCT: Stroop color test; SVLT: Seoul verbal learning test; SAC: Self – assessment of cognitive questionnaire; GOL-AD: Quality of life; GDS: Geriatric Depression Scale; CDR: Clinical Dementia Rate; DPMB: Doors and People memory Battery; SE: Self – efficacy; SAC: Self – assessment of cognitive questionnaire; WMS: Wechsler Memory Scale; CTT: Color Trail Test; GNT: Graded Naming test; VOSP: Visual Object and Space Perception Battery; RBMT: Rivermead Behavioural Memory test; GNT: Graded Naming Test; BT: Brixton test; TT: Token test; DPMB: Doors and People Memory Battery; RSS: Reading Subtest Score; BDI-II: Beck Depression Inventory-2nd Edition; BSRT: Buschke Selective Reminding Test; VR: Visual Reproductions Subtests; LM: Logical Memory Subtests; ROCF: Rey-Osterrieth complex figure test; BriEF-A: Behavior Rating Inventory of Executive Function-Adult version; MEM: Measure Episodic Memory

Volume and duration

Participants completed training programs for a period that ranged from 2 - 6 months. They attended 1 - 2 hours sessions once, twice or three times a week in small groups (4 - 6 patients in each group) or individually. Five of the interventions were administered individually [2,23,24,29] and four were in groups [1,18,25,26,29]. The interventions consisted of 8 to 36 working sessions. The frequency of the sessions varied from 1 to 5 times per week for a duration of 2 to 6 months. The duration of each training session was between 1- 6 hours per week. In one study [18] the duration of the intervention was not reported. Seven of the studies had follow ups conducted after 3 months [29], 4 months [23], 6 months [1,2,5,24] and 12 months [25] after the completion of the intervention and reported that the effects of the interventions remained.

Significant impact of training programs

Eight of the ten studies [1,5,23,24-27,29] reviewed reported improvement in at least one cognitive domain (see Table 3). However, many cognitive abilities, as well as overall cognition were not improved after the intervention.

Specifically, MMSE scores did not increase after training was not in nine out of ten studies ($p > 0.05$ to $p = 0.09$), with the exception of one study [24] ($p < 0.005$). Three of ten studies reported improvement in working ($p < 0.05$) [1,24] and delay memory ($p < 0.01$) [24,25] and another two studies reported improvement in attention [26,27]. These studies used computer-based cognitive training. Only two studies found evidence of improvement in verbal fluency, semantic ($p = 0.04$) (Rojas., *et al*.) and phonemic ($p = 0.01$) [5,25] following pen-and paper strategies without mentioning information regarding the content of the training exercises. Viola., *et al*. (2011) found improvements in mood, following computer-based multi-component cognitive training [26]. On the other hand, Greenaway., *et al*. (2013) did not find any improvement in mood and quality of life using computer- based memory exercises [2].

Results from the present selective review suggest that studies in which multi domain cognitive training was administered had positive impact in more than one domain of cognitive function [1,24]. Additionally, pen- and paper exercises [25] had positive effects on language abilities (naming and semantic fluency). Greater duration of training was associated with greater improvement on global cognitive measures [1,23,24,27,26,29]. It was not possible to infer whether individual versus group sessions had greater benefits on cognition. Mean score and p-value of memory performance, global cognitive function and mood in patients with MCI and early stage AD are presented in table 3.

Study	Outcome measures	Training Group (TG)		Control Group (CG)		p-value post assessment		Test statistics
						TG	CG	
1. Barnes., *et al*. 2009	RBANS delay	PRE:84.8 (12.6) POST:.32 (-.18to.83)		PRE:74.6 (21.4) POST:-.13 (-.47to.20)		p > 0.05	p > 0.05	pair t TEST
	VF	PRE: 35.0 (13.7) POST: -.20 (-.68to.28)		PRE: 40.2 (16.0) POST: .02 (-.37to.41)		p > 0.05	p > 0.05	
	BN	PRE: 26.4 (3.8) POST: -.05 (-.51to.42)		PRE: 26.8 (2.4) POST: -.19 (-.61to.31)		p > 0.05	p > 0.05	
	TMT	PRE:137.0 (51.2) POST: -.11 (-.56to.35)		PRE:149.0 (58.6) POST: -.08 (-.49to.33)		p > 0.05	p > 0.05	
	SS	PRE: 13.0 (3.5) POST:.53 (.02to1.03)		PRE: 12.2 (1.9) POST:.32 (-59to-.05)		p < 0.05	p > 0.05	
2. Viola., *et al*. 2011	MMSE	PRE:22.6 (2.9) POST:22.5 (3.8)		PRE:23.3 (3.9) POST:22.4 (2.8)		p = 0.1	p = 0.9	pair t TEST
	MEMORY	PRE: 5.2 (2.2) POST: 4.9 (2.6)		PRE: 5.5 (1.9) POST: 5.2 (2.2)		p = 0.4	p = 0.5	
	ATTENTION	PRE: 9.3 (4.3) POST: 9.6 (4.7)		PRE: 7.1 (5.0) POST: 8.6 (4.8)		p = 0.01	p = 0.5	
	GDS	PRE:4.7 (3.1) POST: 3.4 (3.0)		PRE:4.3 (3.2) POST: 4.7 (3.4)		p = 0.7	p = 0.001	
	QOL-AD	PRE: 35.2 (5.0) POST:37.3 (4.4)		PRE: 36.1 (5.8) POST:35.4 (6.1)		p = 0.5	p = 0.004	
3. Herrera., *et al*. 2012	MMSE	PRE:1.73 (0.20) POST:2.45 (0.17)		PRE:1.82 (0.24) POST:1.55 (0.22)		p < 0.05	p > 0.05	t TEST
	ROCF	PRE:10.09 (1.52) POST: 10.45 (1.36)		PRE:11.86 (1.27) POST:10.23 (0.87)		p > 0.05	p > 0.05	
	MEM 12	PRE:6.23 (0.35) POST:7.28 (0.26)		PRE:6.40 (0.46) POST:6.05 (0.25)		p < 0.05	p > 0.05	
	DPMTB	PRE:4.91 (0.41) POST:6.36 (0.66)		PRE:4.82 (0.44) POST:4.64 (0.45)		p < 0.05	p > 0.05	
	DSFT	PRE:4.45 (0.31) POST:4.91 (0.21)		PRE:4.36 (0.24) POST:4.18 (0.12)		p < 0.05	p > 0.05	
	DSBT	PRE:3.36 (0.24) POST:4.00 (0.19)		PRE:3.82 (0.18)|POST:3.64 (0.20)		p > 0.05	p > 0.05	
		MCI	Early stage AD	MCI	Early stage AD	MCI	Early stage AD	
4. Hwang., *et al*. 2012	MMSE	PRE: 26.2 (3.6)	18.8 (0.5)	PRE: 25.0 (3.1)	19.3 (4.7)	TG p > 0.05	p > 0.05	Wilcoxon signed- rank test
		POST: 27.0 (2.6)	21.8 (4.1)	POST: 23.6 (4.6)	17.7 (3.8)	CG p > 0.05	p > 0.05	
	BNT	PRE: 10.6 (1.9)	9.3 (2.2)	PRE: 11.2 (1.9)	7.7 (1.2)	p > 0.05	p > 0.05	
		POST: 12.0 (2.0)	9.3 (2.2)	POST: 10.0 (2.2)	8.0 (1.0)	p = 0.07	p > 0.05	
	ROCF	PRE: 34.6 (1.3)	4.3 (4.2)	PRE: 28.9 (8.5)	1.2 (2.0)	p > 0.05	p > 0.05	
		POST: 34.2 (1.6)	3.6 (4.3)	POST: 26.2 (8.8)	0.2 (0.3)	p > 0.05	p > 0.05	
	DSFT	PRE: 6.2 (1.1)	5.8 (1.3)	PRE: 5.8 (1.1)	7.3 (1.2)	p > 0.05	p > 0.05	
		POST: 7.2 (1.10)	6.0 (1.4)	POST: 6.4 (1.5)	7.0 (2.0)	p > 0.05	p > 0.05	
	DSBT	PRE: 3.8 (0.8)	1.5 (1.0)	PRE: 2.22 (1.3)	3.0 (0.0)	p > 0.05	p > 0.05	
		POST: 3.6 (0.9)	3.0 (0.8)	POST: 2.6 (0.5)	1.0 (1.7)	p > 0.05	p > 0.05	
	VF	PRE: 9.0 (3.7)	4.5 (0.6)	PRE: 8.8 (5.1)	3.7 (1.5)	p > 0.07	p > 0.05	
		POST: 10.0 (2.6)	6.5 (0.6)	POST: 8.8 (5.0)	4.0 (1.0)	p > 0.05	p > 0.05	
	SCT	PRE: 73.4 (35.2)	13.0 (13.1)	PRE: 70.6 (23.4)	31.79 (18.0)	p > 0.05	p = 0.07	
		POST: 86 (23.3)	29.0 (9.4)	POST: 59.8 (39.9)	30.3 (23.5)	p > 0.05	p > 0.05	
	VLT	PRE: 1.6 (1.5)	0.0 (0.0)	PRE:2.2 (1.5)	0.0 (0.0)	p > 0.05	p > 0.05	
		POST: 4.6 (2.3)	1.0 (1.4)	POST:2.4 (2.6)	0.0 (0.0)	p < 0.05	p > 0.05	
	SAC	PRE: 3.5 (0.7)	3.1 (1.0)	No reported	No reported	p > 0.05	p > 0.05	
		POST: 4.1 (0.7)	4.2 (0.4)					
5. Rojas., *et al*. 2013	MMSE	PRE:27.53 (2.33) POST:27.53 (2.00)		PRE:27.13 (2.10) POST:25.36 (2.53)		p > 0.05	p = 0.002	pair TEST, Wilcoxon Test
	BOSTON	PRE:44.2. (7.25) POST:47.07 (9.20)		PRE:42.93 (6.78) POST:43.14 (8.10)		p = 0.04	p > 0.05	
	SF	PRE:13.47 (3.09) POST:16.50 (3.67)		PRE:13.47 (3.66) POST:11.07 (3.40)		p = 0.004	p = 0.01	
	PF	PRE:10.47 (4.64) POST:11.93 (4.46)		PRE:10.50 (3.91) POST:9.07 (3.91)		p > 0.05	p > 0.05	
	MEM-REC	PRE:11.07 (1.33) POST:10.64 (1.74)		PRE:9.64 (2.22) POST:8.64 (2.34|)		p > 0.05	p = 0.03	
	CDR	PRE:0.5 (0) POST:0.54 (0.13)		PRE:0.5| (0) POST:0.60 (0.21)		p > 0.05	p = 0.02	
6. Greenaway., *et al*. 2013	MMSE	PRE:26.4 (2.2) POST:26.0 (2..9)		PRE:27.2 (2.4):POST: 27.3 (2.2)		p > 0.05	p > 0.05	Independent t-TEST
	E-Cog	PRE:21.2 (5.9) POST:17.8 (5.4)		NO MENTION				
	SE	PRE:74.9 (12.9) POST:80.2 (9.0)		PRE:79.3 (11.2) POST:77.6 (12.3)		p > 0.05	p > 0.05	
	GOL-AD	PRE:43.4 (6.0) POST:43.4 (5.5)		PRE:43.0 (5.1) POST:41.5 (5.6)		p > 0.05	p > 0.05	
7. Shomaly., *et al*. 2013	N-Back 1	PRE:250.143 (190.937) POST:243.766 (161.457)		PRE: 315.420 (290.987) POST:269.915 (153.983)		No reported		MANCOVA
	N-Back 2	PRE:350.626 (202.243) POST:8.133 (3.719)		PRE:264.979 (64.583) POST:345.801 (184.001)				
8. Gooding *et al*. 2015	BDI-II	PRE:6.39 (4.13) POST:7.38 (3.69)		NO REPORTED		p = 0.09		ANOVA
	MMSE	PRE:50.58 (2.72) POST:51.85 (2.31)				p < 0.01		
	BSRT	PRE: 40.52 (12.48) POST: 47.36 (11.85)				p < 0.01		
	VR	PRE:46.58 (24.24) POST:45.91 (25.54)				p = 0.07		
	LM	PRE:47.61 (26.15) POST:52.66 (27.01)				p = 0.07		
9. Cavallo., *et al*. 2016	MMSE	PRE:22.65 (1.74) POST:22.32 (0.97)		PRE:23.05 (2.44) POST:22.64 (0.96)		p > 0.05		t-TEST
	GNT	PRE: 21.95 (2.57) POST:22.04 (2.53)		PRE:22.15 (217) POST:22.18 (2.27)		p > 0.05		
	VOSP	PRE:35.88 (2.66) POST:36.57 (2.46)		PRE:36.52 (2.45POST:37.35 (2.26)		p > 0.05		
	VF	PRE:17.10 (1.88) POST:16.27 (1.71)		PRE:17.27 (1.76) POST:15.95 (1.60)		p > 0.05		
	RBMT delay	PRE:5.35 (1.73) POST:6.35 (1.73)		PRE:6.52 (1.66) POST:4.52 (1.44)		p < 0.05		
	DSFT	PRE:4.85 (1.60) POST:5.95 (1.80)		PRE:5.20 (1.85) POST:5.18 (1.82)		p < 0.05		
	DSBT	PRE:3.20 (1.26) POST:5.78 (1.44)		PRE:4.10 (0.63) POST:4.02 (0.88)		p < 0.05		
	BT	PRE:4.95 (0.85) POST:5.95 (1.34)		PRE:5.22 (1.32) POST:3.82 (1.65)		p < 0.05		
	TT	PRE:30.30 (2.42) POST:32.30 (2.42)		PRE:30.69 (2.10) POST:27.69 (2.10)		p < 0.05		
10. Barekatan., *et al*. 2016	MMSE	PRE:27.67 (1.49) POST:28.2. (1.01)		PRE:37.53 (1.99) POST:27.60 (1.63)		p = 0.09	p = 0.09	MANCOVA-tTEST
	BriEF-A	PRE:124.27 (25.21) POST:116.20 (24.86)		PRE:110.79 (13.60) POST:103.57 (12.41)		p = 0.14	p > 0.5	
	CTT	PRE: 1.1 (0.7) POST:0.9 (0.6)		PRE:1.1 (0.4) POST:0.9 (0.4)		p = 0.7	p = 0.8	
	SF	PRE:9.7 (4.9) POST:12 (4)		PRE:14 (5.6) POST:16.5 (8.8)		p = 0.20	p = 0.20	
	PF	PRE:16 (4.44) POST:18.40 (4.95)		PRE:19.67 (3.5) POST:18.40 (2.7)		p = 0.01	p = 1	

Table 3: *Mean (SD) and p- value of memory performance, global cognitive function and mood in patients with MCI and early stage AD.*

MMSE: Mini Mental Stage Test; BNT: Boston Naming Test; RT: Rey test; DSFT: Digit Span forward Test; DSBT: Digit Span Backward Test; VF: Verbal fluency; SF: Semantic Fluency; PF; Phonemic Fluency; SCT: Stroop color test; SVLT: Seoul verbal learning test; SAC: Self – assessment of cognitive questionnaire; GOL-AD: Quality of life; GDS: Geriatric Depression Scale; CDR: Clinical Dementia Rate; DPMB: Doors and People memory Battery; SE: Self – efficacy; SAC: Self – assessment of cognitive questionnaire; WMS: Wechsler Memory Scale; CTT: Color Trail Test; GNT: Graded Naming test; VOSP: Visual Object and Space Perception Battery; RBMT: Rivermead Behavioural Memory test; GNT: Graded Naming Test; BT: Brixton test; TT: Token test; DPMB: Doors and People Memory Battery; RSS: Reading Subtest Score; BDI-II,Beck Depression Inventory–2nd Edition; BSRT: Buschke Selective Reminding Test; VR: Visual Reproductions Subtests; LM: Logical Memory Subtests; Rey-Osterrieth complex figure test; BriEF-A: Behavior Rating Inventory of Executive Function-Adult version; MEM: Measure Episodic Memory; TG: Training group; CG: Control Group

Discussion

In the present review, we summarized studies on the effectiveness of cognitive and language rehabilitation in MCI and early stage AD. We identified ten studies that investigated the effectiveness of cognitive rehabilitation in which participants were diagnosed according to Petersen's criteria for persons with MCI and NINCDS-ADRAA criteria for probable AD.

From the selective review we found that five of the ten studies used training programs for memory [1,2,1823,24,29]. Two studies [25] used a multi-domain training program for memory, attention, processing speed, executive function and one study [5] did not report the training program used. Only one study [1] used language training without reporting any information about the kind of language exercises that were used.

The fact that language abilities were not targeted is also confirmed by the lack of neuropsychological tests used to assess language abilities in the studies. Indeed, most of the studies did not use outcomes measures to assess language domains. Specifically, five of ten studies evaluated only the domains of naming and verbal fluency [1,25,27,29].

The results indicated that cognitive interventions were not associated with significant improvement in overall cognitive status. On the other hand, some studies reported that MCI and early stage AD patients in the training groups showed significant improvement of memory (working, verbal and delay) and recall. This may have happened because most studies put emphasis on the practice of memory. Only two studies reported significant improvement on verbal fluency, semantic knowledge and naming. This may be because no interventions contained linguistic exercises according to the details of the studies.

Furthermore, training group showed significant improvement of semantic fluency, memory (delay and working), visuospatial ability, naming and executive function. On the other hand, there are no significant improvements in phonemic fluency, and attention/processing speed. In the intervention group was observed improvement in the specific domains (working memory, executive function, naming, and design fluency) relative to the control group.

According to the above, cognitive training interventions had a positive effect in at least one cognitive domain (i.e. attention, naming, working memory, spatial abilities) while, on the other hand, there were domains in which both patients with AD and MCI did not show any improvement after training (i.e. delay- episodic memory, attention/processing speed, language, verbal fluency). It is important to point out that no cognitive training used multi-component approach simultaneously focusing on the cognitive functions and linguistics. Possibly, multi-component cognitive training with simultaneously emphasis on the cognitive and language impairments are expected to have better results on overall cognitive and linguistic abilities by improving the specific cognitive domain in patients with MCI and early stage AD. Future studies would be appropriate to investigate the benefits of a multi-component cognitive training in the cognitive performance of patients with MCI and early-stage AD. This review must be considered in the context of some limitations. Firstly, the studies consisted of heterogeneous interventions and designs. Secondly, there was no information on the content of some interventions. Lastly, the duration and frequency of the interventions were not the same.

Conclusion

The present selective review revealed that the different kinds of cognitive training had positive impact in only one cognitive domain after training while there were domains in which both patients with AD and MCI did not show any improvement. Possibly, the multicomponent cognitive training with an emphasis on language deficits are expected to have concurrently improvement in more than one domain.

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