

RESEARCH ARTICLE

BDNF mediates improvement in cognitive performance after computerized cognitive training in healthy older adults

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Abstract

Introduction: The often-cited mechanism linking brain-derived neurotrophic factor (BDNF) to cognitive health has received limited experimental study. There is evidence that cognitive training, physical exercise, and mindfulness meditation may improve cognition. Here, we investigated whether improvements in cognition after these three types of structured interventions are facilitated by increases in BDNF.

Methods: A total of 144 healthy older adults completed a 5-week intervention involving working memory/cognitive training, physical exercise, mindfulness meditation, or an active control condition. Serum BDNF levels and Digit Symbol Test (DST) performance were measured pre- and post-intervention.

Results: Linear mixed models suggested that only the cognitive training group demonstrated augmentation of BDNF and DST performance relative to the control condition. Path analysis revealed that changes in BDNF mediate intervention-related improvement in task performance. Regression analyses showed that, across all intervention conditions, increased BDNF levels were associated with increased DST scores.

Discussion: This study appears to be the first to suggest that BDNF helps mediate improvements in cognition after working memory training in healthy older adults.

KEYWORDS

Brain-derived neurotrophic factor (BDNF), cognition, cognitive training, cognitively stimulating activities, mindfulness meditation, older adults, physical exercise, processing speed, working memory

Highlights

- Older adults were randomized to physical activity, mindfulness, cognitive training (computerized cognitive training (CCT), or control.
- CCT, but no other condition, led to increased serum brain-derived neurotrophic factor (BDNF) levels.

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- CCT led to improvement on the untrained Digit Symbol Test (DST) of speed/working memory.
- Path analysis: increases in BDNF mediate intervention-related improvement on DST.
- Increases in BDNF associated with improved DST across all experimental groups.

1 | INTRODUCTION

Our aging population has led to an increasing number of older adults developing mental decline and dementia. In this context, there is growing interest in finding ways to enhance cognitive functioning and to understand the biological mechanisms underlying these improvements. The current investigation focused on the relationship between changes in serum levels of brain-derived neurotrophic factor (BDNF) and improvements in cognitive performance in older individuals.

BDNF has garnered considerable attention because of its important role in brain development and maintenance of function.¹ In comparison to other members of the neurotrophin family of growth factors,² BDNF is highly expressed in the cerebral cortex and hippocampus.³ Extensive research has shown that BDNF promotes neural plasticity, facilitating synaptic transmission,⁴ dendritic modification,⁵ receptor trafficking,⁶ and the process of long-term potentiation.⁶ Moreover, BDNF is known to support neurogenesis⁷ and synaptic growth⁸ and repair.⁹ In longitudinal observational studies of older adults, higher BDNF levels at baseline have been associated with decreased odds of developing dementia.¹⁰ Particularly relevant to the present study is the idea that BDNF contributes to activity-dependent changes in the brain, making it a strong candidate for mediating changes in cognition.

Animal research has provided insight into the potential ways that BDNF can support enhanced cognitive activity. Rodents in enriched (i.e., complex) environments have opportunities for increased cognitive, sensory, and motor stimulation.³ Rodents exposed to these conditions exhibit the gross morphological and biochemical changes required for neural plasticity.^{7,11-13} BDNF levels have been shown consistently to increase in response to enriched environments and aerobic exercise.^{7,11} Animals with augmented BDNF levels, resulting from both enriched environments and exercise, have been shown to perform better on behavioral testing. For example, performance on the Morris water maze, a test of spatial learning and memory, improves significantly in the presence of elevated BDNF levels.¹⁴ Moreover, rats treated with BDNF antibodies have much longer escape latencies and swim paths than their control counterparts.¹⁵ Rats that have completed wheel running training also exhibit elevated BDNF levels, that when blocked by a tropomyosin receptor kinase B-immunoglobulin G (TrkB-IgG) BDNF antagonist during exercise, experience increased escape latencies compared to control animals.¹⁶

The biological and cognitive advantages associated with increased BDNF levels in animals have led to the assumption of similar benefits in humans. Recent research has focused on how different kinds of interventions may affect BDNF levels.¹⁷ Physical exercise, which

has received the most attention, has been associated with increased hippocampal volume,¹⁸ improved memory and executive function,^{19,20} and reduced risk of cognitive impairment,²¹ all of which may be supported by BDNF-facilitated neuroplasticity. Although there are many reports that aerobic exercise increases BDNF levels,^{22,23} outcomes have varied²⁴ and additional research is needed.

Cognitive training and mindfulness interventions have also garnered interest, as they have shown potentially beneficial effects on cognitive functioning and mental well-being in healthy adults as well as those with Alzheimer's disease (AD).^{25,26} Several studies indicate that cognitive training can increase BDNF levels, with most of the available evidence derived from the investigation of patient populations.²⁷⁻²⁹ A recent review suggested that mindfulness interventions are associated with increased BDNF levels, but the number of studies is small and the results have been inconsistent.³⁰ Research has suggested that after mindfulness training, participants exhibit improved performance on tasks requiring attentional control.²⁵

The relationship between intervention-related changes in BDNF and improvement in cognitive performance has not been widely studied or clearly established in humans. Some investigations have reported direct links between physical activity, change in BDNF, and enhancement of cognition. For example, after a 7-week walking intervention, Rahe et al. found that the interaction between change in physical fitness and change in BDNF predicted gains in verbal letter fluency.³¹ Leckie et al.³² demonstrated that BDNF mediates the effect of exercise on task-switch accuracy cost, and Erickson et al.³³ reported that in an aerobic exercise group, changes in hippocampal volume correlated with changes in BDNF and working memory (WM).

Reports about cognitively stimulating or mindfulness activity-induced enhancement in BDNF levels influencing changes in cognition are extremely sparse. To our knowledge, a small study ($n = 11$) of older women with mild cognitive impairment (MCI)³⁴ is the only report that has provided direct evidence of the relationship between cognitive stimulation, BDNF, and improvements in cognitive performance. This study found a significant relationship between change in BDNF and a change in processing speed after subjects participated in an 8-week cognitive training program. We found no studies that have reported whether there is an association between changes in BDNF and cognitive performance after interventions employing mindfulness meditation.

The current investigation aimed to explore the relationship between intervention-associated changes in BDNF and improvement in cognitive performance in a relatively large sample of healthy adults randomly assigned to adaptive computerized cognitive training (CCT),

physical exercise, mindfulness meditation, or an active control condition. Our previous research demonstrated that only participants in the CCT condition exhibited a significant increase in serum BDNF relative to those in the active control condition.³⁵ Based on these BDNF findings, we tested the hypothesis that, compared to an active control group, only the CCT intervention group would exhibit improvement in cognitive performance, which would be mediated by an augmentation of BDNF. Furthermore, we examined the hypothesis that across intervention groups, participants who demonstrated the largest change in BDNF would exhibit the largest improvement in cognition.

2 | METHODS

The current report examined data that had been collected from the Successful Aging and Enrichment (SAGE) study, a randomized, two-site (Boston, USA and Växjö, Sweden) controlled trial, involving three experimental conditions (CCT, physical exercise training, and mindfulness meditation training) and an active control condition, which has been the subject of three previous publications.³⁵⁻³⁷ Here, we investigated the relationship between intervention-related changes in BDNF levels and changes in performance on an untrained test of WM and processing speed (the Digit Symbol Test [DST]³⁸). Our prior work suggested that the active CCT condition is associated with a reliable improvement in performance on the DST³⁶ but no other cognitive outcome measures, which led this test to become the focus of our analysis.

2.1 | Participants

Participants had to be 65 years or older, with a Mini-Mental State Examination (MMSE) score ≥ 26 , an estimated baseline intelligence quotient (IQ) based on the American or Sweden National Adult Reading Test³⁹ (AmNART, NART-SWE) ≥ 90 , and perform within one standard deviation (SD) of mean for published age-based norms on the Logical Memory delayed recall test from the Wechsler Memory Scale, Third Edition (WMS-III).⁴⁰ Participants were excluded if they had major ongoing psychiatric disorders based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria or a history of a central nervous system disorder. The study was approved by the local institutional review board (IRB) committees for each site. The ClinicalTrials.gov number is NCT05128396. All participants completed written informed consent. (See Ledreux et al.³⁵ for a summary of the detailed screening evaluation and the participant inclusion/exclusion criteria.)

2.2 | Interventions

Participants were randomized into one of four intervention groups prior to the baseline assessment. Each of the interventions was structurally similar and conducted in subjects' homes, using interactive,

RESEARCH IN CONTEXT

- 1. Systematic Review:** The authors reviewed the physical exercise, mindfulness, and cognitive training literature available in the major databases. Findings are mixed on whether these interventions affect brain-derived neurotrophic factor (BDNF) levels, and there is a striking paucity of human studies that explore the link between intervention-associated changes in BDNF and changes in cognitive performance.
- 2. Interpretation:** Our study appears to be the first in healthy older adults to demonstrate that BDNF helps mediate improvements in cognitive performance after participation in adaptive computerized cognitive training (CCT) of working memory. These findings provide a potential mechanism for the cognitive benefit of staying mentally active as individuals grow older.
- 3. Future directions:** Lengthier interventions are needed to determine if the elevation of BDNF levels and performance improvements in working memory/processing speed occur in experimental groups other than CCT. Additional research is necessary to understand how the study's findings were influenced by the specific cognitive intervention and outcome variables used, and the demographic characteristics of participants.

web-based software over the course of 5 weeks. Participants completed five sessions per week (a total of 25 individual training sessions) on a laptop provided by the study team, with each session lasting for ≈ 40 minutes. This duration and frequency of training was chosen in accordance with the procedures recommended by Cogmed[®] (Pearson Education, Inc.), a commercially available CCT program.

The PACE-Yourself exercise program is a subject-controlled interactive exercise program that utilizes 12 aerobic exercise routines pre-recorded by the study team.³⁸ During exercise, participants were asked to exert themselves "somewhat hard," which is equivalent to 11 to 13 on the Borg Rating of Perceived Exertion Scale.³⁷ Participants were able to modify exercise intensity every few minutes by indicating via button press whether the exercises were "too hard," "too easy," or "somewhat hard," which determined the pace of the next set of exercises.

The mindfulness meditation training consisted of guided meditation and mindfulness-in-action tasks aimed at improving attention and awareness.³⁵ Each session consisted of one mindful attending session and three mindfulness-in-action tasks, followed by a written reflection. Mindfulness-in-action tasks included mindful walking, mindful music listening, and mindful visual observation.

Adaptive CCT and active control participants completed Cogmed[®] training. Training sessions were based on 12 different verbal and visuospatial tasks, which included remembering a sequence of numbers,

letters, shapes, or spatial locations for immediate recall.³⁶ Participants worked on 8 of the possible 12 tasks on each day of training. The tasks completed each day were predetermined by the training program and balanced across subjects. Under Adaptive CCT, task difficulty was revised on a trial-by-trial basis, with the goal of establishing 60% accuracy, thereby creating a consistently challenging level of subjective difficulty for each individual. Task difficulty was modulated by increasing or decreasing the WM load for each trial. In the active control condition, the task difficulty remained at a constant, relatively low level. (See Ledreux et al.³⁵ for a detailed summary of each intervention condition.)

2.3 | Outcome measures

There were two main outcome measures: (1) change in serum BDNF level, post-intervention minus pre-intervention; and (2) change in Digit Symbol Test (DST) performance, post-intervention minus pre-intervention.

2.3.1 | BDNF measurement

Participants completed a blood draw and neuropsychological testing pre- and post-intervention. Venous blood was collected from a suitable distal arm vein into Vacutainer tubes at baseline and after the 5-week intervention had ended. The blood samples were kept at room temperature for 30 minutes to allow for clotting and then centrifuged at $2000 \times g$ for 15 minutes at 4°C. All blood draws occurred in the morning hours between 8:00 am and 12:00 pm to minimize diurnal variations in BDNF levels.⁴¹

For BDNF analyses, aliquots were kept at -80°C until use. Free BDNF levels were measured in serum samples using a sandwich enzyme-linked immunosorbent assay (Human BDNF Quantikine ELISA, DBD00, R&D Systems, Minneapolis, MN) according to the manufacturer's instructions. All samples were tested in duplicate. Sample BDNF concentrations were determined by non-linear regression from the standard curves using GraphPad Prism v6 (GraphPad, La Jolla, CA). The personnel who ran the analyses were blinded to the experimental conditions.

2.3.2 | Digit Symbol Test

Performance on the DST from the Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV)³⁸ was measured in all participants. The DST is particularly dependent on processing speed and working memory,⁴² two of the cognitive operations emphasized in the Cogmed[®] training tasks.³⁶ Of note, there is evidence that physical exercise as well as mindfulness interventions can also have a beneficial impact these cognitive operations.^{25,31,33}

The baseline visit (in which blood was collected and the DST was completed) occurred ≈ 7 to 10 days before the first intervention ses-

sion. The post-training visit was scheduled as close as possible to the end of each participant's training period (mean days 3.84 ± 0.24 (SD)). It is notable that there was no difference between intervention groups in number of days between the last training session and the date of the post-training visit.

2.4 | Statistical analysis

An intention-to-treat analysis was carried out in which all randomized participants who began the study were included in the statistical analysis.⁴³ No imputations for missing data were made. To examine for demographic differences between the participants in each group, analyses of variance (ANOVAs) were used to compare continuous variables, whereas the Kruskal-Wallis H test was used for dichotomous variables.

The relationship between changes in BDNF and changes in performance on the DST was analyzed in several ways. Linear mixed models (LMMs) were used to model the association between predictors and each of the two outcome measures in comparison to the control condition. The models included fixed main effects and examination for possible two-way or three-way interactions between assessment time (pre- vs post-intervention), site (United States vs Sweden), and intervention condition, run separately for each intervention (adaptive CCT, physical exercise, and mindfulness) versus the active control condition. For any intervention that was associated with both augmentation of BDNF and performance improvement on the DST, a path analysis⁴⁴ was then used to determine if the relationship between intervention group and improvement on the DST was mediated by changes in BDNF level.

In addition, regression analyses were used to further characterize the relationship between changes in BDNF levels and changes in DST performance and to determine whether there was a relationship between serum BDNF levels and DST scores at baseline (pre-intervention).

3 | RESULTS

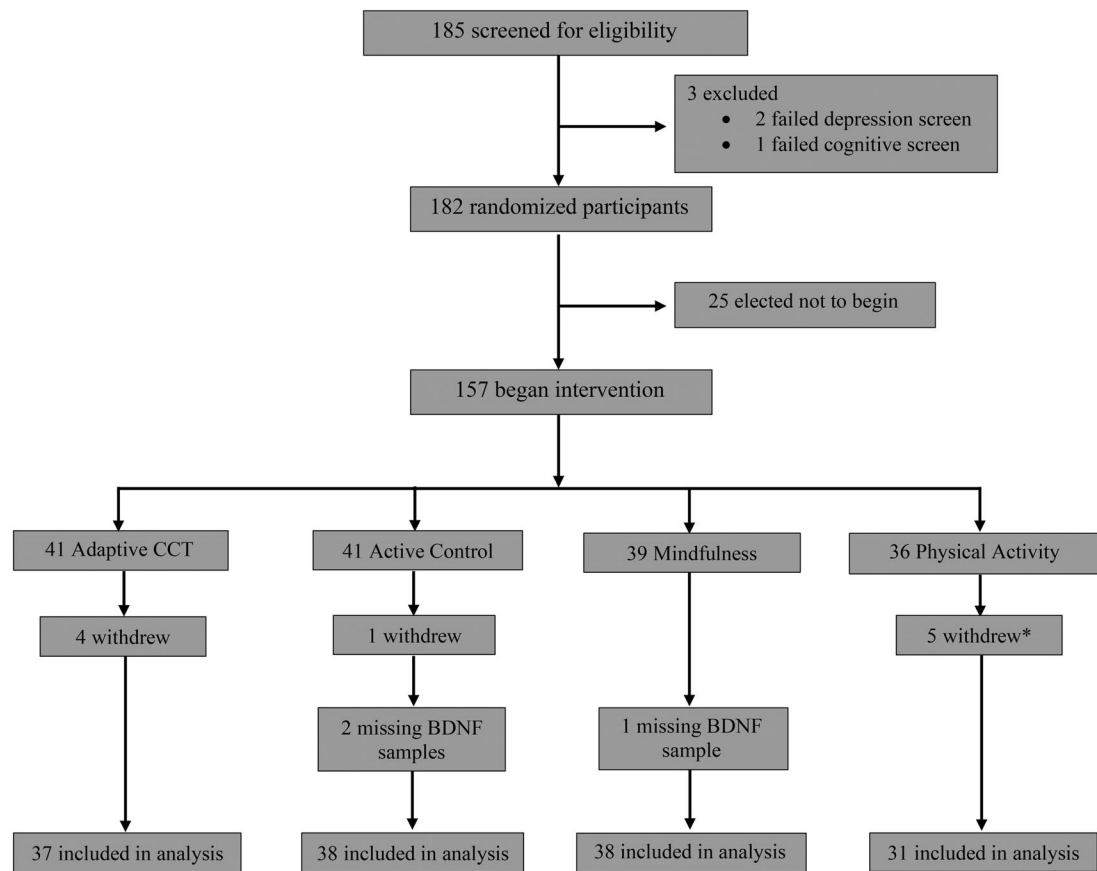
3.1 | Participants and demographics

One hundred eighty-two healthy older adults were randomized into one of four groups prior to the baseline assessment. Twenty-five elected not to begin the intervention, leaving 157 participants in the adaptive CCT ($n = 41$), active control ($n = 41$), mindfulness ($n = 39$), or physical exercise conditions ($n = 36$). Demographic and baseline neuropsychological values were compared between groups (see Table 1). Two subjects randomized to the physical exercise condition later withdrew from the study and their baseline data were lost. There were no differences between the groups in terms of age, sex, or years of education. In addition, the groups did not differ on a test of overall cognitive status (MMSE) or a test of delayed recall (Logical Memory). Mean estimated IQs were in the superior range = 123.21 ± 6.03).

TABLE 1 Demographic and neuropsychological variables of participants who began the intervention

Variables	Adaptive (n = 41)	Control (n = 41)	Mindfulness (n = 39)	Physical (n = 34 ^a)	P value
Age (years)	72.4 (5.6)	73.7 (6.5)	72.3 (5.6)	73.4 (6.7)	.69
Sex (M/F)	(12/29)	(15/26)	(8/31)	(14/20)	.12
Education (years)	15.7 (3.7)	15.2 (3.2)	15.3 (3.7)	15.9 (3.7)	.88
MMSE	29.3 (1.1)	29.1 (1.4)	29.3 (0.9)	29.3 (0.9)	.83
Logical Memory (WMS-III)	26.1 (9.0)	29.0 (1.3)	27.7 (7.1)	26.5 (9.3)	.80
NART	122.6 (5.9)	120.6 (6.0)	124.2 (5.3)	125.4 (5.8)	<.01
Digit Symbol (Baseline)	55.1 (14.9)	53.2 (11.5)	56.1 (13.1)	56.9 (16.4)	.68

^aBaseline data were missing for two of the 36 Physical Exercise participants. Adaptive = Adaptive computerized cognitive training (CCT), Control = Active Control, Mindfulness = Mindfulness Meditation, Physical = Physical Exercise. MMSE = Mini-Mental State Examination, NART = National Adult Reading Test, WMS-III = Wechsler Memory Scale, Third Revision.



* Data from two of these participants were lost.

FIGURE 1 Consolidated Standards of Reporting Trials (CONSORT) flow chart

Participants in the active control group had slightly lower estimated IQ scores than those of the other three groups. However, the adaptive CCT and active control groups did not differ in estimated IQ ($P = .13$). At baseline, the groups did not differ on DST scores ($P = .68$). Ten participants withdrew (including the two noted above) and BDNF data from three other participants were missing (see Figure 1, Consolidated Standards of Reporting Trials [CONSORT] flow chart). A total of 144 participants completed the study for whom there were full data sets.

3.2 | Adherence rates

Adherence rates were calculated for participants in all four interventions. The software for each intervention tracked the number of sessions completed by each participant. Adherence was calculated as the number of sessions completed divided by total number of possible sessions. There was no difference in adherence rate between groups ($P = .46$), with a high average adherence of 96.0%.

TABLE 2 Results of linear mixed models: Main effects and interactions

	Physical Exercise vs Control		Mindfulness vs Control	
	BDNF	Digit Symbol	BDNF	Digit Symbol Test
Time	ns	$\beta = 7.37^{*,a}$	ns	ns
Intervention group	ns	ns	ns	ns
Site	$\beta = 5374.66^{*,b}$	$\beta = 16.44^{*,c}$	$\beta = 5038.79^{**,b}$	ns
Time \times Intervention Group	ns	ns	ns	ns
Time \times Site	ns	ns	ns	ns
Group \times Site	ns	ns	ns	ns
Time \times Group \times Site	ns	ns	ns	ns

Abbreviation: ns, not significant ($P > .05$).

^aDigit Symbol Test scores higher after 5-week intervention.

^bSwedish Cohort had lower brain-derived neurotrophic factor (BDNF) levels.

^cBoston Cohort had higher Digit Symbol Test scores.

* $P < .05$.

** $P = .05$.

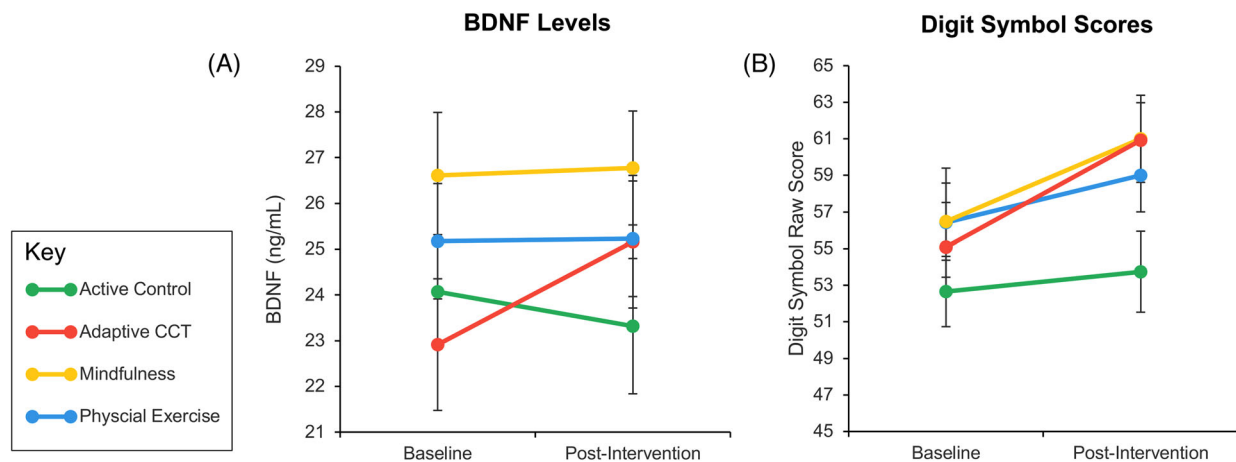


FIGURE 2 (A) Mean brain-derived neurotrophic factor (BDNF) measurements at baseline and post-intervention. (B) Mean Digit Symbol Test scores at baseline and post-intervention. Error bars represent standard errors.

3.3 | Effect of time and intervention

Figure 2 presents each group's baseline and post-intervention data for BDNF levels (Figure 2A) and DST performance (Figure 2B).

3.3.1 | Adaptive CCT versus control

For BDNF levels, LMMs demonstrated no main effects of time, intervention group, or site. It is important to note that there was a time-by-intervention group interaction ($\beta = -2987.96$, $P = .01$). Similarly, for DST scores, there were no main effects of time, intervention group, or site but a time-by-intervention group interaction ($\beta = -4.59$, $P = .04$) (see Figure 2) After 5 weeks of CCT, only the adaptive group exhibited increased BDNF levels [$t(36) = 2.58$, $P = .01$] and improved DST scores [$t(36) = 4.30$, $P < .01$], whereas the active control group demonstrated no reliable changes in BDNF levels [$t(37) = .97$, $P = .34$] or DST scores [$t(37) = .64$, $P = .53$]. There were no time-by-site,

group-by-site, or time-by-group-by-site interactions for either BDNF or DST.

3.3.2 | Physical exercise versus control; mindfulness meditation versus control

Table 2 summarizes the statistical results for comparing these conditions. Of greatest interest, there were no time-by-intervention interactions for BDNF level or DST score when comparing the physical exercise group to the control group, or the mindfulness meditation group to the control group.

3.4 | Path analysis

Compared to the active control group, only the adaptive CCT intervention group exhibited significant increases in BDNF and improvement in

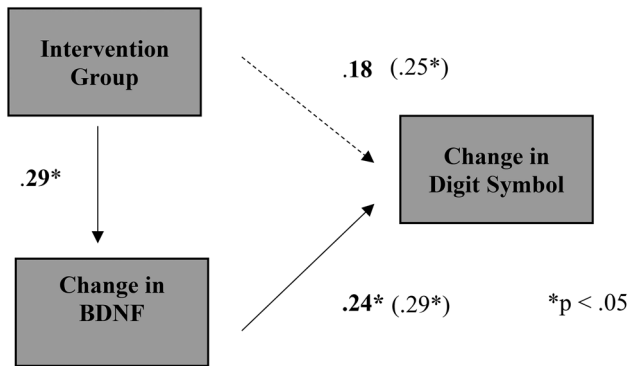


FIGURE 3 Path analysis examining the relationship between intervention group, changes in BDNF levels, and changes in Digit Symbol Test scores. Path coefficients are bolded, and zero-order correlations are presented in parentheses. BDNF, serum brain derived neurotrophic factor; Digit Symbol Test, raw score performance on Digit Symbol Test; change, post- minus pre-intervention values.

DST performance. To further characterize this relationship, the change in BDNF levels was examined as a mediator of the relationship between group (adaptive CCT vs control) and change in performance on the DST (see Figure 3). Path analysis revealed a correlation between group and change in BDNF (path coefficient = $.29$, $P = .01$). There was a correlation between change in BDNF and change in DST performance that survived controlling for the impact of group (path coefficient = $.24$, $P = .04$). In contrast, after controlling for change in BDNF, there was no association between group and change in DST (path coefficient = $.18$, $P = .13$), suggesting that a change in BDNF mediates this relationship. The results of the path analysis were confirmed using a mediation model (see Supplement 1).

3.5 | Relationships between BDNF levels and DST scores

Regression analysis indicated that, collapsing across the sample as a whole, there was a weak association between BDNF levels and DST scores at baseline (pre-intervention). Those participants with higher BDNF levels performed better on the DST ($R^2 = .03$, $P = .03$). However, when each group was examined separately, there was no association between pre-intervention BDNF levels and DST scores (adaptive CCT, $P = .10$; mindfulness, $P = .16$; physical exercise, $P = .17$; active control, $P = .46$).

Of note, collapsing across the sample as a whole, the magnitude of change (post- minus pre-intervention) in BDNF was associated with the magnitude of change in DST score, that is, participants with larger increases in BDNF exhibited greater improvement in DST performance ($R^2 = .10$, $P < .01$). The same relationship was also observed collapsing across all three intervention groups ($R^2 = .14$, $P < .01$) and within each intervention group separately (adaptive CCT: $R^2 = .16$, $P = .01$; mindfulness: $R^2 = .15$, $P = .02$; physical exercise: $R^2 = .09$, $P = .12$), but not the active control group ($R^2 = .01$, $P = .50$) (see Figure 4).

4 | DISCUSSION

This study investigated the relationship between intervention-associated changes in BDNF and improvement in cognitive performance in healthy older adults who were randomly assigned to adaptive CCT, physical exercise, mindfulness meditation, or an active control group. Relative to the control condition, adaptive CCT was the only intervention associated with an increase in BDNF levels. It was also the only intervention linked to improved performance on an untrained task (DST) that emphasizes WM and processing speed. In contrast, neither the physical exercise nor the mindfulness intervention was associated with an increase in BDNF, and neither intervention led to an improvement in performance on the DST compared to the control condition. Taken together, these findings provide support for the idea that changes in BDNF may play an important role in improving performance on a task dependent on WM and processing speed.

Evidence more directly linking BDNF to changes in cognition was derived from our path analysis, showing that the improvement of cognitive performance in the adaptive CCT group (relative to controls) is mediated by intervention-related increases in BDNF, which appears to be the first time this relationship has been demonstrated in healthy adults. Note that although controlling for the impact of intervention group slightly reduced the variance of the change in DST performance explained by the change in BDNF, the relationship between these two variables remained significant. This result suggests that the association between the change in BDNF and change in DST score is not driven solely by the adaptive CCT group.

The connection between BDNF and cognitive functioning was further substantiated by regression analysis, which demonstrated that the greater the increase in BDNF level, the larger the improvement in DST performance. This relationship was found when analyzing the sample as a whole, or when limiting the analysis to only the participants of the three intervention groups, or within each experimental group separately (not only the adaptive CCT group but also the mindfulness and, to a lesser extent, the physical exercise group).

In contrast to research on animals, almost no human studies have directly linked changes in BDNF associated with cognitively stimulating activities to changes in cognitive performance. In fact, there has been a surprisingly limited number of investigations on the subject.^{27–29,34} Vinogradov et al. found that patients with schizophrenia who performed cognitive exercises exhibited an increase in BDNF after a 10-week cognitive exercise intervention.²⁷ Although, there were reliable changes in both BDNF and a score of global cognition, there was no significant relationship between the two variables. Similar results were found by Angelucci et al. in their investigation of patients with Parkinson disease.²⁸ After a cognitive training intervention, participants exhibited increased levels of BDNF and improvement on measures of cognition. However, the relationship between these two factors remained unclear.

In addition, Pressler et al. observed elevated BDNF levels and better cognitive performance after CCT in patients with heart failure²⁹ but did not report a direct link between changes in these variables. Conversely, Darmichi et al. showed that 8 weeks of cognitive training

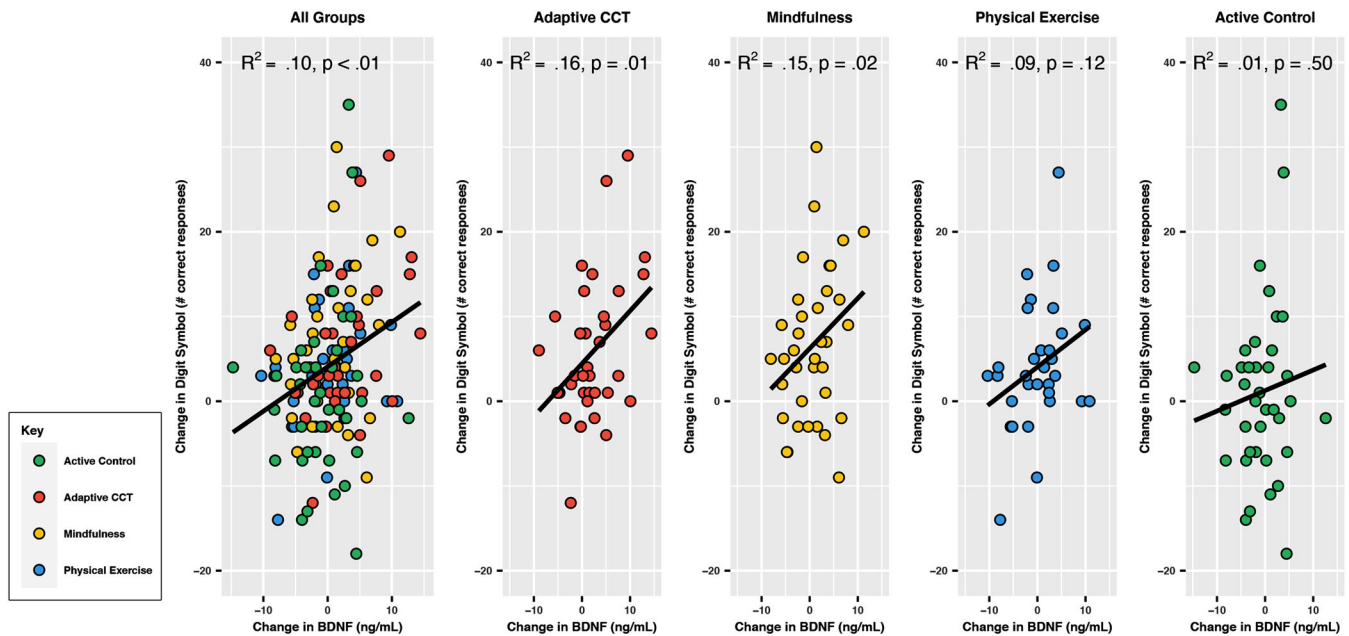


FIGURE 4 Scatterplots depicting change in Digit Symbol Test scores versus change in brain-derived neurotrophic factor (BDNF) levels for each group (Adaptive computerized cognitive training [CCT], Mindfulness, Physical Exercise, Active Control). The first scatterplot collapses across all groups. Each line is representative of results of linear regression.

elevated BDNF levels in 11 older, cognitively impaired women, which correlated with a change in processing speed.³⁴ None of these studies used path or mediation analysis to examine the potential role of BDNF in cognitive change.

Our investigation expanded the very limited research in this area and provided confirmatory evidence that elevations in BDNF linked to 5 weeks of structured cognitively stimulating activity mediate performance improvement on an untrained cognitive task of WM and processing speed. It remains to be determined why our investigation succeeded whereas most prior research did not. Potential contributions include the characteristics and size of our sample, the specific type and intensity of our cognitive intervention, and the primary outcome measures used. Most prior investigations have studied participants with neuropsychiatric conditions (e.g., Parkinson disease and schizophrenia). In contrast, our sample comprised neurologically and physically healthy older adults. Participants came from both urban (Boston) and rural (Växjö) communities, and they tended to be highly intelligent and well educated, which are factors that may have influenced the study's outcomes.⁴⁵ In addition, the 75 participants in the adaptive CCT and active control conditions of the study is a sample substantially larger number than that found in previous work, providing us with greater statistical power to achieve significant results. Our success in linking BDNF changes to training-related improvements in WM and processing speed may be evidence that BDNF is most effective in modulating this particular set of cognitive processes. If so, the previous use of more global cognitive outcome measures in other cognitive intervention studies may have obscured the role of BDNF in influencing cognitive change.

Compared to the control group, the physical exercise intervention group did not exhibit reliable changes in BDNF or improvements in cog-

nitive performance, results that are not consistent with several other investigations that have addressed this topic. For example, in earlier work we have demonstrated that exercise could increase BDNF levels acutely in health older adults after just 30 minutes of moderate physical activity,¹⁷ which is concordant with the outcome of two recent meta-analyses of 52 unique studies.^{22,23} Despite variable outcomes in this research,²⁴ many investigations have shown that acute aerobic exercise^{46,47} and aerobic exercise training programs increase serum BDNF levels.³² Physical exercise has also been shown to increase hippocampal volume,¹⁸ improve memory and executive function^{19,20} and reduce the risk of cognitive impairment.²¹ Although, the mechanisms by which exercise led to these benefits remain unclear, many researchers have hypothesized that BDNF plays an important role.

Reports of investigations have also described direct links between physical activity, change in BDNF, and improvements in cognitive performance. In an interesting, recent study by Nilsson et al.,⁴⁹ healthy older adults completed a 12-week behavioral intervention that involved either physical exercise immediately before cognitive training, physical exercise immediately after cognitive training, physical exercise only, or cognitive training only. They found that greater increases of exercise-induced plasma BDNF were associated with greater cognitive training gains on trained task paradigms, but only when such increases due to exercise preceded cognitive training.

Our inability to demonstrate BDNF or cognitive changes in the physical exercise intervention group may, in part, be due to an important limitation of the study: interventions were structured to follow the recommendations for carrying out the Cogmed[®] CCT program, which involves ≈ 200 minutes per week over 5 weeks (≈ 17 hours total). This duration of activity may have been insufficient to observe changes in BDNF and cognition in the physical exercise and perhaps the

mindfulness interventions relative to an active control condition. For example, a recent systematic review suggested that interventions require at least 52 hours of physical exercise to be associated with cognitive improvement in older adults.⁵⁰ Similarly, many of the mindfulness intervention studies that have reported beneficial effects on cognition were longer than 5 weeks.^{25,30} Interventions may differ in the average time course needed to result in measurable increases in BDNF on a group level. It remains an open question whether longer interventions would have resulted in significant differences between physical exercise or mindfulness interventions and an active control condition. Consistent with our study's finding that, collapsing across interventions, increases in BDNF levels are associated with improvement in performance on the DST, we would hypothesize that programs that successfully augment BDNF levels will also enhance performance on tasks that are dependent on WM and processing speed.

Our study had several other limitations. For example, we purposefully constrained our cognitive outcome variable to performance on the DST. The decision to focus on an untrained task dependent on WM and processing speed was derived from the results of prior work with adaptive CCT³⁶ and was consistent with reports in the literature on the types of cognitive benefit observed with physical exercise and mindfulness interventions.^{19,25} Future studies should include additional cognitive outcome measures to investigate if BDNF plays a modulatory role in other cognitive domains. One issue will be controlling for multiple comparisons, which may make reaching statistical significance more challenging.

In the current study, adaptive CCT augmented BDNF and cognition. Questions remain about the extent to which the specific parameters used in our adaptive CCT intervention led to these results. It is noteworthy that we utilized one kind of cognitively stimulating activity over a specific timeframe. It remains unknown the extent to which the type (e.g., WM training), frequency (e.g., 5 times week), and duration (e.g., ≈40 minutes per session over 5 weeks) of cognitively stimulating activities played a key role in facilitating changes in BDNF and cognitive performance. It will be important to replicate the findings of this study with a different sample of subjects, followed by systematically varying the study's parameters to determine the most critical variables.

Finally, our study lacked follow-up information on our participants. We did not test whether the effect of BDNF levels on WM persisted over time. In addition, because of the relatively short intervention period (5 weeks), we did not try to measure changes in activities of daily living (ADLs). Future research should include longer periods of cognitive stimulation to determine their impact on levels of BDNF and ADLs.

In conclusion, this study demonstrated that 5 weeks of cognitively stimulating activity (through adaptive WM training) can increase serum BDNF levels and cognitive performance in a healthy, geographically diverse, group of older individuals. It is important to note that improvement in cognition after training was mediated by increases in serum BDNF. These results provide evidence that older adults retain the capacity for brain plasticity, which can be elicited by participating in cognitively stimulating activities. The study also revealed that, across the sample as a whole, the greater the increase in BDNF level, the larger the improvement in an untrained task dependent on WM and pro-

cessing speed, suggesting the potentially important role that changes in BDNF may play in cognitive outcomes. Many important questions remain to be answered. Given the increasing numbers of older individuals in our population and growing concerns about the risk of cognitive decline and dementia, the relationships between structured behavioral interventions, alterations in BDNF, and changes in cognition are worthy of additional investigation.

ACKNOWLEDGMENTS

This study was funded by the Kamprad Family Foundation, Växjö, Sweden. In addition, the Laboratory of Healthy Cognitive Aging at Brigham and Women's Hospital has received funding from the Wimberly Family Clinical Care Research Fund, the Gaudet Family Research Fund, and the Alzheimer's Innovation Fund, and has been strongly supported by the Muss family, the Mortimer/Grubman family, and the Herman F. Woerner Trust.

CONFLICTS OF INTEREST

The authors of this manuscript have no activities or interests to disclose related to the content of this submission. Author disclosures are available in the supporting information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Nicastrì CM, McFeeley BM, Simon SS, et al. BDNF mediates improvement in cognitive performance after computerized cognitive training in healthy older adults. *Alzheimer's Dement*. 2022;8:e12337. <https://doi.org/10.1002/trc2.12337>