In Review

Nonpharmacological Treatment of Alzheimer Disease

Clive Ballard, MRC Psych, MD\textsuperscript{1}; Zunera Khan, MSc\textsuperscript{2}; Hannah Clack, BComms\textsuperscript{3}; Anne Corbett, PhD\textsuperscript{4}

**Objective:** To review the key nonpharmacological treatment approaches to the cognitive and functional symptoms of Alzheimer disease (AD).

**Methods:** We searched and critically analyzed the most recent relevant literature pertaining to the nonpharmacological treatment of AD.

**Results:** There is evidence from a modest number of well-conducted randomized controlled trials (RCTs) that various nonpharmacological approaches, including cognitive training, cognitive rehabilitation, and cognitive stimulation therapy (CST), confer modest but significant benefits in the treatment of cognitive symptoms in people with AD, and that there may be additive benefits in combination with cholinesterase inhibitor therapy. Cognitive rehabilitation also appears to result in functional benefits in AD. The modest number of RCTs focusing on cognitive training in AD is consistent with the results of larger cognitive training trials in healthy older people. However, there is no convincing evidence of any benefits associated with brain training games.

**Conclusion:** An emerging evidence base indicates that different approaches to cognitive training and cognitive stimulation in people with AD confer modest but significant benefits. The best evidence base is for CST, although this approach is labour-intensive, and requires further evaluation of cost-effectiveness. There is currently no evidence that brain training games provide any significant benefit to people with AD.


**Clinical Implications**

- Various nonpharmacological interventions confer cognitive benefits to people with AD.
- There may be additive benefits by combining nonpharmacological interventions and cholinesterase inhibitor therapy.

**Limitations**

- Most RCTs evaluating nonpharmacological treatments in people with AD are modest in size.
- Many of the studies use usual treatment as the control.

**Key Words:** cognitive training, cognitive rehabilitation, cognitive stimulation therapy, brain training games, dementia
There is extensive literature regarding nonpharmacological treatment strategies for cognitive and neuropsychiatric symptoms in people with AD. Our article will focus on the treatment of cognitive and functional impairments. Nonpharmacological treatment of neuropsychiatric symptoms is a key topic in its own right (see Ballard and Corbett for a recent review).

There has been tremendous public interest in so-called brain training as a means of preventing cognitive decline, based on the principle of use it or lose it. The foundation of these claims lie in robust evidence from meta-analyses and systematic reviews showing that a higher cognitive reserve is associated with a significantly reduced risk of developing dementia. However, the concept of cognitive reserve encompasses education, occupation, and mental activities throughout life, compared with the more focused short-term interventions provided by marketed brain training products. Therefore, it is unclear whether these products would confer any benefit in later life or in the context of a disease process.

There are numerous different theoretical approaches to cognitive training and cognitive rehabilitation. At the simplest level, often discussed in newspapers and commercial advertising campaigns, this focuses on brain training games and other potentially brain-stimulating activities, such as sudoku and crosswords. Our review will discuss some of the different approaches to neuropsychological and training interventions focusing on cognition, with a specific focus on the evidence for efficacy in people with AD. The key studies are reviewed in the sections below, and summarized in Table 1.

Cognitive Training
Belleville described the essence of cognitive training as teaching theory-based strategies and skills to try and improve cognition functioning. Most cognitive training approaches have employed specific training packages targeting individual cognitive functions, or a cluster of related domains. They are usually received either alone or in groups via a trained individual, and may include computer-based training. Cognitive training has been proposed as a treatment opportunity for people with AD or other dementias, and as a means of preventing cognitive decline in older adults and people with MCI. This concept is extremely attractive, but is there any evidence to support this approach?

Numerous modest-sized studies, including some RCTs, indicate that various cognitive training approaches confer significant and sustained benefit in healthy older adults. A meta-analysis of 10 RCTs indicated a significant but modest overall benefit to healthy older adults (effect size 0.16), which was generally limited to the specific cognitive domain targeted by the training. A common limitation to studies of this type is the absence of an active control group, potentially exaggerating the benefits of the intervention. The largest and most extensive study, the ACTIVE trial, followed more than 2500 older adults during 5 years. Groups of participants received training focused on attention, memory, or reasoning, as well as practice and strategy development. The study reported benefits in the cognitive domain that was the focus of the specific training package, with training in memory and attention predominantly enhancing performance in these specific functions. However, so-called reasoning training was associated with more general improvements across other cognitive domains, and conferred additional benefit on instrumental activities of daily living.

Findings from studies investigating benefits of cognitive training in people with memory impairment and dementia are more conflicting. In the ACTIVE study, training in memory conferred no benefit to people with memory impairment (based on a threshold of a 1.5 standard deviation below normative values on the Rey Auditory Verbal Learning Test), while reasoning training continued to perform well. The benefits of cognitive training for people with AD were reviewed in a recent systematic review and a previous meta-analysis of studies between 1980 and 2004. Both concluded that cognitive training is effective, albeit with a moderate effect size. The meta-analysis included 19 studies, predominantly small in size, and reported a Cohen’s d effect size of 0.38 for general cognitive function. Note that reviews with stricter inclusion criteria have reported less favourable outcomes and that numerous intervention studies have not shown any benefit. For example, an RCT of a specific memory training intervention (practice of mnemonics, organization of items to be recalled into categories, and visualizing and associating memories) involving 34 people with early stage AD did not identify any significant benefit in either memory or cognitive function. It is important to interpret the outcomes of studies into the benefit of cognitive training in people with AD in the context of the wider, more robust literature regarding MCI and healthy older adults.

Alternative approaches to cognitive training include some more innovative approaches and numerous training programs that draw on more specific theoretical frameworks. The most promising of these has provided emerging evidence for the potential benefit of errorless learning in people with AD. This learning paradigm is designed to limit

Abbreviations

ACTIVE: Advance Cognitive Training for Independent and Vital Elderly
AD: Alzheimer disease
Che: cholinesterase inhibitor
CST: cognitive stimulation therapy
FAB: frontal assessment battery
MCI: mild cognitive impairment
MMSE: mini mental status examination
RCT: randomized controlled trial
the accumulation of errors during the acquisition phase of learning, thereby reducing the chances of assimilating incorrect information. This approach has demonstrated benefits in various aspects of memory, with reasonable evidence that benefits are maintained.\(^\text{15}\) However, this evidence is still preliminary, and is largely based on small cohort studies with 3 to 12 participants.\(^\text{16-20}\)

Although the literature regarding cognitive training in AD is limited, studies in people with MCI and healthy older adults do indicate some benefit. However, the effect sizes are modest, with benefits limited to the specific domain on which the training is focused. It should be noted that the most promising studies are those aimed specifically at memory training, as well as approaches that have used a computer package to facilitate a daily training regime. This approach would appear to be worth pursuing, but it may be more profitable to focus on training in specific cognitive or daily functions, as training aimed at more general benefits seem unlikely to be successful, based on the current literature.

### Table 1 Summary of key RCTs of cognitive training, brain training games, and cognitive rehabilitation in people with AD

<table>
<thead>
<tr>
<th>Key studies</th>
<th>Design</th>
<th>Main outcomes</th>
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<tr>
<td><strong>Cognitive training</strong></td>
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<tr>
<td>Sitzer et al(^\text{12})</td>
<td>Meta-analysis of 19 small RCTs of cognitive training in AD; mainly small studies and very broad inclusion criteria</td>
<td>General cognitive function measured in 308 participants, with a Cohen’s (d) standardized effect size of 0.38 favouring cognitive training</td>
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<tr>
<td>Cahn-Weiner et al(^\text{14})</td>
<td>RCT of 34 people with early AD assigned to memory training or control treatment</td>
<td>No significant benefits were seen in memory or function</td>
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<tr>
<td><strong>Cognitive rehabilitation and (or) implicit memory</strong></td>
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<tr>
<td>Zanetti et al(^\text{25})</td>
<td>20 adults with mild-to-moderate AD were randomized to an implicit learning intervention or a control treatment for 3 weeks</td>
<td>The active intervention conferred significant benefit in 20 targeted key activities</td>
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<tr>
<td>Clare et al(^\text{26})</td>
<td>RCT comparing cognitive rehabilitation, relaxation and no treatment during 8 weeks in 69 people with AD or mixed AD–vascular dementia and MMSE score of &gt;18</td>
<td>Cognitive rehabilitation conferred significant benefits in goal performance and satisfaction</td>
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<td><strong>CST</strong></td>
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<tr>
<td>Spector et al(^\text{27})</td>
<td>RCT of 201 people randomized to CST or control treatment for 7 weeks</td>
<td>Significant benefits relative to the control group in cognition and quality of life</td>
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<td>Requena et al(^\text{20})</td>
<td>RCT of CST in 86 people, some followed for 2 years</td>
<td>Significant benefits seen on MMSE, and additive effect with donepezil reported; benefits were seen for 1 year, but not for the full 2 years of follow-up</td>
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<td>Chapman et al(^\text{32})</td>
<td>RCT of CST in 54 people with mild-to-moderate AD comparing donepezil alone with donepezil plus CST</td>
<td>The combination group had significantly had significantly slower decline in MMSE and improved quality of life</td>
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<td><strong>Reality orientation</strong></td>
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<tr>
<td>Spector et al(^\text{34})</td>
<td>Meta-analysis of 6 small RCTs with a total of 125 participants</td>
<td>Overall, reality orientation conferred a significant advantage of about 1 point on the MMSE</td>
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<td>Onder et al(^\text{36})</td>
<td>An RCT of 156 people with mild-to-moderate dementia randomized to reality orientation plus donepezil or donepezil alone for 25 weeks</td>
<td>The group receiving reality orientation had a 1.3-point advantage on the MMSE, compared with the group receiving donepezil alone</td>
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<td><strong>Brain training games</strong></td>
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<td>No RCTs in people with dementia; in an RCT of 11 340 adults aged 18 to 60 years, Owen et al(^\text{23}) demonstrated no benefits during 6 weeks of treatment; in a small nonrandomized study of 32 people with AD, Kawashima et al(^\text{21}) suggested that the brain training games conferred modest benefits</td>
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<td><strong>Memory aids</strong></td>
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<td>No RCTs; several case series and small comparative studies suggest possible benefits</td>
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**Brain Training Games**

Many commercial companies have developed and marketed brain training games (for example, Nintendo, Luminosity, Mindfit, and Neuro-Programmer 2), based on the concept...
of use it or lose it. Promotional materials frequently suggest that these products have the potential to improve cognition or even to reverse or reduce cognitive decline based on performance on specific training tasks. The key difference between brain training games and cognitive training is the absence of a therapist or another person to deliver the training. Therefore, this approach is far less demanding on resources and, if effective, could be made available to a large number of people. Despite the publicity and hype surrounding the benefits of brain training games, there is extremely limited evidence to support the value of any of the current commercially available products in any group of people. Evidence of benefit to people with cognitive impairment is particularly lacking. For example, the Nintendo brain training product has been tested in a comparative trial of 32 people with AD, who were assigned to either brain training or no training for 6 months. The active treatment group performed simple calculations and language tests, while the control group received no training. Assessment of cognitive status, pre- and posttesting, was carried out with the MMSE and the FAB. The active treatment group showed improvement in FAB score, no change in MMSE score, and became more communicative and independent. The control group showed no change in FAB score and a decline in MMSE score.\textsuperscript{21} A larger study with an open design tested the Memory65+ computer training program, with 127 people with and without cognitive impairment.\textsuperscript{22} Participants were tested at baseline, posttraining, and at 9 months. The study reported significant improvements in working memory at posttest assessment and at 9 months both in impaired and in nonimpaired people. There was also significant improvement in performance in the Wechsler Adult Intelligence Scale III battery at the posttraining test, but this was only sustained among nonimpaired people at 9 months.

By far, the largest intervention study of brain training is Brain Test Britain, a collaborative study conducted in the United Kingdom by the British Broadcasting Corporation and the Alzheimer’s Society. In a 6-week online study, 11 430 participants aged between 18 and 60 years were randomized to receive brain training in reasoning (with an emphasis on training games involving executive function), general brain training (similar to commercially available brain training games), or control (Internet search tasks). On average, participants completed 24 training sessions during the 6 weeks of the intervention. Participants showed a 25% improvement in performance in the actual brain training games, but this was not translated to significant benefit in standardized cognitive assessments of executive function, attention, or working memory, even when the tasks assessed cognitive functions that were related to those included in the brain training games.\textsuperscript{23} A 12-month study of the same brain training games in adults aged 60 years and older is still ongoing.

Overall, there is currently strong evidence that brain training games do not improve cognition in adults aged 60 years and younger. The potential value in older adults or people with cognitive impairment has not yet been determined.

Cognitive Rehabilitation and Implicit Learning

Numerous interventions have been developed based on implicit learning approaches, such as the spaced-retrieval technique or broader cognitive rehabilitation interventions. One novel study assessed a computer-based touch screen training program designed to improve specific functional tasks.\textsuperscript{24} The tasks were broken into clear steps, and photographs were taken of each of these steps and scanned into a computer. The approach was tested with 4 adults with mild-to-moderate AD, with a facilitator to assist, although participants were encouraged to work as independently as possible. Performance on the specific tasks improved substantially, but there was no improvement in global cognitive performance. Additional research into implicit learning techniques included a small RCT with 20 people with mild-to-moderate AD randomized to an active treatment group receiving an intervention that targeted 20 key activities designed to improve motor skills, or to a control group.\textsuperscript{25} During 3 weeks, the active treatment group learned these activities more successfully than the control group.

A more recent, larger single-blind RCT of 69 people with AD or mixed AD–vascular dementia, who had MMSE scores of more than 18, evaluated a cognitive rehabilitation approach based on similar principles to improve individualized outcomes.\textsuperscript{26} The intervention consisted of 8 weekly individual sessions of cognitive rehabilitation, teaching strategies and techniques for learning new information, maintaining attention and concentration, managing stress, and using appropriate aids. Performance of participants receiving this intervention was compared with groups receiving relaxation therapy or no treatment during 8 weeks. The cognitive rehabilitation intervention conferred significant benefits in goal performance and satisfaction, compared with the other 2 groups.

CST and Reality Orientation

CST is a group-based approach for people with mild-to-moderate dementia, based on the theoretical concepts of reality orientation and cognitive stimulation. The first group to develop CST designed a very specific operationalized approach with 14 sessions of themed activities that typically run twice a week during a 7-week period.\textsuperscript{27} Other groups have used similar principles with slightly modified implementation protocols. A single-blind RCT of 201 people with dementia (115 people receiving CST and 86 control subjects) reported significant improvements in MMSE ($P = 0.04$) and the Alzheimer Disease Assessment Scale—Cognition (commonly referred to as ADAS-Cog [$P = 0.01$]) in the treatment group relative to the control group, with additional benefits in quality of life.\textsuperscript{27} A further subanalysis of cognitive outcomes showed additional key benefits in language function.\textsuperscript{28} These initial cognitive improvements following CST were only sustained when the intervention was maintained in the long term.\textsuperscript{29}
A further RCT of CST in 86 people with AD, some of whom were followed up for 2 years, also reported that CST conferred significant benefit on the MMSE. Interestingly, the study also observed an additive effect in people who were prescribed donepezil. However, these benefits were only sustained for up to 1 year. A similar study in the United States compared the effects of CST in combination with donepezil, with donepezil alone, in a group of 54 adults with mild-to-moderate AD. Participants in the combination group showed slower decline in MMSE scores, less irritability, less apathy, and improved quality of life after completion of the training. Additional small studies also support an additive effect with a combined treatment, with ChEIs and CST.

One component of CST is reality orientation, an approach that aims to relate accurate information regarding basic but important information, such as person, place, and time to people with AD. Reality orientation has also been investigated as an independent therapy. Meta-analyses have identified 6 RCTs that analyzed the effect of reality orientation. These studies involved a total of 125 participants (67 people receiving reality orientation and 58 control subjects) and indicate a significant effect in favour of reality orientation treatment of about 1 MMSE point. A larger study compared the combined effect of reality orientation and donepezil, with donepezil alone, in 156 participants with mild-to-moderate dementia during 25 weeks. The treatment group showed a 1.3-point MMSE advantage, compared with the control group, providing further support for an additive effect between pharmacological and nonpharmacological interventions.

The overall evidence for reality orientation and CST is convincing, and indicates that significant benefits in cognition and quality of life in people with AD can be achieved with this approach. The RCTs evaluating CST are larger and therefore suggest that this would be the preferred approach. Interestingly, there is a strong indication of an additive effect between these treatment approaches and pharmacological therapy with ChEIs.

Memory Aids
Memory aids, such as digital clocks, memory books, and diaries, could provide a simple and pragmatic approach to aiding memory and improving performance. It is also likely that new innovative products will be developed as technology moves forward. The efficacy of memory aids has been investigated in small samples of people with early stage AD. Several case series and very small comparative studies with less than 20 participants have suggested that this approach may have some potential clinical utility, particularly for promoting improved functioning. Although the evidence base is preliminary, this approach appears to be initially valid and is simple and practical to implement.

Conclusion
An emerging evidence base indicates that different approaches to cognitive training and cognitive stimulation in people with AD confer modest but significant benefits. However, the benefits of in-person cognitive training are modest and mainly limited to the cognitive domains on which the intervention is focused. The best evidence base is CST, although this approach is labour-intensive, and requires further evaluation of cost-effectiveness. There is currently no evidence that brain training games provide any significant benefit to people with AD. Numerous potentially exciting and more innovative approaches to cognitive training have been evaluated in small pilot studies, and may provide the potential for more effective cognitive training interventions in the future.

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References


Résumé : Traitement non pharmacologique de la maladie d’Alzheimer

Objectif : Examiner les principales approches du traitement non pharmacologique des symptômes cognitifs et fonctionnels de la maladie d’Alzheimer (MA).

Méthodes : Nous avons recherché la littérature pertinente la plus récente relative au traitement non pharmacologique de la MA et en avons fait une analyse critique.

Résultats : Des données probantes issues d’un petit nombre d’essais randomisés contrôlés (ERC) bien menés montrent que diverses approches non pharmacologiques, dont l’entraînement cognitif, la réadaptation cognitive, et la thérapie de stimulation cognitive (TSC), procurent des bénéfices modestes mais significatifs dans le traitement des symptômes cognitifs des personnes souffrant de la MA, et qu’il peut y avoir des bénéfices additionnels en les combinant avec un traitement aux inhibiteurs de la cholinestérase. La réadaptation cognitive semble également entraîner des bénéfices fonctionnels dans la MA. Le petit nombre d’ERC portant sur l’entraînement cognitif dans la MA concorde avec les résultats d’essais plus vastes sur l’entraînement cognitif chez les personnes âgées en santé. Toutefois, il n’y a aucune donnée probante convaincante d’un bénéfice quelconque associé aux jeux d’exercice pour le cerveau.

Conclusion : Une nouvelle base de données probantes indique que les différentes approches de l’entraînement cognitif et de la stimulation cognitive chez les personnes souffrant de la MA procurent des bénéfices modestes mais significatifs. Les meilleures données probantes concernent la TSC, bien que cette approche soit exigeante en main-d’œuvre et qu’elle nécessite plus d’évaluation de rentabilité. Aucune donnée probante ne prouve actuellement que les jeux d’exercice pour le cerveau procurent un bénéfice significatif quelconque aux personnes souffrant de la MA.