Can Cognitive Exercise Prevent the Onset of Dementia? Systematic Review of Randomized Clinical Trials with Longitudinal Follow-up

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Objectives: *Epidemiological and preclinical studies suggest that mental activity levels may alter dementia risk. Clinical trials are now beginning to address the key issues of persistence of effect over extended follow-up and transfer of effect to nontrained domains. The aim of this report was to therefore systematically review results from clinical trials, which have examined the effect of cognitive exercise on longitudinal cognitive performance in healthy elderly individuals.* **Methods:** *MEDLINE, PubMed, and key references were used to generate an initial list of relevant studies (N = 54). These were reviewed to identify randomized controlled trials, which tested the effect of a discrete cognitive exercise training regime on longitudinal (>3 months) posttraining neuropsychological performance in healthy older adults. Seven RCTs met entry criteria. Prechange and postchange scores were integrated using a random effects weighted mean difference (WMD) meta-analytic approach (Review Manager Version 4.2).* **Results:** *A strong effect size was observed for cognitive exercise interventions compared with wait-and-see control conditions (WMD = 1.07, CI: 0.32–1.83, z = 2.78, N = 7, p = 0.006, N = 3,194). RCTs with follow-up greater than 2 years did not appear to produce lower effect size estimates than those with less extended follow-up. Quality of reporting of trials was in general low.* **Conclusion:** *Cognitive exercise training in healthy older individuals produces strong and persistent protective effects on longitudinal neuropsychological performance. Transfer of these effects to dementia-relevant domains such as general cognition and daily functioning has also been reported in some studies. Importantly, cognitive exercise has yet to be shown to prevent incident dementia in an appropriately designed trial and this is now an international priority.* (Am J Geriatr Psychiatry 2009; 17:179–187)

Key Words: Dementia, prevention, cognitive exercise, mental activity, cognitive training, brain reserve, cognitive reserve

There are an estimated 27 million individuals affected by dementia worldwide,[1] with the cost of care in many developed countries already outstripping those associated with cardiovascular disease and cancer combined. The rate of new dementia diagnosis is set to rise because of the shifting age profile of the population, with projections in the U.S. of over 7.7 million demented individuals by 2030. There is therefore an urgent need for development of strategies for the prevention of dementia. Within this context, delay of symptom onset is a modest yet potentially powerful goal: delay of dementia presentation by 5 years would effectively halve the burden of disease.[2] In this article, clinical trials that have examined the impact of cognitive training on longitudinal neuropsychological performance will be systematically reviewed. When combined with preclinical and epidemiological evidence, there are reasonable grounds to expect that mental activity may be a safe and effective strategy for delaying the onset of cognitive impairment in late life.

Epidemiological Evidence for a Protective Role of Mental Activity

Several international community-based cohort studies have now examined the link between mental activity and dementia risk. Typically, these studies compare incidence rates in groups with either high or low levels of educational attainment, occupational complexity, or participation in cognitive life style activities. A meta-analysis of 22 such studies integrated data from over 29,000 individuals and found consistent results[3]: an overall risk reduction of 46% for high mental activity levels compared to low activity (OR 0.54, CI: 0.49–0.59). Interestingly, the independent effects of education (OR 0.53), occupational complexity (OR 0.56), and cognitive life style (OR 0.50) were similar in magnitude.

More recent studies suggest that activity in the later stage of life may also have a beneficial effect independent of earlier life experiences. Six cohort studies to examine this issue have replicated a protective effect in the order of approximately 40%–50%, even after simultaneous control for other risk factors including education level.[4] Moreover, a number of these studies also point to dose-dependent effects.[3,5,6] One group, for example, found that the risk for dementia in a group with a moderate level of leisure activities was 50% compared to the low activity group, whereas those with the highest activity levels had their risk reduced to 33%.[7]

These findings can now be assessed against six of the key etiological criteria posed by Hill in 1965[8]—association, consistency, dose dependency, biological plausibility, coherency, and temporal primacy. Meta-analysis has clearly shown a robust association between mental activity and dementia incidence, and that these are highly consistent. More recent studies have furthermore pointed to a dose-dependent pattern in this association. In terms of biological plausibility, there is an embarrassment of riches from animal and human studies indicating the action of several potential mechanisms. These have been reviewed in detail elsewhere in conjunction with the introduction of a more coherent theoretical framework for their interpretation.[4] Potential mediatory mechanisms will only briefly be addressed in Discussion.

An important conceptual question therefore remains as to the direction of causality: is active cognitive life style a prospective predictor of dementia, or low activity levels in fact an early sign of preclinical disease.[9] This was partially addressed in a meta-analysis of studies focused on cognitive decline rather than dementia incidence,[10] after adjusting for baseline level of cognition. Individuals with high levels of mental activities were found to have significantly less risk for prospective cognitive decline than those with lower activity levels, complementing the results from the first meta-analysis. While persuasive, such a correlational approach does not exclusively rule out reverse causality. For this reason, results from intervention studies are critical to development of any future dementia prevention programs and are systematically reviewed here.

METHODS

Search Strategy

We searched MEDLINE (1950-November Wk 2 2007) and PubMed (www.pubmed.gov) databases for original research articles in any language which met our criteria. Our initial search strategy included the intersection of the following terms: ["randomized control trial" or "randomized"], ["cognitive" or

"mental"], ["training" or "exercise"], ["longitudinal" or "follow-up"], and ["older adults" or "elderly"]. This search produced 50 studies. This list was supplemented by manual searches through reference lists of published reports. Abstracts from a final total of 54 studies were then reviewed to assess suitability for inclusion.

Entry Criteria

Inclusion criteria were as follows: i) RCT design, ii) intervention through a cognitive exercise regime, which includes any type of training using repetitive cognitive tasks over separate days for more than 1 week, iii) longitudinal neuropsychological follow-up after cessation of training, defined as greater than 3 months, and iv) participation by healthy, community dwelling older adults greater than 50 years of age. The single additional exclusion criterion used was participation by patients with clinical dementia, cognitive impairment, or other major neurological or psychiatric condition. The three most common reasons for rejecting studies from our initial list were as follows: failure to investigate a cognitive training intervention, not using healthy elderly, and not reporting a primary longitudinal cognitive outcome.

Appraisal of Study Quality and Data Extraction

Seven RCTs met entry criteria and were individually scored on their published adherence to the CONSORT 2001 reporting criteria (www.consort-statement.org; see Table 1). Given the modest number of relevant papers, key information was extracted by a single reviewer onto a standard template. Where key information was missing from the published version, contact was made with the lead author and information requested.

Quantitative Meta-Analysis

A random effects weighted mean difference (WMD) model was used to estimate the integrated effect size across trials using Review Manager (Version 4.2 for Windows. Copenhagen, Denmark: The Nordic Cochrane Centre, The Cochrane Collaboration, 2003). Review Manager uses the Hedges adjusted g formula for estimation of the standardized mean difference of individual studies which is simi-

lar to Cohen's *d* but adjusts for potential bias from studies with small sample size.[11] Because results from individual studies were represented by relative mean change scores in the training versus control groups, negative scores indicate decline over time and positive scores a longitudinal increase. Inverse variance methods are then used to combine results across studies, whereby individual effect sizes are weighted according to the reciprocal of their variance. Finally, statistical inferences are made on the basis of the *z* test, which represents the overall effect size estimate relative to its SE.[12] A single primary neuropsychological outcome variable was used for each study to minimize colinearity bias.

RESULTS

Seven studies met inclusion criteria and represented a cumulative sample of 3,194 individuals. Only three studies met more than 12 of the 22 CONSORT reporting criteria for RCTs. More details about these studies are available in Table 1.

The relative effect sizes from longitudinal RCTs of cognitive exercise are shown in Figure 1. All studies have found effects in a protective direction, with four out of seven showing statistically significant effects. The cumulative WMD effect size estimate was 1.07 with a 95% confidence interval between 0.32 and 1.83 ($z = 2.78$. N = 7, p = 0.006, N = 3,194).

Sensitivity analysis was confined to examining the effect of medium-term (<2 years) versus long-term (≥ 2 years) follow-up. The average effect size from RCTs with long-term follow-up (WMD: 1.02 CI:0.14–1.89, $z = 2.28$, N = 5, p = 0.02, N = 3,040) was within the 95% confidence interval of those with less than 2-year follow-up (WMD: 1.16 CI: 0.37–1.96, $z = 2.88$, N = 2, p = 0.004, N = 154).

DISCUSSION

Longitudinal RCTs of Cognitive Exercise

Cognitive exercise in older adults is undoubtedly effective for improving performance in the trained task if one conducts follow-up assessment immedi-

TABLE 1. Details of Longitudinal RCTs of Mental Activity Training Included in Meta-Analysis
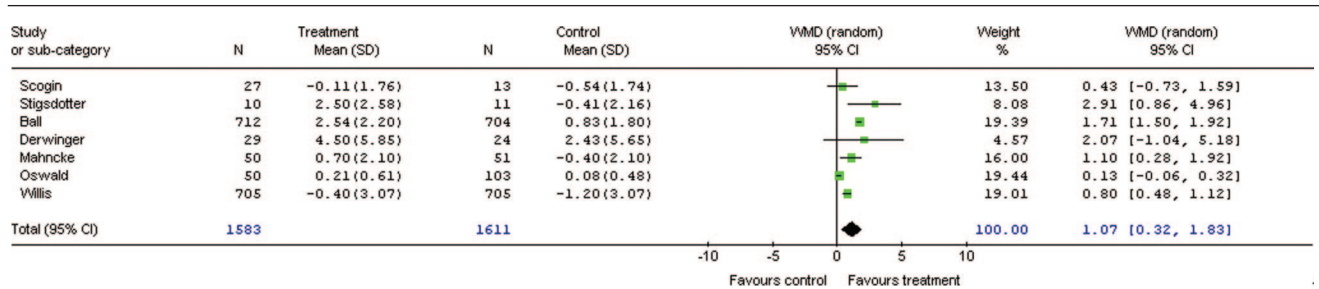
Study	Intervention	Control	Initial Sample Size (N) and Type	Follow-up Time (Months)	Main Outcome
Mahncke et al. (18)	Computer-based training on several cognitive tasks—40 sessions of 60 m over 10 weeks	Active contact	162 Healthy elders	3	Digit span
Willis et al. (17)	Reasoning training—10 sessions of 60 m over 5 weeks	No contact	2,832 Healthy elders	72	IADLs
Oswald et al. (19)	Paper and pencil training on memory, problem solving, and information processing speed tasks—30 sessions of 90 m over 30 weeks	No contact	375 Healthy elders	72	Composite cognitive score
Derwinger et al. (20)	Self-generated strategy training—10 1 hour sessions twice/week for 5 weeks	No contact	81 Healthy elders	8	Recall of short number sequences
Ball et al. (16)	Information processing speed, memory, and problem solving training—10 sessions of 60 m over 5 weeks	No contact	2,832 Healthy elders	24	Information processing speed
Stigsdotter et al. (54)	Multifactorial training covering encoding with imagery and method of loci, attentional task exercises and relaxation—8 weekly sessions	No contact	30 Healthy elders	42	Buschke selective reminding test
Scogin et al. (21)	Manual completion focusing on learning mnemonic skills, increasing encoding time, and practice exercises	No contact	27 Healthy elders with self-report memory complaints	36	Benton visual retention test

ately after the end of training.[13,14] Two central questions, however, need to be addressed in order to hypothesize whether a similar strategy may be effective for the prevention of dementia onset. These are a) transfer of effect: do improvements from particular training regime generalize to other nontrained domains and functions over time, and b) persistence of effect: do such effects last beyond the proximal posttraining period?

Our meta-analysis suggests that a discrete "dose" of cognitive exercise in the order of 2–3 months may have long-lasting and persistent protective effects on cognition over a number of years in healthy older individuals. The overall integrated effect size was strong in magnitude, estimated to be 1.07 (CI: 0.32–1.83). In more common clinical terms, this effect ap-

proximates a relative improvement of 1.2/2.6 points in the MMSE, or 4.1/9.9 ADAS-Cog points, when extrapolated to a community-based sample of either older cognitively intact individuals or those with Mild Cognitive Impairment (MCI), respectively.[15] Before discussing the pros and cons of this analytical approach, salient individual studies will be examined in more detail.

The largest trial so far has been the ACTIVE study,[16] which examined the effect of 10 sessions of cognitive training on 2,832 healthy older individuals divided into three different intervention groups: memory training, reasoning training, and processing speed training. Each intervention improved cognitive ability in the targeted area 2 years later. However, there was neither evidence of transfer of gain to

FIGURE 1. **Summary of Key Findings From RCTs of Mental Activity Training on Longitudinal Cognitive and Functional Change**

Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	WMD (random) 95% CI	Weight %	WMD (random) 95% CI
Scogin	27	-0.11(1.76)	13	-0.54(1.74)		13.50	0.43 [-0.73, 1.59]
Stigsdotter	10	2.50(2.58)	11	-0.41(2.16)		8.08	2.91 [0.86, 4.96]
Ball	712	2.54(2.20)	704	0.83(1.80)		19.39	1.71 [1.50, 1.92]
Derwinger	29	4.50(5.85)	24	2.43(5.65)		4.57	2.07 [-1.04, 5.18]
Mahncke	50	0.70(2.10)	51	-0.40(2.10)		16.00	1.10 [0.28, 1.92]
Oswald	50	0.21(0.61)	103	0.08(0.48)		19.44	0.13 [-0.06, 0.32]
Willis	705	-0.40(3.07)	705	-1.20(3.07)		19.01	0.80 [0.48, 1.12]
Total (95% CI)	1583		1611			100.00	1.07 [0.32, 1.83]

$$-10 \quad -5 \quad 0 \quad 5 \quad 10$$

Favours control   Favours treatment

Notes: Treatment and control means refer to posttest–pretest differences and SD to SD. Studies are listed in chronological order from earliest to most recent. Method of integration is weighted mean difference (WMD), which represents the overall standardized difference between treatment and control post-pre effects. See Table 1 for study details.

other domains nor any effect on instrumental activities of daily living (IADLs).

A 5-year follow-up to the ACTIVE study has, however, been recently reported with change in IADLs used as a main outcome measure.[17] Reasoning training specifically protected against functional decline over this extended follow-up period compared with any of the other interventions or the control wait-and-see condition. This is therefore the first major clinical trial to show a significant transfer of effect: directed cognitive exercise producing robust and enduring benefits on a general functional outcome that is highly relevant to dementia onset.

Mahncke et al.[18] conducted a RCT that was notable for the use of computer-based cognitive exercises, allowing individuals to face tasks of increasing difficulty as their skill levels progress. Neuropsychological tests immediately after the end of the training period found verbal memory performance improved by up to 25% of a SD, and testing 3 months later showed that short-term memory performance remained enhanced.

The Sim-A clinical trial compared the effects of cognitive, physical, and combined training in healthy older individuals over a 5-year period.[19] Despite the randomization procedure being incomplete, 30 paper-and-pencil cognitive training sessions produced a significant effect over both the 12 month and 5-year follow-up periods. Moreover, this effect seemed to transfer to a measure of general cognition. Other smaller studies with samples of less than 100 individuals have found positive trends but have lacked power[20,21] (see Fig. 1).

Although the cumulative effect size and concordance across longitudinal trials of cognitive exercise is promising, some caution against over interpretation is recommended. Primary outcome measures, for example, differed widely across the trials, as did the duration, precise nature, and frequency of the interventions (Table 1). Second, only the single most clinically relevant primary outcome variable was entered into this meta-analysis per trial, generally at the exclusion of secondary outcomes which tended to be less robust. Third, rigorous adherence to CONSORT clinical trials guidelines has been an exception rather than the rule. In general, the quality of trials in this area has been disappointing.

On the other hand, it is encouraging that those studies with longer term follow-up showed no evidence of less potent effects than those with more modest follow-up. Claims for persistence of effect would therefore appear justified. Finally and perhaps most significantly, two of the more recent clinical trials have shown that their training protocols generalize to domains beyond the narrow focus of the exercise regime.[17,19] Well-designed cognitive exercise interventions may thereby have potential to transfer to those domains critical for the development, and thus prevention, of dementia such as general cognitive function and instrumental activities of daily activity.

Could Mental and Physical Activity Be Synergistic?

A systematic review by Colcombe and Kramer[22] of RCTs examined the effects of physical exercise on the

cognitive abilities of older adults. The overall effect size from this review was 0.48 for exercisers and 0.16 across the control groups, indicative of a relative effect size of approximately 0.32, less than half the effect seen in the current meta-analysis of longitudinal cognitive training studies. It is important to note that RCTs integrated by these authors did not feature longitudinal follow-up, and thus the applicability of these findings for the prevention of dementia remains unclear.

The issue of potential interactive effects has been assessed in two RCTs who studied cognitive training, physical training, and their combination in comparison to a control condition. A preliminary study without longitudinal follow-up found that the average difference between pretraining and posttraining memory scores was significantly higher in the combined group than in either the aerobic or mental training alone.[23] As mentioned, the Sim-A trial also examined the effect of 30 sessions of combined training after 5 years of follow-up. Cognitive training alone produced a prepost effect size of $d = 0.13$ (p <0.001), whereas the control and physical training conditions alone had no significant longitudinal effects. The combined physical and cognitive training condition, however, resulted in an effect size more than thrice the cognitive training alone of $d = 0.75$ (p <0.001). Preliminary clinical trials evidence suggests that combining physical and mental exercise may produce greater cognitive benefits over time than either intervention alone. Capacity for such synergistic potentiation clearly needs further evaluation.

Biological Mechanisms Underlying These Benefits

For over four decades, the "environmental enrichment" paradigm has been the dominant experimental technique for analyzing the combined effects of mental and physical activity on the mammalian brain.[24] Enrichment involves changing the home conditions of the animal to include greater opportunities for exploration of novel toys and mazes, more contact with other animals and additional opportunities for voluntary exercise.[25,26] Comprehensive accounts of the biological changes induced by mental[4] and physical exercise[27] are available elsewhere.

Mental stimulation is a robust trigger for the induction of brain-derived neurotrophic factor and nerve growth factor.[24,28] These molecules are vital for neural cell survival and proliferation, and knockout of these genes leads to severe impairments in learning and synaptic plasticity.[29,30] Electrophysiological measures of synaptic plasticity such as long-term potentiation are also augmented.[31] Similarly, enrichment induces profound increases in synaptogenesis, by as much as 150%–200% in quantitative studies.[32] This effect is especially salient to clinical dementia, as synaptic density is arguably the most accurate biophysical correlate of cognitive impairment.[33,34] Furthermore, dozens of studies have now shown that enrichment can increase neurogenesis in the adult hippocampus.[35] There remain, however, a number of unresolved issues,[36] not least whether generation of new neurons in the adult brain is of any functional significance.[37,38]

Early studies in animals found that the mass and girth of the brain increased after a period of enrichment.[39] Remarkably, similar regional effects have been found in humans using volumetric MRI techniques after a period of behavioral training[40] and physical exercise.[41] Whether mental or physical training can retard the rate of hippocampal atrophy seen in A.D. is unknown, yet we have shown that lifetime levels of mental activity are inversely related to rate of hippocampal atrophy in healthy older individuals[42] and that cognitive exercise by healthy older individuals can increase levels of putatively neuroprotective metabolites in the hippocampus specifically.[43] Cognitive training has also been shown to increase the efficiency of resting state metabolism in the frontal lobe.[44]

Perhaps the most intriguing data has come from reports that mental or physical activity may directly interfere with A.D. pathophysiology. Enrichment and voluntary running in transgenic A.D. mice have been associated with decreased levels of amyloid pathology in several studies, by as much as 50%.[45–47] Conflicting data,[48] however, means that replication of such an effect in humans using molecular imaging is a high priority.

Challenges Facing RCTs of Cognitive Exercise

The balance of available data suggests that prevention of dementia is a realistic ambition for interven-

tions based on cognitive exercise. Importantly, this claim has yet to be tested in a prospective, double-blind randomized control trial. This is therefore an international priority. Several key challenges will need to be addressed for these to proceed efficiently and effectively.

Careful selection of the initial cohort has emerged as a primary issue. One reason that the ACTIVE study did not find any effects on functional outcomes at 2-year follow-up was because the control group exhibited almost no decline over this time. Given that interventions in this context are unlikely to increase functional performance, but rather slow or halt the rate of impairment, a level of naturalistic decline in the comparison group proves to be vital. Moreover, the type of "supernormal" participants that often volunteer for these types of trials can severely limit generalization of results. The average baseline MMSE score in the ACTIVE study was, for example 27.3, significantly greater than the reference population. This begs the question as to what one expects to achieve through intervention on a 75-year old person with a MMSE of 28/30 and no functional limitations?

For these reasons, an "at-risk" group is preferable, yet how one defines this has its own challenges. MCI, for example, has a number of practical and ontological difficulties, including competing definitions and highly onerous screening requirements.[49] Other options include raising the minimum age of entry, using "borderline" MMSE entry cut-offs, or selecting on APOE4 or presence of other risk factors. Counterbalancing the at-risk selection strategy is a perceived fear that these individuals may already be "too far down" a pathological process for behavioral interventions to work. Yet as a number of studies have found,[50–52] it is possible to slow the rate of cognitive decline through mental activity even in early dementia. This concern may therefore be overemphasized and borderline cognitive function does not appear to exclude individuals from completing cognitive training. Indeed, to maximize generalization of results to community and clinical settings, exclusion on the basis of comorbidities should be minimized. It is, however, acknowledged that those with visual impairment will find it difficult to learn and practice cognitive exercises that rely on visual, written, and spatial stimuli.

Details of the intervention also need close attention for there remains no consensus on the nature of the optimal cognitive exercise. In general, multidomain cognitive exercises seem to produce more robust results than single-domain training. Computerized delivery of such training so that individuals can be continually challenged across the training period at a personalized level also makes intuitive sense and will assist in standardized and replicable administration.

Attrition of participants is an important issue as for any longitudinal clinical trial. In the ACTIVE study, 294 of the original 2,832 participants were not able to complete 2-year follow-up assessment, an average attrition rate of 5% per annum. Interestingly, this compares favorably with attrition rates from MCI drug studies that vary from 12% to 27% per annum.[53] Similarly, the potential for adverse events from trials of cognitive exercise is probably low, with none reported thus far, yet this may reflect general poor reporting standards rather than a true absence of adverse events.

Finally, improved design of the control condition is required. The experiences of those on no contact waiting lists are vastly different from the intervention experience beyond the cognitive factors, which investigators assume are etiologically salient. Coming into to the research institute to see investigators and study staff, talking and interacting with other participants and the general sense of "doing something positive" all need to be better accounted for through use of active control arms in future RCTs.

How Should We Advise Our Older Patients?

Given the minimal risk for harm from taking on additional mental activities—and the high likelihood that this may in fact prove beneficial from a longitudinal cognitive perspective—it is suggested that older adults maintain a robust level and range of mental activities, particularly after retirement. It is also important to emphasize that no amount of mental activity is sufficient to guarantee against developing dementia or age-related cognitive decline.

CONCLUSIONS

Growing epidemiological and clinical trials evidence suggests that cognitive exercise may be an

effective strategy for delaying the onset of cognitive impairment in older adults. A number of plausible neurobiological mechanisms may account for these benefits. Clinical trials that address the remaining issues are therefore required. Trials will need careful attention to patient selection, to design of cognitive exercise and control conditions, and importantly, to improve quality of reporting. While awaiting such corroborating results, it may be prudent to advise older individuals to maintain robust mental activity, particularly after retirement for optimal cognitive health.

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