RESEARCH ARTICLE

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Protecting cognition from aging and Alzheimer's disease: a computerized cognitive training combined with reminiscence therapy

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Objective: The aim of this paper was to assess the efficacy of process-based cognitive training (pb-CT) combined with reminiscence therapy (RT) in patients with mild Alzheimer's disease (mAD) and mild cognitive impairment (MCI) and in healthy elderly (HE) subjects.

Methods: This multicenter, randomized, controlled trial involved 348 participants with mAD, MCI, and HE from four European countries. Participants were randomly assigned to two arms of a crossover design: those in arm A underwent 3 months of computerized pb-CT for memory and executive functions combined with RT and 3 months of rest; those in arm B underwent the reverse. The primary outcome was the effect of the training on memory and executive functions performance. The secondary outcome was the effect of the training on functional abilities in mAD assessed with the instrumental activities of daily living.

Results: We found a significant effect of the training for memory in all three groups on delayed recall of the Rey Auditory Verbal Learning Test and for executive functions in HE on the phonological fluency test. MCI and HE participants maintained these effects at follow-up. MCI and mAD participants also showed a significant effect of the training on the Mini-mental state examination scale. Participants with mAD showed more stable instrumental activities of daily living during the training versus the rest period.

Conclusions: Our results corroborate the positive effect of pb-CT and its maintenance primarily on memory in HE and MCI participants that did not seem to be potentiated by RT. Moreover, our results are very promising for the mAD participants. Copyright © 2015 John Wiley & Sons, Ltd.

Key words: cognitive training; reminiscence therapy; computerized training; Alzheimer's disease; mild cognitive impairment; aging
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Introduction

Cognitive decay is associated with physiological aging (Hedden and Gabrieli, 2004) and dementia syndromes, particularly Alzheimer's disease (AD). The late-life changes characterizing physiological aging occur particularly in the frontostriatal system connected with the medial temporal regions (Hedden and Gabrieli, 2004; Salthouse, 2009), thus involving memory and executive functions (EFs). Mild cognitive impairment (MCI) (Petersen *et al.*, 1999; Petersen, 2004) is a condition in which a cognitive disorder is objectively documented in

the absence of dementia. Particularly, amnestic multi-domain MCI is a transitional stage between physiological aging and AD in more than 50% of cases within 2 years (Gainotti *et al.*, 2014). Indeed, the early stages of AD are characterized by a significant episodic memory deficit often associated with EF deficits (Perry and Hodges, 1999; Baddeley *et al.*, 2001). Therefore, memory and EFs seem to be an eligible target to be treated.

Because pharmacological interventions showed modest effects (Massoud and Léger, 2011), non-pharmacological approaches received increased attention as a preventive or enhancing treatment (Gates *et al.*, 2011; Bahar-Fuchs *et al.*, 2013; Lampit *et al.*, 2014a). These involve different approaches (Lustig *et al.*, 2009). General cognitive stimulation or individualized rehabilitation protocols (Wilson, 2002) have shown widespread benefits but often small transfer effects (Lustig *et al.*, 2009). Alternatively, cognitive training (CT) consists of repeated practice on standardized tasks relying on specific cognitive domains (Gates and Valenzuela, 2010). This can be distinguished in learning and practicing memory strategies, that is, strategy-based CT (sb-CT), and repetitive cognitive exercises without explicit strategies, that is, process-based CT (pb-CT) (Lustig *et al.*, 2009; Gates *et al.*, 2011). The sb-CT showed large benefits but limited transfer effects, whereas the pb-CT seems to obtain larger transfer effects (Lustig *et al.*, 2009). At present, about 30 reviews and meta-analyses have evaluated the efficacy of CT in the healthy elderly (HE; Papp *et al.*, 2009; Valenzuela and Sachdev, 2009; Gates and Valenzuela, 2010; Martin *et al.*, 2011; Tardif and Simard, 2011; Kueider *et al.*, 2012; Reijnders *et al.*, 2013; Kelly *et al.*, 2014; Lampit *et al.*, 2014a), MCI (Faucounau *et al.*, 2010; Jean *et al.*, 2010; Gates *et al.*, 2011; Li *et al.*, 2011; Martin *et al.*, 2011; Huckans *et al.*, 2013; Reijnders *et al.*, 2013; Coyle *et al.*, 2015), and AD (De Vreese *et al.*, 2001; Clare *et al.*, 2003; Sitzer *et al.*, 2006; Buschert *et al.*, 2010; Olazarán *et al.*, 2010; Yamaguchi *et al.*, 2010; Ballard *et al.*, 2011; Spector *et al.*, 2012; Woods *et al.*, 2012; Bahar-Fuchs *et al.*, 2013; Herholz *et al.*, 2013). The discrepancies that emerged in the conclusions were due to the methodological heterogeneity in the studies and, notably, the different intervention protocols. Selecting pb-CT trials for memory and EFs, we found an average medium positive effect for memory in HE and MCI and, regarding EFs, small-medium effects only for HE. AD patients showed no relevant results for memory and EFs and some positive results for global cognition (Davis *et al.*, 2001; Günther *et al.*, 2003; Loewenstein *et al.*, 2004; Cipriani *et al.*, 2006; Galante *et al.*, 2007; Rozzini *et al.*, 2007; Talassi *et al.*, 2007; Peretz *et al.*, 2011; Miller *et al.*, 2013; Shatil, 2013; Lampit *et al.*, 2014b).

Another non-pharmacological approach used in dementia care is the reminiscence therapy (RT) (Woods *et al.*, 2005). This is a non-specific stimulation activity consisting of recalling personal past events supported by memory triggers (e.g., audio-visual materials). Reminiscence is a naturally occurring process initially adopted in psychotherapy as a "life review" (Butler, 1963), stimulating subjects to review their life by reflecting on their own experiences. Moreover, RT is used to train memory. Because the remote memories are better preserved than recent episodic memories in both the older and dementia patients, recall mechanisms of the memory system might be stimulated by using preserved material, thus avoiding frustration. Furthermore, benefits for global cognition have been shown in dementia patients (Woods *et al.*, 2005; Wang, 2007; Okumura *et al.*, 2008) and in the HE (Akhoondzadeh *et al.*, 2014; Sok, 2015).

The novelty of our randomized controlled trial (RCT) is the coupling of a pb-CT with RT. To our knowledge, this is the first attempt to evaluate the efficacy of the combination of these approaches to protect late-life cognition. We evaluated the efficacy of a pb-CT focused on memory and EFs combined with RT in a large sample including patients with mild AD (mAD), during MCI and HE. Another innovative aspect was the use of a computerized support to administer both interventions. This offered advantages such as the availability of feedback and tailoring programs on the users' performance (Kueider *et al.*, 2012). Most of the exercises trained memory and EFs, but we also included exercises aimed at improving those domains (i.e., orientation, constructional praxis, abstract reasoning, and language) that might be affected by physiological aging and AD. RT consisted of producing a storybook in which participants were guided through their life experiences with questions concerning the entire life cycle.

The primary aim of this study was to evaluate whether a pb-CT on memory and EFs combined with RT would provide similar or better findings on memory and EF outcomes than studies evaluating pb-CT only. The secondary aim was to determine whether the effects were maintained at follow-up. A final aim was to evaluate generalization of the training effects on the functional abilities of mAD.

Methods

Eligibility criteria

Inclusion criteria for participants were age ≥65 years and formal education ≥5 years. Participants were

divided into three samples according to the following criteria:

(1) mAD: Subjects satisfying the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria for diagnosis of probable AD (McKhann *et al.*, 2011) at a mild stage of cognitive impairment and who had a Mini-mental state examination (MMSE) (Folstein *et al.*, 1975) score ≥20 and a global score equal to 1 on the Clinical Dementia Rating (CDR) scale (Hughes *et al.*, 1982) with a subscore of at least 1 in memory domain; stable antidementia pharmacological treatment for at least 1 month; and presence of a primary caregiver.
(2) MCI: Subjects satisfying the operational criteria for MCI (Petersen, 2004) with an MMSE (Folstein *et al.*, 1975) score ≥25 and a global score equal to 0.5 on the CDR (Hughes *et al.*, 1982) with a subscore of 0.5 in the memory domain and presence of an informant.
(3) HE: Healthy elderly with no history of neurological or psychiatric deficits with an MMSE (Folstein *et al.*, 1975) score ≥26 and a global score equal to 0 on the CDR (Hughes *et al.*, 1982) and presence of an informant.

All participants gave their written informed consent. The study was approved by the local ethical committees in the pilot sites.

Study design

We carried out a multicenter RCT by using a stratified randomization by sample (AD, MCI, and HE) and center of recruitment. Participants were recruited in medical centers and municipalities in four countries (Italy, Greece, Norway, and Spain). Participants were allocated in two arms according to a crossover design: arm A, participants began with a training period of about 3 months and then underwent a length-equivalent period of rest; arm B, participants started with the rest followed by the training.

All participants were followed up for 6 months, and all outcome assessments were conducted at baseline, at 3 months (at the switch between periods), and at 6 months (after the study conclusion) by trained raters.

Training

All participants attended 24 one-hour treatment sessions twice weekly for a total of about 3 months. Sessions were carried out in groups of up to three participants under the supervision of a trained cognitive therapist. Each session was divided into 30 min of multi-component pb-CT (10 min for memory, 10 min for EFs, and 10 min for other cognitive domains, i.e., logical reasoning, orientation, language, and constructional praxis) and 30 min of RT during which participants were asked to answer questions concerning semantic autobiographical data (e.g., the name of their primary school) or episodic autobiographical questions (e.g., a nice situation during childhood). The training was administered using a software that resulted from a project co-funded by the European Union (CIP-ICT-PSP) called SOCIABLE (http://www.cognitivetraining.eu) and operating on a touch screen computer. This software was designed for individuals with cognitive impairments as well as for HE. It includes the exercises for the pb-CT and an electronic book called "Book of Life" for the RT. Exercises trained are as follows: episodic memory, for example, remembering a list (Galante *et al.*, 2007), remembering object locations in domestic environments (Schreiber, 1999), and finding pairs of images (Xeno Rasmusson *et al.*, 1999; Peretz *et al.*, 2011; Shatil, 2013); attentional EFs, for example, selective attention by paying attention to stimuli avoiding distractors (Mayas *et al.*, 2014), and abstraction, explaining similarities (Dubois *et al.*, 2000; Bergamaschi *et al.*, 2013), categorizing objects (Nelson, 1976), or deducting a target by excluding the distractors (Gaitán *et al.*, 2013); orientation, for example, moving into a house (Bergamaschi *et al.*, 2013); logical reasoning (Raven, 1947), for example, completing a visual pattern with a missing element; constructional praxis, for example, doing a puzzle (Peretz *et al.*, 2011); and language, for example, coupling synonyms or antonyms (see Supporting Information for a full description). Each exercise featured three progressive difficulty levels adjustable according to users' performance.

Study outcomes

The primary outcome of the study was the effect of the training compared with the rest on neuropsychological test scores of memory and EFs. Memory was assessed with the Rey Auditory Verbal Learning Test (RAVLT) (Rey, 1958) and the Rey–Osterrieth Complex Figure Test (Rey, 1941), and EFs were assessed with the Trail Making Test (Reitan and Wolfson, 1985) and the Phonological Verbal Fluency Test (Borkowski *et al.*, 1967). Global cognition was assessed with the MMSE.

As a secondary outcome (only for the mAD group), the study included the effect of the training compared

with the rest on functional abilities assessed with the instrumental activities of daily living (IADL) (Lawton and Brody, 1969).

Randomization

The randomization of participants between the two arms of the study was carried out by center and sample (mAD, MCI, and HE) and with a block size of four to prevent imbalance between the allocation groups. The allocation procedure was concealed from the raters.

Statistics

The primary aim of our analyses was to determine (separately for each sample of participants) whether there was a differential effect between the training and the rest period for each neuropsychological test. Therefore, we analyzed the interaction arm × time of a mixed analysis of variance (ANOVA) with arms (A and B) as between-subjects factor and time of assessment (baseline, month 3, and month 6) as within-subjects factor. To account for multiple comparisons, we used a Bonferroni correction of the significance level of $p < 0.05$ for the number of measures tested, resulting in $p < 0.008$. To account for the equivalence on demographic and primary outcomes between the two arms of the study (A and B), for each sample, we calculated Student's *t*-test comparisons for continuous variables and the χ^2 test for sex. We used a Bonferroni correction of the significance level of $p < 0.05$ for the number of measures tested, resulting in $p < 0.006$. Then we evaluated the specific effects of the training and rest periods with *post hoc* analyses only for significant interactions. We calculated *post hoc* Student's *t*-tests between the pre-treatment and post-treatment and the pre-rest and post-rest. To account for multiple comparisons, we used a Bonferroni correction of the significance level of $p < 0.05$ for the number of measures tested, resulting in $p < 0.013$. We evaluated the directions of significant effects by calculating Cohen's *d* effect size (Cohen, 1992). Our study was not meant to evaluate a proper follow-up effect; nevertheless, the participants in arm A first received the training and then the rest; therefore, we considered the post-rest assessment as a follow-up. We evaluated the follow-up effect with Student's *t*-tests between baseline and month 6 assessments for subjects of arm A.

Results

Characteristics of participants

A total of 348 participants were randomized, and 301 completed the conclusive assessment (14% dropout) (Figure 1). Demographics and primary outcomes at baseline, stratified by sample (HE, MCI, and mAD) and allocation groups (arm A and arm B), are presented in Table 1.

Primary outcome: cognitive abilities

The ANOVAs (Figure 2) showed a significant time × arm interaction, indicating a general differential effect between the treatment and the rest for MMSE in MCI [$F(2,208) = 7.572$, $p = 0.001$] and mAD [$F(2,158) = 6.085$, $p = 0.004$], for the memory tests of RAVLT delayed for all three groups, that is, HE [$F(2,224) = 6.362$, $p = 0.002$], MCI [$F(2,208) = 6.041$, $p = 0.003$], and mAD [$F(2,158) = 8.009$, $p = 0.001$], and for the test of verbal fluency for HE [$F(2,224) = 5.683$, $p = 0.006$]. We found no significant main effects of arm except for HE on the Rey–Osterrieth Complex Figure Test delayed memory test [$F(1,112) = 15.199$, $p < 0.001$] in agreement with the significant difference detected at baseline (Table 1). Conversely, on each test, the main effect of time was significant for HE [$F(2,224) > 6.547$, $p < 0.004$] with the exception of Trail Making Test A and for MCI [$F(2,\ 170–208) > 6.043$, $p < 0.004$]. For mAD, the main effect of time was never significant.

Table 2 shows results of *post hoc* Student's *t*-test between pre-training/post-training and pre-rest/post-rest periods for outcomes that showed significant interactions on ANOVA. The pre-training/post-training difference in the memory outcome was significant in almost all groups, whereas pre-rest/post-rest difference was never significant. We obtained similar results for the EF outcome in HE and in MMSE scores of MCI

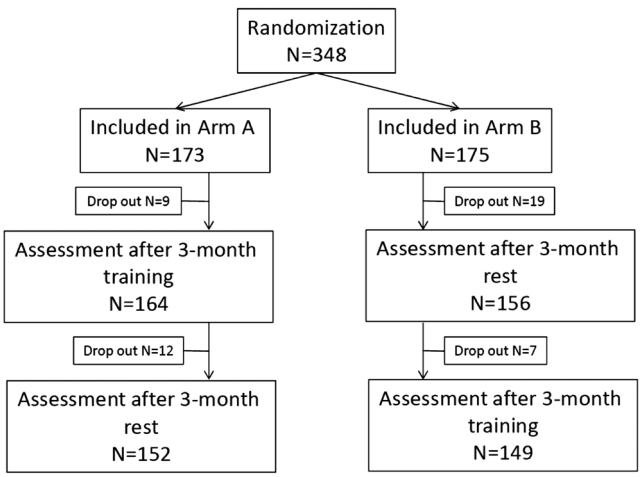

Figure 1 Flow chart of participants in the study.

Table 1 Baseline demographics and primary outcomes means and standard deviations in brackets stratified by sample, HE, MCI participants, and mAD participants and allocation groups training-rest (arm A) and rest-training (arm B)

	HE ($n=114$)			MCI ($n=106$)			mAD ($n=81$)		
	Training-rest ($n=61$)	Rest-training ($n=53$)	p	Training-rest ($n=46$)	Rest-training ($n=60$)	p	Training-rest ($n=42$)	Rest-training ($n=39$)	p
Age	70.9 (6.2)	72 (6.6)	ns	74.4 (5.7)	72.9 (6)	ns	76.7 (5.7)	76.9(5.7)	ns
Education	9.9 (3.7)	10.6 (4.1)	ns	9 (4.3)	11 (4.7)	ns	8.8 (3.6)	9.2 (3.7)	ns
Sex (male/female)	27/34	22/31	ns	25/21	31/29	ns	13/29	11/28	ns
MMSE	29.1 (1.4)	29.1 (1.2)	ns	27.3 (2.1)	28.1 (1.4)	ns	23.4 (1.9)	23.4 (1.7)	ns
Memory									
Rey Words—delayed	9.1 (3)	9.4 (3.5)	ns	4.1 (3.2)	5 (3.2)	ns	1.2 (1.7)	1.5 (1.7)	ns
Rey Figure—delayed	15.1 (6.9)	11.3 (6.9)	0.003	8 (6.8)	9.4 (6)	ns	3.3 (3.1)	2.6 (3)	ns
Executive functions									
Phonological fluency	44.5 (17)	38 (20.2)	ns	25.4 (10.5)	28.8 (10.6)	ns	24.9 (8.9)	25.7 (9.2)	ns
Trail Making Test A	81.1 (45)	93.5 (37.6)	ns	96 (43.4)	84.3 (32.2)	ns	96 (47.9)	94.1 (45.5)	ns
Trail Making Test B	173.3 (86.2)	179.2 (76.4)	ns	211.8 (73.3)	188.1 (76.8)	ns	187.1 (48.1)	261.6 (78.9)	0.001

ns, not significant; p, probability of two sample t-tests; MMSE, Mini-mental state examination; HE, healthy elderly; MCI, mild cognitive impairment; mAD, mild Alzheimer's disease.

and mAD. We also derived Cohen's d (Cohen, 1992) of the training periods showing significant effects (Table 2). Effects of the training for significant results of RAVLT delayed recall ranged between 0.26 and 0.48 and for MMSE between 0.30 and 0.53, whereas phonological fluency was on average 0.17 for HE. Significant positive effects of the training for memory and EF outcomes were maintained during the following rest period in HE and MCI (Table 2, right columns).

Secondary outcome: functional abilities in the mild Alzheimer's disease sample

Half of our mAD sample (comprising both arms A and B) (54%, $n=41$) showed variability on the IADL at all three time points. In this subsample, we found a difference approaching significance between the training and the rest in the ratio between the number of participants who showed increased/stable IADL and the number who showed decreased IADL ($\chi^2=3.190$, $p<0.07$). Specifically, during the training, 68% of the participants showed increased/stable IADL versus 32% who showed decreased IADL, and during the rest, 46% of the participants showed increased/stable IADL versus 54% who showed decreased IADL (Figure 3).

Discussion

This RCT shows a medium positive effect during the training for episodic verbal memory in all three groups. HE also showed a small positive effect for EFs. During the rest, no effects were detected. Furthermore, the MCI and HE subjects' improvements in memory and the HE subjects' improvement in EFs were maintained during the 3 months of post-training rest. mAD and MCI subjects also showed a positive effect on MMSE scores, not maintained during the rest. Finally, during the training, mAD showed an approaching significance positive effect on functional abilities.

The first aim of this study was to evaluate the effect of the training on memory and EFs. As to memory, our findings are consistent with the positive results previously reported in which pb-CT was administered to HE and MCI, and they are very promising for mAD when compared with the lack of significant positive results previously reported in pb-CT studies. Indeed, two studies in HE (Peretz *et al.*, 2011; Miller *et al.*, 2013) found positive effects when they compared

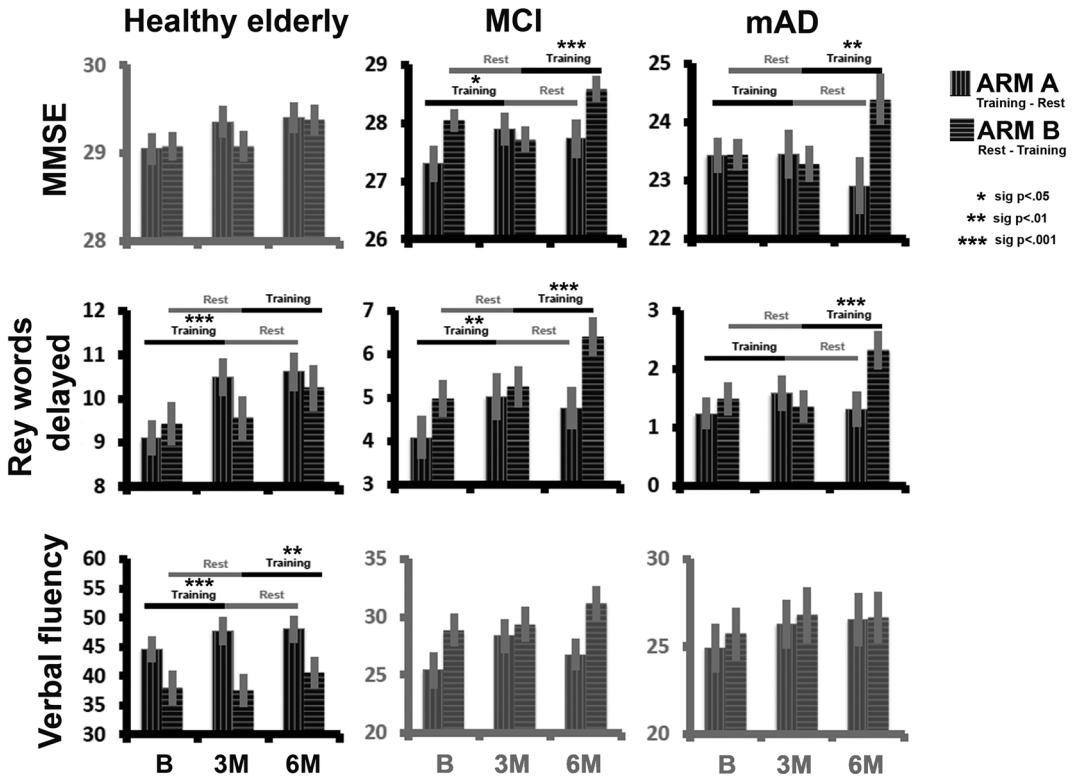

Figure 2 Plots show raw data pertaining to different neuropsychological tests and in the different samples: healthy elderly participants, mild cognitive impairment participants (MCI), and mild Alzheimer's disease participants (mAD). Each graph shows data obtained at three assessments (B, assessment at baseline; 3M, assessment at 3 months after baseline; 6M, assessment at 6 months after baseline) separately for the two arms of the study: arm A is shown with vertical lines and arm B with horizontal lines. Plots showing significant arm × time interactions are in dark gray, and plots showing non-significant arm × time interactions are in light gray. Bars represent standard errors. For significant interactions, *post hoc t*-tests are reported by showing the different levels of significance with a different number of asterisks (see legend). MMSE, Mini-mental state examination.

pre-pb-CT and post-pb-CT ($d = 0.33$ and $d = 0.25$, respectively). Two other studies (Shatil, 2013; Lampit *et al.*, 2014b) showed similar effects when they compared the training period with a comparable period of active placebo (AP) ($d = 0.64$ and $d = 0.49$, respectively). In the former, the placebo showed no effectiveness ($d = -0.02$) (Shatil, 2013), but in the latter, in which the placebo consisted of a memory task, the placebo showed a small-medium effect ($d = 0.38$) (Lampit *et al.*, 2014b). Similar results were reported for MCI subjects (Günther *et al.*, 2003; Cipriani *et al.*, 2006; Talassi *et al.*, 2007) showing an average positive medium effect ($d = 0.72$, $d = 0.56$, and $d = 0.31$, respectively). Finally, previous studies in AD patients reported a lack of relevant effects (Heiss *et al.*, 1994; Davis *et al.*, 2001; Loewenstein *et al.*, 2004; Cipriani *et al.*, 2006; Galante *et al.*, 2007; Talassi *et al.*, 2007).

Regarding EFs, our HE sample showed a positive but small effect consistently with two previous similar studies (Peretz *et al.*, 2011; Shatil *et al.*, 2014) comparing pre-pb-CT and post-pb-CT ($d = 0.26$ and $d = 0.38$, respectively). By contrast, two other studies (Shatil, 2013; Lampit *et al.*, 2014b) comparing the pb-CT with an AP reported non-significant results. Our lack of relevant significant effects in MCI and AD patients is consistent with most previous studies adopting the pb-CT (Loewenstein *et al.*, 2004; Cipriani *et al.*, 2006; Galante *et al.*, 2007; Talassi *et al.*, 2007). Indeed, only Günther *et al.* (2003) found a small positive effect ($d = 0.27$) when they compared pre-pb-CT with post-pb-CT in MCI.

As to global cognition, our MMSE results in MCI participants are very promising because previous studies comparing pre-pb-CT with post-pb-CT reported no significant effects (Cipriani *et al.*, 2006; Talassi *et al.*, 2007). Conversely, our data on mAD patients are consistent with previous findings (Cipriani *et al.*, 2006; Talassi *et al.*, 2007) of a medium-high effect ($d = 1.01$ and $d = 0.54$, respectively).

Our secondary aim was to determine whether the effects were maintained at the follow-up. Our results suggest that the memory improvements of MCI and HE and the EF gains in HE were maintained during the 3 months post-training. These results agree with those

Table 2 *Post hoc* comparison of pre-training/post-training and pre-rest/post-rest in outcomes showing significant time × arm interaction

			Training period					Rest period					Follow-up		
Outcome	Group	Arm	Pre *M* (*SD*)	Post *M* (*SD*)	*t*	*p*	*d*	Pre *M* (*SD*)	Post *M* (*SD*)	*t*	*p*	*d*	*t*	*p*	*d*
RW-del	HE	A	9.1 (3)	10.5 (3.3)	−5.8	<0.001	0.44	10.5 (3.3)	10.6 (3.4)	−0.9	ns	—	−6.7	<0.001	0.47
		B	9.6 (3.6)	10.3 (3.7)	−2.3	ns	—	9.4 (3.5)	9.6 (3.6)	−0.6	ns	—			
	MCI	A	4.1 (3.2)	5 (3.6)	−2.7	0.009	0.26	5 (3.6)	4.8 (3.2)	1.0	ns	—	−2.2	0.03	0.22
		B	5.3 (3.6)	6.4 (3.3)	−4.0	<0.001	0.32	5 (3.2)	5.3 (3.6)	−1.2	ns	—			
	mAD	A	1.2 (1.8)	1.6 (1.9)	−1.7	ns	—	1.6 (1.9)	1.3 (1.9)	1.4	ns	—			
		B	1.4 (1.7)	2.3 (2)	−4.1	<0.001	0.48	1.5 (1.8)	1.4 (1.7)	1.4	ns	—			
PF	HE	A	44.5 (17)	47.7 (17.9)	−4.8	<0.001	0.18	47.7 (17.9)	48 (17.5)	−0.6	ns	—	−4.3	<0.001	0.2
		B	37.5 (19.7)	40.6 (19)	−3.2	0.003	0.16	38 (20.3)	37.5 (19.7)	0.7	ns	—			
MMSE	MCI	A	27.3 (2.1)	27.9 (1.9)	−2.7	0.01	0.30	27.9 (1.9)	27.7 (2.2)	0.7	ns	—	−1.6	ns	—
		B	27.7 (1.7)	28.6 (1.7)	−4.7	<0.001	0.53	28.1 (1.4)	27.7 (1.7)	2.3	ns	—			
	mAD	A	23.4 (1.9)	23.5 (2.7)	−0.1	ns	—	23.5 (2.7)	22.9 (3.1)	1.5	ns	—			
		B	23.3 (1.9)	24.4 (2.7)	−3.0	0.005	0.47	23.4 (1.7)	23.3 (1.9)	0.7	ns	—			

RW-del, Rey words delayed recall; PF, phonological fluency; MMSE, Mini-mental state examination; M, mean; SD, standard deviation; *t*, *t*-test; *p*, probability of the paired *t*-tests; *d*, Cohen's *d*; ns, not significant.

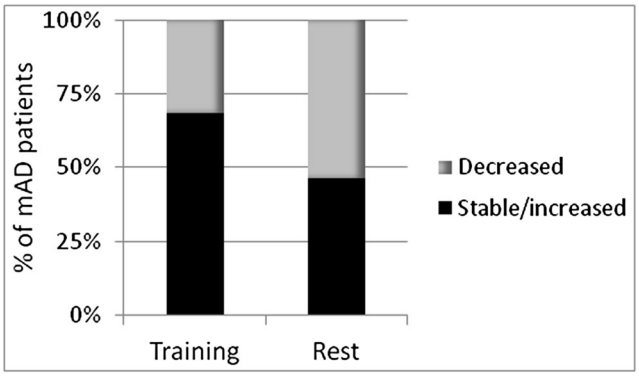

Figure 3 Percentages of mild Alzheimer's disease (mAD)* patients who showed decreased (gray) or stable/increased (black) functional abilities measured with instrumental activities of daily living during the training and the rest periods. *mAD subsample ($n = 41$) showing variability on the instrumental activities of daily living across the three time points (i.e., we did not consider participants who obtained the same scores at all three time points).

previously reported showing that cognitive gains in the HE may last for years (Willis *et al.*, 2006). Indeed, a longitudinal study (Lampit *et al.*, 2014b) in HE subjects showed a significant medium effect on global cognition 3 months post-training ($d = 0.30$) and a small one after 1 year ($d = 0.21$). Moreover, a study on MCI (Günther *et al.*, 2003) showed significant medium effects 5 months post-training ($d = 0.45$) for memory. Finally, a study in mAD (Galante *et al.*, 2007) showed that at month 9 follow-up, the treated group obtained stable MMSE scores compared with the untreated patients who showed a significant decrease.

A final aim was to evaluate the generalization of the training effects on the functional abilities of the mAD. Our results are promising when compared with the lack of positive effects previously reported (Loewenstein *et al.*, 2004; Galante *et al.*, 2007; Talassi *et al.*, 2007).

In conclusion, our training showed in HE and MCI subjects positive medium effects on memory after training that were also maintained at follow-up. Although two recent studies in HE evidenced significant positive effects after RT on global cognition and memory (Akhoondzadeh *et al.*, 2014; Sok, 2015), in our study, the addition of RT does not seem to increase the effectiveness. Indeed, the effects in HE and MCI participants on memory are similar to those reported in previous pb-CT trials. Positive medium effects on memory outcomes were also obtained in mAD. These are very promising considering the lack of positive results in mAD previously reported and the positive effects also on the functional abilities. Because RT in moderate-severe AD patients was previously reported to show positive but non-significant effects on global cognition (Baines *et al.*, 1987; Thorgrimsen *et al.*, 2002; Lai *et al.*, 2004), our results might be due to the

combination of RT and pb-CT. Our results are promising but inconclusive because our study did not compare the training with an AP. Indeed, the cognitive gains of the HE and MCI subjects could not be attributed specifically to CT but to the increased attention that subjects received because these effects might disappear when compared with an AP (Martin *et al.*, 2011). Nevertheless, there are indications in the literature that an AP does not improve cognition (van Muijden *et al.*, 2012; Shatil, 2013) or it shows small effects (Lampit *et al.*, 2014b; Shatil *et al.*, 2014) when the involvement of an active memory component is present. We are currently evaluating the effect of our pb-CT compared with an AP condition not involving memory (i.e., filling a database). However, another RCT is needed to separately compare pb-CT, RT, and their combination with an AP to assess the specificity of their effectiveness.

Finally, the small effect on EFs limited to HE is partially consistent with previous evidence. Nevertheless, our protocol was probably unbalanced toward memory because of the combination of memory pb-CT and RT.

In conclusion, this study is the first attempt to combine pb-CT and RT. In agreement with previous evidence, we found that the training had a positive effect on memory in mAD, MCI, and HE, and in HE also on EFs. Further trials are needed to compare single and combined trainings using an active control condition to assess the specificity of their effectiveness.

Conflict of interest

None declared.

Key points

- This study demonstrates the positive effect of combined treatment with cognitive training and reminiscence therapy on memory in mild Alzheimer's disease patients, MCI, and healthy elderly participants. This positive effect on memory was maintained during the follow-up period in MCI and healthy elderly participants.
- This study demonstrates the positive effect of combined treatment with cognitive training and reminiscence therapy on executive functions in healthy elderly participants and maintenance of the effect during the follow-up period.
- Mild Alzheimer's disease patients tended to maintain more stable functional abilities during the combined treatment than during the rest period.

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Supporting information

Additional supporting information may be found in the online version of this article.