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Does Cognitive Training Prevent Cognitive Decline?

A Systematic Review

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Background: Structured activities to stimulate brain function—that is, cognitive training exercises—are promoted to slow or prevent cognitive decline, including dementia, but their effectiveness is highly debated.

Purpose: To summarize evidence on the effects of cognitive training on cognitive performance and incident dementia outcomes for adults with normal cognition or mild cognitive impairment (MCI).

Data Sources: Ovid MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, and PsycINFO through July 2017, supplemented by hand-searches.

Study Selection: Trials (published in English) lasting at least 6 months that compared cognitive training with usual care, waitlist, information, or attention controls in adults without dementia.

Data Extraction: Single-reviewer extraction of study characteristics confirmed by a second reviewer; dual-reviewer risk-of-bias assessment; consensus determination of strength of evidence. Only studies with low or medium risk of bias were analyzed.

Data Synthesis: Of 11 trials with low or medium risk of bias, 6 enrolled healthy adults with normal cognition and 5 enrolled adults with MCI. Trainings for healthy older adults were mostly computer based; those for adults with MCI were mostly held in group sessions. The MCI trials used attention controls more often than trials with healthy populations. For healthy older adults, training improved cognitive performance in the domain trained but not in other domains (moderate-strength evidence). Results for populations with MCI suggested no effect of training on performance (low-strength and insufficient evidence). Evidence for prevention of cognitive decline or dementia was insufficient. Adverse events were not reported.

Limitation: Heterogeneous interventions and outcome measures; outcomes that mostly assessed test performance rather than global function or dementia diagnosis; potential publication bias.

Conclusion: In older adults with normal cognition, training improves cognitive performance in the domain trained. Evidence regarding prevention or delay of cognitive decline or dementia is insufficient.

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Fear of losing one's cognitive ability to Alzheimer disease and related dementias (ADRD) and ultimately declining to a state considered by many to be worse than death (1) is driving a growing "brain-training" industry. Cognitive training programs, marketed to otherwise healthy adults and persons with a recent diagnosis of mild cognitive impairment (MCI), make bold claims for reversing brain aging. Such claims include the ability to boost "cognitive reserve" in midlife (with *cognitive reserve* referring to both the mismatch between clinical symptoms of dementia and pathologic brain lesion load at death and the repeatedly demonstrated association between educational achievement and dementia risk). However, few studies have evaluated the effect of cognitive training programs on cognitive decline or the onset of dementia, which is the outcome of interest for most people who buy these programs.

This review systematically evaluates the existing literature on the effectiveness of cognitive training in preventing cognitive decline and ADRD. It is part of a larger systematic review commissioned by the National Institute on Aging to address a range of potential interventions to slow cognitive decline and prevent or delay dementia.

METHODS

We developed and followed a standard protocol that was posted on the Agency for Healthcare Research and Quality (AHRQ) Web site (www.effectivehealthcare.ahrq.gov). Full details of the methods, including literature searches, findings, and evidence tables, are available in the final report (2).

Data Sources and Searches

We searched Ovid MEDLINE, PsycINFO, EMBASE, and the Cochrane Central Register of Controlled Trials for relevant literature published between January 2009 and July 2017 (see Part A of the Supplement, available at Annals.org, for searches) and hand-searched reference lists of selected articles. We identified studies published before 2009 by reviewing studies included

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and excluded from the 2010 AHRQ review on preventing Alzheimer disease and cognitive decline (3).

Study Selection

Two investigators independently reviewed titles and abstracts of search results and screened the full text of potentially eligible references. We included randomized trials of cognitive training interventions enrolling adults with either normal cognition or MCI if the studies followed participants for at least 6 months, provided cognitive performance or incident dementia outcomes, and were published in English. We excluded studies that enrolled only persons diagnosed with dementia. The final health outcome of interest was incident ADRD. Intermediate health outcomes of interest included performance on cognitive testing, biomarker protein levels, brain matter volume, and brain cell activity level. No restrictions were placed on sample size or comparator type.

Data Extraction and Quality Assessment

One reviewer extracted study, population, intervention, comparator, and setting characteristics as well as the funding source from all eligible studies. Risk of bias was assessed independently from full texts by 2 investigators using an instrument based on AHRQ guidance (4). Risk of bias was individually reviewed overall and for each outcome and time point, and was summarized as low, medium, or high on the basis of a summary of bias risk across risk-of-bias domains and confidence that results were credible given the study's limitations. Outcomes and adverse events were extracted from studies with low to medium risk of bias. A second reviewer checked the quality of all data.

Data Synthesis and Analysis

Only studies with low or medium risk of bias were summarized, because we judged findings from studies with high risk of bias to lack validity, have little meaning, or be easily misinterpreted. Because studies used a highly varied set of outcome measures, neuropsychological tests were categorized by the following specific cognitive domains to facilitate analysis: executive function, attention, and processing speed; memory; language; and visuospatial abilities (Supplement Table A1). The domains of executive function, attention, and processing speed were grouped together because cognitive tests frequently measure all 3 of these related domains. Because studies analyzed and reported cognitive test results in many different ways, making it difficult or impossible to determine effect size or to assess whether between-group differences in scores or subscores were clinically meaningful (Supplement Table A2), we analyzed and reported cognitive test results by direction of effect and statistical significance. When we identified at least 2 studies or 1 large study (>500 participants) for a treatment comparison, 2 reviewers graded strength of evidence for each outcome on the basis of study limitations, directness, consistency, and precision; otherwise, strength of evidence was graded as insufficient. Assessments were confirmed by consensus.

Role of the Funding Source

The National Institute on Aging of the National Institutes of Health requested this report from the AHRQ Evidence-based Practice Center Program. The funding agencies provided comments on draft reports but had no role in data collection, analysis, interpretation, or manuscript development.

RESULTS

We identified 35 publications of 34 unique randomized controlled trials of cognitive training interventions, 11 of which had medium or low risk of bias (5–16). Only 1 trial was industry funded (8), whereas in 3 cases, trial funding was not reported (9, 15, 16). (See the Supplement Figure and Supplement Tables C1 to C4 for the literature flow diagram, evidence tables, and risk-of-bias assessments.)

The Table summarizes the overall strength-of-evidence findings. For cognitively normal adults, moderate-strength evidence suggests that cognitive training in a particular domain improves performance in that domain compared with inactive or attention control populations. These results are driven largely by the results from the ACTIVE (Advanced Cognitive Training for Independent and Vital Elderly) trial. Low-strength evidence suggests that for persons with MCI, cognitive training in a particular domain does not improve performance in that domain compared with controls. The MCI trials have more limitations and are less precise than the studies conducted with cognitively normal participants. Evidence is insufficient for incident MCI or ADRD outcomes.

Studies in Cognitively Normal Populations

Six trials with low to medium risk of bias tested training interventions in cognitively normal older adults (5–10). Sample sizes for the selected studies ranged from 40 to 2832 participants. Interventions lasted from 2 weeks to 6 months; follow-up ranged from 6 months to 2 years. Three of the 6 trials used only computer-based interventions (6–8), 2 used a combination of computer and noncomputer (paper-and-pencil) interventions (5, 9), and 1 used group-based competition to increase divergent thinking (10). Three of the computer-based interventions were designed to increase performance on a specific cognitive domain (such as processing speed) (5, 6, 9), 1 used computers for cognitive stimulation more generally (7), and 1 used a computer program designed to train several cognitive domains (8). Comparators included both inactive (5, 7, 8, 10) and attention controls (6, 9). No studies reported adverse effects.

The largest trial of cognitive training, ACTIVE, randomly assigned 2832 older adults (mean age, 74 years) without clinically significant cognitive impairment to 1 of 3 training groups or a no-contact control group (5). In each training group, a different cognitive domain was targeted: memory, reasoning, or processing speed. Participants in the intervention groups received 10 trainings of 60 to 70 minutes over 6 weeks. Cogni-

Table. Summary of Conclusions and Strength of Evidence for Cognitive Training in Adults With Normal Cognition or MCI*

Outcome	Conclusion for Normal Cognition	Strength of Evidence (Justification)	Conclusion for MCI	Strength of Evidence (Justification)
Dementia	No data	Insufficient	Unable to draw conclusion (k = 1; n = 24; 28 mo)	Insufficient (high study limitations, imprecise)
MCI	No data	Insufficient	Not applicable	Not applicable
Reasoning	ACTIVE trial: Improvement with reasoning training; no differences with memory or processing speed training Other trials: Improvement with reasoning training (k = 2; n = 3293; 24 mo)	Moderate (medium study limitations, indirect)	No data	Insufficient
Executive function/attention/ processing speed	ACTIVE trial: Improvement with processing speed training; no differences with reasoning or memory training Other trials: Improvement with executive function, attention, or processing speed training (2 of 3 tests significant); less improvement with training in other domains or general cognitive training (4 of 12 tests significant) (k = 4; n = 4233; 24 mo)	Moderate (medium study limitations, indirect)	No improvement in executive function, attention, or processing speed with training (1 of 14 tests significant) (k = 4; n = 429; 28 mo)	Low (medium study limitations, indirect, imprecise)
Memory	ACTIVE trial: Improvement with memory training intervention; no differences with reasoning or processing speed training Other trials: Some improvement with memory-specific training (6 of 11 tests significant) (k = 5; n = 3676; 24 mo)	Moderate (medium study limitations, indirect)	No improvement in memory with training (3 of 19 tests significant) (k = 5; n = 448; 28 mo)	Low (medium study limitations, indirect, imprecise)
Verbal	ACTIVE trial: No data Other trials: No improvement with nonverbal-specific training (0 of 3 tests significant) (k = 3; n = 1024; 12 mo)	Low (medium study limitations, indirect, imprecise)	No improvement in verbal skills with training (0 of 1 test significant) (k = 1; n = 160; 12 mo)	Insufficient (high study limitations, imprecise)

ACTIVE = Advanced Cognitive Training for Independent and Vital Elderly; MCI = mild cognitive impairment.
* "No differences" refers to no statistically significant differences.

tive testing outcomes included measuring changes in domain-specific test performance. Patient-centered cognitive outcomes included measuring changes in everyday problem solving (such as the ability to identify information on medication bottles), everyday speed (such as the time required to find food items on a grocery shelf), driving, and degree of dependency in completing activities of daily living and instrumental activities of daily living. Incident MCI or ADRD was not a prespecified outcome.

Although 5- and 10-year outcomes from the ACTIVE trial have been published (17, 18), only the results from the 2-year study had a medium risk of bias (5). At 2 years, ACTIVE participants showed improvement in the cognitive domains in which they were trained (for example, those who received memory training improved on memory-related tasks compared with control participants), but no statistically significant differences were found among groups with regard to other cognitive outcomes (for example, persons who received training in memory did not do better than control participants on reasoning tasks). Intervention and control groups did not differ in other patient-centered cognitive outcomes at 2-year follow-up.

Modeled on the visual process and speed training group of the ACTIVE trial, IHAMS (the Iowa Healthy and Active Minds Study) (n = 681) (6) randomly assigned adults by age group (50 to 64 years vs. ≥65 years) to visual processing speed training at the study center, visual processing speed training on the participant's home computer, or computerized crossword puzzles (attention control group). Two-hour training sessions were held once a week for 5 weeks. Participants assigned to the intervention at the training center also received a booster training at 11 months. One year after training, both intervention groups showed statistically significant improvement in the primary outcome of the Useful Field of View test compared with the attention control group.

The IHAMS participants also were administered 8 secondary cognitive tests on which they had not been trained. These tests were primarily within the executive functioning, attention, or processing speed domains. The intervention groups showed improvement in the Symbol Digit Modalities and Stroop Word tests compared with the attention control participants. The home training group showed improvement in parts A and B of the Trail Making Test compared with the control group. However, the training center–only group showed improvement only in Trails A, whereas the training center–booster group showed improvement only in Trails B, compared with the control group. No differences were found among groups with regard to the other 4 secondary tests.

Miller and colleagues (8) (n = 84) randomly assigned participants to a computerized brain-training

program addressing 6 domains (short- and long-term memory, language, visuospatial processing, reasoning, and calculation) or to a waitlist control group. Cognitively normal participants were asked to use the program 20 to 25 minutes a day, 5 days a week, for 8 weeks. Outcomes were evaluated by domain-specific tests of delayed memory, immediate memory, and language (visuospatial processing, reasoning, and calculation were not evaluated). Outcomes were evaluated at baseline and at 2 and 6 months. Only overall domain scores were reported, of which only delayed memory showed statistically significant improvement from training.

Carretti and colleagues (9) (n = 40) randomly assigned volunteers to individual-level working-memory training using audio recordings for word recall and computers for text recall versus a no-intervention control. Participants in the intervention group were asked to complete three 50- to 70-minute training sessions over 2 weeks. At 6 months, those receiving working-memory training showed statistically significant improvement in working memory and listening comprehension compared with the control participants. No statistically significant differences were found in reading comprehension or fluid intelligence between groups.

Klusmann and colleagues (7) (n = 259) randomly assigned women older than 70 years to a computer-based cognitive intervention or a nonintervention control group. (A physical exercise group is not included in this review.) The cognitive intervention group attended 90-minute computer courses taught approximately 3 times per week for 6 months. Course activities included learning to use e-mail and the Internet, taking and editing pictures or videos, playing games, word processing, and drawing. Six months after the intervention, the cognitive training group had a statistically significant improvement in immediate and delayed story recall, long-delay free recall, and Trail Making Test parts A and B compared with control participants. Groups did not differ in short-delay free recall, semantic verbal fluency, or Stroop test results.

Stine-Morrow and colleagues (10) (n = 461) randomly assigned older adults (mean age, 73 years) to a group intervention aimed at engagement and problem solving, an individual intervention with cognitive training in reasoning, or a waitlist control group. Participants in the group intervention were divided into teams, attended weekly practice sessions, and competed in a tournament in which teams were judged on their ability to develop novel solutions to problems. The individual training consisted of paper-and-pencil weekly lessons and activities focused on inductive reasoning. Both active interventions lasted for 16 weeks. Posttests were conducted between 30 and 32 weeks. At 8 months, participants in the individual training showed greater improvement in reasoning (the skill in which they were trained) than the engagement or control group. Participants in the group intervention showed greater improvement in divergent thinking (also the skill they practiced) than those in the training and waitlist groups. No generalized treatment effects were observed on composites of processing speed, visuospatial abilities, or verbal episodic memory in either intervention group.

Studies in Adults With MCI

We identified 5 trials with low to medium risk of bias that enrolled adults with MCI (11–16). Sample sizes ranged from 19 to 223 participants. Nearly all the interventions included a component that provided memory training; however, additional components varied. Interventions lasted 6 weeks to 6 months; follow-up was 6 to 28 months. Most interventions were delivered in small groups (11–14, 16); 1 was delivered individually through a computer (15). Only 1 trial measured conversion to ADRD or biomarkers related to ADRD pathology (13, 14). Two of the 5 trials used an educational control (11, 12), 2 used an attention control (13–15), and 1 had an inactive control group (16). No studies reported adverse effects.

Kwok and colleagues (1) (n = 223) randomly assigned persons with subjective memory problems (mean Mini-Mental State Examination [MMSE] score, 26 points) to receive cognitive training based on the ACTIVE protocol or to attend health-related educational lectures (12). Small-group cognitive training classes were led by occupational therapists 1.5 hours per week for 12 weeks. Groups did not differ on 5 subscales of the Chinese version of the Mattis Dementia Rating Scale after the intervention or at 1 year. However, some subgroup analyses by education level showed that training was more effective for participants with less education.

Vidovich and colleagues (11) (n = 160) randomly assigned older adults with MCI to a multidomain cognitive activity program or an educational control group. The small-group cognitive strategy training sessions, led by a clinical psychologist, focused on attention, memory, and executive processes. Participants attended 90-minute sessions twice a week for 5 weeks. Of the 11 cognitive tests reported, none showed a statistically significant effect of the intervention compared with the educational control.

Buschert and Förster and their colleagues (13, 14) (n = 24) randomly assigned participants with MCI (mean MMSE score, 26 points) to either memory training and social engagement or a control condition that involved monthly paper-and-pencil activities. A crossover design was used. For 6 months, participants in the intervention group received 120 minutes per week of training and engagement in a small-group setting. Of the 2 reported global measures of cognition, only the Alzheimer's Disease Assessment Scale–Cognitive Subscale showed improvement in the intervention group compared with the control group. This improvement was sustained for 22 months after the intervention. One of the 4 domain-specific tests, the Repeatable Battery for Neuropsychological Status (RBANS) Immediate Memory Index, showed statistically significant improvement with the intervention compared with the control; RBANS Delayed Memory and Trail Making Test A and B results were not statistically significantly improved by

the intervention. Conversion to Alzheimer disease occurred in half the participants in the control or delayed-intervention group and none of those in the early-intervention group during the 28-month follow-up.

Herrera and colleagues (15) (n = 22) randomly assigned adults with MCI (mean MMSE score, 27 points) to computer-based memory and attention training or computer-based cognitive activities (such as organizing a list of purchases in categories) as a control condition. Participants received 2 hours of training per week for 12 weeks. The authors categorized the measured cognitive tests as recognition (Doors Recognition Sets A and B, DMS48), working memory (Digit Span Forward and Backward), and recall (BEM-144 12-word list, 16 items free and cued, MMSE-3 words, Rey Complex Figure). Results were mixed. Compared with participants in the control group, those receiving the intervention had improvement in 1 of 3 recognition tests (Doors, Set A), 1 of 2 working memory tests (Digit Span Forward), and 2 of 4 recall tests (BEM-144 and MMSE).

Rapp and colleagues (16) (n = 19) randomly assigned participants with MCI (mean MMSE score, 28 points) to either memory training and education or a no-intervention control group. The memory training was delivered in small groups by clinical geropsychologists 2 hours per week for 6 weeks. The study reported 8 objective memory measures, both immediate and delayed: word lists, shopping lists, names and faces, and paragraphs. No statistically significant effects of training were seen at 6 months on any of the measures.

DISCUSSION

Many consumers of cognitive training programs wish to stave off dementia or slow the progression of an already-diagnosed cognitive deficit. However, only 1 small trial (12 participants per group) measured progression to ADRD, and no included trials reported incident MCI among cognitively normal participants. Instead of reporting incident MCI or ADRD, most of the trials measured intermediate outcomes of test performance. The evidence suggests that cognitive training improves cognitive test performance in otherwise healthy older adults, for the domain trained (5, 6, 9, 10). The ACTIVE trial provides the most compelling evidence for domain-specific improvements in performance after cognitive training, particularly for processing speed training (effect sizes were larger for speed of processing than for memory or reasoning training) (5). However, these gains do not seem to generalize to domains not trained.

Evidence for an effect of cognitive training on adults who already have MCI or other subjective memory loss seems less encouraging. Three of the 5 trials found no statistically significant effects of the training on cognitive testing (24 comparisons between intervention and control groups) (11, 12, 16). The other 2 small trials found mixed results of training on cognitive testing outcomes for people with MCI (13, 15).

Attrition is a major barrier to conducting cognitive training trials to assess long-term, patient-centered outcomes. In the ACTIVE trial, attrition at 5 years was 33% and was similar for all groups, including control participants (17); attrition at 10 years was 57% and, again, was similar across groups (18). Only about 18% of the sample loss at 5 years was attributable to death (17). Efforts were made to assess the effect of attrition, but none adequately addressed potential bias. Regular contact with the cohorts was not maintained, and reasons for sample loss were not well-established.

The evidence base for this review has limitations beyond attrition. Selected studies used many different validated and investigator-designed cognitive measures that often were combined into aggregate scores, making comparisons difficult and statistical summarization impossible. Trials sometimes included many performance test outcomes; whether positive performance test results were preferentially reported (publication bias) could not be assessed. Most studies were small and were not designed to evaluate clinically meaningful changes in global function or prevention of cognitive decline and dementia. Participants' adherence to the interventions was not directly reported in most cases.

Our findings are more positive than those of the other systematic reviews of randomized controlled trials of cognitive interventions that we identified in our literature searches (19–21). Clare and colleagues (20) and Bahar-Fuchs and coworkers (19) found no benefit from cognitive training and insufficient evidence for cognitive rehabilitation. Both reviews focused on persons with Alzheimer disease and vascular dementia, whereas our review focused on those with healthy cognition or MCI. Although Martin and colleagues (21) found some improvements in memory outcomes for persons with healthy cognition or MCI who received memory training, these gains did not exceed those in the active control groups. However, the authors did not require at least 6 months of follow-up in their inclusion criteria. In addition, their review did not evaluate nonmemory outcomes because of insufficient data for pooling. Because of data limitations, we did not pool, but we did qualitatively analyze all available evidence, providing a more comprehensive assessment of intermediate outcomes. All 3 reviews note substantial limitations in the consistency and methodological quality of the literature on cognitive training interventions.

We found that in older adults with presumed normal cognition, cognitive training seems to provide some protection against diminishing performance in the domain of training but no broader cognitive or functional benefit. Evidence was insufficient regarding whether cognitive training reduces the risk for future MCI or dementia. At this time, not enough evidence is available for health care providers to endorse or encourage any specific cognitive training to reduce the risk for cognitive decline or incident dementia. Patients may require education about how to interpret advertising for cognitive training programs and products.

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