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Computerized Structured Cognitive Training in Patients Affected by Early-Stage Alzheimer's Disease is Feasible and Effective: A Randomized Controlled Study

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Abstract

Introduction: Alzheimer's disease (AD) presents with significant neuropsychological deficits. Cognitive training in AD has recently started to demonstrate its efficacy. In this study, we implemented computerized cognitive training of a large group of early-stage AD patients, to identify its effects at a neuropsychological level and to investigate whether they were stable after 6 months.

Method: Overall, 80 AD patients were randomized in two groups. Patients in the experimental group used a structured rehabilitative software three times a week for 12 consecutive weeks aimed at training memory, attention, executive function and language skills, whereas patients in the control group underwent a control intervention.

Results: A Repeated Measures General Linear Model considering groups' performance at the three assessment points (before training, after training and at the 6-month follow-up) showed a significant interaction effect for: digit span forward ($F_{(2,74)} = 2.785$, $p = 0.03$) and backward ($F_{(2,74)} = 3.183$, $p = 0.02$), two-syllable words test ($F_{(2,74)} = 3.491$, $p = 0.004$), Rivermead Behavioural Memory Test immediate ($F_{(2,74)} = 2.877$, $p = 0.03$) and delayed ($F_{(2,74)} = 3.783$, $p = 0.003$), Token test ($F_{(2,74)} = 4.783$, $p = 0.001$), and Brixton test ($F_{(2,74)} = 8.783$, $p < 0.001$). For all of them, experimental group performed better than controls.

Conclusions: Patients in the experimental group showed a significant improvement in various neuropsychological domains, and their achievements were stable after 6 months. This study suggests an useful computerized training in AD, and should prompt further investigations about the generalizability of patients' acquired skills to more ecologically oriented tasks.

Keywords: Alzheimer's disease; Cognitive training; Memory; Neuropsychology; Rehabilitation

Introduction

Several neurological and neuropsychiatric conditions, such as Parkinson's disease, multiple sclerosis and dementias are typically characterized by important deficits that reduce significantly patients' skills and their overall quality of life (Cavallo, Enrici & Adenzato, 2011; Enrici et al., 2015; Ostacoli et al., 2013). Amongst them, Alzheimer's disease (AD) is the most common form of dementia, and it accounts for an estimated 60%–80% of all cases. AD affects the patient, their family and their wider social network through its deep effects at cognitive, behavioural and social levels (Cheston & Bender, 1999; Dourado et al., 2014). Clinical manifestation of AD typically includes significant neuropsychological deficits such as memory problems, frequently associated to other cognitive deficits such as aphasia, apraxia and/or agnosia, that significantly interfere with everyday life (McKhann et al., 1984, 2011).

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In recent years, cognitive training in AD has started to show its potentialities. The rationale for cognitive training in AD is based on evidence regarding the neuropsychology and neuroanatomy of memory impairments in AD and the capacity of the patients with AD to acquire new knowledge (Cavallo et al., 2013a; Cavallo, Zanalda, Johnston, Bonansea & Angilletta, 2016; Clare, Wilson, Carter, Hodges & Adams, 2001). It is relevant to note that converging evidence clearly indicates that some cognitive subsystems (e.g., procedural memory) remain relatively intact, whilst others (e.g., episodic memory) are dramatically impaired (Pause et al., 2013; Salmon & Bondi, 2009). These dissociations are indeed supported also by a developing understanding of the role played by different brain areas in the cognitive processes of memory encoding, storing and retrieval (Glisky, 1998; Graham & Hodges, 1997; Nadel & Moscovitch, 1997).

Very recently, computerized cognitive training has started to show interesting evidence in this clinical domain. In one of the first studies on this topic, Gaitán and colleagues (2013) investigated the effect of a computer-based cognitive training (CBCT) program, adjunctive to traditional cognitive training (TCT) based on pen-and-paper exercises. Patients in the combined treatment group (CBCT + TCT) showed less anxiety symptoms and less disadvantageous choices in decision making than the TCT group at 12 months. The authors noted that no significant improvement or worsening was observed in memory or emotional tests, whereas positive effect sizes favoring the CBCT + TCT group were observed in all variables.

In another study, Lee, Yip, Yu and Man (2013) investigated the effects of a computerized errorless learning-based memory training program (CELP) for persons with early AD, and compared its outcomes with those of a therapist-led errorless learning program (TELP) group and a waiting-list control group. Small groups were assigned to the CELP ($n = 6$), TELP ($n = 6$) and waiting-list control ($n = 7$) groups. Evaluation of patients' status before and after testing, and at 3-month follow-up was achieved using various neuropsychological and functional tests, such as the Chinese Mini-Mental State Examination, Chinese Dementia Rating Scale, Hong Kong List Learning Test, and the Brief Assessment of Prospective Memory-Short Form as cognitive measures, and the Modified Barthel Index, Hong Kong Lawton Instrumental Activities of Daily Living Scale and Geriatric Depression Scale-Short Form as functional measures. Interestingly, the authors noted that positive treatment effects on cognition were found in both errorless learning-based memory groups (i.e., computer-assisted and therapist-led) and at a functional level in patients receiving TELP. However, the small group size was a significant limit of this study.

More recently, a systematic review of the literature (Coyle, Traynor & Solowij, 2015) focused on computerized cognitive training (CCT) and virtual reality cognitive training (VRCT) for individuals at high risk of cognitive decline. The studies evaluated ($N = 16$) were categorized as CCT ($N = 10$), VRCT ($N = 3$) and multimodal interventions ($N = 3$). The authors concluded that CCT and VRCT were moderately effective in long-term improvement of cognition. As general limitations of the studies included in this review, was underlined the need to improve study design by including larger samples, to apply longitudinal designs, and to assess the wider effect of cognitive training on cognitive decline.

To try and overcome these limitations, in the present study we recruited a large group of early-stage AD patients ($N = 80$), performed a detailed neuropsychological assessment, and then randomly assigned them to two groups: an experimental group ($N = 40$), undergoing a computerized structured cognitive training using the rehabilitation software Brainer1, which had been fruitfully used in an our previous study (Cavallo et al., 2013b) and included memory, attention, executive function, and language tasks of increasing difficulty and tailored on patient's performance; and a control group ($N = 40$), undergoing a computerized general cognitive intervention encompassing different exercises (such as reading online newspaper articles and discussing them with the neuropsychologists, navigating web-sites of interest, and so on). In both groups the medium was the same (computer) to allow a strict comparability of interventions; however, in one case, the training was structured and oriented towards rehabilitation purposes (experimental group), whereas in the other the intervention was non-specific and unstructured (control group). Our 2-fold aim was to identify the effects of the computerized structured cognitive training in the experimental group as compared to controls at a neuropsychological level, and to investigate whether its effects were stable after 6 months.

Methods

Participants

The present study involved 80 patients with early-stage AD They were consecutively recruited over three years (from January 2012 until October 2014) in the Assisted Health Residence "Ville Roddolo" (Moncalieri, Italy). Exclusion criteria were the additional presence of other neurological and/or psychiatric disorders such as traumatic brain injury, stroke or psychosis; a positive history of alcohol or drug abuse; the presence of any significant general health co-morbidities that could influence patients' cognitive profile (e.g., diabetes or hypertension); and the presence of significant sensorial impairments and/or extremely severe communication problems that could seriously compromise both the administration of cognitive tests and

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the interpretation of the relative results, and the implementation of the computerized cognitive training. All patients were referred for progressing memory problems, which often resulted in embarrassing (e.g., they tended to forget names of members of the family, or very basic information about their recent past) or dangerous (e.g., they forgot to shut off the gas a few times after cooking, and they tended to forget where the car had been parked) behaviours. Before the beginning of the present study, a comprehensive clinical assessment, including neurological examination, neuropsychological assessment and consecutive brain MRI scans, was arranged by Consultant Neurologists, who made a diagnosis of early-stage probable AD, according to standard NINCDS-ADRDA diagnostic criteria (McKhann et al., 1984, 2011) and after the exclusion of possible neuropsychiatric confounders. After the diagnosis and prior to the beginning of the present study, most of them commenced pharmacotherapy with acetylcholinesterase inhibitors, if tolerated. Patients were then randomized in two separate groups (experimental and control groups) by means of a random number generator with mixed block sizes (the block size could be two, four or eight). There was no significant differences in usage, as well as type and dosage of inhibitors between the two groups.

The study was granted approval by the local Research Ethics Committee. Informed written consent was obtained from all patients and from their caregivers.

Neuropsychological Assessment

All participants underwent detailed neuropsychological assessments by experienced neuropsychologists before training, after training and after 6 months, in order to obtain detailed information about their performance across a wide range of cognitive domains. Neuropsychologists were blind to the purposes of the study, and to the group each patient belonged to. More precisely, the Mini-Mental State Examination (MMSE, Folstein, Folstein & McHugh, 1975) and the Short Intelligence Test (Test di Intelligenza Breve, T.I.B., Colombo, Sartori & Brivio, 2002) were administered, as screening measures for cognitive impairment and pre-morbid intelligence, respectively. Memory was assessed by administering digit span forwards and backwards (Wechsler, 1987), the two-syllable words repetition test (Spinnler & Tognoni, 1987) and the Rivermead Behavioural Memory Test (RBMT, Wilson, Cockburn & Baddeley, 1985). Semantic knowledge was assessed by the Graded Naming test (McKenna & Warrington, 1983). Language was assessed by the Token test (De Renzi & Vignolo, 1962). Visuospatial abilities were assessed using three subtests of the Visual Object and Space Perception Battery (VOSP) (Warrington & James, 1991): object decision, position discrimination, and number location. Executive tasks included both timed and untimed tests. Timed tests encompassed letter (F, A, S) and category (animals) spoken verbal fluency tasks (Novelli et al., 1986), as well as the Hayling Sentence Completion test (Burgess & Shallice, 1997). As an untimed executive test, participants were administered the Brixton test (Burgess & Shallice, 1997).

Neuropsychiatric Assessment

Emotional disturbances were investigated by administering the Hospital Anxiety and Depression Scale (HADS, Zigmond & Snaith, 1983), a brief self-assessment scale that provides a valid and reliable measure of severity of anxiety and depression. As for neuropsychological measures, also the HADS was administered three times to each patient: before training, after training and after 6 months.

Computerized Cognitive Training (Experimental Group)

Each patient received an individual computerized cognitive training (three 30-min sessions per week, for 12 consecutive weeks). Each session was performed by the patient together with a neuropsychologist, as we wanted to conduct the training in an interpersonal context instead of delegating completely the training to the patient in isolation. This frequency of sessions had been chosen as previous research demonstrated that the intensity and frequency of training are the crucial issues in planning effective rehabilitation programs: in fact, frequent 30–45 min sessions appear to be necessary to efficiently drive neuroplastic changes (Jensen, Marstrand & Nielsen, 2005). The cognitive intervention used the rehabilitative software Brainer1 (https://www.brainer.it/), that allows the person to go through exercises tapping different cognitive functions and of increasing difficulty as long as the person's performance improves. The software Brainer1 has been specifically designed by an expert panel of Italian neuropsychologists, neurologists and speech therapists for rehabilitation purposes of neurological patients. Thus, it was designed with the goal of developing a training program and a complex intellectual stimulation system targeting patients in need of cognitive rehabilitation, and it has been fruitfully used in our previous study (Cavallo et al., 2013b). Before the beginning of the computerized training, an individual session with each patient was planned, to show them the software and to teach them how to use it. Brainer is composed by a set of more than 100 exercises covering several cognitive

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domains: visual perception, auditory perception, attention, language, reading and writing, calculations, logic and deduction, memory, sensory motor skills. Before the beginning of the study, exercises tapping the cognitive domains typically impaired in early-stage AD (i.e., memory, attention, executive function and language) were selected, and two parallel versions of the training (versions 1 and 2) were created. Half of the patients started the training with version 1; after 6 weeks, version 2 was proposed to patients for the remaining 6 weeks, in order to avoid the repetition of the same pattern of exercises throughout the whole training and minimizing the mere repetition of the same exercises. The remaining patients started with version 2, and switched to version 1 after 6 weeks of training, for the reasons just mentioned. Each session included one exercise per cognitive domain (memory, attention, executive function and language), in random order.

Control Cognitive Intervention (Control Group)

Patients in the control group followed the same frequency of sessions (three 30-min session per week, for 12 weeks) together with a neuropsychologist. During the sessions, a computer connected to the Internet was used and the patient was free to choose to read electronic newspaper articles and discuss them with the neuropsychologist, or to play games and solve puzzles, and/or reach sites and contents of interest for him/her. The idea was to maintain the same setting as for the treatment condition (using a computer in the presence of a neuropsychologist), but without proposing a structured cognitive training specifically designed having rehabilitation purposes in mind.

Statistical Analyses

Descriptive statistical analyses were performed using IBM SPSS Statistics (Statistical Package for the Social Sciences) version 22.0. As the graphical and statistical exploration of the data by means of box plots, histograms, Q–Q plots and normality tests indicated normal distributions, parametric tests were used. Firstly, comparisons of the patients' scores on background neuropsychological and neuropsychiatric measures were performed by means of *t*-tests for independent samples. Then, in order to investigate the effect of training on neuropsychological performance, a Repeated Measures General Linear Model (RM-GLM) was run by considering participants' performance on each test at the three assessment points (i.e., T_0, T_1 and T_2) as the within-subjects variable, and "group" (i.e., patients and controls) as the between-subjects factor. Lastly, single-case analyses via modified *t*-test (Crawford & Garthwaite, 2002) was conducted too, to investigate computerized training effects also at individual patient's level. A $p < 0.05$ was considered statistically significant throughout the analyses.

Results

Baseline Neuropsychological Assessment

The two groups of participants underwent a detailed neuropsychological assessment before the beginning of the cognitive training. Patients' scores in the two groups were similar. The only differences were detected on the following tests: digit span-backward ($t_{(78)} = 2.185$, $p = 0.03$), two-syllable words repetition test ($t_{(78)} = 2.077$, $p = 0.02$), and RBMT-story delayed ($t_{(78)} = 3.155$, $p = 0.01$), with patients in the experimental group showing a worse performance than controls. Regarding all of the other demographic data and neuropsychological measures administered, patients did not differ significantly between groups. Participants' scores and the statistical comparisons of interest are shown in Table 1.

Baseline Neuropsychiatric Assessment

The comparison of patients' scores on the HADS did not show any statistically significant difference (anxiety*:* patients' score = 8.60 ± 2.77, controls' score = 7.97 ± 1.29; $t_{(78)} = 0.847$, NS; depression*:* patients' score = 6.87 ± 2.41, controls' score = 6.05 ± 2.31; $t_{(78)} = 1.119$, NS).

Post-Treatment Neuropsychological Assessment

The two groups of participants underwent a detailed neuropsychological assessment after the cognitive interventions. Patients' scores in the two groups differed in a number of tests, with patients in the experimental group getting higher scores, as compared to the control group. Significant differences were detected on the following tests: digit span-forward

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Table 1. Demographic data and participants' baseline performance on background neuropsychological measures (means and standard deviations are shown)

	Experimental group ($N = 40$)	Control group ($N = 40$)	t-Test
Age in years	76.50 (2.88)	76.33 (3.83)	1.096 NS
Gender (M:F)	13:27	16:24	Chi-squared NS
Education—years	8.53 (3.00)	8.12 (2.79)	1.148 NS
Duration of illness—years	2.29 (0.72)	1.95 (1.42)	1.789 NS
Under acetylcholinesterase inhibitors (YES/NO)	36/4	38/2	Chi-squared NS
MMSE	22.65 (1.74)	23.05 (2.44)	1.487 NS
T.I.B. (Pre-morbid IQ)	115.22 (4.01)	116.27 (2.49)	1.693 NS
Digit span (forward)	4.85 (1.60)	5.20 (1.85)	1.532 NS
Digit span (backward)	3.20 (1.26)	4.10 (0.63)	2.185*
Two-syllable words test	4.80 (1.72)	6.00 (2.15)	2.077*
RBMT (standardized profile score)	8.60 (1.12)	8.80 (1.36)	1.146 NS
RBMT (story immediate)	6.72 (1.09)	7.04 (1.66)	1.782 NS
RBMT (story delayed)	5.35 (1.73)	6.52 (1.66)	3.155*
GNT	21.95 (2.57)	22.15 (2.17)	1.289 NS
Token test	30.30 (2.42)	30.69 (2.10)	1.187 NS
VOSP (object decision)	18.20 (0.72)	18.42 (0.81)	1.214 NS
VOSP (position discrimination)	19.22 (0.70)	19.29 (0.72)	1.085 NS
VOSP (number location)	8.87 (0.69)	9.00 (0.68)	1.329 NS
Verbal fluency (letters)	35.88 (2.66)	36.52 (2.45)	1.429 NS
Verbal fluency (category)	17.10 (1.88)	17.27 (1.76)	1.108 NS
Hayling test (overall score)	5.82 (1.24)	5.95 (1.15)	1.289 NS
Brixton test	4.95 (0.85)	5.22 (1.32)	1.307 NS

*$p < 0.05$; IQ = Intelligence Quotient; GNT = Graded Naming Test; MMSE = Mini-Mental State Examination; NS = not significant; RBMT = Rivermead Behavioural Memory Test; SD = standard deviation; T.I.B. = Test di Intelligenza Breve (short intelligence test); VOSP = Visual Object and Space Perception battery.

($t_{(78)} = 2.493$, $p = 0.02$), digit span-backward ($t_{(78)} = 3.485$, $p = 0.01$), two-syllable words repetition test ($t_{(78)} = 2.278$, $p = 0.03$), RBMT-story immediate ($t_{(78)} = 3.748$, $p = 0.004$), RBMT-story delayed ($t_{(78)} = 3.452$, $p = 0.001$), Token test ($t_{(78)} = 3.155$, $p = 0.01$), and Brixton test ($t_{(78)} = 3.555$, $p = 0.001$).

To rule out the unlikely possibility that patients in the experimental group starting with version 1 of the training and then switching to version 2 differed from patients starting with version 2 and then switching to version 1, we compared statistically the two sub-groups of patients, as expected, they did not differ significantly in any way (data not shown).

Post-Treatment Neuropsychiatric Assessment

The comparison of patients' scores on the HADS did not show any statistically significant difference (anxiety: patients' score = 7.65 ± 2.41, controls' score = 7.57 ± 1.33; $t_{(78)} = 0.589$, NS; depression: patients' score = 6.42 ± 2.21, controls' score = 6.35 ± 2.21; $t_{(78)} = 1.019$, NS).

As a typical issue in follow-up studies, not all participants were available at the scheduled follow-up. However, it is relevant to note that only two AD patients per group were missing at the 6-month assessment, as their families preferred to move them from our Health Assisted Residence to another one closer to their places. As a result, 38 out of 40 patients for both group were available at follow-up, allowing us to assess the vast majority of treated patients also 6 months from the end of the experimental and control interventions.

6-Month Follow-up Neuropsychological Assessment

The two groups of participants underwent for the last time the detailed neuropsychological assessment 6 months after the end of the cognitive interventions. During this time frame, all of the patients were involved in the daily standard activities of the Health Assisted Residence, with no specific focus on cognitive stimulation. Interestingly, the pattern of significant differences remained the same already detected at the post-treatment assessment, with patients in the experimental group showing a better performance than controls on the following tests: digit span-forward, digit span-backward, two-syllable words repetition test, RBMT-story immediate, RBMT-story delayed, Token test and Brixton test. Participants' scores and the statistical comparisons of interest at follow-up are shown in Table 2.

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Table 2. Participants' scores on background neuropsychological measures at the 6-month follow-up (means and standard deviations are shown)

	Experimental group ($N = 38$)	Control group ($N = 38$)	*t*-Test
MMSE	22.32 (0.97)	22.64 (0.96)	0.987 NS
Digit span (forward)	5.95 (1.80)	5.18 (1.82)	2.493*
Digit span (backward)	5.78 (1.44)	4.02 (0.88)	3.485*
Two-syllable words test	6.14 (1.42)	5.05 (2.15)	2.278*
RBMT (standardized profile score)	8.60 (1.12)	8.80 (1.36)	1.087 NS
RBMT (story immediate)	8.72 (1.24)	6.00 (1.41)	3.748*
RBMT (story delayed)	6.35 (1.73)	4.52 (1.44)	3.452*
GNT	22.04 (2.53)	22.18 (2.27)	0.645 NS
Token test	32.30 (2.42)	27.69 (2.10)	3.155*
VOSP (object decision)	18.25 (0.93)	18.45 (0.81)	0.745 NS
VOSP (position discrimination)	19.15 (0.74)	19.22 (0.70)	0.872 NS
VOSP (number location)	8.85 (0.58)	9.02 (0.62)	1.004 NS
Verbal fluency (letters)	36.57 (2.46)	37.35 (2.26)	1.245 NS
Verbal fluency (category)	16.27 (1.71)	15.95 (1.60)	1.374 NS
Hayling test (overall score)	5.42 (0.98)	5.37 (0.86)	0.874 NS
Brixton test	5.95 (1.34)	3.82 (1.65)	3.555*

*$p < 0.05$; IQ = Intelligence Quotient; GNT = Graded Naming Test; MMSE = Mini-Mental State Examination; NS = not significant; RBMT = Rivermead Behavioural Memory Test; SD = standard deviation; T.I.B. = Test di Intelligenza Breve (short intelligence test); VOSP = Visual Object and Space Perception battery.

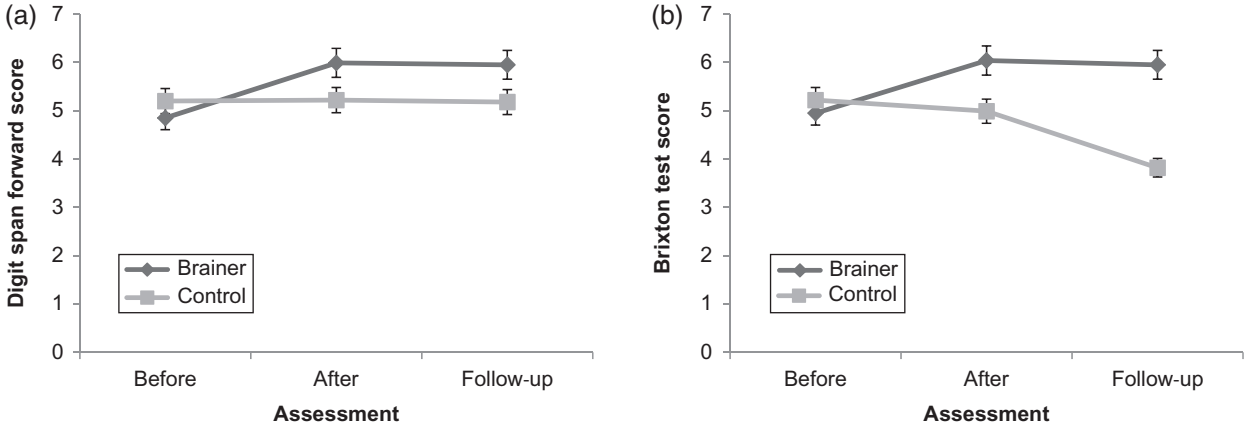

Fig. 1. Groups' performance at the three assessment points (before, after, follow-up) on the digit span forward (a) and Brixton (b) tests.

6-Month Follow-up Neuropsychiatric Assessment

The comparison of patients' scores on the HADS did not show any statistically significant difference on anxiety and depression.

Lastly, to investigate the possible longitudinal effect of treatment on neuropsychological measures, a Repeated Measures General Linear Model (RM-GLM) was run by considering participants' performance on each test at the three assessment points (before training, after training and at the 6-month follow-up) as the within-subjects variable, and "group" (i.e., experimental versus control groups) as the between-subjects factor. *p*-Values were adjusted for multiple comparisons using the false-discovery rate approach. There was a statistically significant interaction between time and group on patients' performance on the following tests: digit span forward ($F_{(2,74)} = 2.785$, $p = 0.03$, $d = 0.42$), digit span backward ($F_{(2,74)} = 3.183$, $p = 0.02$, $d = 0.49$), two-syllable words test ($F_{(2,74)} = 3.491$, $p = 0.004$, $d = 0.53$), RBMT story immediate ($F_{(2,74)} = 2.877$, $p = 0.03$, $d = 0.44$), RBMT story delayed ($F_{(2,74)} = 3.783$, $p = 0.003$, $d = 0.51$), Token test ($F_{(2,74)} = 4.783$, $p = 0.001$, $d = 0.60$) and Brixton test ($F_{(2,74)} = 8.783$, $p < 0.001$, $d = 0.63$). Simple main effects analysis showed that patients' cognitive performance in the experimental group were more influenced positively by the training than patients in the control group both at the post-treatment assessment and at the 6-month follow-up. In all these measures, patients' performance was better than controls' performances. Figure 1 reports groups' performances on two of these tasks (e.g., digit span forward and Brixton tests).

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In order to investigate neuropsychological individual changes in the treatment group versus controls' scores, single-case analyses were performed using the procedure formalized by Crawford and Garthwaite (2002) to deal with single cases in cognitive neuropsychology appropriately. More precisely, modified *t*-tests were used to determine whether each individual's performance at follow-up was significantly better than the corresponding control group's scores for the seven cognitive tasks that were significantly influenced by the computerized training. This is considered a very conservative approach, and aims at making it more difficult (and then more reliable) to reject the null hypothesis of absence of differences between a single patient and a control group. Interestingly, the vast majority of patients belonging to the experimental group got better test scores at follow-up, as compared to control group. More precisely, for each neuropsychological tests of interest the number of patients showing a better performance at follow-up was: for digit span forward, 30/38; for digit span backward, 32/38; for two-syllable words test, 32/38; for RBMT story immediate, 30/38; for RBMT story delayed, 32/38; for Token test, 33/38; and for Brixton test, 35/38.

Discussion

During the last decades, cognitive training in AD has started to show its beneficial effects. Computerized cognitive training has started to show interesting evidence, even if at this point in time evidence in favour of it still remains weak and in need of more robust studies. The two important issues at hand pertain to the possibility for patients to acquire new procedural skills, and to maintain them once the training comes to an end.

In the present randomized, clinical study we recruited a large group of early-stage AD patients ($N = 80$), performed a detailed neuropsychological assessment, and then randomly assigned them to two groups: an experimental group ($N = 40$) undergoing a computerized structured cognitive intervention tailored on the most vulnerable cognitive functions to early-stage AD, and a control group ($N = 40$) undergoing a computerized general cognitive intervention not specifically tailored on patients' cognitive needs. In order to maintain the two interventions as comparable as possible, it is important to note that in both of them the medium was the same (computer). However, in one case, the training was structured and oriented towards rehabilitation purposes (experimental group), whereas in the other the intervention was non-specific and unstructured (control group). Our 2-fold aim was to identify the effects of the computerized structured cognitive training in the experimental group as compared to controls, and to investigate whether its effects were stable after 6 months. After randomization, the two groups of patients were well-matched in terms of age, gender, pre-morbid IQ, and level of formal education. In addition, the comparison of patients' performance on the neuropsychological measures administered showed the presence of significant differences between the two groups only on few neuropsychological measures (with patients in the experimental group getting lower scores than controls), corroborating also from a neuropsychological standpoint that patients were at the early stages of their condition and that there were no substantive differences between groups. Thus, we were confident that the patients were not too cognitively compromised to be involved in this type of cognitive training, and that there was not a significant difference in group composition. In order to take into account the possibility that cognitive performance was influenced by neuropsychiatric factors, we investigated the presence of possible differences between groups in terms of levels of anxiety and depressive symptoms at each assessment point, as measured by the HADS. Of note, levels of anxiety and depression did not differ significantly between the two groups either at the beginning of the training or at the follow-up, allowing us to exclude significant differences between the two groups in terms of mood state.

The strength of the software Brainer1 is that it allows one to select a battery of exercises that tap specific cognitive functions. Before the beginning of the study, various exercises of increasing difficulty and tapping the cognitive domains typically impaired in early-stage AD (i.e., memory, attention, executive function and language) were selected, and two parallel versions of training were defined. In doing so, we were able to schedule a structured cognitive training specifically oriented towards patients' needs, and we could administer different sets of exercise during the course of the 12-week cognitive intervention. Conversely, patients in the control group underwent a computerized general cognitive intervention encompassing different exercises such as reading online newspaper articles and discussing them with the neuropsychologist, navigating web-sites of interest, watching videos and listening to music: these cognitive activities were comparable in terms of time and frequency to the structured intervention, but were not driven and tailored on patients' neuropsychological profile.

After the cognitive interventions, we were able to see a significant effect of the structured computerized cognitive intervention on different neuropsychological measures. More precisely, digit span-forward, digit span-backward, two-syllable words repetition test, RBMT-story immediate, RBMT-story delayed, Token test and Brixton test were performed significantly better by patients in the experimental group than controls. Interestingly, this pattern of results was maintained at the 6-month follow-up. To corroborate this evidence, we showed a significant longitudinal effect in patients' performance, compared to controls, providing strong evidence of the stability over a long period of time (at least 6 months) of the results achieved

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immediately after the training. For most of these tests (i.e., two-syllable words repetition test, RBMT-story immediate, RBMT-story delayed, Token test, and Brixton test) controls' performance over time decreased, whereas trained patients' performance improved after the training: this is both scientifically and clinically very important, as these results suggest that the structured cognitive training realized would not only be useful in contrasting the decay in these neuropsychological abilities due to the clinical condition, but it would also allow patients to improve their performance on some neuropsychological tests, at least within the time interval considered here. However, further studies should address specifically this important issue. In addition, using single-case analysis we were able to demonstrate that these significant differences between trained patients and controls depended on the vast majority of them, and not just on the mere presence of few patients influencing groups' comparison.

Previous studies have already highlighted that specific neuropsychological domains, such as episodic memory, executive function, language and attention, are particularly vulnerable to AD (Bondi et al., 2008), and that some of these domains can be positively affected by cognitive intervention (Cavallo et al., 2013a; Huntley, Gould, Liu, Smith & Howard, 2015), even if to date evidence in this direction is still growing. To the best of our knowledge, our study is one of the first showing at a large scale a clear and stable pattern of improved neuropsychological performances in AD patients due to the cognitive training implemented. We were able to demonstrate stable training effects not only at a group level, but at an individual level too. Our results suggest that an intense and structured cognitive training tailored on patients' cognitive needs can lead to a significant improvement of performance in at least some neuropsychological tests, and above all, that these achievements can be maintained for at least 6 months after the end of the training.

There are several strengths of this study. Firstly, a very detailed neuropsychological assessment was conducted at the beginning of the study, at the end of the cognitive interventions, and at the 6-month follow-up. Although various studies included shorter neuropsychological batteries, we were confident that our assessment was able to show strengths and weaknesses of patients' neuropsychological profile. Secondly, we were able to recruit and treat a large number of patients ($N = 80$), overcoming a frequent limitation of previous studies that actually involved smaller samples of participants. Lastly, the follow-up allowed us to investigate the stability of the results achieved during the training after 6 months: the vast majority of participants were available at follow-up (76/80, i.e., 95%), and we were happy to see that patients belonging to the experimental group were able to maintain an improved performance on some neuropsychological tests after such a long period of time.

This study also has some limitations. Firstly, we were able to demonstrate that patients' performance on neuropsychological tests improved and was maintained over time, but we did not investigate a possible improvement in patients' everyday life skills. In addition, it would have been interesting to know whether these acquired skills could be maintained over a longer period of time (e.g., 1 or 2 years).

In conclusion, in the present study we were able to provide to patients a structured cognitive training that lead to a stable improvement of performance on memory, language and executive function tests. These findings should prompt further investigations in order to identify the degree of learning that patients affected by early-stage AD can achieve, and the degree of generalizability of their newly acquired skills to everyday life tasks.

Conflict of Interest

None declared.

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