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The ACTIVE Cognitive Training Trial and Health-Related Quality of Life: Protection That Lasts for 5 Years

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Objective. We evaluated the ability of the three cognitive training interventions (memory, reasoning, or speed of processing) fielded in the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) multisite randomized controlled trial to protect against two thresholds of extensive decline in health-related quality of life (HRQoL) at 2 and 5 years post-training.

Method. Adults aged 65 years or older (2802) were enrolled and randomized to three cognitive interventions or a no-contact control group. Data on 1804 participants were available at both the 2- and 5-year follow-ups. HRQoL was measured by the eight MOS 36-Item Short-Form Health Survey (SF-36) scales. Clinically relevant decline on each scale was defined as a drop of $\geq$ 0.5 standard deviations from baseline. Extensive HRQoL decline was defined as clinically relevant drops on (i) $\geq$ 4 SF-36 scales, and (ii) $\geq$ 3 SF-36 scales, and was assessed using multiple logistic regressions, weighted to adjust for potential attrition bias.

Results. At 2 years post-training, 23.7% and 36.6% had clinically relevant drops on $\geq$ 4 and $\geq$ 3 SF-36 scales, respectively. At 5 years post-training, 32.9% and 47.3% had clinically relevant drops on $\geq$ 4 and $\geq$ 3 SF-36 scales, respectively. Participants in the speed of processing intervention arm were significantly less likely to have extensive HRQoL decline compared to participants in the control group regardless of the threshold or time period, whereas participants in the memory and reasoning intervention arms were significantly less like to have extensive HRQoL decline only at 5 years post-training and only at the lower threshold.

Conclusion. The effect of the speed of processing intervention was stronger and evident earlier than those for the memory and reasoning interventions. This result stems from the speed of processing intervention being the most procedural intervention, operating through sensory-motor elaboration and repetition, bringing about a broader pattern of regional brain activation. At 5 years post-training, however, all three interventions were successful in protecting against a lower threshold of age-related extensive declines in HRQoL.

OLDER adults face declining cognitive ability and increasing difficulty with activities of daily living (ADLs) and instrumental ADLs (IADLs) (1), which are the primary risk factors for nursing home placement (2–4). After nursing home placement occurs, the risk for mortality increases (3,5), most likely due to failure to thrive (6,7). Moreover, after cognitive decline has been documented, there is evidence suggesting that triage results in decreased proclivity for both inpatient and outpatient health services (8,9). Thus, it is not surprising that cognitive decline is the greatest fear of older adults.

Even before institutionalization is considered, however, declining cognitive ability is a major risk for disability (10). It is well known that the prevalence of cognitive and functional impairment increases with age (11). Indeed, it is estimated that 4–5 million Americans (about 2% overall and 15% of those older than 65 years) have some form and degree of cognitive failure (12). With cognitive and functional loss comes decreased social interaction, and reduced leisure-time physical activity with accompanying decrements in quality of life and active life expectancy (13). Therefore, noninvasive interventions that can delay the pace of cognitive decline have much to contribute both to public health and to quality of life among older people.

It is not surprising, then, that numerous cognitive enhancement interventions for older adults exist (14), although few of those target prevention in cognitively intact elderly persons (15). Reports from the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) (16) study, a large multisite randomized controlled trial (RCT) of cognitively intact older adults, have strongly supported the effectiveness of its three distinct cognitive training interventions in improving targeted cognitive ability (15). In addition, ACTIVE's speed of processing intervention was observed to have a protective effect against extensive clinically relevant declines in health-related quality of life

(HRQoL) at 2 years post-training (17). However, this effect was not observed at 2 years post-training for the memory and reasoning interventions.

Two plausible explanations were posited for this. First, of the three cognitive interventions, speed of processing is the most clearly procedural, operating through sensory-motor elaboration and repetition, whereas the memory and reasoning interventions emphasize or require the explicit learning of new concepts. Procedural tasks have a broader pattern of regional brain activation (18); this may account for the greater sense of well-being captured by the HRQoL ratings. The second explanation suggested that the lack of protective effects from the memory and reasoning interventions may have occurred from a combination of the low rate (25%) of extensive decline in HRQoL observed at 2 years post-training, and because 2 years may not have been sufficient time for an effect targeted at delaying decline (rather than improving current status) to materialize.

The purpose of this study is to determine if the three ACTIVE cognitive interventions were effective in delaying extensive clinically relevant decline in HRQoL at 5 years post-training. To do this, we use data from both the 2-year and the recently completed 5-year post-training follow-up interviews. Moreover, we also consider two definitional thresholds for extensive decline in HRQoL.

Methods

Design

ACTIVE was a single-blind RCT with three treatment arms (memory, reasoning, or speed of processing) and a no-contact control group. All treatment arms involved 10 equal-length, standardized intervention sessions. Those researchers conducting the outcome assessments were blinded to the treatment assignment of their participants. In addition to outcome assessments immediately following completion of the training, outcomes were assessed at 1, 2, 3, and 5 years post-training (16).

Sample

At each of the six sites, participants were recruited who were 65 years old or older and were living independent of formal care. These participants, however, were at risk for loss of functional independence. Each site used slightly different recruitment strategies from March 1998 through October 1999 (16), and a total of 4970 potential participants were identified. Exclusion criteria were (a) cognitive impairment (Mini-Mental State Examination [MMSE] score < 23) (19), (b) vision $< 20/50$, (c) hygiene, bathing, or dressing dependence, (d) Alzheimer's disease, (e) strokes occurring in the prior year, (f) limited life expectancy from cancer, (g) chemotherapy or radiation treatment ongoing at enrollment, (h) difficulty communicating, (i) intent to move, (j) scheduling conflicts, and (k) prior participation in cognitive training. These exclusion criteria were met by 905 individuals (18.2%), and another 1263 individuals (25.4%) refused either to be screened or to be enrolled. Of the 2802 participants screened, enrolled, and randomized, 1804 (64.4%) were successfully reassessed on all outcomes at 5 years post-training. Attrition was not associated with treatment status.

Interventions

In each of the three treatment arms, sessions 1–5 focused on strategy instruction and practice exercises, whereas sessions 6–10 provided additional practice. Content was scripted in a trainer's manual and involved laboratory-type and everyday activities (16). Reasoning training focused on inductive reasoning, the ability to solve problems that follow a serial pattern and are manifest in executive functioning. Memory training focused on verbal episodic memory, with participants taught mnemonic strategies for remembering lists, sequences of items, text material, and main ideas and story details. Speed training focused on visual search and the ability to identify and locate visual information in a divided attention format, with and without distraction.

HRQoL

HRQoL was measured with the widely used MOS 36-Item Short-Form Health Survey (SF-36) (20). Detailed descriptions and procedures, as well as the exact wording of the SF-36 items are available elsewhere (21–26). Thirty-five of the 36 items make up eight scales: physical functioning (10 items), role limitations due to physical functioning (4 items), bodily pain (2 items), general health perceptions (5 items), vitality (4 items), social functioning (2 items), role limitations due to emotional problems (3 items), and mental health (5 items). Within scales, missing data are imputed using a prorated method. Scores are transformed to range from 0 (worst health) to 100 (best health).

Clinically relevant changes in HRQoL were defined as a decline of ≥ 0.50 standard deviations (*SD*) between baseline and the 5-year follow-up, as suggested by Cohen (27). Although different cut points have been recommended, the most widely cited are very close to Cohen's .50 *SD* level (28–30), and a recent meta-analysis found that the mean estimated meaningfully important difference was 0.50 *SD* (31). Moreover, given seven response options per scale question, 0.50 *SD* is close to the estimated maximum human ability to discriminate between two feeling states (32). Thus, the 0.50 *SD* effect size is used here to define clinically relevant change in a single SF-36 scale. We used two definitional thresholds for extensive HRQoL decline. As in our previous report (17), the first is defined as clinically relevant change in four or more of the eight SF-36 scales, which reflects decline in a majority of the SF-36 domains. Our second definitional threshold for extensive HRQoL decline requires clinically relevant change in only three or more of the eight SF-36 scales. This lower threshold is included to evaluate whether the memory and reasoning interventions are also protective, but only against somewhat less robust HRQoL declines.

Attrition Bias

Of the 2802 ACTIVE participants, 1804 (64.4%) were reassessed on the HRQoL outcomes at the 5-year follow-up, creating the potential for attrition bias. Therefore, propensity score methods were used to adjust for it (33–35). Simply

Table 1. Means or Percentages of Sociodemographic, Functional Status, and SF-36 Scales Scores at Baseline, by Treatment Arm, Weighted to Adjust for Attrition Bias ($N = 1804$)

Variables	Memory Intervention $N = 453$	Reasoning Intervention $N = 447$	Speed Intervention $N = 448$	Control Group $N = 456$	p Value
Sociodemographics					
Age	73.9	74.0	73.3	74.2	.123
Women, %	74.6	73.0	75.4	74.0	.845
African American, %	26.1	27.6	30.4	30.0	.434
Functional status					
ADLs	0.36	0.27	0.26	0.30	.327
IADLs	4.43	4.51	4.36	4.08	.564
MMSE score	27.1	27.2	27.2	27.3	.792
EPT	18.5	18.1	18.2	18.1	.644
Depressive symptoms	5.2	5.9	5.4	4.9	.044
Chronic conditions	2.3	2.4	2.3	2.2	.281
SF-36 scales					
Physical function	68.4	65.6	68.0	67.9	.314
Role physical	59.2	52.7	63.2	60.1	.001
Bodily pain	67.1	63.3	66.1	66.2	.045
Social function	86.6	82.8	85.8	88.1	.001
Mental health	80.2	78.1	79.4	80.4	.123
Role emotional	73.9	69.5	74.6	75.8	.055
Vitality	61.2	59.3	62.1	61.4	.173
General health	68.3	65.8	69.6	68.6	.026

Note: SF-36 = MOS 36-Item Short-Form Health Survey; ADL = Activities of Daily Living; IADLs = Instrumental ADLs; MMSE = Mini-Mental State Examination; EPT = Everyday Performance Test.

put, a multivariable logistic regression model of whether outcome data were available at the 5-year follow-up was estimated, and the predicted probabilities of inclusion in the analytic sample were computed. The average participation rate within each propensity score (predicted probability) quintile was then determined, and the inverse (1 − the participation rate) was used to weight the data, giving greater influence to retained participants who were most like those participants who were not followed. The propensity score model included binary indicators for each of the three cognitive intervention arms, baseline age, sex, race, cognitive function, basic ADLs, IADLs, cognitive ADLs, depressive symptoms, comorbid medical conditions, and SF-36 scale scores.

Analysis

After weighting the data to adjust for potential attrition bias, a simple intent-to-treat analysis was conducted. A multivariable regression model was estimated that included binary indicators for each of the three cognitive intervention arms. This regression model was estimated using HRQoL change data derived from both the 2- and 5-year post-training interviews, first for the more stringent definitional threshold used previously (17), and then for the less stringent definitional threshold. All analyses include only the 1804 ACTIVE participants who were successfully re-interviewed at both 2 years and 5 years post-training.

Results

Descriptive Results

Table 1 contains means or percentages for selected sociodemographic and functional status characteristics, as well as the eight SF-36 scale scores at baseline, by treatment group. Overall, the 1804 ACTIVE participants who were successfully interviewed at both the 2-year and 5-year follow-ups were 73.0 years old, 78% were women, and 23.5% were African American. The mean MMSE (19) score was 27.6, the average number of ADLs with difficulty (36) was 0.3, and the average number of IADLs with difficulty (37) was 4.1. The mean number of successful answers on the Everyday Performance Test (38) was 18.2, the average number of depressive symptoms (39) was 5.4, and the mean number of chronic conditions (40) was 2.3. As shown, the only significant difference was on depressive symptoms, for which the control group was favored. In contrast, data in Table 1 show significant differences in baseline SF-36 scale scores by treatment group. These differences, however, form no consistent pattern in advantaging or disadvantaging any of the treatment groups. Moreover, it is important to remember that it is the extent of clinically relevant decline over time, not at baseline, that is under examination.

Propensity Score Model

Table 2 contains the results of the multiple logistic regression analysis predicting follow-up at 5 years. As shown, none of the cognitive intervention treatment arms were significantly associated with retention to the 5-year follow-up. Among the other factors in the model, loss to follow-up was associated with older age, being African American, and male gender. Retention to the 5-year follow-up was associated with better MMSE scores, better Everyday Performance Test scores (cognitive ADL function), and better scores on the SF-36 physical function scale. The not statistically significant ($p = .594$) Hosmer–

Table 2. Multiple Logistic Regression Analysis of Completion of the 5-Year Follow-Up Interview ($N = 2802$)

Independent Variables	Adjusted Odds Ratio	95% Confidence Interval	*p* Value
Treatment arms			
Memory	1.114	.885, 1.403	.358
Reasoning	1.163	.922, 1.467	.202
Speed	1.131	.897, 1.426	.298
Baseline covariates			
Age	.969	.955, .984	.001
Women	1.620	1.295, 2.026	.001
African American	.804	.653, .989	.039
MMSE	1.086	1.035, 1.139	.001
ADLs	1.002	.911, 1.103	.960
IADLs	.993	.974, 1.012	.458
EPT	1.042	1.023, 1.062	.001
CES-D	1.005	.983, 1.028	.638
Chronic conditions	.986	.927, 1.048	.645
Baseline SF-36 scale scores			
Physical function	1.007	1.003, 1.012	.003
Role physical	.998	.995, 1.001	.289
Bodily pain	.996	.991, 1.001	.102
Social function	1.003	.997, 1.009	.299
Mental health	.999	.991, 1.006	.731
Role emotional	1.001	.999, 1.004	.318
Vitality	1.005	.999, 1.011	.119
General health	1.001	.995, 1.006	.851

Note: MMSE = Mini-Mental State Examination; ADL = Activities of Daily Living; IADLs = Instrumental ADLs; EPT = Everyday Performance Test; CES-D = Centers for Epidemiological Studies–Depression Scale; SF-36 = MOS 36-Item Short-Form Health Survey.

Lemeshow statistic (41) and the C-statistic (.658) (42), respectively, indicate that the propensity score model fit the data well (i.e., had no evidence of heteroscedastic error) and was moderately successful in accurately distinguishing between those followed and not followed for 5 years.

Clinically Relevant Declines in SF-36 Scales

Table 3 shows the percentage of participants at each number (0–8) of clinically relevant declines (i.e., ≥ 0.50 *SD*) between baseline and the 2- and 5-year follow-ups on the eight SF-36 scales. These data indicate that there was considerable decline in HRQoL by 2 years post-training and that, as expected, this decline increased substantially by 5 years post-training. At 2 years post-training, 23.7% and 36.6% had clinically relevant drops on ≥ 4 and ≥ 3 SF-36 scales, respectively. At 5 years post-training, 32.9% and 47.3% had clinically relevant drops on ≥ 4 and ≥ 3 SF-36 scales, respectively.

Extensive Decline in HRQoL

Table 4 contains the results from the multiple logistic regression analysis of whether the ACTIVE participants had extensive declines in HRQoL at 2 years and 5 years post-training. In this analysis, extensive declines were defined as clinically relevant change on four or more of the SF-36 scales between baseline and the 2- or 5-year follow-ups. The results of this intent-to-treat analysis show that participants in the speed of processing intervention treatment arm were significantly protected from extensive declines in HRQoL at both 2 and 5 years post-training (adjusted odds ratios [AORs] = 0.617 and 0.744, *p* values = .004 and .038, respectively). Participants in the memory and reasoning treatment arms, however, were not significantly protected from extensive HRQoL decline at either period.

Table 3. Percentage Distribution of the Number of Clinically Important Declines (i.e., ≥ 0.5 *SD*) on the SF-36 Scales at the 2- and 5-Year Follow-Ups, Weighted to Adjust for Attrition Bias ($N = 1804$)

Number of Clinically Important Declines	At the 2-Year Follow-Up	At the 5-Year Follow-Up
None	25.7%	18.6%
One	21.0%	18.7%
Two	16.7%	15.5%
Three	12.9%	15.0%
Four	9.2%	11.9%
Five	7.1%	9.2%
Six	4.2%	5.7%
Seven	2.6%	3.7%
All Eight	0.6%	1.7%
	100.0%	100.0%

Note: *SD* = Standard deviation; SF-36 = MOS 36-Item Short-Form Health Survey.

Table 5 contains the results when extensive declines were defined as clinically relevant change on three or more of the SF-36 scales between baseline and the 2- or 5-year follow-ups. The results of this intent-to-treat analysis again show that participants in the speed of processing intervention treatment arm were significantly protected from extensive declines in HRQoL at both 2 and 5 years post-training (AORs = 0.740 and 0.737, *p* values = .033 and .022, respectively) and that the amount of risk reduction was virtually identical over time. Participants in the memory and reasoning treatment arms, however, were not significantly protected from extensive HRQoL decline at 2 years post-training, but were significantly protected from extensive HRQoL decline at 5 years post-training (AORs = 0.664 and 0.762, *p* values = .002 and .041, respectively).

Discussion

Inasmuch as ACTIVE is the largest multisite RCT ever conducted that focuses on improving or maintaining cognitive performance among older adults (16), the results reported here are especially important. At both 2 and 5 years post-training, the speed of processing intervention provided significant protection against extensive declines in HRQoL, and this was the case regardless of whether that outcome was defined as clinically important declines on four or more or on three or more of the eight SF-36 scales. Moreover, the risk reduction for participants in the speed of processing intervention treatment arm was nearly identical over time for the less robust definitional threshold, and only modestly lower for the more rigorous definitional threshold. In contrast, memory and reasoning had significant protective effects against extensive decline in HRQoL at 5 years post-training, but only when the less robust definitional threshold was used. However, under those circumstances, the pro-

Table 4. Adjusted Odds Ratios of Extensive Decline in HRQoL at the 2- and 5-Year Follow-Ups (i.e., ≥ 0.5 *SD* Decline on ≥ 4 SF-36 Scale Scores) for Each Cognitive Intervention Group Versus Control Group, Weighted to Adjust for Attrition Bias ($N = 1804$)

Two-Year and Five-Year Outcomes	Percentage With ≥ 4 CIDs	Adjusted Odds Ratio	95% Confidence Interval	*p* Value
2-Year				
Memory	26.5%	1.117	0.829, 1.506	.468
Reasoning	27.4%	1.169	0.868, 1.574	.305
Speed	16.6%	0.617	0.444, 0.856	.004
Control (Reference)	24.4%	1.000		
5-Year				
Memory	32.3%	.851	.647, 1.120	.250
Reasoning	31.2%	.809	.614, 1.067	.133
Speed	29.5%	.744	.563, .983	.038
Control (Reference)	36.0%	1.000		

Note: HRQoL = Health-Related Quality of Life; *SD* = standard deviation; SF-36 = MOS 36-Item Short-Form Health Survey; CIDs = clinically important differences.

Table 5. Adjusted Odds Ratios of Extensive Decline in HRQoL at the 2- and 5-Year Follow-Ups (i.e., ≥ 0.5 *SD* Decline on ≥ 3 SF-36 Scale Scores) for Each Cognitive Intervention Group Versus Control Group, Weighted to Adjust for Attrition Bias ($N = 1804$)

Two-Year and Five-Year Outcomes	Percentage With ≥ 3 CIDs	Adjusted Odds Ratio	95% Confidence Interval	*p* value
2-Year				
Memory	39.3%	1.099	0.841, 1.436	.491
Reasoning	39.7%	1.117	0.854, 1.460	.419
Speed	30.4%	0.740	0.561, 0.976	.033
Control (Reference)	37.1%	1.000		
5-Year				
Memory	43.9%	0.664	0.511, 0.862	.002
Reasoning	46.7%	0.762	0.586, 0.989	.041
Speed	45.8%	0.737	0.567, 0.957	.022
Control (Reference)	53.5%	1.000		

Note: HRQoL = Health-Related Quality of Life; *SD* = standard deviation; SF-36 = MOS 36-Item Short-Form Health Survey; CIDs = clinically important differences.

tective effects of memory and reasoning were comparable to that of speed of processing.

On the one hand, we believe that the speed of processing intervention has its effect at both definitional thresholds, and has it sooner than do the memory and reasoning interventions, because speed of processing operates through sensory-motor elaboration and repetition. It has been shown that such procedural tasks have a broader pattern of regional brain activation than explicit memory tasks (18). Improved brain activation or structure may delay the onset of (if not reduce the risk for) ''slowing down.'' Because slowing down is the single most dreaded fear of older adults (43), the tempo reductions delayed or avoided by participants in the speed of processing intervention may have helped these older adults retain higher (i.e., baseline) perceptions of their HRQoL compared to their counterparts.

On the other hand, it is not surprising that all three cognitive interventions—memory, reasoning, and speed of processing—ultimately had protective effects against extensive decline in HRQoL. Declining cognitive ability is a major risk for disability (10), and decreased social interaction, reduced leisure-time physical activity, and accompanying decrements in quality of life and active life expectancy are known sequelae of cognitive and functional loss (13), and it has been shown that each of the three cognitive interventions had significant effects on their targeted cognitive abilities (15). Why, though, were the protective effects of memory and reasoning against extensive HRQoL decline manifest only at 5 years post-training, and why did they only occur for the less robust definitional threshold? Based on the data shown in Tables 4 and 5, we can unequivocally say that the failure to detect significant protective effects for the memory and reasoning interventions at 2 years post-training was not due to statistical power, as previously assumed (17). That is, the 2-year post-training AORs for the memory and reasoning cognitive interventions, regardless of the definitional threshold, were greater than unity, not less than it. Issues related to statistical power would have affected the confidence intervals around the point estimates, but not the point estimates themselves.

But why was the speed of processing effect observed sooner, and at the higher definitional threshold? It has already been noted that speed of processing was the most procedural of the interventions, and its computer-based delivery allowed participants to proceed at their own pace. We believe that the former transferred across more HRQoL domains, and that the latter allowed maximal effective dosing. As a result, the speed of processing intervention provided protection across a wider spectrum of HRQoL domains and provided that protection sooner than did the memory and reasoning interventions.

What is less clear is whether the indisputable and protective effects of the speed of processing intervention will be observed when more distal outcomes are examined. Specifically, it will be important to determine whether these protective effects translate into more appropriate and reduced levels of health services utilization and resource consumption, and ultimately into greater longevity. Examining these outcomes is the next step.

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