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The ACTIVE conceptual framework as a structural equation model

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Abstract

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Background/Study Context—Conceptual frameworks are analytic models at a high level of abstraction. Their operationalization can inform randomized trial design and sample size considerations.

Methods—The Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) conceptual framework was empirically tested using structural equation modeling (N=2,802). ACTIVE was guided by a conceptual framework for cognitive training in which proximal cognitive abilities (memory, inductive reasoning, speed of processing) mediate treatment-related improvement in primary outcomes (everyday problem-solving, difficulty with activities of daily living, everyday speed, driving difficulty), which in turn lead to improved secondary outcomes (health-related quality of life, health service utilization, mobility). Measurement models for each proximal, primary, and secondary outcome were developed and tested using baseline data. Each construct was then combined in one model to evaluate fit (RMSEA, CFI, normalized residuals of each indicator). To expand the conceptual model and potentially inform future trials, evidence of modification of structural model parameters was evaluated by age, years of education, sex, race, and self-rated health status.

Results—Preconceived measurement models for memory, reasoning, speed of processing, everyday problem-solving, instrumental activities of daily living (IADL) difficulty, everyday speed, driving difficulty, and health-related quality of life each fit well to the data (all RMSEA < .05; all CFI > .95). Fit of the full model was excellent (RMSEA = .038; CFI = .924). In contrast with previous findings from ACTIVE regarding who benefits from training, interaction testing revealed associations between proximal abilities and primary outcomes are stronger on average by nonwhite race, worse health, older age, and less education ($p < .005$).

Conclusions—Empirical data confirm the hypothesized ACTIVE conceptual model. Findings suggest that the types of people who show intervention effects on cognitive performance potentially may be different from those with the greatest chance of transfer to real-world activities.

A conceptual framework is the totality of concepts that categorize observations and predictions (Kluge, 2006). Conceptual frameworks help researchers organize and communicate hypothesized relationships and complex phenomena by generating testable hypotheses that can be falsified. They bring significance and context to findings from studies. Conceptual frameworks in cognitive aging research guide the conceptualization of results and inform ongoing and future research. They provide opportunities to reflect on the original design, adequacy of sample sizes, and intensity of study follow-up. Insights from conceptual frameworks can guide innovation in future intervention research and pilot studies.

The Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) project proceeded along a plan of intervention research by presuming a causal structure implied by a conceptual framework (Jobe et al., 2001). This conceptual framework, reproduced in Figure 1, specifies presumed relationships among proximal abilities (e.g., memory, inductive reasoning, and speed of processing), primary outcomes (e.g., everyday problem-solving, instrumental activities of daily living [IADL] functioning, everyday speed, driving habits), and secondary outcomes, including health-related quality of life (HRQOL) and health services utilization. For example, memory should be related to everyday problem-solving

ability (solid lines in Figure 1), but not speed of processing (dotted lines in Figure 1). Memory and reasoning should be indirectly associated with HRQOL through everyday problem-solving and IADL functioning but not through everyday speed (Jobe et al., 2001).

Individual studies published from ACTIVE examined parts of the conceptual framework. Major publications from the ACTIVE study have focused on the effect of ACTIVE training on proximal cognitive outcomes (Ball et al., 2002; Rebok et al., 2014; Willis et al., 2006). Some have reported evidence of cognitive training on primary outcomes, including IADL functioning (Rebok et al., 2014; Willis et al., 2006). Other publications in ACTIVE have characterized associations between proximal and primary abilities, including memory with IADL functioning and everyday problem-solving (Gross, Rebok, Unverzagt, Willis, & Brandt, 2011a); memory and reasoning with everyday problem-solving (Yen, Rebok, Gallo, Jones, & Tennstedt, 2011); memory, reasoning, and speed with IADL functioning (Gross, Rebok, Unverzagt, Willis, & Brandt, 2011b), proximal cognitive abilities and driving cessation (Ackerman, Edwards, Ross, Ball, & Lunsman, 2008); and proximal cognitive abilities and everyday speed (Owsley, Sloane, McGwin, & Ball, 2002). McArdle and Prindle (2008) directly tested the transfer of training gains from proximal to primary outcomes. With respect to secondary outcomes, studies have linked cognitive impairment with mobility limitations (O'Connor, Edwards, Wadley, & Crowe, 2010) and everyday functioning (Wadley et al., 2007), speed of processing with health-related quality of life (Wolinsky et al., 2010), health and driving cessation (Edwards, Lunsman, Perkins, Rebok, & Roth, 2009), and proximal cognitive abilities with health-related quality of life (Wolinsky et al., 2006).

We are aware of no study that has comprehensively tested the ACTIVE conceptual framework, which is the goal of this study. ACTIVE and other cognitive intervention studies are predicated on the veracity of this presumed structure and our ability to adequately measure constructs in it. If relationships between proximal and primary outcomes are weak or nonexistent, then the feasibility of attempting to demonstrate transfer of training to primary and then secondary outcomes is dubious. In this study, we analyzed between-persons correlations among constructs in the model using baseline data. Although no causal directions can be concluded from this analysis alone, such cross-sectional models define potential upper limits to longitudinal effects, and thus the most optimistic estimates of effect sizes.

In addition to testing hypothesized relationships in the ACTIVE conceptual model, we further tested for moderators of relationships that were not originally hypothesized in ACTIVE, as subsequent research has suggested that relationships may differ by demographic and health characteristics (e.g., Ball et al., 2013; Rebok et al., 2013; Willis et al., 2013). Given its role in disease processes and individual differences, the National Institutes of Health (NIH) has recently emphasized the importance of reporting sex-specific effects of interventions (NIH, 2015). Recent studies have shown persons with lower self-rated health have steeper decline in memory (Bendayan et al., 2016). These effect modification analyses can potentially inform whether or not specific subgroups may show transfer in future trials, thus informing who to target for public health interventions (e.g., Kraemer, Wilson, Fairburn, & Agras, 2002). Such differences have theoretical and public health importance and offer a natural way for the conceptual framework to evolve in future

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trials. These tests of moderation represent indirect evaluations of whether associations between proximal, primary, and secondary outcomes may be stronger (compensatory) or weaker (amplification) for groups who perform poorly in initial testing (Verhaeghen et al., 1996). If associations between proximal outcomes and primary/secondary outcomes are weaker in groups who generally perform poorly on cognitive tests at baseline, then a cognitive training intervention might show greater effects on primary and secondary outcomes in higher-performers, whereas low performers might benefit only in proximal outcomes. Alternatively, associations that are stronger in lower-performing groups than in higher-performing groups could lead to compensation, or observable reductions in group differences in outcomes, as a consequence of intervention.

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In the present study, we used structural equation modeling (SEM) to model hypothesized as well as novel relationships between constructs using available measures in ACTIVE based on the ACTIVE conceptual framework (Jobe et al., 2001; Figure 1). Each construct was first separately factor-analyzed in a measurement model to optimize fit to the data. We then combined measurement models for all constructs together in a single model to explore hypothesized and additional pathways. In an extension to the ACTIVE conceptual framework, we tested effect modification by demographic and health variables. We hypothesized that the data would fit well to the framework but did not specify a priori hypotheses about effect modifiers.

Methods

Participants

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ACTIVE was a randomized, controlled, single-masked trial that tested training interventions in memory, reasoning, and speed of processing in adults aged 65 and older across six university-based sites (University of Alabama at Birmingham, Johns Hopkins University, Penn State University, Wayne State University, Hebrew Rehabilitation Center for the Aged, Indiana University). Participants were randomized to receive training in memory, inductive reasoning, or speed of processing, or to a no-contact control group following their baseline visit and followed up immediately after training, and 1, 2, 3, 5, and 10 years later. The present study uses baseline data for $N = 2802$ older adults.

Variables

We constructed factors based on measures of memory, reasoning, speed of processing, everyday problem-solving, IADL difficulty, everyday speed, driving difficulty, and HRQOL. Health services utilization questions were also included.

Memory performance (proximal outcome)—The memory factor was constructed using immediate recall from three memory tests: the Hopkins Verbal Learning Test (HVL; Brandt, 1991), Auditory Verbal Learning Test (AVLT; Rey, 1964), and paragraph recall of the Rivermead Behavioral Memory Test (RBMT; Wilson, Cockburn, & Baddeley, 1985). Because of differences in versions used for the HVL and AVLT in ACTIVE (Gross et al., 2012), we used equipercentile-equated versions of the scores.

Reasoning performance (proximal outcome)—The reasoning factor was represented by the Letter Series, Word Series, and Letter Sets tasks (Ekstrom, French, Harman, & Derman, 1976; Gonda & Schaie, 1985; Thurstone & Thurstone, 1949; Willis, 1996).

Speed of processing performance (proximal outcome)—We used the last three subscales from the Useful Field of View task (Owsley et al., 2002), which has been described and used previously in the ACTIVE study (Willis et al., 2006).

Everyday problem-solving (primary outcome)—The primary outcome factor for everyday problem-solving was represented by the Everyday Problems Test (EPT; Marsiske & Willis, 1995; Willis & Marsiske, 1993), the Observed Tasks of Daily Living (OTDL; Diehl et al., 2005), and the Timed Instrumental Activities of Daily Living test (TIADLs; Ball, 2000; Owsley, Sloane, McGwin, & Ball, 2002).

IADL difficulty (primary outcome)—We used 12 IADL indicators representing difficulty planning meals, cooking, washing dishes, doing laundry, balancing a checkbook, keeping records of expenses, taking medications, taking injections, remembering phone numbers, remembering numbers, shopping, and traveling by vehicle.

Everyday speed (primary outcome)—The outcome of everyday speed was represented by two subtasks of the Road Sign Complex Reaction Time task (Ball et al., 2000).

Driving difficulty (primary outcome)—Driving difficulty was assessed by a factor analysis of eight items from the Driving Habits Questionnaire (Owsley, Stalvey, Wells, & Sloane, 1999; Stalvey, Owsley, Sloane, & Ball, 1999). These self-reported Likert-scaled items gauged whether participants in the last 12 months have driven alone, driven in the rain, driven on high-traffic roads, driven at night, made lane changes, made left-hand turns, merged into traffic, and driven in rush-hour traffic.

Health-related quality of life (secondary outcome)—The Medical Outcomes Study 36-item Short-Form Health Survey (SF-36) is a widely used measure of HRQOL and uses eight core dimensions to define HRQOL: physical function, role limitations due to physical problems, social functioning, bodily pain, mental health, role limitations due to emotional problems, vitality, and general health (Ware & Sherbourne, 1992). We used a general factor to represent HRQOL from the SF-36 items and included secondary factors for each of the eight subdomains but only report associations of the general HRQOL domain with other constructs.

Health care utilization (secondary outcome)—Health care utilization was represented in the operationalization of the ACTIVE conceptual framework using three yes/no questions: “Do you see a physician regularly?” “Have you ever been in a hospital overnight?” and “Have you ever been in a nursing home?” We did not construct a factor from these questions because health care utilization is too heterogeneous a construct for factor analysis.

Effect modifiers—Age, years of education, sex, race, and baseline self-rated health status were considered as effect modifiers in an extension of the original ACTIVE conceptual framework. We used tests of effect modification to evaluate the relative strength of associations among primary, proximal, and distal outcomes across strata of demographic and health characteristics. There was no missingness in these variables.

Analysis plan

To test hypothesized relationships (Figure 1), analyses were conducted in three steps. First, in a measurement model step for each construct, we constructed factors using component measures. For each construct, we estimated a factor analysis using maximum likelihood estimation for continuous indicators and weighted least squares estimation for categorical estimators in Mplus version 7.3 software (Muthén & Muthén, 2014). We evaluated contributions of each item to the overall fit by evaluating normalized residuals (calculated by the difference between sample and model-estimated correlations) to determine item-level fit of each indicator to each model to help pinpoint any areas of model misfit (Bollen, 1989). We also report overall model fit with the root mean square error of approximation (RMSEA; Steiger, 1989) and the comparative fit index (CFI; Hu & Bentler, 1999).

Second, guided by the ACTIVE conceptual diagram (Figure 1), we assembled each construct from the first step (memory, reasoning, speed of processing, everyday problem-solving, IADL difficulty, everyday speed, driving difficulty, health-related quality of life) in one overall model to test structural relationships among the factors. We tested alternative models by adding regressions among constructs that were not originally hypothesized, and we dropped relationships hypothesized a priori that were estimated to be small and not significantly ($p < .05$) different from 0. Third, to evaluate support for compensatory versus amplification hypotheses that were not part of the original ACTIVE conceptual framework, we tested for effect modification of associations in the ACTIVE conceptual model by age (65–74 vs. 75 years), years of education (<12 vs. 12 years), sex, race (white vs. nonwhite), and self-rated health (excellent, very good vs. good, fair, poor). Cutoffs for age, years of education, and self-rated health were based on median splits of the sample on these variables. Effect modification was evaluated using multiple-group SEM in Mplus version 7.3 software (Muthén & Muthén, 2014). Specifically, we allowed parameters to vary by group and tested for any differences by calculating the difference in coefficients and the standard error of the differences using the Delta method. Because the tests of effect modification involved regression comparisons for each of five models, we used an adjusted $p < .005$ to determine statistical significance in these models. For continuous variable factor analyses, data are assumed to be missing at random conditional on variables in the model.

Sensitivity analyses

Tests of effect modification by demographic and health subgroups are potentially vulnerable to ceiling or floor effects in the proximal, primary, and distal outcome measures: if ceiling effects are greater in one group than another, then correlations with other variables may be weaker in that group. For example, if there is a ceiling effect in the speed of processing factor, and if highly educated participants are overrepresented at that ceiling, then we might expect stronger associations between speed of processing and primary outcomes among the

group with less years of education. To address this, we calculated factor scores from Mplus for each score and evaluated histograms of them for evidence of ceiling effects. We reran multiple-group SEM analyses excluding data on a construct's measurement model for participants at the ceiling of the factor score if histograms demonstrated a ceiling or floor effect.

Results

Descriptive statistics

ACTIVE ($N = 2802$) is a mostly white (72%), female (76%), and well-educated sample (mean age: 14 years; range: 4–20 years). Self-related health was mostly good, fair, or poor (56%). The mean age at study baseline was 74 years (range: 65–94 years), with 80% of the sample falling between the ages of 66 and 82. There were no missing data for descriptive variables, and there were minimal (<15%) missing data for indicators used in factor analyses.

Model fitting for each factor

Factor analyses for each construct fit well to the data based on RMSEA, CFI, and normalized residuals of each pairwise correlation among indicators (see Supplemental Tables 3–9). Based on normalized residuals, which are scaled to a $N(0, 1)$ distribution, we included a methods factor in IADL difficulty for items related to money management; resulting overall fit was excellent (RMSEA = .041, CFI = .955). For HRQOL, we included specific factors for the eight subdomains of the SF-36, and resulting model fit of that measurement model was acceptable (RMSEA = .057, CFI = .952). Aside from these and from health care utilization variables for which we did not attempt to construct a reflective factor model, unidimensional models were sufficient for the other constructs (see normalized residuals in the supplemental tables).

Full model in ACTIVE

The full model in ACTIVE fit well (RMSEA = .042, CFI = .906; results not presented). We expanded the full model to include associations not originally hypothesized by Jobe and colleagues (2001) between proximal and primary outcomes; this model fit well also (RMSEA = .038, CFI = .924). Specifically, we modeled nonhypothesized associations between memory performance and everyday speed as well as driving difficulty, between reasoning performance and everyday speed as well as driving difficulty, and between speed of processing and everyday problem-solving. Strengths of associations are shown in Table 1. Hypothesized associations between all proximal and primary outcomes were statistically significant (Table 1). Better performance on all proximal outcomes were associated with less IADL difficulty, better everyday problem-solving ability, faster everyday speed, and less driving difficulty. In the expanded model, associations between speed of processing and everyday problem-solving, between memory and reasoning and everyday speed, and between memory and reasoning and driving difficulty were also significant.

With respect to secondary outcomes, high overall HRQOL was associated with less IADL difficulty and faster everyday speed, but not with driving difficulty or everyday problem-

solving (Table 1). There were relatively few associations of primary outcomes with health care utilization.

Hypothesized associations of HRQOL with driving difficulty and with everyday problem-solving did not reach statistical significance. Further, only two associations between health services utilization and primary outcomes were significant. When we removed these structural relationships, overall model fit remained excellent (RMSEA = .038, CFI = .925), although model fit compared with the full model was worse (χ^2 difference test = 220.30, df = 12, p < .05).

Effect modification

With respect to race, memory and reasoning ability were more strongly associated with everyday problem-solving in nonwhite participants (Tables 2–6). Better memory predicted faster everyday speed more strongly in nonwhite participants.

With respect to effect modification by sex, relationships between proximal and primary outcomes did not differ between men and women. For secondary outcomes, IADL difficulty was more strongly associated with HRQOL in women. Higher everyday speed was associated with spending a night in the hospital only among women (Table 3).

With respect to effect modification of pathways by self-rated health status (Table 4), associations tended to be stronger among the less healthy: in that group, reasoning ability was more strongly coupled with better everyday problem-solving and faster everyday speed, and slower speed of processing was more strongly coupled with greater IADL difficulty.

With respect to effect modification by age (Table 5), better reasoning performance was linked to higher everyday problem-solving most strongly in adults aged 75 and older. Better memory was associated with less IADL difficulty only in the older age group. Better memory and reasoning ability were both more strongly related to faster everyday speed in the older age group.

With respect to effect modification by years of education (Table 6), better memory and reasoning ability were more strongly associated with everyday problem-solving ability in participants with a high school education or less, although these predictors were also still important in the more highly educated group.

Sensitivity analyses

Supplemental Figures 1–8 show density plots of estimated factor scores for each construct tested, stratified by the demographic and health characteristics we tested in effect modification analyses. There was a ceiling effect (indicating slow performance) for the speed of processing proximal outcome for n = 138 participants (Supplemental Figure 3). More of these participants were in the 75+ age group than in the younger group. There was a floor effect (indicating less difficulty) for the IADL difficulty primary outcome, affecting n = 1438 participants (Supplemental Figure 5). A larger number of these participants were in the groups with better self-rated health, younger age group, and the group with more than 12 years of education. Finally, there was a floor effect (indicating less difficulty) for the driving

difficulty secondary outcome, affecting $n = 1496$ participants (Supplemental Figure 5). On average, participant characteristics associated with performance at the floor of driving difficulty included white race, male sex, high self-rated health, age less than 75 years, and higher amount of education.

When we reran effect modification analyses excluding speed of processing data for participants at the ceiling for speed of processing (see Supplemental Table 1 for the overall results table), IADL difficulty data for participants at the floor for IADL difficulty, and driving difficulty data for participants at the floor for driving difficulty, the association of speed of processing with IADL difficulty no longer differed by self-rated health status (Supplemental Table 2). The association between memory and everyday speed no longer differed by age. Otherwise, no inferences changed.

Discussion

We tested a conceptual framework that has guided ACTIVE, a large study of cognitive training for older adults, as well as many subsequent cognitive training research programs. Model fit statistics confirmed that each construct is essentially unidimensional, and well-indicated by content-valid measures. Given the statistical significance of nonhypothesized associations between proximal and primary ACTIVE outcomes, the specificity of relationships suggested by the original ACTIVE conceptual framework is not supported. We further explored effect modification, which was not originally hypothesized in the ACTIVE conceptual model but supported by subsequent research, and uncovered remarkable group differences in associations—mostly between proximal and primary outcomes. Promising cross-sectional associations between proximal measures and secondary outcomes are suggestive of potential causal links, but the associations must be replicated using longitudinal data. The potential value of this study is the ability to examine the extent to which transfer may be expected based on the magnitude of cross-sectional associations among proximal, primary, and secondary outcomes in empirical data.

A consensus among psychologists and neuroscientists recently issued a critical statement regarding salutary effects of computerized cognitive training in older adults (Stanford Center on Longevity, 2014). Key to their skepticism was the lack of evidence for transfer of abilities trained to other outcomes in traditional training programs. This study provides standardized effect sizes in Tables 1 and 2 that can be used to determine sample sizes needed to detect transfer. For example, from Table 1, the fully standardized regression coefficient linking memory with everyday problem-solving is 0.49 (95% confidence interval [CI]: 0.46, 0.51). We also know the standardized effect of memory training on memory was 0.23 *SD* (95% CI: 0.11, 0.35) after 5 years (Willis et al., 2006) and -0.06 *SD* (95% CI: -0.14 , 0.27) after 10 years (Rebok et al., 2014). Thus, we can presume the upper-bound effect of a training intervention resulting in a 0.23 *SD* improvement on memory at 5 years can have at most a $0.23 \times 0.49 = 0.11$ *SD* gain in everyday problem-solving at 5 years. Interestingly, Willis and colleagues (2006, table 4) reported a 0.15 effect size (99% CI: -0.02 , 0.28) for memory training in everyday problem-solving at 5 years, illustrating that the baseline path analysis can produce a reasonable and perhaps conservative estimate of expected treatment effects. This bound would be $0.23 \times 0.42 = 0.10$ among nonwhite participants and $0.23 \times 0.44 =$

0.10 in a sample with less than 12 years of education (Table 6). These calculations assume that cognitive training does not directly affect gains in everyday problem-solving or through other mediators, and further that there is negligible measurement error in any of the variables.

Overall, results suggest that it is reasonable to anticipate improvement in primary abilities given improvement in proximal cognitive abilities, as those relationships are strong. Transfer to secondary outcomes, however, is smaller and more difficult to detect, particularly for characteristics of health care utilization. Findings from tests of effect modification can inform the types of participants who should be recruited to observe transfer. Our findings are consistent with the notion of compensation, in which less advantaged groups may show more transfer of cognitive training to other proximal and distal outcomes. One potential explanation for this effect is that training may disproportionately bolster self-efficacy in less advantaged groups, as has been found in caregiving research (Gitlin, Corcoran, Winter, Boyce, & Hauck, 2001). Another explanation is that associations among cognitive abilities are stronger in less advantaged groups of older adults (i.e., elevated dedifferentiation; see Anstey, Hofer, & Luszcz, 2003).

Tests of effect modification in the ACTIVE conceptual framework revealed that associations between proximal and primary cognitive abilities were stronger in racial minorities, the older age group, and less educated and less healthy participants. These findings suggest that transfer of training, regardless of the magnitude of a training effect itself, may be greater in less advantaged groups that are often underrepresented in cognitive aging research. Findings were unchanged after accounting for ceiling and floor effects in sensitivity analyses.

Intuitively, this pattern appears to contrast with previous findings from ACTIVE. Namely, higher initial cognitive status has been associated with larger training effects for reasoning ability (Willis & Caskie, 2013). Younger age, more years of education, and better health are associated with larger memory training effects for memory ability (Rebok et al., 2013). On average, younger age is associated with maintenance of appropriate memory strategies over time (Gross & Rebok, 2011), and participants who were younger and had more education were more likely to learn high-level strategies such as the method of loci (Gross et al., 2014).

Coupling these previous findings regarding training effects with findings from the present study, it is worth distinguishing between *demonstrating benefit from training*, as measured by effects of a training intervention on proximal cognitive abilities, and *demonstrating transfer from proximal to primary outcomes*: certain groups may show treatment gains but minimal transfer, whereas others may show modest training gains on proximal outcomes but have greater hope of transfer to everyday activities. The latter appears plausible given the present results, although this study does not definitively prove that less advantaged groups will show greater transfer of training. Ultimately, future work is needed to model the effect of training across subgroups and its transfer to downstream abilities across subgroups of participants. Any expectation of greater transfer effects in less advantaged groups based on our model must be balanced against evidence that training gains are reduced in these same groups. Thus, recruitment of certain groups on the basis of promise for transfer as demonstrated here may not produce expected greater transfer effects because training gains

may be inversely related to group status. Despite this caveat, the present results suggest that training programs should include diverse groups of older adults, especially if the programs fail to show far transfer in homogeneous samples (e.g., high socioeconomic status, high educational attainment).

There are several caveats of our study. First, we analyzed between-persons correlations among these constructs, so causal directions should be approached with care. Second, we represented most of the key proximal, primary, and secondary outcomes in the ACTIVE conceptual framework as best we could as latent variables using data collected in ACTIVE. We did not include mobility impairment in our operationalization because the baseline sample excluded low-functioning persons who would have had mobility impairments. Similarly, we considered difficulty with IADLs instead of ADL difficulty because too few participants at baseline reported ADL difficulty. Other latent variables, such as for reasoning ability, may be represented by other equally salient indicators of the construct. A final limitation is that although there was minimal (<15%) missing data for variables used in the main analyses, we excluded data in our sensitivity analysis that evaluated the robustness of results to floor and ceiling effects of some of the indicators. Although this sensitivity analysis was consistent with our conclusions, by virtue of excluding data based on outcomes, we induced a bias that was probably inconsistent with the assumption that data were truly missing at random. Thus, results of the sensitivity analysis should only be viewed as a confirmation of the main findings and not necessarily trustworthy on its own.

In conclusion, ACTIVE is the largest, longest-running study of cognitive training for older adults. In the present study, we operationalized the ACTIVE conceptual framework using structural equation modeling, tested additional pathways, and evaluated invariance of associations across health and demographic groups. The data support the framework with several modifications. The overall and stratified effects we report can be used to determine necessary sample sizes and sampling frames in future cognitive intervention work designed to detect transfer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

ACTIVE conceptual framework operationalized. The ACTIVE conceptual framework adapted from Jobe and colleagues (2001). Solid lines indicate hypothesized pathways. Dashed lines indicate pathways not originally hypothesized. For the present study, each circle represents a measurement model of a factor analysis using available indicators; see Methods for details.

Table 1

Empirical associations among proximal (e.g., memory, speed, reasoning), primary, and secondary outcomes in the ACTIVE conceptual model ($N = 2802$).

Outcome	Predictor	Estimate	95% CI
<i>Primary outcomes</i>			
Everyday problem-solving	Memory	0.49 [*]	(0.46, 0.51)
Everyday problem-solving	Reasoning	0.55 [*]	(0.53, 0.57)
Everyday problem-solving	Speed (X)	-0.38 [*]	(-0.41, -0.35)
IADL difficulty	Memory	-0.20 [*]	(-0.25, -0.15)
IADL difficulty	Reasoning	-0.21 [*]	(-0.26, -0.16)
IADL difficulty	Speed	0.19 [*]	(0.13, 0.24)
Everyday speed	Memory (X)	-0.36 [*]	(-0.39, -0.33)
Everyday speed	Reasoning (X)	-0.42 [*]	(-0.45, -0.39)
Everyday speed	Speed	0.41 [*]	(0.38, 0.44)
Driving difficulty	Memory (X)	-0.16 [*]	(-0.22, -0.10)
Driving difficulty	Reasoning (X)	-0.18 [*]	(-0.24, -0.13)
Driving difficulty	Speed	0.19 [*]	(0.12, 0.25)
<i>Secondary outcomes</i>			
HRQOL	Driving difficulty	-0.02	(-0.09, 0.05)
HRQOL	IADL difficulty	-0.64 [*]	(-0.68, -0.59)
HRQOL	Everyday problem-solving	0.03	(-0.03, 0.10)
HRQOL	Everyday speed	-0.09 [*]	(-0.14, -0.03)
<i>Health services utilization</i>			
Regularly see a physician	Driving difficulty	0.05	(-0.09, 0.19)
Regularly see a physician	IADL difficulty	-0.06	(-0.20, 0.08)
Regularly see a physician	Everyday speed	-0.04	(-0.17, 0.08)
Ever been in a hospital overnight	Driving difficulty	0.09	(-0.02, 0.20)
Ever been in a hospital overnight	IADL difficulty	-0.09	(-0.20, 0.02)
Ever been in a hospital overnight	Everyday speed	-0.11 [*]	(-0.21, -0.02)
Ever been in a nursing home	Driving difficulty	-0.13	(-0.32, 0.07)
Ever been in a nursing home	IADL difficulty	-0.24 [*]	(-0.42, -0.06)
Ever been in a nursing home	Everyday speed	0.04	(-0.13, 0.21)
<i>Model fit statistics</i>			
RMSEA	.038		
CFI	.924		

Note. (X) = association not hypothesized in the original ACTIVE conceptual framework (Jobe et al., 2001). Estimates represent standardized $N(0, 1)$ effect sizes. Data from the ACTIVE baseline were used.

^{*}
 $p < .05$.

Table 2

Effect modification by race/ethnicity of baseline empirical associations among proximal, primary, and secondary outcomes in the ACTIVE conceptual model ($N = 2802$).

Outcome	Predictor	Race/ethnicity	
		Nonwhite (<i>n</i> = 774)	White (<i>n</i> = 2028)
		Estimate (95% CI)	Estimate (95% CI)
<i>Primary outcomes</i>			
Everyday problem-solving	Memory	0.42 (0.35, 0.50)	0.36 (0.31, 0.41) *
Everyday problem-solving	Reasoning	0.64 (0.57, 0.70)	0.59 (0.54, 0.63) *
Everyday problem-solving	Speed (X)	−0.14 (−0.21, −0.07)	−0.14 (−0.19, −0.09)
IADL difficulty	Memory	−0.01 (−0.12, 0.10)	−0.15 (−0.22, −0.07)
IADL difficulty	Reasoning	−0.16 (−0.27, −0.05)	−0.07 (−0.14, 0.01)
IADL difficulty	Speed	0.13 (0.03, 0.23)	0.14 (0.06, 0.21)
Everyday speed	Memory (X)	−0.32 (−0.40, −0.23)	−0.17 (−0.22, −0.11) *
Everyday speed	Reasoning (X)	−0.3 (−0.38, −0.22)	−0.33 (−0.38, −0.28)
Everyday speed	Speed	0.31 (0.24, 0.39)	0.34 (0.28, 0.39)
Driving difficulty	Memory (X)	−0.08 (−0.22, 0.06)	−0.01 (−0.09, 0.06)
Driving difficulty	Reasoning (X)	−0.17 (−0.30, −0.05)	−0.18 (−0.25, −0.11)
Driving difficulty	Speed	0.05 (−0.07, 0.17)	0.12 (0.04, 0.19)
<i>Secondary outcomes</i>			
HRQOL	Driving difficulty	−0.02 (−0.11, 0.07)	−0.05 (−0.11, 0.00)
HRQOL	IADL difficulty	−0.51 (−0.58, −0.44)	−0.52 (−0.56, −0.47)
HRQOL	Everyday problem-solving	0.14 (0.05, 0.24)	0.07 (0.01, 0.12)
HRQOL	Everyday speed	−0.04 (−0.13, 0.04)	−0.09 (−0.14, −0.03)
Health services utilization			
Regularly see a physician	Driving difficulty	−0.01 (−0.10, 0.09)	−0.01 (−0.07, 0.06)
Regularly see a physician	IADL difficulty	−0.05 (−0.14, 0.04)	−0.01 (−0.07, 0.04)
Regularly see a physician	Everyday speed	−0.02 (−0.11, 0.06)	−0.03 (−0.08, 0.03)
Ever been in a hospital overnight	Driving difficulty	0.04 (−0.05, 0.13)	0.04 (−0.02, 0.10)
Ever been in a hospital overnight	IADL difficulty	−0.11 (−0.20, −0.02)	−0.01 (−0.07, 0.04)
Ever been in a hospital overnight	Everyday speed	−0.02 (−0.11, 0.06)	−0.06 (−0.12, −0.01) *
Ever been in a nursing home	Driving difficulty	−0.03 (−0.12, 0.06)	−0.04 (−0.10, 0.03)
Ever been in a nursing home	IADL difficulty	−0.1 (−0.19, −0.01)	−0.09 (−0.14, −0.03)
Ever been in a nursing home	Everyday speed	0.05 (−0.04, 0.14)	−0.04 (−0.10, 0.02)
<i>Model fit statistics</i>			
RMSEA	.041		
CFI	.842		

Note. Estimates represent standardized $N(0, 1)$ effect sizes. Data from the ACTIVE baseline were used.

* $p < .005$.

Table 3

Effect modification by sex of baseline empirical associations among proximal, primary, and secondary outcomes in the ACTIVE conceptual model ($N = 2802$).

Outcome	Predictor	Sex	
		Male (<i>n</i> = 676)	Female (<i>n</i> = 2126)
		Estimate (95% CI)	Estimate (95% CI)
<i>Primary outcomes</i>			
Everyday problem-solving	Memory	0.43 (0.34, 0.52)	0.42 (0.37, 0.47)
Everyday problem-solving	Reasoning	0.57 (0.49, 0.65)	0.58 (0.54, 0.63)
Everyday problem-solving	Speed (X)	−0.08 (−0.16, 0.01)	−0.11 (−0.15, −0.06)
IADL difficulty	Memory	−0.08 (−0.21, 0.05)	−0.17 (−0.25, −0.10)
IADL difficulty	Reasoning	0.01 (−0.11, 0.14)	−0.05 (−0.12, 0.02)
IADL difficulty	Speed	0.11 (−0.01, 0.24)	0.14 (0.07, 0.20)
Everyday speed	Memory (X)	−0.26 (−0.36, −0.16)	−0.29 (−0.34, −0.24)
Everyday speed	Reasoning (X)	−0.35 (−0.45, −0.26)	−0.3 (−0.35, −0.25)
Everyday speed	Speed	0.26 (0.16, 0.36)	0.31 (0.26, 0.36)
Driving difficulty	Memory (X)	−0.09 (−0.21, 0.03)	−0.21 (−0.30, −0.12)
Driving difficulty	Reasoning (X)	−0.02 (−0.14, 0.09)	−0.14 (−0.22, −0.06)
Driving difficulty	Speed	0.09 (−0.03, 0.20)	0.08 (0.00, 0.16)
<i>Secondary outcomes</i>			
HRQOL	Driving difficulty	−0.17 (−0.29, −0.05)	−0.01 (−0.06, 0.05)
HRQOL	IADL difficulty	−0.4 (−0.48, −0.32)	−0.54 (−0.58, −0.50) *
HRQOL	Everyday problem-solving	0.19 (0.08, 0.30)	0.09 (0.03, 0.15)
HRQOL	Everyday speed	0 (−0.10, 0.11)	−0.08 (−0.13, −0.03)
Health services utilization			
Regularly see a physician	Driving difficulty	0.18 (0.06, 0.31)	−0.02 (−0.08, 0.04)
Regularly see a physician	IADL difficulty	−0.01 (−0.11, 0.08)	−0.02 (−0.08, 0.03)
Regularly see a physician	Everyday speed	−0.02 (−0.13, 0.08)	−0.03 (−0.08, 0.03)
Ever been in a hospital overnight	Driving difficulty	−0.04 (−0.17, 0.09)	0.04 (−0.02, 0.09)
Ever been in a hospital overnight	IADL difficulty	−0.02 (−0.12, 0.08)	−0.06 (−0.11, −0.00)
Ever been in a hospital overnight	Everyday speed	0.02 (−0.09, 0.13)	−0.07 (−0.13, −0.02) *
Ever been in a nursing home	Driving difficulty	−0.04 (−0.16, 0.08)	−0.05 (−0.11, 0.01)
Ever been in a nursing home	IADL difficulty	−0.08 (−0.18, 0.02)	−0.11 (−0.16, −0.06)
Ever been in a nursing home	Everyday speed	−0.06 (−0.17, 0.05)	−0.01 (−0.06, 0.05)
<i>Model fit statistics</i>			
RMSEA	.042		
CFI	.838		

Note. Estimates represent standardized $N(0, 1)$ effect sizes. Data from the ACTIVE baseline were used.

* $p < .005$.

Table 4

Effect modification by self-rated health status of baseline empirical associations among proximal, primary, and secondary outcomes in the ACTIVE conceptual model ($N = 2802$).

Outcome	Predictor	Self-rated health	
		Low (<i>n</i> = 1548)	High (<i>n</i> = 1205)
		Estimate (95% CI)	Estimate (95% CI)
<i>Primary outcomes</i>			
Everyday problem-solving	Memory	0.38 (0.32, 0.43)	0.35 (0.28, 0.42)
Everyday problem-solving	Reasoning	0.65 (0.60, 0.69)	0.58 (0.52, 0.64) *
Everyday problem-solving	Speed (X)	−0.1 (−0.16, −0.05)	−0.15 (−0.22, −0.08)
IADL difficulty	Memory	−0.1 (−0.19, −0.01)	−0.06 (−0.15, 0.02)
IADL difficulty	Reasoning	0.01 (−0.07, 0.10)	−0.04 (−0.12, 0.05)
IADL difficulty	Speed	0.21 (0.13, 0.30)	0.06 (−0.02, 0.15) *
Everyday speed	Memory (X)	−0.2 (−0.26, −0.14)	−0.19 (−0.26, −0.11)
Everyday speed	Reasoning (X)	−0.38 (−0.44, −0.33)	−0.29 (−0.36, −0.22) *
Everyday speed	Speed	0.31 (0.25, 0.37)	0.33 (0.27, 0.40)
Driving difficulty	Memory (X)	0.02 (−0.08, 0.13)	−0.04 (−0.13, 0.05)
Driving difficulty	Reasoning (X)	−0.2 (−0.30, −0.11)	−0.12 (−0.20, −0.04)
Driving difficulty	Speed	0.11 (0.01, 0.21)	0.12 (0.03, 0.20)
<i>Secondary outcomes</i>			
HRQOL	Driving difficulty	0.02 (−0.05, 0.09)	−0.02 (−0.10, 0.07)
HRQOL	IADL difficulty	−0.63 (−0.67, −0.58)	−0.34 (−0.42, −0.27) *
HRQOL	Everyday problem-solving	0.03 (−0.04, 0.10)	0 (−0.08, 0.07)
HRQOL	Everyday speed	−0.02 (−0.08, 0.05)	−0.1 (−0.17, −0.03)
Health services utilization			
Regularly see a physician	Driving difficulty	−0.01 (−0.07, 0.06)	0.03 (−0.07, 0.12)
Regularly see a physician	IADL difficulty	−0.02 (−0.08, 0.03)	0.01 (−0.08, 0.09)
Regularly see a physician	Everyday speed	−0.04 (−0.10, 0.03)	−0.03 (−0.10, 0.05)
Ever been in a hospital overnight	Driving difficulty	0.03 (−0.04, 0.09)	0.08 (−0.01, 0.17)
Ever been in a hospital overnight	IADL difficulty	−0.04 (−0.09, 0.02)	−0.04 (−0.13, 0.04)
Ever been in a hospital overnight	Everyday speed	−0.03 (−0.09, 0.04)	−0.05 (−0.13, 0.02) *
Ever been in a nursing home	Driving difficulty	−0.09 (−0.16, −0.02)	0.07 (−0.02, 0.16)
Ever been in a nursing home	IADL difficulty	−0.11 (−0.17, −0.06)	−0.05 (−0.14, 0.03)
Ever been in a nursing home	Everyday speed	−0.01 (−0.07, 0.06)	−0.05 (−0.12, 0.03)
<i>Model fit statistics</i>			
RMSEA	.043		
CFI	.799		

Note. Estimates represent standardized $N(0, 1)$ effect sizes. Data from the ACTIVE baseline were used.

* $p < .005$.

Table 5

Effect modification by age of baseline empirical associations among proximal, primary, and secondary outcomes in the ACTIVE conceptual model ($N = 2802$).

Outcome	Predictor	Age	
		Less than 75 (<i>n</i> = 1683)	75 or greater (<i>n</i> = 1119)
		Estimate (95% CI)	Estimate (95% CI)
<i>Primary outcomes</i>			
Everyday problem-solving	Memory	0.38 (0.33, 0.43)	0.4 (0.33, 0.47)
Everyday problem-solving	Reasoning	0.61 (0.56, 0.66)	0.64 (0.58, 0.70) *
Everyday problem-solving	Speed (X)	−0.14 (−0.20, −0.09)	−0.13 (−0.20, −0.07)
IADL difficulty	Memory	0 (−0.08, 0.07)	−0.19 (−0.29, −0.09)
IADL difficulty	Reasoning	−0.04 (−0.11, 0.03)	−0.13 (−0.23, −0.03)
IADL difficulty	Speed	0.13 (0.06, 0.20)	0.07 (−0.03, 0.17)
Everyday speed	Memory (X)	−0.14 (−0.20, −0.08)	−0.26 (−0.33, −0.19) *
Everyday speed	Reasoning (X)	−0.34 (−0.40, −0.28)	−0.41 (−0.48, −0.35) *
Everyday speed	Speed	0.31 (0.25, 0.37)	0.25 (0.17, 0.32)
Driving difficulty	Memory (X)	−0.01 (−0.10, 0.07)	0.02 (−0.09, 0.12)
Driving difficulty	Reasoning (X)	−0.15 (−0.23, −0.08)	−0.24 (−0.34, −0.13)
Driving difficulty	Speed	0.08 (0.00, 0.16)	0.04 (−0.06, 0.15)
<i>Secondary outcomes</i>			
HRQOL	Driving difficulty	−0.07 (−0.13, −0.01)	−0.01 (−0.09, 0.07)
HRQOL	IADL difficulty	−0.52 (−0.57, −0.47)	−0.51 (−0.57, −0.46)
HRQOL	Everyday problem-solving	0.09 (0.03, 0.15)	0.11 (0.03, 0.18)
HRQOL	Everyday speed	−0.09 (−0.15, −0.03)	−0.06 (−0.12, 0.01)
Health services utilization			
Regularly see a physician	Driving difficulty	0.02 (−0.05, 0.08)	−0.03 (−0.11, 0.05)
Regularly see a physician	IADL difficulty	−0.02 (−0.08, 0.04)	−0.02 (−0.09, 0.05)
Regularly see a physician	Everyday speed	−0.02 (−0.08, 0.05)	−0.03 (−0.10, 0.05)
Ever been in a hospital overnight	Driving difficulty	0.01 (−0.05, 0.07)	0.09 (0.01, 0.17)
Ever been in a hospital overnight	IADL difficulty	−0.04 (−0.10, 0.02)	−0.07 (−0.15, −0.00)
Ever been in a hospital overnight	Everyday speed	−0.07 (−0.13, −0.00)	−0.01 (−0.08, 0.06) *
Ever been in a nursing home	Driving difficulty	−0.01 (−0.08, 0.05)	−0.04 (−0.13, 0.05)
Ever been in a nursing home	IADL difficulty	−0.07 (−0.13, −0.01)	−0.11 (−0.18, −0.03)
Ever been in a nursing home	Everyday speed	0 (−0.06, 0.07)	−0.01 (−0.09, 0.06)
<i>Model fit statistics</i>			
RMSEA	.041		
CFI	.839		

Note. Estimates represent standardized $N(0, 1)$ effect sizes. Data from the ACTIVE baseline were used.

* $p < .005$.

Table 6

Effect modification by years of education of baseline empirical associations among proximal, primary, and secondary outcomes in the ACTIVE conceptual model ($N = 2802$).

		Years of education	
		12 years or less (<i>n</i> = 1117)	13 years or more (<i>n</i> = 1683)
Outcome	Predictor	Estimate (95% CI)	Estimate (95% CI)
Primary outcomes			
Everyday problem-solving	Memory	0.44 (0.37, 0.50)	0.35 (0.29, 0.40) *
Everyday problem-solving	Reasoning	0.61 (0.55, 0.67)	0.58 (0.53, 0.63) *
Everyday problem-solving	Speed (X)	−0.11 (−0.17, −0.04)	−0.17 (−0.22, −0.11)
IADL difficulty	Memory	−0.12 (−0.22, −0.02)	−0.09 (−0.17, −0.02)
IADL difficulty	Reasoning	−0.03 (−0.13, 0.07)	−0.06 (−0.14, 0.01)
IADL difficulty	Speed	0.15 (0.05, 0.24)	0.14 (0.07, 0.22)
Everyday speed	Memory (X)	−0.23 (−0.30, −0.15)	−0.2 (−0.26, −0.14)
Everyday speed	Reasoning (X)	−0.37 (−0.44, −0.30)	−0.35 (−0.40, −0.30)
Everyday speed	Speed	0.3 (0.23, 0.37)	0.32 (0.26, 0.37)
Driving difficulty	Memory (X)	0.04 (−0.09, 0.17)	−0.04 (−0.12, 0.04)
Driving difficulty	Reasoning (X)	−0.15 (−0.27, −0.03)	−0.11 (−0.18, −0.04)
Driving difficulty	Speed	0.13 (0.01, 0.26)	0.13 (0.06, 0.21)
Secondary outcomes			
HRQOL	Driving difficulty	−0.04 (−0.11, 0.03)	−0.03 (−0.09, 0.03)
HRQOL	IADL difficulty	−0.54 (−0.60, −0.49)	−0.5 (−0.55, −0.45)
HRQOL	Everyday problem-solving	0.05 (−0.03, 0.13)	0.09 (0.02, 0.15)
HRQOL	Everyday speed	−0.08 (−0.15, −0.01)	−0.08 (−0.14, −0.02)
Health services utilization			
Regularly see a physician	Driving difficulty	−0.01 (−0.09, 0.06)	0 (−0.07, 0.07)
Regularly see a physician	IADL difficulty	−0.02 (−0.09, 0.05)	−0.02 (−0.08, 0.04)
Regularly see a physician	Everyday speed	−0.02 (−0.10, 0.06)	−0.02 (−0.09, 0.04)
Ever been in a hospital overnight	Driving difficulty	0.08 (0.01, 0.15)	−0.01 (−0.08, 0.05)
Ever been in a hospital overnight	IADL difficulty	−0.08 (−0.16, −0.01)	−0.02 (−0.08, 0.04) *
Ever been in a hospital overnight	Everyday speed	−0.04 (−0.11, 0.04)	−0.06 (−0.12, 0.01) *
Ever been in a nursing home	Driving difficulty	0.01 (−0.06, 0.09)	−0.1 (−0.18, −0.03)
Ever been in a nursing home	IADL difficulty	−0.13 (−0.20, −0.05)	−0.08 (−0.14, −0.02)
Ever been in a nursing home	Everyday speed	−0.01 (−0.09, 0.07)	0 (−0.07, 0.07)
Model fit statistics			
RMSEA	.041		
CFI	.841		

Note. Estimates represent standardized $N(0, 1)$ effect sizes. Data from the ACTIVE baseline were used.

* $p < .005$.