
Article:
De Marco, M., Meneghello, F., Duzzi, D. et al. (3 more authors) (2016) Cognitive stimulation of the default-mode network modulates functional connectivity in healthy aging. Brain Research Bulletin, 121. pp. 26-41. ISSN 0361-9230

https://doi.org/10.1016/j.brainresbull.2015.12.001

Cognitive Stimulation: The Evidence Base for its Application in Neurodegenerative Disease

Matteo De Marco[1, 2], Michael F Shanks[2], Annalena Venneri[1, 2]

[1] IRCCS San Camillo Foundation, Venice, Italy
[2] Department of Neuroscience, University of Sheffield, UK

Corresponding Author
Prof. Annalena Venneri
Department of Neuroscience - Medical School
University of Sheffield
Beech Hill Road
Royal Hallamshire Hospital, N floor, room N130
Sheffield - S10 2RX - United Kingdom
a.venneri@sheffield.ac.uk
Tel: +44 114 2713430

Abstract

Multiple modalities of cognitive stimulation (CS) have been designed and tested in samples of patients with probable Alzheimer's disease (AD). Despite the substantial inter-study variability, an overall positive impact of CS is reported. This impact has been especially observed in general measures of cognition. The mechanisms by which cognitive exercises would be beneficial for high-order cortical functions are still largely undetermined, however.

When CS has been applied to patients with Mild Cognitive Impairment (who are at the prodromal stage of AD) more stringent methodological criteria and designs were used and studies have been of greater clinical and research relevance. At this disease stage, a positive impact of CS has been reported in a range of different cognitive domains, and even at a neuro-computational level by the measurement of test-retest modifications of brain function.

The effects of CS in healthy adults have also been studied. This population allows researchers to explore and test specific neural mechanisms possibly underlying the effect of pen-and-paper or computerised exercises. The evidence from these studies and those contributing to a better understanding of the pathophysiology of AD has led to devising forms of CS as preventive and therapeutical measures for neurodegenerative diseases based on novel frameworks of brain structure, function and connectivity.

An extensive review of the literature was carried out to clarify whether CS is effective in AD and mild cognitive impairment and, together with the evidence from studies in healthy participants, to identify the relevant mechanisms that might sustain this effectiveness.

Keywords

Alzheimer's Disease; Cognitive Stimulation; Cognitive Training; Mild Cognitive Impairment; Neural Changes; Non-pharmacological Treatment;

Introduction

Alzheimer's disease (AD) is a neurodegenerative condition associated with multidimensional de-regulation of neurobiological and neurobehavioural variables [1]. Although no decisive treatment for AD is available at present, the study of therapeutics is a vast frontier of research that is addressing the scarcity of findings with translational applicability to clinical settings. One major area of investigation is represented by non-pharmacological interventions based on pen-and-paper or computerised exercises with significant computational demands, and specifically designed to improve cerebral and cognitive parameters. This type of approach is normally indicated as "cognitive stimulation" (CS), although other labels have been sometimes proposed (e.g. "cognitive training" or "cognitive rehabilitation"), depending on the distinct theoretical purpose that may drive the design of a programme of intervention [2-4].

Observational studies carried out on large cohorts have reported that engaging in various types of cognitive activities is protective against the onset of AD later in life [5-8]. These findings are statistically robust, as they derive from longitudinal designs and the recruitment of remarkably large samples. However, they also suffer from significant methodological limitations associated with the inability to manipulate the independent variables in observational designs (above all, the inability to define a statistical cause and effect relationship between CS and cognitive benefit). In this respect, clinical trials represent a valuable complementary source of evidence. While the number of participants included in such studies is more limited, research teams can manipulate CS in accordance with their experimental hypothesis.

Although other publications have reviewed the available experimental evidence of published trials of CS in relation with a diagnosis of AD [2, 9], to our knowledge no reviews have covered the literature on CS in association with a model of AD that accounts for the progression of the pathology from the preclinical stage onwards, and includes neuroimaging markers. Neuroimaging measures are gaining more and more attention in the characterisation of AD neurodegeneration in ageing. The main reason behind this lies in the profound association that appears to exist between the neurobiology of this neurodegenerative disease and measures of brain atrophy and functional connectivity [10]. In AD, in fact, the Beta Amyloid neurotoxic plaques tend to accumulate following a regional distribution that overlaps with the default-mode network [11], a brain network

that activates in the absence of explicit mental tasks. Based on this, measures of neuroimaging might become an important marker of treatment effects of CS, similarly to the way they can track down the impact of pharmacological treatment [12-14]. Our objective was, therefore, to summarise the main experimental findings in this research field, with particular focus on the timeline of AD and on its neural involvement. Dementia is the most prominent cognitive feature of later-stage AD. However, it is important to highlight that in this review we did not include papers that report studies carried out on patients having a general form of dementia, unless necessary for the purpose of describing methodological aspects. The reason behind this choice lies in the fact that multiple aetiologies may contribute to a diagnosis of dementia [15]. Although the cognitive phenotype of two forms of dementia may be equivalent, the underlying neural and patho-physiological mechanisms of distinct diagnostic entities are considerably different. For this reason, the identification of a robust framework to operationalise CS requires a critical review of evidence collected in a set of studies carried out on a homogeneous population of individuals whose recruitment is based on recognised criteria for AD [16-17]. Since the main objective of this study was reviewing the mechanisms of CS in AD, studies focusing on treatments specifically designed for patient-caregiver dyads or based on interventions of profound non-cognitive signatures were not included.

Part 1: Cognitive Stimulation in the Presence of a Diagnosis of Clinically Established Alzheimer's Disease

It is clear that CS does not represent a unitary entity, and meta-analytical procedures do not capture this heterogeneity. Cochrane criteria were used to meta-analyse the effectiveness of CS trials in early-stage [18] and mild-to-moderate AD [19]. Both systematic studies featured stringent methodologies and both studies reported no impact of CS on cognitive abilities. Conversely, a third meta-analysis featuring less strict constraints for inclusion in the analysis revealed that CS exerts beneficial effects over learning and executive functions in AD patients [20]. The trade-off between compliance to methodological rigidity and evidence of an effect suggests that there must be several studies that suffer from design shortcomings. The reason behind these shortcomings may be found in the medical background of AD patients. Unfortunately, patients diagnosed with clinically-established dementia of AD type also have multiple problematic aspects in their medical, familiar, and psychosocial histories. In this respect, breaches of methodological rigidity are a necessary evil in the quest for a compromise between clinical obligations and the experimental study of the topic. A control group (or condition)

is very often absent, and it is frequently impossible to separate the effect of CS from that of other forms of concurrent pharmacological or non-pharmacological treatment (which might, in turn, show intra-sample variability, for instance with regard to drug type or dosage). Although the presence of methodological shortcomings in an experimental design might compromise the scientific rigour of its findings, it has to be acknowledged that this field of research is still in its early stages, and no well-established pattern of findings or methodological gold-standard exists. For this reason any study may be informative and useful in the definition of potential candidate CS mechanisms, test-retest indices of treatment effectiveness and CS features (programme duration, session duration and intensity, definition of the exercises, difficulty levels, multimedial implementation, individual vs group training, etc.). As a consequence, an extensive review of a large number of studies would represent a complimentary overview to other reviews and meta-analyses that have focused exclusively on studies abiding by strict methodology. Moreover, the inclusion in the review of exploratory studies and of studies which are less strong methodologically offers the opportunity to give a comprehensive overview of this research field and not just a more restrictive perspective delimited by a small number of reviewed studies.

The first section of studies reviewed in Part 1 will introduce a set of studies in which CS aimed to exercise aspects of cognition of extremely basic importance (i.e.. orientation in space and time). In the subsequent section the methodological issue of separating the impact of CS from that of concurrent types of interventions (i.e. pharmacological medication) will be introduced. Following that, specific focus will be given first to studies in which the additive effects of CS and pharmacological stimulation were investigated, and then to those in which the control group received medication treatment together with a control CS. The final section will examine in depth the research paradigms based on hypothesis that take into account the notion of neuroplasticity.

Engaging in everyday activities which require a substantial computational load is associated with slower cognitive decline, when AD has been already diagnosed [21]. Often programmes of CS have been operationalised as sets of exercises aiming at enhancing those aspects of cognition that are still open to change. Reality Orientation Therapy (ROT), for example, is a stimulation technique that focuses on the sense of reality of the patient, who may have lost their orientation in space and time. The aim of ROT is reorienting constantly the patient in space and time, providing the person also with some memory information related to themselves. This type of stimulation is extremely basic, and is beneficial for patients diagnosed with various forms of

dementia [21-24]. Arguably, ROT does not involve considerable high-order cognitive aspects (like memory retrieval or executive processes). This reflects the first main problematic aspect of CS designed for and administered to samples of fully demented AD patients: the lack of training exercises strongly associated with skills that are strictly cognitive in nature. The conceptualisation of CS as exercises based on "colouring and drawing" [25], "waltz-lessons" [26] or "the game of Bingo" [27] takes a highly pragmatic approach to programmes of non pharmacological treatment. Patients may fully engage in these exercises, but at the same time such tasks present indeterminate processing demands and have questionable reference to models of cortical cognitive functions like memory or executive abilities. There is a further problem with such approaches. The improvement associated with CS in samples of demented patients often has been studied just as a function of a change in general measures of cognition, with no focus on specific functions. In the following paragraphs studies of CS in AD will be reviewed in detail (see Table 1 for an overview).

- Insert Table 1 about here -

A programme which aimed to stimulate those cognitive skills which were still spared was administered to a sample of moderate-severe AD patients (with a Global-Deterioration-Scale (GDS) score of 5-6) over a 2 year period. No improvement was detected [28]. In the same study, patients with GDS scores of 3-4 (thus classifiable as minimal-mild AD) were trained with exercises targeting various cognitive functions and activities of daily living. Again, no improvements in cognitive abilities were registered [28]. A similar experimental attempt was made by Farina and colleagues [29-30], who piloted a protocol of CS targeting "residual cognitive functions" in a sample of mild-to-moderate AD. Again, no improvements of specific cognitive abilities emerged. Multicomponential non-pharmacological stimulation (including CS) was administered to a group of 10 mild AD in a third research study. This led to no significant impact on either verbal or visuospatial memory [31]. These were the only cognitive components investigated in this study. In an additional study, mildly-moderately demented ex-career soldiers with AD were assigned either to a stimulation of various cognitive functions or to a control group involved only in stimulation through communication. Although this study included methodological control, no specific cognitive testing was performed except for the general Mini-Mental State Examination (MMSE), which showed a significant improvement triggered by CS [32].

No mention of concomitant pharmacological treatment was made in the studies by Yanguas et al. [28], Farina et al. [29] and Kurz et al. [31]. In the other study by Farina and colleagues [30] part of the sample had treatment with a cholinergic enhancer, while with Niu and colleagues [32] all patients were receiving cholinesterase inhibitors. Although the study of CS in the presence of a diagnosis of AD is usually driven by an interest in the clinical efficacy of the treatment rather than in the understanding of the mechanisms that lead to positive changes, it is important to estimate at least the extent to which CS contributes to any improvements when CS is only one component of a multimodal treatment. The use of cholinergic treatment for AD is based on specific hypotheses and is associated to an extensive literature that has described the specific changes at a neural level in patients with AD [12-14]. In contrast, the mechanisms of CS are not fully known. For this reason it is important to take into account any variable that can account for changes in cognitive abilities, and discuss the results carefully, without omitting any potential cause of benefit. Paradoxically, in the five studies previously reported, the concurrent administration of CS and pharmacological treatment were interpreted in terms of benefit from the non pharmacological stimulation (CS), the mechanisms of which are even less understood.

Other papers have described the effects of a combination of the two types of treatment (pharmacological and CS) administered together. In these studies two treatment options were compared, and both groups (experimental and control) were exclusively composed of patients having pharmacological therapy. The combination of drugs and ROT was tested by Giordano et al. [33] in a sample of mild-to-moderate AD. The authors reported a beneficial effect of this treatment regime on the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-COG) score after 3 weeks, in comparison with the control group who received only pharmacological treatment. A more elaborate CS protocol was designed by Bottino and coworkers [34]. They recruited a mild, pharmacologically-treated, AD sample, who engaged in 5 months of various types of exercise, including ROT, errorless learning, communication and training of activities of daily living. The experimental group obtained improvement in the MMSE score and the digit span backwards when compared with the drug-only group. Further studies did not include ROT but were centred on other paradigms of CS. A study of cognitive-communication training was carried out by Chapman and colleagues [35]. After 2 months of treatment, mild-to-moderate AD individuals in the experimental group showed no improvement in either the MMSE, or the ADAS-COG score when compared with controls. Another study similarly centred on communication, but which also involved learning exercises and verbal fluency tasks was completed in Japan [36]. A small sample of AD patients was split into an experimental group based on this mixed treatment and

donepezil therapy and a drug-only condition. After 20 sessions (first administered at a weekly rate, then one session every two weeks) a significant group-by-time interaction revealed a positive synergic effect of medication and CS on MMSE scores [36]. The same pattern of findings was replicated in a shorter intervention, with only a 30-minute session of specific exercises for seven weeks [37]. A programme more focused on high-order cognitive skills, rather than orientation or communication was published in Spanish. Following intervention with stimulation which focused on reasoning, attention, memory, language, calculation, praxis and gnosis a group of mild AD (mean MMSE at baseline: 22.89) showed benefits in verbal learning and fluency tests when compared with drug-only controls (baseline mean MMSE score: 20.12) [38]. In a more recent controlled trial the marketed videogame Big Brain Academy (Nintendo) was used as the CS programme with mild AD patients for 3 months. A significant increase in ADAS-COG score (indicating decline) was found at follow up in the control group; in the experimental group ADAS-COG scores remained stable [39]. In a recent study, a group of mild AD patients were assigned either to a control condition only receiving medication or to one of two experimental groups in which medication was combined with working-memory training. The first of the two programmes consisted of exercises of manipulation of complex material, whereas the second one was based on a model of executive functions having a dynamic-psychology signature. After 6 months, an effect of condition was found for measures of daily-life activities, language, memory and executive functions, although the post-hoc comparisons indicated that the "dynamic" training triggered the largest benefit. Despite the promising results, the authors highlighted that the sample included in this study was unfortunately characterised by lack of homogeneity in test performance at both baseline and retest [40]. All these studies included a control group whose members did not engage in any CS but only received pharmacological treatment.

There are other studies that have reported a different type of experimental-control comparison, with controls receiving medication and also engaging in a control CS. A paper published more than 10 years ago described a randomised controlled trial in which an experimental group received 6 weeks of a previously published CS programme based on memory strategies [41] and was compared with a control group exposed to educational material. All patients recruited were on pharmacological treatment and the mean MMSE score of the two groups was 24 and 25, respectively, indicating very mild AD. No significant impact of the training was found on any of the measures of cognition investigated [42]. Löwenstein and colleagues [43] recruited mild AD patients under cholinergic treatment and assigned them either to an experimental group who trained with exercises of memory, attention, mental calculation, decision making and spatial-temporal orientation, or to a control group who

exercised with recreational activities. After 3 months the experimental group showed a significant improvement in verbal long-term memory, and the group-by-time interaction revealed a beneficial effect on the MMSE score. Tarraga and colleagues [44] trained mild AD participants for 3 months with a multidimensional programme including cholinesterase inhibitors, various forms of non-pharmacological treatments, and multimedia CS ("Smartbrain" tool; http://www.educamigos.com). The authors reported slight, yet significant, drug-exercise synergic benefits on global measures of cognition in comparison with a control group that received all forms of stimulation but did not engage in their computerised CS exercises. None of the tests which assessed specific cognitive skills rather than general cognitive levels were affected by the treatment. This was the first study among those so far described that introduced the use of computerised CS in samples of AD patients. A recent study focused on the additional benefits from computerised CS in a group of prodromal-to-mild AD patients in addition to ordinary pen-and-paper CS, in comparison with a group receiving pen-and-paper CS only. The authors reported no significant differences in cognitive functioning between the two groups after treatment [45].

We have reviewed 17 studies which report the findings of CS intervention in samples of patients with clinical AD dementia. A variety of interventions were described, such as ROT, communication training, exercises focused on high-order cognitive skills, pen-and-paper treatments, computerised programmes, commercialised videogames. Variability in methodological control was observed, as was variability in concurrent pharmacological treatment. Baseline disease severity levels were also heterogeneous. Overall, however, there is converging evidence which suggests that CS exerts some benefits in AD, at least in general measures of cognition.

More recent studies have introduced a novel, computerised implementation of cognitive tasks. Tasks of this type may offer a number of important advantages (e.g. for adjustment of difficulty levels, the opportunity to convert CS into home-based telemedicine, the concurrent treatment of multiple participants at the same time despite the individual nature of the treatment). However, we believe that it does not represent the kind of breakthrough in the study of CS that transcends classic pen-and-paper CS. All studies characterise CS as an instrument designed to improve the clinical status of the patients (either with or without technological support), but rarely describe the mechanisms by which engaging in pen-and-paper or computerised cognitive stimulation would result in some sort of computational modulation. We suggest that the most crucial problem in the study of CS in clinical AD does not stem from any of the methodological shortcomings identified in the earlier literature. We would

suggest that the main issue in this area of research is the absence of an adequate interpretational framework capable of operationalising the disease and CS. An appropriate framework would indicate what measures of test-retest changes have to be analysed to test the experimental hypotheses, and would also suggest how to design the exercises of CS. At present, the exact mechanisms by which CS should be effective and beneficial are unknown. More research is needed to study the specific mechanisms by which behaviours may translate into neurobiological changes, which can alter the progression of the disease. The often tacit rationale by which the proposed exercises are meant to benefit cognitive functions in AD is based on a model according to which the simple exercise of cognitive functions will lead to improvement. The mechanisms by which exercising in one or more tasks improves the performance in trained and/or untrained tasks refer to the concepts of practice effect and transfer [46]. However, a cognitive framework is not the sole option to approach CS in the presence of a neurodegenerative disease. On a theoretical level CS is often associated and compared with physical activity, as both types of stimulation have been investigated in association with normal and abnormal ageing. However, whereas specific physiological mechanisms have been put forward to study the benefits of physical exercise [47], CS has been rarely studied with a similar approach. The study of animal models show that CS (conceptualised as environmental enrichment) triggers neurogenic benefits such as adult neurogenesis and cellular proliferation [48]. Such cellular mechanisms cannot be studied in vivo in a human model, but alternative variables can be investigated. Modern techniques of neuroimage acquisition and analysis offer the chance to study measures of brain structure and brain function, and to hypothesise and test mechanisms by which CS may have a specific impact on these measures. This theoretical chance is particularly relevant in AD because AD is associated with known patterns of structural and functional modifications of the brain, which could be targeted and slowed down, stopped or perhaps even reverted by CS. AD is a pathology that causes progressive and unstoppable neurodegeneration and deregulation of brain signal [49-51]. More sophisticated knowledge of the characteristics of brain structure and function in the various stages of AD pathology yields important information about the areas and connections of the brain that are fully, partially, or not functional when AD patients have entered the stage of dementia. As a consequence, it seems possible to design a programme of CS based on objectives determined by looking at the status of brain connectivity, and by choosing exercises that tap the desired target regions. Experimental hypotheses based on this framework have been scarce. There have been some studies that have looked at task-associated fMRI paradigms as a vehicle to evaluate treatment effects [52], but we are aware of only 2 studies that have investigated the effect of CS designed based on evidence of brain function in established AD dementia. In a paper published relatively early for this type of approach, a

programme of CS has been described by a Japanese team [53]. They recruited a small sample of patients diagnosed with AD of variable severity and assigned them either to a no-contact control group or to a training programme consisting of reading and simple arithmetic. The purpose of the exercises was to enhance activation in dorsolateral prefrontal cortex, parietal and temporal areas, the main regions in which hypometabolism is detected in AD [54]. After 6 months of training the experimental group showed a significant improvement in the Frontal Assessment Battery and stable MMSE scores, which declined in the controls [53]. Seven years later, an Italian team enrolled minimal-to-mild AD patients in a pen-and-paper intervention based on a specific hypothesis. They stimulated lexical-semantic abilities in order to regulate brain networks involved in verbal processing and semantic memory. After 3 months an improvement was registered in measures of global cognition, verbal skills, and long-term memory, in comparison with the control group, who engaged in a programme stimulating creativeness [55]. This study is also paradigmatic because none of the participants were having pharmacological treatment, and the benefits were not a synergic effect of drug and CS.

The overall conclusion that we draw from the multifaceted literature on CS in AD dementia indicates that CS interventions result in sporadic moderate improvements in general measures of cognition. Studies have been often constructed in an exploratory fashion, without a specific rationale based on structural and functional progression of neurodegeneration in AD. The only two studies stemming from rationales based on neuroimaging suggest that this avenue of research deserves more attention. In addition, remarkably time-consuming programmes of CS do not induce dramatic benefits in cognitive skills. Most of the studies consisted of programmes of several weeks, and the improvements are limited to one or a few, often global, measures of cognition. While these changes may be significant from a statistical perspective, they do not always reflect a substantial improvement in clinical variables related to everyday life. The simplest explanation for the disappointing outcome of any cost-benefit qualitative analysis, suggests that AD-dementia is too late a stage for obtaining meaningful positive changes against the advance of neurodegeneration and breakdown of connectivity. This unavoidable conclusion is actually supported by disease models which account for the nature of neural modifications observed in AD. According to Mesulam's theory [56], the disruptive propagation of AD pathology in the brain is counteracted by mechanisms of structural and circuital rearrangement of compensatory nature. These mechanisms are indicated as "neuroplasticity", and would be largely succesful during the early stages of the disease as long as the neuronal de-regulation is limited, but would become less and less effective and even maladaptively detrimental as the disease progresses through its later stages. According to this view,

any experimental or clinical attempt to trigger neuroplasticity during the dementia stage of AD would be largely ineffective. This, however, does not rule out the possibility of cognitive improvement or slower cognitive decline through non-neuroplastic mechanisms. In a detailed theoretical framework, Lövdén and colleagues set some specific boundaries to distinguish neuroplastic from non-neuroplastic changes in brain function and cognitive function: a change is promoted by neuroplasticity only when it is implemented by structural modifications (e.g. alteration of connections, neurogenesis, axonal growth) [57]. On the other hand, examples of non-neuroplastic phenomena are transient changes in intra/intercellular processes (e.g release of neurotransmitter or action potentials), or enhanced flexibility in the use of mental representations [57]. This latter form of computational change will be further discussed in Part 2 in association with the use of cognitive strategies as form of CS. Referring back to the idea of progressive failure of neuroplasticity observed in AD, interventions administered at an earlier stage of the disease would occur in a context of a greater residual capacity for neuroplastic responsiveness, and therefore would be more likely to have positive and lasting effects on cognition.

Part 2: Cognitive Stimulation in the Presence of a Diagnosis of Mild Cognitive Impairment

Common models describing the timeline of AD biomarkers depict the prodromal stage of AD as characterised by the absence of dementia, but detection of cognitive deficits in one or more domains [1]. This cognitive phenotype is labelled as Mild Cognitive Impairment (MCI). A patient with MCI has objective impairment in one or more aspects of cognition (often accompanied by subjective complaints) without dementia, and retains everyday life independence [58]. AD is only one of the possible underlying aetiologies of MCI [59] and for this reason there is no automatic correspondence between MCI and AD. This means that MCI patients with an amnestic phenotype (which, theoretically, might predicts future conversion to AD dementia) do not necessarily convert to AD dementia and, vice versa, non-amnestic MCI might convert to AD dementia [60]. This suggests that the population of MCI patients is quite heterogeneous with regard to the neural and cognitive status, and, therefore it might have a heterogeneous response to CS, whatever the rationale of the exercises is. Nonetheless, despite this large expected variability, it is of some value to review the main findings associated with CS in samples of MCI (See Table 1 for an overview). Similarly to Part 1, Part 2 is also subdivided into sections. The

first part will cover the use of mental strategy as a form of CS, while the second part will focus on CS programmes aimed to stimulate and enhance specific computational processes.

MCI individuals are still independent in their daily life activities, and for this reason their clinical problems are not as severe as those experienced by demented patients. This allows experimenters to use more rigorous methodologies and to test the impact of CS in the absence of pharmacological treatment (not normally administered to MCI patients). As the most common cognitive problem in MCI is impairment in memory, most of the computerised and non-computerised designs have been based on memory exercises and have tried to improve this function. The overall pattern of findings is characterised by only sporadic success [61], although reviews often report optimistic conclusions [62], and the findings of a meta-analysis of 17 studies, taken together, appear to indicate that there might be significant beneficial results in executive functioning, memory and overall cognition [63]. A closer look at this meta-analysis reveals considerable variation in the methodological and theoretical aspects of the studies examined. Six of the 17 studies had no control group and experimental groups ranged from 9 to 67 participants. Moreover, some of the included studies did not have a programme with sufficient cognitive signature (occupational therapy, cognitive-behavioural therapy, educational programmes). Stott and Spector [61] carried out a second meta-analysis but only included interventions on memory. Again, a critical review of available evidence is necessary to understand what the most fruitful deployment of CS is likely to be.

A large component of the literature on CS in MCI has studied the effect of training programmes in which patients were trained with specific strategies to improve cognitive performance (especially memory). An early study describes the effect of a multi-componential protocol lasting 6 weeks and consisting of tutorials teaching the use of memory strategies together with relaxation and other forms of non-cognitive stimulation. The comparison with a no-contact control group reported no changes in objective measures of memory [64]. A similar study was carried out by Troyer and colleagues [65], who planned an educational intervention centred on teaching strategies in order to enhance memory in everyday life, but including other various didactic aspects such as relaxation and nutrition. Like the former study, no impact on neuropsychological tests of memory was reported. In a third study a mixed sample of older adults with subjective memory complaints or objective memory impairment was recruited in order to test a 3-month programme of CS based on memory strategies. None of the a priori planned statistical comparisons revealed significant changes in cognition, but additional

exploratory analyses suggested a positive impact of this type of treatment [66]. A moderately more successful attempt was made by a Swedish team, who recruited 15 amnestic single-domain MCI participants and treated them with a cognitive strategy-based training for everyday life goals for 8 weeks. No control group was included in this study. No benefit was reported in memory and executive tasks, but an improvement in processing speed was registered [67]. More positive findings have been reported by other teams. Eight weeks of teaching memory strategies, with complementary exercises for attention and processing speed led to improvement in a face-name association task and in verbal delayed recall, in comparison with untreated MCI patients [68]. The team of Unverzagt and colleagues [69] tested the effectiveness of a package of strategy-oriented CS previously tested on an extremely large sample of healthy elderly adults [41, 70] and a smaller sample of AD patients [42]. Domain-specific improvements were observed in all the subgroups of MCI patients (each subgroup trained with strategies of executive functions, executive speed or memory) in comparison with the three control groups who only received a booster training. However, improvements were transferred to none of the untrained domains. Moro et al. [71] designed a programme of CS based on the learning of strategies for memory and the development of metacognitive competence. They trained MCI patients for 6 months in the constant presence of their caregivers. The comparison between the training-dependent change in cognitive performance in the experimental group and that in the control group (who received no training) revealed a significant and positive impact of the training programme on various measures of attention and verbal memory. However, as no post-hoc correction for multiple comparisons was used, a more conservative re-interpretation of these findings (and their respective p values) would indicate that memory was the cognitive domain which benefited the most from the training.. In a recent study authored by Olchick and colleagues [72], samples of MCI and healthy adults were enrolled. Some were taught and exercised with strategies. Two control groups were also recruited for each diagnostic group. One only took part in educational sessions about memory and ageing, while the other was a no-contact control group. No clear evidence of improvement in objective measures of cognition was reported, as the active control group showed changes similar to the experimental group. A recent and much shorter intervention was designed by Hampstead and colleagues [73]. They trained MCI individuals for 2 weeks with a task in which learning of associations between object and location was requested. A structural MRI was also acquired. Significantly better performance was reported for those MCI participants who were taught a mnemonic strategy, compared with those who had a normal exposure to the material but did not train with strategies. This change in performance was negatively correlated with the size of the inferior lateral ventricles, but did not correlate with the total volume of the lateral ventricles, hippocampi or amygdalae.

Finally, results from a study investigating the efficacy of strategy learning for improving memory performance were associated with changes in brain function in a sample of 15 MCI patients. Encoding- and retrieval-related resources benefitted from training and a rearrangement of activation in a complex pattern of areas was observed after only 12 hours of intervention [74]. This indicates that strategy learning triggers quick modifications in brain function.

This corpus of research is characterised by a common interventional framework based on teaching cognitive strategies to patients to improve their performance. In educational settings, a strategy is a routine that aims to enhance the acquisition and use of knowledge about the world [75]. Strategies can be either task-specific or transferrable to other tasks and situations [76]. Although any form of improvement is a desirable goal in MCI and dementia, strategies that are generalisable to other domains and settings would be preferred over task-speficic strategies. However, the set of findings reviewed above suggests that the benefits triggered by strategy training in MCI have had limited, or no transfer to other tasks and domains. As a consequence, it is likely that most of the strategies taught to MCI patients have been task-specific. In their model, Lövdén and colleagues specify that the use of strategies, albeit being able to trigger improvement in performance, does not generate neuroplastic changes, because strategy training is based on the use and manipulation of representations (used as a synonim for knowledge), and circumvents computational processes [57]. The definitions of representation and process are a fundamental distinction in cognitive psychology. Representations are "embodiments or interpretations of ideas" [75], whereas processes are entities required to "help in keeping the integrity of the goal representation" [77]. There are processes which play a central role in human cognition and are associated with the activity of areas and circuits, which, in turn are involved in multiple tasks of diverse nature (e.g. working memory and executive functions). Training such processes would facilitate transfer to those untrained tasks whose activity is associated with a completely or partially overlappable set of areas [78] (see also [79] for a retraction of the published findings. This retraction does not affect the theoretical rationale of the study). On the other hand, strategy training would bypass processes and rely on simple acquisition of knowledge and flexibility in the use of representations [57]. Based on this view, as intended by the model of Lövdén and colleagues, it seems unlikely that changes in brain functions observed after strategy training (i.e. [74]) are the result of neuroplastic mechanisms. It is instead suggested that training with strategies facilitates the acquisition and use of knowledge about task material so that this ability can be transfered to other tasks (e.g. cognitive tests administered at the end of the CS programme) based on similar computations. This, however, does not rule out the possibility that a brain in the MCI stage of neurodegeneration has potential for neuroplastic changes.

In conclusion, these studies are relevant to AD and MCI patients, as clinically significant improvements in memory might be associated with improved quality of life. Improvements in memory performance might not always involve any overt mechanisms of neurobiological nature, but would, however, be of dramatic importance for variables associated to everyday mood, quality of life and general wellbeing of both patients and caregivers. For this reason, any improvement in these non-cognitive, non-neural variables is a clinical success. Since the ultimate aim of the scientific study of neurodegenerative disorders is to translate findings into the clinical setting, a hypothetical code of "good translational practice" would suggest measuring these variables within all randomised trials of CS with potential benefits in everyday life.

A parallel body of research exists, including trials of CS administered on samples of MCI patients which are not centred on the use of strategies but based on exercises intended to stimulate sets of computations, repeatedly. A review was published four years ago, reviewing four recent studies of this kind in which CS was implemented using computerised material [80]. In the first study reviewed, Gunther et al. [81] reported the findings of a pilot study done with a programme of CS based on a German software commercialised in 1992 (Cognition I, version 3.93 [82]). After 14 weeks the sample (not specifically diagnosed with MCI but with "age-associated memory impairment") improved on various cognitive measures, including processing speed, long-term memory and learning. There was no control, however. In a second study, two small (n = 10) samples of AD patients with an MMSE score higher than 22 (on medication) and MCI patients (not on medication) were administered a modified version of the TNP software [83], a software originally developed to treat aphasia. Significant (but uncorrected for multiple comparisons) increases in scores on the MMSE, phonemic fluency and Trail Making Test-Part B were found in the AD sample after two 4-week periods of treatment spaced out by a 6-week break, whilst the MCI group showed a significant increase in the Rivermead Behavioural Memory Test [84]. The same software was used by Talassi and colleagues [85] together with occupational and behavioural therapy on a sample of MCI and mildly demented patients (MMSE score: 15-23). The only positive impact after 3 weeks was an improvement in the delayed recall score of the Rey Figure, but the reported significance would not have survived adjustments for multiple comparisons. Finally, in the last of the four studies in the review, Rozzini and co-workers [86] also used this same software, to train MCI individuals who were also medicated with one of the three available cholinesterase inhibitors. Four weeks of intensive stimulation constituted a block, and three

subsequent blocks were administered with two-month inter-block distance. The mix of ChEI treatment and this programme which focused on various aspects of cognition led to an improvement in scores on the short story recall and the Raven progressive matrices task compared with the drugs-only and the no-treatment groups. The TNP software was also used by Galante and colleagues [87] as stimulation material in a further study on a small sample of mild AD patients. They were assigned either to the TNP condition or to an aspecific treatment consisting of conversational activity. However, after four weeks of training, no significant changes in cognition emerged.

Other studies have investigated the benefits of CS in MCI. Training material based on principles of neuroplasticity [88-89] was used in a controlled trial by Barnes and colleagues [90] with a sample of MCI patients. Positive trends in the predicted direction were reported in several measures of cognition, albeit not reaching significance. The authors concluded that larger samples were needed. A Brazilian team tested the effectiveness of a CS protocol consisting of memory, attention, proper names retrieval, mental calculation and orientation exercises, based on multiple types of exercise, some of which used strategies and required the use of external aids [91]. Improvements were reported in various measures of cognition. These findings, however, are vitiated by a methodological problem, since participants were treated in parallel with lithium. The study with AD patients by Kurz et al. [31] mentioned above also included two groups of MCI participants; one of these MCI groups was treated with the same multidimensional protocol administered to the subgroup with dementia. Both verbal and non-verbal memory skills improved. More recently, small samples of South Korean AD and amnestic MCI patients were treated with a package of multidimensional cognitive stimulation including numerous modalities of task. Test-retest improvements were registered in several sub-components of cognition albeit these benefits were minimal [92]. Finally, in an Italian study a small sample of MCI patients was treated with five sessions of working memory exercises completed over two weeks [93]. Changes were found in the working memory target test and in a test of fluid intelligence in comparison with the control group who had five educational sessions about memory including advice on the use of strategies. These findings seem to contrast with the earlier negative evidence from studies which focused on the effects of strategy usage. When CS does not exclusively focus on improving knowledge of training material, it appears to have a larger impact on cognitive skills, even though there is no well-defined pattern of consistent findings.

All of the above studies suggest that CS may be more easily implemented in samples of patients who have only mild cognitive problems and who are not demented. Significant benefits induced by CS indicate that the central nervous system of individuals with MCI might retain sufficient neural plasticity to trigger organic changes of brain structure and reorganisation of brain function and benefit, therefore, from this type of intervention. This hypothesis has been investigated by those teams who have recruited samples of MCI patients and analysed changes induced by CS using measures of neuroimaging. To date, we are aware of three studies that report alterations of fMRI task-associated activation due to the effect of a programme of CS. The study by Belleville and colleagues that reported changes in activation following strategy training [74] has already been discussed above with regard to the nature of strategies. Hampstead and colleagues [94] piloted a small CS programme on a sample of 6 amnestic multidomain MCI patients (with no control group). Five sessions of face-name association training were administered over a period of 2 weeks. The first and the fifth sessions were recorded in the fMRI scanner and compared. Measures of effective connectivity, a parameter similar to functional connectivity, but aimed at detecting a causal relationship between the activities of two separate hubs, were used. The authors interpreted the wide-spread increase in task-related activation as enhancement of function of structures within the default mode network (whose system of interconnected brain structures is disrupted in Alzheimer's disease), with enhanced connectivity between the middle temporal gyrus and precuneus/posterior cingulate and other parietal areas. Rosen et al. [95] treated a small sample of MCI patients (of various subtypes, some of them treated also with AD-related medication) with the same programme of exercises based on principles of neuroplasticity (reviewed above) used by Barnes and colleagues [90]. An intense regime was chosen, with 24 sessions of individually-tailored difficulty and gradually-increased duration. Efficacy was assessed as a change in activation during performance in a verbal encoding task. Increases in activation were reported in the hippocampus, suggesting that this area, although being extremely susceptible to AD pathology, still retains some residual capacity for plasticity at the MCI stage. These three studies, albeit not representing a substantial body of research, suggest that individuals in the MCI stage retain capacity for neural plasticity, and suggest that even the changes in cognition reported in studies that did not include neuroimaging recordings may have been triggered by neuroplastic effects. More studies are needed to understand what the most effective types of exercise are for this diagnostic group, to observe structured changes in neural and cognitive variables and to formulate benefit in parameters of clinical relevance, for example an attenuation of cognitive decline, or stable levels of cognition over a timespan.

The priority of studies with MCI patients has always been given to improving cognition and variables related to daily life. Unless they are markedly focused on a specific mechanism, most of the studies have an explicit or implicit objective directed towards the improvement of everyday life conditions for patients and caregivers. Studying CS with a focus on neuroplasticity would mean identifying structural mechanisms that could be modified via training and lead to significant improvements, measurable through analysis of both cognitive functions and brain physiological parameters. The literature on changes in brain structure and function due to CS is limited, and remarkably no study has specifically investigated changes in brain structure triggered by CS in samples of AD or MCI patients. In conclusion there is some evidence suggesting that people in the MCI stage still retain capacity for neuroplasticity, but more and more specific evidence is needed from bigger samples and with whole-brain methodologies of investigations.

Part 3: The Importance of Studies Investigating Cognitive Stimulation in Healthy Individuals

An overview of parallel studies of CS in AD and MCI groups suggests that there is an inverse relation between progression of disease severity and the brain's retained capacity for plasticity. This would imply that healthy individuals should show even greater neurocognitive changes than diseased groups due to neuroplastic processes. The population of healthy young and old adults represents the best target groups to test specific hypotheses of the effect of forms of non-pharmacological treatment based on neuroplasticity. A large number of publications have reported neural changes following CS in samples of healthy individuals. The first studies which investigated structural changes triggered by behavioural treatments reported that motor training induced regional changes in brain anatomy of both young and old adults [96-97]. Research has then looked at programmes of stimulation of cognitive skills. Training based on learning through the use of a cognitive strategy was associated with specific cortical thickening [98]. Another team found structural changes with Voxel-Based Morphometry (VBM) in young adults after just 5 days of intensive (4 hours every day) cognitive workout [99-100]. This indicates that in young healthy brains neuroplastic processes are not as "sluggish" as initially hypothesised [57]. Diffusion Tensor Imaging (DTI) was also applied to the study of CS in healthy adults, and changes in parameters of white matter diffusivity were reported following cognitive interventions [101-102], even after training with memory strategies [103]. The use of VBM and DTI in the study of CS in samples of AD and MCI may represent an important frontier in the study of the effects of therapeutics in neurodegenerative

processes. AD has been associated with specific patterns of atrophy and structural disconnection [104-105]. However, no specific study has investigated the effects of CS on structural parameters in the presence or in the potential presence of AD pathology. Two studies of healthy participants also found changes in functional connectivity following CS [99, 106] and at least two studies have found regional changes in resting-state blood flow [107-108]. Similarly, the impact of AD on resting state function and connectivity is well known [54, 109], but, as reviewed above, only a few studies have investigated the impact of CS on these parameters. For this reason, samples of healthy participants may represent an initial target to test the effectiveness of experimental programmes of CS specifically designed to treat patients with MCI or AD.

Final Considerations

The study of CS is moving towards models describing changes in brain structure and function that are the result of neuroplastic effects [110]. For this reason, the study of CS in AD pathology should move in the same direction, incorporating designs with neuroimaging measurements and experimental hypotheses linking cognitive exercises with specific mechanisms of neural modifications. Most studies based on neuroimaging measures have been explorative and, albeit describing remarkable changes in brain structure and/or function, have not detailed the exact mechanism by which the repeated administration of training exercises would influence the neural substrate by inducing specific expected changes. Along these lines, participating in cognitively stimulating activities has also been reported to be associated with lower Beta Amyloid burden in a large set of brain areas [111]. The suggestion that CS might attenuate the pathophysiological burden of AD is extremely interesting. In fact, according to this hypothesis, CS could be contextualised as an instrument not meant to target cognitive functions or the neural system, but disease processes at the cellular level. Arguably, this opportunity would not become a major breakthrough in this literature as long as CS is not designed and tested as a function of a specific mechanism based on neuroplasticity.

To date only a few of these mechanisms have been hypothesised. The stimulation of specific neuronal regions showing hypometabolism in AD [53] appears to be a reasonable interventional option, as it aims to regulate a well-determined process disrupted by the pathology. The use of training material design to target semantic-lexical networks [55] appears as another option with a strong theoretical motivation, as lexical-semantic

difficulties are an early-stage impairment in AD [112]. An opposite approach to these two hypotheses could be the stimulation of computational units that are not primarily affected by AD, which could thus represent a healthy substrate to "fortify" retained cognitive skills. Stimulation of procedural memory [113], for instance, might reflect the regulation of networks that are affected by AD at later stages. This network regulation, however, seems to be more indicated at disease stages in which restorative network regulation (i.e. and up-regulation of areas with hypometabolism) is no longer possible, and the sole avenue of treatment is either compensative or aims to maintain a high level of functionality in the cognitive functions that are relatively spared by the disease. However, a comparable approach adopted in the study by Herrera and colleagues [114] suggests that a more sophisticated implementation of this rationale (stimulation of preserved functions) may lead to benefits even in the prodromal stages of neurodegeneration. These authors designed a computerised programme for MCI patients focused on recognition memory, being this function "still preserved or slightly impaired in MCI" (page 1872). In this study the aim was not to stimulate a function relatively spared by AD (like procedural memory, supported by implicit memory processes), but rather to exercise a relatively preserved form of recollection (recognition), an aspect of this function that relies on explicit memory processes which are negatively affected by AD (episodic memory). Although the target of CS was a spared sub-component of cognition, improvements generalised even to measures of episodic recall. This finding suggests that training of relatively intact cognitive functions can be particularly beneficial in MCI when the network sustaining them (sufficiently preserved to allow normal recognition abilities) also supports other functions that are more susceptible to AD neuropathology. In addition to the approaches suggested above, there also are studies which have explored different perspectives. One study which used a CS approach based on a mechanism specifically focused on the auditory channel, suggested that specific exercises might regulate and enhance the pattern of neuromodulation (normally down-regulated by ageing) of a series of structures involved in attention, perception, and memory [88]. A fifth and final mechanism has been recently proposed by Martinez and colleagues, who postulated that resting-state connectivity between two areas might be enhanced by co-activation of those two areas induced by specific, muti-componential tasks [115].

Future studies should attempt to identify new potential mechanisms of CS and should also include the appropriate measurement of benefits triggered by this form of intervention, using the most fitting neuroimaging techniques, in association with classical testing of cognitive function and, possibly, daily-life functionality. In addition, changes in neuropsychological functions should be carefully examined in relation to the nature of the training. Indeed, cognitive improvement in AD or MCI partients has been reported almost exclusively in

domains directly stimulated by the training exercises. A CS programme inducing significant changes in untrained cognitive skills would undoubtedly be a large success. Within the set of neuroimaging variables, measures of functional connectivity appear to be particularly indicated in the study of neurodegenerative diseases as brain networks appear to be associated with their pathophysiological progression [10]. Within this general picture, the identification of a candidate mechanism responsible for neurocognitive improvement would also allow the recognition of the main intervenient variables (e.g. cognitive reserve) that may play a significant role in modulating treatment effectiveness.

Conflict of Interest

MDM has no conflict of interest. MFS and AV have received educational support, travel support and consultancy fees from manufacturers of treatments for AD

Acknowledgements

This study has been partially supported by grant No. 42/RF-2010-2321718 from the Italian Ministry of Health to AV

References

[1] Jack CR, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, et al. Hypothetical Model of Dynamic Biomarkers of the Alzheimer's Pathological Cascade. Lancet Neurol 9(1): 119-128 (2010).

[2] Clare L, Woods RT. Cognitive Training and Cognitive Rehabilitation for People with Early-Stage Alzheimer's Disease: A review. Neuropsychol Rehabil 14(4): 385-401 (2004).

[3] Steinerman JR. Minding the Aging Brain: Technology-Enabled Cognitive Training for Healthy Elders. Curr Neurol Neurosci 10(5): 374-380 (2010).

[4] Vidovich MR, Lautenschlager NT, Flicker L, Clare L, Almeida OP. The PACE Study: A Randomised Clinical Trial of Cognitive Activity (CA) for Older Adults with Mild Cognitive Impairment (MCI). Trials

10.1186/1745-6215-10-114. 2009 Dec 14; Available from www.trialsjournal.com/content/pdf/1745-6215-10-114.pdf

[5] Crowe M, Andel R, Pedersen NL, Johansson B, Gatz M. Does Participation in Leisure Activities Lead to Reduced Risk of Alzheimer's Disease? A Prospective Study of Swedish Twins. J Gerontol B Psychol Sci Soc Sci 58(5): P249-P255 (2003).

[6] Scarmeas N, Levy G, Tang MX, Manly J, Stern Y. Influence of Leisure Activity on the Incidence of Alzheimer's Disease. Neurology 57(12): 2236-2242 (2001).

[7] Wilson RS, Barnes LL, Aggarwal NT, Boyle PA, Hebert LE, de Leon CFM, et al. Cognitive Activity and the Cognitive Morbidity of Alzheimer Disease. Neurology 75(11): 990-996 (2010).

[8] Wilson RS, de Leon CFM, Barnes LL, Schneider JA, Bienias JL, Evans DA, et al. Participation in Cognitively Stimulating Activities and Risk of Incident Alzheimer Disease. JAMA 287(6): 742-748 (2002).

[9] Grandmaison E, Simard M. A Critical Review of Memory Stimulation Programs in Alzheimer's Disease. J Neuropsychiatry Clin Neurosci 15(2): 130-144 (2003).

[10] Seeley WW, Crawford RK, Zhou J, Miller BL, Greicius MD. Neurodegenerative Diseases Target Large-Scale Human Brain Networks. Neuron 62(1): 42-52 (2009).

[11] Sperling RA, Laviolette PS, O'Keefe K, O'Brien J, Rentz DM, Pihlajamaki M, et al. Amyloid Deposition is Associated with Impaired Default Mode Network Function in Older Persons Without Dementia. Neuron 63(2): 178-188 (2009).

[12] Venneri A. Imaging Treatment Effects in Alzheimer's Disease. Magn Reson Imaging 25: 953-968 (2007).

[13] Venneri A, Shanks MF. Using MRI Neuroimaging Methods to Detect Treatment Responses in Alzheimer's Disease. Neurodegen Dis Manage 1(3): 235-243 (2011).

[14] Venneri A, Shanks MF. Central Effects of Cholinesterase Inhibitors in Alzheimer's Disease: Insights from Advanced Neuroimaging. Imaging Med 5(5): 441-452 (2013).

[15] Fratiglioni L, Launer LJ, Andersen K, Breteler MM, Copeland JR, Dartigues JF, et al. Incidence of Dementia and Major Subtypes in Europe: A Collaborative Study of Population-Based Cohorts. Neurologic Diseases in the Elderly Research Group. Neurology 54(11, Suppl 5): S10-S15 (2000).

[16] McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical-Diagnosis of Alzheimers-Disease - Report of the Nincds-Adrda Work Group under the Auspices of Department-of-Health-and-Human-Services Task-Force on Alzheimers-Disease. Neurology 34(7): 939-944 (1984).

[17] Dubois B, Feldman HH, Jacova C, Dekosky ST, Barberger-Gateau P, Cummings J, et al. Research Criteria for the Diagnosis of Alzheimer"s Disease: Revising the NINCDS-ADRDA Criteria. Lancet Neurol 6(8): 734-746 (2007).

[18] Clare L, Woods RT, Moniz Cook ED, Orrell M, Spector A. Cognitive Rehabilitation and Cognitive Training for Early-Stage Alzheimer's Disease and Vascular Dementia. Cochrane Database Syst Rev 4: CD003260 (2003).

[19] Bahar-Fuchs A, Clare L, Woodb B. Cognitive Training and Cognitive Rehabilitation for Mild to Moderate Alzheimer’s Disease and Vascular Dementia. Cochrane Database Syst Rev 6: CD003260 (2013).

[20] Sitzer DI, Twamley EW, Jeste DV. Cognitive Training in Alzheimer's Disease: A Meta-Analysis of the Literature. Acta Psychiatr Scand 114(2): 75-90 (2006).

[21] Treiber KA, Carlson MC, Corcoran C, Norton MC, Breitner JCS, Piercy KW, et al. Cognitive Stimulation and Cognitive and Functional Decline in Alzheimer's Disease: The Cache County Dementia Progression Study. J Gerontol B Psychol Sci Soc Sci 66(4): 416-425 (2011).

[22] Metitieri T, Zanetti O, Geroldi C, Frisoni GB, De Leo D, Dello Buono M, et al. Reality Orientation Therapy to Delay Outcomes of Progression in Patients with Dementia. A Retrospective Study. Clin Rehabil 15(5): 471-478 (2001).

[23] Onder G, Zanetti O, Giacobini E, Frisoni GB, Bartorelli L, Carbone G, et al. Reality Orientation Therapy Combined with Cholinesterase Inhibitors in Alzheimer's Disease: Randomised Controlled Trial. Br J Psychiatry 187: 450-455 (2005).

[24] Spector A, Davies S, Woods B, Orrell M. Reality Orientation for Dementia: A Systematic Review of the Evidence of Effectiveness from Randomized Controlled Trials. Gerontologist 40(2): 206-212 (2000).

[25] Hattori H, Hattori C, Hokao C, Mizushima K, Mase T. Controlled Study on the Cognitive and Psychological Effect of Coloring and Drawing in Mild Alzheimer's Disease Patients. Geriatr Gerontol Int 11(4): 431-437 (2011).

[26] Rösler A, Seifritz E, Krauchi K, Spoerl D, Brokuslaus I, Proserpi SM, et al. Skill Learning in Patients with Moderate Alzheimer's Disease: A Prospective Pilot-Study of Waltz-Lessons. Int J Geriatr Psychiatry 17(12): 1155-1156 (2002).

[27] Sobel BP. Bingo vs. Physical Intervention in Stimulating Short-Term Cognition in Alzheimer's Disease Patients. Am J Alzheimer Dis Other Demen 16(2): 115-1120 (2001).

[28] Yanguas JJ, Buiza C, Etxeberria I, Galdona N, Gonzalez MF, Urdaneta E. A Randomized, Placebo-Controlled Study of the Efficacy of Cognitive Intervention on Elderly People and on Patient's with Alzheimer's Disease: 2006: Proceedings of the 10th International Conference of ICCHP; 2006 July 11-13; Linz, Austria. Volume 4061: 759-765 (2006).

[29] Farina E, Fioravanti R, Chiavari L, Imbornone E, Alberoni M, Pomati S, et al. Comparing Two Programs of Cognitive Training in Alzheimer's Disease: A Pilot Study. Acta Neurol Scand 105(5): 365-371 (2002).

[30] Farina E, Mantovani F, Fioravanti R, Pignatti R, Chiavari L, Imbornone E, et al. Evaluating Two Group Programmes of Cognitive Training in Mild-to-Moderate AD: Is There Any Difference between a 'Global' Stimulation and a 'Cognitive-Specific' One? Aging Ment Health 10(3): 211-218 (2006).

[31] Kurz A, Pohl C, Ramsenthaler M, Sorg C. Cognitive Rehabilitation in Patients with Mild Cognitive Impairment. Int J Geriatr Psychiatry 24(2): 163-168 (2009).

[32] Niu YX, Tan JP, Guan JQ, Zhang ZQ, Wang LN. Cognitive Stimulation Therapy in the Treatment of Neuropsychiatric Symptoms in Alzheimer's Disease: A Randomized Controlled Trial. Clin Rehabil 24(12): 1102-1111 (2010).

[33]Giordano M, Dominguez LJ, Vitrano T, Curatolo M, Ferlisi A, Di Prima A, et al. Combination of Intensive Cognitive Rehabilitation and Donepezil Therapy in Alzheimer's Disease (AD). Arch Gerontol Geriatr 51(3): 245-249 (2010).

[34] Bottino CMC, Carvalho IAM, Alvarez AMMA, Avila R, Zukauskas PR, Bustamante SEZ, et al. Cognitive Rehabilitation Combined with Drug Treatment in Alzheimer's Disease Patients: a Pilot Study. Clin Rehabil 19(8): 861-869 (2005).

[35] Chapman SB, Weiner ME, Rackley A, Hynan LS, Zientz J. Effects of Cognitive-Communication-Stimulation for Alzheimer's Disease Patients Treated with Donepezil. J Speech Lang Hear Res 47(5): 1149-1163 (2004).

[36] Matsuda O. Cognitive Stimulation Therapy for Alzheimer's Disease: The Effect of Cognitive Stimulation Therapy on the Progression of Mild Alzheimer's Disease in Patients Treated with Donepezil. Int Psychogeriatr 19(2): 241-252 (2007).

[37] Matsuda O, Shido E, Hashikai A, Shibuya H, Kouno M, Hara C, Saito M. Short-Term Effect of Combined Drug Therapy and Cognitive Stimulation Therapy on the Cognitive Function of Alzheimer's Disease. Psychogeriatrics 10(4): 167-172 (2010).

[38] Zamarrón Cassinello MD, Mestre LT, Fernandez-Ballesteros R. Cognitive Plasticity in Alzheimer's Disease Patients Receiving Cognitive Stimulation Programs. Psicothema 20(3): 432-437 (2008).

[39] Fernandez-Calvo B, Rodriguez-Perez R, Contador I, Rubio-Santorum A, Ramos F. Efficacy of Cognitive Training Programs Based on New Software Technologies in Patients with Alzheimer-Type Dementia. Psicothema 23(1): 44-50 (2011).

[40] Schecker M, Pirnay-Dummer P, Schmidtke K, Hentrich-Hesse T, Borchart D. Cognitive Interventions in Mild Alzheimer's Disease: A Therapy-Evaluation Study on the Interaction of Medication and Cognitive Treatment. Dement Geriatr Cogn Disord Extra 3: 301-311 (2013).

[41] Jobe JB, Smith DM, Ball K, Tennstedt SL, Marsiske M, Willis SL, et al. ACTIVE: A Cognitive Intervention Trial to Promote Independence in Older Adults. Contr Clin Trials 22(4): 453-479 (2001).

[42] Cahn-Weiner DA, Malloy PF, Rebok GW, Ott BR. Results of a Randomized Placebo-Controlled Study of Memory Training for Mildly Impaired Alzheimer's Disease Patients. Appl Neuropsychol 10(4): 215-223 (2003).

[43] Löwenstein DA, Acevedo A, Czaja SJ, Duara R. Cognitive Rehabilitation of Mildly Impaired Alzheimer Disease Patients on Cholinesterase Inhibitors. Am J Geriatr Psychiatry 12(4): 395-402 (2004).

[44] Tarraga L, Boada M, Modinos G, Espinosa A, Diego S, Morera A, et al. A Randomised Pilot Study to Assess the Efficacy of an Interactive, Multimedia Tool of Cognitive Stimulation in Alzheimer's Disease. J Neurol Neurosurg Psychiatry 77(10): 1116-1121 (2006).

[45] Gaitan A, Garolera M, Cerulla N, Chico G, Rodriguez-Querol M, Canela-Soler J. Efficacy of an Adjunctive Computer-Based Cognitive Training Program in Amnestic Mild Cognitive Impairment and Alzheimer's Disease: A Single-Blind, Randomized Clinical Trial. Int J Geriatr Psychiatry 28: 91-99 (2013).

[46] Barnett SM, Ceci SJ. When and Where Do We Apply What We Learn? A Taxonomy for Far Transfer. Psychol Bull 128(4): 612-637 (2002).

[47] Ahlskog JE, Geda YE, Graff-Radford NR, Petersen RC. Physical Exercise as a Preventative or Disease-Modifying Treatment of Dementia and Brain Aging. Mayo Clin Proc 86(9): 876-884 (2011).

[48] Kempermann G, Fabel K, Ehninger D, Babu H, Leal-Galicia P, Garthe A, et al. Why and How Physical Activity Promotes Experience-Induced Brain Plasticity. Front Neurosci 4: 189 (2010).

[49] Braak H, Braak E. Neuropathological Stageing of Alzheimer-Related Changes. Acta Neuropathol 82(4): 239-259 (1991).

[50] Greicius MD, Srivastava G, Reiss AL, Menon V. Default-Mode Network Activity Distinguishes Alzheimer's Disease from Healthy Aging: Evidence from Functional MRI. Proc Natl Acad Sci USA 101(13): 4637-4642 (2004).

[51] Schroeter ML, Stein T, Maslowski N, Neumann J. Neural correlates of Alzheimer's Disease and Mild Cognitive Impairment: A Systematic and Quantitative Meta-Analysis Involving 1351 Patients. Neuroimage 47(4): 1196-1206 (2009).

[52] van Paasschen J, Clare L, Woods RT, Linden DEJ. Can we change brain functioning with cognition-focused interventions in Alzheimer's disease? The Role of Functional Neuroimaging. Restor Neurol Neurosci 27(5): 473-491 (2009).

[53] Kawashima R, Okita K, Yamazaki R, Tajima N, Yoshida H, Taira M, et al. Reading Aloud and Arithmetic Calculation Improve Frontal Function of People with Dementia. J Gerontol A Biol Sci Med Sci 60(3): 380-384 (2005).

[54] Mosconi L. Brain Glucose Metabolism in the Early and Specific Diagnosis of Alzheimer's Disease - FDG-PET Studies in MCI and AD. European J Nucl Med Mol Imaging 32(4): 486-510 (2005).

[55] Jelcic N, Cagnin A, Meneghello F, Turolla A, Ermani M, Dam M. Effects of Lexical-Semantic Treatment on Memory in Early Alzheimer Disease: An Observer-Blinded Randomized Controlled Trial. Neurorehabil Neural Repair 26(8): 949-956 (2012).

[56] Mesulam MM. A Plasticity-Based Theory of the Pathogenesis of Alzheimer's Disease. Alzeheimer's Disease Ann NY Acad Sci 924: 42-52 (2000).

[57] Lövdén M, Backman L, Lindenberger U, Schaefer S, Schmiedek F. A Theoretical Framework for the Study of Adult Cognitive Plasticity. Psychol Bull 136(4): 659-676 (2010).

[58] Petersen RC, Doody R, Kurz A, Mohs C, Morris JC, Rabins PV. Current Concepts in Mild Cognitive Impairment. Arch Neurol 58: 1985-92 (2001).

[59] Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, et al. Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J Intern Med 256(3): 240-246 (2004).

[60] Hussain H. Conversion from Subtypes of Mild Cognitive Impairment to Alzheimer Dementia. Neurology 69(4): 409-409 (2007).

[61] Stott J, Spector A. A Review of the Effectiveness of Memory Interventions in Mild Cognitive Impairment (MCI). Int Psychogeriatr 23(4): 526-538 (2011).

[62] Gates NJ, Sachdev PS, Fiatarone Singh MA, Valenzuela M. Cognitive and Memory Training in Adults at Risk of Dementia: A Systematic Review. BMC Geriatr 11: 55 (2011).

[63] Li HJ, Li JA, Li NX, Li B, Wang PY, Zhou T. Cognitive Intervention for Persons with Mild Cognitive Impairment: A Meta-Analysis. Ageing Res Rev 10(2): 285-296 (2011).

[64] Rapp S, Breenes G, Marsch AP. Memory Enhancement Training for Older Adults with Mild Cognitive Impairment: A Preliminary Study. Aging Ment Health 6: 5-11 (2002).

[65] Troyer AK, Murphy KJ, Anderson ND, Moscovitch M, Craik FI. Changing Everyday Memory Behaviour in Amnestic Mild Cognitive Impairment: A Randomised Controlled Trial. Neuropsychol Rehabil 18(1): 65-88 (2008).

[66] Craik FIM, Winocur G, Palmer H, Binns MA, Edwards M, Bridges K, et al. Cognitive Rehabilitation in the Elderly: Effects on Memory. J Int Neuropsychol Soc 13(1): 132-142 (2007).

[67] Londos E, Boschian K, Linden A, Persson C, Minthon L, Lexell J. Effects of a Goal-Oriented Rehabilitation Program in Mild Cognitive Impairment: A Pilot Study. Am J Alzheimers Dis Other Demen 23(2): 177-183 (2008).

[68] Belleville S, Gilbert B, Fontaine F, Gagnon L, Menard E, Gauthier S. Improvement of Episodic Memory in Persons with Mild Cognitive Impairment and Healthy Older Adults: Evidence from a Cognitive Intervention Program. Dem Geriatr Cogn Disord 22(5-6): 486-499 (2006).

[69] Unverzagt FW, Smith DM, Rebok GW, Marsiske M, Morris JN, Jones R, et al. The Indiana Alzheimer Disease Center's Symposium on Mild Cognitive Impairment. Cognitive Training in Older Adults Lessons from the ACTIVE Study. Curr Alzheimer Res 6(4): 375-383 (2009).

[70] Ball K, Berch DB, Helmers KF, Jobe JB, Leveck MD, Marsiske M, et al. Effects of Cognitive Training Interventions with Older Adults - A Randomized Controlled Trial. JAMA 288(18): 2271-2281 (2002).

[71] Moro V, Condoleo MT, Sala F, Pernigo S, Moretto G, Gambina G. Cognitive Stimulation in a-MCI: An Experimental Study. Am J Alz Dis Other Demen 27(2): 121-130 (2012).

[72] Olchik MR, Farina J, Steibel N, Teixeira AR, Yassuda MS. Memory training (MT) in Mild Cognitive Impairment (MCI) Generates Change in Cognitive Performance. Arch Gerontol Geriatr 56: 442-447 (2013).

[73] Hampstead BM, Sathian K, Phillips PA, Amaraneni A, Delaune WR, Stringer AY. Mnemonic Strategy Training Improves Memory for Object Location Associations in Both Healthy Elderly and Patients with Amnestic Mild Cognitive Impairment: A Randomized, Single-Blind Study. Neuropsychology 26(3): 385-399 (2012).

[74] Belleville S, Clement F, Mellah S, Gilbert B, Fontaine F, Gauthier S. Training-Related Brain Plasticity in Subjects at Risk of Developing Alzheimer's Disease. Brain 134: 1623-1634 (2011).

[75] Prawat RS. Promoting Access to Knowledge, Strategy, and Disposition in Students: A Research Synthesis. Rev Educ Res 59(1): 1-41 (1989).

[76] Singer RN, Chen DP. A Classification Scheme for Cognitive Strategies: Implications for Learning and Teaching Psychomotor Skills. Res Q Exerc Sport 65(2): 143-151 (1994).

[77] Davelaar EJ. Processes Versus Representations: Cognitive Control as Emergent, Yet Componential. Top Cogn Sci 3: 247-252 (2011).

[78] Persson J, Reuter-Lorenz PA. Gaining Control Training Executive Function and Far Transfer of the Ability to Resolve Interference. Psychol Sci 19(9): 881-888 (2008).

[79] Persson J, Reuter-Lorenz PA. Gaining Control Training Executive Function and Far Transfer of the Ability to Resolve Interference (Retraction of vol 19, page 881, 2008). Psychol Sci 22(4): 562-562 (2011).

[80] Faucounau V, Wu YH, Boulay M, De Rotrou J, Rigaud AS. Cognitive Intervention Programmes on Patients Affected by Mild Cognitive Impairment: A Promising Intervention Tool for Mci? J Nutr Health Aging 14(1): 31-35 (2010).

[81] Gunther VK, Schafer P, Holzner BJ, Kemmler GW. Long-Term Improvements in Cognitive Performance through Computer-Assisted Cognitive Training: A Pilot Study in a Residential Home for Older People. Aging Ment Health 7(3): 200-206 (2003).

[82] Marker KR. Handbuch zum Programmpaket Cognition-1. Ladenburg: Marker Software (1992).

[83] Tonetta M. Il TNP, un Software che Opera in Ambiente Windows. Atti del 4 Convegno Internazionale Informatica, Didattica e Disabilità. Naples (Italy) (1995).

[84] Cipriani G, Bianchetti A, Trabucchi M. Outcomes of a Computer-Based Cognitive Rehabilitation Program on Alzheimer's Disease Patients Compared with Those on Patients Affected by Mild Cognitive Impairment. Arch Gerontol Geriatr 43(3): 327-335 (2006).

[85] Talassi E, Guerreschi M, Feriani M, Fedi V, Bianchetti A, Trabucchi M. Effectiveness of a Cognitive Rehabilitation Program in Mild Dementia (MD) and Mild Cognitive Impairment (MCI): A Case Control Study. Arch Gerontol Geriatr 44: 391-399 (2007).

[86] Rozzini L, Costardi D, Chilovi BV, Franzoni S, Trabucchi M, Padovani A. Efficacy of Cognitive Rehabilitation in Patients with Mild Cognitive Impairment Treated with Cholinesterase Inhibitors. Int J Geriatr Psychiatry 22(4): 356-360 (2007).

[87] Galante E, Venturini G, Fiaccadori C. Computer-Based Cognitive Intervention for Dementia: Preliminary Results of a Randomized Clinical Trial. G Ital Med Lav Erg, Suppl B, Psicologia 3: B26-B32 (2007).

[88] Mahncke HW, Connor BB, Appelman J, Ahsanuddin ON, Hardy JL, Wood RA, et al. Memory Enhancement in Healthy Older Adults Using a Brain Plasticity-Based Training Program: A Randomized, Controlled Study. Proc Natl Acad Sci USA 103(33): 12523-12528 (2006).

[89] Smith GE, Housen P, Yaffe K, Ruff R, Kennison RF, Mahncke HW, Zelinski EM. A Cognitive Training Program Based on Principles of Brain Plasticity: Results from the Improvement in Memory with Plasticity-Based Adaptive Cognitive Training (IMPACT) Study. J Am Geriatr Soc 57(4): 594-603 (2009).

[90] Barnes DE, Yaffe K, Belfor N, Jagust WJ, DeCarli C, Reed BR, Kramer JH. Computer-based Cognitive Training for Mild Cognitive Impairment Results from a Pilot Randomized, Controlled Trial. Alzheimer Dis Assoc Disord 23(3): 205-210 (2009).

[91] Brum PS, Forlenza OV, Yassuda MS. Cognitive Training in Older Adults with Mild Cognitive Impairment. Dem Neuropsy 3(2): 124-131 (2009).

[92] Hwang HR, Choi SH, Yoon DH, Yoon BN, Suh YJ, Lee DH, et al. The Effect of Cognitive Training in Patients with Mild Cognitive Impairment and Early Alzheimer's Disease: A Preliminary Study. J Clin Neurol 8: 190-197 (2012).

[93] Carretti B, Borella E, Fostinelli S, Zavagnin M. Benefits of Training Working Memory in Amnestic Mild Cognitive Impairment: Specific and Transfer Effects. Int Psychogeriatr 24(5): 617-626 (2013).

[94] Hampstead BM, Stringer AY, Stilla RF, Deshpande G, Hu XP, Moore AB, Sathian K. Activation and Effective Connectivity Changes Following Explicit-Memory Training for Face-Name Pairs in Patients With Mild Cognitive Impairment: A Pilot Study. Neurorehabil Neural Repair 25(3): 210-222 (2011).

[95] Rosen AC, Sugiura L, Kramer JH, Whitfield-Gabrieli S, Gabrieli JD. Cognitive Training Changes Hippocampal Function in Mild Cognitive Impairment: A Pilot Study. J Alzh Dis 26: 349-357 (2011).

[96] Draganski B, Gaser C, Busch V, Schuierer G, Bogdahn U, May A. Neuroplasticity: Changes in Grey Matter Induced by Training - Newly Honed Juggling Skills Show up as a Transient Feature on a Brain-Imaging Scan. Nature 427(6972): 311-312 (2004).

[97] Boyke J, Driemeyer J, Gaser C, Buechel C, May A. Training-Induced Brain Structure Changes in the Elderly. J Neurosci 28(28): 7031-7035 (2008).

[98] Engvig A, Fjell AM, Westlye LT, Moberget T, Sundseth O, Larsen VA, Walhovd KB. Effects of Memory Training on Cortical Thickness in the Elderly. Neuroimage 52(4): 1667-1676 (2010).

[99] Takeuchi H, Taki Y, Hashizume H, Sassa Y, Nagase T, Nouchi R, Kawashima R. Effects of Training of Processing Speed on Neural Systems. J Neurosci 31(34): 12139-12148 (2011).

[100] Takeuchi H, Taki Y, Sassa Y, Hashizume H, Sekiguchi A, Fukushima A, Kawashima R. Working Memory Training Using Mental Calculation Impacts Regional Gray Matter of the Frontal and Parietal Regions. PLOS ONE 6(8): e23175 (2011).

[101] Sagi Y, Tavor I, Hofstetter S, Tzur-Moryosef S, Blumenfeld-Katzir T, Assaf Y. Learning in the Fast Lane: New Insights into Neuroplasticity. Neuron 73(6): 1195-1203 (2012).

[102] Takeuchi H, Sekiguchi A, Taki Y, Yokoyama S, Yomogida Y, Komuro N, et al. Training of Working Memory Impacts Structural Connectivity. J Neurosci 30(9): 3297-3303 (2010).

[103] Engvig A, Fjell AM, Westlye LT, Moberget T, Sundseth Ø, Larsen VA, Walhovd KB. Memory Training Impacts Short-Term Changes in Aging White Matter: A Longitudinal Diffusion Tensor Imaging Study. Hum Brain Mapp 33: 2390-2406 (2012).

[104] Ferreira LK, Diniz BS, Forlenza OV, Busatto GF, Zanetti MV. Neurostructural Predictors of Alzheimer's Disease: A Meta-Analysis of VBM Studies. Neurobiol Aging 32: 1733-1741 (2011).

[105] Sexton CE, Kalu UG, Filippini N, Mackay CE, Ebmeier KP. A Meta-Analysis of Diffusion Tensor Imaging in Mild Cognitive Impairment and Alzheimer's Disease. Neurobiol Aging 35: 2322.e5–e18 (2011).

[106] Wei DT, Yang JY, Li WF, Wang KC, Zhang QL, Qiu J. Increased Resting Functional Connectivity of the Medial Prefrontal Cortex in Creativity by Means of Cognitive Stimulation. Cortex 51: 92-102 (2014).

[107] Mazoyer B, Houde O, Joliot M, Mellet E, Tzourio-Mazoyer N. Regional Cerebral Blood Flow Increases During Wakeful Rest Following Cognitive Training. Brain Res Bull 80(3): 133-138 (2009).

[108] Mozolic JL, Hayasaka S, Laurienti PJ. A Cognitive Training Intervention Increases Resting Cerebral Blood Flow in Healthy Older Adults. Front Hum Neurosci 4: 16 (2010).

[109] Buckner RL, Andrews-Hanna JR, Schacter DL. The Brain's Default Network: Anatomy, Function, and Relevance to Disease. Ann NY Acad Sci 1124: 1-38 (2008).

[110] Fu WT, Lee H, Boot WR, Kramer AF. Bridging Across Cognitive Training and Brain Plasticity: A Neurally Inspired Computational Model of Interactive Skill Learning. WIREs Cogn Sci 4: 225-236 (2013).

[111] Landau SM, Marks SM, Mormino EC, Rabinovici GD, Oh H, O'Neil JP, et al. Association of Lifetime Cognitive Engagement and Low β-Amyloid Deposition. Arch Neurol 69(5): 623-629 (2012).

[112] Wilson RS, Leurgans SE, Boyle PA, Bennett DA. Cognitive Decline in Prodromal Alzheimer's Disease and Mild Cognitive Impairment. Arch Neurol 68(3): 351-356 (2011).

[113] Zanetti O, Zanieri G, Di Giovanni G, De Vreese LP, Pezzini A, Metitieri T, et al. Effectiveness of Procedural Memory Stimulation in Mild Alzheimer's Disease Patients: A Controlled Study. Neuropsychol Rehabil 11(3/4): 263-272 (2001).

[114] Herrera C, Chambon C, Michel BF, Paban V, Alescio-Lautier B. Positive Effects of Computer-Based Cognitive Training in Adults with Mild Cognitive Impairment. Neuropsychologia 50: 1871-1881 (2012).

[115] Martinez K, Solana AB, Burgaleta M, Hernández-Tamames JA, Álvarez-Linera J, Román FJ, et al. Changes in Resting-State Functionally Connected Parietofrontal Networks After Videogame Practice. Hum Brain Mapp 34: 3143-3157 (2013).

Table 1. List (#) of studies which report specifically structured and cognitively based CS programmes included in the review.

Authors	Group	Number of Participants	Methods	Use of ChEI	Imaging	Control (Y/N)
Participants with probable Alzheimer's disease						
			CS based on spared functions			
Yanguas et al., 2006 (1st sub-group)	Minimal-mild AD	Not indicated (part of a the complete recruited sample of 390 individuals)	Training of various cognitive functions and ADL	Not specified (reasonably all)	No	Yes (not described)
Yanguas et al., 2006 (2nd sub-group)	Moderate-severe AD	Not indicated (part of a the complete recruited sample of 390 individuals)	Training of residual cognitive abilities and ADL	Not specified (reasonably all)	No	Yes (not described)
Farina et al., 2002	Mild-moderate AD	Experimental sub-group 2 of the study: 11	Training of residual cognitive abilities	Not specified (reasonably all)	No	No
Farina et al., 2006	Mild-moderate AD	Experimental sub-group 2 of the study: 16	Training of residual cognitive abilities	Experimental sub-group: 11 out of 16	No	No
			Combination of CS and pharmacological treatment (control group not receiving CS)			
Giordano et al., 2010	Mild-moderate AD	Experimental sub-group: 62 Control sub-group: 38	ROT	All	No	Yes: No treatment

Bottino et al., 2005	Mild AD	Experimental sub-group: 6 Control sub-group: 7	ROT, learning, memory, communication and ADL training	All	No	Yes: No treatment
Chapman et al., 2004	Mild-moderate AD	Experimental sub-group: 26 Control sub-group: 28	Communication, functional activities and quality of life training	All	No	Yes: No treatment
Matsuda, 2007	AD	Experimental sub-group: 17 Control sub-group: 13	Fluency, communication, verbal learning training	All	No	Yes: No treatment
Matsuda et al., 2010	Mild AD	Experimental sub-group: 31 Control sub-group: 18	Mental control, verbal learning and fluency training	All	No	Yes: No treatment
Cassinello et al., 2008	Mild AD	Experimental sub-group: 17 Control sub-group: 9	Reasoning and attention, language, praxias, gnosias, calculation and association-ordering training	All	No	Yes: No treatment
Fernandez-Calvo et al., 2011	Mild AD	Experimental sub-group: 15 Control sub-group: 15	"Big Brain Academy" videogame	All	No	Yes: No treatment
Scheckter et al., 2013	Mild AD	Experimental sub-group 1: 15; Experimental sub-group 2: 12; Control sub-group: 15	Training of working memory: Manipulation of complex material (sub-group 1); "Dynamic" training on the self as "the highest executive and metacogntiive authority" (sub-group 2)	All	No	Yes: No treatment

Hwang et al., 2012 (1st sub-group)	Mild AD	Experimental sub-group: 6 Control sub-group: 3	ROT, attention, memory, executive functions, visuoconstructional skills training	All	No	Yes: No treatment
Combination of CS and pharmacological treatment (control group receiving CS)						
Niu et al., 2010	Mild-moderate AD	Experimental sub-group: 16 Control sub-group: 16	ROT, Fluency, perception and memory training	All	No	Yes: Educational, conversational sessions
Cahn-Weiner et al., 2003	Mild AD	Experimental sub-group: 17 Control sub-group: 17	Memory strategies	All	No	Yes: Educational material
Löwenstein et al., 2004	Mild AD	Experimental sub-group: 25 Control sub-group: 19	Orientation, learning, attention and calculation training	All	No	Yes: Recreational activities and computerised games
Tarraga et al., 2006	Mild AD	Experimental sub-group: 15 1st control sub-group: 16 2nd control sub-group: 12	Training of various cognitive functions, ADL training, workshops and "Smartbrain" computerised exercises	All	No	Yes: - 1st sub-group: cognitive and ADL training, workshops - 2nd sub-group: No treatment
Galante et al, 2007	Mild AD	Experimental sub-group: 7 Control sub-group: 4	Computerised multidimensional cognitive stimulation	All	No	Yes: Conversational activities

Gaitan et al., 2013	Multidomain MCI-Mild AD	Experimental sub-group: 23 Control sub-group: 16	Computerised multidimensional and pen-and-paper cognitive stimulation	Experimental sub-group: 3 out of 16; Control sub-group: 5 out of 22	No	Yes: Multidimensional pen-and-paper cognitive stimulation
Studies based on evidence of brain function						
Kawashima et al., 2005	Mild-to-severe AD	Experimental sub-group: 16 Control sub-group: 16	Reading and arithmetic	Not specified (reasonably all)	No	Yes: No treatment
Jelcic et al., 2012	Mild AD	Experimental sub-group: 20 Control sub-group: 20	Lexical-semantic training	None	No	Yes: Creative, communication and recreational activities
Studies with no control condition/group						
Cipriani et al., 2006 (1st sub-group)	Mild AD	Experimental sub-group: 10	Computerised multidimensional cognitive stimulation	All	No	No
Kurz et al., 2009 (1st sub-group)	Mild AD	Experimental sub-group: 10	Multi-componentiall cognitive and non-cognitive training	Not specified (reasonably all)	No	No

Participants with Mild Cognitive Impairment

Studies based on cognitive strategies

Rapp et al., 2002	MCI	Experimental sub-group: 9 Control sub-group: 10	Metacognitive and memory strategy training	None	No	Yes: No treatment
Troyer et al., 2008	MCI	Experimental sub-group: 24 Control sub-group: 26	Strategy training and lifestyle education	Not specified	No	Yes: No treatment
Craik et al., 2007	Aduts with subjective/objective memory impairment	Experimental sub-group: 29 Control sub-group: 20	Memory strategy training	Not specified (reasonably none)	No	Yes: No treatment
Londos et al., 2008	MCI	Experimental sub-group: 15	Memory strategy training	None	No	No
Belleville et al., 2006	Amnestic MCI	Experimental sub-group: 20 Control sub-group: 8	Memory strategy training	Not specified	No	Yes: No treatment
Unverzagt et al., 2009	MCI	Memory sub-group: 703; Reasoning sub-group: 699; Processing speed sub-group: 702; Control sub-group: 698	Strategy training	Not specified	No	Yes: No treatment
Moro et al., 2012	Amnestic MCI	Experimental sub-group: 15 Control sub-group: 15	Metacognitive and memory strategy training	None	No	Yes: No treatment Cross-over design (30 participants in total)

Olchik et al., 2013	MCI	Experimental sub-group: 16; 1st control sub-group: 17; 2nd control sub-group: 14	Memory Strategies	Not specified (reasonably none)	No	Yes: - 1st sub-group: Educational Material - 2nd sub-group: No treatment
Hampstead et al., 2011	Amnestic MCI	Experimental sub-group: 6	Face-name association memory strategy training	Not specified	Yes	No
Hampstead et al., 2012	Amnestic MCI	Experimental sub-group: 13 Control sub-group: 14	Visuo-spatial memory strategy training	Not specified	Yes	Yes: Exposure to training material with no strategy learning
Belleville et al., 2011	Amnestic MCI	Experimental sub-group: 15	Memory strategy training	Not specified	Yes	No
		CS based on computational exercises				
Gunther et al., 2003	Patients with age-associated memory impairment	Experimental sub-group: 19	Computerised multidimensional cognitive stimulation	Not specified (reasonably none)	No	No
Cipriani et al., 2006 (2nd sub-group)	MCI	Experimental sub-group: 10	Computerised multidimensional cognitive stimulation	Not specified (reasonably none)	No	No
Talassi et al., 2007	MCI	Experimental sub-group: 30 Control sub-group: 7	Computerised multidimensional cognitive stimultation, ADL and behavioural training	Not specified (reasonably none)	No	Yes: Physical, ADL and behavioural training

Rozzini et al., 2007	MCI	Experimental sub-group: 15 1st control sub-group: 22 2nd control sub-group: 22	Computerised multidimensional cognitive stimulation	Experimental and 1st control sub-group	No	Yes: - 1st sub-group: only ChEI - 2nd sub-group: No treatment
Barnes et al., 2009	MCI	Experimental sub-group: 22 Control sub-group: 25	Computerised processing speed and accuracy training	None	No	Yes: Passive computerised tasks
Brum et al., 2009	MCI	Experimental sub-group: 16 Control sub-group: 18	Memory, attention, orientation and calculation training, and lithium	Experimental sub-group: 4 out of 16; Control sub-group: 3 out of 18	No	Yes: lithium
Kurz et al., 2009 (2nd and 3rd sub-grous)	MCI	Experimental sub-group: 18 Control sub-group: 12	Multi-componentiall cognitive and non-cognitive training	Not specified	No	Yes: No treatment
Hwang et al., 2012 (2nd sub-group)	Amnestic MCI	Experimental sub-group: 6 Control sub-group: 5	ROT, attention, memory, executive functions, visuoconstructional skills training	Not specified (reasonably none)	No	Yes: No treatment
Carretti et al., 2013	Amnestic MCI	Experimental sub-group: 10 Control sub-group: 10	Verbal working memory training	None	No	Yes: Educational training on memory and memory strategies

Rosen et al., 2011	MCI	Experimental sub-group: 6 Control sub-group: 6	Computerised processing speed and accuracy training	Not specified (eligible, if on medication)	Yes	Yes: No treatment

studies are listed following the order of presentation in text within each subsection