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One-year repeated cycles of cognitive training (CT) for Alzheimer's disease

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Abstract

Background Recent research suggests that a combination of both pharmacological and psychosocial treatments targeting cognitive functions improves cognition in patients with Alzheimer's disease (AD). The present study evaluated the effectiveness of a 1-year cognitive training (CT) by comparing the cognitive performance of 16 patients with AD treated with CT and cholinesterase inhibitors (ChEIs) (experimental group) with the performance of 16 patients treated with a non-specific cognitive treatment and ChEIs (control group).

Methods This study was a single-blind randomized controlled trial. The patients in the experimental group received pharmacological treatment and repeated cycles of CT for 1 year, whereas the control group received pharmacological treatment and repeated cycles of non-specific cognitive exercises. The patients in the two groups were administered a variety of neuropsychological tests measuring several cognitive functions (i.e. memory, language, reasoning, executive function, working memory and apraxia), activities of daily living, and depression.

Results After 1 year of training, the experimental group scored significantly higher on the Mini Mental State

Examination, the Milan Overall Dementia Assessment battery and in other five neuropsychological tests, compared to the control group.

Conclusions Present results suggest that repeated cycles of CT in patients with AD treated with ChEIs are associated with benefits in several areas of cognitive function.

Keywords Dementia · Cognitive impairment · Neuropsychological assessment · Non-pharmacological interventions

Introduction

Alzheimer's disease (AD) is characterised by the insidious onset of cognitive deficits that progress over the course of several years. The nature of the cognitive impairment and its severity varies greatly throughout the different stages of the disease. Impairments in functional abilities of daily living have a dramatic impact on the quality of life of both the patients and their caregivers (e.g. [1]). Improving patients' cognitive function can delay hospitalisation and, therefore, reduce the costs for the national health care and improve patients' and carers' well-being [2].

Studies evaluating the effects of pharmacological treatment for AD have produced conflicting results. For example, although some authors (e.g. [3]) conclude that cholinesterase inhibitors (ChEIs) significantly improve clinical outcomes such as cognition, global assessment and behaviour, other studies (e.g. [4]) find that results can be limited due to methodological problems. Evidence indicates that pharmacological treatments for AD can benefit patients but important side effects have led to the development of non-pharmacological interventions and their widespread use.

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Among these, cognitive training (CT) programmes for patients with mild to moderate AD have received increasing attention. CT can be either an individual or group intervention, in which people with AD perform tasks involving a variety of functions such as memory, attention, language, logical reasoning and activities of daily living [5]. A recent systematic review, however, has found no support for the use of CT for people with early stage AD [6], mainly due to small sample sizes (e.g., [7]) and low frequency and duration of CT interventions, for example, weekly 1 hour sessions for 5 weeks [8, 9]. These findings appear to contrast results of studies reporting that people in the early stages of dementia can (a) learn or re-learn important and personally relevant information; (b) maintain this learning over time; and (c) have the ability to apply this learning to an everyday context (e.g. [10–13]).

Although previous studies [5] have recently reported lack of support for the use of CT for people with early stage AD, they have underlined that this intervention may produce modest benefits in certain domains of cognitive functioning. In line with this, Mondini and colleagues [14] have reported a pilot study evaluating the efficacy of a month-long CT programme (2 h every day), comparing the cognitive performance of three patients with AD undergoing pharmacological therapy and CT and three patients with AD receiving only pharmacological treatment. The patients who had received CT showed improvement and obtained significantly better scores on a variety of neuropsychological tests. However, follow-up assessments 3 months after the end of treatment showed that cognitive performance had reverted to baseline level. It appears, therefore, that the benefits provided by one cycle of CT cannot be maintained over time, indicating that patients with a neurodegenerative disease (such as AD) may require continuous cognitive stimulation without interruptions in treatment to gain cognitive function benefits.

Thus, in the present study, we tested the hypothesis that additional and repeated treatments of CT would limit progressive cognitive decline in patients with AD and lead to improved cognition. We specifically examined the effectiveness of repeated cycles of CT by comparing the performance of patients with mild to moderate AD before and after a 1-year CT treatment (experimental group). We evaluated cognition on the MMSE (Italian version, [15]) and on a neuropsychological battery, the Milan Overall Dementia Assessment (MODA, [16]), widely used in Italy to measure general cognition. Additional neuropsychological tests included measures of working memory, abstraction, executive function and language. The hypothesis was that well-structured activities of CT repeated over a 1-year period would maintain cognitive performance in patients with AD.

Materials and methods

Participants

Thirty-two people with mild to moderate AD were recruited from the Alzheimer's Evaluation Unit of Cremona (Northern Italy). The patients underwent neurological examination, which included either magnetic resonance or computed tomography brain scans, and further laboratory tests to rule out other causes of decline. All participants underwent complete neuropsychological evaluations and met diagnostic criteria of DSM-IV (Diagnostic and Statistical Manual of Mental Disorders; [17]) and NINCDS-ADRDA (National Institute of Neurological Disorders and Stroke-Alzheimer's disease and Related Disorders Association; [18, 19]).

All patients had been taking ChEIs (donepezil, 5 or 10 mg/day) for almost 1 month prior to being recruited for our research, and over the 1-year period none of them changed their dosage and none of them dropped out. Patients were assigned to two groups using a computer randomization programme: 16 formed the experimental group and 16 the control group. Stratification according to age and education was not used when selecting participants that were randomly sampled from a pool of patients with MMSE ranging 18–24/30.

Programmes

The experimental (i.e. combined treatment) group participated in five 1 month cycles of CT (one cycle: 20 sessions, 2 h per day, 5 days a week) with a break of 4 weeks in between each cycle. The control group received non-specific cognitive activity at a Day Centre. All patients underwent two identical neuropsychological evaluations, at the beginning (T0) and after 1 year at the end of the study (T1). The experimental group participated in daily multiple-session training, in small 4-patient groups which were formed according to age and severity of dementia. An expert neuropsychologist administered the CT to each group daily for a total of 2 h, either in the morning or the afternoon session.

The structure of the CT programme and the types of activities involved were very similar to the CT described in the literature and has been reported in detail elsewhere (e.g. [6, 7]). All paper-and-pencil tasks were taken from Bergamaschi et al. [20]. The specific exercises were designed to stimulate spatial orientation, memory, attention, perception and visual analysis, as well as recognition of emotional expressions. Examples of CT exercises are given below:

In the *time orientation* exercises, patients performed recognition and naming tasks of images of clothing, and tasks requiring associating clothing with images of the four

seasons. In tasks of *spatial orientation*, patients were asked to imagine that they were going into different rooms of a house drawn on a plan and were required to indicate the direction of their moves (for example, forwards, right or left). In the *logical reasoning* exercises, patients were asked either to complete puzzles or to rearrange sentences in a logical sequence (e.g. *I went to the supermarket, I bought vegetables, I cooked the soup, I ate it, I washed the dishes*). Throughout the training, the difficulty of the CT exercises increased gradually.

The control group participated in daily multiple sessions of non-specific cognitive activities at a Day Centre. Small groups (four patients in each control group) were formed according to age and severity of dementia. The main aim of this programme was to involve the patients in recreational entertaining activities like reading the newspaper, playing group games, and listening to music.

Neuropsychological assessment

To assess patients' neuropsychological abilities, the following tests were administered:

- The MMSE (Italian version [15]), a very short test producing a “global” score of cognitive impairment by assessing different areas of cognitive function.
- The MODA [16], an extensive battery widely used in Italy as a cognitive deterioration screening test. Three sections compose the battery: (a) “Orientations” including time, spatial, personal and family orientation; (b) “Personal autonomy in daily living”; (c) “Neuropsychological Tests”, which includes learning reversal tasks, attention and verbal intelligence tests, immediate story recall, semantic fluency, and visual recognition tests (range of scores 0–100).

Five tests from the Esame Neuropsicologico Breve—ENB-2 (tr. Short Neuropsychological Examination—ENB-2; [21]) were also selected:

- Memory Test with Interference, based on the Brown–Peterson paradigm (range of scores 0–9).
- Story Recall-Immediate, testing the ability to recall a short story composed of 28 elements (range of scores 0–28).
- Overlapping Figure Test, measuring the ability to reorganise and select figures and reorganise complex visual patterns (range of scores 0–50).
- Verbal Fluency Test, which taps cognitive flexibility, organisation and selection of words using a search strategy and inhibiting preceding categories (range of scores 0–34).
- Clock Drawing Test, involving image retrieval, reasoning and praxic abilities (range of scores 0–10).

Depression was assessed through:

- The Cornell Scale for Depression in Dementia (CSDD; [22]), designed to assess depression in older people with dementia. Previous studies have shown the CSDD to have proven reliability and validity in community, hospital and care home settings (scores range from 0 to 38).

Everyday functioning was assessed through:

- Activities of Daily Living (ADL; [23]), checking the presence of activities that are essential for self-care, such as bathing and dressing.
- Instrumental Activities of Daily Living (IADL; [24]), assessing ability in activities such as shopping, cooking, transportation and housekeeping.

All patients were administered the tests at the beginning of the study (T0) and 1 year later (T1). They were individually tested in a 1-hour session with fixed-order tasks by an examiner unaware of which group the patients were in. All tasks were presented using a paper-and-pencil modality and all responses were recorded manually.

Statistical method

All analyses were carried out to investigate differences between the experimental and the control group before and after treatment. A *t* test analysis showed that the two groups did not differ in terms of age [$t(30) = 0.43$, n.s.], years of education [$t(30) = 1.54$, n.s.], and level of cognitive impairment (e.g. MMSE score), [$t(30) = -1.98$, n.s.] (see Table 1). Differences between the two groups before the training (T0) and after the training (T1) were assessed by separate mixed ANOVAs for each test, with the within-variable Time (T0 vs. T1) and the between-variable Group (experimental vs. control) as independent variables. The η_p^2 was employed as a measure of effect size. Post-hoc analyses were carried out by means of pairwise *t* tests by comparing the scores between groups on a given time (e.g. experimental group vs. control group at T0), and by comparing the scores within the same group at different times (e.g. experimental group at T0 vs.

Table 1 Means (M) and standard deviations (SD) for demographic information and differences between groups at T0

	Experimental group (<i>N</i> = 16) Mean (SD)	Control group (<i>N</i> = 16) Mean (SD)	Differences between groups (T0)	
Age	78.19 (5.50)	77.72 (5.06)	$t(30) = 0.43$	n.s.
Education	7.25 (3.24)	5.61 (2.30)	$t(30) = 1.54$	n.s.
MMSE	20.25 (2.95)	21.94 (2.01)	$t(30) = -1.98$	n.s.

experimental group at T1). All p values were adjusted to the false discovery rate (FDR) correction [25, 26]. All statistical analyses were performed on raw scores using R, release 2.15.1 [27]. Only significant results are reported.

Results

The mean and standard deviations of the two groups of patients on the neuropsychological tests at T0 and T1 are reported in Table 2. At T0, the two groups did not differ significantly on any of the tests.

In the ANOVA on the MMSE scores, the Time \times Group interaction was significant [$F(1, 30) = 60.48, p < 0.001, \eta_p^2 = 0.67$]. Post-hoc tests investigating this interaction showed that at T1 the experimental group had significantly higher scores compared to the control group ($p < 0.001$). Moreover, the experimental group showed a significant increase in MMSE scores ($p < 0.001$), whereas the control group showed a significant decline from T0 to T1 ($p < 0.001$).

The ANOVA on the MODA showed a significant Time \times Group interaction [$F(1, 30) = 13.59, p < 0.001, \eta_p^2 = 0.31$]. Post-hoc tests investigating this interaction showed that the experimental group had higher scores than the control group at T1 ($p < 0.05$). This difference was associated with a decline of MODA scores from T0 to T1 in the control group ($p < 0.05$), but not in the experimental group.

The analysis on Memory Test with Interference showed a significant Time \times Group interaction [$F(1, 30) = 8.8, p < 0.01, \eta_p^2 = 0.23$]. Post-hoc results indicated that at T1 the experimental group performed better than the control

group ($p < 0.05$). There were no significant differences between the experimental and the control group between T0 and T1.

In the ANOVA on Story Recall-Immediate no significant effects were observed.

The analysis on Overlapping Figures revealed a significant Time \times Group interaction [$F(1, 30) = 13.08, p < 0.01, \eta_p^2 = 0.30$], with post-hoc analyses indicating that at T1 the experimental group had higher scores than the control group.

An ANOVA on the Verbal Fluency Test showed a significant main effect of Group [$F(1, 30) = 5.98, p < 0.05, \eta_p^2 = 0.17$] and a significant Time \times Group interaction [$F(1, 30) = 14.30, p < 0.001, \eta_p^2 = 0.23$]. Post-hoc tests showed that these effects were related to a difference at T1 between the two groups ($p < 0.01$).

For the Clock Drawing Test a significant main effect of Time [$F(1, 30) = 4.60, p < 0.05, \eta_p^2 = 0.14$] and a significant Time \times Group interaction [$F(1, 30) = 13.94, p < 0.01, \eta_p^2 = 0.14$] were found. Post-hoc comparisons showed that at T1 the experimental group performed better than the control group ($p < 0.01$).

The ANOVAs on ADL showed significant effects of Time [$F(1, 30) = 26.85, p < 0.001, \eta_p^2 = 0.47$] and of Time \times Group interaction [$F(1, 30) = 11.10, p < 0.005, \eta_p^2 = 0.27$]. Post-hoc tests showed that controls experienced a decline in ADL from T0 to T1 ($p < 0.05$).

The ANOVAs on IADL showed significant effects of Time [$F(1, 30) = 17.44, p < 0.001, \eta_p^2 = 0.37$] and a significant Time \times Group interaction [$F(1, 30) = 5.38, p < 0.05, \eta_p^2 = 0.15$]. However, the post-hoc comparisons showed no significant differences between the two groups.

Finally, in the ANOVA on CSDD scores no significant differences were observed.

Table 2 Means (M) and standard deviations (SD) for tests and scale scores for each group at T0 and T1, and p value of differences between group at T0 and T1 (from ANOVA analysis)

	Exp. group ($N = 16$) Mean (SD)	Control group ($N = 16$)	Differences between groups	Exp. group ($N = 16$) Mean (SD)	Control group ($N = 16$)	Differences between groups
	T0	T0		T1	T1	
MMSE	20.25 (2.95)	21.94 (2.01)	n.s.	23 (2)	18.37 (2.96)	$p < 0.001^*$
MODA	74.50 (9.66)	75.44 (8.76)	n.s.	78.31 (9.85)	69.95 (8.75)	$p < 0.05^*$
Memory Int.	1.50 (1.97)	1.61 (1.91)	n.s.	2.44 (2.53)	0.75 (1.39)	$p < 0.05^*$
Story Recall	3 (3.18)	3.44 (2.43)	n.s.	4.12 (3.16)	3.31 (2.68)	n.s.
Verbal Flu	7.01 (1.86)	6.28 (3.25)	n.s.	8.07 (2.31)	4.56 (2.88)	$p < 0.01^*$
Over Fig	13.31 (5.36)	13.29 (5.46)	n.s.	16.37 (6.11)	10.56 (5.44)	$p < 0.01^*$
Clock	3.87 (3.75)	3.55 (2.70)	n.s.	6.34 (2.73)	3.06 (2.84)	$p < 0.01^*$
ADL	5.06 (1.12)	5.18 (1.18)	n.s.	4.75 (1.34)	3.75 (1.75)	$p < 0.05^{*1}$
IADL	3.94 (2.51)	3.94 (2.41)	n.s.	3.56 (2.34)	2.62 (1.76)	n.s.
CSDD	29.37 (4.47)	27.19 (8.28)	n.s.	30.44 (4.87)	26.75 (7.73)	n.s.

*¹ In case of ADL, the direction of difference is that at T1 the control group shows a significant decline compared to the experimental group

Discussion

This single-blind, randomized, controlled study investigated the efficacy of a 1-year repeated-cycle CT programme on several areas of cognitive function, mood, and activities of daily living in people with AD. Patients who participated in the CT intervention showed improvement in several cognitive measures and did not experience any decline on neuropsychological tests or in activities of daily living. On the contrary, patients who participated in non-specific activities at a Day Centre showed decline in both cognitive abilities and activities of daily living. These results have significant implications for research in rehabilitation of AD patients, as they strongly suggest gains in several areas of cognition in a group of patients receiving the CT programme.

Recent studies evaluating the effects of Cognitive Stimulation Therapy (CST) in AD (e.g. [28]) have reported significant benefits in cognition and participant-rated quality of life, when comparing CST to treatment as usual. Clare and colleagues [29] have demonstrated the efficacy of cognitive rehabilitation in early stage AD using an individualized approach, that is, helping people with AD and their families to identify personally relevant goals and implement strategies for addressing them [30]. Although CT has been frequently confused with other therapies [31], there is evidence that it can offer benefits to people with early stage AD [32] producing primarily medium effect sizes for learning, general cognition, depression and self-rated general functioning.

An important and very promising outcome of the present study is the maintenance of abilities in measures of activities of daily living among people with AD following a 1-year intervention of CT, compared to a decline in functional abilities in the control group. However, the benefits of CT did not generalise to mood and affective function as measured by the CSDD scale. This could be attributed to the fact that patients took part in the activities with the other people in their group. Even simple team games may have provided opportunities for social stimulation, whereas the positive influence exerted by socialisation in the group may have improved behavioural disorders [33].

Not all studies evaluating a combination of pharmacological and non-pharmacological treatment for patients with AD showed benefits due to CT. Farina and colleagues [33] compared recreational activities (global treatment: e.g. singing, dancing, party games) with a combination of procedural memory training on activities of daily living (e.g. washing hands, setting and clearing the table, writing and sending a letter) and training of 'residual' cognitive functioning (e.g. exercises of attention, language, visuo-spatial abilities). A tendency to improve in behavioural scales was found, but only in the global treatment condition

did behavioural improvement reach statistical significance, even if patients improved also in everyday functioning and verbal fluency. Patients treated with specific CT techniques showed improved functional competence only in daily living (Nurses' Observation Scale for Geriatric Patients, NOSGER). It should be noted, however, that treatment intensity differs between CT interventions. In previous studies, CT was composed of a total of 15 training sessions in 6 weeks, whereas in our study patients participated for a total of 100 training sessions for 1 year.

An important contribution of the present study is the finding that repeated cycles of CT are associated with beneficial effects in several areas of cognition and in particular in tests of executive function. Our findings are consistent with previous studies showing that CT programmes combined with ChEIs could be regarded as complementary therapies in AD treatment and particularly effective for people with mild to moderate AD by improving and maintaining cognitive function [34]. The present results suggest that CT programmes combined with pharmacological treatments can protect patients from functional deterioration by slowing progressive decline. Future research could be directed towards examining the potential benefits of repeated CT for other outcomes such as caregiver burden, institutionalisation, and cost-effectiveness.

These results suggest that repeated cycles of CT may be a useful therapy for people with mild and moderate AD, although they should be interpreted with caution given the small sample size.

This study has been approved by the Ethics Committee of the Departments of Psychology, University of Padua, Italy, and has been conducted in accordance with the ethical standards of the Declaration of Helsinki.

Conflict of interest None.

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