JGS	12607	WILEY	Dispatch: 15.11.13	CE: Sathya
Journal Code	Manuscript No.		No. of pages: 9	PE: Saranya Shree

CLINICAL INVESTIGATIONS

Ten-Year Effects of the Advanced Cognitive Training for Independent and Vital Elderly Cognitive Training Trial on Cognition and Everyday Functioning in Older Adults

George W. Rebok, PhD,† Karlene Ball, PhD,‡ Lin T. Guey, PhD,§ Richard N. Jones, ScD,‖ Hae-Young Kim, DrPH,§ Jonathan W. King, PhD,# Michael Marsiske, PhD,**†† John N. Morris, PhD,‖ Sharon L. Tennstedt, PhD,§ Frederick W. Unverzagt, PhD,‡‡ and Sherry L. Willis, PhD,§§ for the ACTIVE Study Group*

OBJECTIVES: To determine the effects of cognitive training on cognitive abilities and everyday function over 10 years.

DESIGN: Ten-year follow-up of a randomized, controlled single-blind trial (Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE)) with three intervention groups and a no-contact control group.

SETTING: Six U.S. cities.

PARTICIPANTS: A volunteer sample of 2,832 persons (mean baseline age 73.6; 26% African American) living independently.

INTERVENTION: Ten training sessions for memory, reasoning, or speed of processing; four sessions of booster training 11 and 35 months after initial training.

MEASUREMENTS: Objectively measured cognitive abilities and self-reported and performance-based measures of everyday function.

RESULTS: Participants in each intervention group reported less difficulty with instrumental activities of daily living (IADLs) (memory: effect size = 0.48, 99% confidence interval (CI) = 0.12–0.84; reasoning: effect size = 0.38, 99% CI = 0.02–0.74; speed of processing: effect size = 0.36, 99% CI = 0.01–0.72). At a mean age of 82, approximately 60% of trained participants, versus 50% of controls ($P < .05$), were at or above their baseline level of self-reported IADL function at 10 years. The reasoning and speed-of-processing interventions maintained their effects on their targeted cognitive abilities at 10 years (reasoning: effect size = 0.23, 99% CI = 0.09–0.38; speed of processing: effect size = 0.66, 99% CI = 0.43–0.88). Memory training effects were no longer maintained for memory performance. Booster training produced additional and durable improvement for the reasoning intervention for reasoning performance (effect size = 0.21, 99% CI = 0.01–0.41) and the speed-of-processing intervention for speed-of-processing performance (effect size = 0.62, 99% CI = 0.31–0.93).

CONCLUSION: Each Advanced Cognitive Training for Independent and Vital Elderly cognitive intervention resulted in less decline in self-reported IADL compared with the control group. Reasoning and speed, but not memory, training resulted in improved targeted cognitive abilities for 10 years. **J Am Geriatr Soc 2013.**

Key words: cognitive training; elderly; cognitive abilities; everyday function; training maintenance

Cognitive decline is prevalent in older adults and is associated with decline in performance of instrumental activities of daily living (IADLs). Cognitive training has demonstrated utility for reducing cognitive decline in normal aging,[1,2] but evidence of its effectiveness in delaying difficulties in daily function has been limited.[3]

The Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) study is the first large-scale, randomized trial to show that cognitive training improves

From the *Department of Mental Health, Johns Hopkins University, †Center on Aging and Health, Johns Hopkins University, Baltimore, Maryland; ‡Department of Psychology, University of Alabama at Birmingham, Birmingham, Alabama; §New England Research Institutes, Watertown, Massachusetts; ‖Social and Health Policy Research, Hebrew SeniorLife, Boston, Massachusetts; #Division of Behavioral and Social Research, National Institute on Aging, Bethesda, Maryland; **Institute on Aging, University of Florida, ††Department of Clinical and Health Psychology, University of Florida, Gainesville, Florida; ‡‡Department of Psychiatry, School of Medicine, Indiana University, Indianapolis, Indiana; and §§Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, Washington.

The ACTIVE Study Group members are in Appendix A

Address correspondence to George W. Rebok, Department of Mental Health, The Johns Hopkins University, Hampton House 891, 624 North Broadway, Baltimore, MD 21205. E-mail: grebok@jhsph.edu

DOI: 10.1111/jgs.12607

0002-8614/13/$15.00

cognitive function in community-dwelling older adults for up to 5 years and to show evidence of transfer of that training to daily function.[4,5] Given the time lag in the relationship between cognitive change and appearance of functional deficits, it was was expected that the full extent of the intervention effects on daily function would take longer than 5 years to be evident in this well-functioning study population.[5]

Two hypotheses are derived from the trial's conceptual model[4,6] and prior findings; the effects of cognitive training are specific to the trained cognitive ability and durable to 10 years, and the effects of cognitive training will delay difficulties in daily function.[7,8]

METHODS

Design and Participants

ACTIVE is a multisite, randomized, controlled clinical trial (see[4] and[6] for details), with recruitment from March 1998 through October 1999 in six metropolitan areas. Community-dwelling adults aged 65 and older were eligible. Exclusion criteria were significant cognitive dysfunction (Mini-Mental State Examination (MMSE) score <23);[9] functional impairment (dependency or regular assistance in activities of daily living (ADLs) on Minimum Dataset (MDS) Home Care);[10] self-reported diagnoses of Alzheimer's disease, stroke within the last 12 months, or certain cancers; current chemotherapy or radiation therapy; or poor vision, hearing, or communicative ability that would have interfered with the interventions or outcome assessments. Participants (N = 2,832, average age 73.6, average education 13 years, 74% white and 26% African American, 76% female) were randomly assigned to one of three intervention groups (memory, reasoning, or speed-of-processing training) or a no-contact control group. Outcome assessments were conducted immediately and 1, 2, 3, 5, and 10 years after the intervention. Institutional review boards at participating institutions approved study procedures, and all participants provided written informed consent.

Interventions

ACTIVE training focused on memory, reasoning, and speed-of-processing because prior research indicated that these abilities show early age-related decline and are related to ADLs. Training was conducted in small groups in ten 60- to 75-minute sessions over 5 to 6 weeks. Memory training focused on improving verbal episodic memory through instruction and practice in strategy use. Reasoning training focused on improving ability to solve problems that contain a serial pattern. Speed-of-processing training focused on visual search and ability to process increasingly more-complex information presented in successively shorter inspection times. Booster training (four 75-minute sessions) was provided 11 and 35 months after training to a random subset (39%) of participants in each training group who completed at least eight of 10 training sessions; 60% of selected participants completed booster training at Years 1 and 3, 19% completed Year 1 booster only, 6% completed Year 3 booster only, and 15% did not complete any booster training. Sixty-one percent of the total sample (n = 1,694) was not selected to receive booster training.

Outcome Measures

Cognitive outcome measures assessed the effect of each cognitive training intervention on its targeted cognitive ability. Memory outcomes involved measures of episodic verbal memory: Rey Auditory-Verbal Learning Test total of five learning trials, the Hopkins Verbal Learning Test total of three learning trials, and the Rivermead Behavioural Paragraph Recall test immediate recall.[11–13] Reasoning outcomes involved measures requiring identification of patterns including total correct for Letter Series,[14] Letter Sets,[15] and Word Series.[16] Speed-of-processing outcomes involved three Useful Field of View (UFOV) tasks requiring identification and location of information, with 75% accuracy, under varying levels of cognitive demand.[17–19]

Functional outcome measures were used to assess whether training-related cognitive improvements improved everyday function. There were three measure of daily function. The self-reported measure of everyday IADL function was the IADL difficulty subscore from the MDS Home Care, which assesses performance in the past 7 days on 19 daily tasks spanning meal preparation, housework, finances, health care, telephone, shopping, travel, and need for assistance in dressing, personal hygiene, and bathing.[20] The validity and clinical utility of MDS scores have been established.[21,22] The two performance-based measures of daily function were Everyday Problem Solving, comprising the Everyday Problems Test[23] and Observed Tasks of Daily Living,[24] and Everyday Speed, comprising Complex Reaction Time[25] and Timed IADL.[26]

There were multiple measures of the cognitive and daily function outcomes. Because training effects on an outcome such as memory function were of interest, rather than the effects on each single test of memory function, composite scores were created for each area of cognitive and daily function using the average of the standardized scores for each test in that composite measure.[4–6]

Analysis

To evaluate the effects of ACTIVE training, an intention-to-treat analysis was conducted using a repeated-measures mixed-effects model[27] for each cognitive and daily function composite outcome. Several design features and three interaction terms were included in these models to measure the net effect of training and the net effect and added effect of booster training. Time was treated as a categorical variable (baseline, 1, 2, 3, 5, 10 years). Baseline measures of age, sex, cognitive status (MMSE score), years of education, and visual acuity were also included.

Training effects were assessed by comparing mean improvement from baseline to Year 10 in each of the three training groups with mean improvement from baseline to Year 10 in the nontrained control group. Effects of booster training were assessed similarly by comparing mean improvement from baseline to Year 10 in subjects receiving booster training with mean improvement from baseline to Year 10 in subjects who did not receive booster training.

This comparison was made for each of the three cognitive interventions. The analyses were first performed using available data.Then the effect of missing data was assessed by repeating the analysis using multiple imputation[28,29] and by conducting a sensitivity analysis that forced missing cognitive and daily function scores to be low. All statistical tests were two-sided. Analyses were conducted at the data coordinating center using R version 2.12.0.[30]

Results are presented as effect sizes, which quantify the size of the difference between a training group and the control group and provide a way to compare this difference between the training groups (e.g., does reasoning training have a better effect than memory training on each cognitive and daily function outcome). Cohen describes an effect size of 0.2 as small, 0.5 as medium, and 0.8 as large.[27] Because the analyses included six comparisons, a corrected significance level[31] of $P < .008$ was used.

In addition, the percentage of participants who showed reliable improvement in each training group was investigated using standard error of measurement (SEM).[32] Participants were classified as having improved reliably on a particular measure if their score at 10 years exceeded their baseline score on that measure by 0.66 SEM or was within 0.66 SEM of the baseline score.[33] For the purposes of this study, this was considered maintenance of performance. For each training group, the percentage with reliable change on each cognitive and daily function outcome was compared with that of the control group.

RESULTS

Sample Characteristics

Of 5,000 individuals contacted for participation, 2,802 were randomized in accordance with the protocol and constitute the analytical sample. Of those not randomized, approximately 41% were ineligible, 57% refused, and 1% were improperly randomized (Figure 1). Participants were less likely than those who refused to be female (76% vs 79%) and younger (mean age 74 vs 75) and more likely to be white (73% vs 60%), married (36% vs 27%), and better educated (mean 13.5 vs 12.3 years). Participants had higher MMSE scores (mean 27.3 vs 26.8) and were less likely to have heart disease (11% vs 14%) and diabetes mellitus (13% vs 17%) than were those who refused.

Baseline characteristics are shown in Table 1 according to intervention group. Eighty-nine percent of participants completed the training intervention. Those who completed the intervention were younger and had more education and higher baseline MMSE and cognitive function scores.

Sixty-seven percent of the sample was retained 5 years after training and 44% at 10 years. Death (40%) was the primary reason for nonparticipation at 10 years, followed by participant decision to withdraw (35%) and site decision to withdraw the participant because of continued missed visits in the absence of explicit refusal (17%). Predictors of attrition at 10 years included older age, male sex, not being married, higher alcohol consumption, more physical and mental health problems, and worse performance on cognitive outcomes. Attrition rates and predictors of attrition were similar between intervention groups.

Training Effects on Cognitive Abilities

Mean scores at baseline, change from baseline to Year 10, and the effect size of the intervention on each cognitive outcome are shown in Table 2. All interventions produced immediate improvement in the trained cognitive ability[6] (Figure 2). This improvement was retained for 10 years in the reasoning and speed trained groups (Table 2). The effect sizes indicate a small effect of the reasoning intervention (0.23) on the reasoning outcome and a medium to large effect of the speed intervention (0.66) on the speed outcome at 10 years. The effect of the memory intervention (0.06) on the memory outcome at 10 years was not significant. Similarly, there were significant effects of booster training for the reasoning (effect size = 0.21, CI = 0.01–0.41) and speed (effect size = 0.62, 99% CI = 0.31–0.93) interventions but not for the memory intervention.

Results of the analyses of reliable maintenance of cognitive function at 10 years (Table 2) show that 73.6% of reasoning-trained participants and 70.7% of speed-trained participants were performing at or above their respective cognitive ability, compared with 61.7% and 48.8%, respectively, of control participants ($P < .01$). The results for memory-trained participants were not significant.

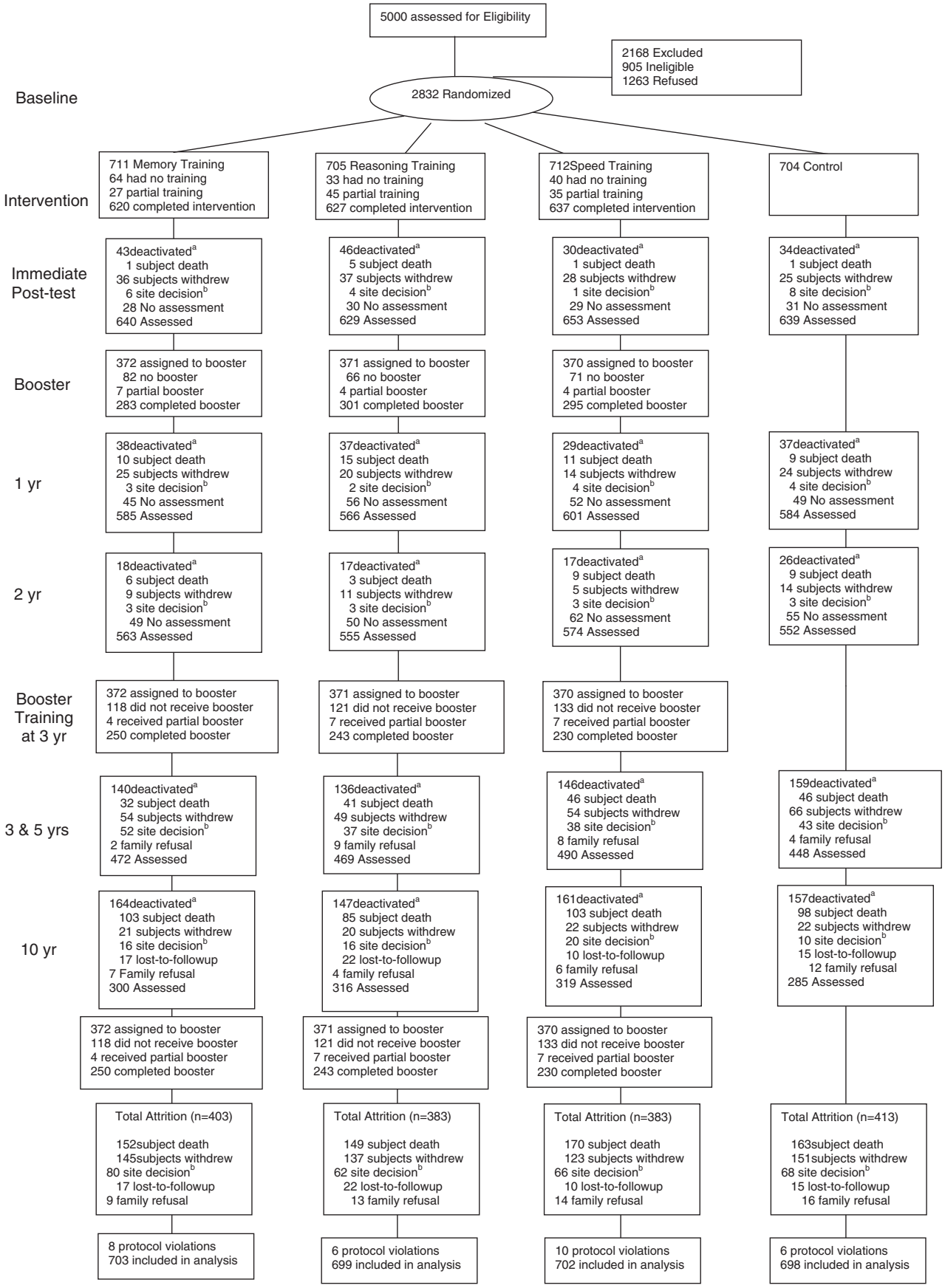
Training Effects on Daily Function

At Year 10, participants in all three intervention groups reported less difficulty performing IADLs than did participants in the control group (Table 2, Figure 3). The effects of the interventions (shaded in Table 2) were small to medium (0.48 for memory, 0.38 for reasoning, 0.36 for speed). Self-reported IADL function improved through 2 years (Figure 3). Then functional decline was first evident between Years 2 and 3 for all groups. From Years 3 to 5, the decline was less in the three intervention groups than in the control group. This difference in self-reported IADL function between trained participants and nontrained control participants was then maintained as all participants continued to decline (report more IADL difficulties) from Years 5 to 10.

Results of the reliable maintenance analysis (Table 2) are consistent with this pattern of temporal decline. Whereas at 10 years, 49.3% of control participants reported the same or improved level of IADL difficulty as at baseline, the proportions of trained participants reporting the same or improved level of IADL difficulty were significantly higher (memory, 61.6%, $P = .003$; reasoning, 60.2%, $P = .008$; speed, 58.5%, $P = .02$). There was no effect of training (Table 2) or added booster training (not shown) on the performance-based measures of everyday function. Finally, the results of models using multiple imputation for missing data and results of the sensitivity analysis (data not shown) were the same as the main results reported above.

DISCUSSION

In the ACTIVE trial, 10 to 14 weeks of organized cognitive training delivered to community-dwelling older adults resulted in significant improvements in cognitive abilities and better preserved functional status than in nontrained



[a]Deactivations include all reasons for discontinued participation: deaths, subject withdrawals, and site decision.

[b]Site decisions for deactivation primarily consisted of continuous missed study visits without explicit subject withdrawal.

Figure 1. Profile of the ACTIVE trial.

Table 1. Baseline Characteristics

Characteristic	Memory, n = 703	Reasoning, n = 699	Speed of Processing, n = 702	Control, n = 698
Age	73.5 ± 6.0 (65–93)	73.5 ± 5.8 (65–91)	73.4 ± 5.8 (65–91)	74.1 ± 6.1 (65–94)
Female, n (%)	537 (76.4)	537 (76.8)	538 (76.6)	514 (73.6)
Race, n (%)				
White	524 (74.5)	504 (72.1)	523 (74.5)	503 (72.1)
Black	176 (25.0)	190 (27.2)	175 (24.9)	187 (26.8)
Other or unknown	3 (0.4)	5 (0.7)	4 (0.6)	8 (1.2)
Years of education, mean ± SD (range)	13.6 ± 2.7 (5–20)	13.5 ± 2.7 (4–20)	13.7 ± 2.7 (5–20)	13.4 ± 2.7 (6–20)
Married, n (%)	257 (36.6)	249 (35.6)	242 (34.5)	259 (37.1)
Mini-Mental State Examination score, mean ± SD (range)	27.3 ± 2.1 (23–30)	27.3 ± 2.0 (23–30)	27.4 ± 2.0 (23–30)	27.3 ± 2.0 (23–30)
Short-Form 36 physical function score, mean ± SD (range)	69.1 ± 23.5 (5–100)	67.4 ± 24.1 (5–100)	69.7 ± 24.1 (0–100)	68.9 ± 24.6 (5–100)
Alcohol consumption, n(%)[a]				
Nondrinker	298 (42.4)	302 (43.2)	295 (42.0)	350 (50.1)
Light drinker	341 (48.5)	347 (49.6)	362 (51.6)	313 (44.8)
Heavy drinker	60 (8.5)	46 (6.6)	42 (6.0)	30 (4.3)
Center for Epidemiologic Studies Depression Scale score, mean ± SD (range)	5.1 ± 5.3 (0–36)	5.5 ± 5.3 (0–36)	5.2 ± 5.0 (0–36)	5.1 ± 4.9 (0–36)
Disease history, n (%)				
Hypertension	372 (53.1)	369 (53.2)	350 (50.1)	337 (48.8)
Diabetes mellitus	95 (13.5)	99 (14.2)	87 (12.4)	77 (11.0)
Transient ischemic attack or stroke	46 (6.6)	54 (7.8)	51 (7.3)	44 (6.3)
Ischemic heart disease	108 (15.5)	117 (17	94 (13.5)	102 (14.7)
Congestive heart failure	30 (4.3)	44 (6.4)	27 (3.9)	37 (5.4)
High cholesterol	309 (44.6)	316 (46.4)	305 (44.3)	296 (43.1)
Myocardial infarction	79 (11.3)	78 (11.2)	76 (10.9)	76 (10.9)

[a]Based on frequency of drinking alcohol and number of drinks on a typical day when drinking.
SD = standard deviation.

persons 10 years later. Each training intervention produced large and significant improvements in the trained cognitive ability. These improvements dissipated slowly but persisted to at least 5 years for memory training and to 10 years for reasoning and speed-of-processing training. This is the first demonstration of long-term transfer of the training effects on cognitive abilities to daily function.

Unlike for the nontrained participants, cognitive function for the majority of the reasoning and speed-trained participants was at or above their baseline level for the trained cognitive ability 10 years later. A significant percentage of participants in all trained groups (≥60%) continued to report less difficulty performing IADLs than nontrained participants (49%). After 10 years, 60% to 70% of participants were as well off as or better off than when they started.

Others have reported the absence of long-term memory training effects.[34] It is possible that the memory training used in ACTIVE requires more-extensive practice or greater dosing to reach durability levels than reasoning and speed training. It is also possible that age-related structural changes in the medial temporal lobe, including age-related neuropathology and even incipient Alzheimer's disease in some participants, limits the durability of memory training is in older adults.[35,36]

There are a number of possible reasons for the finding that training effects on self-reported daily function are maintained over time, whereas the training effects on cognitive abilities dissipate over time. First, this could reflect a cascade relationship between cognitive ability and daily function. Prospective observational studies indicate that changes in cognition precede changes in daily function by several years.[37] Second, improved cognitive processing may alter patterns of neural activation over the long term.[38,39] Third, training-based improvements in cognitive abilities may produce changes in behavior and social interaction that promote broad-based engagement in functional activities and maintenance over many years.

The effects of cognitive training on daily function in this study were modest. This is probably because manyfactors beyond cognition affect daily function and functional independence, including sex, social class, mood, sarcopenia, obesity, chronic diseases, and social isolation.[40,41] Even within the cognitive realm, some domains such as general cognitive status and executive cognitive ability may be more closely related to daily function than other domains (e.g., spatial skills).[42,43]

The current study showed weak to absent effects of cognitive training on performance-based measures of daily function. It is probably a mistake to conceive of these performance-based functional measures as something other than cognitive tests. The administration formats, task demands, and scoring all have more in common with standard cognitive tests than with actual ADLs. In addition,

Table 2. Effect of Training on Cognitive and Functional Outcomes From Baseline to Year 10

Cognitive and Functional Outcomes	Intervention Group			
	Memory	Reasoning	Speed	Control Group
Memory (possible range 0–132, N = 943)				
Score at baseline, mean ± SD	82.1 ± 25.7	79.5 ± 26.3	79.1 ± 25.5	79.8 ± 27.3
Mean change from baseline to year 10	−10.6	−11.2	−12.7	−9.4
Effect size (99% CI)[a]	0.06 (−0.14–0.27)	−0.11 (−0.31–0.10)	−0.05 (−0.25–0.15)	
At or above baseline level,%[b]	35.9	28.6	31.0	31.0
Reasoning (possible range 0–75, N = 938)				
Score at baseline, mean ± SD	31.8 ± 11.7	29.6 ± 12.3	28.9 ± 12.0	30.2 ± 12.8
Mean change from baseline to year 10	−3.2	−0.05	−3.9	−3.0
Effect size (99% CI)[a]	−0.02 (−0.17–0.12)	0.23 (0.09–0.38)	−0.06 (−0.20–0.08)	
At or above baseline level,%[b]	60.0	73.6 ($P < .01$)	59.3	61.7
Speed of Processing (possible range 0–1500, N = 883)				
Score at baseline, mean ± SD	774.1 ± 216.9	800.9 ± 231.0	830.0 ± 231.9	800.6 ± 231.8
Mean change from baseline to year 10	−144.4	−126.2	24.3	−123.3
Effect size (99% CI)[a]	−0.07 (−0.29–0.16)	0.005 (−0.22–0.23)	0.66 (0.43–0.88)	
At or above baseline level,%[b]	47.2	48.5	70.7 ($P < .01$)	47.8
Instrumental activity of daily living difficulty (possible range 0–38[c], N = 1,211)				
Score at baseline, mean ± SD	1.0 ± 1.8	1.2 ± 2.0	1.1 ± 2.0	0.9 ± 2.1
Mean change from baseline to year 10	−3.1	−2.7	−2.3	−3.6
Effect size (99% CI)[a]	0.48 (0.12–0.84)	0.38 (0.02–0.74)	0.36 (0.01–0.72)	
At or above baseline level,%[b]	61.6 ($P < .01$)	60.2 ($P < .01$)	58.5 ($P < .05$)	49.3
Everyday problem solving (possible range 0–56, N = 1,104)				
Score at baseline, mean±SD	40.7 ± 7.7	39.2 ± 8.1	38.7 ± 7.7	39.4 ± 9.1
Mean change from baseline to year 10	−6.1	−5.6	−6.0	−5.7
Effect size (99% CI)[a]	0.004 (−0.23–0.24)	−0.02 (−0.25–0.22)	0.008 (−0.23–0.24)	
At or above baseline level,%[b]	59.6	63.1	61.0	61.4
Everyday speed of processing (possible range −3–100, N = 938)[d]				
Score at baseline, mean ± SD	3.2 ± 1.0	3.3 ± 1.2	3.4 ± 1.3	3.4 ± 1.1
Mean change from baseline to year 10	1.5	−1.4	−1.5	−1.4
Effect size (99% CI)[a]	0.02 (−0.19–0.23)	−0.004 (−0.21–0.21)	−0.05 (−0.26–0.16)	
At or above baseline level,%[b]	34.9	30.5	29.0	30.2

[a]Effect size defined as training improvement from baseline to year 10 minus control improvement from baseline to year 10 divided by the intrasubject standard deviation (SD) of the composite score. Positive effect sizes indicate improvement.
[b]Calculated as the percentage of participants in each group who were ≥0.66 standard errors of measurement above baseline.
[c]Coded as 0 = no difficulty; 1 = some help needed or participant is slow or becomes tired; 2 = great difficulty.
[d]One component of this composite score is a standardized z score, with a potential range of $-\infty$ to ∞.
CI = confidence interval.

these performance-based measures call on multiple cognitive skills. A main lesson of the ACTIVE study and other cognitive intervention trials is that the benefits of cognitive training are specific to the cognitive ability trained. Viewed in this way, it is not surprising that the specific forms of cognitive training used in ACTIVE did not result in improvements on performance-based measures of daily function that are really multi-ability cognitive tests.

The ACTIVE 10-year retention rate was 44%. Death was the primary reason for nonparticipation (40%), followed by the subject's decision to stop participation (35%) and the site's decision to withdraw the subject (17%). In comparison, the Diabetes Prevention Program (DPPP) reported a 10-year retention rate of 59%,[44] although DPPP participants were more than 20 years younger (50.6) at enrollment than were ACTIVE participants at enrollment (73.0). The 10-year retention rate compares favorably with rates in observational studies of similar duration and samples of similar ages and ethnic diversity.[45,46] Although retained subjects were younger and had fewer physical and mental health problems at baseline, there was no difference between groups in attrition. This means that the training effects observed were not an artifact of differential attrition. Furthermore, in recognition of this attrition, appropriate methods were used to test assumptions about missing data and the validity of the inferences. First, the linear mixed-effects models are appropriate for situations with informative missingness and informative censoring.[47] In addition, the effect of missing data on the outcomes were analyzed using multiple imputation and a sensitivity analysis that assumed that missing outcome scores were low. Results of the analysis using multiple imputation and the sensitivity analysis were similar to the results of the mixed-effects models. Therefore, it is likely that the results regarding the effects of cognitive training interventions are robust.

The evaluation of the effect of booster training is limited because the two groups of interest (booster trained and non-booster trained) are not comparable. To be eligible for selection for booster training, participants had to have completed at least 80% of baseline training. In contrast, only 20% of non-booster-trained participants completed baseline training. Therefore, the non-booster-trained group was overrepresented by persons who did not

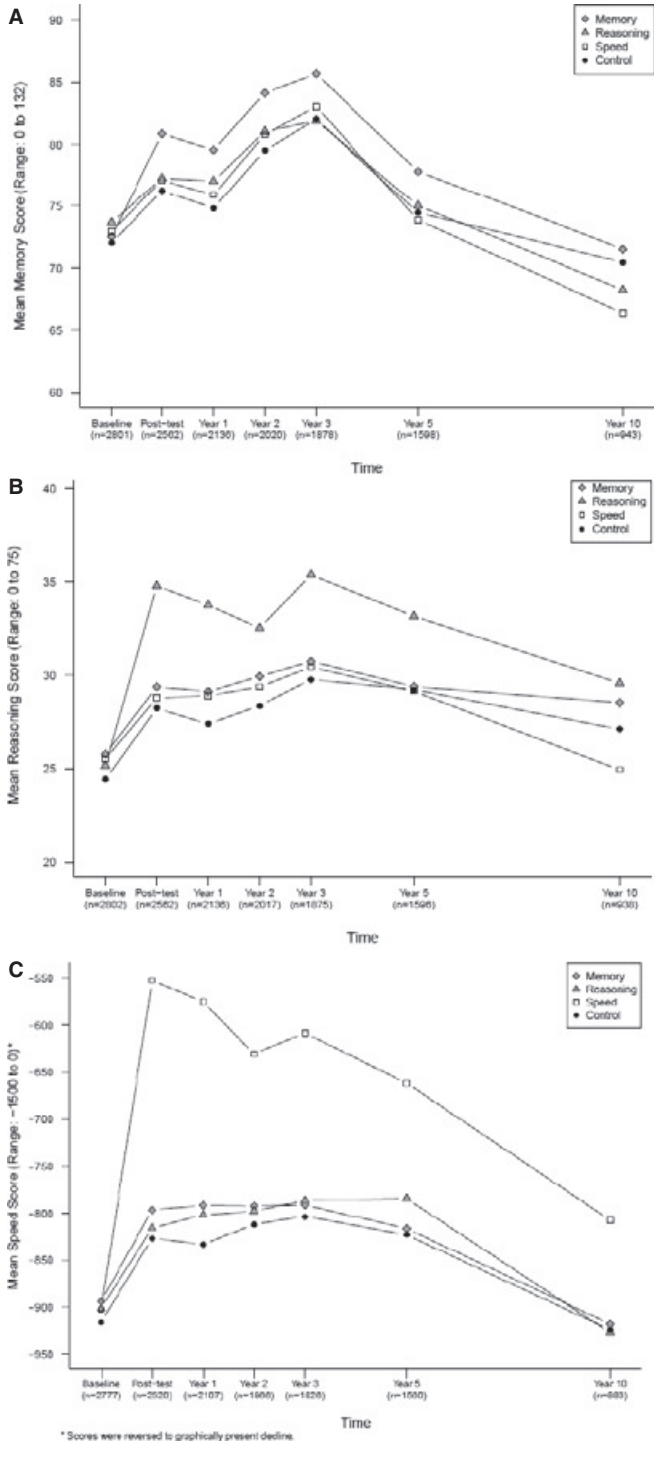


Figure 2. Cognitive outcomes according to time and training group. The figure displays mean scores for the three cognitive outcomes—memory (A), reasoning (B), speed of processing (C)—for each training group at each time point. Higher scores indicate better performance. The sample sizes show the number of participants with complete data for each cognitive outcome at each time point.

complete baseline training and reflected neither participants who completed baseline training nor nontrained participants (the control group) but something in between.

In summary, ACTIVE was the first multisite clinical trial to test the effects of cognitive training interventions

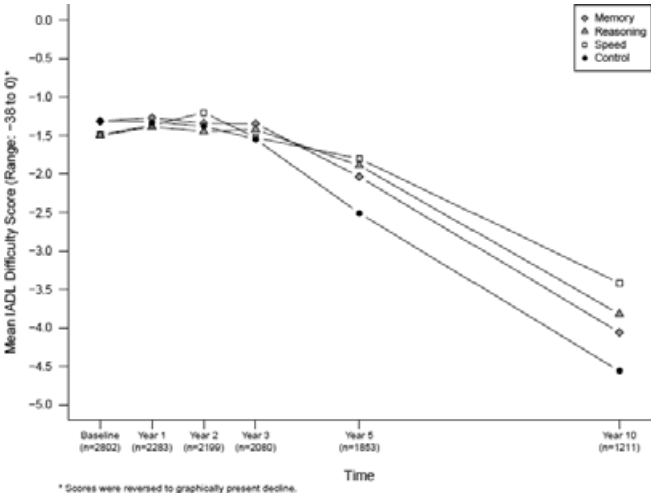


Figure 3. Training effects on self-reported instrumental activity of daily living (IADL) difficulty scores. The figure displays mean IADL difficulty scores for each training group at each time point. Higher scores indicate better functioning. The sample sizes show the number of participants with complete data for the IADL difficulty score at each time point.

on cognitive abilities and daily function. Results at 10 years demonstrate that cognitive training has beneficial effects on cognitive abilities and on self-reported IADL function. These results provide support for the development of other interventions, particularly those that target multiple cognitive abilities and are more likely to have an effect on IADL performance. Such interventions hold the potential to delay onset of functional decline and possibly dementia and are consistent with comprehensive geriatric care that strives to maintain and support functional independence. If interventions that could delay onset of functional impairment by even 6 years were introduced, the number of people affected by 2050 would be reduced by 38%,[48] which would be of great public health significance.

ACKNOWLEDGMENTS

The principal investigators thank the following National Institutes of Health project officers who were at their respective institutes during some or all of the project period: Jared Jobe, Daniel Berch, Jeffrey Elias, Sidney Stahl, and Jonathan King of the National Institute on Aging and Taylor Harden, Karin Helmers, Mary Leveck, Nell Armstrong, Kathy Koepke, and Susan Marden of the National Institute of Nursing Research. We also thank the ACTIVE participants and the research staff at each field site and the data coordinating center.

Conflict of Interest: ACTIVE is supported by grants from the National Institute on Aging and the National Institute of Nursing Research to Hebrew Senior Life (U01 NR04507), Indiana University School of Medicine (U01NR04508), Johns Hopkins University (U01AG-14260), New England Research Institute (U01 AG14282), Pennsylvania State University (U01 AG14263), University of Alabama at Birmingham (U01 AG14289), and University of Florida (U01AG14276). Drs. Unverzagt and Marsiske have received research support from Posit

Science, Inc., in the form of site licenses for cognitive training programs for investigator-initiated research projects. Dr. Marsiske has received research support from Robert Wood Johnson Foundation and McKnight Brain Research Foundation and payment for development of education presentations from the National Academy of Neuropsychology and the International Neuropsychological Society for workshops on cognitive interventions and from the National Institute on Aging and American Society on Aging for overview presentation on cognitive interventions. Dr. Ball is a consultant and owns stock in the Visual Awareness Research Group and Posit Science, Inc., the companies that market the UFOV Test and speed-of-processing training software, now called Insight (the Visual Awareness Research Group invented Insight and the UFOV). Dr. Ball serves as a member of the Posit Science Scientific Advisory Board. Posit Science paid royalties to the Visual Awareness Research Group (unrelated to the study described). The Visual Awareness Research Group is an S Corp; all profits and losses flow to stockholders. Dr. Rebok is an investigator with Compact Disc Incorporated for the development of an electronic version of the ACTIVE memory intervention. Drs. Morris and Jones received support from the Edward Fein Foundation and Vicki and Arthur Loring for research activities. The views expressed in this article are those of the authors and not to be ascribed to the National Institute on Aging, National Institute of Nursing Research or the Department of Health and Human Services.

Author Contributions: Drs. Guey and Kim had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Rebok, Ball, Jones, Marsiske, Morris, Tennstedt, Unverzagt, Willis. Acquisition of data: Rebok, Ball, Marsiske, Morris, Unverzagt, Willis. Analysis and interpretation of data: Rebok, Ball, Jones, King, Marsiske, Morris, Tennstedt, Unverzagt, Willis, Guey, Kim. Drafting of the manuscript: Rebok, Ball, Jones, King, Marsiske, Tennstedt, Unverzagt, Willis, Guey. Critical revision of the manuscript for important intellectual content: Rebok, Ball, Jones, King, Marsiske, Tennstedt, Unverzagt, Willis, Guey, Kim. Statistical analysis: Jones, Marsiske, Guey, Kim. Obtained funding: Rebok, Ball, Marsiske, Morris, Tennstedt, Unverzagt, Willis. Administrative, technical, or material support: Rebok, Ball, Jones, King, Marsiske, Morris, Tennstedt, Unverzagt, Willis, Guey, Kim. Study supervision: Rebok, Ball, Jones, Marsiske, Morris, Tennstedt, Unverzagt, Willis.

Sponsor's Role: Representatives of the National Institute on Aging and the National Institute of Nursing Research were directly involved in the design of the study, interpretation of the data, and preparation, review, and approval of the manuscript. These representatives also monitored the conduct of the study, collection, management, and analysis of the data.

REFERENCES

1. Hertzog C, Kramer A, Wilson R et al. Enrichment effects on adult cognitive development: Can the functional capacity of older adults be preserved and enhanced? Psychol Sci 2008;9:1–65.
2. Rebok G. Cognitive Training: Influence on Neuropsychological and Brain Function in Later Life. State-of-Science Review: SR:E22. London, UK: Government Foresight Mental Capital and Mental Wellbeing Project, Government Office for Science, 2008.
3. Pappa K, Walsh S, Snyder P. Immediate and delayed effects of cognitive interventions in healthy elderly: A review of current literature and future directions. Alzheimers Dement 2009;5:50–60.
4. Ball K, Berch DB, Helmers KF et al. Effects of cognitive training interventions with older adults: A randomized controlled trial. JAMA 2002; 288:2271–2281.
5. Willis SL, Tennstedt SL, Marsiske M et al. Long-term effects of cognitive training on everyday functional outcomes in older adults. JAMA 2006;296:2805–2814.
6. Jobe JB, Smith DM, Ball K et al. ACTIVE: A cognitive intervention trial to promote independence in older adults. Control Clin Trials 2001;22:453–479.
7. Lazaridis EN, Rudberg MA, Furner SE et al. Do activities of daily living have a hierarchical structure? An analysis using the longitudinal study of aging. J Gerontol 1994;49:M47–M51.
8. Wolinsky F, Miller D. Disability concepts and measurement: Contributions of the epidemiology of disability to gerontological inquiry. In: Wilmoth J, Ferraro K, eds. Gerontology: Perspectives and Issues. New York: Springer Publishing. 2006, pp ????–????. 2
9. Folstein MF, Folstein SE, McHugh PR. 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198.
10. Morris J, Morris S. ADL Assessment measures for use with frail elders. In: Teresi J, Lawton M, Holmes D et al., eds. Measurement in Elderly Chronic Care Populations. New York: Springer Publishing Co. 1997, pp ????–????. 3, 4
11. Brandt J. The Hopkins Verbal Learning Test: Development of a new memory test with six equivalent forms. Clin Neuropsychol 1991;5:125–142.
12. Rey A. L'examen psychologique dans les cas d'encéphalopathie traumatique. (Les problems.)./The psychological examination in cases of traumatic encepholopathy. Problems. Arch Psychologie 1941;28:215–285.
13. Wilson B, Cockburn J, Baddeley A. The Rivermead Behavioural Memory Test. Titchfield, Fareham, Hampshire, UK: Thames Valley Test Company, 1985.
14. Thurstone L, Thurstone T. Examiner Manual for the SRA Primary Mental Abilities Test (Form 10–14). Chicago: Science Research Associates, 1949.
15. Ekstrom R, French J, Harman H et al. Kit of Factor-Referenced Cognitive Tests, Rev Ed. Princeton, NJ: Educational Testing Service, 1976.
16. Gonda J, Schaie K. Schaie-Thurstone Mental Abilities Test: Word Series Test. Palo Alto, CA: Consulting Psychologists Press, 1985.
17. Owsley C, Ball K, Sloane ME et al. Visual/cognitive correlates of vehicle accidents in older drivers. Psychol Aging 1991;6:403–415.
18. Owsley C, Ball K, McGwin G Jr et al. Visual processing impairment and risk of motor vehicle crash among older adults. JAMA 1998;279:1083–1088.
19. Ball KK, Beard BL, Roenker DL et al. Age and visual search: Expanding the useful field of view. J Opt Soc Am 1988;5:2210–2219.
20. Morris JN, Fries BE, Steel K et al. Comprehensive clinical assessment in community setting: Applicability of the MDS-HC. J Am Geriatr Soc 1997;45:1017–1024.
21. Landi F, Tua E, Onder G et al. Minimum data set for home care: A valid instrument to assess frail older people living in the community. Med Care 2000;38:1184–1190.
22. Hirdes JP, Fries BE, Morris JN et al. Home care quality indicators (HCQIs) based on the MDS-HC. Gerontologist 2004;44:665–679.
23. Willis S, Marsiske M. Manual for the Everyday Problems Test. University Park, PA: Pennsylvania State University, 1993.
24. Diehl M, Marsiske M, Horgas AL et al. The revised observed tasks of daily living: A performance-based assessment of everyday problem solving in older adults. J Appl Gerontol 2005;24:211–230.
25. Ball K. Increased mobility and reducing accidents of older drivers. In: Schaie K, Pietrucha M, eds. Mobility and Transportation in the Elderly. New York: Springer. 2000, pp ????–????. 5
26. Owsley C, Sloane M, McGwin G Jr et al. Timed instrumental activities of daily living tasks: Relationship to cognitive function and everyday performance assessments in older adults. Gerontology 2002;48:254–265.
27. Brown H, Prescott R. Applied Mixed Models in Medicine, 2nd Ed. Chichester, UK: John Wiley, 2006.
28. Schafer J. Analysis of Incomplete Multivariate Data. London: Chapman & Hall, 1997.
29. van-Buuren S, Oudshoorn C. mice: Multivariate Imputation by Chained Equations in R. J Stat Softw 2011;45:1–67.
30. Team RDC. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing, 2008.

31. Abdi H, ed. Bonferroni and Šidák Corrections for Multiple Comparisons. Thousand Oaks, CA: Sage, 2007.
32. Dudek F. The continuing misinterpretation of the standard error of measurement. Psychol Bull 1979;86:335–337.
33. Garrett H. Statistics in Psychology and Education. New York: Longsman, 1937.
34. Scogin F, Bienias JL. A three-year follow-up of older adult participants in a memory-skills training program. Psychol Aging 1988;3:334–337.
35. Singer T, Lindenberger U, Baltes PB. Plasticity of memory for new learning in very old age: A story of major loss? Psychol Aging 2003;18:306–317.
36. Jack CR Jr, Knopman DS, Jagust WJ et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol 2010;9:119–128.
37. Schaie K. Developmental Influences on Adult Intellectual Development: The Seattle Longitudinal Study. New York: Oxford University Press, 2005.
38. Kelly AM, Garavan H. Human functional neuroimaging of brain changes associated with practice. Cereb Cortex 2005;15:1089–1102.
39. May A, Hajak G, Ganssbauer S et al. Structural brain alterations following 5 days of intervention: Dynamic aspects of neuroplasticity. Cereb Cortex 2007;17:205–210.
40. Beland F, Zunzunegui MV. Predictors of functional status in older people living at home. Age Ageing 1999;28:153–159.
41. Baumgartner RN, Wayne SJ, Waters DL et al. Sarcopenic obesity predicts instrumental activities of daily living disability in the elderly. Obes Res 2004;12:1995–2004.
42. Royall D, Lauterbach E, Kaufer D et al. The cognitive correlates of functional status: A review from the Committee on Research of the American Neuropsychiatric Association. J Neuropsychiatry Clin Neurosci 2007;19:249–265.
43. Johnson JK, Lui LY, Yaffe K. Executive function, more than global cognition, predicts functional decline and mortality in elderly women. J Gerontol A Biol Sci Med Sci 2007;62A:1134–1141.
44. Knowler WC, Fowler SE, Hamman RF et al. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. Lancet 2009;374:1677–1686.
45. Carlson MC, Xue QL, Zhou J et al. Executive decline and dysfunction precedes declines in memory: The Women's Health and Aging Study II. J Gerontol A Biol Sci Med Sci 2009;64A:110–117.
46. Gao S, Thiébaut R. Mixed-effect models for truncated longitudinal outcomes with nonignorable missing data. J Data Sci 2009;7:27–42.
47. Park S, Palta M, Shao J et al. Bias adjustment in analysing longitudinal data with informative missingness. Stat Med 2002;21:277–291.
48. Sloane PD, Zimmerman S, Suchindran C et al. The public health impact of Alzheimer's disease, 2000–2050: Potential implication of treatment advances. Annu Rev Public Health 2002;23:213–231.

APPENDIX A: ACTIVE STUDY INVESTIGATORS

In addition to the principal investigators and program officers, the following persons participated in the ACTIVE study: Hebrew SeniorLife—Adrienne L. Rosenberg, MS; Indiana University School of Medicine—Daniel F. Rexroth, PsyD., David M. Smith, MD, Lyndsi Moser, CCRP, Fredric D. Wolinsky, PhD; Johns Hopkins University—Jason Brandt, PhD, Kay Cresci, PhD, RN, Joseph Gallo, MD, MPH, Laura Talbot, PhD, EdD, RN, CS; New England Research Institutes (Data Coordinating Center)—Kathleen Cannon, BS, Michael Doherty, MS, Henry Feldman, PhD, Patricia Forde, BS, Nancy Gee, MPH, Eric Hartung, EdD, Linda Kasten, MS, Ken Kleinman, ScD, Herman Mitchell, PhD, George Reed, PhD, Anne Stoddard, ScD, Yan Xu, MS, Elizabeth Wright, PhD; Pennsylvania State University—Pamela Davis, MS, Scott Hofer, PhD, K. Warner Schaie, PhD; University of Alabama at Birmingham—Jerri Edwards, PhD, Martha Graham, MA, MGS, Cynthia Owsley, PhD, Dan Roenker, PhD, David Vance, PhD, Virginia Wadley, PhD; University of Florida/Wayne State University—Manfred K. Diehl, PhD, Ann L. Horgas, RN, PhD, FAAN, Peter A. Lichtenberg, PhD, ABPP.

Author Query Form

Journal: JGS
Article: 12607

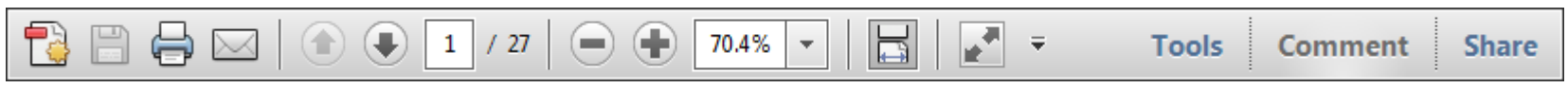
Dear Author,
During the copy-editing of your paper, the following queries arose. Please respond to these by marking up your proofs with the necessary changes/additions. Please write your answers on the query sheet if there is insufficient space on the page proofs. Please write clearly and follow the conventions shown on the attached corrections sheet. If returning the proof by fax do not write too close to the paper's edge. Please remember that illegible mark-ups may delay publication.
Many thanks for your assistance.

Query reference	Query	Remarks
1	AUTHOR: Please check that authors and their affiliations are correct.	
2	AUTHOR: Please provide the page range for reference [8].	
3	AUTHOR: Please provide the page range for reference [10].	
4	AUTHOR: If there are fewer than 4 editors for reference [10], please supply all of their names. If there are 4 or more editors, please supply the first 3 editor names then et al. Please check and update all such references found in the list.	
5	AUTHOR: Please provide the page range for reference [25].	
6	AUTHOR: Figure 2 has been saved at a low resolution of 183 dpi. Please resupply at 600 dpi. Check required artwork specifications at http://authorservices.wiley.com/bauthor/illustration.asp.	
7	AUTHOR: Figure 3 has been saved at a low resolution of 192 dpi. Please resupply at 600 dpi. Check required artwork specifications at http://authorservices.wiley.com/bauthor/illustration.asp.	

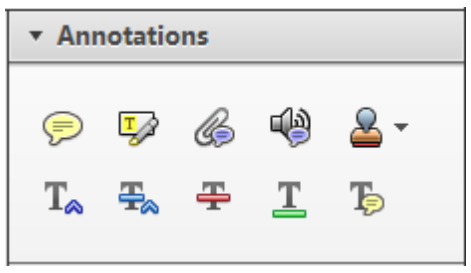
USING e-ANNOTATION TOOLS FOR ELECTRONIC PROOF CORRECTION

Required software to e-Annotate PDFs: Adobe Acrobat Professional or Adobe Reader (version 8.0 or above). (Note that this document uses screenshots from Adobe Reader X)
The latest version of Acrobat Reader can be downloaded for free at: http://get.adobe.com/reader/

Once you have Acrobat Reader open on your computer, click on the Comment tab at the right of the toolbar:



This will open up a panel down the right side of the document. The majority of tools you will use for annotating your proof will be in the Annotations section, pictured opposite. We've picked out some of these tools below:

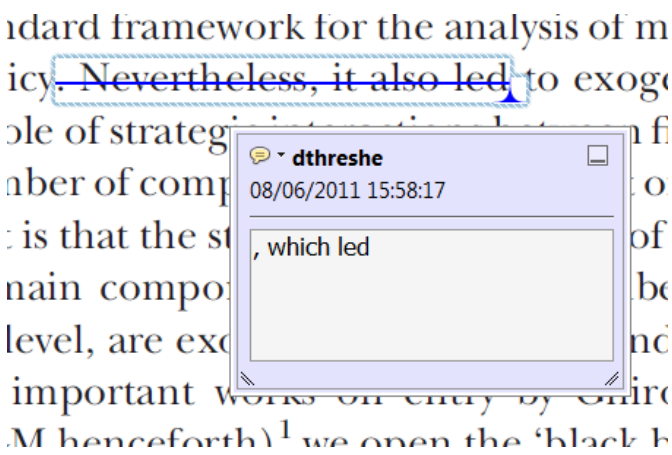


1. Replace (Ins) Tool – for replacing text.

Strikes a line through text and opens up a text box where replacement text can be entered.

How to use it

- Highlight a word or sentence.
- Click on the Replace (Ins) icon in the Annotations section.
- Type the replacement text into the blue box that appears.

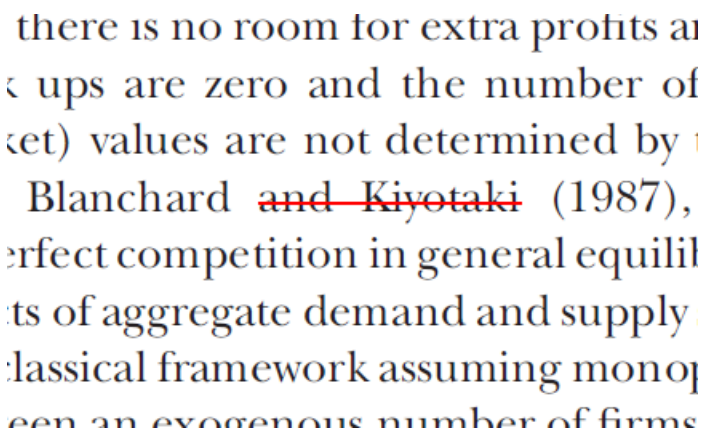


2. Strikethrough (Del) Tool – for deleting text.

Strikes a red line through text that is to be deleted.

How to use it

- Highlight a word or sentence.
- Click on the Strikethrough (Del) icon in the Annotations section.

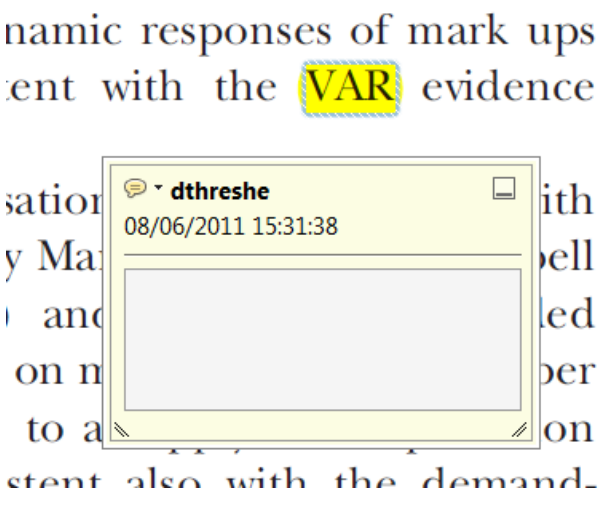


3. Add note to text Tool – for highlighting a section to be changed to bold or italic.

Highlights text in yellow and opens up a text box where comments can be entered.

How to use it

- Highlight the relevant section of text.
- Click on the Add note to text icon in the Annotations section.
- Type instruction on what should be changed regarding the text into the yellow box that appears.

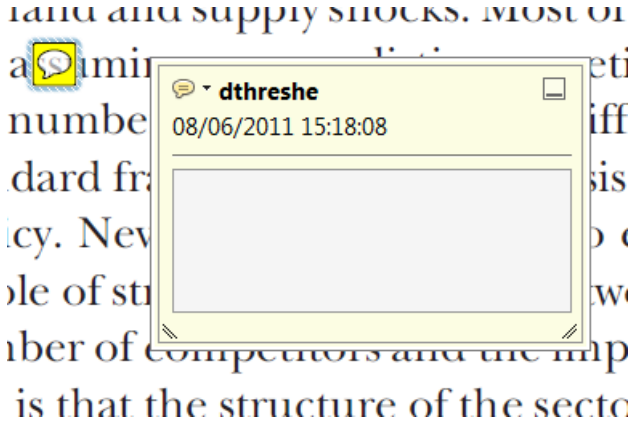


4. Add sticky note Tool – for making notes at specific points in the text.

Marks a point in the proof where a comment needs to be highlighted.

How to use it

- Click on the Add sticky note icon in the Annotations section.
- Click at the point in the proof where the comment should be inserted.
- Type the comment into the yellow box that appears.



WILEY-BLACKWELL

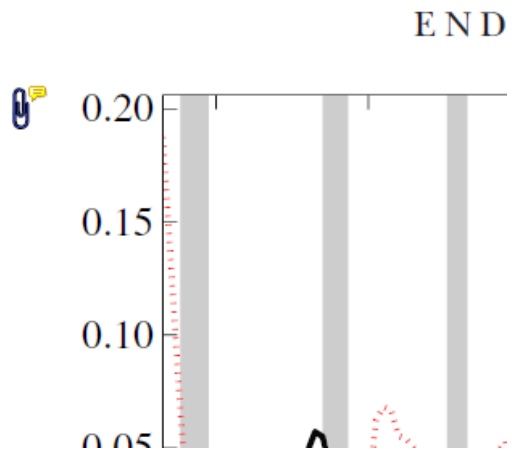
USING e-ANNOTATION TOOLS FOR ELECTRONIC PROOF CORRECTION

5. Attach File Tool – for inserting large amounts of text or replacement figures.

Inserts an icon linking to the attached file in the appropriate pace in the text.

How to use it

- Click on the Attach File icon in the Annotations section.
- Click on the proof to where you'd like the attached file to be linked.
- Select the file to be attached from your computer or network.
- Select the colour and type of icon that will appear in the proof. Click OK.

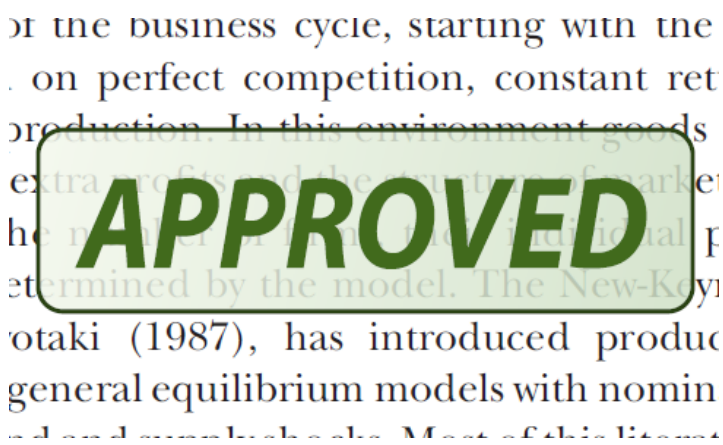


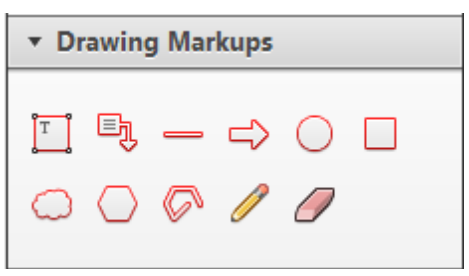
6. Add stamp Tool – for approving a proof if no corrections are required.

Inserts a selected stamp onto an appropriate place in the proof.

How to use it

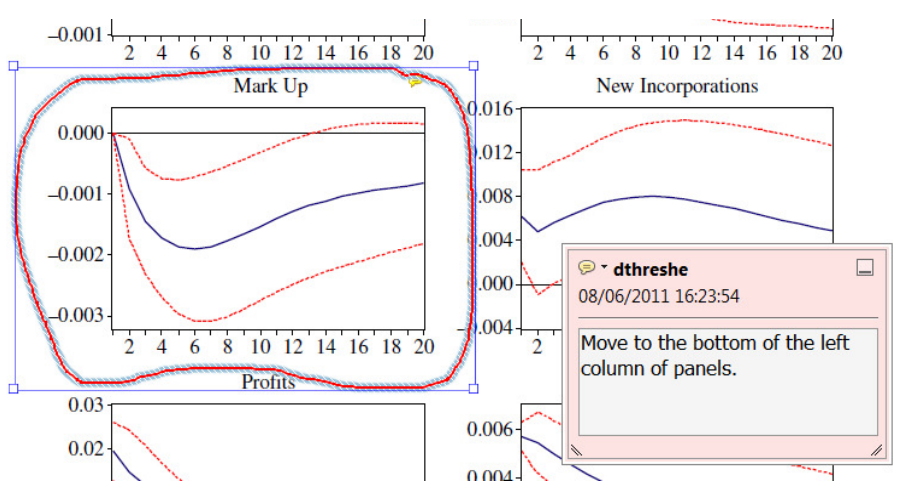
- Click on the Add stamp icon in the Annotations section.
- Select the stamp you want to use. (The Approved stamp is usually available directly in the menu that appears).
- Click on the proof where you'd like the stamp to appear. (Where a proof is to be approved as it is, this would normally be on the first page).





7. Drawing Markups Tools – for drawing shapes, lines and freeform annotations on proofs and commenting on these marks.

Allows shapes, lines and freeform annotations to be drawn on proofs and for comment to be made on these marks..



How to use it

- Click on one of the shapes in the Drawing Markups section.
- Click on the proof at the relevant point and draw the selected shape with the cursor.
- To add a comment to the drawn shape, move the cursor over the shape until an arrowhead appears.
- Double click on the shape and type any text in the red box that appears.

For further information on how to annotate proofs, click on the Help menu to reveal a list of further options: