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Review Article

Immediate and delayed effects of cognitive interventions in healthy elderly: A review of current literature and future directions

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Abstract

Background: Research on the potential effects of cognitive intervention in healthy elderly has been motivated by (1) the apparent effectiveness of cognitive rehabilitation in Alzheimer's disease (AD) patients; (2) the face validity of bolstering skills eventually burdened by disease; (3) interest in low-cost/noninvasive methods of preventing or delaying onset of disease; (4) the epidemiologic research suggesting protective effects of educational attainment and lifelong participation in cognitively stimulating activities; (5) the burgeoning industry of brain training products and requisite media attention; and (6) the aging world population.

Methods: We performed a systematic review with meta-analytic techniques to analyze randomized controlled trials of cognitive interventions in healthy elderly.

Results: The weighted mean effect size (Cohen's *d*) of cognitive intervention across all outcome measures after training was .16 (95% confidence interval, .138 to .186). The existing literature is limited by a lack of consensus on what constitutes the most effective type of cognitive training, insufficient follow-up times, a lack of matched active controls, and few outcome measures showing changes in daily functioning, global cognitive skills, or progression to early AD.

Conclusions: Our review was limited by a small, heterogeneous, and methodologically limited literature. Within this literature, we found no evidence that structured cognitive intervention programs delay or slow progression to AD in healthy elderly. Further work that accounts for the limitations of past efforts and subsequent clear and unbiased reporting to the public of the state and progress of research on this topic will help the elderly make informed decisions about a range of potential preventive lifestyle measures including cognitive intervention.

Keywords: Alzheimer's disease; Lifestyle interventions; Cognitive training; Brain training; Healthy elderly

1. Introduction

The current lack of a disease-modifying treatment to delay onset or slow progression to Alzheimer's disease (AD), the many epidemiologic studies suggesting modifiable protective lifestyle factors (eg, educational achievement), and the robust physical exercise literature have led to an increasing interest in other lifestyle interventions to delay onset and slow progression from healthy elderly to mild cognitive impairment (MCI) and from MCI to AD. Even when effective neuroprotective drugs are eventually developed, lifestyle interventions might still provide additive or potentially synergistic effects. Thal et al [1] estimated that delaying onset of AD by 5 years would reduce the overall prevalence rate by 50%, profoundly reducing caregiver burden and institutional care and enhancing quality of life.

Can structured cognitive training programs lead to enhanced ''brain health''? Can cognitive training programs effectively mimic or supplement the known protective effects of education and lifelong involvement in mentally stimulating activities? Can cognitive training slow the progression or delay onset of MCI or AD?

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1.1. Lifestyle interventions: The case for cognitive training

Cognitive training has strong face validity as a means of offsetting declines in cognition in the elderly. Belleville [2] defined cognitive training as ''teaching theoretically motivated strategies and skills in order to optimize cognition functioning.'' The benefits of teaching rehabilitative and compensatory strategies in elderly who already have memory complaints (AD, dementia, or MCI) have been shown in multiple studies [3]. There is not an extensive literature, however, on the effects of cognitive training on cognition in generally healthy elderly persons (ie, individuals without current diagnosable memory impairments). Cognitive training is different from cognitive rehabilitation in that it attempts to enhance both broad and specific domains of cognitive functions.

Brain aging and AD are characterized by a loss of brain substance and a reduction in synapses and neurotransmitters. Ball and Birge [4] characterized this as an imbalance between neuronal injury (brain aging from oxidative stress, environmental or genetic factors) and repair (expression of neurotrophins, apoE cytokines, β-amyloid). The neuroscientific model supporting the potential effectiveness of cognitive training is that activities and chemical agents that promote neuronal repair are protective and might also promote neuronal growth and plasticity [5]. In a mouse model of AD, environmental enrichment alleviated amyloid burden and altered disease-associated gene expression [6], whereas environmental enrichment in a similar study prevented memory deficit for 12 months and slowed neurodegeneration [7]. Cognitive training could also strengthen synapses that would otherwise be lost to lack of stimulation. Animal models support this ''use it or lose it'' hypothesis; rats exposed in middle age to an enriched environment developed greater brain volumes than those deprived during middle age [8].

Retrospective studies in humans have shown that engagement in mentally stimulating activities from middle age is correlated with lower incidence of AD [9–15].

Epidemiologic evidence also indicates that high educational attainment [4,16] correlates with greater maintenance of memory. Cognitive training might enhance this protective factor. Education could provide more opportunity for lifespan intellectual stimulation that would help maintain neural networks throughout the life course. A cognitive reserve bolstered by education could potentially lead to better coping and compensatory mechanisms [17] or increase the number of Alzheimer's-type lesions or cerebrovascular changes needed before actual expression of dementia.

Evidence-based information regarding cognitive intervention in healthy elderly needs to be amalgamated and presented clearly to both the scientific community and our vulnerable elderly population. The last meta-analysis performed on studies of healthy elderly and memory training was published in 1992 [18]. Since then, the definition of cognitive training has expanded beyond memory training. Moreover, recent media attention has increased public awareness and spending on cognitive interventions [19]. Americans are expected to spend $80 million this year on brain exercise products in comparison to $2 million in 2005 [20]. Brain aging products can be a financial drain, decrease participation in more proven lifestyle interventions, and potentially undermine cognitive health by frustrating the ''worried well'' if poorly designed [21].

Anti–brain aging products such as [m]Power (Dakim, Inc, Santa Monica, CA) claim to be ''a powerful new weapon in the fight against Alzheimer's disease,'' but industry-based research has been criticized for not accounting for placebo effects, for confusing procedural learning with genuine overall cognitive improvement, for generalizing results from nursing home residents to healthy elderly, and for claiming that a brief increase in blood flow can decrease brain aging [21,22]. Given the rapid growth of this industry, it is important to survey available research both to determine whether cognitive interventions are effective in forestalling the onset of cognitive decline and to determine the veracity of the claims made in advertising these products.

The objectives of this review and meta-analysis were (1) to systematically review the literature on cognitive training and healthy elderly, (2) to assess and compare the efficacy of different cognitive interventions on a variety of cognitive and functional areas, and (3) to provide recommendations for future research. The validity of using primarily meta-analytic techniques was limited by the multiple outcome measures per study and their heterogeneity both within and among studies, the lack of any follow-up in half of the studies, and the large variability in sample sizes between studies.

2. Methods

2.1. Search strategy

From September through December 2007, we searched for the terms *cognitive training*, *brain training*, *cognitive intervention*, *healthy elderly*, and *mild cognitive impairment* in various combinations in the following sources: (1) five electronic databases: MEDLINE, Scopus, The Cochrane Collaboration, Dissertation Abstract International, and PsycINFO and (2) two registers: Current Controlled Trials andClinicaltrials.gov. As a second step, we used the Web of Science Cited Reference service to search all of the promising bibliographic citations listed in the articles found during our initial search to identify any additional pertinent studies that might have been inadvertently overlooked.

2.2. Inclusion criteria

Published studies were included if they were randomized controlled trials (RCTs) of a cognitive intervention, conducted among community-dwelling healthy elderly, written in English, and published after 1992.

Table 1
RCTs of cognitive training in healthy elderly

Study sample	n, age, gender, education	Cognitive training intervention	Control condition	Duration & type of training	Outcome measures	Effect sizes (immediate)	Effect sizes (follow-up)	Study quality (maximum score = 8)
RCT1 [27]: musically naïve, healthy elderly recruited in FL from churches and an age-restricted independent residential area	EC, n = 16; CC, n = 15; EC, CC: A = 69.6, 71.4; G = 27%, 25%; E = 16.5, 16.3	(1) Individualized piano instruction: progressive difficulty in performance, technical motor/ dexterity exercises, music theory	No-contact	30-min lesson each week for 6 mo, 24 total sessions, minimum individual practice of 3 h/wk; individual	Trail Making Test Card A Trail Making Test Card B Trails Delta WAIS Digit Symbol WAIS Total Digit Span WAIS Block Design WAIS Letter/Number Sequencing	Initial –.08 .51 .66 .36 .83 .16 .60	3-mo follow-up .54 .75 .58 1.32 .44 .03 .49	6: not double-blinded, no placebo control
RCT2 [28]: community-dwelling healthy elderly recruited from university program for elderly called Medwise in AL	EC, n = 44; CC, n = 47; EC, CC: A = 73.29, 73.85; G = 41%, 42.5%; E = 14.3, 14.8	(1) Group discussion about attentional skills & IADL; (2) modified Useful field of view 3 tasks: speed of processing, divided attention, selective attention with tasks increasing in difficulty over sessions	No-contact	1-h sessions over 6 wk, 10 sessions total; group (2–3)	WAIS Block Design WAIS Information Facial Recognition WAIS Digit Span Rey-Osterrieth Complex Figure Test Benton Visual Retention Controlled Oral Word Association Trail-Making Test Stroop WAIS Digit Symbol Substitution Letter/Pattern Comparison Identical Pictures Finding As Timed IADL Road Sign Test Useful field of view	–.14 –.30 –.11 –.09 –.38 –.02 –.13 –.37 .05 –.22 –.06 –.19 .01 .09 –.13 .72	No follow-up	4: not double-blinded, no placebo control, no method for excluding AD patients, no follow-up
RCT3 [29]: healthy elderly recruited from clubs	EC, n = 8; CC, n = 8; EC, CC: A = 60–76; G = 12.5%, 12.5%; E = data not provided	8 themes, 1/ session: (1) perceptive activities; (2) attention; (3) intellectual structuration; (4) association & imagination; (5) language; (6) spatial marks; (7) temporal marks; (8) associated recruiting	Controls met for equal lengths for leisure activities (eg, painting, singing)	90-min session each week for 8 wk, 8 sessions total; individual	Memory Quotient Paired Associated Learning Digit Span Forward Logical Memory-Immediate Recall Orientation General Information Mental Control Visual Reproductions	.80 .77 –.04 .76 Not calculable Not calculable .07 .18	No follow-up	6: not double-blinded, no follow-up

(*Continued*)

Table 1
RCTs of cognitive training in healthy elderly (*Continued*)

Study sample	n, age, gender, education	Cognitive training intervention	Control condition	Duration & type of training	Outcome measures	Effect sizes (immediate)	Effect sizes (follow-up)	Study quality (maximum score = 8)
RCT4 [30]: healthy elderly from CA with 87% living independently	EC, n = 50; MAC, n = 51; CC, n = 54; A = 70.9; G = 50%; E = 16.3	Posit Science Brain Fitness Program: six computer-based exercises with increasing difficulty: (1) determining the identity (upward vs downward) & sequence of frequency-modulated sweeps; (2) identifying synthetically generated syllable from a confusable pair; (3) matching short spoken confusable consonant-vowel-consonant words from a spatial grid; (4) reconstruct a sequence of short spoken words; (5) reconstruct a spoken series of instructions by using the mouse to drag icons; (6) answering questions about short narratives	MAC & no-contact control (CC)	1 h/day, 5 days/wk for 8–10 wk; computer-based individual			Follow-up after 3 mo	6: no description of withdrawals, dropouts, no method for excluding AD patients
					Digit Span	.28	.08	
					RBANS Global Auditory Memory	.253	ND	
					Speed of Processing	1.047	ND	
					Spatial Syllable Match Memory	Not calculable	ND	
					Forward Word Recognition Span	.424	ND	
					Working Memory	ND	ND	
					Narrative Memory	ND	ND	
RCT5 [31]: healthy community-dwelling elderly couples	EC IT, n = 30; EC CT, n = 34; CC, n = 34; EC IT, EC CT, CC: A = 71.67, 71.79, 70.85; G = 50%, 50%, 50%; E = 16.1, 16.35, 15.41	Inductive Reasoning Training Protocol (same as RCT8): Individual Training (IT) vs Collaborative Training (CT)	No-contact	10 sessions over 4–5 weeks completed in-home; individual or collaborative	Letter Series Test EC IT	1.44	No follow-up	5: not double blinded, no placebo control, no follow-up
					Word Series Test EC IT	.59		
					Letter Sets Test EC IT	1.03		
					Letter Series Test EC CT	1.32		
					Word Series Test EC CT	.52		
					Letter Sets Test EC CT	.79		

(*Continued*)

Table 1
RCTs of cognitive training in healthy elderly (*Continued*)

Study sample	n, age, gender, education	Cognitive training intervention	Control condition	Duration & type of training	Outcome measures	Effect sizes (immediate)	Effect sizes (follow-up)	Study quality (maximum score = 8)
RCT6 [32]: community-dwelling healthy elderly	EC, n=46; CC, n = 97; A = 79.47; G = data not provided; E = data not provided	Memory Training Program based on Multi-Storage Model	No-contact	One 2- to 3-h session per week for 9 mo, 36 sessions total; group of 15–20	Independent Living Cognitive Status	0 1	No follow-up	4: not double blinded, no placebo control, no description of withdrawals/dropouts, no follow-up
RCT7 [33]: ACTIVE Study, healthy elderly from 6 U.S. cities	ECM, n = 703; ECR, n = 699; ECSP, n = 702; CC, n = 698; ECM, ECR, ECS, CC: A = 73.5, 73.5, 73.4, 74.1; G = 23.6, 23.2, 23.4, 26.4; E = 13.6, 13.5, 13.7. 13.4; MMSE = 27.3, 27.3, 27.4, 27.3	(1) Memory-teaching mnemonic strategies (organization, visualization, association for remembering verbal material); (2) Reasoning-teaching strategies for finding the pattern in a letter or word series & identifying the next item in series; (3) Speed of Processing: visual search and divided attention tasks (SP)	No-contact	Ten 60- to 75-min sessions, 4 sessions of ''booster'' training at 11 & 35 mo; group	Memory (ECM) Memory (ECR) Memory (ECSP) Reasoning (ECM) Reasoning (ECR) Reasoning (ECSP) Speed of Processing (ECM) Speed of Processing (ECR) Speed of Processing (ECSP) IADL Difficulty (ECM) IADL Difficulty (ECR) IADL Difficulty (ECSP) Everyday Problem Solving (ECM) Everyday Problem Solving (ECR) Everyday Problem Solving (ECSP) Everyday Speed of Processing (ECM) Everyday Speed of Processing (ECR) Everyday Speed of Processing (ECSP)	.257 –.009 –.012 –.018 .480 –.026 .045 –.003 1.463 ND ND ND ND ND .016 .091 –.004 .016	Follow-up 1, 2 & 5 y .212 .174 .23 −.011 −.030 .05 −.021 −.052 .05 .021 .045 −.01 .402 .257 .26 −.003 −.019 .02 .054 .034 −.01 .033 .043 .15 1.212 .867 .76 ND ND .20 ND ND .29 ND ND .26 −.045 −.073 −.15 .030 −.027 −.08 .008 .031 −.05 .041 .007 .04 −.050 −.030 .09 −.001 .009 .08	6: single-blinded, no placebo control
RCT8 [34]: Donostia Longitudinal Study, healthy elderly recruited from retirement homes in Spain	EC1, n = 85; EC2, n = 68; CC, n = 85; EC1, EC2, CC: A = 73.28, 70.18, 73.14: G = 29, 30, 26; E = data not provided	Training based on Braak & Braak AD staging model (1991); weekly cognitive function training session; monthly session on well-being in EC2 content unstructured	No-contact	1 & 1/2 hour session twice per week; 180 sessions over 2 y; group	Abstraction Ideational Praxis Immediate Execution Memory Ideomotor Praxis Phonetic Fluency Execution Recent Logic Execution Memory Short Term Memory Visuomanual Coordination Speed Visuomanual Coordination Execution	EC1 EC2 .11 .35 .04 .35 .06 .25 –.19 .35 –.24 .16 .32 –.18 .11 .09 .10 .19 .18 –.06	Follow-up after 2 y EC1 EC2 .1 .16 .13 .24 .3 .47 0 .3 –.25 –.29 .28 –.13 .57 .22 .05 –.07 –.38 –.35	6: no description of withdrawals, dropouts, no placebo control

(*Continued*)

Table 1
RCTs of cognitive training in healthy elderly (*Continued*)

Study sample	n, age, gender, education	Cognitive training intervention	Control condition	Duration & type of training	Outcome measures	Effect sizes (immediate)	Effect sizes (follow-up)	Study quality (maximum score = 8)
RCT9 [35]: IMPACT Study	EC, n = 181; CC, n = 208; EC, CC: A = 75.3, 74.9; G = 42.2%, 52.5%; E = 15.7, 15.7; MMSE = 29.1, 29.1	Posit Science Brain Fitness Program (see RCT4)	Active control	60 min/day, 5 days/wk, 8-10 wk; group	RBANS Global Auditory Memory	.09	No follow-up	7: no follow-up assessment
					Overall Memory Composite	.11		
					RBANS Visual Functioning Score	.12		
					RAVLT Trial 1-5	.07		
					RAVLT Delayed Recall	.05		
					WMS-III Digit Span Backward	.19		
					WMS-III Letter Number Sequencing	.16		
					RBMT Story Memory Immediate	.05		
					RBMT Story Memory Delayed	.04		
					Speed of Processing	.52		
RCT10 [36]: elderly in retirement community	EC1, n = 12; EC2, n = 13; EC3, n = 10; CC, n = 11; EC1-3, CC: A = 77.1, 76.6, 80.7, 82.3; G = data not provided; E = 15.8, 16.5, 14.7, 15; MMSE = 28, 28.3, 27.9, 27.2	EC1, group-based memory training; EC2, 1 of 2 self-paced commercially available audiotape memory training; EC3, individualized, microcomputer-based memory training	No-contact	90 min/wk, 9 wk total		EC1 EC2 EC3	No follow-up	5: no blinding, no placebo control, no follow-up
					Memory Controllability Inventory	.53 1 .64		
					Memory Functioning Questionnaire	.66 .5 .51		
					Geriatric Depression Scale-Revised	−.59 −.6 −1.00		
					Hopkins Verbal Learning Test	.25 .31 1.29		
					Hopkins Prospective Memory Test	.16 .33 1.25		
					Rivermead Behavioral Memory Test	−.36 −.3 −.3		

Abbreviations: A (age) = mean years; G (gender) = % male; E (education) = mean years; EC, experimental condition; CC, control condition; ES, effect size; WAIS, Weschsler Adult Intelligence Scale; IADL, independent activities of daily living; MAC, matched active control; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; WMS, Weschler Memory Scale; RAVLT, Rey Auditory Verbal Learning Scale; ND, no data.

NOTE. Positive effect sizes indicate improvement. Table modeled on Sitzer et al [3].

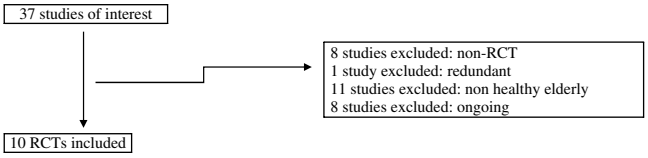

Fig. 1. Study selection process as outlined in Raschetti et al [23].

2.3. Exclusion criteria

Exclusion criteria included studies without an RCT design, ongoing studies, and studies involving subjects with MCI, AD, or dementia (Fig. 1).

2.4. Evaluation of study methodology

Study quality was evaluated by using a combination of items from a modified version of the Scale to Assess Scientific Quality of Investigations (SASQI) as cited in Sitzer et al [3] and items from Jadad et al [24]. Studies were scored by assigning 1 point for presence and 0 points for the absence of the following eight study characteristics: (1) randomized, (2) double-blind, (3) description of withdrawals/dropouts, (4) description of inclusion/exclusion criteria, (5) use of a comparison group controlling for nonspecific therapeutic factors (ie, attention-placebo), (6) methods of statistical analysis described, (7) exclusion of AD patients, and (8) inclusion of a follow-up assessment. Study quality was rated by the authors and separately by an independent researcher, resulting in 100% inter-rater reliability.

2.5. Data/statistical analysis

Results across the 10 studies meeting inclusion and exclusion criteria were combined for the meta-analysis following methods described by Petiti [25]. Effect sizes, when not reported by the study, were calculated by using the mean differences between scores on post-treatment outcome measures. Effect sizes (Cohen's *d*) were found by dividing the mean differences for control and experimental groups by the pooled standard deviation (SD) of each outcome measure (cognitive ability or functional behavior). To combine effect sizes across studies, effect sizes for each outcome measure were weighted to account for study sample size by multiplying by an estimate of 1/variance [25]. Mean weighted effect sizes for type of training intervention were calculated by grouping outcome measures for each type of training intervention (ie, memory, reasoning, speed of processing, and multimodal) across studies and then converting them back to Cohen's *d* by dividing by the total number of observations across studies of each training intervention [3,25].

The meta-analysis was repeated for all outcome measures at baseline to ensure that there were no statistically significant differences between groups at baseline [26].

3. Results

Presented in Table 1 are study, study quality, average study effect size, participant demographics (age, sex, years of education, and Mini-Mental State Examination [MMSE] scores when available), type and form of cognitive intervention training, control conditions, outcome measures, and effect sizes after training intervention and at follow-up. RCTs are referenced according to their assigned number in Table 1.

The mean effect size (Cohen's *d*) was 0.00 for all measures at baseline, indicating overall differences between groups at baseline were negligible. The weighted mean effect size (Cohen's *d*) of cognitive intervention across all outcome measures after training was .16 (95% confidence interval [CI], .138 to .186). Effect sizes (immediate) refer to outcome measurement after intervention. Length of time between the end of the intervention and outcome measurement varied from study to study, with an average between 7 and 14 days. The weighted mean effect size of cognitive intervention across all outcome measures at any follow-up point in time was not calculated because of the high variability in time to follow-up. Of the 10 studies, five had no follow-up assessments at all, and the remaining five had follow-up exams at 5 years (one study), 2 years (one study), 1 year (one study), and after 3 months (two studies).

3.1. Study quality

The average study quality was 5.3 on the 8-point scale. The lowest scoring studies were RCT6 and RCT2, with 4 points each. The highest scoring study was RCT9, with 7 points. Points were most commonly lost for not including a placebo or matched active control and for no follow-up after post-training outcome measures.

3.2. Types of cognitive training

The mean number of hours trained across all 10 studies was 74.89 hours, with a range from 10 hours of training in RCT2 to 540 hours of training during a period of 2 years in RCT8. Five studies used group training methods, with groups ranging from two to 20 participants, three studies used individual training, one study had both individual and group experimental conditions, and one study used both collaborative and individual training in separate experimental groups.

This review categorized cognitive training according to the groups used in the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) study, namely, Memory Training, Reasoning Training, and Speed of Processing Training [33]. We also included Multimodal Training, which involved training in two or more of the above three categories and/or involved two or more sensory systems (Table 2).

The mean weighted effect sizes (Cohen's *d*) were .12 for Memory Training (95% CI, .068 to .167). RCT6 used Memory Training alone, with a program based on the multi-storage model. RCT10 used three different types of training: group-based memory training, self-paced commercially

Table 2
Effect sizes (Cohen's *d*) for type of training after intervention

Type of training	Effect size (Cohen's *d*)	95% CI	No. of RCTs in effect size calculation
Memory	.12	(.068 to .167)	3
Multimodal	.15	(.103 to .194)	5
Reasoning	.16	(.11 to .21)	2
Speed of Processing	.22	(.17 to .26)	2

available audiotape memory training, and computer-based memory training program. Memory training in the ACTIVE study, RCT7, involved verbal episodic memory training and mnemonic strategies for remembering.

The mean weighted effect size for Multimodal Training was .15 (95% CI, .103 to .194). Five studies were classified as having Multimodal Training programs. RCT1 used individualized piano instruction. RCT3 focused on eight training themes: perceptive activities, attention, intellectual structuration, association and imagination, language, spatial marks, temporal marks, and associated recruiting. Most of the tasks involved combining sight and hearing as well as visuospatial skills. For example, in spatial marks, participants had to draw the mirror image of various pictures of objects. RCT4 and RCT9 used what they term brain plasticity–based training. It emphasizes increasing the speed and accuracy of aural information processing. Tasks involve identifying a synthetically generated syllable from a confusable pair (/ba/vs/da/) and reconstructing spoken instructions by dragging and ordering computer icons. RCT8 based their cognitive training on Braak and Braak's model of AD staging. Training was therefore geared toward tasks whose anatomic correlates are affected by AD. They trained on tasks of attention, orientation, memory, language, visuoconstructive ability, executive functions, visuomanual coordination, and ideational and ideomotor praxis.

The mean weighted effect size was .16 for Reasoning Training (95% CI, .11 to .21). Two studies had specific reasoning training groups, RCT5 and RCT7. Both involved the same outcome measures and training on the basis of the ability to solve problems that involve different types of serial patterns.

The mean weighted effect size was .22 for Speed of Processing Training (95% CI, .17 to .26). RCT2 and RCT9 both used speed of processing training involving visual search skills.

3.3. Control conditions

Three of the 10 trials included matched active control groups. In RCT3, controls met for an equal amount of time and participated in leisure activities such as singing and painting. RCT4 and RCT9 also used matched active controls. The weighted mean effect sizes for studies with an attention-placebo control versus a no-contact control were similar, .17 (SD, .32) and .18 (SD, .48), respectively.

3.4. Outcome measures

All studies used multiple outcome measures addressing cognition and functioning from multiple perspectives. We categorized outcome measures according to domain tested: overall cognitive function, Executive Function I (working memory/divided attention), Executive Function II (planning/cognitive flexibility), Executive Function III (inhibitory control/response inhibition), speed of processing, memory, reaction time/motor speed, visuospatial functioning, and performance-based activities of daily living [3,37]. Mean weighted effect sizes for each domain of functioning were not calculated because of the heterogeneity of training paradigms. We intended to calculate the mean weighted effect sizes for each domain of functioning, but we determined that it would not be a valid measure because of the high variability in sample sizes and the large number of outcome measures used in each study.

4. Discussion

Our meta-analysis of 10 studies published between 1996 and January 2008, all with the aim of determining the effectiveness of cognitive training in healthy older adults, resulted in a post-training weighted mean effect size (Cohen's *d*) of .16 (95% CI, .138 to .186). The mean weighted effect sizes for individual types of cognitive training were small: .12 for Memory Training (95% CI, .068 to .167), .15 for Multimodal Training (95% CI, .103 to .194), .16 for Reasoning Training (95% CI, .11 to .21), and .22 for Speed of Processing Training (95% CI, .17 to .26). For five studies examined individually, we found medium effect sizes across outcome measures administered after training. Effect sizes were largest when outcome measures were directly related to type of training. These findings suggest that training improves immediate performance on related tasks, but there was no evidence for any generalizability of training. Because half of the studies did not include follow-up examinations, there is scant evidence for long-term beneficial effects. In general, our ability to compare results across these studies is limited for a number of reasons that, taken together, reflect serious problems with the extant literature on this topic.

4.1. Limitations of this review

The use of multiple outcome measures per study and their heterogeneity both within and among studies make amalgamating data in a useful and statistically valid way difficult.

In addition, the variability in sample size also confounds a meta-analytic analysis. Petiti [25] argued that combining data from small trials with data from larger trials can result in overestimating the precision of smaller studies. The problem of differential sample sizes was partially mediated by using mean weighted effect sizes. Within-study effect size correlations and the small number of studies can also make averaged outcome measures less useful. In addition, the two large trials (RCT7 and RCT9) inevitably dominated

the analysis because they have approximately 10 times the number of participants than the other eight studies combined.

Another limitation encountered in all meta-analyses is obtaining complete study information. In RCT4, it was impossible to calculate effect sizes for three outcome measures because the study design did not involve pre/post measures for every outcome measure but instead used percentage improvement at multiple time points for some self-paced tasks. Despite contact with the authors, we were only able to obtain follow-up data for one outcome measure. RCT7 did not record baseline difficulty with independent activities of daily living or everyday problem solving. In RCT2, effect sizes for two outcome measures were incalculable because of SDs equal to 0; this might have resulted from the small sample size or other methodologic or data-recording limitations.

We also recognized that by combining effect sizes across generalized and specific regimens, we might dampen the effect of gains in specific tasks related to specific training. However, we believe that cognitive interventions must have generalizable effects to be clinically useful.

We did not calculate effect sizes for follow-up measures because only five studies had follow-up. In addition, the highly variable length of follow-up (from 3 months to 5 years) makes the averaging of follow-up scores problematic and, in our perspective, inappropriate.

4.2. Cognitive rehabilitation versus cognitive training and cognitive stimulation

A methodologic limitation seen in many of the RCTs reviewed is that they base their training on the rehabilitation model of training to increase performance for very specific tasks [26]. This seems antithetical to determining whether a cognitive intervention might exert generalized beneficial effects on cognition in healthy older persons. It is imperative that the distinction between specific rehabilitation and generalizable training be recognized, with a greater emphasis on exploring the effects of the latter approach in future work. Clare et al divided cognitive intervention in the elderly into three categories: cognitive stimulation (nonspecific enhancement in activities), cognitive training (attempts to optimize cognitive functioning), and cognitive rehabilitation (specific interventions in elderly to enhance performance in activities of daily living) [2]. Rehabilitation implies application to a functionally impaired population. The effectiveness of interventions in a clinical population has been well-documented [3].

What Clare et al argued is that rehabilitation in those with dementia and possibly MCI is compensatory and does not enhance overall cognitive function, which it has the potential to do in healthy elderly [2]. The goal of training in healthy elderly is to enhance cognition and to thereby enhance the cognitive reserve associated with reduced risk of AD [9].

4.3. Limitations of the current literature and recommendations for future work

4.3.1. The goal of interventions should be to show improvements generalized to more than one specific domain

Showing improvement in specific skills that subjects are specifically trained on in a study might not generalize to improvements or maintenance of overall cognitive functioning and activities of daily living. For example, those who received Memory Training in the ACTIVE study had an effect size for Memory performance of .257 and a Reasoning performance effect size of –.009. Alternatively, those who received Reasoning Training had an effect size for Memory performance of –.018 and an effect size of .480 for Reasoning performance. A current limitation of cognitive intervention studies is whether the outcome measures being used are valid and are able to accurately discriminate between various cognitive functions. We categorized the outcome measures into nine groups as described in Section 3.4. The broad heterogeneity of outcome measures in the literature makes cross-study comparisons difficult.

We would recommend a battery of tests that survey across several key domains (working memory, visuospatial function, episodic memory, executive controls) and that lead to an omnibus composite score. It might be useful to ''borrow'' from those batteries used in pharmaceutical research to measure cognition in healthy populations (eg, Cognitive Drug Research, Ltd, Goring-on-Thames, UK; CogState, Ltd, Melbourne, Australia). The effects of cognitive training on subjective memory complaints as well as participant well-being should also be considered by including measures of depression, anxiety, and subjective memory complaints.

4.3.2. Training interventions should be designed in accordance with key neuropsychological findings

Any effective training program should lead to generalized improvements in cognitive function, and it should be based on the application of sound theory and empirical evidence. The literature might benefit from a consensus on domains of functioning to be trained and tested such as those specified in the ACTIVE study [33,36]. RCT6 uses a training program based on a multi-storage model of memory. RCT4 and RCT9 also take steps in the right direction by basing their intervention and outcome measures on neuroscientific theory of negative brain plasticity (reduced schedules of brain activity, noisy processing, and weakened neuromodulatory control.) Current research on specific cognitive deficits associated with various subtypes of MCI might lead to novel and effective cognitive interventions.

An additional component of training is Psychosocial Training (education about elderly issues, healthy aging, and everyday coping strategies). West et al [38] argued that inclusion of psychosocial, attribution, or self-regulatory factors has beneficial effects on subjective memory appraisal.

4.3.3. The design of cognitive interventions should be tied to the latest neuroscientific evidence

Ample evidence exists at the neuronal, animal model, and neuroimaging levels of investigation to show that ''brain training'' is associated with changes in brain activity and neurochemistry. For example, Valenzuela et al [39] looked at neurobiologic changes of cognitive intervention in healthy elderly. They found elevated creatine and choline signals in the hippocampus by using magnetic resonance spectroscopy after 5 weeks of training with the method of loci, a mnemonic memory training technique. They found the largest increases in creatine and choline signals in those with the highest neural dysfunction at baseline, which suggests that baseline characteristics might influence the effectiveness of an intervention.

4.3.4. Trials of cognitive interventions in the elderly should include matched active control groups

Training effects must be isolated from the potentially confounding benefits of increased social contact (especially in the potentially more isolated elderly). Studies with matched active controls might further decrease the already small effect sizes found in the cognitive training literature. Few outcome measures had Cohen's *d* effect sizes surpassing .2. In contrast, two meta-analyses of cognition and physical exercise found effect sizes of .60 and .57, respectively [40,41].

4.3.5. Longer follow-up intervals are needed to capture cognitive degeneration in aging and AD

Of these 10 trials described, six did not include follow-up exams. Only three studies involved follow-up periods of more than 1 year. Selwood et al [42] argued that results cannot be viewed with confidence when there is less than 1 year of follow-up. In a degenerative illness, finding a true association can be dependent on the length of follow-up [25].

4.4. Noteworthy citations that did not meet inclusion criteria

There were a number of noteworthy studies that did not meet the RCT design inclusion criteria. Belleville et al [43] used a multi-factorial training program for both healthy elderly and those with MCI; they designed the training to promote generalization of tasks by using homework, elaboration to real-life strategies, and exercises with graded difficulty. Results showed large to medium effect sizes for two of three objective measures of episodic memory as well as significant differences in measures of subjective memory and well-being before/after training. Another noteworthy approach has been reported by Jaeggi et al [44], who designed their ''Dual N-Back'' working memory task with the aim of promoting generalized effects in fluid intelligence.

Calero et al [45] found that training gain in 133 healthy elderly was modulated by participants' cognitive plasticity as measured by the ''position test,'' a cognitive plasticity measurement to evaluate memory, spatial learning, and orientation. Although nonrandomized, this trial showed significant gains in working memory both after test and at 9-month follow-up.

Cognitive interventions have increasingly incorporated computers. Bond et al [46] used a computer training program in memory matching in Veterans Administration elderly residential homes. Although nonrandomized, the study showed a statistically significant difference between trained and untrained participants on five outcome measures of cognition after controlling for age, acuity, MMSE score, and length of stay in the residential home. Computer training has been extended to other technologies such as virtual reality that might potentially provide multi-modal training opportunities [47].

To the best of our knowledge, there are currently eight ongoing clinical trials of cognitive training in healthy elderly. Five of these involve computer-based cognitive training programs, and the remaining three use mental activity combined with physical exercise, memory as it relates to mental health, and visual training.

5. Conclusions

The popularity of products designed to slow brain aging might have outpaced credible scientific data to show that these interventions are effective. The majority of the trials showed statistically significant changes in performance on skills trained, but few trials have long enough follow-up periods to show a delay in onset of AD. More RCTs are needed with the cognitive training grounded in robust neuroscientific theory, sufficient follow-up time, matched active control groups, and outcome measures that can show changes in both daily functioning and global cognitive skills. The clinical research community should assist our elderly in making informed decisions about preventive lifestyle interventions. Communicating the state and progress of research in a clear and unbiased manner to the public is vital.

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