Speed of processing training results in lower risk of dementia

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Abstract

INTRODUCTION: Cognitive training improves cognitive performance and delays functional impairment, but effects on dementia are not known. We examined whether three different types of cognitive training lowered risk of dementia across ten years of follow-up relative to control, and if greater number of training sessions attended was associated with lower dementia risk.

METHODS: The Advanced Cognitive Training in Vital Elderly (ACTIVE; NCT00298558) study was a randomized-controlled trial (N=2802) among initially healthy older adults that examined the efficacy of three cognitive training programs (memory, reasoning, or speed of processing) relative to a no-contact control condition. Up to ten training sessions were delivered over six weeks with up to four sessions of booster training delivered at 11 months and a second set of up to four booster sessions at 35 months. Outcome assessments were taken immediately post-intervention and at intervals over 10 years. Dementia was defined using a combination of interview- and performance-based methods.

RESULTS: 260 cases of dementia were identified during the follow-up. Speed training resulted in reduced risk of dementia (HR 0.71, 95%CI 0.50 to 0.998, p=.049) compared to control, but memory and reasoning training did not (HR 0.79, 95%CI 0.57 to 1.11, p=.177 and HR 0.79, 95%CI 0.56 to 1.10, p=.163, respectively). Each additional speed training session was associated with a 10% lower hazard for dementia (unadjusted HR, 0.90; 95%CI, 0.85 to 0.95, p<.001).

DISCUSSION: Initially healthy older adults randomized to speed of processing cognitive training had a 29% reduction in their risk of dementia after 10 years of follow-up compared to the untreated control group.

Keywords

Cognitive training, cognitive intervention, dementia, Useful field of view training

Highlights

- A randomized trial examined the efficacy of three cognitive training programs
- Speed of processing cognitive training significantly reduced dementia risk
- Each session of speed training completed was associated with reduced dementia risk

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1. Introduction

Dementia affects 14% of persons age 71 years and older and 30% of those over age 90 (1). A 2010 study estimated that 34.4 million people have dementia worldwide with estimated formal and informal care costs of $422 billion (2). Interventions that postpone dementia onset by even two years would cut projected dementia prevalence in 2047 by 22% (3).

The Advanced Training in Vital Elderly study (ACTIVE) (4) was a randomized trial on the efficacy of three different types of cognitive training to preserve cognitive and daily function in older adults. Participants were randomized to either strategy-based memory- or reasoning- training; speed of processing training; or no-contact control conditions (5). Cognitive training produced longitudinal improvements on the targeted cognitive outcomes, and trained participants self-reported less difficulty completing instrumental activities of daily living (IADL) 10 years later (6-8). As dementia by definition involves functional impairments, of interest is whether these interventions reduced dementia risk. Previous analysis of ACTIVE using a combination of self-report and performance-based definitions of dementia found no difference in rate of dementia by training arm at 5 years (9).

Importantly, ACTIVE sub-analyses have shown that, as hypothesized (4), exposure to booster training was associated with larger improvements in cognitive performance and wider transfer to daily function, particularly for the reasoning and speed arms (6, 10, 11). Participants randomized to greater doses of speed training demonstrated improved

functional performance at one-, two-, and five- years [5, 9]. Exposure to booster training was associated with additional improvement in targeted cognitive performance at 10 years for participants receiving reasoning and speed training (6, 10, 11). Thus, consideration of training dose is necessary.

Given the additional follow-up in ACTIVE and the indications that booster training enhances outcomes, it was of interest to re-examine the relation between training and dementia across 10 years. We hypothesized that exposure to cognitive training would lower risk of dementia and that the benefit would be greatest for those attending more training sessions (i.e., booster training).

2. Methods

2.1 Study design and participants

ACTIVE was a multi-site, single-blind, 4-arm, randomized trial (NCT00298558, see Figure 1). Participants were community-dwelling adults aged 65 years and older. Participants were excluded if they had significant cognitive dysfunction (MMSE < 23); any functional impairment (self-reported difficulty indexed by the Minimum Data Set Home care); poor vision; self-reported diagnoses of Alzheimer disease, stroke, certain cancers; or communication difficulties (4). Written informed consent was obtained. The study was approved by site Institutional Review Boards.

2.2 Procedures

The study protocol is detailed elsewhere (4). Briefly, eligible participants completed baseline assessments of cognitive (i.e., memory, reasoning, and speed of processing) and functional abilities (i.e., self-report and performance-based measures of functional abilities) and were randomized (Figure 1). Memory training focused on instruction and practice in strategy use for verbal episodic memory. Reasoning training focused on instruction and practice in strategy use related to problem-solving and serial patterns. Speed training focused on computerized, visual-perceptual exercises designed to increase the amount and complexity of information quickly processed. Each training arm consisted of ten 60-75 minute sessions over 5 to 6 weeks delivered to small groups of participants. A subset of participants completing at least 80% of the training sessions were randomly selected to receive booster training (four 75-minute sessions) at 11- and 35- months after completion of the initial training. Thus, the total "dose" of each type of training could range from 0-18 sessions. Outcome assessments occurred immediately post-training, and at 1, 2, 3, 5 and 10 years after training.

2.3 Measures

The measures are detailed elsewhere (4), with brief descriptions of those relevant to analyses provided here. The memory composite outcome included Hopkins Verbal Learning Test, Rey Auditory-Verbal Learning Test, and Rivermead Behavioral Memory Test (immediate recall). The reasoning composite included Letter Series, Letter Sets, and Word Series. The speed composite included the four subtests of the Useful Field of View, reverse-scaled so that higher scores indicated better performance. Participants' vocabulary scores were also considered. Test scores were normalized to the control

group to form Z-scores. The average of the component Z-scores formed four domain-specific cognitive composites.

Baseline demographic and health variables were captured by self-report including age, sex, race, education, marital status, smoking, alcohol consumption, depressive symptoms (assessed by the Center for Epidemiological Scales for Depression; CES-D), and presence of diabetes, myocardial infarction, angina, congestive heart failure (CHF), stroke, hypertension, and high cholesterol.

2.4 Outcome

Adapting our earlier approach (9) and consistent with research-based diagnostic criteria (12), we defined dementia as the first occurrence of any of the following:

1. Cognitive and functional impairment defined as: a) memory composite score at or below -1.5 SD of the baseline sample mean and reasoning composite, speed composite, or vocabulary score at or below -1.5 SD of the baseline mean (for assessment details see (5)), and b) Minimum Data Set Instrumental Activities of Daily Living (IADL) total score at or below the 10^{th} percentile of the baseline (self-reported).
2. A score of <22 on the MMSE, with all subsequent MMSE assessments at < 22 or missing (13).
3. Self- or proxy-report of diagnosis of dementia or Alzheimer disease during the follow-up.

Our earlier approach (9) included two additional criteria, institutionalization and deactivation due to family refusal. We did not include these two criteria in the primary analysis because neither designation is specific to dementia. Dementia is the cause of nursing home placement in only 48% of admissions (14), and families may restrict participant engagement for reasons apart from dementia. For comparability to earlier analyses, we included these two markers in sensitivity analyses (section 2.5.1).

2.5 Statistical Analysis

Statistical analyses were performed using SAS 9.4. Descriptive statistics are presented using means and standard deviations for continuous variables and frequencies and proportions for categorical variables. The effect of cognitive training dementia risk was evaluated using Weibull regression analyses for interval-censored data, as markers of dementia were only known within discrete intervals of time. Accelerated failure time analysis using Weibull regression was used to estimate training effects while controlling for confounding effects of potential risk factors (15). We determined whether randomization to cognitive training lowered dementia risk by comparing each of the training groups to the control arm. Second, we examined whether there was a relationship between dementia and number of sessions attended for each training arm. Training sessions ranged from 0 to 18 and were treated as a time-varying covariate in the model. The approach proposed by Sparling et al. (16) was used to handle the time-varying covariate for interval censored data.

Unadjusted hazard ratios (HR) of risk factors were first estimated and those significant at the .05 level were then included in a multivariable model via a backward elimination

procedure. Adjusted HRs and their 95% confidence intervals (CI) were estimated based on the final model to assess the effect of these factors on dementia risk.

2.5.1. Sensitivity Analyses

Sensitivity analyses were performed to examine the effect of variations in dementia criteria. Training effects were estimated using different combinations of the criteria (section 2.4) including #1, #2, and #3; #1 only; #2 only; #3 only; #1 and #2; #1 and #3; and #2 and #3. In addition, we examined the dementia criteria previously applied (9), which included institutionalization and deactivation from the study due to family refusal. These results were compared to the primary results to examine whether the effects were dependent on the dementia definition.

To further evaluate the effect of training sessions attended, three sets of sensitivity analyses were performed. The first set examined the effect of dementia criteria on the relation between number of sessions attended and dementia risk as detailed above.

The second set of sensitivity analyses for the effect of training sessions attended examined whether unmeasured participant characteristics associated with invitation to booster training may account for the relation between training sessions and dementia risk as there could be differences between participants who completed fewer/more training sessions. Restricting the analysis to two subgroups of more homogeneous participants who initially completed at least 8 sessions of training and were or were not randomized to booster training, we examined the adjusted effect of training sessions on dementia risk and compared results to the primary analysis. The goal was to determine

whether the relation between training and dementia risk was evident in these two subgroups of participants.

The third set of sensitivity analyses examined the effect of different patterns of attrition on the relation between training sessions and dementia risk. Utilizing the ideas of pattern mixture models, we restricted the analysis to three subgroups of participants by dropout patterns: early dropouts (those who dropped out of the study before 5 years), late dropouts (those who dropped out of the study after 5 years), and completers (those who remained in the study at 10 years). The adjusted effect of training sessions on dementia risk was estimated and compared to the primary analysis to determine whether the relation between training sessions and dementia risk was of similar magnitude in these three subgroups of participants.

3. Results

3.1. Demographics

Demographics, health characteristics, and attrition were similar by training arm (*p*s>.05, see Table 1). At baseline, the overall sample had an average age of 73.6 years (SD 5.9), preserved cognitive status as indicated by MMSE (M 27.3, SD 2.0), and included individuals who were predominately white (73.3%) and female (76.2%). Each training arm had comparable rates of health conditions including diabetes, hypertension, myocardial infarction, stroke, and depressive symptoms. The total number of training sessions attended, including the initial and booster sessions, were not different across treatment arms. Of the 2785 participants in the analytic sample, 1220 completed the

10-year follow-up. Among participants who did not complete the 10-year follow-up, 627 were censored due to death, and the remaining 938 were censored prior to the 10-year follow-up due to attrition (30.6% attrition). The rate of nonparticipation due to death, withdrawal, and loss to follow-up were in expected ranges given the age of the sample at baseline, and, *importantly*, did not differ by training arm.

3.2. Characteristics of Participants with Dementia

A total of 260 participants developed dementia during the 10-year follow-up (12% met the psychometric criteria for dementia only, 28% met the MMSE criterion for dementia only, 43% met the reported diagnosis of dementia criterion only, 15% met two of the definitions, and 2% met all three of the definitions). Participants who developed dementia during the follow-up were older, male, of nonwhite race, less educated, more likely non-drinkers, with more depressive symptoms, and more likely to have diabetes or CHF (Table 2).

3.3. Cognitive Training and Number of Sessions Attended

Speed training resulted in lower risk of dementia across 10 years as compared to control (see Table 3). The hazard of dementia was 29% lower for speed training than control (HR, 0.71; 95%CI, 0.50 to 0.998, *p*=.049). The risk of dementia for memory and reasoning training was not significantly different compared to control (see Table 3). A greater number of memory sessions was associated with reduced dementia risk (HR, 0.95; 95%CI, 0.90-1.00, p=.038), but was not significant after adjusting for risk factors. The lower risk of dementia for speed training was more prominent for those who

completed a greater number of training sessions (Table 3). Each additional speed training session was associated with a 10% lower hazard for dementia (unadjusted HR, 0.90, 95%CI, 0.85 to 0.95, $p<.001$). The effect of number of speed training sessions remained significant after controlling for age, sex, race, depressive symptoms, diabetes, and congestive heart failure (adjusted HR, 0.90; 95%CI, 0.85 to 0.95, $p<.001$). Among participants who completed 5 or more booster training sessions, indicators of dementia were evident in 5.9% of participants from the speed arm and 9.7-10.1% among those completing the memory and reasoning booster training arms, respectively (See Supplemental Table 1).

3.4 Sensitivity Analyses for Effects of Cognitive Training

When dementia was defined using all three criteria (section 2.4) in all combinations, and more broadly also using the previously applied (9) criteria (i.e., institutionalization and deactivation due to family refusal) the hazard of dementia was consistently lower for participants in the speed training arm compared to controls. The estimated HR ranged from 0.64 to 0.87, magnitudes consistent with the results from the primary analyses (Supplemental Table 2).

3.5 Sensitivity Analyses for Effect of Training Sessions

3.5.1 Variations in Dementia Definition

For the effect of training sessions, the estimated HRs of dementia were again consistent with the primary analysis when dementia was defined using different combinations of the criteria. The estimated HRs after adjusting for age, sex, race, depressive

symptoms, and diabetes ranged from 0.90 to 0.92 (Supplemental Table 3), indicating that a greater number of speed of processing training was associated with lower dementia risk.

3.5.2. Assignment to Booster

Among 639 participants in the speed training arm who completed at least 8 initial training sessions (hence eligible for booster training), an additional training session was associated with an 11% lower risk of dementia (adjusted HR, 0.89; 95%CI, 0.82 to 0.98). Similarly, the adjusted HR was 0.83 (95%CI, 0.74 to 0.92) for an additional training session among 365 participants in the speed training arm who completed at least 8 initial training sessions and were randomized to booster training. These results are consistent with the primary analyses. That is, when two relatively homogeneous subgroups (8-10 initial sessions attended, 8-10 initial sessions attended and randomized to booster) were selected from the speed training arm, we still see the same trend for decreased risk of dementia with increased training session exposure.

3.5.3 Patterns of Attrition

The three dropout patterns (prior to 5-year follow-up, after 5-year follow-up, and completers) all had HRs of similar magnitude as found in the primary analysis. The HRs for each additional training session were 0.89 for early dropouts, 0.94 for late dropouts, and 0.89 for completers. Although the statistical significance was not consistent as in the primary analysis (due to limited power from small subsamples),

results for dropout patterns yielded effect sizes similar in magnitude indicating lower risk of dementia associated with attending more speed training sessions.

4. Discussion

Initially healthy, well-functioning older adults randomized to speed of processing cognitive training had a 29% reduction in their risk of dementia after 10 years of follow-up compared to an untreated control group. This relationship seemed to be driven in part by number of training sessions attended (greater risk reduction with more training sessions attended). Cognitive training focused on memory or reasoning was not associated with decreased risk of dementia. To our knowledge, this is the first study to show any intervention (behavioral or pharmacologic) can lower risk of dementia.

This relationship was not detectable in the ACTIVE sample after 5 years of follow-up (9). At 5 years, there were 189 dementia cases compared to 260 cases at 10 years. The increased number of outcomes improved our power to detect a relationship. We also applied new analysis by examining the role of number of training sessions attended, and found that is an important driver of the effect.

Speed training is distinct from memory and reasoning training as a perceptual/cognitive technique aimed at enhancing basic information processing efficiency with implicit learning mechanisms. In contrast, the memory and reasoning training arms are strategy-based and operate through explicit memory systems. Older adults at higher risk for dementia due to older age, low education, or mild cognitive impairment are

actually *more* likely to benefit from speed training (10, 17, 18). Meta-analysis of speed training indicates effects are broad (19) including enhanced quality of life (20, 21), lower risk of depression (22), and improved physical function (23). Importantly, multiple randomized trials indicate that speed training results in improved everyday functioning including both performance-based and self-report indices of IADL (18, 24-27). Given that functional decline is a hallmark of dementia (28), it is logical that speed training reduces dementia risk. A recent critique of cognitive training in general is that participants beliefs and expectations may influence their performance (29). However, results across randomized trials indicate that speed of processing training produces equivalent training gains as compared to either active control conditions or no-contact controls, and that speed training effects *cannot* be attributed to beliefs or expectations (19, 30, 31).

To place our results in a broader context, the dementia risk reduction of 22.7% for speed training vs. 28.8% for control yields a relative risk of 78.8% across 10 years. The magnitude of this effect is greater than the relative risk reduction antihypertensive medications provide against major cardiovascular events like stroke, coronary heart disease, or heart failure, in which treatment is associated with a 20-40% relative risk reduction over 3 to 5 years (32).

The underlying mechanism for the dementia risk reduction is not yet clear, but could relate to positive changes in brain reserve as a result of cognitive training (33). The brain reserve concept arose, in part, as a way to understand the well-documented

protective effect of education on the display of clinical brain diseases in epidemiological studies. Speed training may lower dementia risk by increasing brain reserve capacity through compensatory changes in function (e.g., enhanced capacity or efficiency of the brain) or via direct effects promoting viability of healthy tissue or decreasing the amount or effect of pathologic proteins and processes (9, 34). Biomarker studies or changes in brain structure and function taken at intervals during training may help identify mechanisms of action underlying the protective effects of speed training.

This study includes strengths such as the experimental design, a large diverse sample, multi-center treatment delivery and outcome assessments, and longitudinal follow-up. Limitations are also noted including the absence of a clinical diagnosis, attrition during follow-up, and the method of booster training assignment. ACTIVE did not have dementia as a primary outcome, so results are from secondary analyses. We acknowledge that the association between number of training sessions and the risk for dementia could be due to reverse causality. As such, we have appropriately moderated the interpretation of the exposure to training results toward association with risk. Our dementia criteria were defined a priori (9). There are of course limitations to these criteria, for example, self- and proxy-reports of dementia diagnosis are not infallible, MDS-IADL function was self-reported and thus biased, low MMSE is not a sensitive dementia marker, and overlap among the dementia criteria was low. A definitive study of the efficacy of cognitive training on dementia requires a clinical diagnosis as the primary outcome. That said, our approach to approximating a clinical diagnosis of dementia is reasonable and yielded a similar proportion of cases with dementia as prior

research (1). Our criteria were based on standard diagnostic criteria and published quantitative cutpoints. The psychometric criteria tie directly to the definition of dementia from the National Institute on Aging/Alzheimer's Association- loss of cognitive function associated with impairment in activities of daily living (35). Furthermore, results confirmed that known risk factors for dementia (e.g., age, education, CHF, diabetes) were similarly associated with our dementia criteria (36, 37). Lastly, sensitivity analyses systematically examined variations in the dementia definition and found effects of similar magnitude with every variant.

Attrition always presents a challenge when the sample comprises adults over age 65 and the follow-up interval is long. Typically, such studies see attrition rates of 2.5-9% per year (38-40). The overall attrition rate in ACTIVE of 5.5% per year over a ten-year period falls within this range. Importantly, in ACTIVE there was no differential attrition by training arm, either quantitatively or by reason for participant loss. Finally, our sensitivity analyses comparing effects of early dropout, late dropouts, and completers consistently indicated similar magnitude of speed training effects on dementia risk reduction regardless of timing of dropout. Thus, the results are robust and are likely a valid indication of the influence of speed training on dementia.

A design limitation in ACTIVE was the method of assigning participants to booster training after the initial training was completed. Participants were randomized to booster, but invitation to complete booster was conditioned on initial training adherence. While this helps to assure delivery of the treatment, it also opens the range of

interpretation of booster effects. One of the sensitivity analyses we conducted examined if participant factors related to completing 8+ initial sessions and hence being eligible for booster training could explain the dementia risk reduction. The relation of increased training exposure to lower risk of dementia was detected in each group to the same degree; therefore, differential participant characteristics linked to booster assignment is likely not responsible for our pattern of findings.

We have shown that a specific form of cognitive training, speed of processing, reduced the risk of dementia in initially well-functioning older adults followed up to 10 years. This is the first report of an intervention significantly reducing dementia risk. Future research should examine ways to increase the potency of this form of training intrinsically (e.g., increasing dose) and possibly by adding other putative protective interventions (e.g., exercise, diet). Replication of results using clinical diagnosis of dementia as a primary outcome is needed. Further examination to elucidate mechanisms of action is also warranted.

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Declaration of interests. Dr. Edwards worked between 1996 to 2005 as a consultant conducting related research studies for Visual Awareness, Inc., who owned the intellectual property surrounding the speed of processing training software. Posit Science now markets the newest version of the training program. Over an approximate three-month period in 2008, Dr. Edwards worked as a limited consultant to Posit Science, Inc. to analyze data and prepare a publication. Dr. Edwards currently serves on the data safety and monitoring board of NIH grants awarded to employees of Posit Science. Dr. Edwards worked as a consultant to Wilson, Sonsini, Goodrich & Rosati across an approximate three month period between May-August of 2015. Dr. Guey is employed by Moderna Therapeutics. Dr. Unverzagt received research support from Posit Science, Inc., in the form of site licenses for cognitive training programs for investigator-initiated research projects (2009-2012). Drs. Clark, Xu, and Ross have no conflicts of interest relevant to these analyses.

Contributions to the Manuscript. Jerri D. Edwards, study design, data collection, literature searches, data analysis and interpretation, writing of the manuscript Huiping Xu, statistical analyses, data analysis and interpretation, figures, writing of the manuscript. Daniel O. Clark, literature searches, data interpretation, writing of the manuscript. Lin T. Guey – data analysis and interpretation. Lesley A. Ross – data collection, literature searches, writing of the manuscript. Frederick W. Unverzagt – obtaining funding, study design, data collection, data analysis and interpretation, writing of the manuscript.

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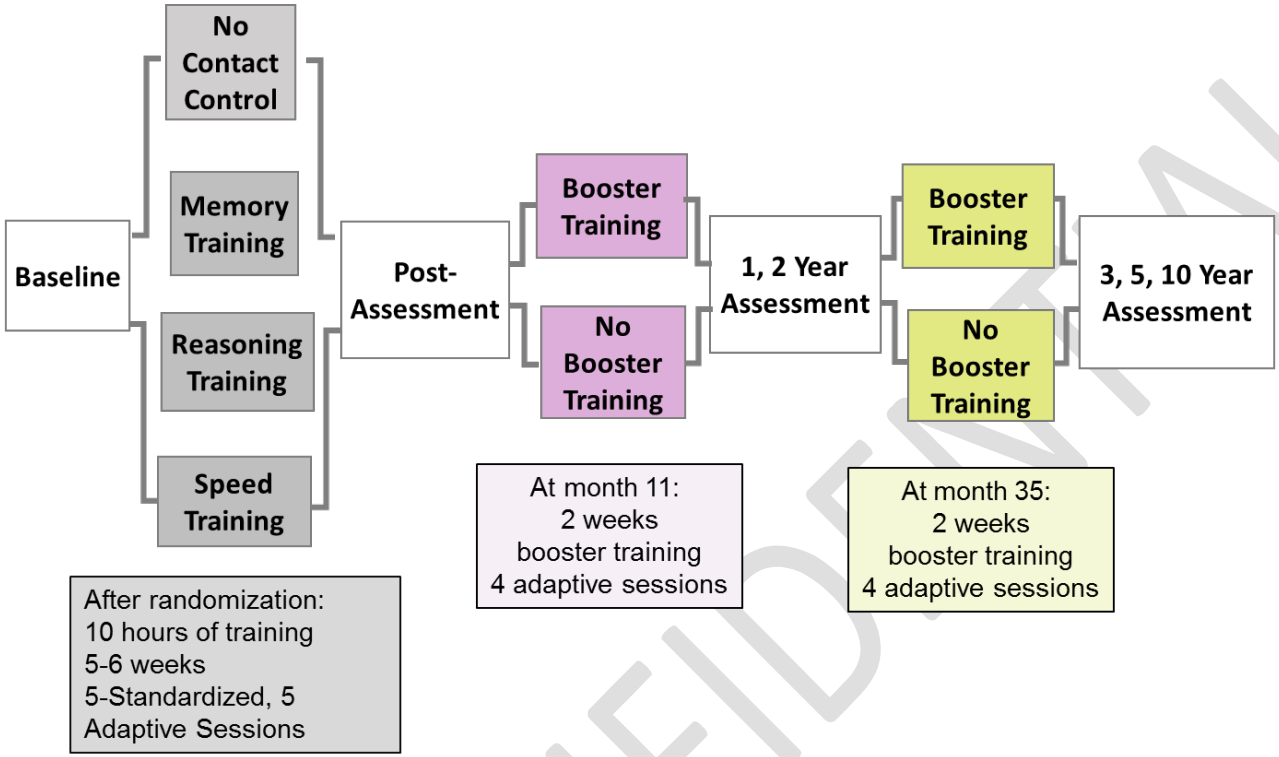

Figure 1. The Advanced Cognitive Training in Vital Elderly (ACTIVE) study design. Participants were randomized to one of four training arms and assessed immediately after training or an equivalent delay. Assessments were completed at 1, 2, 3, 5, and 10 years. A subset of participants completed four additional booster training sessions at 11 months and again at 35 months.

Table 1. Participant characteristics by training arm (count and % unless otherwise noted).

	Memory (N = 702)	**Reasoning (N = 690)**	**Speed (N = 698)**	**Control (N = 695)**
Demographics				
Age, yrs, M (SD)	73.5 (6.0)	73.5 (5.7)	73.4 (5.8)	74.0 (6.0)
Female	537 (76.5)	536 (77.7)	537 (76.9)	513 (73.8)
White	523 (74.5)	497 (72)	520 (74.5)	501 (72.1)
Education, yrs, M (SD)	13.6 (2.7)	13.5 (2.7)	13.6 (2.7)	13.4 (2.7)
Married	256 (36.5)	241 (34.9)	238 (34.2)	257 (37.0)
Health				
Smoking	57 (8.1)	46 (6.7)	50 (7.2)	54 (7.8)
Alcohol consumption				
Nondrinker	297 (42.4)	296 (43.1)	292 (42.0)	350 (50.7)
Light drinker	343 (49.0)	344 (50.2)	362 (52.0)	312 (45.2)
Heavy drinker	60 (8.6)	46 (6.7)	42 (6.0)	29 (4.2)
MMSE, M (SD)	27.3 (2.1)	27.3 (1.9)	27.4 (1.9)	27.3 (2.0)
CES-D, M (SD)	5.1 (5.3)	5.5 (5.3)	5.2 (4.9)	5.07 (4.9)
Chronic Conditions				
Diabetes	95 (13.5)	97 (14.1)	87 (12.5)	76 (11.0)
Myocardial infarction	79 (11.3)	78 (11.4)	76 (11.0)	74 (10.7)
Angina	108 (15.5)	115 (16.9)	93 (13.5)	102 (14.8)
CHF	30 (4.3)	44 (6.5)	27 (3.9)	37 (5.4)
Stroke	46 (6.6)	53 (7.8)	50 (7.2)	44 (6.4)
Hypertension	372 (53.2)	365 (53.3)	350 (50.4)	336 (48.8)
Participation Status				
Participated at 10-years	300 (42.7)	316 (45.8)	319 (45.7)	285 (41.0)
Censored at death	151 (21.5)	145 (21.0)	168 (24.1)	163 (23.5)
Participant withdrew	145 (20.7)	135 (19.6)	121 (17.3)	148 (21.3)
Site's decision to withdraw	80 (11.4)	60 (8.7)	66 (9.5)	68 (9.8)
Loss to follow-up	17 (2.4)	22 (3.2)	9 (1.3)	13 (2.9)
Family refusal	9 (1.3)	12 (1.7)	14 (2)	15 (2.2)

Note. MMSE = Mini-mental State Examination, CES-D = Center for Epidemiological Studies Depression Scale range 0-36, CHF = congestive heart failure.

Table 2. Demographic and clinical characteristics by dementia status (count and % unless otherwise noted).

	No dementia (N = 2525)	**Dementia (N = 260)**	**Hazard ratio (95%CI)**	**P value**
Demographics				
Age, years, M (SD)	73.4 (5.8)	75.8 (6.0)	1.10 (1.08 - 1.13)	<0.001
Female	1885 (76.8)	183 (70.4)	0.65 (0.49 - 0.85)	0.002
White	1871 (74.1)	170 (65.4)	0.59 (0.45 – 0.76)	<0.001
Education, years, M (SD)	13.6 (2.7)	13.1 (2.7)	0.90 (0.86 - 0.95)	<0.001
Married	898 (35.6)	94 (36.3)	0.91 (0.7 - 1.17)	0.444
Health				
Smoking	191 (7.6)	16 (6.2)	1.14 (0.69 - 1.9)	0.603
Alcohol consumption				
None	1104 (43.9)	131 (50.6)	1.00 (reference)	
Light	1243 (49.4)	118 (45.6)	0.77 (0.60 - 0.99)	0.042
Heavy	167 (6.6)	10 (3.9)	0.54 (0.28 - 1.04)	0.065
MMSE, M (SD)	27.4 (1.9)	26.2 (2.1)	0.71 (0.67 - 0.76)	<0.001
CES-D, M (SD)	5.1 (5.1)	6.5 (5.4)	1.06 (1.04 - 1.08)	<0.001
Memory, M (SD)	0.1 (0.3)	0.1 (0.3)	0.99 (0.66 – 1.49)	0.98
Reasoning, M (SD)	0.1 (0.3)	0.1 (0.3)	1.23 (0.83 – 1.83)	0.31
Speed, M (SD)	0.1 (0.3)	0.1 (0.3)	1.08 (0.73 – 1.59)	0.70
Vocabulary, M (SD)	0.7 (0.2)	0.6 (0.2)	0.18 (0.10 – 0.31)	<0.001
Chronic conditions				
Diabetes	313 (12.4)	42 (16.2)	1.56 (1.12 - 2.17)	0.009
Myocardial infarction	280 (11.2)	27 (10.4)	1.20 (0.80 - 1.79)	0.374
Angina	380 (15.2)	38 (14.8)	1.10 (0.78 - 1.55)	0.586
CHF	123 (4.9)	15 (5.8)	2.02 (1.20 - 3.40)	0.009
Stroke	172 (6.9)	21 (8.1)	1.3 (0.83 – 2.03)	0.252
Hypertension	1308 (52.1)	115 (44.6)	0.84 (0.65 - 1.07)	0.156

Note: MMSE = Mini-mental State Examination, CES-D = Center for Epidemiological Studies Depression Scale, CHF = congestive heart failure.

Table 3. Effect of training and number of training sessions attended on risk of dementia.

	No dementia (N = 2525)	**Dementia (N = 260)**	**Hazard ratio (95%CI)**	**P value**
Training group, N (%)				
Control	620 (24.6)	75 (28.8)	1.00 (reference)	
Memory	639 (25.3)	63 (24.2)	0.79 (0.57 - 1.11)	0.177
Reasoning	627 (24.8)	63 (24.2)	0.79 (0.56 - 1.10)	0.163
Speed	639 (25.3)	59 (22.7)	0.71 (0.50 – 0.998)	0.049
Number of training sessions, M (SD)*				
Memory	11.9 (5.2)	11.6 (5.7)	0.95 (0.90 – 1.00)	0.038
Reasoning	12.0 (5.0)	12.9 (4.1)	0.96 (0.91 – 1.02)	0.240
Speed	12.1 (4.9)	10.8 (4.8)	0.90 (0.85 - 0.95)	<0.001

Note. * Hazard ratios for number of training sessions indicate association with dementia per each training session attended.

Supplemental Table 1. Risk of dementia by training arm and number of sessions completed.

	N	Dementia, n (%)
Memory training		
0-7 initial sessions	84	10 (11.9%)
8-10 initial sessions		
No booster	246	21 (8.5%)
4 or fewer booster sessions	144	10 (6.9%)
5-8 booster sessions	228	22 (9.7%)
Reasoning training		
0-7 initial sessions	65	2 (3.1%)
8-10 initial sessions		
No booster	256	26 (10.2%)
4 or fewer booster sessions	141	12 (8.5%)
5-8 booster sessions	228	23 (10.1%)
Speed training		
0-7 initial sessions	66	7 (10.6%)
8-10 initial sessions		
No booster	267	25 (9.4%)
4 or fewer booster sessions	145	14 (9.7%)
5-8 booster sessions	220	13 (5.9%)
Control	695	75 (10.8%)

Supplemental Table 2. Sensitivity Analyses for Randomization to Speed Training

	Total N	Dementia Cases	Hazard Ratio (95%CI)	P Value
Primary analysis	2785	260	0.71 (0.50 – 0.998)	0.049
#1	2785	54	0.87 (0.42 – 1.80)	0.70
#2	2785	111	0.81 (0.49 – 1.34)	0.42
#3	2785	142	0.64 (0.39 – 1.06)	0.08
#1 and #2	2785	148	0.79 (0.51 – 1.24)	0.31
#1 and #3	2785	187	0.70 (0.46 – 1.07)	0.09
#2 and #3	2785	228	0.69 (0.48 – 1.00)	0.05
#1, #2, #3, institutionalization, deactivation from study due to family refusal to access to participant	2785	332	0.67 (0.49 – 0.91)	0.009

Supplemental Table 3. Sensitivity Analyses for Speed Training Sessions Attended

	Total N	Dementia Cases	Hazard Ratio (95%CI)	P Value
Primary analysis	2785	260	0.90 (0.85 - 0.95)	<0.001
Sensitivity 1: Dementia Definition				
#1	2785	54	0.91 (0.82 - 1.02)	0.11
#2	2785	111	0.91 (0.84 - 0.98)	0.01
#3	2785	142	0.90 (0.83 - 0.97)	0.007
#1 and #2	2785	148	0.91 (0.85 - 0.98)	0.01
#1 and #3	2785	187	0.90 (0.85 - 0.97)	0.003
#2 and #3	2785	228	0.90 (0.85 - 0.95)	<0.001
#1, #2, #3, institutionalization, deactivation from study due to family refusal to access to participant	2785	332	0.92 (0.87 - 0.96)	<0.001
Sensitivity 2: Assignment to Booster				
Speed training with 8+ initial sessions	631	51	0.89 (0.82 - 0.98)	0.01
Speed training with booster training	365	27	0.83 (0.74 - 0.92)	<0.001
Sensitivity 3: Patterns of Attrition				
Speed training with early dropouts (dropout before 5 years)	214	16	0.89 (0.78 - 1.02)	0.10
Speed training with late dropouts (dropout after 5 years)	165	18	0.94 (0.84 - 1.05)	0.28
Speed training with completers (complete 10-year visit)	319	25	0.89 (0.81 - 0.98)	0.02

Note. Hazard ratios indicate association with dementia per each training session attended.