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The Efficacy of Cognitive Intervention Programs for Mild Cognitive Impairment: A Systematic Review

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Abstract: Mild cognitive impairment (MCI) describes a transitional state in progression from normal aging to dementia, especially Alzheimer's disease (AD). Currently, there is no effective pharmacological treatment that offers a long-term beneficial effect to delay the progression to dementia. There is growing evidence that supports an important role of non-pharmacological cognitive interventions. Therefore, it is warranted to clarify the distinct forms of cognitive interventions and their effects based on previous clinical trials. We aimed to provide a review of clinical trials of non-pharmacological cognitive interventions for MCI and to address the characteristics of the study patients, cognitive intervention programs and short-term / long-term benefits of the interventions. A total of 32 articles were identified according to the inclusion criteria. The results showed positive effects for both objective and subjective outcome variables, and these effects persisted from 1 month up to 5 years. Although many of the positive effects were related to improvement in trained tasks, alterations in neuroimaging and the transfer effects shown by some studies are encouraging. Future research in this area requires a larger sample size with a wider spectrum of MCI, more instructive outcome measures and a longer follow up duration.

Keywords: Alzheimer's disease, cognitive intervention, cognitive outcome, functional brain imaging, mild cognitive impairment, progression.

INTRODUCTION

Mild cognitive impairment (MCI) describes a transitional state in the progression from normal aging to dementia, particularly Alzheimer's disease (AD). MCI is characterized by memory and other cognitive dysfunctions with preserved general cognitive function and functional independency [1, 2]. A systematic review based on previous epidemiological studies reported that the prevalence of MCI ranges from 3% to 42%, and the global incidence rate ranges from 21.5 to 71.3 per 1000 person-years [3]. MCI is an important clinical state because the progression rate to AD or other dementia has been reported to be as high as 12-15% per year, compared to 1-2% in healthy adults [4]. In memory clinics, more than 50% of MCI converts to dementia in 4 to 5 years [5] although many individuals also revert to normal or do not progress [6]. Because MCI is a heterogeneous state, early detection of MCI individuals at risk of eventually progressing to dementia will provide clinicians with more treatment options [7]. Luis *et al.* suggested that interventions that could moderately decrease the rate of progression from MCI to dementia would save billions of dollars, which is attributable to decreased utilization of healthcare, special needs transportation, long-term care, and daycare facilities [8].

Considering these data, developing treatment strategies for this state is crucial. Currently, there is no effective pharmacological treatment for MCI that offers a long-term benefit to delay the progression to dementia [9]. Growing evidence supports important roles of non-pharmacological interventions such as cognitive intervention, occupational therapy, psychoeducation, and psychotherapy in MCI [10]. Such non-pharmacological intervention, if it is found to be successful at the MCI stage, may serve as a good adjunct to pharmacological intervention [11]. A recent review also recommends engagement in cognitive activities and social activities for MCI patients [12]. Recommendations for non-pharmacological interventions in persons with MCI who retain a large range of cognitive capacities are based on recent reports demonstrating that the brain is highly plastic and capable of generating new synaptic connections and neurons throughout life [13]. Cognitive interventions to enhance cognitive reserve will potentially delay the onset and progression of dementia [14] and attenuate cognitive decline [15-17].

Therefore, it is warranted to clarify the distinct forms of cognitive interventions in MCI and their effects in previous clinical trials. We aimed to provide a review of previous clinical trials of non-pharmacological cognitive interventions for MCI and to address which outcome variables benefit from the interventions.

METHODS

A literature search was performed using both electronic and manual methods. MEDLINE (via PubMed) and EM-

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BASE were searched using the key words "mild cognitive impairment" AND "cognitive training OR cognitive exercise OR cognitive intervention OR memory training". The search was performed for human studies in English between January 1, 2000 and June 30, 2014. Additionally, we searched the reference lists within the articles identified by our electronic search. Articles were selected for our review if they met the following inclusion criteria: (1) clinical trials primarily evaluating the effects of the cognitive intervention; (2) the subjects met criteria for MCI that showed cognitive disorders evidenced by objective evaluation and the absence of dementia; (3) cognitive assessments and/or brain imaging based analysis were completed at pre- and post-intervention; and (4) longitudinal clinical trials. Cognitive intervention in our study means all kinds of non-pharmacological cognitive programs including cognitive training, rehabilitation and stimulation. No exclusion criteria were initially applied because we aimed to review all clinical trials using cognitive interventions that have been studied to date.

RESULTS

Initially, the literature search identified 250 articles of which 160 articles were excluded due to their emphasis on different themes or different disease stages in the titles. Among the 90 articles finally selected, after checking the abstracts, 53 articles did not match the inclusion criteria because they had different themes, used pharmacological interventions, or employed mixed samples with normal cognition or AD. An additional five articles were also excluded before the analysis because four articles did not match the inclusion criteria due to the absence of objective cognitive measures, and another study was excluded because the full text was not provided electronically. Based on the criteria proposed for this review, 32 articles ultimately met the inclusion criteria and were subjected to our review. Fig. (**1**) represents a graphical flowchart of the selection of the articles.

What are the Characteristics of Study Patients?

Before comparing the treatment efficacy across studies, the diagnostic criteria and characteristics of the enrolled patients were investigated. First, the diagnostic criteria that studies adopted for the inclusion of MCI were reviewed. The inclusion criteria in each study are summarized in (Table **1**). The most commonly used criteria are some versions of the MCI criteria by Petersen and colleagues (26 studies, 81%) including (1) self-reported memory/ cognitive complaints, (2) objective memory/ cognitive deficits, (3) relatively preserved global cognitive and functional abilities, and (4) the absence of dementia [1, 2, 4, 18]. However, closer examination of each study's inclusion criteria showed discrepancies in the patient's symptoms and impaired domains. Some studies enrolled patients who complained of memory problem and objective memory impairment according to the Petersen's criteria reported in 1997 and 1999, while other studies enrolled all patients who complained of any cognitive problem and at least one objective cognitive impairment according to the criteria in 2001 and 2004. The remaining six studies [19-24] used other criteria, although the criteria [25, 26] used in the 5 studies were comparable to the Petersen's criteria in 2004. Only 1 study [22] used neuropsychological criteria, but did not consider subjective memory complaints or functional decline. Totally, 19 studies (59%) enrolled only the amnestic form of MCI and twelve studies (38%) also included patients with non-amnestic forms of MCI. Two studies enrolled only patients with amnestic multiple domain MCI.

More than half of the studies (21 of 32) enrolled elderly aged at least 50 years old; the other 11 studies did not restrict

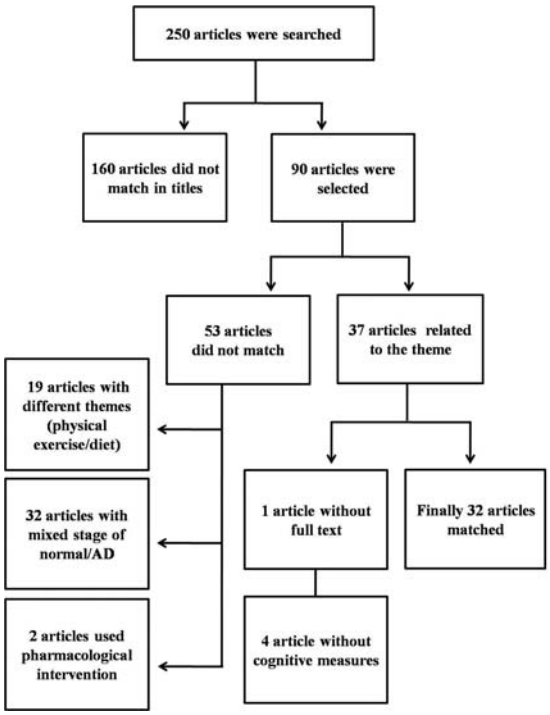

Fig. (1). A graphical flowchart of the selection of the articles.

Table 1. A summary of the studies reviewed.

Author, Year	Sample Size	Criteria	Age	Blind	Components of Intervention	Setting	Duration
RCT: Level A							
Rapp, 2002	aMCI =19 (IG=9, CG=10)	Petersen, 1999	Old adults (mean: 73.3±6.6)	No	Multifaceted intervention (education about memory loss, relaxation training, memory skills, cognitive restructuring)	Group	6 session (6wks), 2hr/session
Rozzini, 2007	aMCI=59 (ChEI+TNP =15, ChEI only=22, CG=22)	Petersen, 2001	63-78 yrs old	No	Computerized training (TNP software) for multiple cognitive functions	Individual	60 session (9mo), 1hr/session
Barnes, 2009	MCI=47 (IG=22, CG=25)	Winblad, 2004	≥50 yrs old	Single	Computer-based training designed to improve processing speed and accuracy, auditory memory task	Group	30 session (6wks), 100min/session
Kinsella, 2009	aMCI=46 (IG=22, CG=24)	Petersen, 2004	All	Single	Education about cognitive problem-solving approach and practice of memory strategies	Group	5 session (5wks), 1.5 hr/session
Jean, 2010	aMCI=22 (IG=11, CG=11)	Petersen, 2004	≥50 yrs old	Single	Learning about face-name associations using memory strategies	Individual	6 session (3wks), 45min/session
Buschert, 2011	aMCI=24 (IG=12, CG=12)	Petersen, 2001	≥50 yrs old	No	Multicomponent training including memory exercise, mnemonic technique, information about meta-cognition and social engagement	Group	20 session (6 mo), 2hr/session
Förster, 2011	aMCI=21 (IG=9, CG=12)	Petersen, 1999	≥50 yrs old	No	Group based multicomponent cognitive intervention	Group	20 session (6 mo), 2hr/session
Rosen, 2011	MCI=12 (IG=?)	Winblad, 2004	All (mean:70.7±10.6)	Single	Computer-based training for processing speed, accuracy in auditory processing	Individual	24 session (5days/wk), 100min/session
Tsolaki, 2011	aMCI=176 (IG=104, CG=72)	Petersen, 2001	All (mean: 68.5±7.0)	No	Multi-component approach including cognitive training, cognitive stimulation, memory strategies, psycho-therapeutic approach	Group (5 / group)	60 session (6mo), 90min/session
Buschert, 2012	aMCI=24 (IG=12, CG=12)	Petersen, 2001	≥50 yrs old	No	Multi-component cognitive training including memory exercise, mnemonic technique and social engagement	Group	20 session (6 mo), 2hr/session
Gagnon, 2012	MCI=24 (IG 1=12, IG 2=12)	Petersen,1999	Old adults (mean: 67±7.8)	Double	Computer-based divided attention training on the dual-task (Intervention 1: Fixed priority condition; Intervention 2: Variable priority condition)	Individual	6 session (2wks), 1 hr/session
Hampstead, 2012	aMCI=28 (IC=14, CG=14)	Petersen, 2004	All (mean: 71.7±10.2)	Single	Training for mnemonic strategy (intervention group) in object-location-association task or matched simple exposure to object-location- associations	Individual	3 session (2wks), 60-90 min/session
Herrera, 2012	Multiple domain aMCI=22 (IG=11, CG=11)	Petersen, 2004	65-90 yrs old	No	Computer-based memory-attention training (visual memory task, visual attention task)	Individual	24 session(12wks), 1hr/session
Moro, 2012	aMCI=30 (early IG=15, late IG=15)	Petersen, 2001	All (mean: 73.3±6.9)	No	Training for mnemonic strategy, external memory aid, cognitive exercise (memory task), Cross-over design	Individual	32 session (6mo)

(Table 1) contd….

Author, Year	Sample Size	Criteria	Age	Blind	Components of Intervention	Setting	Duration
Valdes, 2012	MCI=195 (IG=85, CG=110)	Neuropsy-cho-logical criteria	≥65 yrs old	No	Computer-based, non-verbal, group exercise of visual attention	Individual	2 session/wk (over 5 wks)
Carretti, 2013	aMCI=20 (IG=10, active CG=10)	Petersen, 1999	65-75yrs old	No	Verbal working memory training	Not presented	3 session, 30-40 min/session
Greenaway, 2013	Single domain aMCI=40 (IG=?)	Petersen, 2004	All	No	Education for Memory Support System (MSS) and homework assignment	Individual (pt+partner)	12 session (6wks), 1hr/session
Olchik, 2013	MCI=62 (IG 1=22, IG 2=20, CG=20)	Gauthier and Touchon, 2005	≥60 yrs old	Single	IG 1 (MT)=Education on memory, mnemonic strategy + memory exercise, IG 2 (EI)=Education on memory only	Group (up to 10/group)	8 session (4wks), 90min/session
Rojas, 2013	MCI=30 (IG=15, CG=15)	Petersen, 1999	All (mean: 72±14.3)	No	Multi-modal cognitive intervention (teaching cognitive strategies, cognitive stimulation for memory, attention, speed, cognitive training and use of external aids)	Group (4-5/group)	48 session (6mo), 2hr/session
Suzuki, 2013	MCI=92 (IG=47, CG=45)	Petersen, 2004	≥65 yrs old	Single	Multi-component exercise program including exercise and dual-task training (cognitive tasks during exercise)	Group (16-17 /group)	40 session (6 mo), 60min/session
Vidovich, 2014	MCI=160 (IG=80, CG=80)	Portet, 2006	≥65 yrs old	Single	Multi-component intervention of cognitive rehabilitation, stimulation and training (discussion about cognition, cognitive activity using strategies to enhance cognition)	Group (6-9 /group)	10 session (5wks), 90min/session
Non-randomized CT: Level B							
Belleville, 2006	aMCI=28 (IG=20, CG=8), Normal elderly=17	Petersen, 2001	Old adults (mean: 62.3±7.3)	No	Teaching episodic memory strategies and stress management, computer assisted attention training	Group (4-5 /group)	8 session (8 wks), 2hr/session
Talassi, 2007	aMCI=37 (IG=30, CG=7)	Petersen, 1997	Old adults (mean: 76.2±7.3)	No	Computerized cognitive training, occupational therapy and behavioral training	Individual	12 session (3 wks), 30-45min/session
Kurz, 2009	MCI=30 (IG=18, CG=12)	Winblad, 2004	All (mean: 70.4±8.4)	No	Multi-component intervention (cognitive rehabilitation, education on meta-memory, health, relaxation techniques, stress management, external memory aids, self-assertiveness training, , memory training, motor exercise)	Group (10 / group)	4wks, 22hrs/wk, from 9:00 to 15:00 per day
Banningh, 2011	MCI=93 (IG=63, CG=30)	Petersen, 2004	>50 yrs old	No	Cognitive behavioral group therapy with psycho-educational and memory rehabilitation (using of memory strategies, making notes and personal goals)	Group	10 session(10wks), 2hr/session
Banningh, 2013	MCI=84 (early IG=57, late IG=27)	Petersen, 2004	>50 yrs old	No	Cognitive behavioral group therapy with psycho-educational and memory rehabilitation	Group	10 session(10wks), 2hr/session
Non-randomized, no CG: Level C							
Wenisch, 2007	aMCI=12,	Petersen, 2001	60-87 yrs old	No	Teaching techniques about reality orientation, categorization and mental imagery, cognitive exercises for memory and executive function	Group (8-10 /group)	12 session (3 mo), 1.5hr/session

(Table 1) contd….

Author, Year	Sample Size	Criteria	Age	Blind	Components of Intervention	Setting	Duration
Greenaway, 2008	aMCI=20	Petersen, 1999	All (mean: 78.2±.8)	No	Education for calendar/note system (Memory Support System (MSS)) and homework assignment	Individual (pt+partner)	12 session (6wks), 1hr/session
Hampstead, 2008	Multi-domain aMCI=8	Petersen, 2004	All (mean: 75±6.7)	No	Training the use of explicit memory strategies with face-name association training	Individual	3 session (2wks), 2.8 days/session
Banningh, 2008	MCI=22,	Petersen, 2004	>50 yrs old	No	Cognitive behavioral therapy (discussion about the session's theme and self-monitoring tasks, discussion about memory, memory skills, activities for social skills)	Group	10 session(10wks), 2 hrs/session
Londos, 2008	aMCI=15	Petersen, 2001	50-80 yrs old	No	Memory strategy group training, education about brain, memory, factors influence memory, external memory aids	Group	16 session (8wks), 2.5hrs/session
Belleville, 2011	aMCI=15 (IG=15)	Petersen, 2001	All (mean: 70.1±7.3)	No	Teaching mnemonic strategies and psycho-educational information, episodic memory training	Group (4-5 /group)	6 session (6wks), 2hr/session

range of age, but the mean age of the patients was between the 7th or 8th decades of life. Memory/cognitive scores below -1.0 or -1.5 SD were considered to be abnormal in all of the studies, but the memory/cognitive measures used varied from study to study. No study limited the educational level of patients in their inclusion criteria, although a few studies excluded illiterates. Mean educational levels ranged from 4 [7] to 18 [21] years; most studies included highly educated patients (26 out of 32, 81%) with the exception of a few studies [7, 27-31] that included low-educated patients having less than a mean of 10 years of education.

Consistent diagnostic criteria and similarity of the enrolled patients might enable an accurate comparison of the treatment efficacies. Although there was variability in the diagnostic criteria, cutoff scores of neuropsychological tests, age, and educational levels of enrolled patients, the studies reviewed here had some consistent similarities in that 81% used some versions by Petersen *et al.* and more than half of the studies enrolled high-educated MCI patients aged 50 years old or older with the amnestic form of the disease.

What Kind of Cognitive Intervention Programs have been Applied to MCI Patients?

A summary of the cognitive intervention programs and study designs is described in (Table **1**). For the present review, we created specific criteria to appropriately classify the quality level of each study as follows: Level A) randomized controlled trials including the control group (no intervention); B) non-randomized, controlled trials involving comparisons between intervention groups and no intervention group; C) non-randomized, non-controlled trials based on comparisons before and after cognitive interventions. More than half of the reviewed studies (21, 66%) used randomized controlled designs (level A), and 9 out of 21 additionally used single-or double-blinded designs. Five studies used only controlled designs without randomization (level B) [15, 20, 27, 32, 33]. Only six studies used neither a control group nor randomization (level C) [7, 34-38]. Two group comparisons between an intervention group and a control group accounted for 92% of the studies for 92% (24 out of 26). The other two studies compared three groups; intervention 1, intervention 2, and a control (no intervention) group [17, 23]. Sample sizes varied from 8 to 195, but most ranged from 21 to 30. The mean sample size was 47.4. Most studies used training in small groups because this was thought to be more effective than individual training or training in larger groups [15]. Study durations ranged from 2 weeks to 9 months, but the mean duration was 11.1 weeks. Because amnestic MCI is the strongest risk factor for AD [4] and memory problems the main reason of help seeking, most interventions aimed to manage memory loss. Very few studies focused on speed improvement or attention training. All programs except four (88%) focused on memory enhancement by including education about memory strategy and memory training. The other three studies targeted only attention [22, 39] or improvement of speed and accuracy [19]. One study used cognitive stimulation in non-specific manner [40]. Eight studies used a computer for cognitive training programs [15, 17, 19, 21, 22, 27, 29, 39], in which patients received individual computer-based training for memory, attention, or combined multiple cognitive functions. Combined interventions of education about memory/memory strategies and cognitive training accounted for 78.6% of the studies which targeted memory function (22 out of 28), and the other 21.4% did not teach mnemonic strategies before cognitive intervention (6 out of 28). Mnemonic strategies included education about compensatory and restorative strategies such as visual imagery, method of loci, mind mapping, categorization, organization, chunking, cueing, memory aids, errorless learning, spaced retrieval, vanishing cues, reality orientation therapy, and reminiscence therapy [41]. Various mnemonic strategies were taught simultaneously in all of the studies; hence, comparisons of effects among the various strategies are difficult.

Some studies educated about using external memory aids such as a calendar, a notes system, cell phone functions, and timers [11, 35, 37, 42]. A few studies used different programs such as cognitive behavioral group therapy with psychoeducational and memory rehabilitation [7] or combined programs with physical exercise and cognitive stimulation [40].

In summary, the majority of studies were randomized controlled trials which enrolled 21-30 patients with MCI, adopted grouped cognitive interventions targeting memory enhancement, and compared effects between two groups (cognitive intervention vs. no intervention). Most of the intervention programs were as follows: 1-2 hours of cognitive programs containing cognitive training with education about mnemonic strategies over a period of approximately 11.1 weeks. However, the reviewed studies varied considerably in terms of group setting, number of training sessions, duration of intervention, overall period of the intervention, and the content of the intervention.

Can Cognitive Interventions Improve any Cognitive Outcome Measures?

Outcome measures and the results are listed in (Tables **2** and **3**). We divided outcome measures into three categories: objective cognitive outcomes, subjective perception, and changes in brain imaging findings. Changes in brain imaging will be explained in the next section. Twenty studies (63%) measured both objective and subjective scales. Most studies with the exception of 4 studies (28 of 32, 88%) showed significant improvement in objective cognitive measures; however, many of these improved cognitive measures were related to the trained tasks or only part of the measured outcomes [11, 15, 17, 19, 22-24, 27, 29-31, 34-37, 39, 40, 42, 43-45]. The 4 studies showed no significant improvement in objective cognitive outcomes [7, 32, 46, 47] although they showed improvement in subjective perception or a trend toward improvement [46, 32].

Effects of cognitive intervention on each cognitive domain are summarized in Table **3**. We categorized cognitive intervention programs as single, combined and multiple approaches to summarize the intervention programs and compare the effects according to the programs; if a study used a single method such as computerized cognitive exercise, classical cognitive training, education about mnemonic strategies, non-specific cognitive stimulation, physical exercise, psycho-education or behavioral therapy, then the study was categorized as 'single', if a study combined two of the former methods, then it was categorized as 'combined', if a study used at least three methods, then it was categorized as 'multiple'. We divided various cognitive outcomes into attention, executive function, working memory function, delayed memory recall, prospective memory function, language function, visuospatial function and general cognition excluding subjective outcomes. In our reviewed studies, delayed memory recall function (including both visual and verbal memory) was most commonly assessed (21 out of 32). Among the studies which measured delayed memory recall tests, 14 studies (67%) reported significant effects of cognitive intervention. All of the studies that reported positive effects on delayed memory function adopted programs for memory enhancement with memory strategies except for one study by Carretti *et al.* The study adopted working memory training without educating for memory strategies in intervention group and showed transfer effects in delayed memory recall [31].

Another issue to be clarified is whether a cognitive intervention might improve general cognitive function or other tasks that the patients were not trained to improve. However, only 14 (44%) studies measured general cognitive function or performed a battery of neuropsychological tests combined with multiple cognitive function tasks. A Mini-Mental State Exam (MMSE) was the most commonly used tool (ten studies); the other measures were the Alzheimer's Disease Assessment Scale (ADAS-cog, four studies), the dementia rating scale-2 (DRS-2, three studies), the Montreal Cognitive Assessment (MoCA, one study), Repeatable Battery for Assessment of Cognitive Status (RBANS, one study) and the Cambridge Cognitive Examination-Revised (CAMCOG-R, one study). Among the 14 studies, six randomized controlled trials [14, 28, 40, 45, 48, 49] reported improvement of general cognitive measures (MMSE / MoCA / CDR) or detailed neuropsychological test scores (ADAS-cog). Most of the six studies that reported a generalized cognitive effect used a group-based multiple component cognitive intervention including education about memory, memory strategies, use of external memory aids, and cognitive training of multiple domains. The durations of the cognitive interventions were 6-months in common, relatively long duration. Intervention durations less than 6 months might not be sufficient for MCI patients to show significant effects. The other four studies reported promising results in that they showed some improvement in the activities of daily living (ADL) or transfer effects on non-trained domains: Kurz *et al.* showed improvement of ADL and verbal/non-verbal episodic memory function using multiple component cognitive rehabilitation [20]. Three studies [19, 21, 31] reported some transfer effects on non-trained measures. When we summarize the results of level A - studies in isolation, delayed memory recall improved in 53% of the studies (8 out of 15), working memory function in 54% (7 out of 13), general cognition in 50% (6 out of 12), executive function in 37.5% (3 out of 8), attention in 83.3% (5 out of 6), language function in 33.3% (2 out of 6), visuospatial function in 33.3% (1 out of 3) and prospective memory function in one study. Delayed memory function is the most commonly measured in level A studies, and over half of the studies showed significant improvement in intervention group. On the other hand, attention scores improved in most of the level A ranked studies according to our review.

In summary, most effects after cognitive intervention were the same or related to the trained tasks, particularly, the memory function. However, some studies reported transfer effects of cognitive intervention to general cognitive function, ADL function, or other cognitive domains. A few randomized controlled trials with relatively long study durations (6 months) that used group-based multi-component intervention showed improvement in general cognitive functions. Improvement in attention might be another favorable effect of cognitive intervention. However, the variability of outcome measures in each study, the use of only a few cognitive outcome measures and the lack of measurements for general

Table 2. A summary of the outcome measures and results.

Author, Year	Follow Up	Outcome Measures	Results
RCT: Level A			
Rapp, 2002	6 mo	Objective measure: CERAD, MMSE, memory recall tests Subjective measure: MFQ*, MCI[§]*, scale for mood	Trend of improvement of word delayed recall only after 6months post-intervention. Improvement in self-perception did not persist until follow up
Rozzini, 2007	3 mo	Objective measure: MMSE, short story recall*, verbal fluency test, Raven's colored matrices*, Rey's figure copy and recall, B-ADL, I-ADL Subjective measure: NPI*, GDS*	TNP+ChEIs group: improvement in episodic memory (story recall) and abstract reasoning (Raven's colored matrices) and NPI, GDS
Barnes, 2009	No	Objective measure: RBANS, CVLT, verbal fluency, Boston naming, Design fluency, TMT, Spatial span*	Trends of improvement in learning/memory and RBANS delayed recall ($p>0.05$). Improvement in attention (spatial span)
Kinsella, 2009	4 mo	Objective measure: Envelope task*, Reminding task, Strategy Knowledge Repertoire* Subjective measure: MMQ-Ability, MMQ-Strategy*, MMQ-Contentment	Improvement in prospective memory task and knowledge and use of memory strategies Persistent improvement in prospective memory and knowledge of memory strategy
Jean, 2010	4wks	Objective measure: TM (Training measure)*, DRS-2, CVLT-II, MMSE, RBMT Subjective measure: MMQ, SES	Improvement was shown only in TM: no persistence until follow up
Buschert, 2011	No	Objective measure: ADAS-cog*, MMSE, TMT-B, RBANS story recall Subjective measure: QoL-AD, MADRS*	Improvement in ADAS-cog and MADRS
Förster, 2011	No	Objective measure: ADAS-cog*, MMSE*, FDG-PET*	Improvement in ADAS-cog, MMSE. Attenuated decline in FDG uptake
Rosen, 2011	No	Objective measure: RBANS memory immediate recall*, fMRI imaging*	Improvement in memory (RBANS) Increased activation in left hippocampus
Tsolaki, 2011	No	Objective measure: MMSE*, MoCA*, RBMT, RAVLT, ROCFT*, TEA, FUCAS*, TMT-B, FAS, Boston naming, clock drawing*, FRSSD (total daily functioning)*	Improvement in executive, verbal memory, visual-constructive, ADL and general cognitive performance
Buschert, 2012	9 & 22mo	Objective measure: ADAS-cog*, MMSE, TMT-B, RBANS story memory*, story recall Subjective measure: QoL-AD, MADRS*	Improvement in ADAS-cog, RBANS story memory and MADRS: persistent effects in ADAS-cog and RBANS story memory Early intervention group showed no progression to AD
Gagnon, 2012	No	Objective measure: TEA, TMT-A, TMT-B, Alpha-arithmetic and visual detection task* Subjective measure: Well-being scale	Improvement in accuracy of visual detection task
Hampstead, 2012	1 mo	Objective measure: Object-location association test*, fMRI*	Improvement in object-location association test at end-point and follow up. Increased hippocampal activity in fMRI
Herrera, 2012	6 mo	Objective measure: Digit span test*, 12-word-recall test*, 16-FR/CR test*, recall score of MMSE*, visual recognition subtest from Doors and People memory battery*, ROCFT recall	Improvement in forward digit span, episodic recall and recognition: persisted after 6 months (recall score of MMSE, forward digit span, 12-word recall test, visual recognition test)
Moro, 2012	6mo	Objective measure: Attentional matrices*, TMT, Bourdon test, verbal span*, AVLT*, listening span test*, story recall*, Tower of London test, verbal fluency test, stroop test	Improvement in trained function tests (memory and attention) and persisted after 6 months
Valdes, 2012	1, 2, 3 & 5 yrs	Objective measure: Useful Field of View performance (UFOV) test*	Improvement in UFOV performance: persisted until 5 years

(Table 2) contd….

Author, Year	Follow Up	Outcome Measures	Results
Carretti, 2013	No	Objective measure: CWMS*, digit span, Dot matrix, List recall*, Pattern comparison, Cattell test*	Improvement in trained task (working memory) and some transfer effects on other working memory, delayed recall and fluid intelligence
Greenaway, 2013	6 mo	Objective measure: DRS-2, MMSE, E-Cog-memory subscale*, Subjective measure: CES-D*, QOL-AD, CB, Self-Efficacy in MCI scale*, Adherence assessment	Improvement in adherence scores and ADLs (E-Cog) : did not persist until follow up, Improvement in mood (self-efficacy, CES-D): persisted until follow up
Olchik, 2013	No	Objective measure: Categorical verbal fluency*, FAS, RAVLT*, RBMT	Improvement in categorical verbal fluency, RAVLT immediate and delayed recall scores
Rojas, 2013	No	Objective measure: MMSE*, CDR*, Signoret's Memory Battery, Boston naming test*, verbal fluency test*, conversion to dementia Subjective measure: QoL Questionnaire, NPI	Improvement in Boston naming and semantic fluency, intervention effects in MMSE, CDR Trained group showed lower progression to dementia
Suzuki, 2013	No	Objective measure: ADAS-cog, MMSE, logical memory test, MRI (cortical atrophy)	Improvement in MMSE, logical immediate memory score and whole brain cortical atrophy in amnestic MCI subtype
Vidovich, 2014	10, 52 & 104 wks	Objective measure: CAMCOG-R, digit span*, symbol search, TMT, COWAT, LAQ, PAQ, SNSQ Subjective measure: MFQ, QoL-AD*	Improvement in digit span forward and quality of life No significant effect on progression
Non-randomized CT: Level B			
Belleville, 2006	No	Objective measure: Word list recall*, face-name association*, Memo-text recall, verbal fluency test, computerized test for attention Subjective measure: Subjective memory questionnaire*, measures of well-being*	Improvement on delayed list recall, face-name association, measures of subjective memory and well-being
Talassi, 2007	No	Objective measure: MMSE, digit span, verbal fluency, episodic memory test, visual search, digit symbol test, ROCFT*, clock-drawing test, physical performance test*, basic ADL, instrumental ADL Subjective measure: GDS*, Anxiety inventory*	Improvement on RCFT copy and recall, physical performance test, GDS, anxiety inventory
Kurz, 2009	No	Objective measure: Bayer-ADL scale*, CVLT*, ROCFT* Subjective measure: Beck Depression Inventory*	Improvement in ADL, mood, verbal and nonverbal episodic memory delayed recall (CVLT, RCF)
Banningh, 2011	No	Objective measure: RAND-36 Subjective measure: ICQ (acceptance*, helplessness), GDS-15	Improvement in ICQ (acceptance)
Banningh, 2013	No	Objective measure: RAND-36, RMBPC Subjective measure: Sense of Competence Questionnaire, ICQ, IQCODE-short form, GDS-15	No significant effect in outcome variables
Non-randomized, no CG: Level C			
Wenisch, 2007	No	Objective measure: Wechsler memory scale (Logical memory test and word paired associate learning task*), TMT part B, verbal fluency test Subjective measure: Goldberg scale (anxiety and depression)	Improvement in associative learning task
Greenaway, 2008	8 wks	Objective measure: DRS-2, measures for functional ability* (Every Day Cognition, Record of Independent Living) Subjective measure: Caregiver Burden scale	Improvement in functional ability (independence, self-confidence and mood)
Hampstead, 2008	1 mo	Objective measure: Face-name association test*	Improvement in face-name recognition (persisted only in trained pairs)

(Table 2) contd….

Author, Year	Follow Up	Outcome Measures	Results
Banningh, 2008	No	Objective measure: RAND-36 Subjective measure: GDS, Subscales Acceptance* and Helplessness (ICQ), Maudsley Marital Questionnaire*, Alertness to memory failure (IQCODE) and behavior changes, sense of competence questionnaire	Improvement in acceptance and marital satisfaction
Londos, 2008	6 mo	Objective measure: WAIS III Digit span, WAIS NI Spatial span, WAIS-R Digit Symbol, RCFT, A Quick Test (AQT)* Subjective measure: QoL-AD*	Improvement in cognitive processing speed (AQT), occupational performance and some of QoL domains (persisted until follow up)
Belleville, 2011	No	Objective measure: Word list recall using computer*, fMRI*	Improvement in word recall, Increased fMRI activation

* Significant improvement in intervention group ($p<0.05$); MCI[§] = Memory Controllability Inventory

cognition and other cognitive domains not trained for may have hampered the appropriate estimation of the study results.

Subjective scales included perception of self-memory function, scales for mood, measures of well-being, caregiver burden scales, and quality of life scales. Nine studies used scales for subjective memory function although the scales varied. Six of nine studies reported positive effects in subjective memory scales; the other three reported no significant changes in subjective memory function [24, 33, 44]. The three studies which showed no positive effect in subjective memory function also showed partial or no significant effects in objective cognitive outcomes. Among eight studies which measured quality of life or well-being scales, only three studies reported significant improvement [15, 24, 37]. Among fourteen studies which measured emotion, only six studies reported significant improvement especially in depression [14, 17, 20, 27, 42, 49].

In summary, among 19 studies that measured subjective outcomes, 13 reported positive effects [7, 11, 14, 15, 17, 20, 24, 27, 32, 37, 42, 46, 49]. The positive effects were mainly in subjective memory function and partially depression, and not in other emotion or quality of life.

Can Cognitive Interventions Induce Favorable Changes in Brain Imaging?

A total of five studies investigated the effects of cognitive intervention using functional or structural brain imaging [21, 38, 48, 50]. The patterns of brain volume changes, activation or metabolism changes before and after cognitive intervention were compared. Although the intervention program and protocols of MRI were different among the studies, all reported positive effects after cognitive intervention (Table **4**). Belleville *et al.* reported increased activation in multiple areas during memory encoding and retrieval after cognitive intervention, although there was no control group [38]. Rosen *et al.* showed greater activation of the left hippocampus in the cognitive intervention group compared with that of the control group [21]. In a study by Forster and colleagues, FDG-PET imaging showed an attenuated decline in the temporal, prefrontal, and anterior cingulate cortices [51]. In a pilot study of six MCI patients, the authors reported significantly increased brain activation in extensive cortical areas after cognitive intervention including the medial frontal, parietal, and occipital lobes close to the temporo-parietal junction, the left frontal operculum, and part of left temporal cortex [52]. This study was not reviewed because cognitive outcomes were not reported. On the other hand, in a recent study, the authors focused on hippocampal activation. An fMRI during a memory retrieval task showed significant activation of the hippocampus in the cognitive intervention group compared with that in the control group [50]. Suzuki *et al.* reported that whole brain volume improved after cognitive intervention in patients with amnestic MCI [40]. The paucity of studies that have investigated alterations in brain imaging may be due to methodological difficulties; however, all of the studies that are available reported positive effects such as activation of memory related structures or attenuated metabolic decline. Persistent effects in brain imaging need to be replicated through further investigations with a larger sample size.

Is there any Long-Term Benefit of Cognitive Intervention?

Verifying whether the effects could be maintained over time was another important issue to be clarified. A total of 12 studies (38%) investigated whether the effects of cognitive intervention lasted until a follow-up examination after cognitive intervention. The follow-up duration ranged from 1 month to 5 years. Eight of twelve studies (67%) showed that the improvement persisted until follow-up examination, although they are mostly limited to part of the cognitive domains or the trained tasks. A few studies reported that the improvements in quality of life remained significant [24, 37], or the positive effects in general cognitive measures (ADAS-cog) persisted [49]. Valdes *et al.* showed that the effects were maintained for up to 5 years following the intervention regardless of subtypes of MCI, although it was limited to the trained task [22].

Decreasing or delaying progression to dementia or AD might be a true target of cognitive intervention trials [53], however the progression rates were assessed in only 3 studies mainly due to the short follow-up durations in most studies [24, 45, 49]. Buschert *et al.* showed that none of the early intervention group progressed to AD; whereas, six (50%) of late intervention group (control group) progressed [49]. Rojas *et al.* also reported positive effects of cognitive intervention on clinical progression to dementia; only one patient in

Table 3. Effects of cognitive intervention on cognitive domains and clinical progression.

Author, Year	Intervention	Progression	Global Cognition	Executive Function	Attention	Working Memory	Delayed Recall	Language Function	Visuospatial Function	Prospective Memory
RCT: Level A										
Rapp, 2002	Multiple		○			○	○			
Rozzini, 2007	Single		○	●			○	○	○	
Barnes, 2009	Single		○	○	●	○	○	○	○	
Kinsella, 2009	Combined									●
Jean, 2010	Combined		○			○	●			
Buschert, 2011	Multiple		●	○		○	○			
Förster, 2011	Multiple		●							
Rosen, 2011	Single					●				
Tsolaki, 2011	Multiple		●	●	○	○	●	○	●	
Buschert, 2012	Multiple	●	●	○		●	○			
Gagnon, 2012	Single				●					
Hampstead, 2012	Combined						●			
Herrera, 2012	Single					●	●			
Moro, 2012	Combined			○	●	●	●			
Valdes, 2012	Single				●					
Carretti, 2013	Single			●		●	●			
Greenaway, 2013	Single		○							
Olchik, 2013	Combined					●	●	●		
Rojas, 2013	Multiple	●	●				●	●		
Suzuki, 2013	Combined		●			●	○			
Vidovich, 2014	Multiple	○	○	○	●	○	○	○		
Non-randomized CT: Level B										
Belleville, 2006	Combined				○	○	●	○		
Talassi, 2007	Multiple		○	○	○	○	●	○	●	
Kurz, 2009	Multiple						●			
Banningh, 2011	Multiple									
Banningh, 2013	Multiple									
Non-randomized, no CG: Level C										
Wenisch, 2007	Combined			○			●	○		
Greenaway, 2008	Single		○							
Hampstead, 2008	Combined						●			
Banningh, 2008	Single									
Londos, 2008	Combined			●	○				○	
Belleville, 2011	Combined						●			

○ This domain was assessed but not affected by cognitive intervention; ● This domain was assessed and improved by cognitive intervention.

Table 4. Results of brain imaging after cognitive intervention

Author, Year	Sample Size	Examination, Time	Tasks	Results
Belleville, 2011	aMCI=15 (IG=15)	fMRI at Baseline, 1 week after Endpoint	Memory encoding, Memory retrieval	Activation during encoding: Post-training> Pre-training ($p<0.001$, uncorrected) Lt. superior temporal gyrus and insula, Lt. thalamus, putamen and globus pallidus, Rt. inferior parietal lobule, Rt. superior frontal gyrus, Rt. cerebellum Activation during retrieval: Post-training> Pre-training ($p<0.001$, uncorrected) Lt. postcentral gyrus and inferior parietal lobule, Lt. inferior parietal lobule, Both posterior cingulate, Lt. superior temporal gyrus, Rt. insula, Rt. superior temporal gyrus, Lt. precuneus, Lt. middle frontal gyrus
Förster, 2011	aMCI=21 (IG=9, CG=12)	FDG-PET at Baseline, Endpoint	None	Decreased metabolism in bilateral occipito-temporal, parietal and prefrontal area only in CG, Attenuated decline in both temporal, prefrontal and anterior cingulate cortex in IG ($p<0.001$, uncorrected)
Rosen, 2011	MCI=12	fMRI at Baseline, Endpoint	Auditory word list stimulation	Activation of left hippocampus in intervention group
Hampstead, 2012	aMCI=18 (IG=9, CG=9)	fMRI at Baseline, Endpoint	Memory encoding (object-location-association task), Memory retrieval	Activation during encoding: Intervention> Control no significant difference between group Activation during retrieval: Intervention> Control for trained stimulus, activation in left hippocampal body and right hippocampus for untrained stimulus, activation in right hippocampal body
Suzuki, 2013	MCI=92	MRI at Baseline, Endpoint	None	Whole brain cortical volume increased in IG with aMCI subtype

intervention group progressed to dementia, whereas three in control group progressed after 1 year [45]. Conversely, in a recent study by Vidovich and colleagues, cognitive intervention did not affect progression to dementia [24]. However, the follow up durations were 12 months [45], 18 months [49] and 26 months [24], which might not be sufficient to confirm the effects of cognitive intervention considering the progression rate of MCI is 12-15% per year [4]. The cognitive intervention effects on progression warrant further studies with a longer follow-up period.

DISCUSSION

We have reviewed the characteristics of MCI patients, the various cognitive intervention programs applied, short-term effects, and long-term benefits of cognitive interventions in 32 clinical trials since January 2000 to June 2014.

Because MCI is a heterogeneous syndrome that may remain stable, revert to normal cognition, or progress to a dementia syndrome, treatment efficacy may vary according to patient inclusion criteria. In the reviewed studies, most of them used similar enrollment criteria in which the patients complained of memory / cognitive decline, objective memory / cognitive impairment, and lacked dementia. However, there was some discrepancy between the subtypes of MCI (amnestic vs. non-amnestic type; single-domain vs. multiple-domain) across the reviewed studies. In addition, the term "MCI spectrum" is broad, and contains both "early" and "late" stage MCI; the treatment efficacy and goals may be different according to the severity of disease [54]. Demographic factors of the participants might also influence the treatment effects. Belleville *et al.* reported that younger age and a higher level of education were associated with a larger benefit after cognitive intervention [15]. This observation is consistent with a meta-analysis that reported higher mental status and younger age were positively correlated with a greater efficacy of cognitive interventions [55]. Factors related with cognitive reserve such as educational level, occupation, leisure activity, and cognitive activity might modulate the effects after cognitive interventions [41], but these factors were not considered in the previous studies we reviewed. Assessing the effects of cognitive therapy according to patients' characteristics like these should be the avenue of research exploring further.

Regarding the sample size, most studies had a small sample size with a mean of 47.4 patients; only 8 studies exceeded 50. Considering the sample size of intervention group, only 3 studies among randomized controlled trials enrolled more than 50 MCI patients for intervention group. Large study samples were scarce in the reviewed studies and this might interfere with the external validity of the results. Enrollment of larger sample size is not easy for many reasons: 1) Same expert clinician administering the cognitive intervention using standardized instructions through all of the sessions might be needed for the internal validity of the results; 2) Cognitive intervention program is very time-

consuming and labor-intensive to accomplish for both the trainers and the patients; 3) Patients with MCI are still active in social and occupational functioning and have difficulty finding time to participate in the study; 4) Patients with MCI might not be keenly interested in the study because their cognitive decline does not have a significant impact on their daily life.

As shown from our current literature review, multiple training programs could be used either alone or in combination for cognitive enhancement. Previous studies have identified three approaches to cognitive interventions including the followings: (1) cognitive stimulation that encompasses group activities designed to increase general cognitive and social functioning in a non-specific manner, (2) cognitive rehabilitation that involves therapeutic activities based on the patient's deficits encompassing individually tailored programs on specific ADL, and (3) cognitive training aimed at improving, maintaining, or restoring specific neuropsychological functions through repeated and structured practice of cognitive tasks [56]. The trained cognitive function might be attention, executive function, perception, language, or memory. Classification of the type of intervention according to these definitions is often difficult because many studies employ a mix of different intervention strategies [57]. The reviewed study trials that combined cognitive stimulation and cognitive training reported improvement in multiple cognitive domains and general cognitive measures. This is consistent with the recent study suggesting that combined cognitive training, cognitive stimulation, and psychotherapeutic techniques might be better for the improvement of multiple cognitive functions and ADL [28]. On the other hand, cognitive rehabilitation would be more suitable for people with dementia because that approach takes into consideration the impairment of each individual.

There was no identifiable consensus regarding study design, standardized routine programs, or duration and setting of cognitive intervention. Hence, it remains to be sought using larger samples. There are some important issues to consider about the programs of the cognitive intervention. First, group settings varied in each study. In the reviewed studies, no comparisons were made between group interventions vs. individual interventions or between large group vs. small group interventions. Generally, a small group intervention was believed to be more effective than individual or large-group interventions [15]. Group intervention has benefits in terms of the cost-benefit ratio, mood, and social interaction among the patients. Verhaeghen *et al.* reported that cognitive training with small groups in short sessions was more effective than individual training in a healthy aged population [55]. On the other hand, individualized intervention has benefits in that personal needs and preferences can be considered [41]. Second, mnemonic strategies were taught in only approximately half of the reviewed studies. Some studies taught external aids for memory. The mnemonic strategies and external aids provide some benefits. Mnemonic strategies supply internal compensatory ways that facilitate the organization and association of new information [54]. This approach engages several cognitive processes possibly including other "normal" brain areas and/or compensatory regions to achieve improvement. The mnemonic strategies can be effective in MCI, especially in the early stage because early stage patients still have capabilities to use compensatory techniques. Patients may use this "internal aid" for other situations across settings, although it is time-consuming and requires considerable efforts. As such, more severely cognitively compromised patients cannot use such strategies [54]. External aids for memory are probably most effective for prospective tasks. Greenaway and colleagues reported that external aids improved ADL and memory self-efficacy in MCI, although high dependency on the aids might occur [42]. Whether the strategies contributed to the overall efficacy of the cognitive interventions is unclear, because studies that did not teach memory strategies also showed some improvement. Third, we included all studies using computer-based and non-computer-based (classical) interventions. Computer-based cognitive intervention seems to be promising in that quality-controlled, individualized programs that are tailored to the patient can be used widely [58]. However, benefits from social interaction would be lost in computer-based intervention. Based on our current review, group-based multi-component cognitive intervention including cognitive exercise of multiple domains, education for memory strategies and meta-memory with long durations of intervention might be beneficial in improving multiple cognitive domains including memory function, attention, executive function, visuospatial function and general cognition. Cognitive interventions focused on specific cognitive abilities might not show improvement in multiple cognitive domains or generalization probably due to a heterogeneity of cognitive deficits in an MCI stage. Further research comparing individual vs. group settings, with vs. without memory aids, and teaching vs. no teaching memory strategies might be required to determine an appropriate setting for cognitive intervention in MCI.

Because there is no gold standard for assessing cognitive impairment, selecting the appropriate outcome variables is a big challenge in cognitive intervention studies. Outcome measures should be sensitive to the effects of the cognitive intervention and include multiple cognitive function tests. Variable outcome measures in each study make it difficult to compare the effects across the studies. Most studies in our current review reported positive effects of cognitive intervention through objective cognitive measures or subjective perception of memory function, although the outcome measures were considerably different across the studies, and many of the objective measures were related to the trained tasks or only part of the measured outcomes. Although there have been a limited number of studies that investigated brain imaging changes, all of them reported positive effects including increased whole brain volume, activation of memory-related structures or attenuated metabolic decline. These favorable outcomes might be attributed to neuronal plasticity and cognitive reserve. Neuronal plasticity is defined as the neuron's ability to adapt its structure in response to environmental changes [59]. Similarly, cognitive plasticity is defined as the changed patterns of cognitive behavior through neural plasticity [60]. Previous studies have shown that cognitive plasticity in MCI is associated with less cognitive decline [61]. Cognitive reserve is a concept that provides an explanation for different susceptibilities to pathologic changes related to AD [62]. Cognitive reserve is affected by the subject's educational level, occupational attainment, lei-

sure activities, and social activities. Because patients with MCI still have the ability to learn new information and adapt their behaviors, cognitive intervention might attenuate the risk of cognitive decline by increasing cognitive reserve. An earlier meta-analysis showed that people with high cognitive reserve have a 46% reduced risk of developing dementia compared to individuals with low cognitive reserve, and the effect persisted over a median 7.1 years [63]. In another recent review, the authors suggested that repeated exposure to activities related with cognitive reserve may not only help the brain adapt to pathologic changes, but also prevent those changes [64]. Moreover, animal studies have found that mice in an 'enriched' environment generate more new neurons [65] and display reduced beta amyloid deposition in the brain [66].

Most favorable results are shown in memory function, especially in the delayed recall task. Given that the majority of the patients had an amnestic form of MCI and that the memory problem was the main complaint of the patients, improving memory function should be a main target of the cognitive intervention. Based on the results of level A - ranked studies, attention also showed a favorable cognitive improvement in the intervention group. Successful improvement in attention via cognitive intervention may enhance cognitive functioning and allow patients to benefit from other forms of intervention. However, the clinical significance and confirmation of this gain in attention via cognitive intervention programs need further studies because only 6 studies focused on measuring changes in attention.

Another alternative method to detect the effects of cognitive intervention is to evaluate neuroimaging changes. All of the studies we reviewed showed positive effects in brain imaging. These findings provide evidences for neuronal plasticity in MCI patients. Increased brain activities and attenuated metabolic decline in our reviewed studies mainly indicate compensation and partial normalization of the affected functions. Brain imaging can additionally identify the brain regions related to training and determine the task that is more transferable and effective [67]. In the plastic brain, relevant structural areas that mediate the cognitive changes may also be altered [59], although only one study measured structural changes.

Results are mixed considering the extent of the impact and the intervention's capacity to delay conversion to AD. Only a few studies additionally showed transfer effects of the cognitive intervention to general cognitive function, ADL functions, or other cognitive domains. However, only 38 of the studies we assessed measured general cognition, and the most commonly used tool, MMSE, might not be suitable to measure improved general cognition because of the non-specific nature and potential ceiling effects in people with MCI [54]. A lack of long-term follow-up studies was also another limitation of the previous studies.

CONCLUSION

Most studies of cognitive training in MCI subjects demonstrated positive effects of cognitive training on both objective and subjective outcome variables, and these effects persisted from 1 month to 5 years. Although many of the positive effects were noted in previously trained tasks or part of measurements, favorable changes in neuroimaging and the transfer effects shown by some studies are encouraging because they indicate the potential efficacy of cognitive intervention in MCI patients. Future studies with a larger sample size and more specified criteria in a wider spectrum of MCI will allow understanding of the effects of cognitive intervention on MCI patients. More characterization of subjects, assessment of cognitive reserve in each patient and identification of the most instructive outcome measures will be topics to move the field forward. The ultimate goal of cognitive intervention is to improve "real functioning" within everyday life and to delay clinical progression. Future research, therefore, should also focus on demonstrating these goals. MCI might be a suitable state for cognitive intervention because patients with MCI have a high probability of progression but still have sufficient functional activities remaining to respond to cognitive intervention. Moreover, the human brain is highly plastic and capable of generating new synaptic connections throughout life and new neurons under selective conditions. Therefore, selecting appropriate cognitive interventions for specified subjects and measuring proper outcomes will achieve maximal benefits from non-pharmacological treatment in patients with MCI.

ABBREVIATIONS

16-FR/CR test	=	16-item free and cued reminding test
AD	=	Alzheimer's disease
ADAS-cog	=	Alzheimer's Disease Assessment Scale
CAMCOG-R	=	Cambridge Cognitive Examination-Revised
CB	=	Caregiver Burden questionnaire
CDR	=	Clinical Dementia Rating
CERAD	=	The Consortium for the Registry of Alzheimer's Disease
CES-D	=	Center for Epidemiological Studies-Depression
CG	=	Control group
ChEI	=	Cholinesterase inhibitors
COWAT	=	Controlled Oral Word Association Test
CT	=	Controlled trial
CVLT	=	California verbal learning test
CWMS	=	Categorization Working Memory Span test
DRS-2	=	Dementia Rating Scale-2
FAS	=	F-A-S verbal fluency test
FDG-PET	=	Fluorodeoxyglucose-Positron emission tomography
FRSSD	=	Functional Rating Scale of Symptoms of Dementia
FUCAS	=	Functional Cognitive Assessment Scale
GDS	=	Geriatric depression scale
ICQ	=	Illness Cognition Questionnaire

IG = Intervention group

IQCODE = Information Questionnaire on Cognitive Decline in the Elderly

LAQ = Leisure Activity Questionnaire

MADRS = Montgomery-Asberg Depression Rating Scale

MCI = Mild cognitive impairment

MCI§ = Memory Controllability Inventory

MFQ = Memory Functioning Questionnaire

MMQ = Multifactorial Metamemory Questionnaire

MMSE = Mini-Mental State Examination

MoCA = Montreal Cognitive Assessment

NPI = Neuropsychiatric inventory

PAQ = Physical Activity Questionnaire

QoL-AD = Quality of Life-AD

RAND-36 = Research ANd Development-36

RAVLT = Rey auditory verbal learning test

RBANS = Repeatable battery for assessment of cognitive status

RBANS = Repeatable Battery for the assessment of Neuropsychological Status

RBMT = Rivermead Behavioural Memory Test

RCFT = Rey Complex Figure test

RCT = Randomized controlled trial

RMBPC = Revised Memory and Behavior Problems Checklist

ROCFT = Rey-Osterrieth Complex Figure Test

SES = Self-Esteem Scale

SNSQ = Social Network Satisfaction Questionnaire

TEA = Test of Everyday Attention

TMT = Trail-making test

TNP = NeuroPsychological Training

WAIS = Wechsler Adult Intelligence Scale

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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