



# Non-pharmacological intervention for memory decline

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Non-pharmacological intervention of memory difficulties in healthy older adults, as well as those with brain damage and neurodegenerative disorders, has gained much attention in recent years. The two main reasons that explain this growing interest in memory rehabilitation are the limited efficacy of current drug therapies and the plasticity of the human central nervous and the discovery that during aging, the connections in the brain are not fixed but retain the capacity to change with learning. Moreover, several studies have reported enhanced cognitive performance in patients with neurological disease, following non-invasive brain stimulation [i.e., repetitive transcranial magnetic stimulation and transcranial direct current stimulation to specific cortical areas]. The present review provides an overview of memory rehabilitation in individuals with mild cognitive impairment and in patients with Alzheimer's disease with particular regard to cognitive rehabilitation interventions focused on memory and non-invasive brain stimulation. Reviewed data suggest that in patients with memory deficits, memory intervention therapy could lead to performance improvements in memory, nevertheless further studies need to be conducted in order to establish the real value of this approach.

**Keywords:** training, Alzheimer, MCI, aging, brain stimulation

Memory is the ability to store, maintain, and retrieve information from the mind. In other words, it is the human ability to construct a virtual bridge between the past, the present, and the future.

Memory declines with physiological aging, and memory loss is characteristic of several clinical conditions such as mild cognitive impairment (MCI) and Alzheimer's disease (AD). Non-pharmacological interventions for memory difficulties in healthy older adults, as well as those with brain damage and neurodegenerative disorders, have gained much attention in recent years (Ball et al., 2002; Willis et al., 2006; Acevedo and Loewenstein, 2007). The limited efficacy of the current drug therapies and the recent advances of knowledge in the field of human central nervous system plasticity are two of the main reasons for the growing interest in rehabilitation (Landi and Rossini, 2010; Buschert et al., 2011). The ability to learn and remember new information declines with physiological aging (Grady and Craik, 2000). In particular, older adults show impairments in episodic memory tasks (Tulving, 1983), which involve encoding and retrieving information from previously experienced events. These reductions in cognitive performance most likely reflect age-related changes in the brain, which undergoes significant structural and functional modifications during the aging process (Creasey and Rapoport, 1985). These modifications may be due to decreased cell metabolism, which is characterized by a reduced activity of networks dedicated to carrying out a given function.

Due to the rapidly aging demographic, the mean age of the general population is increasing, with a corresponding increase in the number of people that will develop cognitive disabilities related to aging. Therefore, it is extremely important to identify effective interventions to reduce the incidence of these disabilities

in older adults. Interestingly, memory functions in some older subjects are able to compensate for the structural losses that occur during aging; these individuals show performance improvements comparable to those of young subjects. Accordingly, understanding the basis of minor vs. major age-related cognitive declines is of great interest.

Several imaging studies have addressed the neural mechanisms underlying memory decline in older adults (Grady et al., 1995, 1998; Schacter et al., 1996; Cabeza et al., 1997, 2000; Rosen et al., 2002; Gutchess et al., 2005; Dennis et al., 2008). Based on these age-related changes, an amendment to the hemispherical encoding retrieval asymmetry (HERA) theory (Tulving et al., 1994) was proposed for older adults. The HERA model predicts that the left prefrontal cortex (PFC) specializes in encoding while the right PFC specializes in retrieval. Accordingly, functional magnetic resonance imaging (fMRI) studies in older adults led to a proposal of the hemispheric asymmetry reduction in older adults (HAROLD) model (Cabeza, 2002). Although activation of the right PFC during retrieval was less pronounced, bilateral involvement of the PFC during both encoding and retrieval was observed in healthy elders, which differed from young participants who exhibited only left hemisphere activity during retrieval tasks. Overall, the significance of these changes is intriguing because they could be caused either by an effective functional compensation strategy or by inadequate and/or less efficient processing in the contralateral hemisphere.

Despite numerous studies on the role of the dorsolateral PFC (DLPFC) in episodic memory, neuroimaging studies have demonstrated the involvement of a distributed neural network constituted by the DLPFCs, the medial temporal lobes, the parietal cortices (PARCs), and the precuneus (Wagner et al., 1998; Rugg

and Wilding, 2000; Buckner et al., 2001; Fletcher and Henson, 2001; Cabeza and Nyberg, 2003; Cabeza et al., 2003; Simons and Spiers, 2003).

Recently, repetitive transcranial magnetic stimulation (rTMS) has been used to investigate prefrontal asymmetry in healthy aging individuals (Rossi et al., 2004), thereby confirming the reduction in asymmetry previously shown by fMRI (Cabeza, 2002). Moreover, a recent brain stimulation study showed that older adults with higher memory performance showed less prefrontal asymmetry, which has led to the hypothesis that decreased asymmetry could represent an efficient strategy for counteracting age-related memory decline (Manenti et al., 2011). In line with these data, several studies have suggested that cerebral plasticity and cognitive reserves play important roles in physiological aging and rehabilitation (Stern, 2002, 2006; Stern et al., 2005; Valenzuela and Sachdev, 2006, 2009; Noack et al., 2009).

Many researchers are interested in helping older adults maintain their cognitive abilities and quality of life (Fratiglioni et al., 2004; Salthouse, 2006; Willis and Schaie, 1986; Rasmusson et al., 1999; Ball et al., 2002; Salthouse, 2006; Willis et al., 2006; Craik et al., 2007; Lovden et al., 2010, for a review see Tardif and Simard, 2011).

The advanced cognitive training for independent and vital elderly (ACTIVE) study was a multicentre, randomized, controlled trial conducted by Ball et al. (2002) that examined the long-term outcomes of cognitive interventions in older individuals who were living independently. This work showed that each of the three cognitive interventions used in the trial improved the cognitive ability of older individuals and that these improvements were maintained throughout the following 2 years of follow-up. Subsequently, Willis et al. (2006) confirmed that cognitive training improved cognitive functions in well-functioning older adults and that the improvement lasted for up to 5 years from the beginning of the intervention. In addition, this trial provided some evidence that improvements in cognitive function can have a positive effect on daily living skills. Moreover, recent multisite, randomized, controlled, double-blind studies have confirmed the positive effects resulting from computerized cognitive training programs on memory and attention in older adults (Smith et al., 2009; Zelinski et al., 2011).

A systematic review of the literature conducted by Zehnder et al. (2009) demonstrated significant improvements for specific memory tasks (paired associate learning and immediate and delayed recall) as a result of training effects. However, the authors concluded that the evidence supporting the effectiveness and specificity of training intervention is scarce. Is it possible to develop prosthetics to correct poor memory, equivalent to spectacles for poor vision? The present review provides an overview of rehabilitation programs focusing on memory improvement for individuals with MCI and patients with AD. Particular emphasis is placed on cognitive rehabilitation interventions focused on episodic memory, as well as the application of non-invasive brain stimulation techniques such as rTMS and transcranial direct current stimulation (tDCS) to improve memory performance.

In regard to the application of cognitive rehabilitation, we divided interventions into the following four principal approaches:

(a) memory exercises, (b) teaching memory strategies, (c) procedural memory, and (d) errorless learning techniques.

The aim is to highlight the most important aspects of these rehabilitation approaches and to suggest the opportunity of combining a cognitive rehabilitation intervention with non-invasive brain stimulation to increase the effectiveness of intervention.

## MEMORY INTERVENTIONS IN MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE

Studies on normal subjects (young and elderly participants) and on patients affected by neurological disease have shown that the improvement and recovery of function after cerebral deficits or environmental changes could involve a reorganization of the central nervous system. Functional neuroimaging studies have shown that cerebral reorganization occurs after rehabilitation interventions (Warburton et al., 1999; Nyberg et al., 2003; Shaywitz et al., 2003; Strangman et al., 2005).

Importantly, previous studies on healthy aging have focused on prevention; this concept is even more relevant if we apply it to a particular elderly adult population afflicted with MCI or more specifically, amnesic MCI (aMCI; Petersen, 2004). MCI is widely used to define a disorder among individuals who have subjective cognitive deficits, objective memory impairments, or other cognitive deficits without impairments in daily activities (Petersen et al., 1999). Given the increased risk of developing AD in this population, there is a strong argument for developing cognitive interventions aimed at reducing memory difficulties in MCI patients. A recent review of cognitive intervention strategies for MCI patients indicated that memory impairment might be best targeted by interventions that develop compensatory strategies and induce the learning of specific information relevant to the affected individual (Stott and Spector, 2011).

Along these lines, several studies have utilized cognitive training aimed at improving memory in MCI patients (Table 1).

Using computer-assisted cognitive training for aging-associated memory deficits, Gunther et al. (2003) found significant improvements in short- and long-term memory for verbal and visual stimuli. Cipriani et al. (2006) evaluated a computer-based cognitive training program in AD patients compared with patients affected by MCI, as well as a control group of patients with the diagnosis of multiple system atrophy (MSA). The computer-based cognitive training included exercises designed to stimulate the learning of new information and exercises involving information retrieval from semantic memory. The MCI participants showed a significant improvement in working memory tasks, psychomotor learning, and behavioral memory. In contrast, the AD patients improved in global cognitive status (MMSE), verbal fluency and executive functions. The MSA patients did not benefit from cognitive training. Importantly, this study indicated a general beneficial effect of the training because participants not only improved in computer-based trained exercises but also in cognitive tests (Cipriani et al., 2006).

Furthermore, computer-based cognitive training has been shown to lead to cognitive and mood benefits in MCI individuals treated with cholinesterase inhibitors (ChEIs; Rozzini et al., 2007). In this study, the authors evaluated the efficacy of computer-based cognitive training that included several exercises designed

Table 1 | Memory intervention in individuals with mild cognitive impairment.

Reference	Intervention	Participants	Study design	Frequency/duration	Outcome	Follow-up	Results
<b>MEMORY EXERCISES</b>							
Gunther et al. (2003)	II: computer-assisted cognitive training	19 MCI	U	Fourteen 45-min sessions (1/week)	Speed and attention, memory, learning, interference tendency	5 months	↑ Speed, short- and long-term memory, learning, interference tendency. At FU: ↑ learning, interference tendency
Cipriani et al. (2006)	II: computer cognitive training	10 MCI; 10 AD; 3 MSA	U	Two blocks of 16 13/45-min sessions (4/week). Break: 6 weeks	Language, attention, executive functions, memory, mood, behavior	None	MCI: ↑ short- and long-term memory. AD: ↑ language, executive functions
Rozzini et al. (2007)	II: computer cognitive training (CT)	59 MCI (15 CT plus ChEIs, 22 ChEIs, 22 POB)	RC	Three blocks of 20 60-min sessions (5/week)	Long-term memory, language, reasoning, praxis, behavior, mood, functional living skills	None	CT: ↑ long-term memory, reasoning, behavior, mood. ChEIs group: ↑ mood
Talassi et al. (2007)	II: computer training plus behavioral therapies (CT) vs. physical and behavioral therapies (POB)	37 MCI (30 CT, 7 POB); 29 MID (24 CT, 5 POB)	C	Twelve 45-min sessions (4/week)	Memory, language, praxis, mood, behavior, functional living skills, processing speed, executive function	None	MD CT: ↑ short-term memory, mood, behavior; MCI CT: ↑ praxis, long-term memory, mood, behavior, processing speed
Wenisch et al. (2007)	GI: reality orientation, cognitive exercises, memory strategy use	12 MCI; 12 HE	U	Ten 90-min sessions (1/week)	Long-term memory, attention, language, mood	None	MCI vs. HE: ↑ long-term memory
Barnes et al. (2009)	II: computer working auditory memory (WAM) training vs. computer control activities (CG)	47 MCI	RC	Thirty 100-min sessions (5/week)	Memory, language, attention, visuospatial abilities, mood	None	WAM: ↑ visuospatial abilities, long-term memory, short-term memory
Kurz et al. (2009)	GI: multi-component training and memory training	28 MCI (18 TG, 10 CG); 10 AD	C	22 h/week over 4 weeks	Functional living skills, long-term memory, mood, praxis	None	MCI TG: ↑ mood, long-term memory, functional living skills

(Continued)

Table 1 | Continued

Reference	Intervention	Participants	Study design	Frequency/ duration	Outcome	Follow-up	Results
<b>TEACHING MEMORY STRATEGIES</b>							
Rapp et al. (2002)	GI: education and training about memory skills	19 MCI (9 TG, 10 CG)	RC	Six 120-min sessions (1/w/week)	Long-term memory, language, praxis, metamemory, perceived control over memory, mood	6 months	TG at end: ↑ metamemory, +control over memory; TG at FU: ↑ metamemory
Belleville et al. (2006)	GI: teaching episodic memory strategies	28 MCI (20 TG, 8 CG); 17 HE (9 TG, 8 CG)	C	Eight 120-min sessions (1/w/week)	Learning, associative memory, quality of life, metamemory, attention, language	None	MCI TG: ↑ associative memory, learning, quality of life, metamemory. HE TG: ↑ long-term memory
Hampstead et al. (2008)	II: teaching episodic memory strategies	8 MCI	WS	Three 180-min sessions over 2 weeks	Face-name associative memory (trained and untrained), mood	1 month	↑ Trained and untrained associations. At FU: ↑ trained associations
Londos et al. (2008)	GI: teaching episodic memory strategies	15 MCI	U	Eight 150-min sessions (2/w/week)	Memory, executive functions, praxis, processing speed, quality of life, occupational skills	6 months	At end and FU: ↑ occupational skills, processing speed, quality of life
Troyer et al. (2008)	GI: teaching memory strategies plus lifestyle education	54 MCI (27 TG, 27 CG)	RC	Ten 120-min session over 6 months	Strategies knowledge and use, functional skills, long-term memory, associative memory	3 months	TG at end and FU: ↑ strategies knowledge and use
Kinsella et al. (2009)	GI: teaching episodic memory strategies	47 MCI (22 TG, 25 CG)	RC	Five 90-min sessions (1/w/week)	Prospective memory, metamemory, strategies knowledge	4 months	TG at end and FU: ↑ prospective memory, strategies knowledge
Belleville et al. (2011)	GI: teaching episodic memory strategies	15 MCI; 15 HE	U	Six 120-min sessions (1/w/week)	Long-term memory	None	MCI: ↑ long-term memory
<b>ERRORLESS LEARNING TECHNIQUES</b>							
Akhtar et al. (2006)	II: errorless or errorful learning for word lists	16 MCI; 16 HE	WS	One 40/60-min session	Long-term memory, metamemory	None	MCI and HE: ↑ long-term memory; errorless > errorful
Jean et al. (2007)	II: errorless learning for face-name associations	2 MCI	WS	Six 45-min sessions (2/w/week)	Memory, associative memory	5 weeks	At end and FU: ↑ associative memory

RC, randomized controlled study; C, controlled study; U, uncontrolled pre-post study; FU, follow-up; WS, within subject study; II, individual intervention; GI, group intervention; HE, healthy elders; AD, Alzheimer's disease patients; MCI, mild cognitive impairment patients; MD, mild dementia of different type; MSA, multi-system atrophy; ↑, improvement.

to stimulate memory, attention, language, abstract reasoning and visuospatial abilities in MCI patients who were either treated or not treated with ChEIs. The results showed that MCI individuals without any treatment were stable in cognitive, functional and behavioral status after 1 year while MCI patients treated only with ChEIs improved in depressive symptoms. However, individuals treated with cognitive training and ChEIs showed improvements in two different cognitive areas (memory and abstract reasoning), as well as in depressive symptoms. Talassi et al. (2007) compared the effectiveness of the cognitive training protocol used by Rozzini et al. (2007) plus occupational and behavioral therapies with that of physical rehabilitation plus occupational and behavioral therapies. They tested MCI and mild dementia (predominantly AD) patients. The study demonstrated that only computer-based training plus occupational and behavioral therapies provided an improvement in the cognitive and affective status of individuals with MCI and dementia. In contrast, a rehabilitation program that did not stimulate cognitive function did not have significant effects (Talassi et al., 2007). Similarity, a randomized, controlled pilot trial of intensive, computer-based cognitive training concluded that this intervention was effective in subjects with MCI (Barnes et al., 2009).

Using multi-component cognitive training that included memory exercises, Kurz et al. (2009) showed improved episodic memory measures in MCI individuals (California Verbal Learning Test and Rey Complex Figure Recall Test), as well as increases in daily living activities and mood. Furthermore, Wenisch et al. (2007) showed that programs that included memory exercises resulted in an improvement of associative memory abilities in MCI and normal subjects (although a greater improvement was observed in MCI cases).

Several studies have investigated the effect of training in the use of memory strategies on individuals with MCI, showing prospective memory (Kinsella et al., 2009), quality of life (Londos et al., 2008) and metamemory (Rapp et al., 2002) improvements. A randomized controlled trial for individuals with aMCI explored the efficacy of a memory intervention as measured by the acquisition and application of everyday memory strategies (Troyer et al., 2008). This study found an improvement after the use of memory strategies. Another relevant study, conducted by Belleville et al. (2006), aimed to assess the efficacy of a 2-month, multi-factorial cognitive training protocol designed to teach episodic memory strategies in individuals with MCI. The study included healthy elderly and MCI individuals. The training was comprised of episodic memory strategy training, meta-cognition, and computer-based training of attention. The authors found a significant effect on episodic memory tests (delayed list recall and face-name association) in both the control and MCI participants (Belleville et al., 2006).

Moreover, studies using errorless learning techniques for subjects with MCI have shown that this approach can facilitate the learning of information and associations (Akhtar et al., 2006; Jean et al., 2007). This technique refers to a learning condition in which patients are prevented from making errors. Baddeley and Wilson (1994) demonstrated that amnesic patients learn better under errorless conditions. This principle has proven successful over a range of tasks, including learning word lists (Hunkin et al., 1998a),

person and object names (Wilson et al., 1994; Parkin et al., 1998; Evans et al., 2000), word processing skills (Hunkin et al., 1998a), semantic concepts (McKenna and Gerhand, 2002), word pair associations (Squires et al., 1997), and electronic diary programming (Wilson et al., 1994). The general principles of errorless learning incorporate specific techniques for vanishing cues and spaced retrieval (Landauer and Bjork, 1978; Glisky et al., 1986; Glisky, 1992; Camp et al., 1993, 1996). In general, the method of vanishing cues involves the gradual addition and then reduction of cues across learning trials, whereas the spaced retrieval method requires the recall of the target item after short but gradually increased intervals.

The use of these methods in MCI individuals led to an improvement in associative memory (Jean et al., 2007) and word list recall (Akhtar et al., 2006), which supports the effectiveness of these techniques in patients with memory deficits.

Recently, studies have been conducted using functional imaging techniques to examine how brain activity changes in response to cognitive training programs with MCI participants. In a study conducted by Hampstead et al. (2011), fMRI was used to test whether there were training-specific changes in the activation and connectivity within memory-related areas of patients with multidomain MCI. The findings suggested that the effectiveness of explicit memory strategy training in subjects with MCI (associative memory) is associated with training-specific increases in activation and connectivity across a distributed neural system, which included areas involved in explicit memory function.

The significant neural activity changes observed after explicit memory strategy training in MCI and healthy participants were confirmed in a recent fMRI study (Belleville et al., 2011). This study demonstrated increased brain activation after training that correlated with increased performance in long-term episodic memory abilities. The activations included a large network involving the frontal, temporal, and parietal areas (Belleville et al., 2011). These data provide empirical support for the use of cognitive training as an intervention for individuals with MCI.

The main limitation of these studies is the heterogeneity of the target population. MCI is a controversial label describing a range of age-related intellectual declines that includes people presenting with and without a dementia prodrome state (Schneider, 2005; Gauthier et al., 2006; Visser et al., 2006; Whitehouse and Brodaty, 2006; Chertkow et al., 2007; Whitehouse, 2007). Moreover, the use of different types of interventions and different outcome measures makes direct comparisons difficult (Stott and Spector, 2011). Nevertheless, the results of these studies highlight the value of prevention in the older adult population.

Memory problems are typically one of the first warning signs of cognitive decline in AD. AD is the most common cause of dementia and results in a slow and progressive loss of memory, language, reasoning, and other cognitive functions, which eventually become completely impaired.

Behavioral and functional dysfunctions following AD constitute some of the major causes of disability worldwide and have a significant impact on the lives of the affected individuals and their families. However, this process is not an "all or none" phenomenon. Importantly, during the first stage of the disease process, some cognitive functions are preserved (i.e., procedural memory) and can

be the target of cognitive interventions (Beck et al., 1988; Zanetti et al., 1998, 2001, 2002; Clare et al., 2001; De Vreese et al., 2001; Olazaran et al., 2004, 2010; Onder et al., 2005; Souchay et al., 2008). Moreover, several studies have demonstrated at least a modest benefit from specific interventions designed to improve functioning in select cognitive tasks.

The application of cognitive rehabilitation during early dementia is based on evidence regarding the neuropsychological profile of patients with AD. AD patients show short-term forgetfulness, whereas long-term memory and implicit memory appear to be relatively unaffected (Perry and Hodges, 1996). These patients exhibit a profound impairment in episodic memory, as demonstrated by free recall and recognition tests, especially after delays (Greene et al., 1996). Moreover, episodic memory difficulties in AD patients are primarily the result of defective information encoding and storage (Kopelman, 1985).

Despite the memory deficits associated with AD, the facilitation of episodic memory can be used when adequate support is provided (Backman and Dixon, 1992; Backman, 1996).

Plasticity mechanisms also play a role in AD. In patients with AD, an increase in the activation of areas involved in memory, or a recruitment of new areas, has been shown (Becker et al., 1996; Woodard et al., 1998; Backman et al., 1999). However, cognitive rehabilitation and cognitive training focusing on memory functioning in dementia patients remain somewhat controversial. A recent Cochrane Library report (Clare et al., 2003b) suggested that the present findings do not provide a strong rationale for the application of cognitive training interventions for people with early-stage AD or vascular dementia. These conclusions must be viewed with caution due to the limited number of randomized controlled trials evaluating the individual cognitive rehabilitation approaches available and the associated methodological limitations. To date, it is not possible to draw conclusions about the efficacy of such interventions for people with early-stage dementia (Clare et al., 2003b).

Nevertheless, several studies have demonstrated benefits from specific interventions designed to improve functioning on select cognitive tasks (Table 2). For example, Cahn-Weiner et al. (2003) suggested that AD patients who are taught specific memory strategies (i.e., memory training to learn word lists) can benefit at least modestly, even if non-significantly, from training exercises.

The main cognitive methods used in AD rehabilitation include *procedural memory training* and *errorless learning techniques*. Neuropsychology findings have suggested that, especially during the first stages of the disease, relatively well preserved skills should be the target of rehabilitative interventions that are aimed at delaying the decline of cognitive functioning. There is evidence that procedural memory, which involves the cognitive use of previous experiences without recognition, is relatively well preserved in AD. Following this evidence, a study conducted by Zanetti et al. (2001) confirmed the effectiveness of *procedural memory training* consisting of three consecutive weeks in 13 basic and instrumental activities of daily living in mild and mild-to-moderate AD patients. The trained group, in comparison to an untrained group, showed a significant reduction in the time needed to perform these activities, whereas the control group showed a non-significant increase (Zanetti et al., 2001).

Similarly, results from Farina et al. (2002) provide further support for the stimulation of procedural memory. In their first study, the authors compared the stimulation of procedural memory with the training of partially spared cognitive functions. Their findings demonstrated that both training exercises induced a substantial improvement in everyday functioning, even if the results of cognitive tests suggested that the training of procedural memory may have been more effective (Farina et al., 2002). In a subsequent study, Farina et al. (2006) compared the effect of recreational activities with gains induced by specific cognitive programs (i.e., procedural memory training vs. neuropsychological rehabilitation of “residual functions”). These results showed that AD patients exposed to recreational activities reported a significant improvement in behavioral disturbances, memory, and functional living skills, as well as reduced caregiver distress at the 6-month follow-up. However, this study did not show improvements as a result of cognitive-specific intervention (Farina et al., 2006), thus highlighting that the benefits from this therapy were usually confined to the treatment period and that there was a rapid loss of improvement after the end of training.

A different method is applied for the treatment of memory in AD patients during errorless learning because some previous studies have suggested that cognitive rehabilitation approaches may have positive effects on memory functioning during the early-stages of AD (Backman and Dixon, 1992; Backman, 1996; Clare et al., 1999, 2000, 2001, 2002, 2003a, 2009). This technique employs learning conditions in which patients are prevented from making errors and is based on various techniques (e.g., vanishing cues and spaced retrieval) that have been previously described for MCI studies. In particular, Clare and collaborators used a combination of methods to successfully produce long-lasting memories for a specific set of face–name pairs (Clare et al., 1999, 2000, 2001, 2002, 2003a). Furthermore, a single case study by Winter and Hunkin (1999) provided descriptive evidence that errorless learning in AD may lead to better re-learning of familiar names compared to learning with errors. Davis et al. (2001) evaluated a 5-week cognitive intervention using training in face–name associations, spaced retrieval, and cognitive stimulation in a group of AD patients. In this study, the patients were randomly assigned to either a cognitive or placebo intervention. Although the patients in the intervention group showed improvements in face–name information and in a measure of attention, the beneficial results did not extend to additional neuropsychological measures or caregiver-rated patient quality of life.

A single case study by Clare et al. (1999; Clare et al., 2003a) tested the hypothesis that a patient in the early-stages of AD can learn face–name associations by applying errorless learning techniques. The results of the study showed a striking improvement in a patient’s recall of the face–name association that was maintained up to 9 months after the end of the study. Subsequent studies demonstrated that improvements in patient recall remained relatively stable over the following year, and the patient’s performance on the trained items remained well above baseline levels even after 2 years (Clare et al., 2001). The same authors confirmed an improvement in face–name memory in six individuals with AD (Clare et al., 2000). These interesting findings were extended in a controlled trial that involved 12 participants with AD

Table 2 | Memory intervention in patients with Alzheimer's disease.

Reference	Intervention	Participants	Study design	Frequency/ duration	Outcome	Follow-up	Results
<b>MEMORY EXERCISES</b>							
Beck et al. (1988)	II: exercises in attention and reading, concentration, and remembering	20 AD (10 TG, 10 CG)	RC	Eighteen 30/40-min sessions (3/week)	Attention, memory, visuospatial	None	TG: ↑ short-term memory
<b>TEACHING MEMORY STRATEGIES</b>							
Cahn-Weiner et al. (2003)	GI: teaching memory strategies (AT) vs. educational formation (EF)	34 AD (17 AT vs. 17 EF)	RC	Six 45-min sessions (1/week)	Learning, long-term memory, language, visuospatial, executive abilities, functional living skills, metamemory	8 weeks	No significant changes
<b>PROCEDURAL MEMORY</b>							
Zanetti et al. (2001)	II: 13 basic and instrumental activities of daily living training	18 AD (11 TG, 7 CG)	RC	Fifteen 60-min sessions (5/week)	Execution time and number of cues	4 months	TG: ?performing of the activities
Farina et al. (2002)	II: procedural memory training (PM) vs. training of cognitive functions (CF)	22 AD (11 PM vs. 11 CF)	RC	Thirty 45-min sessions (2/day, 3 days/week)	Memory, attention, praxis, behavior, language, quality of life	None	PM: ↑ functional living skills, language; CF: ↑ functional living skills
Farina et al. (2006)	GI: recreational activities (RA) vs. procedural memory training and neuropsychological rehabilitation (PM)	32 AD (16 RA vs. 16 PM)	RC	Fifteen 180-min sessions (3/week for 4 weeks, 2/week the fifth week, and 1/week the last week)	Short and long-term memory, attention, praxis, behavior, language, functional living skills, quality of life, mood, caregiver burden	6 months	RA at end: ↑ behavior, short- and long-term memory, functional living skills, language. RA at FU: ↑ caregiver burden. PM at end: ↑ functional living skills
<b>ERRORLESS LEARNING TECHNIQUES</b>							
Clare et al. (1999)	II: errorless learning for face-name associations	1 AD	U	Twenty-one sessions (2/week)	Intelligence, reasoning, language, visuospatial, memory, mood, associative memory	3, 6, 9 months	At end and FU: ↑ associative memory
Winter and Hunkin (1999)	II: errorless learning for face-name associations	1 AD	U	Four sessions	Associative memory	None	↑ Associative memory
Clare et al. (2000)	II: errorless learning for face-name associations, personal information, or calendar	6 AD	U	One session per item to be treated	Mood, memory, caregiver burden, reasoning, intelligence, language, visuospatial, associative memory (treated and untreated), personal information, or calendar	3, 6 months	At end and FU: ↑ treated associative memory

(Continued)

Table 2 | Continued

Reference	Intervention	Participants	Study design	Frequency/ duration	Outcome	Follow-up	Results
Clare et al. (2001)	II: errorless learning for face-name associations	1 AD	U	Six sessions	Mood, memory, caregiver burden, reasoning, intelligence, language, visuospatial, associative memory (treated and untreated)	1, 2 years	At end and at 1 year: ↑ treated and untreated, at 2 year: ↑ treated
Davis et al. (2001)	II: training in face-name associations and personal information	37 AD (19 TG, 18 CG)	RC	Five 60-min sessions (1/week). In TG, continued at home	Memory, attention, language, mood, quality of life, processing speed, associative memory, personal information	None	TG: ↑ treated items performance, long-term memory, attention, language; CG: ↑ long-term memory, attention, language
Clare et al. (2002)	II: errorless learning for face-name associations	12 AD	WS	Six sessions	Mood, metamemory, memory, behavior, caregiver burden, associative memory (treated and untreated)	1, 3.6, 12 months	↑ Treated and untreated; at 3.6 months: ↑ treated
Clare et al. (2003b)	II: errorless learning for face-name associations	1 AD	U	Six sessions	Mood, memory, caregiver burden, reasoning, language, visuospatial, associative memory	3.6 months	↑ Associative memory; at FU: ↑ associative memory
Hawley and Cherry (2004)	II: spaced retrieval for name-face associations	6 AD	U	Six 60-min sessions across 2 weeks	Associative memory, face recognition, live-person transfer task	None	↑ Associative memory, live-person transfer task
Loewenstein et al. (2004)	II: face-name association in cognitive rehabilitation (CR) vs. mental stimulation (MS)	44 AD (25 CR vs. 19 MS)	RC	Twenty-four two 45-min sessions (2/day, 2 days/week)	Associative memory, processing speed, functional living skills, memory, executive functions, language	3 months	CR at end and FU: ↑ associative memory, orientation, processing speed
Cherry and Simmons-D'Gerolamo (2005)	II: spaced retrieval for object memory	15 AD	U	Six 60-min sessions over 3 weeks	Long-term memory	None	↑ Long-term memory

Dunn and Clare (2007)	II: vanishing (VC) vs. forward cues (FC) vs. target selection (TS) vs. paired associate (PA) learning for associations	8 AD; 1 VD; 1 MD	WS	Six 60-min sessions (2/week)	novel and familiar associative memory, visual face-name recognition	none	↑ Novel and familiar associative memory. VC = FC = TS = PA
Metzler-Baddeley and Snowden (2005)	II: errorless vs. errorful learning for greeble- or face-name associations	4 AD	WS	Eight sessions (1/day) over 8 days	Name-object (familiar) and face-name (novel) associations	None	↑ Associative memory; errorless = errorful; familiar = novel
Hawley et al. (2008)	II: adjusted (AS) vs. uniform expanded (UE) spaced retrieval for face-name associations	12 AD (6 AS, 6 UE)	RC	Nine 60/190-min sessions (3/week) across 3 weeks	Associative memory, face recognition, live-person transfer task	None	AS: ↑ associative memory, live-person transfer task; UE: ↑ associative memory
Souchay et al. (2008)	II: rehearsal strategy for learning word lists	16 AD, 16 HE, 16 HY	WS	One session	Long-term memory	None	AD: ↑ long-term memory; HE: ↑ long-term memory; HY: ↑ long-term memory
Cherry et al. (2010)	II: spaced retrieval for name-face-occupation associations	4 AD	U	Six 60-min sessions over 2 weeks	Face-name-occupation memory	None	↑ Associative memory, occupation > name
Haslam et al. (2010)	II: errorless learning (EL) plus vanishing cues (VC) vs. EL vs. VC for greeble- or face-name associations	22 AD; 60 HE	WS	Two 90-min sessions	Associative memory	None	AD: ↑ associative memory; EL + VC > EL or VC
Hopper et al. (2010)	II: spaced retrieval for face-name associations	30 AD; 2 VD	WS	Up to forty 30-min sessions (4/week)	Known and novel associative memory	None	↑ Associative memory
Laffan et al. (2010)	II: standard vs. self-generated errorless learning for famous face-name associations	20 AD	WS	Ten sessions (2/week)	Associative memory	None	Self-generated > standard

RC, randomized controlled study; C, controlled study; U, uncontrolled pre-post study; WS, within subject study; FU, follow-up after treatment end; II, individual intervention; GI, group intervention; HE, healthy elders; AD, Alzheimer's disease patients; VD, vascular dementia; MD, mild dementia; HE, healthy elderly; HY, healthy young; ↑, improvement.

(Clare et al., 2002) in which a significant recall improvement was obtained for trained face–name associations but not for control items (i.e., untreated items). Interestingly, the gains were maintained for 6 months after rehabilitation (for a review see Werheid and Clare, 2007). These findings are consistent with the literature demonstrating that errorless learning is more effective than learning with error among other patient populations (Squires et al., 1997; Hunkin et al., 1998b; Tailby and Haslam, 2003).

Dunn and Clare (2007) conducted a study comparing the effects of four different learning techniques (vanishing cues, forward cues, target selection, and paired associate learning) on the acquisition of name–face associations among patients in the early-stage of AD, patients with vascular dementia and patients with mixed dementia. Overall, these findings showed that each learning method was effective and provided further evidence that learning is possible in AD and vascular dementia patients, which had been shown in previous studies (Camp et al., 1993; Bird and Kinsella, 1996). In addition, several other studies have investigated the usefulness of errorless learning for memory training in AD, which demonstrated improvements in memory for associations and compared the efficacy of different errorless learning methods (Clare and Wilson, 2004; Metzler-Baddeley and Snowden, 2005; Haslam et al., 2010; Laffan et al., 2010; Thom and Clare, 2011).

Another promising intervention for helping individuals with AD during learning is the use of spaced retrieval training (SRT). In SRT exercises, the subject is asked to repeatedly recall a target after increasingly longer intervals of time. This technique is based on the method of expanding retrieval abilities originally described by Landauer and Bjork (1978). Camp and Stevens (1990) adapted the original procedure and applied it to patients with AD. In this form, the intervals were adjusted according to the patient's performance. Several studies have demonstrated that adjusted SRT is efficacious in individuals with probable AD and leads to an improvement in associative memory (Hawley and Cherry, 2004; Cherry and Simmons-D'Gerolamo, 2005; Hopper et al., 2005, 2010; Hawley et al., 2008; Cherry et al., 2010).

Finally, Loewenstein et al. (2004) combined specific cognitive techniques (spaced retrieval, dual cognitive support, procedural memory activation, visuo-motor processing, and functional skills training) into a single cognitive rehabilitation treatment for mildly impaired AD patients. The results of this study indicated that AD patients benefited from cognitive rehabilitation intervention and demonstrated improvements in the learning of face–name associations, processing speed, functional abilities, and orientation.

Because cognitive rehabilitation and cognitive training focusing on memory functioning in dementia patients remain somewhat controversial, the recent Cochrane Library report (Clare et al., 2003b) suggests that the present findings do not provide a strong rationale for the application of cognitive training interventions for people with early-stage AD or vascular dementia and that well-designed trials would help provide more definitive evidence.

Based on the literature, a cognitive rehabilitation approach focusing on individualized, personally meaningful goals that combine errorless learning with a number of other memory techniques seems to be a promising strategy for patients with AD (Cotelli et al., 2006, 2011c).

## NON-INVASIVE BRAIN STIMULATION TO IMPROVE EPISODIC MEMORY IN MCI AND AD PATIENTS

Episodic memory and encoding and retrieval processes have been linked to different networks. Specifically, lesion and functional imaging studies have indicated that episodic memory involves a widespread network of brain structures, including the PFC and PARCs (Cabeza et al., 2008). In elderly subjects, successful memory encoding, and retrieval are associated with activation of the left inferior parietal lobules (IPLs) and the anterior hippocampus (Kircher et al., 2008).

In healthy participants, rTMS studies have confirmed the role of the PFC during the encoding and retrieval of verbal or non-verbal material (Rossi et al., 2001; Sandrini et al., 2003; Manenti et al., 2010a). However, rTMS studies in posterior brain areas have not yet elucidated this mechanism. Previous studies have demonstrated the involvement of PARCs, which is in contrast to rTMS studies. In particular, Rossi et al. (2006) found that the activity of the intraparietal sulci, unlike that of the DLPFC, is not causally involved in the encoding and retrieval of visual scenes. However, by combining fMRI and rTMS, Manenti et al. (2010b) provided the first evidence of a causal role of not only the PFC but also PARCs during word retrieval. Recently, the use of non-invasive brain stimulation to study cognitive functions and dysfunctions in stroke and neurodegenerative patients has attracted much attention. Specifically, rTMS has been shown to transiently modulate neural excitability. Since the introduction of rTMS, it has become evident that the modulatory effects of cortical stimulation may outlast the immediate stimulation period, with effects from repeated sessions lasting for days and even weeks. Along these lines, the use of tDCS has also been shown to have potential for the treatment of neurological diseases (Miniussi et al., 2008; Boggio et al., 2011b; Cotelli et al., 2011b; Miniussi and Rossini, 2011; Miniussi and Vallar, 2011).

Non-invasive brain stimulation techniques for modulating cortical activity include TMS (Wassermann et al., 2008a) and tDCS (Nitsche et al., 2008). Both TMS and tDCS can transiently influence behavior by altering spontaneous neuronal activity (Wassermann et al., 2008a), which may have facilitatory or inhibitory effects.

TMS involves the delivery of a brief (shorter than 1 ms) and powerful (approximately 2 T) magnetic pulse to the scalp through a coil. The magnetic pulse induces a transitory electric current in the cortical surface under the coil, which causes the depolarization of cell membranes (Barker et al., 1985, 1987) and transynaptic depolarization of a population of cortical neurons (Wassermann et al., 2008b).

TMS initially involved the delivery of single magnetic pulses (Barker et al., 1985). In the nineties, it became possible to deliver trains of magnetic pulses with a rhythmic repetition rate of up to 100 Hz. This has been referred as rTMS. Studies have shown that rTMS interacts with cortical activity in a repetition frequency-dependent manner. Empirical evidence has indicated that continuous rTMS below 1 Hz reduces cortical excitability, whereas intermittent rTMS trains above 5 Hz have the opposite effect (Pascual-Leone et al., 1994; Chen et al., 1997; Maeda et al., 2000). Therefore, rTMS allows for transient modulation of neural excitability. Changes last for several minutes beyond the

end of stimulation, depending on the stimulation duration and parameters (see Rossi et al., 2009) for guidelines).

The tDCS technique (Priori, 2003; Nitsche et al., 2008) involves applying weak electrical currents ( $\sim 0.5\text{--}2$  mA) directly to the head for several minutes ( $\sim 5\text{--}20$  min). These currents generate an electrical field that modulates neuronal activity according to the modality of the application. Neurons respond to tDCS by altering their firing rates. Several studies using animal models (Creutzfeldt et al., 1962; Bindman et al., 1964) have suggested that cathodal tDCS reduces spontaneous neuronal firing rates, while anodal tDCS has the opposite effect. Accordingly, similar effects have been observed (Nitsche and Paulus, 2000) in humans. Cathodal polarization over the motor cortex can induce motor cortex excitability reductions, while anodal polarization increases motor cortex excitability (Nitsche and Paulus, 2000). Similar to rTMS, these changes last for minutes to hours beyond the end of stimulation, depending on the stimulation parameters.

Non-invasive brain stimulation techniques exert their effects on neuronal excitation through different mechanisms. TMS induces a current that can elicit action potentials in neurons. tDCS induces a polarization that is too weak to elicit action potentials in cortical neurons. However, it effectively modifies the evoked cortical response to afferent stimulation as well as the postsynaptic activity level of cortical neurons, presumably by inducing a shift in intrinsic neuronal excitability (as shown in tDCS studies on animals, Bindman et al., 1962, 1964, 1979; Purpura and McMurtry, 1965). In spite of this difference, it is likely that both techniques induce cerebral plasticity effects that are comparable in many aspects (Ridding and Ziemann, 2010). Both long-term potentiation and its opposite, long-term depression, have also been postulated to explain the persistent effects of non-invasive brain stimulation on cortical activity (Cooke and Bliss, 2006; Thickbroom, 2007; Ziemann and Siebner, 2008).

In sum, these techniques have been shown to induce modifications of cortical plasticity that may outlast the stimulation period itself. Given this potential, there is currently a growing interest in therapeutically applying these methodologies to reduce cognitive deficits in patients with stroke and chronic neurodegenerative diseases.

The potential for inducing behavioral improvement in patients with memory deficits, and the further possibility that these effects may be long-lasting, is intriguing to many researchers and clinicians. Furthermore, the results of these studies could lead to the development of completely new therapeutic approaches (Table 3).

Solé-Padullés et al. (2006) demonstrated a beneficial role of high-frequency rTMS in associative memory among elderly subjects with memory deficits and low performance on neuropsychological memory tests. This study combined rTMS and fMRI to show behavioral improvement in a face–name association memory task following a single session of off-line stimulation over the bilateral PFC that was not evident in the placebo group. This improvement was associated with the recruitment of the right PFC and the bilateral posterior cortices as shown by fMRI (Solé-Padullés et al., 2006). Moreover, a recent study by Cotelli et al. (2011a) assessed whether the application of daily high-frequency rTMS to the left parietal area for 2 weeks could lead to significant

improvements in memory for face–name associations in an individual with aMCI. The rationale for examining face–name associations was that an early symptom of memory impairment in AD is a particular problem with forgetting or failing to learn people's names (Greene and Hodges, 1996; Holzer and Warshaw, 2000). A significant improvement was found, providing evidence for a putative role of the left parietal area in associative memory and its enhancement by rTMS (Cotelli et al., 2011a).

With respect to AD patients, three tDCS studies have been conducted. First, Ferrucci et al. (2008) found that word recognition memory task (WRT) accuracy increased after a single session of anodal tDCS applied bilaterally over temporal-parietal areas in AD patients, while WRT performance worsened after cathodal tDCS. Moreover, in two subsequent studies, Boggio et al. (2009, 2011a) investigated the effects of anodal tDCS on long-term memory performance among AD patients. Boggio et al. (2009) applied a single anodal tDCS session over the left DLPFC or over the left temporal cortex and reported improved recognition memory (visual recognition memory task). Recently, Boggio et al. (2011b) demonstrated that repeated sessions of anodal tDCS applied bilaterally over the temporal area resulted in a performance increase in a group of AD patients for visual recognition memory tasks. Importantly, this effect was also present at the 4-week follow-up (Boggio et al., 2011b).

In summary, non-invasive brain stimulation techniques may play a role in designing multidimensional models for interventional therapies for individuals with memory impairments. A recent review concluded that stimulation techniques appear safe in AD patients, but the long-term risks have not been sufficiently evaluated (Freitas et al., 2011). Further studies are needed to identify the optimal responders to specific non-invasive brain stimulation interventions (Boggio et al., 2011b; Guerra et al., 2011; Vallar and Bolognini, 2011). However, these initial studies indicate that, while further randomized, placebo-controlled studies are needed, these interventions appear to have the potential to significantly contribute to the improvement and provision of care for people with AD and MCI. Moreover, further lines of inquiry should evaluate the functional changes in cortical reactivity and effective connectivity induced by cognitive plasticity as assessed by the co-registration of TMS or tDCS and EEG, fMRI, DTI, or MEG before, during and after intervention.

## CONCLUSION

In conclusion, the studies described above have shown that non-pharmacological intervention can enhance the effect of ChEI treatment. Generally, these studies compared a combined treatment with pharmacological intervention alone. However, several studies included more than one control condition to verify the improvements induced by the specific cognitive training used (Cotelli et al., 2011c). Moreover, a crucial issue in non-pharmacological rehabilitation is the duration of the induced effects; given the demanding nature of these studies, thus far, only a few have considered long-term follow-up.

Although further controlled studies are needed to demonstrate the efficacy of cognitive training and stimulation interventions, the present review highlights that both of these interventions might be useful in enhancing memory functioning in individuals with

Table 3 | Brain stimulation intervention in patients with Alzheimer disease and individuals with mild cognitive impairment.

Study	Participants	Stimulation technique	Target area	Study design	Frequency/duration	Outcome	Follow-up	Results
<b>REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (rTMS)</b>								
Solé-Padullés et al. (2006)	39 Elders with memory impairment	High-frequency rTMS (20), placebo rTMS (19); 5 Hz, 80% MT, 500 pulses	Bilateral prefrontal	RC	One 50-min session	Associative memory	None	↑ Associative memory
Cotelli et al. (2011a)	1 MCI	High-frequency rTMS; 20 Hz, 100% MT, 2000 pulses/session	Left parietal	U	Ten 25-min sessions (5/week)	Associative memory, reasoning, language, learning, short- and long-term memory, praxis, attention, executive functions	24 weeks	At end and FU: ↑ associative memory, long-term memory
<b>TRANSCRANIAL DIRECT CURRENT STIMULATION (tDCS)</b>								
Ferrucci et al. (2008)	10 AD	atDCS, ctDCS or ptDCS; reference over the right deltoid muscle (two 25 cm <sup>2</sup> electrodes)	Bilateral temporo-parietal	WS	Three 30-min sessions (1.5 mA)	Long-term memory, attention	None	atDCS: ↑ long-term memory, ctDCS: ↓ long-term memory
Boggio et al. (2009)	10 AD	atDCS vs. ptDCS; reference over the right supraorbital area (two 35 cm <sup>2</sup> electrodes)	Left DLPF, left temporal	WS	Three 30-min sessions (2 mA)	Executive functions, memory	None	atDCS: ↑ long-term memory
Cognitive training (Boggio et al., 2011a)	15 AD	atDCS – ptDCS or ptDCS – atDCS; reference over the right deltoid muscle (35 cm <sup>2</sup> for cephalic electrode, 64 cm <sup>2</sup> for extracephalic electrode)	Bilateral temporal	RC	Five 30-min sessions over 5 days (2 mA)	Language, praxis, long-term memory, attention	4 weeks	atDCS at end and FU: ↑ long-term memory

RC, randomized controlled study; U, uncontrolled pre-post study; WS, within subject study; MT, motor threshold; FU, follow-up after treatment end; AD, Alzheimer's disease patients; MCI, mild cognitive impairment patients; DLPF, dorsolateral prefrontal; atDCS, anodal transcranial direct current stimulation, ptDCS, cathodal transcranial direct current stimulation, ctDCS: cathodal transcranial direct current stimulation; rTMS, repetitive transcranial magnetic stimulation; ↑, improvement; ↓, worsening.

memory disorders. A comprehensive and uniform rehabilitation program should be designed with memory improvement as the primary target. Furthermore, unification of the gains obtained by these two interventions should increase the usefulness of these training protocols among these patients. Accordingly, it is reasonable to suggest that combined treatment paradigms (tDCS or rTMS during cognitive training) may ameliorate the cognitive decline associated with aMCI/AD more effectively than either one

of these techniques alone. Further studies, based on larger patient samples and including placebo and control conditions, should be conducted to identify the optimal parameters for such a combined treatment protocol.

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