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Computer-Based Cognitive Training for Mild Cognitive Impairment: Results from a Pilot Randomized, Controlled Trial

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Abstract

We performed a pilot randomized, controlled trial of intensive, computer-based cognitive training in 47 subjects with mild cognitive impairment (MCI). The intervention group performed exercises specifically designed to improve auditory processing speed and accuracy for 100 minutes/day, 5 days/week for 6 weeks; the control group performed more passive computer activities (reading, listening, visuospatial game) for similar amounts of time. Subjects had a mean age of 74 years and 60% were men; 77% successfully completed training. On our primary outcome, Repeatable Battery for Assessment of Neuropsychological Status (RBANS) total scores improved 0.36 standard deviations (SD) in the intervention group (p=0.097) compared to 0.03 SD in the control group (p=0.88) for a non-significant difference between the groups of 0.33 SD (p=0.26). On 12 secondary outcome measures, most differences between the groups were not statistically significant. However, we observed a pattern in which effect sizes for verbal learning and memory measures tended to favor the intervention group while effect sizes for language and visuospatial function measures tended to favor the control group, which raises the possibility that these training programs may have domain-specific effects. We conclude that intensive, computer-based mental activity is feasible in subjects with MCI and that larger trials are warranted.

Keywords

human; aged; cognition; cognitive rehabilitation; memory; neuropsychological tests; randomized controlled trial; mild cognitive impairment

INTRODUCTION

There is growing interest in the potential for lifestyle interventions such as mental activity to improve cognitive function in the short term and possibly slow cognitive decline and delay onset of dementia in the long term. The Alzheimer's Association Maintain Your Brain® campaign recommends staying mentally active as one of the key components of a `brain healthy' lifestyle. In addition, the Alzheimer's Association has recently partnered with the Centers for Disease Control and Prevention to develop the *Healthy Brain Initiative*, which recommends studying the effects of mental activity as part of its Road Map for maintaining or improving the cognitive performance of all adults.

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These recommendations are based on recent studies demonstrating that the brain is highly plastic and capable of generating new synaptic connections and neurons throughout life (1). Studies in mice have found that animals raised in an `enriched' environment—which includes access to `mental activities' such as colorful toys and tunnels—generate more new neurons in the dentate gyrus of the hippocampus (2) and experience reduced cerebral deposition of β-amyloid, a pathological hallmark of Alzheimer's disease (3). In humans, several prospective observational studies have found that older adults who engage in more mental activity—such as reading or playing games—are less likely to develop dementia and Alzheimer's disease (4, 5).

However, relatively few randomized, controlled trials (RCTs) of mental activity interventions have been performed, especially in elders with mild cognitive impairment (MCI), who are at increased risk of developing dementia. The largest mental activity RCT conducted to date included only healthy elders and found that training in memory, speed of processing or reasoning was associated with domain-specific improvements in cognition that were maintained for up to five years (6,7). More recently, several small cognitive training RCTs have been performed in subjects with dementia (8-19) or MCI (20,21-26), with mixed results. Therefore, it remains critically important to study the effects of specific cognitive interventions, especially in high-risk elders.

The primary objective of our study was to perform a pilot RCT to compare the effects of a formal computer-based, cognitive training program (Posit Science Corporation, San Francisco, CA) with more passive computer-based activities in older adults with MCI. Our goal was to determine whether intensive computer-based cognitive training is feasible in subjects with MCI and to estimate the size of its effect on cognition.

METHODS

Subjects

Subjects were recruited from Memory Disorders Clinics at the four University Clinics in the San Francisco Bay Area. At each site, all current MCI patients who were ≥ 50 years old, fluent in English and not currently enrolled in another research study were invited to participate. MCI was diagnosed at each center using standardized clinical criteria and was defined as having a significant cognitive complaint in at least one cognitive domain and the absence of dementia, which is consistent with the recommendations of an international consensus committee (27). All MCI subtypes were eligible. Subjects were excluded if they had clinically significant cerebrovascular disease or were starting an acetylcholinesterase inhibitor; those on a steady dose were eligible. All study procedures were approved by Institutional Review Boards at the participating universities, and all subjects provided written informed consent.

Randomization and blinding

Subjects were randomly assigned to the intervention or control group in site-specific blocks that varied randomly in size to ensure adequate randomization. The randomization sequence was concealed from research personnel who enrolled subjects. Research personnel who administered cognitive tests were blinded to group assignment. Subjects were told that the purpose of the study was to compare the effects of two computer-based cognitive training programs.

Cognitive training

All cognitive training was performed in participants' homes on study-provided computers. Subjects were contacted weekly to make sure they were progressing through the training and to solve problems if necessary related to computer difficulties and issues of compliance.

The intervention group completed a computer-based, cognitive training program developed by Posit Science Corporation (San Francisco, CA) that is based on the principles of brain plasticity. The program involved seven exercises that were designed to improve processing speed and accuracy in the auditory cortex; primary and working auditory memory tasks were woven implicitly into the exercises. Specifically, subjects 1) determined whether two sounds were sweeping upward or downward, 2) identified a target syllable when it interrupted a repeated, similar sounding syllable, 3) distinguished between two similar sounds (e.g., bo and do), 4) matched sounds on a spatial grid, 5) distinguished between two similar sounding words (e.g., rake and lake), 6) followed a series of instructions that increased in complexity and 7) identified the picture that corresponded to the sentence. Each exercise employed adaptive tracking methods to continuously adjust task difficulty based on the subject's performance. Subjects used the program for 100 minutes per day, five days per week until either achievement of asymptotic performance levels over a several day period or completion of 80% of the training material in a given exercise. Progress was monitored automatically through weekly electronic data upload.

The control group performed three types of computer-based activities to control for the time intensity of the intervention and to keep subjects `blind' as to their group assignment. Specifically, subjects were given weekly `assignments' that involved listening to audio books, reading online newspapers and playing a visuospatially-oriented computer game (Myst) for 30 minutes each, for a total of 90 minutes/day, 5 days/week. Progress was monitored through self-report.

Cognitive outcomes

We administered a comprehensive neuropsychological test battery before and after the intervention period. Our primary outcome was the Repeatable Battery for Assessment of Cognitive Status (RBANS) total score (28). We selected this test because it has well-developed norms and alternate versions and provides both the total score and five index scores, which are composites based on 11 specific tests. In accordance with the RBANS instruction manual (28), all subjects received Form A during the first visit and Form B during the second visit and all RBANS scores were standardized (mean of 100, standard deviation (SD) of 15).

Secondary outcomes included the 5 RBANS index scores (immediate memory, visuospatial/constructional, language, attention, and delayed memory) as well as 7 other standard neuropsychological measures: the California Verbal Learning Test - II (CVLT-II) (29), in which subjects must learn and recall a list of 16 words that are grouped into four semantic categories (variables analyzed: total number of words learned and long-delay free recall); Controlled Oral Word Association Test (COWAT) (30), in which subjects are asked to generate as many words as possible that begin with a given letter within one minute (variable analyzed: total number of correct words generated); the Boston Naming Test (BNT) (31), in which subjects are asked to name the items shown in a series of ink drawings that range in familiarity (variable analyzed: total number named correctly); the California Trail Making Test and Design Fluency tests from the Delis-Kaplan Executive Function Scale (32) (variables analyzed: time to complete number/letter switch task and number of different designs completed on switch task); and the Spatial Span test (33), which is a visual working memory measure in which subjects must remember the location of objects on a spatial grid (variable analyzed: total number from forward and backward span tests combined). For all subjects, the CVLT-II was administered first and the RBANS list learning task was administered last to minimize interference between the two lists. Alternate forms were used for the CVLT-II, COWAT and BNT but were not available for other measures. Secondary outcomes were grouped into the domains of learning/memory, language/visuospatial function, and attention/executive

function. We hypothesized a priori that the effect of the intervention would be strongest for measures of learning/memory.

Other measures

Other measures included age and number of years of education. Depressive symptomatology was assessed with the Geriatric Depression Scale (GDS) (34).

Statistical analyses

Intention-to-treat analyses were performed using the last observation carried forward method for subjects who were lost to follow-up or had missing data. Baseline characteristics of intervention and control groups were compared using t-tests for continuous variables and χ^2 tests for categorical variables. Paired t-tests were performed to determine whether cognitive test scores changed within intervention or control groups. Standardized change scores were calculated by subtracting pre-intervention from post-intervention scores and dividing by the standard deviation (SD) for all subjects combined. Effect sizes were calculated by subtracting mean standardized change scores in the control group from those in the intervention group, so that positive effect sizes favor the intervention group while negative effect sizes favor the control group. Unpaired tests were performed to calculate p-values and 95% confidence intervals for effect sizes. Linear regression analyses were used to adjust effect sizes for baseline cognitive test scores, study site and randomization block.

RESULTS

Forty-eight subjects were enrolled from April 2004 to April 2005, one of whom withdrew during baseline testing and was excluded from all analyses. The remaining 47 subjects had a mean age of 74 years at baseline (range: 54-91) and a median of 17 years of education (range: 8-20); 60% were men. Twenty-two subjects were randomly assigned to the intervention group and 25 to the control group. Demographic and cognitive function variables at baseline were similar in the intervention and control groups (all $p > 0.20$, Table 1).

Thirty-six of the 47 subjects (77%) successfully completed the cognitive training protocol while 5 intervention and 6 control subjects dropped out. Subjects who dropped out did not differ from those who completed the study in terms of age, sex, education, depressive symptoms or cognitive function scores. The primary reasons for drop-out included the time commitment involved (3 intervention, 2 control), unrelated medical or personal issues (3 control), negative experiences with training (2 intervention) and none provided (1 control). Intervention subjects took a mean ± SD of 5.9 ± 1.3 weeks to progress through the exercises compared to 6.2 ± 2.0 weeks in the control group.

For our primary outcome, RBANS total scores improved 0.36 SD in the intervention group ($p=0.097$) compared to 0.03 SD in the control group ($p=0.88$) for a non-significant difference between the groups (effect size) of 0.33 SD ($p=0.26$) (Table 2).

For our secondary outcomes, most differences between the groups were not statistically significant. However, effect sizes for measures of learning/memory consistently favored the intervention group (range: 0.16 to 0.53 SD) and the effect size for the RBANS delayed memory test was nearly statistically significant in favor of the intervention group ($p=0.07$) (Table 2). In contrast, effect sizes for measures of language/visuospatial function tended to favor the control group (range: -0.51 to 0.01), and the effect size for RBANS visuospatial function was nearly statistically significant in favor of the control group ($p=0.08$). There was no consistent pattern for measures of attention/executive function. However, the largest effect size was observed for the Spatial Span test, on which scores improved significantly in the intervention

group (0.53 SD, p=0.04) and declined significantly in the control group (-0.32 SD, p=0.02) for a significant effect size of 0.85 SD (p=0.003) (Table 2).

All results were similar after adjustment for baseline cognitive test scores, study site and randomization block.

DISCUSSION

We found that intensive computer-based cognitive training is feasible in at least a subgroup of people with MCI. Seventy-seven percent of subjects completed the training, even though it involved a substantial time commitment of 90-100 minutes/day, 5 days/week for 6 weeks. Although most subjects in our study were highly educated, some had not previously used a computer.

For our primary outcome of global cognitive function as measured by the RBANS total score, we observed an effect size of 0.33 SD, which is similar in magnitude to cholinesterase inhibitors (ChEIs) for treatment of Alzheimer's disease (35). Although this effect was not statistically significant, its size suggests that a larger trial may be warranted. A sample size of 145 subjects per group would be required to detect this effect size with two-sided alpha = 0.05 and 80% power.

For our secondary outcomes, although most differences between the intervention and control groups were not statistically significant, we observed a pattern in which effect sizes for measures of verbal learning and memory consistently favored the intervention, which we had hypothesized a priori. This is consistent with an RCT of a related Posit Science program that was studied in healthy elders, in which significant improvement was observed in auditory memory, especially in subjects who started out with scores below the mean (36). In contrast, effect sizes for measures of language and visuospatial function tended to favor the control condition, which involved listening to books, reading and playing the visuospatially-oriented computer game Myst. This pattern is consistent with the hypothesis that these training programs may have domain-specific effects. Larger studies are needed to determine whether these observations are real or due to random variation.

Interestingly, the largest effect size was observed on the Spatial Span test, which requires subjects to remember the location of different items on a spatial grid. Although we did not hypothesize a priori that this test would be particularly sensitive to our intervention, in retrospect, the Spatial Span test is similar to the fourth exercise in our intervention, in which subjects must remember the location of sounds on a spatial grid in order to match them. However, additional studies are needed to determine whether this finding reflects a true effect or whether it was due to chance.

Most prior RCTs of cognitive training interventions in older adults with MCI have been relatively small (≤100 subjects), and results have been mixed. Several studies have found that memory training improves subjective but not objective memory measures. In a study of 54 elders with amnestic MCI, Troyer et al. (37) found that those who received training in practical, everyday memory techniques increased knowledge and use of memory strategies but not memory test performance compared to a waitlist control group. Similarly, Rapp et al. (22) found that memory training improved perceptions of memory capabilities but not objective measures of memory performance compared with a no-training control group. It remains unclear whether these negative findings are real or due to low statistical power.

Several other studies have reported that various cognitive training programs are associated with significant improvements in cognitive outcomes, but they have suffered from various methodological limitations that make interpretation of results more difficult. One study did not

include a control group (23), another study included a control group but did not randomize study participants (21), and several studies did not report between-group comparisons (24-26). For example, in a study of 59 elders with MCI, Rozzini et al. (25) found that the participants who received neuropsychological training plus ChEIs experienced significant improvements in measures of memory, abstract reasoning, mood and behavioral symptoms whereas those who received ChEIs alone improved only in depressive symptoms and those who received no treatment experienced no changes, but differences between the groups were not reported. Another study that included 84 elders with MCI or mild to moderate AD found that those who received a cognitive-motor plus psychosocial support intervention experienced stabilization of cognitive status over the first 6 months of the study compared to significant decline in the group that received psychosocial support alone, but between group differences for cognitive measures appear to have been non-significant.(24) Taken together, our results combined with the results from these other studies indicate that a larger trial with adequate statistical power is warranted.

Strengths of our study include evaluation of a novel, cognitive training intervention to enhance cognitive function in subjects with MCI, who are a vulnerable group with a high risk of developing dementia. Limitations include the small sample size, which restricts our ability to determine whether our findings are due to chance or lack of power. In particular, we examined 12 secondary outcomes measures and, using the $p<0.05$ criterion for statistical significance, one would expect one in 20 `statistically significant' findings to be false positives.

In addition, it is likely that our study population included primarily highly motivated subjects, and it is unclear whether our results would generalize to less motivated subjects. It is possible that our subjects were more compliant than other subjects, which could magnify the effects of our intervention. On the other hand, our subjects may have been engaging in higher levels of concurrent cognitively and physically stimulating lifestyle activities, which could have `washed out' the effects of our intervention. Future studies should determine the role that co-interventions may play on the results of cognitive training trials.

Finally, the active control utilized for our study may have been too active. We had hypothesized that the activities performed by the control group would be the equivalent of an inert placebo; however, our trial suggests that these activities also may have resulted in domain-specific cognitive improvements. Future studies should either include a no-contact control group (in a three-arm design) or confirm that any active control activities are, in fact, inert before commencing a trial.

In summary, we found that intensive computer-based mental activity training is feasible in elders with MCI and that larger trials are warranted.

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Table 1

Baseline characteristics of intervention and control groups*

	Intervention (N=22)	Control (N=25)	*p* Value
Age, y	74.1 (8.7)	74.8 (7.2)	0.78
Sex (% male)	59.1	60.0	0.95
Education, y	16.8 (3.2)	16.6 (2.9)	0.85
Depression score	2.7 (2.8)	2.8 (3.0)	0.89
Cognitive Function			
Primary Outcome			
RBANS total	85.2 (11.5)	87.8 (13.6)	0.48
Secondary Outcomes			
Learning/Memory			
RBANS immediate memory	84.8 (12.6)	85.7 (18.4)	0.84
RBANS delayed memory	71.4 (19.2)	74.6 (21.4)	0.59
CVLT total learned	35.3 (11.5)	33.9 (13.7)	0.71
CVLT delayed free recall	5.1 (3.9)	5.3 (4.3)	0.90
Language/Visuospatial			
RBANS language	91.5 (10.3)	93.6 (12.1)	0.51
RBANS visuospatial	103.4 (14.3)	103.4 (14.6)	0.99
Verbal fluency	35.0 (13.7)	40.2 (16.0)	0.25
Boston naming	26.4 (3.8)	26.8 (2.4)	0.67
Attention/Executive			
RBANS attention	93.3 (14.0)	95.3 (16.0)	0.65
Design fluency	5.0 (3.0)	4.0 (2.4)	0.23
Trail making test	137.0 (51.2)	149.0 (58.6)	0.46
Spatial span	13.0 (3.5)	12.2 (1.9)	0.30

* Data are presented as means (standard deviations) or percentages.

Table 2

Mean standardized change in intervention and control groups*

	Mean Change (95% CI)		
	Intervention (N=22)	**Control (N=25)**	**Difference (Effect Size)**
Primary outcome			
RBANS total	.36 (-.07 to .80)‡	.03 (-.39 to .45)	.33 (-.26 to .92)
Secondary outcomes			
Learning/Memory			
RBANS immediate memory	.32 (-.18 to .83)	-.05 (-.40 to .30)	.38 (-.21 to .96)
RBANS delayed memory	.40 (-.11 to .90)	-.13 (-.47 to .20)	.53 (-.05 to 1.10)‡
CVLT total learned	-.08 (-.42 to .26)	-.24 (-.72 to .25)	.16 (-.43 to .75)
CVLT delayed free recall	.07 (-.32 to .46)	-.19 (-.64 to .26)	.26 (-.33 to .85)
Language/Visuospatial			
RBANS language	.30 (-.13 to .74)	.29 (-.14 to .72)	.01 (-.59 to .60)
RBANS visuospatial	-.07 (-.39 to .26)	.44 (-.03 to .92)‡	-.51 (-1.08 to .07)‡
Verbal fluency	-.20 (-.68 to .28)	.02 (-.37 to .41)	-.22 (-.81 to .37)
Boston naming	-.05 (-.51 to .42)	.19 (-.21 to .59)	-.23 (-.82 to .36)
Attention/Executive Function			
RBANS attention	-.11 (-.50 to .28)	-.15 (-.61 to .31)	.04 (-.56 to .63)
California trail making test	-.11 (-.56 to .35)	-.08 (-.49 to .33)	-.03 (-.62 to .57)
Design fluency	.08 (-.33 to .49)	.19 (-.26 to .63)	-.11 (-.71 to .48)
Spatial span	.53 (.02 to 1.03)†	-.32 (-.59 to -.05)†	.85 (.31 to 1.39)†

*All values are in standard deviation units. Difference is intervention - control; positive values favor intervention group, negative values favor control group. RBANS, Repeatable Battery for Assessment of Neuropsychological Status; CVLT, California Verbal Learning Test; CI, Confidence Interval.

†$p < 0.05$

‡$0.05 \leq p < 0.10$