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Effect of memory impairment on training outcomes in ACTIVE

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Abstract

Cognitive training improves mental abilities in older adults, but the trainability of persons with memory impairment is unclear. We conducted a subgroup analysis of subjects in the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) trial to examine this issue. ACTIVE enrolled 2802 non-demented, community-dwelling adults aged 65 years and older and randomly assigned them to one of four groups: Memory training, reasoning training, speed-of-processing training, or no-contact control. For this study, participants were defined as memory-impaired if baseline Rey Auditory Verbal Learning Test (AVLT) sum recall score was 1.5 SD or more below predicted AVLT sum recall score from a regression-derived formula using age, education, ethnicity, and vocabulary from all subjects at baseline. Assessments were taken at baseline (BL), post-test, first annual (A1), and second annual (A2) follow-up. One hundred and ninety-three subjects were defined as memory-impaired and 2580 were memory-normal. Training gain as a function memory status (impaired *vs*. normal) was compared in a mixed effects model. Results indicated that memory-impaired participants failed to benefit from Memory training but did show normal training gains after reasoning and speed training. Memory function appears to mediate response to structured cognitive interventions in older adults.

Keywords

Cognition; Memory; Mild cognitive impairment; Aging; Therapeutics; Clinical trial; Psychological technique

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INTRODUCTION

The mental abilities of healthy older adults can be improved by systematic training programs focused on those skills (Willis et al., 2006). Training programs vary in the degree to which the interventions rely on or target visual perceptual skills (Ball et al., 1988) *versus* cognitive abilities like memory (Rebok & Balcerak, 1989) or reasoning (Baltes & Willis, 1982).

Recent studies suggest that there may be a large reservoir of mildly cognitively impaired persons in the community (DiCarlo et al., 2000; Ganguli et al., 2004a; Graham et al., 1997; Lopez et al., 2003; Unverzagt et al., 2001). A major cause of abnormal cognitive aging is Alzheimer disease (AD) which, in its initial stages, is characterized clinically by impairment in declarative memory and neuropathologically by intracellular deposits of tau, in the form of neurofibrillary tangles, extracellular deposits of beta-amyloid, and neuronal loss in the medial temporal lobe including the hippocampus and entorhinal cortex. AD is a slowly progressive process and the transition between normal aging and the earliest stages of AD is difficult to discern by most routine medical evaluations (Callahan et al., 1995; Ganguli et al., 2004b).

A basic taxonomy in neuropsychology is the bifurcation of memory into declarative and procedural forms (Squire, 1987). This distinction recognizes differences in the role of conscious effort in encoding and recall. Declarative memory requires conscious attention during the encoding and recall phases and an ability to specify the contingencies under consideration. Procedural memory, on the other hand, is characterized by repetitive exposures and actions by the organism with no requirement of awareness of the contingencies at play. The psychological and neurological parameters underlying these operations have been the subject of intense research interest with reasonable agreement that the formation and recall of new declarative memories is dependent on a network involving medial temporal lobe structures and posterior neocortical association areas (Squire et al., 1993). In contrast, procedural memories are believed to reflect neural plasticity of cortical and subcortical pathways outside the medial temporal lobe (Squire et al., 1993).

The Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) study is a randomized, controlled trial of the effectiveness of three forms of cognitive intervention (memory, reasoning, and visual attention) on improving basic cognitive ability and performance of activities of daily living of normal older people (Jobe et al., 2001). The ACTIVE trial focused on non-demented, older adults who were at-risk for loss of independence but who had not yet experienced loss. The sample was selected from the population of community-dwelling elders who did not require formal care at the point of entry into the study. The specific methods used and strategies taught in these three modules were tailored to be specific to the cognitive ability targeted. The Memory training module focused on improving participants' abilities to consciously learn new information and as a result relies very heavily on declarative memory operations. The Reasoning training module emphasized pattern detection and inductive reasoning abilities and required some element of declarative processing in the training. The Speed training module focused on repetitive, visually guided manual responding and had essentially no reliance on declarative memory.

ACTIVE screened out participants with obvious dementia using typical methods (mental status examination and interview-based assessment of daily function); however, some participants with mild memory impairment are expected to have passed these typical but rather rudimentary exclusion procedures and entered the study. Some of these persons would be expected to have subtle medial temporal lobe pathology caused by early changes associated with AD (Morris et al., 2001). Because the neural substrate required for declarative learning in these participants is likely compromised, we hypothesized that, compared to those with “normal” memory, they would not benefit, or would benefit less, from memory training, which has a high requirement

for declarative-type conscious processing. Further, we hypothesized these same "memory impaired" participants would show a normal training gain when the intervention did not rely heavily on declarative learning processes, such as in speed training.

METHODS

Participants

This study was approved by and subject to ongoing review by the institutional review boards of all grantee institutions and all participants provided IRB-approved informed consent. Community volunteers were recruited from six metropolitan areas in the Midwest and Eastern part of the United States (Baltimore, MD, Birmingham, AL, Boston, MA, Detroit, MI, State College, PA, and Indianapolis, IN) using a variety of sources including community centers, churches, senior housing sites, driver's license registries, outpatient medical clinic rosters, and social service program rosters. Each site contributed 400 to 500 participants to the trial. Participants were enrolled in waves or replicates (six in total) over approximately 18 months. Reasonably well-functioning persons aged 65 years and older were eligible. Exclusion criteria were as follows: (1) presence of substantial cognitive impairment [Mini-mental State Examination, MMSE; (Folstein et al., 1975)] <23, with serial seven subtraction from 100 as the attention item), (2) presence of substantial functional impairment (e.g., regular need for significant assistance in dressing, personal hygiene, or bathing because of any cause), (3) self-reported diagnosis of Alzheimer disease, stroke within the last 12 months, or certain cancers, (4) current chemotherapy or radiation therapy, (5) prior exposure to systematic cognitive interventions, (6) participants who did not plan to be residentially stable, (7) low vision (worse than 20/70 with best correction), (8) low auditory acuity (interviewer rated), or (9) low communicative ability (interviewer rated).

Design

ACTIVE is a randomized, controlled, single-blind trial. Participants were randomly assigned to one of three treatment arms (Memory, Reasoning, or Speed training) or a no-contact control group (Figure 1). Assessments were conducted at baseline (BL), following the intervention (immediate post-test, PT), and annually at 1 (A1) and 2 (A2) years after the intervention. Assessors were blind to treatment assignment.

Interventions

The rationale for the intervention and detailed descriptions of the training modules can be found elsewhere (Ball et al., 2002; Jobe et al., 2001; Willis et al., 2006). In brief, the training in ACTIVE focused on memory, reasoning, and speed of processing because prior research had indicated that these abilities exhibit early age-related decline and because these skills are associated with performance of activities of daily living. The interventions were conducted in small groups. Ten sessions lasting 60 to75 minutes were conducted over 5 to 6 weeks. Memory training focused on improving verbal episodic memory. Participants were instructed in strategies for recalling word lists and short narratives (e.g., organization, visualization, association). Reasoning training focused on improving the ability to solve problems that contained a serial pattern. Participants were taught how to identify, block, and mark patterns in abstract series of letters and words in order to induce the next item in a series. Speed training focused on visual search and the ability to process increasingly more information presented in successively shorter inspection times. On a touch computer screen, participants identify briefly appearing visual objects. At the first level this involves a single target. At the second level, this involves simultaneously appearing central and peripheral visual targets. At higher levels, the simultaneous identifications are made more difficult by overlaying visual masks and auditory demands. At each level, massed repetition occurs and when a plateau of responding is reached, cues are added (e.g., segmented response field, brighter target colors) to improve performance.

For each of the three intervention conditions, booster training was provided to a subset of participants approximately 11 months after the end of the primary training. A 60% random subsample of participants in each intervention condition were selected, with the restriction that they had to have completed 80% of the initial training sessions, to receive booster training. The booster training was delivered in four 75-minute sessions over a three-week period. The structure and content of the sessions were similar to those used in the primary training.

Measures

An extensive measurement battery was developed for this trial tapping a range of demographic, sensory, motor, cognitive, functional, mood, health, health service utilization, and quality of life variables with self-report and direct performance measurements obtained in individual and group formats (Jobe et al., 2001). For this investigation, we focused on demographic variables of age (in years), education (years of school completed), gender, ethnicity, overall intellectual ability (Vocabulary test; (Ekstrom et al., 1976), and cognitive tests that formed the main outcome measure for each intervention as follows. *Memory training outcomes* were measured by verbal memory tasks: Hopkins Verbal Learning Test total of the 3 learning trials (Brandt, 1991), Rey Auditory-Verbal Learning Test total of the 5 learning trials (Rey, 1941), and the Rivermead Behavioral Memory Test immediate recall (Wilson et al., 1985). *Speed of Processing training outcomes* were measured using computer-based visual attention tasks, the Useful Field of View (Owsley et al., 1998), with the key dependent variable being the shortest display time required to achieve 80% correct response rate. *Reasoning training outcomes* were measured by tasks requiring the identification of patterns in letter and word series problems: Letter Series total correct (Thurstone & Thurstone, 1949), Letter Sets total correct (Ekstrom et al., 1976), and Word Series total correct (Gonda & Schaie, 1985).

Individual test scores were standardized at each time point to the BL mean and standard deviation (each participant's test score was subtracted from the group mean score at pretreatment baseline and the difference was divided by the group standard deviation at BL). The resultant *z*-score has a mean of 0 and standard deviation (SD) of 1 at baseline. Composites were formed for each outcome domain as follows: (a) the average of the Rey Auditory Verbal Learning Test, Hopkins Verbal learning Test, and Rivermead Behavioral Memory Test *z*-scores formed the memory composite, (b) the average of Letter Series, Letter Sets, and Word Series tests formed the reasoning composite, and (c) the average of the UFOV tasks formed the speed composite. If one or more tests of a composite were missing, the composite score was calculated as the average of the non-missing tests. Scores were normalized by pooling scores at all time points and applying a Blom transformation which standardizes the components to have equal weight and reduced skewness (Blom, 1958).

Memory Impairment

For the purposes of this study, memory impairment was defined in reference to the baseline Rey Auditory Verbal Learning Test (AVLT) sum recall scores. Specifically, baseline age, education, ethnicity, and vocabulary score were regressed against (AVLT) sum recall and predicted AVLT scores were computed for each participant. Participants with actual AVLT scores 1.5 SD or more below the predicted score were defined as memory-impaired; all others were defined as memory-normal.

Statistical Analysis

The effects of ACTIVE training over 2 years were analyzed with a repeated measures, mixed-effects model (Cnaan et al., 1997). The SAS program used the Mixed Procedure. For each of the three dependent outcome variables (memory composite, reasoning composite, and speed composite) a separate model was run that had these specifications: covariance structure was compound symmetry; subject effect was NID; estimation method was REML; residual variance

method was profile; fixed effects SE method was model-based; and degrees of freedom method was between-within. There were 2 levels of memory impairment (yes and no); 2 levels of booster (yes and no); 4 levels of time (or occasion of measurement-baseline, post-test, A1, and A2); 4 levels of treatment (control, memory, reasoning, speed); 6 levels of site (the six performance sites); and 6 levels of replicate (replicates 1 through 6). The following 11 effects were chosen for interpretability and included in each model: main effects for memory impairment, time, treatment, booster, and site; 2-way interactions for time × treatment, booster × treatment, site × replicate, and memory impairment × treatment; and 3-way interactions for booster × time × treatment and memory impairment × time × treatment. The hypotheses in this study focuses on the 3-way interactions of memory impairment × time × treatment for each of the three main outcome composites.

In mixed-effect models, all training groups are in each model and a significant 3-way interaction would indicate that not all intervention-by-time-by-impairment curves are the same. Our hypotheses are focused on the memory-trained with the memory composite, the reasoning-trained with the reasoning composite, and the speed-trained with the speed composite, but in fact all the other training groups are in each model. Thus a significant 3-way interaction could suggest that memory-status interacted with treatment over time (i.e., training was not equally effective for the memory-impaired and memory normal participants over time) and examination of the cells of interest would be needed to confirm or refute the hypothesis. A non-significant 3-way interaction would suggest that training was not differentially effective for the memory-impaired and memory normal participants over time.

The analyses used net difference scores from the composite outcomes. The net effect of training on the composite outcome variable is defined as: (trained mean – control mean at a later time point) – (trained mean – control mean at BL). These net difference scores are converted into effect sizes by dividing by the intra-subject *SD*, thus allowing for direct comparison of different outcomes. Any treatment-related gain is by definition a gain beyond that achieved by the control subjects (from any cause including practice or self-initiated treatments or training).

Contrasts were specified as the comparison of trained group effect size minus control from baseline to time point of interest (PT, A1, and A2) in the memory-impaired *versus* the memory-normal participants on the specific composite outcome measure. The contrast tests the hypothesis of interest: that the training gain is different for memory-impaired subjects who received certain training than for memory-normal subjects who received the same training, relative to controls. Because this investigation had specific, *a priori* hypotheses, including a predicted interaction, statistical significance was set at $p < .05$.

RESULTS

A total of 5000 persons were contacted for participation, 2832 (57%) were eligible, 905 (18%) were ineligible, and 1263 (25%) refused. Thirty eligible persons were randomized incorrectly resulting in 2802 participants in the clinical trial. Participants had an average age of 73.6 years (*SD* = 5.9, range 65–94), average education of 13.5 years (*SD* = 2.7, range 4–20), and average MMSE of 27.3 (*SD* = 2.0, range 23–30) and were predominantly white (73.3%) females (75.9%), although a significant proportion were African American (26%). There were no significant differences in any demographic or health factors between the four treatment groups (see (Willis et al., 2006).

The AVLT was administered with an 8 second inter-stimulus interval during the first replicate; thereafter, the inter-stimulus interval was set at 2 seconds. To accommodate the difference in administration, regressions were conducted separately for participants in replicate 1. The model with age, education, gender, ethnicity, and vocabulary score in replicate 1 participants was

significant (F[6,267] = 18.7, $p < .001$, $R^2 = .2959$). The model was also significant for the participants in replicates 2 through 6 (F[6,2492] = 197.3, $p < .001$, $R^2 = .3221$).

A total of 193 participants were identified by this algorithm as having memory-impairment at BL. When divided by AVLT memory groupings, the memory groups (impaired *vs*. normal) did not differ significantly in years of education, gender or ethnicity, but the memory-impaired participants were slightly older and had lower MMSE scores (see Table 1).

The hypothesis that training gain would be mediated by memory status was supported by the mixed-effects, general linear model showing a significant three-way interaction of memory status × intervention group × time. This interaction indicates that not all treatment-by-time-by-impairment curves are the same. This interaction was significant for the Memory trained participants on the memory composite outcome measure (F[12,6360] = 2.30, $p < .01$), nonsignificant for the Reasoning trained participants on the reasoning composite outcome measure (F[12,6618] = 1.16, $p = .31$), and significant for the Speed trained group on the speed composite outcome measure (F[12,6482] = 2.52, $p < .01$).

In reviewing the left-hand portion of Table 2, it can be seen that each training program produced a specific effect on its corresponding cognitive composite outcome measure among the memory-normal participants. Memory trained participants with normal memory function at BL improved significantly on the memory composite relative to Control participants at PT (effect size, $ES = .300$, $p < .001$), A1 ($ES = .254$, $p < .001$), and A2 ($ES = .214$, $p < .001$; see the darkly outlined group of three cells in the upper left portion of Table 2). The effect of Memory training was specific to memory ability as the composite outcome measures for reasoning and speed were no different from Controls at any time point (the six cells to the right of the darkly outlined group in upper left area of Table 2). Similarly, in the memory-normal group, Reasoning trained participants improved significantly on the reasoning composite relative to Control participants at PT ($ES = .477$, $p < .001$), A1 ($ES = .416$, $p < .001$), and A2 ($ES = .262$, $p < .001$). The effect of Reasoning training was specific to reasoning ability as the composite outcome measures for memory and speed were no different from Controls at any time point (three cells to either side of the darkly outlined group in the middle portion of the left side of Table 2). Finally, in the memory-normal group, Speed trained participants improved significantly on the speed composite relative to Control participants at PT ($ES = -1.488$, $p < .001$), A1 ($ES = -1.238$, $p < .001$), and A2 ($ES = -.886$, $p < .001$). Note that negative effect sizes in this context reflect the fact that lower raw scores indicate better performance in this domain. The effect of Speed training was specific to speed ability as the composite outcome measures for memory and reasoning were no different from Controls at any time point (six cells to the left of the darkly outlined group in the lower right portion of the left-side panel in Table 2).

In reviewing the right-side panel of Table 2, it is clear that in contrast to the memory-normal group, the memory-impaired participants in Memory training showed no benefit of training at any time point relative to controls (darkly outlined cells in the upper left portion of the right panel of Table 2). All these effect sizes are nonsignificant and hover around zero at PT ($ES = -.012$), A1 (ES = −.175), and A2 ($ES = -.100$; all p's > .30). In contrast to Memory training, Reasoning training was effective in memory-impaired participants at PT ($ES = .573$, $p < .001$) and A2 ($ES = .276$, $p < .05$, see the darkly outlined cells in the center portion of the right panel of Table 2). Again, in contrast to Memory training, Speed training was effective in memory-impaired participants at all time points: PT ($ES = -1.420$, $p < .001$), A1 ($ES = -1.100$, $p < .001$), and A2 ($ES = -.755$, $p < .001$, see the darkly outlined cells in the lower right corner of the right panel of Table 2).

Figure 2 shows graphically the failure of memory-impaired participants to benefit from Memory training. There is clear separation between the groups, with the memory-impaired effect sizes hovering near zero (i.e., no different from Controls who received no training). On the other hand, memory-impaired participants showed significant treatment gains after Reasoning and Speed training, with lines clearly outside the zero-effect size region. In these training arms, memory-impaired and memory-normal participants benefited approximately equally (lines largely overlapping at each time point).

DISCUSSION

In this study, we have demonstrated that older adults with objectively-defined memory impairment can benefit, to the same degree as their normal-memory peers, from programs of cognitive training focused on instruction and practice in inductive reasoning and speed of information processing. On the other hand, memory-impaired older adults did not benefit from a training program that was focused on learning strategies that required explicit, conscious, associative linking (declarative memory).

The ACTIVE participants that had objective memory impairment also had generally intact intellectual function (i.e., normal range MMSE) and normal ADLs at baseline. While our study did not provide a clinical diagnosis, it is likely that a large proportion of the memory-impaired participants would be classified as having Mild Cognitive Impairment (MCI) single domain amnestic or multi-domain amnestic (Petersen, 2004) since they meet key elements of the diagnostic criteria for that disorder.

Studies of Memory training in older adults with MCI have been mixed. A clinical trial of memory training in 19 MCI patients did not show a positive effect of training at immediate post-test or six month follow-up (only 1 of 16 comparisons were significant; (Rapp et al., 2002). In another study that included mnemonic training techniques similar to those used in ACTIVE (e.g., imagery, organization, method of loci) that were imbedded within dual-task attention training, MCI adults benefited from training on some immediate post-test measures of face-name associations but not on measures of paragraph recall or immediate word list recall (Belleville et al., 2006). Although the Belleville et al. study had a small sample size (20 MCI subjects and 9 controls), their results suggest that to improve memory function in MCI patients, a more multi-factorial approach than the ACTIVE training may be required.

It may be that memory-impaired participants as defined either by algorithm, as in this study, or clinical diagnosis, as in the other studies, do not profit from Memory training because they have early Alzheimer disease pathology or other structural defects within the medial temporal lobes (Morris et al., 2001). If this were true, a key component of the neural substrate targeted by the intervention would be compromised and training might be ineffective as a result. On the other hand, it is also possible that the memory training module we used in ACTIVE was not well suited to memory-impaired participants and that modifications in its content or process might have resulted in a different pattern of results.

The memory-impaired participants in ACTIVE were able to benefit from training, to the same degree as their memory-normal peers, in the computer-based visual attention training (Speed) and, to a lesser extent, in the strategy training in inductive reasoning (Reasoning). The computer-based visual attention intervention has features that are comparable in many ways to procedural training approaches that have been used successfully in amnesics (Cavaco et al., 2004) and dementia patients (Camp et al., 1996; Davis et al., 2001; Grandmaison & Simard, 2003). Taken together, these findings suggest that a functioning hippocampal-medial temporal lobe network may not be required to show training gain when the training does not rely upon declarative memory.

The Reasoning training produced intermediate results. This module requires both declarative (e.g., focus on teaching strategies such as underlining repeating letters, saying the letters aloud, inserting symbols for "skips") and procedural memory. As these operations, learned through declarative memory, were repetitively practiced, it is possible they became "automatized," thus invoking procedural plasticity and no longer being entirely dependent on formation and recall of new declarative memories for their execution. Further, the main response output in this module, (i.e., inducing the next item in the series, is generated out of working memory and as such would not be dependent on a hippocampal-medial temporal lobe network.

Limitations of this study include the lack of a clinical diagnosis of MCI in persons objectively defined as having memory impairment. This group is likely to be heterogeneous, including persons with non-AD forms of memory impairment as well as persons who are transiently cognitively impaired (Unverzagt et al., 2001). Such heterogeneity would undermine the assumption of medial temporal lobe pathology in the memory-impaired participants and make it less likely we would find the hypothesized pattern of effects. Second, the ACTIVE study specifically excluded persons with dementia, so even in this large study of over 2800 persons, few participants had significantly impaired memory, thus preventing potentially interesting subgroup analyses in the memory-impaired group (e.g., stable *versus* declining MCI, multi-domain *versus* single domain MCI, etc.).

CONCLUSION

In conclusion, this study establishes that memory status may mediate response to some forms of cognitive intervention and training. Future research should examine the effect of other cognitive subgroups (low reasoning, low speed of processing) on trainability.

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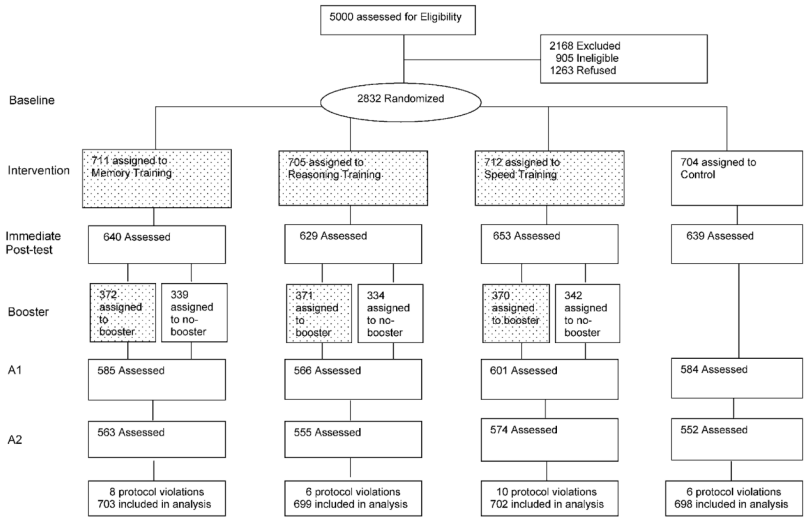

Fig. 1.
Study design.

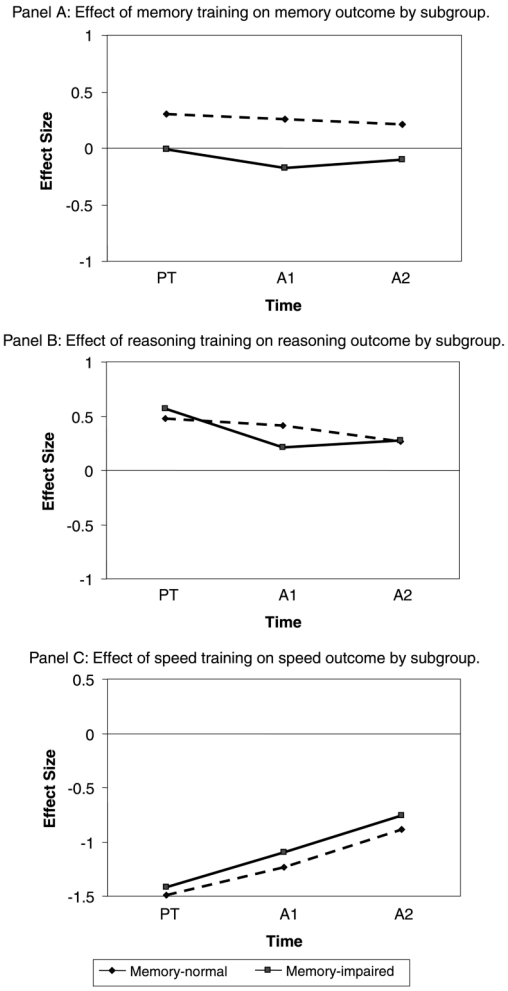

Fig. 2.

Cognitive training effects as a function of participant's memory status (normal *vs*. impaired). Panel A: Memory trained participants on the memory composite outcome measure. Panel B: Reasoning trained participants on the reasoning composite outcome measure. Panel C: Speed trained participants on the speed composite outcome measure. PT = Immediate post-test assessment, A1 = first annual assessment, A2 = second annual assessment.

Table 1

Sample characteristics by memory group

	Memory-normal (*n* = 2580)		Memory-impaired (*n* = 193)		
	M	***SD***	***M***	***SD***	***p***
Age, years	73.5	5.8	74.5	6.4	.02
Education, years	13.5	2.7	13.6	2.6	ns
MMSE	27.4	2.0	26.2	1.9	.0001
Gender, % female	75.9	—	74.6	—	ns
Ethnicity, % white	72.9	—	73.6	—	ns

Note: MMSE = Mini-mental State Examination.

Table 2

Training effect size for Memory-normal and Memory-impaired participants by intervention group and composite outcome measure

Intervention	Time	Composite outcome measures					
		Memory-normal			Memory-impaired		
		Memory	Reasoning	Speed	Memory	Reasoning	Speed
Memory	PT	.300**	−.009	−.050	−.012	−.117	.105
	A1	.254**	.033	−.061	−.175	−.163	.107
	A2	.214**	.052	−.057	−.100	−.015	.400*
Reasoning	PT	.001	.477**	.025	−.048	.573**	−.277
	A1	.013	.416**	−.026	−.230	.208	−.155
	A2	−.003	.262**	−.021	−.331	.276*	−.434*
Speed	PT	.004	−.017	−1.488**	−.108	−.111	−1.420**
	A1	.004	.009	−1.238**	−.163	−.097	−1.100**
	A2	−.024	−.013	−.886**	−.298	.079	−.755**

Note. PT = post-test, A1 = first annual assessment, A2 = second annual assessment.

* $p < .05$.

** $p < .001$.