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The Indiana Alzheimer Disease Center's Symposium on Mild Cognitive Impairment. Cognitive Training in Older Adults: Lessons from the ACTIVE Study

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Abstract

This paper is based on a presentation made during the Indiana Alzheimer Disease Center's *Symposium on Mild Cognitive Impairment* on April 19, 2008. The results of the ACTIVE study (Advanced Cognitive Training for Independent and Vital Elderly) were presented at the symposium including review of previously published study findings. The ACTIVE study is a multicenter, randomized, controlled clinical trial that has been examining the long-term effectiveness of cognitive training on enhancing mental abilities (memory, reasoning, and attention) and preserving activities of daily living (managing finances, taking medication, using the telephone, and driving) in older adults. Six centers across the eastern United States enrolled nearly 3000 people initially. Participants underwent detailed assessments of mental and functional ability on multiple occasions over several years of follow-up. ACTIVE has shown positive effects of cognitive training at 5 years post-intervention for basic mental abilities, health-related quality of life, and improved ability to perform instrumental activities of daily living (IADL). A subgroup analysis through 2 years of follow-up suggested that subjects with mild cognitive impairment (MCI) did not benefit from memory training; however, they did benefit, to the same degree as cognitively normal participants, from training in reasoning and speed of processing. This finding suggests that MCI may interfere with a person's ability to benefit from some forms of cognitive enhancement. Limitations of ACTIVE and directions for future research are reviewed.

INTRODUCTION

This paper is based on a presentation made during the Indiana Alzheimer Disease Center's *Symposium on Mild Cognitive Impairment* on April 19, 2008. The results and important lessons learned regarding cognitive aging from the ACTIVE study (Advanced Cognitive Training for

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Independent and Vital Elderly) were presented including review of previously published findings from ACTIVE.

In September 1995, the National Institutes of Health (NIH) sought applications for a cooperative field trial of cognitive interventions to maintain and promote independent functioning among older adults (RFA AG-96-001). The mechanism of support was a cooperative agreement (U01) funded via the National Institute on Aging and the National Institute of Nursing Research.

The RFA occurred in the context of a broad literature showing the presence of significant age-related cognitive decline at the level of self-report (e.g., rates over 50% in one large community study [1]) and at the level of objective, psychometric tests showing performance losses beyond 50% compared to younger adults, depending on the age groups and tests used (e.g., [2,3]). The assumption, later demonstrated in longitudinal studies, was that declines in cognitive function lead to incident functional loss (i.e., decline in activities in daily living) in older adults [4].

At the same time, effective pharmacological treatments for age-related cognitive loss did not exist (and still do not). The RFA noted that the impetus for the trial came from “recent success of a number of different cognitive, or related perceptual, intervention techniques at enhancing some aspects of ability or functioning; the increasing evidence that cognitive factors are associated with key public health outcomes such as hospitalization and death; and the increasing need to find preventative techniques that successfully maintain the quality of life of the older population. (RFA AG-96-001).” These early studies on cognitive intervention tended to be limited by small sample size, lack of random assignment, or absence of control groups.

The proposed NIH cooperative trial was envisioned as a way to rectify these limitations and resulted in ACTIVE (Advanced Cognitive Training for Independent and Vital Elderly). The goal of ACTIVE was to provide a large scale, multi-center, randomized, controlled trial of the effectiveness of three forms of cognitive intervention in maintaining cognitive health and functional independence in older adults (see Figure 1).

Embedded in the ACTIVE conceptual model is the assumption that the effects of training on the cognitive abilities would be highly specific, whereas effects on functional status would be less so. That is, each intervention is expected to show greater and specific improvement on measures of the ability trained relative to all other interventions and control groups. On the other hand, intervention effects are expected to be more general (less specific) for primary and secondary functional outcomes.

METHOD

Design

ACTIVE is a randomized, controlled, single-blind trial. Participants were randomly assigned to one of three treatment arms (Memory, Reasoning, or Speed training) or a no-contact control group. Assessments were conducted at baseline (BL), immediately following the intervention (post-test, PT), and annually at 1 (A1), 2 (A2), 3 (A3), and 5 (A5) years after the intervention. A final annual assessment is underway 10 years after intervention (A10). Assessors are blind to treatment assignment.

Participants

The study was approved by the Institutional Review Boards of all grantee institutions; all participants provided informed consent. Participants were recruited from six metropolitan areas in the Midwest and Eastern part of the United States (Baltimore, MD, Birmingham, AL, Boston, MA, Detroit, MI, State College, PA, and Indianapolis, IN) using a variety of sources including:

community centers, churches, senior housing sites, driver's license registries, outpatient medical clinic rosters, and social service program rosters. Each site contributed 400–500 participants to the trial. Participants were enrolled in six replicates over approximately 18 months. Reasonably well-functioning persons aged 65 years and older were eligible. Exclusionary criteria were as follows: 1) substantial cognitive impairment (Mini-mental State Examination, MMSE; [5]] < 23), 2) regular need for significant assistance in dressing, personal hygiene, or bathing, 3) diagnosis of Alzheimer disease, stroke within the last 12 months, or certain cancers, 4) current chemotherapy or radiation therapy, and 5) low vision (worse than 20/70 with correction) or low auditory acuity.

Interventions

The training modules selected for ACTIVE focused on memory, reasoning, and speed of processing. Earlier research indicated these abilities show age-related decline and are associated with performance of activities of daily living [6]. All treatment modules were standardized to consist of 10 sessions lasting 60–75 minutes completed over a 5 to 6 week interval. Memory training focused on verbal episodic memory, and participants were instructed in the use of organization, visualization, and association to improve registration and recall of word lists and short narratives. Reasoning training focused on problem solving for serial patterns, and participants were taught how to identify, block, and mark patterns in abstract series of letters and words and to predict the next items in the series. Speed training focused on visual search. Participants identified visual objects on a computer screen with tasks made progressively more difficult by shortening presentation times and overlaying masks. Booster training was provided to a subset of trained participants approximately 11 and 35 months after training. The booster training was delivered in four, 75-minute sessions over a 3-week period. The structure and content of the sessions were similar to those used in the primary training (see [6] for details).

Measures

The measurement battery tapped a range of demographic, sensory, motor, cognitive, functional, mood, health, health service utilization, and quality of life variables. Self-report and direct performance measurements were obtained in individual and group formats [6]. Measures are grouped into four major categories: *proximal outcomes* (cognitive abilities that were direct targets of training), *primary outcomes* (daily functioning), *secondary outcomes* (e.g., driving and health-related quality of life), and *covariates*.

Proximal outcomes were formed for each training arm. Memory outcomes were measured by verbal memory tasks: Hopkins Verbal Learning Test total of the 3 learning trials [7], Rey Auditory-Verbal Learning Test total of the 5 learning trials [8], and the Rivermead Behavioral Memory Test immediate recall [9]. Reasoning outcomes were measured by tasks requiring the identification of patterns in letter and word series problems: Letter Series total correct [10], Letter Sets total correct [11], and Word Series total correct [12]. Speed of Processing outcomes were measured with the Useful Field of View [13], a computer-based set of visual attention tasks, with the key dependent variable being the shortest display time required to achieve 80% correct response rate.

Primary outcome included the Minimum Data Set - Home Care (MDS-HC, [14]) which provides a measure of functional status, specifically participant self-report of instrumental activities of daily living (IADL). The Performance subscale assesses the degree of independent completion of 19 daily subtasks over the past seven days (major domains include: meals, housework, finances, health care, telephone, shopping, and travel). The Difficulty subscale assesses the perceived degree of difficulty in completing these subtasks. In addition, performance-based measures of daily functioning were also included as follows: Everyday

Problems Test (EPT) assesses ability to utilize information in 14 everyday stimuli (e.g., medication labels, transportation schedules)[15]; Observed Tasks of Daily Living (OTDL) [16] requires participants to perform actions required to solve everyday tasks (e.g., searching medication label for side effects, making change, using a telephone); Complex Reaction Time (CRT), a computer-administered test measures reaction time to traffic signs [17]; and Timed IADL (TIADL) measures the time to successfully complete 5 tasks (e.g., finding a number in telephone book, finding items on a simulated grocery shelf) [18]. The EPT and OTDL were combined to form an Everyday Problem Solving Composite. The CRT and TIADL were combined to form an Everyday Speed Composite.

Secondary outcomes included, among other measures, assessment of health-related quality of life (HRQOL) via the SF-36 [19].

Statistical Analysis

Training effects were determined using repeated-measures, mixed-effects analytic models. Composites were formed for each cognitive outcome domain. If one or more tests of a composite were missing, the composite score was calculated as the average of the non-missing tests. Scores were normalized by pooling scores at all time points and applying a Blom transformation which standardizes the components to have equal weight and reduced skewness [20]. Contrasts for the net effect of a specific training (Memory, Reasoning, Speed) were determined separately by trained arm as follows: ([Trained mean at follow-up – Control mean at follow-up] – [BL Trained mean – BL Control mean]). Contrasts were converted to effect sizes by dividing by σ, where σ^2 is the intra-subject variance as estimated by the model.

To control for multiple comparisons, α denoting significance is set to $p \leq .001$. Also, due to baseline differences in boosted and non-boosted subjects, booster analyses are adjusted for baseline age and MMSE.

RESULTS

A total of 5000 persons were contacted for participation: 1263 refused, 905 were ineligible, and 2832 persons were willing and eligible for participation in ACTIVE [6]. The analytic sample consisted of 2802 persons who were randomly assigned to non-contact control, memory training, reasoning training, or speed training groups (30 eligible persons were excluded from the analysis because they were randomized inappropriately). There were no significant group differences in any major demographic or clinical status variables. The average age of the sample was approximately 74 years, women were over-represented (approximately 76%), just over one-quarter of the sample was African American, average education was approximately 13 years, and cognitive function was well within normal limits (MMSE M = 27.3, SD 2.0). At the A5 post-test, retention was 67% (n=1,877) [21].

Proximal Outcomes

Table 2 shows effect sizes for the net effect of ACTIVE training and booster training on the proximal outcome composites. As can be seen in the left-side columns under each group, each intervention produced an immediate improvement in the cognitive ability trained (all $p < .001$) that was durable to 5 years (all $p < .001$). Training produced ability-specific effects; for example, Reasoning training did not improve memory performance indicating that training effects are not explained by social contact. The right-side columns show that booster training resulted in significant gains (after adjusting for baseline age and MMSE) for the reasoning and speed treatment arms that remained significant through all 5 years of follow-up.

Primary Outcomes

Table 3 shows effect sizes for the net effect of ACTIVE training on the primary outcome composites. While each of the ACTIVE training programs produced roughly comparable positive effects on self-reported difficulty in performing IADL by A5, between .202 and .289, only the reasoning training arm was significant beyond $p \leq .001$. These data support the hypothesized time lagged transfer of cognitive training improvements to daily function. The performance-based functional composites (Everyday Problem Solving and Everyday Speed) did not show transfer of training effects to function. Booster training effects are presented in the right-side columns under each group in Table 3. Only Subjects assigned to Speed booster training produced significant improvement at A5 on the hypothesized functional composite (Everyday Speed effect size = .302, $p \leq .001$). We suspect that these performance-based measures are more highly saturated with the specific basic ability (more so than IADL Difficulty ratings), explaining why more intensive training (booster) was required to show an effect.

These data are consistent with the model and hypotheses set out in the initial RFA and operationalized by ACTIVE nearly 10 years ago. ACTIVE is the first large-scale, controlled clinical trial to show that improvements in basic cognitive abilities transfer to daily activities.

Secondary Outcomes

The ability of the ACTIVE training programs to protect against decline in health-related quality of life (HRQOL) was investigated recently [22]. Data from 1804 participants with both A2 and A5 follow-ups completed were used. HRQOL was measured by the SF-36 which contains 8 scales. Clinically relevant decline on a scale was defined as a drop of 0.5 standard deviations or more from baseline. Significant HRQOL decline was defined as clinically relevant drops on 3 or more SF-36 scales. At A2, 36.6% of the sample had clinically relevant drops on 3 or more SF-36 scales; at A5 that number increased to 47.3%. Logistic regression at A2 indicated that participants receiving speed of processing were significantly less likely to have HRQOL decline compared to participants in the control group, and by A5 all trained participants were significantly less likely to have HRQOL declines. The basis for the earlier and stronger positive effect of speed of processing compared to the other interventions is unclear, but it may relate to that intervention being the most “procedural” of the three which might bring about broader regional brain activation.

Selected Subgroup Analyses

The ACTIVE results are clear in demonstrating that cognitive training improves mental abilities in older adults; however, the trainability of persons with memory impairment is unclear. We performed subgroup analysis in ACTIVE using an algorithm-based definition of mild cognitive impairment (MCI) [23]. Participants were defined as MCI if baseline Rey Auditory Verbal Learning Test (AVLT) sum recall score was 1.5 SD or more below predicted AVLT sum recall score from a regression-derived formula using age, education, ethnicity, and vocabulary from all subjects at baseline. A total of 193 subjects were defined as MCI using this criterion; the rest (n = 2580) were memory-normal. Training gain as a function of MCI status (yes vs. no) was compared in a mixed effects model. Results indicated that MCI participants failed to benefit from Memory training but did show normal training gains after Reasoning and Speed training (see Figure 3). MCI status appeared to mediate response to ACTIVE interventions.

CONCLUSION

The ACTIVE study is the largest, randomized-controlled trial of a cognitive intervention ever conducted in older adults. Results to date clearly support the effectiveness of three cognitive interventions (memory, reasoning, and speed of processing) in maintaining cognitive health. Training produces immediate positive effects that are modality specific. These cognitive improvements do dissipate over time but are still detectable at least 5 years after training. Additional booster training does enhance training gain. ACTIVE is the first study of its kind to demonstrate modest but detectable far transfer to health-related quality of life and instrumental activities of daily living.

Results from ACTIVE also suggest that older adults with significant memory impairment, including those that meet an algorithm-based definition of amnestic MCI, can benefit from training protocols like ACTIVE as long as the interventions do not require declarative memory. Amnestic MCI subjects within the ACTIVE cohort did benefit from training in reasoning and speed of processing to the same degree as cognitively normal subjects; however, they did not benefit if the training was focus on memory. This study suggests that MCI interferes with a person's ability to benefit from some forms of cognitive enhancement. This distinction is important because it begins to bring specificity to the question of who benefits from what kind of treatment. In addition, it demonstrates the need to study cognitive interventions in cognitively normal older adults and in those with neurodegenerative processes.

This large project did have limitations. The representativeness of the ACTIVE sample can be questioned. ACTIVE was a large volunteer cohort and the risk of self-selection bias exists. The ACTIVE sample was advantaged to a small extent relative to the general population in terms of age, education, and MMSE; therefore, the results of ACTIVE cannot be freely generalized to the population. The effectiveness of these interventions in very old persons and those with lower education remain to be determined. Also, the design of the booster training made it difficult to fully examine the role of additional training (a dose effect) on treatment outcomes. Finally, subgroup analyses focused on clinical conditions is hampered by lack of a medical assessment and diagnosis component at baseline and throughout the follow-up. Examinations of this kind would have been particularly interesting in uncovering the role of dementia in training effectiveness.

Ongoing research with the ACTIVE sample is focused on establishing the limits and determinants of transfer of the ACTIVE cognitive training programs to cognitive, functional, and other distal outcomes (e.g., health care utilization). The results from ACTIVE will be extended by extrapolating the effects of cognitive training to a representative national sample and in so doing providing a direction for the development of new training programs.

Further research is needed to examine the dose-response effect of training more clearly. Is there an asymptote in response as a function of intensity of training in terms of length (30, 60, or 90 minute sessions), frequency (1, 2, or 5 days per week), and duration (1, 3, or 6 month versus constantly ongoing) of training? The role of combinatorial interventions should be explored. Would a multimodal cognitive intervention, one that combined training in memory, reasoning, and speed of processing, produce stronger results? The effectiveness of combinatorial treatments beyond cognitive training is an area for profitable research. Do combinations of specific forms of mental training with diet or physical training produce a synergistic effect on treatment outcomes? Is training on IADLs a more direct and sustainable path to preserving functional independence?

By being the first study to demonstrate the long-term potency of specific programs of cognitive training on mental ability and to show far transfer to important outcomes in daily life of older adults, ACTIVE will hopefully stimulate new programs of research on non-pharmacologic interventions in older adults.

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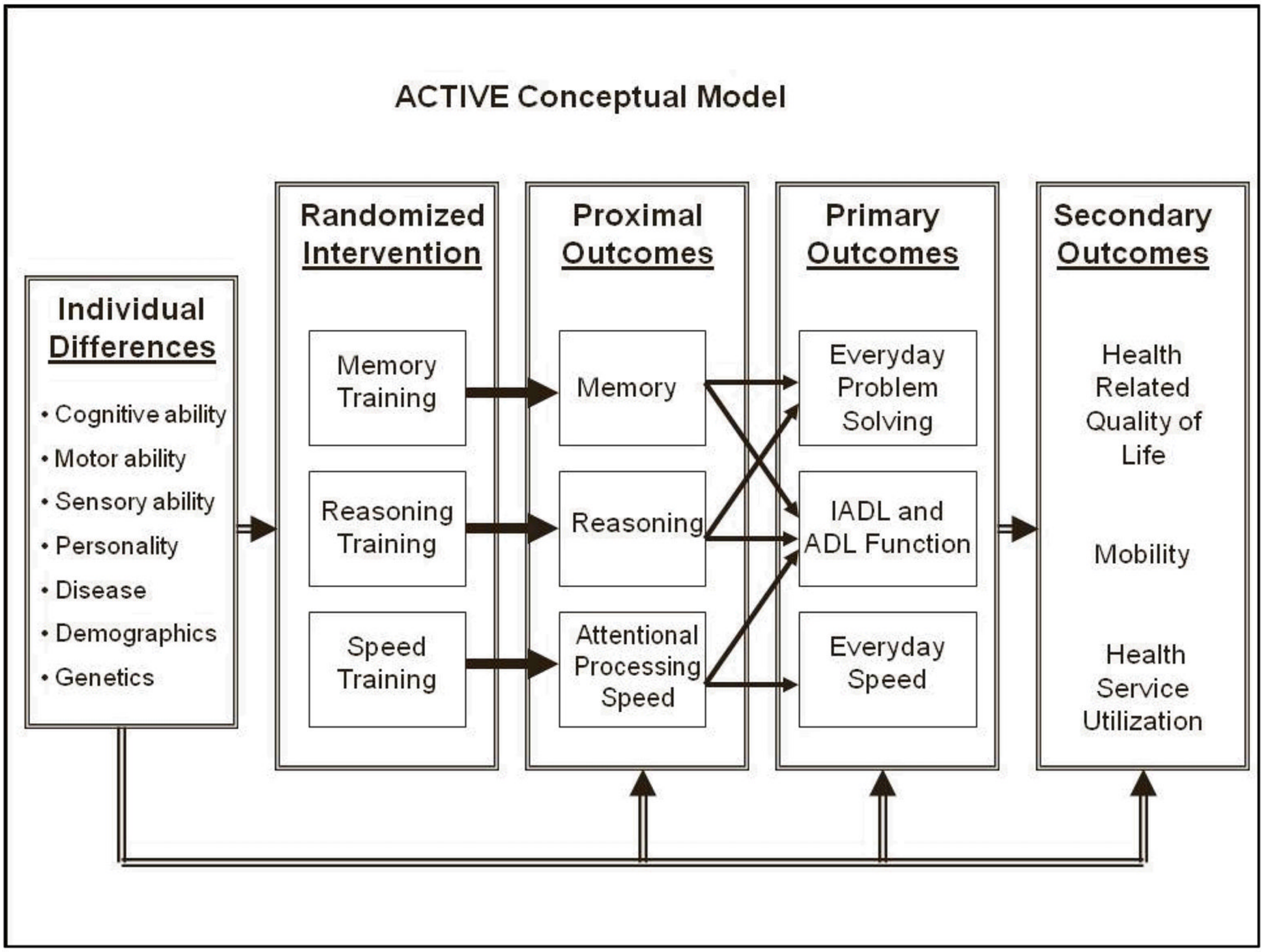

Figure 1.
ACTIVE conceptual model (IADL = Instrumental Activities of Daily Living).

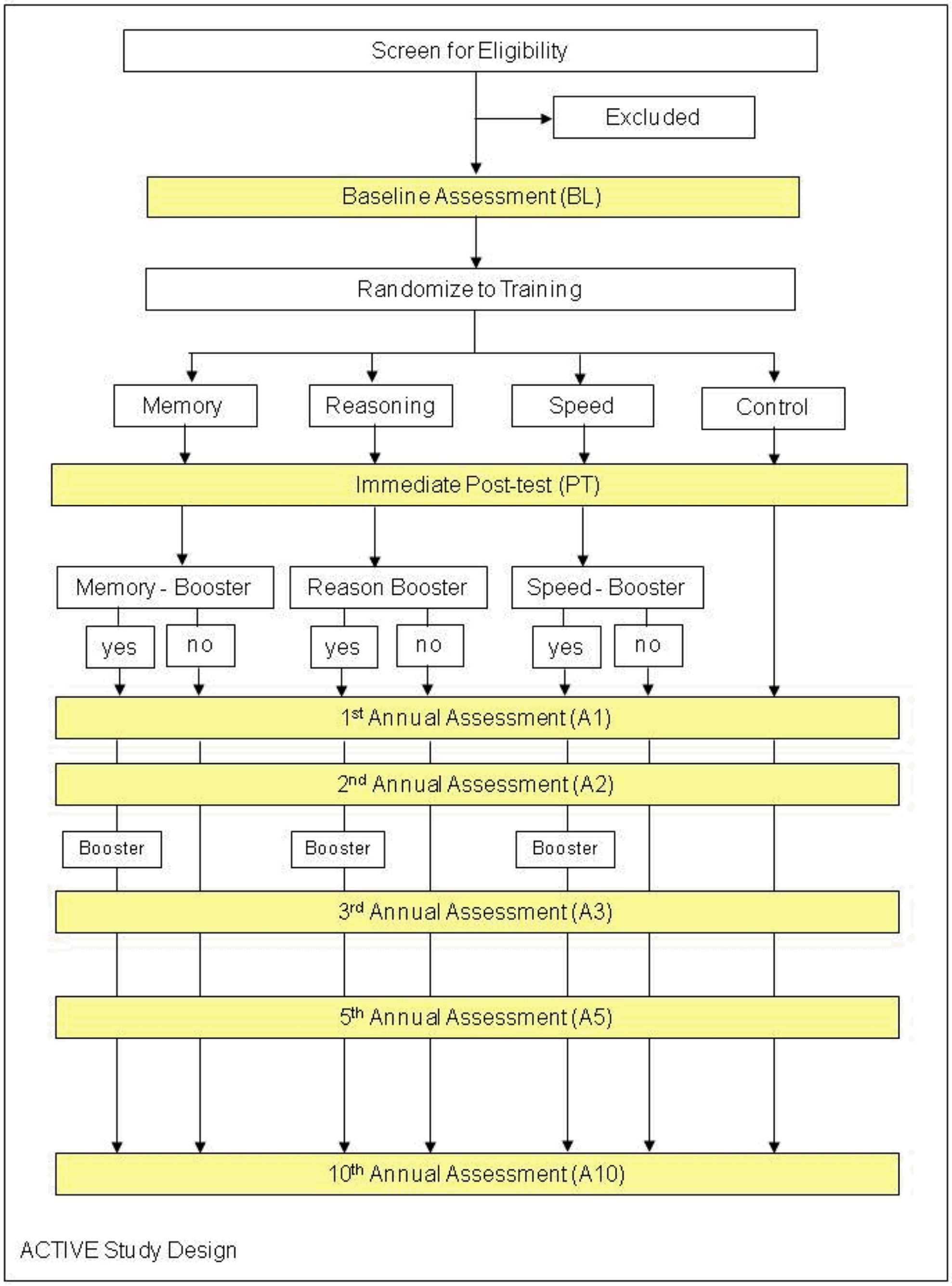

Figure 2.
ACTIVE study design.

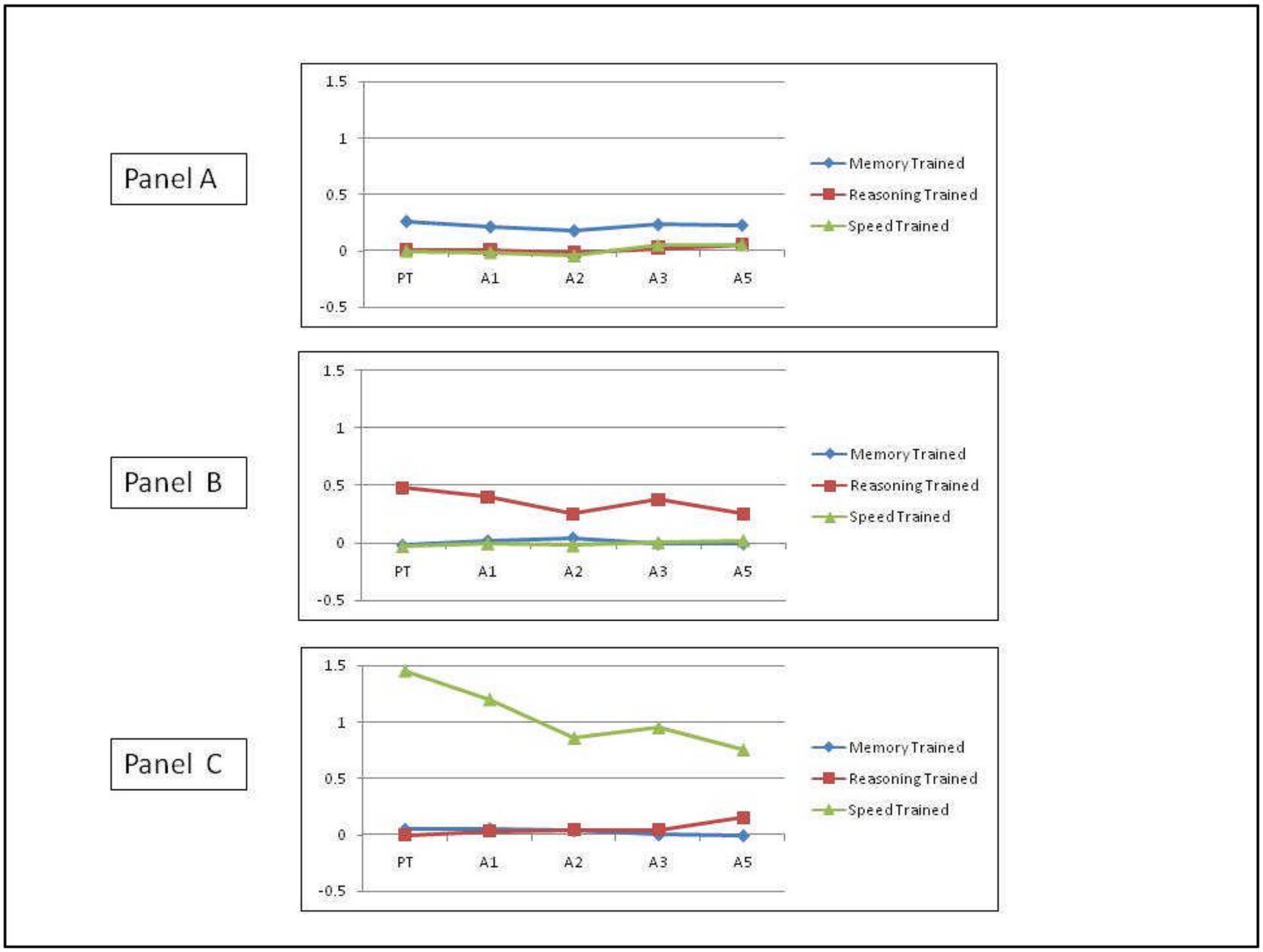

Figure 3.
Proximal Outcomes. Panel A shows training effect size on the Memory composite outcome by group over time. Panel B shows training effect size on the Reasoning composite outcome by group over time. Panel C shows training effect size on the Speed composite outcome by group over time.

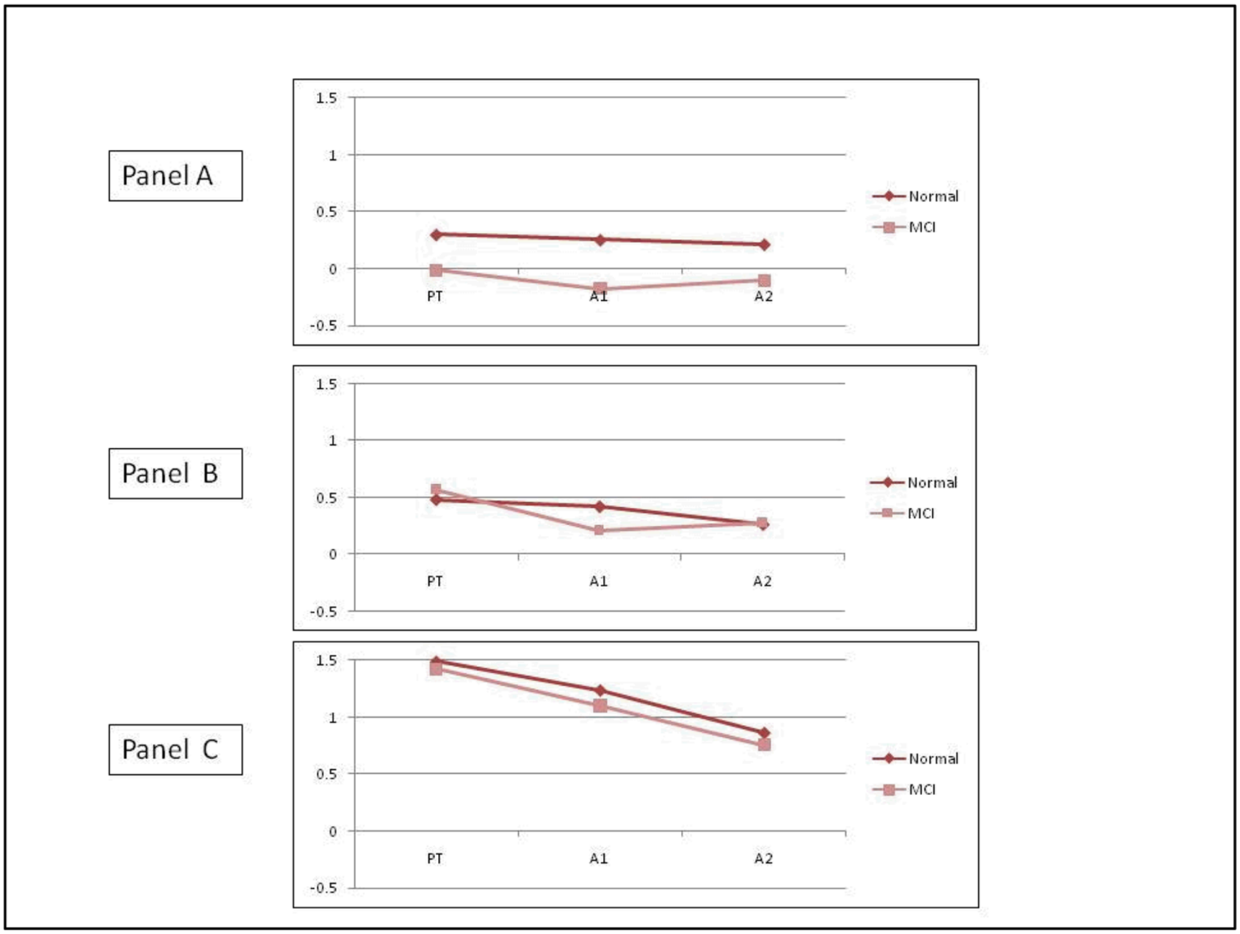

Figure 4.
MCI Subgroup Analysis on Proximal Outcomes. Panel A shows training effects for MCI and Normal subjects for memory trained subjects on the memory composite through A2. Panel B shows training effects for MCI and Normal subjects for reasoning trained subjects on the reasoning composite through A2. Panel C shows training effects for MCI and Normal subjects for speed trained subjects on the speed composite through A2.

Table 1

Sample characteristics.

	Control (n = 698)	Memory (n = 703)	Reasoning (n = 699)	Speed (n = 702)
Age, M (SD)	74.1 (6.1)	73.5 (6.0)	73.5 (5.8)	73.4 (5.8)
Education, M (SD)	13.4 (2.7)	13.6 (2.7)	13.5 (2.7)	13.7 (2.7)
Gender, % F	73.6	76.4	76.8	76.6
Ethnicity, % AA	26.8	25.0	27.2	24.9
MMSE, M (SD)	27.3 (2.0)	27.3 (2.1)	27.3 (2.0)	27.4 (2.0)

Notes: F = female; AA = African American; MMSE = Mini-mental State Examination

Table 2

Effects of ACTIVE training on proximal outcomes by training group and occasion.

Outcome Measure by Occasion	Intervention Group					
	Memory		Reasoning		Speed	
	All[1]	Booster-only[2]	All[1]	Booster-only[2]	All[1]	Booster-only[2]
Memory						
PT, effect size[3]	0.259***	0.007	0.003	0.077	−0.004	−0.051
A1	0.212***	0.059	0.003	−0.047	−0.016	−0.021
A2	0.179***	0.086	−0.016	−0.013	−0.047	0.048
A3	0.231***	0.210**	0.021	0.021	0.049	0.032
A5	0.226***	0.076	0.050	0.144	0.054	0.052
Reasoning						
PT	−0.020	−0.018	0.480***	0.076	−0.027	0.037
A1	0.018	−0.002	0.399***	0.370***	−0.002	0.150**
A2	0.043	−0.043	0.256***	0.190***	−0.019	−0.050
A3	−0.009	−0.090	0.381***	0.480***	0.006	0.107
A5	−0.008	0.092	0.257***	0.277***	0.024	0.081
Speed of Processing						
PT	0.045	0.018	−0.001	0.008	1.454***	0.202*
A1	0.051	0.051	0.031	0.061	1.203***	1.107***
A2	0.034	0.031	0.042	0.080	0.864***	0.417***
A3	−0.002	−0.060	0.041	0.027	0.955***	1.215***
A5	−0.010	0.011	0.151**	0.031	0.758***	0.848***

[1] Notes: Net effect size defined as [(Training improvement from BL to post-test occasion) - (Control improvement from BL to post-test occasion)]/intra-subject standard deviation of the Blom transformed composite score.

[2] Net effect size defined as [(Booster improvement from BL to post-test occasion) - (Non-boosted improvement from BL to post-test occasion)]/intra-subject standard deviation of the Blom transformed composite score. Covariates being adjusted: baseline age and MMSE score.

[3] Positive effect sizes indicate improvement.

* $p < .05$,

** $p < .01$,

*** $p < .001$.

Table 3

Effect of ACTIVE training on primary outcomes by training group and occasion.

	Intervention Group					
	Memory		Reasoning		Speed	
Outcome Measure by Occasion	**All[1]**	**Booster-only[2]**	**All[1]**	**Booster-only[2]**	**All[1]**	**Booster-only[2]**
IADL Difficulty						
A1, effect size[3]	−0.011	0.169	0.106	0.262	0.080	0.073
A2	0.011	−0.062	0.031	0.175	0.124	0.073
A3	0.096	−0.069	0.105	0.174	0.127	−0.070
A5	0.202*	−0.087	0.289***	0.240	0.256*	−0.287
Everyday Problem Solving						
A1	−0.045	−0.013	0.034	0.042	0.015	0.017
A2	−0.075	−0.039	−0.029	−0.015	0.028	−0.102
A3	−0.057	−0.029	−0.060	0.017	−0.011	0.045
A5	−0.152**	0.038	−0.080	0.219*	−0.054	−0.019
Everyday Speed						
PT	0.084*	−0.060	−0.002	0.033	0.019	0.024
A1	0.034	−0.032	−0.045	0.067	0.001	0.179*
A2	0.010	0.043	−0.026	0.024	0.014	0.117
A3	0.036	0.016	−0.026	0.032	0.048	0.08
A5	0.040	−0.008	0.088	0.081	0.077	0.302***

[1] Notes: Net effect size defined as [(Training improvement from BL to post-test occasion) - (Control improvement from BL to post-test occasion)]/intra-subject standard deviation of the Blom transformed composite score.

[2] Net effect size defined as [(Booster improvement from BL to post-test occasion) - (Non-boosted improvement from BL to post-test occasion)]/intra-subject standard deviation of the Blom transformed composite score. Covariates being adjusted: baseline age and MMSE score.

[3] Positive effect sizes indicate improvement.

* $p < .05$,

** $p < .01$.

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$p < .001$