Efficacy of cognitive intervention programs in amnesic Mild Cognitive Impairment: A Systematic Review

Gómez-Soria I[1], Peralta-Marrupe P[2*], Calatayud Sanz E[1], Latorre E[3,4]

[1] Department de Physiatry and Nursery, Faculty of Health Sciences. University of Zaragoza, Spain.

[2] Reyes de Aragón Orpea Care Home. Zaragoza, Spain.

[3] Department of Biochemistry and Cell Biology. Faculty of Science. University of Zaragoza, Zaragoza. Spain

[4] Institute of Health Research of Aragón (IIS Aragón), Zaragoza, Spain

***Corresponding Author**

Patricia Peralta-Marrupe
San Juan de la Cruz 22
50006 Zaragoza (Spain)
peraltamarrupe@hotmail.com

Declarations of interest: none

Highlights

1. Amnesic mild cognitive impairment (aMCI) do not have effective pharmacological treatment.

2. Cognitive interventions could be an effective way to delay aMCI.

3. Cognitive training programs show positive effects on global cognition in aMCI.

4. It is essential to continue investigating cognitive interventions in aMCI.

Efficacy of cognitive intervention programs in amnesic Mild Cognitive Impairment: A Systematic Review

Gómez-Soria I[1], Peralta-Marrupe P[2*], Calatayud Sanz E[1], Latorre E[3,4]

[1] Department de Physiatry and Nursery, Faculty of Health Sciences. University of Zaragoza, Spain.

[2] Reyes de Aragón Orpea Care Home. Zaragoza, Spain.

[3] Department of Biochemistry and Cell Biology. Faculty of Science. University of Zaragoza, Zaragoza. Spain

[4] Institute of Health Research of Aragón (IIS Aragón), Zaragoza, Spain

***Corresponding Author**

Patricia Peralta-Marrupe
San Juan de la Cruz 22
50006 Zaragoza (Spain)
peraltamarrupe@hotmail.com

Declarations of interest: none

Abstract

Background: Amnesic mild cognitive impairment (aMCI) is considered a prodromal stage of Alzheimer's disease. Given the absence of an effective pharmacological treatment for aMCI, increasing numbers of studies are attempting to understand how cognitive interventions could benefit these patients. The aim of the present review was to evaluate the efficacy of cognitive interventions programs in older adults with aMCI that assess global cognition using the Mini Mental State Examination (MMSE).

Methods: We searched for randomized controlled trials (RCTs) and clinical trials published before March 2020 on PubMed, Web of Science, Cochrane Library, SCOPUS, and OTseeker. A total of 454 papers were identified and 7 studies that met the inclusion criteria, were included in this review. PRISMA guidelines were followed and PEDro scale was included for the measurement of the quality of the selected studies.

Results: Cognitive training programs show positive effects on global cognition measured by MMSE. Cognitive training and cognitive rehabilitation programs seem to improve several cognitive domains in aMCI patient in both post-training and follow-up analysis.

Conclusions: Our findings support that cognitive interventions may be an effective option for people with aMCI. Cognitive interventions led to improve global cognitive function post-intervention, but also could enhance some cognitive domains post-intervention and at follow-up. However, more RCTs are needed to analyze the potential benefits of cognitive intervention on aMCI.

Keywords: Cognition, Cognitive Training, Cognitive Rehabilitation, Cognitive Stimulation, Mini-Mental State Examination.

1. INTRODUCTION

Amnesic mild cognitive impairment (aMCI) is considered a prodromal stage of Alzheimer's disease (AD); actually around 75%-80% of aMCI patients finally develop AD[1]. The incidence of aMCI substantially varies between 8.5-25.9 per 1,000 person and its prevalence is increasing among elderly groups[2]. aMCI patients can be divided in two groups based in their deficits. Some patients have only memory impairment, called amnestic MCI single domain (aMCIs)[3], whereas in others, aMCI is characterized by slight impairment in at least two cognitive domains[4], for example in executive functions, verbal or visual memory, language, attention[5-7], speed of processing, problem solving or visuospatial abilities[5] , called amnestic MCI multiple domain (aMCImd).

In patients with lower performances in tests of episodic memory and executive functions, it can predict the time to progression from aMCI to clinical diagnosis of AD[8,9]. Given the absence of an effective pharmacological treatment for aMCI[10], clinical research is working on attempting to understand how effective cognitive interventions may be for patients with aMCI[11] to optimize cognition[12], and improve some cognitive domains[13]. Clare et al identified 3 possible approaches to cognitive interventions: 1) Cognitive stimulation, referring to the involvement in group activities designed to increase cognitive and social functioning[14,15], 2) Cognitive rehabilitation, individualized interventions based on the assessment and understanding of the patient's cognitive behavioral deficits[16], 3) Cognitive training, computer or paper and pencil-based cognitive exercises aiming to provide a set of standardized tasks[10].

Several systematic reviews and meta-analysis[13,17-24] have studied the cognitive intervention effects on cognition. However, only two included exclusively patients with aMCI[19,20] and in both studies patients were also treated with pharmacological treatments. Since then, more than 1000 articles (randomized controlled trials and clinical trials) in elderly with MCI have been indexed in Pubmed.

Therefore, it is necessary to update the systematic reviews of Simon et al, (2012)[19] and Jean et al, (2010)[20] and analyze the current knowledge about cognitive interventions on aMCI patients. This

type of intervention may optimize cognitive functioning, contribute to slow cognitive decline and delay the onset of dementia. The aim of the present review was to evaluate the efficacy of cognitive interventions programs in older adults with aMCI that assess global cognition using the Mini Mental State Examination (MMSE).

2. METHODS

This work adheres the PRISMA [Preferred Reporting Items for Systematic Reviews and Meta-Analyses] guidelines[25] and was registered in PROSPERO (CRD42020189135).

2.1. Information Sources and Study Selection: Literature search

We searched for randomized controlled trials (RCTs) and clinical trials published up to March 2020, exploring the effects of non-pharmacological interventions that included cognitive stimulation, cognitive rehabilitation and cognitive training, on cognitive outcomes in older adults diagnosed with aMCI. The databases of PubMed, Web of Science, Cochrane Collaborative Central Register of Controlled Trials, SCOPUS, and OTseeker were used in this search. The terms "cognitive stimulation", "cognitive rehabilitation", "cognitive training", "memory training", "memory intervention", "cognitive dysfunction", "mild cognitive impairment", "amnesic mild cognitive impairment", "Mini-Mental State Examination", "MMSE") were combined with boolean operators. The filters "Type of article" (randomized controlled trials and clinical trials), "Languages" (English or Spanish); "Ages" (65+ years) and "Species" (Humans) were applied.

In addition to the previous search, we conducted a manual search from the reference lists of previously published systematic reviews and meta-analysis found in the literature and we included studies by hand that were not found through the search but did meet the inclusion criteria.

2.2. Inclusion and exclusion criteria

The inclusion criteria were:

1) Randomized controlled trials and clinical trials.

2) Studies that include participants who were diagnosed with aMCI and mean age over 65 years.

3) Cognitive interventions based on cognitive stimulation, cognitive rehabilitation or cognitive training.

4) Primary or secondary outcomes should measure global cognition by MMSE.

The exclusion criteria were:

1) Studies that included diagnosis of other cognitive impairments and not only aMCI.

2) Studies based of multicomponent interventions that included motor intervention, physical exercise or psychotherapeutic techniques.

3) Studies that included healthy participants and it did not perform independently statistical analysis.

2.3. Data Collection and Coding

Two independent reviewers (I G-S., P P-M.) initially evaluated the studies according to titles and abstracts, identified by the search strategy. Then, the reviewers evaluated the completed articles and selected studies according to the specified eligibility criteria. Disagreements between the reviewers were resolved by a third reviewer (E L.).

Three of the authors of the study (I G-S., P P-M. and E L.) independently extracted data from reading the full text articles to complete a priori data tables. Extracted data tables and articles were then reviewed by a four person for accuracy to ensure no errors. The following data was extracted from the selected studies: sample size, design study, setting study, characteristics of the participants (mean age), tools used to assess cognitive function, intervention, control group frequency if there were, blindness, intervention frequency, significant effect for intervention group, duration of follow-up, and information about the professional who applied the intervention.

The PEDro scale[26] was included for the measurement of the quality of the studies included in the review (Table 1). The total scores for methodological quality ranged from 7 to 9 points. The PEDro scale to indicate good quality equal to or greater than 5 points; therefore all studies included are from moderate to high quality.

Study (Author, year)	Eligibility criteria	Random allocation	Concealed allocation	Similar at baseline	Blind subjects	Blind therapist	Blind assessors	< 15% dropout	Intention-to treat-analysis	Between group comparison	Point measures and variability	Total
Jean et al. 2010[27]	1	1	-	1	-	-	1	1	1	1	1	8
Greenaway et al. 2012[32]	1	1	-	1	-	-	-	1	1	1	1	7
Hampstead et al. 2012[33]	1	1	1	1	-	-	1	1	1	1	1	9
Tarnanas et al. 2014[28]	1	1	-	1	1	-	1	1	1	1	1	9
Savulich et al. 2017[29]	1	1	1	1	-	-	-	1	1	1	1	8
Poptsi et al. 2019[30]	1	1	1	1	-	-	1	-	1	1	1	8
Park et al. 2019[31]	1	1	1	1	-	-	-	1	1	1	1	8

Table 1: PEDro scale of quality for eligible randomized controlled trials and randomized trials.

3. RESULTS

3.1. Literature Search- Studies included

The initial search provided a total of 454 records. After removing duplicates, 353 potentially relevant studies were found, of which 28 articles was selected based on title and abstract. After reading them, only 11 studies were included based on the full-text. Finally, seven studies[27-33] were eligible for inclusion in the review: 5 studies[27-31] were focused on cognitive training (two about computerized training), and 2 studies[32,33] were focused on cognitive rehabilitation. Studies about cognitive stimulation were not included. Selection process are detailed in Figure 1.

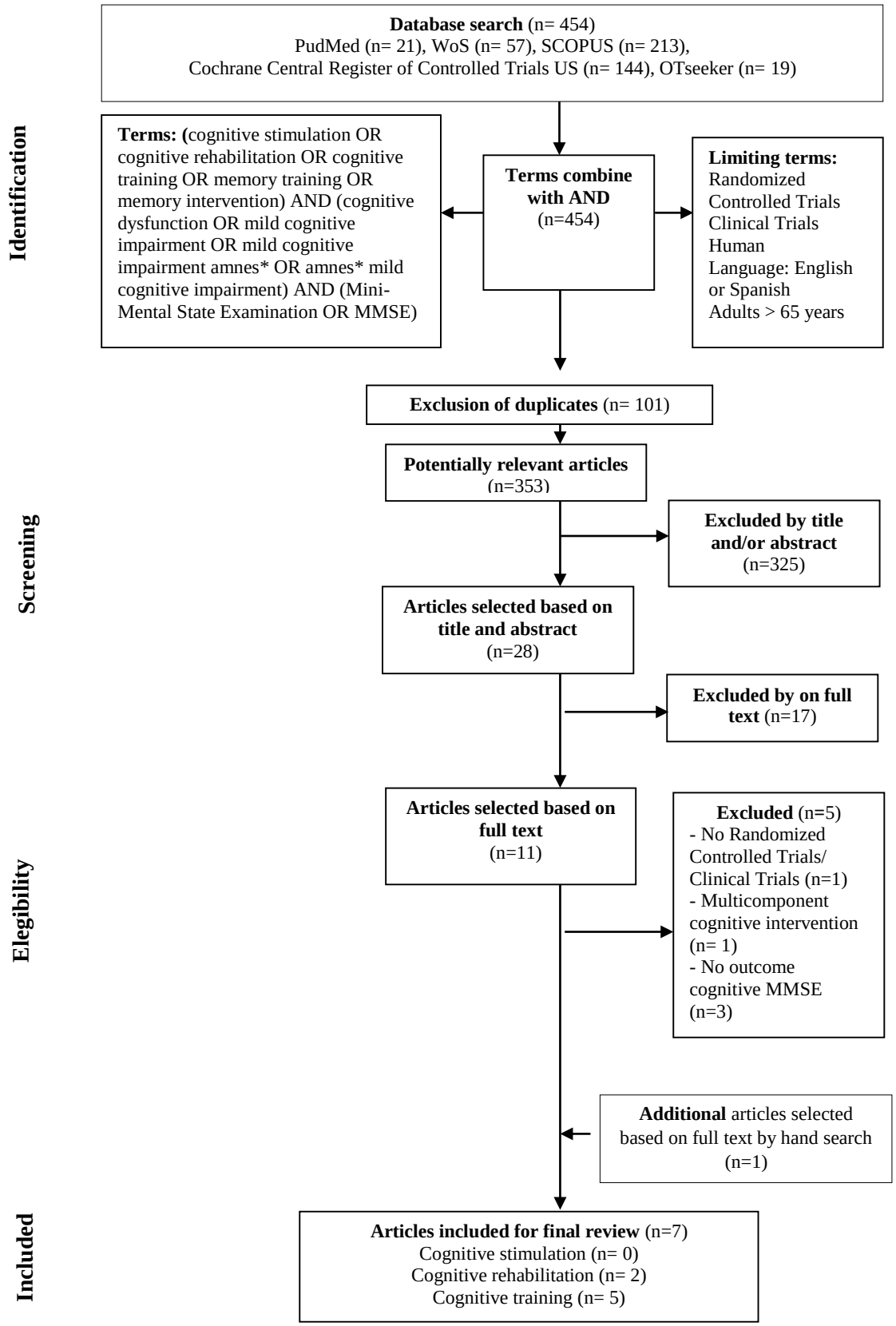

Figure 1: Information flow through the different phases of this systematic review.

3.2. Studies Characteristics

3.2.1. Participant characteristics and sample size.

The main characteristics of the included studies are described in Table 2. Participants were mainly recruited from medical/ research settings such as medical center, clinics or hospitals. In the 7 studies included in the present review, the number of individuals with aMCI enrolled in the cognitive intervention varied from 22[27] to 95[28], being 48.3 the mean of participants. The mean age of the participants in the experimental group was 71 ranged from 68.5[27] to 75.2[29] years old. The education years ranged from 10.1[31] to 17.4[33] years, with a 14.4 education years as mean. The most patients were female; 8.5 males and 11.8 females of average in the experimental group.

3.2.1. Experimental Design of studies reviewed.

The studies were randomized controlled trials and clinical trials, however their design were quite different. Three studies offered no follow-up (FU) evaluation and only performed post-intervention[28,29,33] analysis, two studies performed a FU at 4 weeks[27] or 6 months[30] after the intervention and two studies evaluated two FU at 8 weeks-6 months[32] and 12 weeks-24 weeks[31]. Only one study had higher than annual FU sessions[31]. All studies evaluated both within (experimental group) and between group findings.

3.3. Cognitive intervention characteristics.

The cognitive intervention is normally lead by a qualified professional, being a neuropsychologist, occupational therapist or psychologist. However, only one study specified that they have been specifically trained[30]. Intervention characteristics varied widely (Table 2). Studies were grouped according to the type of intervention assessed: cognitive training (CT) and cognitive rehabilitation (CR). The number of aMCI older adults in the experimental groups was between 9[33] and 32[28], being 18.8 participants of mean. The duration of interventions also varied greatly between studies, ranged from 5[33] to 48[30] sessions and from 30[31] to 90[28] min/session. The type of intervention in the cognitive training was focused on: 1) Memory training that included: to re-learn face–name associations (first and last names)[27]; error exclusion learning, categorization,

three-phasic method, face recognition, imagery, exercise, and interactive methods[31]; completion time, digit span, learning ability[30]; errorless learning (EL) and spaced-retrieval (SR)[27]. 2) Frontal training that included: behavior modification, ordering, abstract thinking training, and goal-directed training. 3) Attention training as attention processing, sudoku, color-diagram finding, shape diagram finding and word finding. 4) Visuospatial function training including direction training and localization training. 5) Language training: word naming test, country naming test, memory, writing, speaking events[31]; tasks ecologically valid derived from activities of daily living (ADLs), focused in the training and enhancement of semantic expression of language, semantic comprehension of language and phonemic expression of language[30]. 6) Orientation trainings that included: real sense training and drawing a clock and calculation training (calculation of price and pin money)[31]. The cognitive computerized training was focused on playing virtual reality cognitive training games (some simple memory exercises inside an ecologically valid 3D environment)[28] and play Game Show on an iPad[29]. The type of intervention in the cognitive rehabilitation was focused on: mnemonic strategy training[33] and memory compensatory strategy external memory aids such as calendars[32].

Study (Autor, year)	Subtype aMCI	N	Mean Age year (SD)	Education years (SD)	Gender male /female	Mean MMSE baseline	Setting study	Intervention group (Frequency)	Control group	Blindness	Lead by	Follow-up
Jean et al. 2010[27]	s/md	N: 22 IG: 11 CG: 11	 68.5 (9.2) 68.5 (5.9)	 14.4 (3.2) 14.5 (4.2)	 4/7 5/6	29.5	NS	**CT (Errorless and Spaced retrieval: memory training)** + **Pychoeducational content** 45-min session Twice a week 6 sessions	**Active** CT (Errorful) + Pychoeducational content 45-min session Twice a week 6 sessions	Single (Research assistant)	NS	4 weeks
Greenaway et al. 2012[32]	s	N: 40 IG: 20 CG: 20	 72.7 (6,9) 72.3 (7.9)	 16.4 (2.8) 16.4 (2.8)	 8/12 7/13	26.8	Medical center	**CR (Notebook/calendar: memory support system training)** 60-min session Twice a week 6 weeks 12 sessions	**Passive**	NS	Licensed occupational therapist specializing and a Master's level psychologist	6 months
Hampstead et al. 2012[33]	md	N: 18 MS:9 XP:9	 71.7 (10,2) 70.8 (7.2)	 17.4 (1.8) 16.8 (2.4)	 NS NS	26.7	Medical center	**CR (memory training)** 2 weeks 5 sessions	**Passive**	Single	NS	No
Tarnanas et al. 2014[28]	s	N: 95 IG: 32 AC/G: 39 CG: 34	 70.5 (4.3) 69.7 (4.5) 70.9 (4.4)	 NS NS NS	 12/20 16/23 13/21	26.4	Day Clinic	**CCT (Virtual reality museum: memory training)** 90-min session Twice a week 5 months 40 sessions	**Active** CT (learning,based memory training) 90-min session Twice a week 5 months 40 sessions/ **Passive**	Double	Psychologists	No
Savulich et al. 2017[29]	NS	N: 42 IG: 21 CG: 21	 75.2 (7.4) 76.9 (8.3)	 15.9 (1.3) 16.0 (2.1)	 11/10 14/7	26.7	Hospital	**CCT (Memory game for use on an iPad: memory training)** 60-min session Twice a week 4 weeks 8 sessions	**Passive**	NS	Cognitive experimental psychologist and professional game developer	No

Study (Autor, year)	Subtype aMCI	N	Mean Age year (SD)	Education years (SD)	Gender male /female	Mean MMSE baseline	Setting study	Intervention group (Frequency)	Control group	Blindness	Lead by	Follow-up
Poptsi et al. 2019[30]	md	N: 71 PC/G:14 PP/G:18 OR/G:10 AC/G:15 CG: 14	 67.9 (9.8) 70.1 (5.5) 71.8 (3.9) 65.7 (6.6) 68.1 (6.9)	 12.1 (3.2) 11.2 (3.2) 9.7 (5.8) 11.1 (4.5) 10.4 (4.8)	 5/9 4/14 5/15 4/11 4/10	27.2	Day Care Centre	**CT (language training program)** 60-min session Twice a week 6 months 48 sessions	**Active** The same tasks of intervention orally **Passive**	Single (assessor)	Expert psychologists trained in cognitive interventions	6 months
Park et al. 2019[31]	NS	N: 50 HCI: 25 CG: 25	 70.7 (7.5) 69.7 (8.4)	 10.1 (3.3) 10.0 (3.5)	 12/13 10/15	26.1	Hospital	**CT (memory training and language training)** 30-min session 12 weeks 12 sessions	**Passive**	NS	NS	24 weeks

aMCI: amnestic mild cognitive impairment. s: single domain. md: multiple domain. IG: Intervention Group. CG: Control Group. MS: Mnemonic Strategy Training. XP: Matched-Exposure Control Group. AC/G: Active control group. PC/G: Computer-based program of language tasks intervention group. PP/G: Paper and pencil intervention group. OR/G: Oral intervention group. HCI: Home based cognitive intervention group. CT: Cognitive Training. CR: Cognitive rehabilitation. CCCT: Computer based cognitive training. NS: Not specified. FU: Follow-up.

Table 2. Characteristics of participants, format and content of cognitive interventions programs in aMCI.

3.4. Control group type.

There are many differences on control groups included in the studies: 42.9% of the studies included an active control group which involved participants in different activities to the intervention group, or participants performed the same tasks of intervention but orally and 57.1% of the studies included only a passive control group. Only one of the studies combined analysis of healthy participants with aMCI, including on the experimental subgroups and control group

3.5. Measured outcomes.

The main outcome of this review was to assess the global cognitive function by MMSE. The MMSE is a universal cognitive screening test, commonly used in both clinical and research settings[34]. This tool is composed by 20 short individual tests covering 11 domains as orientation, attention or calculation, with a maximun of 30 points[35]. The sensitivity of MMSE is 0.58 and specificity 0.82. Based on optimal cut-off values, scoring lower than 28 would suggest MCI[36]. Specific cognitive domains were also evaluated by different instruments. All studies evaluated the memory on individuals with aMCI (verbal, episodic, visuospatial, semantic and subjective memory); 71.4% of selected studies also analysed other cognitive domains as language (repetition, semantic and phonemic comprehension)[30-33], visuospatial (abilities, skills)[28,29,32,33], attention[28,31-33], constructional abilities[32,33], executive function[28,31,33], praxis[28] or motor speed[29]. All studies included neurocognitive outcome measures to assess the effect of cognitive intervention on domain-specific cognitive measures. However, it should be noted that there is considerable overlap between the cognitive functions assessed by each test, some outcome measures tapping into multiple cognitive domains; as such, memory, attention, language, visuospatial abilities, visuospatial skills, praxis, attention and executive function.

3.6. Effect of cognitive interventions on aMCI

3.6.1. Mini-Mental State Examination

The Mini-Mental State Examination or MMSE was the main tool to assess general cognitive screening. Table 3 describes the baseline, post-intervention and follow-up data of MMSE in the

intervention and control group (active and passive) and reflecting the significant positive effects observed in the experimental group, between groups and by time interactions. At baseline, the average of MMSE ranged from 26.05[31] to 29.5[27] points. The studies based on computerized CT of Tarnanas et al.[28] and Savulich et al.[29] showed significant improvements between experimental group and control group in the global cognition measured with MMSE and also the study of Savulich et al.[29] in group by time interactions analysis. This is particularly remarkable since the duration total of the intervention in both programs was quite different 8 – 40 sessions and 60 -90 min/session respectively. There is no evidence that the higher educational level groups obtained more significant improvements. However, mean education years (data only provided in one of the two studies) would need to take into account, as several authors comment the influence of educational level on the performance of MMSE[37,38]. The rest of the studies analyzed showed no statistically significant differences in global cognition measured by MMSE.

3.6.2. Other global cognitive instruments

Other tools have also been used to assess general cognitive screening as Dementia Rating Scale 2nd Edition (DRS-2)27,32 or the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog Scale)31 (Table 4). Although some studies showed significant improvements in MMSE scores, neither showed significant differences on these instruments after the intervention or at follow-up.

	Baseline			Post-intervention			Follow-up		
Study (Autor, year)	Experimental group	Active Control group	Passive Control group	Experimental group	Active Control group	Passive Control group	Experimental Group	Active Control group	Passive Control group
Jean et al. 2010[27]	29.45 (0.82)	29.55 (0.52)	n/a	29.36 (1.29)	29.33 (0.87)	n/a	28.82 (1.47)	29.44 (0.73)	n/a
Greenaway et al. 2012[32]	26.40 (2.20)	n/a	27.2 (2.40)	26.00 (2.90)	n/a	27.30 (2.20)	26.10 (2.20)	n/a	27.30 (1.80)
Hampstead et al. 2012[33]	26.90 (1.80)	26.10 (2.10)	27.7 (2.20)	ND	ND	ND	ND	ND	ND
Tarnanas et al. 2014[28]	26.80 (3.60)	26.20 (3.60)	26.2 (3.10)	28.20 (2.50) [a,b]	27.0 (2.60) [a,b]	24.60 (4.60) [a,b]	n/a	n/a	n/a
Savulich et al. 2017[29]	26.60 (2.90)	n/a	26.80 (2.20)	27.4 (1.50) [b,*]	n/a	26.10 (2.40) [b,*]	n/a	n/a	n/a
Poptsi et al. 2019[30]	28,07 (1.63)[1]	27.20 (1.93)	26.07(3.05)	28.92 (1.32)[1]	27.40 (1.99)	26.92 (2.73)	n/a	n/a	n/a
	27.89 (1.28)[2]			28.33 (1.37)[2]					
	26.90 (2.47)[3]			26.70 (2.54)[3]					
Park et al. 2019[31]	25.90 (2.70)	n/a	26.20 (2.60)	26.00 (2.40)	n/a	25.00 (1.90)	26.20 (2.4)	n/a	26.10 (3.10)

[1]: PC/G: Computer-based program of language tasks intervention group. [2]: PP/G: Paper and pencil intervention group. [3]: OR/G: Oral intervention group.
n/a: not applicable. ND: data not available
[a] Significant positive effect in the experimental group
[b] Significant positive effect between groups
[*] Significant group by time interactions

Table 3. Summary of Mini-Mental State Examination (MMSE) scores in the selected studies

3.6.3 Specific domain- cognitive function

Table 4 describes the post-intervention and follow-up data of cognitive measures used. All studies based in CT[27-30] showed significant improvements in memory (verbal memory, verbal episodic memory, episodic memory,) after intervention[27-31] and in some of them, the benefits even remain at follow-up[27,31]; these effects were observed in the experimental group[27-30], between groups[27-29,31] and by time interactions[27,29]. Savulich et al.[29] demonstrated benefits in the experimental group, between group and group by time in episodic memory by the Cambridge Neuropsychological Test Automated Battery Paired (CANTAB PAL) and between group and group by time in visuospatial memory on the Brief Visuospatial Memory Test-Revised (BVMT-R) after training. Moreover, Tarnanas et al.[28] showed positives changes in verbal memory by Rey Auditory Verbal Learning Test (RAVLT) Delayed Recall in the experimental group and between group post-intervention and Poptsi et al.[30] too found gains on the RAVLT in the experimental group after intervention. Jean et al.[27] showed subjective memory enhancement from baseline to training end and at 4-weeks FU measured by Multifactorial Memory Questionnaire (MMQ) Contentment and Strategy in the experimental group and group by time. In another CT study, Park et al.[31] found significant improvements between groups, both post-intervention and at FU in a questionnaire (COWAT) that assesses memory, attention and executive functions. There was not significant differences in the verbal episodic memory after the intervention nor at FU on California Verbal Learning Test 2nd Edition (CVLT-II) or subjective memory in MMQ Ability in the study of Jean et al.[27]. In Tarnanas et al[28], with an intervention based in a computerized CT, the authors did not found differences in the verbal memory by RAVLT Immediate Recall, Recognition and Copy. When memory is associated with other cognitive domains, as in the case of the study of Greenaway et al.[32] the experimental group and group by time showed significant changes on the Everyday Cognition (Ecog) memory scales in memory, language, visuospatial abilities and attention post-intervention and at FU analysis. However, in the CT program of Park et al.[31] did not observed significant changes after the intervention or at FU in memory, attention or executive function measured by Digit Span Memory Test, Story Memory, Digit-symbol, Color word strop and

COWAT. Similarly, the CR program of Hampstead et al.[33] did not show benefits in memory, language, attention or visuospatial/constructional with the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).

The language were also assessed by two studies[28,30] based on CT programs. Statistically significant differences were observed in both studies. In the study of Poptsi et al.[30] language showed significant differences between groups and in experimental group analysis by Verbal Fluency Test (FAS), Boston Diagnostic Aphasia Examination (BDAE)1 and BDAE2 after intervention. On the other hand, in the computerized program of Tarnanas et al.[28] language was associated with semantic memory, and also significant changes were observed by Boston Naming Test (BNT) in the experimental group post-intervention.

Study (Autor,year)	Outcome Measures	Outcome Cognitive Domain (s)	Post-intervention		Follow-up	
			Experimental group	Between group findings	Experimental group	Between group findings
Jean et al. 2010[27]	**MMSE**	**Global Cognitive Function**	↔	↔	↔	↔
	CVLT-II	Verbal Episodic Memory	n/a	↔	n/a	↔
	DRS-2	**Global Cognitive Function**	n/a	↔	n/a	↔
	MMQ	Subjective memory				
	- Contentment		↑	↔*	↑	↔*
	- Ability		↔	↔	↔	↔
	- Strategy		↑	↔*	↑	↔*
	RBMT	Verbal Episodic Memory	↔	↔	↔	↔
Greenaway et al. 2012[32]	**MMSE**	**Global Cognitive Function**	↔	↔	↔[1]/↔[2]	↔[1]/↔[2]
	ECog memory scales	Memory, Language, Visuospatial Abilities, and Attention	↑	↔*	↑[1]/↑[2]	↔[1]*/↔[2]
	DRS-2	**Global Cognitive Function**	↔	↔	↔[1]/↔[2]	↔[1]/↔[2]
Hampstead et al. 2012[33]	**MMSE**	**Global Cognitive Function**	n/a	↔	n/a	n/a
	RBANS	Memory, Visuospatial/Constructional, Language and Attention	n/a	↔	n/a	n/a
	TMT	Attention and Executive Function				
	- Trails A		n/a	↔	n/a	n/a
	- Trails B		n/a	↔	n/a	n/a
Tarnanas et al. 2014[28]	**MMSE**	**Global Cognitive Function**	↑	↑	n/a	n/a
	RAVLT	Verbal Memory				
	- Immediate Recall		↔	↔	n/a	n/a
	- Delayed Recall		↑	↑	n/a	n/a
	- Recognition		↔	↔	n/a	n/a
	- Copy		↔	↔	n/a	n/a
	BNT	Language and Semantic Memory	↑	↔	n/a	n/a
	ROCF	Praxis and Visuospatial Abilities				
	- Copy		↔	↔	n/a	n/a
	- Immediate Recall		↑	↑	n/a	n/a
	- Delayed Recall		↔	↔	n/a	n/a
	- Recognition		↔	↔	n/a	n/a
	Symbol Digit Modalities Test	Attention and Executive Function	↔	↔	n/a	n/a
	TMT: Trails B	Attention and Executive Function	↑	↑	n/a	n/a
	Stroop interference Test	Attention and Executive Function	↔	↔	n/a	n/a
	Letter Fluency	Attention and Executive Function	↔	↔	n/a	n/a

Study (Autor,year)	Outcome Measures	Outcome Cognitive Domain (s)	Post-intervention		Follow-up	
			Experimental group	Between group findings	Experimental group	Between group findings
Savulich et al. 201729	**MMSE**	**Global Cognitive Function**	↔	↑*	n/a	n/a
	CANTAB PAL	Episodic Memory	↑	↑*	n/a	n/a
	BVMT-R	Visuospatial Memory	↔	↑*	n/a	n/a
Poptsi et al. 2019[30]	**MMSE**	**Global Cognitive Function**	↔	↔	n/a	n/a
	RAVLT	Verbal Memory	↑	↔	n/a	n/a
	RBMT	Verbal Episodic Memory	↑	↔	n/a	n/a
	FAS	Verbal Fluency (semantic and phonemic)	↑	↑	n/a	n/a
	BDAE 1- Repetition	Language, repetition	↑	↔	n/a	n/a
	BDAE 2- **Phonemic Correlation**	Language, phonemic comprehension	↑	↔	n/a	n/a
	PPT	Executive function	↑	↔	n/a	n/a
Park et al. 2019[31]	**MMSE**	**Global Cognitive Function**	n/a	↔	n/a	↔
	ADAS-Cog Scale	**Global Cognitive Function**	n/a	↔	n/a	↔
	Digit Span Memory Test	Memory, attention and executive function	n/a		n/a	
	- Forward			↔		↔
	- Backward			↔		↔
	- Total score			↔		↔
	Story Memory	Memory, attention and executive function	n/a		n/a	
	- Recall			↔		↔
	- Delayed Recall			↔		↔
	- Recognition			↔		↔
	- Total score			↔	n/a	↔
	COWAT	Memory, attention and executive function	n/a			
	- Category			↔		↔
	- Letter score			↔		↔
	- Total score			↑		↑
	Color-word strop	Memory, attention and executive function	n/a	↔	n/a	↔
	Digit-symbol test	Memory, attention and executive function	n/a	↔	n/a	↔

MMSE: Mini mental state examination. CVLT-II: California Verbal Learning Test 2nd Edition. DRS-2: Dementia Rating Scale 2nd Edition MMQ: Multifactorial Memory Questionnaire. RBMT: Rivermead Behavioral Memory Test. RBANS: The Repeatable Battery for the Assessment of Neuropsychological Status. TMT: Trail Making Test. ECog: Everyday Cognition. CANTAB PAL: The Cambridge Neuropsychological Test Automated Battery Paired. BVMT-R: The Brief Visuospatial Memory Test-Revised. CANTAB CRT: CANTAB Choice Reaction Time. RAVLT: Rey Auditory Verbal Learning Test. BNT: Boston Naming Test. ROCF: Rey Complex Figure Copy. COWAT: Controlled oral word association test. FAS: Verbal Fluency test. FAS: Verbal Fluency test. BDAE: Boston Diagnostic Aphasia Examination. PPT: Pyramids and Palm Trees. [1]: 8 weeks. [2]: 6 months.
↑: significant positive effect. ↔: no change. n/a: not applicable. *: Significant group by time interactions.

Table 4. Cognitive intervention programs in aMCI: Measures and results of cognitive function.

The executive function was analyzed in four studies[28,30,31,33] based on CT programs; one study[30] without associating to other cognitive domains and two studies[28,33] associated with attention and one[31] study associated with attention and memory. The study of Poptsi et al.[30] evaluated the executive functions by Pyramid and Palm Trees (PPT), finding statistically significant differences in the experimental group after intervention. In the computerized program of Tarnanas et al.[28] it evaluated executive function and attention, and significant differences were observed by TMT Trails B. However, improvements were not observed in attention and executive functions in the study of Park et al.[31] by TMT (Trails A and B).

Other cognitive domains as praxis or visuospatial abilities were evaluated in the computerized CT program of Tarnanas et al.[28] showing significant changes by Rey Complex Figure Copy (ROCF) immediate recall in the experimental group and between groups post-training.

4. DISCUSSION

The aim of this systematic review was to evaluate the efficacy of cognitive intervention programs in older adults with aMCI. We have analyzed seven studies and six of them evidenced positive effects in cognition. In particular, computerized cognitive training programs yield significant improvements on global cognitive function measured by MMSE in participants with aMCI. In agreement, some randomized controlled trials based in multicomponent cognitive interventions programs also found benefits in MMSE scores. Tsolaki et al.[12] described significant differences carrying out an intervention for 5 months (60 sessions with 90 min per session) in younger participants and also Foster et al.[39] showed benefits on global cognition after a 6-months program (120 minutes each session). In contrast, in Jeong et al.[40], based on multicomponent intervention, observed no differences in MMSE in younger aMCI participants. However, participants in our study and also in Tsolaki et al.[12] and Foster et al.[39], had higher MMSE scores at baseline than participants in Jeong et al.[40] (27.1 versus 25.7). This point could suggest that cognitive interventions may be beneficial only in a group of participants with a certain cognitive level.

Memory decline could be detected prior to the dementia stage of AD, therefore it is important to analyze memory-binding deficiencies[41]. In this systematic review, we have observed that cognitive interventions show improvements in episodic, verbal, visuospatial, semantic and visuospatial memory, which could be promising for slowing cognitive impairment in people with aMCI. All studies based in CT programs[27-31] included in this review showed significant improvements in memory in the experimental group[27-30], between groups[27-29,31] and by time interactions[27,29] measured by MMQ, RAVLT, CANTAB PAL, BVMT-R, RBVMT, COWAT. In agreement, other studies based on CT also showed significant improvements in prospective and episodic memory.[42], working memory[11,43-45], long term memory[11]; or subjective memory[42,45]. Moreover, several studies based on computerized CR programs also obtained significant changes in short and long memory and in visual and verbal episodic memory[46,47]. Similarly, studies based on CE showed positive effects on memory abilities, especially on short-term and working memory as demonstrated by Moro et al.[48] or Wenish et al.[49]. The study of Unverzagt et al.[50] based on a

computer visual attention intervention failed to benefited memory training but showed gains after reasoning and speed training.

Poptsi et al.[30], through a traditional cognitive intervention and Tarnanas et al.[28], based on computerized intervention, evidenced significant changes in language. Supporting that, several studies also showed benefits in language domain as Rozenfeld Olchik et al.[51] in a program based on memory training and Cipriani et al.[48] based on a computer CR program. Moreover, Poptsi et al.[30] and Tarnanas et al.[28] also evaluated executive function demonstrating positive effects measured by PPT and TMT: Trails B. Similarly, the study of Moro et al.[48] proved the efficacy of a CE program on the executive functions in patients with aMCI, suggesting that an improvement in those functions benefit memory at least at a 6 month FU. Other cognitive domains such as attention, praxis, or visuospatial abilities were also analyzed. The computerized CT program of Tarnanas et al.[28] showed significant differences in those cognitive domains measured by RCOF-Immediate recall after intervention. However, the study of Talassi et al.[47], with a CR program, found no differences in participants with MCI.

Although the presented studies have evidenced a significant improvement either in global cognitive function and cognitive domains, we should highlight some limitations that can affect our conclusions: 1) Small sample size (18-22 participants). 2) Cognitive interventions are quite heterogeneous in terms of techniques, session duration and total intervention time. 3) Lack of specific training of some health-care professionals. 4) Wide variety of assessment tool and instruments. 5) Differences in follow-up assessments.

Since aMCI is a degenerative condition in some patients, it is crucial to assess the longitudinal progression of clinical findings[20]. In light of the present findings, further recommendations to improve cognitive interventions in the aMCI population are suggested. It is need to perform randomized trials with large samples based on cognitive interventions programs which are designed and adapted to the cognitive level of the participants. The cognitive intervention programs should be carried out under supervision of trained and qualified professionals, using assessments for global cognition and cognitive domains, and evaluate at different times and at

long term. It would be interesting to specify the MCI subtypes included in the studies as well as analyze separately the results for each MCI subtype[20]. Educational levels and occupations of patients must be considered when analyzing the effects of cognitive interventions because both factors could have an impact on cognitive reserve[52]. Since 57.14% of the studies included in this review has an average educational level equal to or greater than 12 years, it is possible that the positive results are somehow related to this aspect. Therefore, studies in individuals with lower educational level also need to be performed to investigate this hypothesis.

5. CONCLUSIONS

Our finding support that cognitive interventions seems to be an effective option for people with aMCI. Cognitive interventions programs led to improvements in the global cognitive function measured by MMSE after intervention and showed improvements in cognitive domains as memory, language, attention, executive function, visuospatial abilities or praxis. A critical comparison between studies is difficult due to the heterogeneity of the characteristics the cognitive intervention programs and assessment tools. Showing these promising results and with the lack of pharmacological treatments, it is essential to continue investigating the effects of the cognitive interventions, especially about cognitive rehabilitation and cognitive stimulation programs, in controlled randomized trials with large samples and with long-term follow-up.

Funding:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declarations of interest: none

REFERENCES

1. Hu Z, Wu L, Jia J, Han Y. Advances in longitudinal studies of amnestic mild cognitive impairment and Alzheimer's disease based on multi-modal MRI techniques. Neurosci Bull. 2014;30(2):198-206. doi:10.1002/gps.4075.

2. Ward A, Arrighi HM, Michels S, Cedarbaum JM. Mild cognitive impairment: disparity of incidence and prevalence estimates. Alzheimers Dement. 2012;8(1):14-21. doi:10.1016/j.jalz.2011.01.002.

3. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol. 1999;56(3):303-8. doi:10.1001/archneur.56.3.303.

4. Gauthier S, Reisberg B, Zaudig M, Petersen RC, Ritchie K, Broich K, et al. Mild cognitive impairment. Lancet. 2006. 367(9518):1262-70. https://doi.org/10.1016/S0140-6736(06)68542-5.

5. Petersen RC. Clinical practice. Mild cognitive impairment. N Engl J Med. 2011. 364:2227-34. doi:10.1056/NEJMcp0910237.

6. Clément F, Gauthier S, Belleville S. Executive functions in mild cognitive impairment: emergence and breakdown of neural plasticity. Cortex. 2013;49(5):1268-79. https://doi.org/10.1016/j.cortex.2012.06.004.

7. Taler V, Phillips NA. Language performance in Alzheimer's disease and mild cognitive impairment: a comparative review. J Clin Exp Neuropsychol. 2008;30(5):501-56. doi:10.1080/13803390701550128.

8. Blacker D, Lee H, Muzikansky A, Martin EC, Tanzi R, McArdle JJ, et al. Neuropsychological measures in normal individuals that predict subsequent cognitive decline. Arch Neurol. 2007;64:862-71. doi:10.1001/archneur.64.6.862.

9. Saunders NL, ~~J~~ Summers MJ. Longitudinal deficits to attention, executive, and working memory in subtypes of mild cognitive impairment. Neuropsychology. 2011;25:237-48. https://doi.org/10.1037/a0021134.

10. Sitzer D, Twamley E, Jeste D. Cognitive training in Alzheimer's disease: a meta-analysis of the literature. Acta Psychiatr Scand. 2006;114(2):75-90. doi:10.1111/j.1600-0447.2006.00789.x..

11. Carretti B, Borella E, Fostinelli S, Zavagnin, M. Benefits of training working memory in amnestic mild cognitive impairment: specific and transfer effects. Int Psychogeriatr. 2013;25(4):617-26. doi:10.1017/S1041610212002177.

12. Tsolaki M, Kounti F, Agogiatou C, Poptsi E, Bakoglidou E, Zafeiropoulou M, et al. Effectiveness of nonpharmacological approaches in patients with mild cognitive impairment. Neurodegenerative Dis. 2011;8(3):138-45. doi:10.1159/000320575.

13. Li H, Li J, Li N, Li B, Wang P, Zhou T. Cognitive intervention for persons with mild cognitive impairment: A meta-analysis. Ageing Res Rev. 2011;10(2):285-96. doi: 10.1016/j.arr.2010.11.003.

14. Clare L, Woods RT, Moniz Cook ED, Orrell M, Spector A- Cognitive rehabilitation and cognitive training for early-stage Alzheimer's disease and vascular dementia (Cochrane Review). Cochrane Database Syst Rev. 2003;4:CD003260. doi:10.1002/14651858.CD003260.

15. Clare L, Woods RT. Cognitive training and cognitive rehabilitation for people with early-stage Alzheimer's disease: a review. Neuropsychol Rehabil. 2004;14:385-401. https://doi.org/10.1080/09602010443000074.

16. Vidovich MR, Lautenschlager NT, Flicker L, Clare L, Almeida OP. The PACE study: a randomised clinical trial of cognitive activity (CA) for older adults with mild cognitive impairment (MCI). Trials. 2009;10(1):114. doi:10.1186/1745-6215-10-114.

17. Reijnders J, van Heugten C, van Boxtel M. Cognitive interventions in healthy older adults and people with mild cognitive impairment: a systematic review. Ageing Res Rev. 2013;12(1):263-75. https://doi.org/10.1016/j.arr.2012.07.003.

18. Hong JAY, Hye Jang E, Hwang J, Hoon Roh J, Lee JH. The efficacy of cognitive intervention programs for mild cognitive impairment: a systematic review. Curr Alzheimer Res. 2015;12(6):527-42. doi:10.2174/1567205012666150530201636.

19. Simon SS, Yokomizo JE, Bottino CM. Cognitive intervention in amnestic Mild Cognitive Impairment: a systematic review. Neurosci Biobehav Rev. 2012;36(4):1163-78. doi:10.1016/j.neubiorev.2012.01.007.

20. Jean L, Marie-Eve Bergeron MP, Thivierge S, Simard M. Cognitive Intervention Programs for Individuals with Mild Cognitive Impairment: Systematic Review of the Literature. Am J Geriatr Psychiatry. 2010;18:281-96. doi:10.1097/JGP.0b013e3181c37ce9

21. Cooper C, Li R, Lyketsos C, Livingston G. Treatment for mild cognitive impairment: systematic review. Br J Psychiatry. 2013;203(4):255-64. doi 10.1192/bjp.bp.113.127811.

22. Teixeira CVL, Gobbi LTB, Corazza DI, Stella F, Costa JLR, Gobbi S. Non-pharmacological interventions on cognitive functions in older people with mild cognitive impairment (MCI). Arch Gerontol Geriatr. 2012; 54(1):175-80. doi:10.1016/j.archger.2011.02.014.

23. Chandler MJ, Parks AC, Marsiske M, Rotblatt LJ, Smith GE. Everyday impact of cognitive interventions in mild cognitive impairment: a systematic review and meta-analysis. Neuropsychol Rev. 2016;26(3):225-51. doi:10.1007/s11065-016-9330-4.

24. Sherman DS, Mauser J, Nuno M, Sherzai D. The efficacy of cognitive intervention in mild cognitive impairment (MCI): A meta-analysis of outcomes on neuropsychological measures. Neuropsychol Rev. 2017;27(4):440-84. https://doi.org/10.1007/s11065-017-9363-3.

25. Moher D, Liberati A, Tetzlaff J, Altman DG, Prisma Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS med. 2009;6(7):e1000097. https://doi.org/10.1371/journal.pmed.1000097.

26. Maher CG, Sherrington C, Herbert RD, Moseley AM, Elkins M. Reliability of the PEDro scale for rating quality of randomized controlled trials. Phys Ther. 2003;83(8):713-21. https://doi.org/10.1093/ptj/83.8.713.

27. Jean L, Simard M, Wiederkehr S, Bergeron M, Turgeon Y, Hudon C, et al. Efficacy of a cognitive training programme for mild cognitive impairment: Results of a randomised controlled study. Neuropsychol Rehabil. 2010; 20(3):377-405. https://doi.org/10.1080/09602010903343012.

28. Tarnanas I, Tsolakis A, Tsolaki M. Assessing virtual reality environments as cognitive stimulation method for patients with MCI. Technologies of Inclusive Well-Being: Serious Games, Alternative Realities, and Play Therapy. 2014;536:39-74. doi: 10.1007/978-3-642-45432-5_4.

29. Savulich G, Piercy T, Fox C, Suckling J, Rowe JB, O'Brien JT, et al. Cognitive training using a novel memory game on an iPad in patients with amnestic mild cognitive impairment (aMCI). Int J Neuropsychopharmacol.2017;20(8):624-33. https://doi.org/10.1093/ijnp/pyx040.

30. Poptsi E, Lazarou I, Markou N, Vassiloglou M, Nikolaidou E, Diamantidou A, et al. A comparative single-blind randomized controlled trial with language training in people with mild cognitive impairment. Am J Alzheimers Dis Other Demen. 2019;34(3):176-87. doi: 10.1177/1533317518813554.

31. Park J, Kim SE, Kim EJ, Lee BI, Jeong JH, Na HR, et al. Effect of 12-week home-based cognitive training on cognitive function and brain metabolism in patients with amnestic mild cognitive impairment. Clin Interv Aging. 2019;14:1167-75. doi: 10.2147/CIA.S200269.

32. Greenaway MC, Duncan NL, Smith GE. The memory support system for mild cognitive impairment: randomized trial of a cognitive rehabilitation intervention. Int J Geriatr Psychiatry. 2013;28(4):402-9. doi: 10.1002/gps.3838.

33. Hampstead BM,Stringer AY, Stilla RF, Giddens M, Sathian K. Mnemonic strategy training partially restores hippocampal activity in patients with mild cognitive impairment. Hippocampus. 2012;22(8):1652-8. doi: 10.1002/hipo.22006.

34. Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. J Am Geriatr Soc. 1992;40:922-35. doi: 10.1111/j.1532-5415.1992.tb01992.x.

35. Mitchell Alex J. The Mini-Mental State Examination (MMSE): an update on its diagnostic validity for cognitive disorders. Cognitive screening instruments. Springer, London, 2013. 15-46. doi: 10.1007/978-1-4471-2452-8-2.

36. Van Patten R, Britton K, Tremont G. Comparing the Mini-Mental State Examination and the modified Mini-Mental State Examination in the detection of mild cognitive impairment in older adults. Int Psychogeriatr. 2018;31(5):693-701. doi:10.1017/S1041610218001023.

37. Freitas S, Simões MR, Alves L, Santana I. The relevance of sociodemographic and health variables on MMSE normative data. Appl. Neuropsychol Adult. 2015;22:311-9. doi: 10.1080/23279095.2014.926455.

38. Xie H, Zhang C, Wang Y, Huang S, Cui W, Yang W. Distinct patterns of cognitive aging modified by education level and gender among adults with limited or no formal education: a normative study of the mini-mental state examination. J Alzheimers Dis. 2016;49:961-9. doi: 10.3233/JAD-143066.

39. Förster S, Buschert VC, Teipel SJ, Friese U, Buchholz HG, Drzezga A, et al. Effects of a 6-month cognitive intervention on brain metabolism in patients with amnestic MCI and mild Alzheimer's disease. J Alzheimers Dis. 2011;26(s3):337-48. doi: 10.3233/JAD-2011-0025.

40. ~~41~~. Jeong JH, Na HR, Choi SH, Kim J, Na DL, Seo SW, et al. Group-and home-based cognitive intervention for patients with mild cognitive impairment: a randomized controlled trial. Psychother Psychosom. 2016; 85(4):198-207. doi:10.1159/000442261.

41. Parra MA, Calia C, García AF, Olazarán-Rodríguez J, Hernandez-Tamames JA, AlvarezLinera J, et al. Refining memory assessment of elderly people with cognitive impairment: insights from the short-term memory binding test. Arch Gerontol Geriatr. 2019;83:114-20. https://doi.org/10.1016/j.archger.2019.03.025.

42. Kinsella GJ, Ames D, Storey E, Ong B, Pike KE, Saling MM, et al. Strategies for improving memory: a randomized trial of memory groups for older people, including those with mild cognitive impairment. J Alzheimers Dis. 2016;49(1):31-43. doi:10.3233/JAD-150378.

43. Finn M, McDonald S. Computerised cognitive training for older persons with mild cognitive impairment: a pilot study using a randomised controlled trial design. Brain Impairment. 2011;12(3):187-99. doi:10.1375/brim.12.3.187.

44. Vermeij A, Claassen JA, Dautzenberg PL, Kessels RP. Transfer and maintenance effects of online working-memory training in normal ageing and mild cognitive impairment. Neuropsychol Rehabil. 2016;26(5-6):783-809. doi: 10.1080/09602011.2015.1048694.

45. Hyer L, Scott C, Atkinson MM, Mullen CM, Lee A, Johnson A, et al. Cognitive training program to improve working memory in older adults with MCI. Clin Gerontol. 2016;39(5):410-27. doi: 10.1080/07317115.2015.1120257.

46. Cipriani G, Bianchetti A, Trabucchi M. Outcomes of a computer-based cognitive rehabilitation program on Alzheimer's disease patients compared with those on patients affected by mild cognitive impairment. Arch Gerontol Geriatr. 2006;43(3)327-35. doi:10.1016/j.archger.2005.12.003.

47. Talassi E, Guerreschi M, Feriani M, Fedi V, Bianchetti, Trabucchi M. Effectiveness of a cognitive rehabilitation program in mild dementia (MD) and mild cognitive impairment (MCI): a case control study. Arch Gerontol Geriatr. 2007;44:391-9. doi: 10.1016/j.archger.2007.01.055.

48. Moro V, Condoleo MT, Sala F, Pernigo S, Moretto G, Gambina G. Cognitive stimulation in a-MCI: an experimental study. Am J Alzheimers Dis Other Demen. 2012;27(2):121-30. doi:10.1177/1533317512441386.

49. Wenisch E, Cantegreil-Kallen I, De Rotrou J, Garrigue P, Moulin F, Batouche F, et al. Cognitive stimulation intervention for elders with mild cognitive impairment compared with normal aged subjects: preliminary results. Aging Clin Exp Res. 2007;19(4):316-22. doi:10.1007/BF03324708.

50. Unverzagt FW, Kasten L, Johnson KE, Rebok GW, Marsiske M, Koepke KM, et al. Effect of memory impairment on training outcomes in ACTIVE. Journal of the International Neuropsychological Society. 2007;13(6):953-60. doi:10.1017/S1355617707071512.

51. Rozenfeld Olchik M, Farina J, Steibel N, Ribeiro Teixeira A, Sanches Yasuda M. Memory training (MT) in mild cognitive impairment (MCI) generates change in cognitive performance. Arch Gerontol Geriatr. 2013; 56(3):442-7. https://doi.org/10.1016/j.archger.2012.11.007.

52. Solé-Paddulés C, Bartrés-Faz D, Junqué C, Vendrell P, Rami L, Clemente IC, et al. Brain structure and function related to cognitive reserve variables in normal aging, mild cognitive

impairment and Alzheimer disease. Neurobiol Aging. 2009;30:1114-24. https://doi.org/10.1016/j.neurobiolaging.2007.10.008.

Declarations of interest: none

Credit Author Statement

I G-S: Conceptualization, Methodology, Data curation, Writing- Original draft preparation

P P-M: Data curation, Formal analysis, Writing- Reviewing and Editing,

E C-S: Data curation, Writing-Reviewing and Editing

E L: Supervision, Writing- Reviewing and Editing,