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Featured Article

The effects of 7-week cognitive training in patients with vascular cognitive impairment, no dementia (the Cog-VACCINE study): A randomized controlled trial

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Abstract

Introduction: Evidence for the efficacy of cognitive training in patients with subcortical vascular cognitive impairment no dementia is still lacking.

Methods: A randomized, active controlled design using multidomain, adaptive, computerized cognitive training for 30 minutes, 5 days/week for 7 weeks. Assessments included global cognitive function and executive function (primary outcomes) and brain functional connectivity and structural changes (secondary outcomes).

Results: Sixty patients were randomized across three medical centers in Beijing. At the end of the intervention, the cognitive training group showed significant improvement in Montreal Cognitive Assessment relative to the active control group ($P = .013$) and significantly increased functional connectivity between the left dorsolateral prefrontal cortex and medial prefrontal cortex, which was significantly correlated with Montreal Cognitive Assessment change ($P = .017$).

Discussion: Computerized cognitive training significantly improved global cognitive function, which was supported by the improved brain plasticity. Incorporation of biomarkers should be implemented in cognitive training trials.

Keywords: Vascular cognitive impairment no dementia; Computerized cognitive training; Randomized controlled trial; Brain plasticity

Zude Zhu provides consulting to Wispirits Inc. about scientific program.

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1. Introduction

Vascular cognitive impairment (VCI) is one of the most common causes of acquired cognitive impairment, second only to Alzheimer's disease (AD) [1]. Vascular cognitive impairment no dementia (VCIND) refers to cognitive deficits associated with underlying vascular causes that are insufficient to confirm a diagnosis of dementia. According to the China Cognition and Aging Study, VCIND accounts for 42.0% of cases of mild cognitive impairment (MCI) in China, rendering it the most common subtype of MCI therein [2]. A 5-year follow-up of patients with VCIND revealed that 50.0% of the patients developed dementia, including AD [3].

Although VCIND is potentially a key stage at which early intervention may delay or prevent dementia, an approved method of intervention has yet to be developed. Recent advances in cognitive training, however, may inform strategies to treat VCIND. In a healthy elderly population, the Advanced Cognitive Training for Independent and Vital Elderly trial led to improvement in targeted domains and daily function, which was maintained across long-term follow-up [4]. In addition, computerized cognitive training has demonstrated potential as an effective intervention for patients with MCI or early AD [5]. Despite the promise of such findings, far fewer resources have been allocated to nonpharmacological approaches to treating dementia, including cognitive training, than to the development of pharmacological disease-modifying therapies [6]. Evidence for the efficacy of cognitive training in patients with VCIND is consequently lacking. Considering the significant heterogeneity of VCIND, research must address the dearth of data on the efficacy of intervention trials with respect to VCIND subtypes.

The present study focused on the most common subtype of the disorder, VCIND caused by subcortical ischemic small vessel disease (subcortical VCIND), as its relatively homogenous features render it a suitable target condition for intervention trials. We conducted a randomized, active controlled trial to determine the efficacy of a 7-week multidomain, adaptive, computerized cognitive training regimen in patients with subcortical VCIND (the Cog-VACCINE study). As executive dysfunction is the primary impairment associated with subcortical VCIND [7], we used the Trail Making Test (TMT) in tandem with assessing global cognitive function via the Montreal Cognitive Assessment (MoCA) as an additional primary outcome to confirm whether cognitive training could attenuate executive dysfunction in patients with subcortical VCIND. Observed alleviation of cognitive dysfunction would likely be accounted for by changes to brain plasticity [8], including increased gray matter volume, improved white matter integrity, and changes in neuronal functional connectivity. To assess these secondary outcomes and elucidate the mechanism underlying a possible effect of cognitive training, we performed structural magnetic resonance imaging (sMRI) and functional magnetic resonance imaging (fMRI).

2. Methods

2.1. Study design and registrations

The present randomized, active controlled clinical trial was conducted in accordance with both the CONSORT statement and the CONSORT statement for nonpharmacological interventions. Participants with subcortical VCIND were recruited from three centers: Xuanwu Hospital; Beijing Friendship Hospital; and Fu Xing Hospital, Capital Medical University. All participants provided written informed consent. Ethical approval was obtained from the Ethics Committee of Xuanwu Hospital, Capital Medical University (2015010). The trial was registered under ClinicalTrials.gov (NCT02640716) and its protocol has been published previously [9].

2.2. Participants

The diagnosis of VCIND was based on evidence of both cognitive impairment without dementia and small vessel ischemic disease. All patients were diagnosed by a consensus panel including three senior neurologists and met the following inclusion criteria: (1) literate in Han Chinese with a consistent caregiver (>4 days/week); (2) complaint and/or informant report of cognitive impairment involving memory and/or other cognitive domains with a duration of at least 3 months; (3) according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, the patients were neither normal nor demented as indicated by a clinical dementia rating of $\geq$0.5 on at least one domain, a global score of $\leq$0.5, and a Mini–Mental State Examination score of $\geq$20 (primary school) or $\geq$24 (junior school or above); and (4) normal or slightly impaired daily living activities as defined by a total score of $\leq$1.5 for the three functional clinical dementia rating domains (home and hobbies, community affairs, and personal care). We excluded participants who exhibited any condition that would preclude completion of neuropsychological testing or disorders other than subcortical VCIND that would affect cognition.

The MRI-based inclusion criteria details were as follows: (1) multiple ($\geq$3) supratentorial subcortical small infarcts (3–20 mm in diameter) with/without white matter lesions of any degree or moderate-to-severe white matter lesions (score of $\geq$2 according to the Fazekas rating scale [10]) with/without small infarct; (2) absence of cortical or watershed infarcts, hemorrhages, hydrocephalus, or white matter lesions with specific causes (e.g., multiple sclerosis); and (3) no hippocampal or entorhinal cortex atrophy (score of zero according to the medial temporal lobe atrophy scale of Scheltens [11]).

Exclusion criteria included the following: (1) severe aphasia or other factors that might preclude completion of

neuropsychological assessments or MRI; (2) clinically significant gastrointestinal, renal, hepatic, respiratory, or other systemic diseases; and (3) other disorders or use of medication that might affect cognitive functions.

2.3. Blinding

The participants were randomly assigned to training or active control group. The personnel involved in conducting the study and data analysis were masked to the patient randomization. Study participants, their caregiver, and all assessors were blinded to treatment assignment throughout the study.

2.4. Procedures

Patients in the intervention group received a computerized, multidomain, adaptive training program for 7 weeks. The training domains included processing speed, attention, perception, long-term memory, working memory, calculation, executive control, reasoning, and problem solving. The rigor with which each domain was trained differed according to each task and informed the grouping of the tasks. Participants were required to complete 30 min of training per day (five 2-min tasks completed thrice), 5 days a week. Within each task, high accuracy (>80%) was required to upgrade to the next difficulty level.

The active control group received five processing speed and attention tasks, whose duration totaled to 30 min each training day. However, these tasks were set to a fixed, primary difficulty level across the study.

The training of all participants was completed at home and supervised by an independent neurologist over the Internet (www.66nao.com) to guarantee the fulfillment of the training.

The intervention began directly after randomization. All the outcomes were assessed at the baseline, end of intervention, and 6 months after randomization to measure long-term resilience of the effect. For the details of the interventions, see Methods in Supplementary Materials.

2.5. Outcomes

The primary outcome measures were global cognitive function, measured by MoCA, and executive function, measured by TMT B-A; both were centrally assessed.

Based on previous studies, we hypothesized that cognitive training could enhance functional and structural connectivity and/or local morphometry. The secondary outcomes of the present study therefore included structural and functional indices: the gray-matter volume of the hippocampus, a key brain structure linked with memory impairment [12]; and white-matter (WM) integrity, which is associated with cognitive decline [13]. Functional connectivity was assessed in the default mode network (DMN) and the executive control network (ECN), two neurocognitive networks critical to the cognitive functions. Prior research has shown that the DMN and ECN are associated with pathological disconnection in cognitive decline and the progression of dementia [14], and cognitive training was found to modulate them [15].

In addition to the primary outcomes, we conducted other neuropsychological evaluations: the Digit Span, the WHO-UCLA Auditory Verbal Learning Test [16], the Boston Naming Test (BNT), the Hachinski Ischemic Scale, the Geriatric Depression Scale, the Neuropsychiatric Inventory, and an assessment of activities of daily living.

2.6. MRI data

2.6.1. MRI data collection

The MRI data were acquired via a 3.0 T Siemens scanner. High-resolution T1-weighted images of the whole brain were obtained using a sagittal 3D magnetization-prepared rapid gradient echo sequence. Resting-state fMRI was conducted using a multiband echo-planar imaging sequence. DTI images were acquired by using a diffusion-weighted double spin-echo-planar imaging sequence. See Supplementary Materials for sequence details.

2.6.2. Volumetric analysis of the hippocampus

Volumetric analysis was performed using FSL-integrated registration and segmentation toolbox (FIRST; https://fsl.fmrib.ox.ac.uk). Followed the FIRST processing guideline, the volume of the bilateral hippocampus was extracted and compared across groups via the linear mixed effect model (see Supplementary Materials for details).

2.6.3. White matter microstructure

DTI data preprocessing was implemented using PANDA software (a pipeline tool for analyzing brain diffusion images; http://www.nitrc.org/projects/panda/) [17]. Following the processing guideline, the fractional anisotropy was estimated and calculated. Fractional anisotropy of WM tracts associated with cognitive decline in VCI [13,18] was then extracted for analysis (see Supplementary Fig. 1 for details).

2.6.4. Functional connectivity

Resting-state fMRI data were preprocessed by using the DPARSF (a toolbox for Data Processing and Analysis of Brain Imaging; http://www.rfmri.org) following the guideline (see Supplementary Materials for details) [19]. A seed-based approach was performed first for baseline data to identify the DMN (seed in the posterior cingulate cortex, PCC) and ECN (seed in the left dorsolateral prefrontal cortex, DLPFC.L). Based on the identified network, the mean time courses were extracted from bilateral DLPFC, inferior parietal lobule in the ECN, medial prefrontal cortex, and PCC in the DMN (blue in Supplementary Fig. 2), and the functional connectivity (Pearson's correlation coefficients) was calculated between each pair of regions for the baseline, end of intervention, and 6-month follow-up data. The

Fisher's Z transformation correlation coefficients were then extracted for each pair in each time point and used as inputs for the corresponding linear mixed effect models.

2.7. Statistical analyses

All data were analyzed according to intent-to-treat principles. The effects of cognitive training on neuropsychological scores and MRI data were examined using linear mixed effect models nested within individuals. Time was assigned as the repeated variable. Group, time, and group-by-time were included as fixed effects. We analyzed the changes in the neuropsychological scores and MRI data from the baseline to the end of intervention and from baseline to 6-month follow-up. A statistically significant difference (two tailed, $P < .05$) for any of the two primary outcomes at the end of the intervention would be considered as preliminary evidence of efficacy. Correlation analyses between significant brain functional changes and neuropsychological scores were then performed to explore a potential neural mechanism for cognitive functional changes.

3. Results

3.1. Participants' characteristics

Participants were enrolled from December 22, 2015 through November 7, 2016. The last follow-up measurements were obtained in May 8, 2017. The flow of participants through the study is shown in Fig. 1. A total of 212 individuals from the neurology and geriatric clinics were included and assessed for eligibility. Of these, 152 were excluded and the present study therefore enrolled a total of 60 patients. They were randomly assigned to the cognitive training or active control groups. A total of 54 participants (27 in each group) finished the trial with good compliance. A total of 44 participants (23 in the training group and 21 in the active control group) completed the 6-month follow-up. Of the 16 participants (26.7%) who withdrew from the study, five reported health issues, four reported time constraints, five were dissatisfied, and two reported personal issues. Baseline characteristics and neuropsychological assessment data are shown in Table 1. We found no group differences in age, sex, or duration of education. Except for immediate recall, the neuropsychological testing scores were matched between the two groups. All participants completed more than 90% of the training requirement. There was no significant group difference in both training days ($P = .167$) and training time per day ($P = .134$) (Table 1).

3.2. Primary outcome measures

The changes from the baseline to the end of the 7-week intervention and from the baseline to the end of the 6-month follow-up for the primary outcomes are shown in Fig. 2 and Table 2. There was a significant group × time interaction in MoCA at the end of the intervention period. After 7 weeks, MoCA had significantly improved in the cognitive training group (from 21.87 to 25.22) relative to

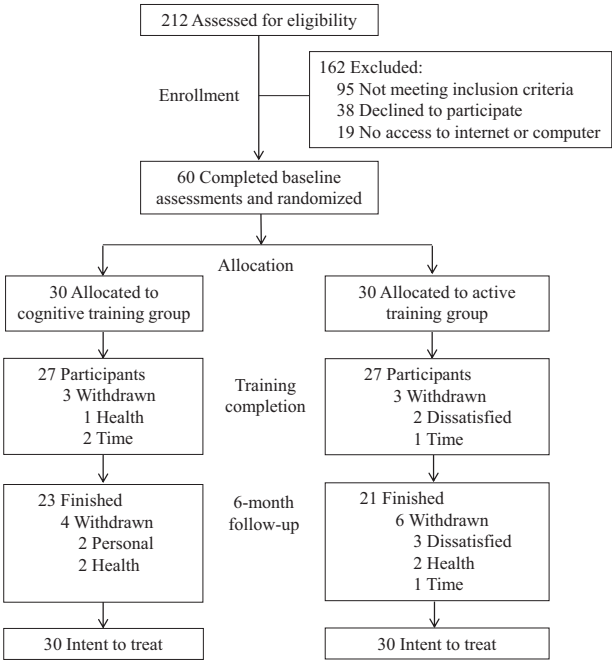

Fig. 1. The flowchart for the Cog-VACCINE study.

Table 1
Baseline characteristics and training adherence of the two groups

Variables	Training group (n = 30)	Active control group (n = 30)
Age, y	63.9 (7.9)	64.9 (6.6)
Female	12 (40.0%)	8 (26.7%)
Education, y	10.8 (3.5)	10.0 (2.8)
MoCA	21.9 (3.8)	21.2 (3.8)
ADL	21.7 (3.1)	21.5 (2.8)
Digit span forward	7.4 (1.6)	7.2 (1.1)
Digit span backward	4.3 (1.5)	4.2 (1.1)
BNT	22.2 (3.7)	23.4 (3.6)
WHO-UCLA AVLT		
Immediate recall	22.9 (5.8)	19.2 (6.7)
Delayed recall	7.3 (2.7)	6.3 (3.3)
Recognition	10.9 (2.7)	9.9 (2.9)
TMT B-A	74.0 (56.6)	77.0 (65.3)
Hachinski Ischemic Scale	3.5 (3.0)	2.3 (2.7)
NPI*	3.9 (3.9)	2.7 (4.4)
GDS	8.9 (6.7)	7.4 (5.7)
Training days (days)	34.0 (1.0)	33.6 (1.1)
Training time/day (minutes)	29.2 (1.9)	28.3 (2.1)

Abbreviations: MoCA, Montreal Cognitive Assessment; ADL, activities of daily living; BNT, Boston Naming Test; WHO-UCLA AVLT, WHO-UCLA Auditory Verbal Learning Test; TMT B-A, Trail Making Test B-A; NPI, Neuropsychiatric Inventory; GSD, Geriatric Depression Scale.

*Though the data are not normally distributed, the means and standard deviations of scores are represented the same as in previous research. Mann-Whitney tests were used to compare group differences in the total NPI score.

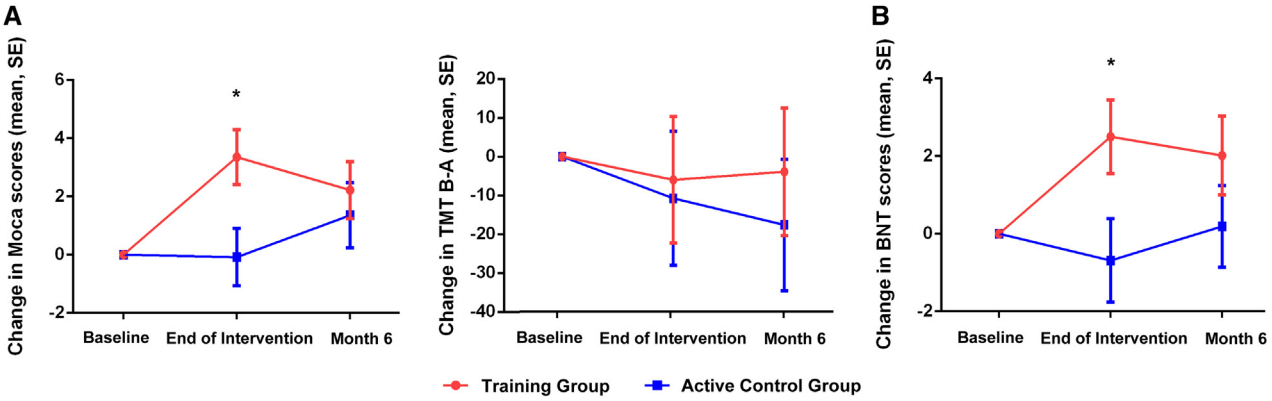

Fig. 2. Training effect on cognitive function. (A) Training effect on primary outcomes (MoCA and TMT B-A), showing significant increase in MoCA at the end of intervention relative to the baseline in the cognitive training group. (B) Training effect on the BNT, showing a significant increase by the end of intervention relative to the baseline in the training group. *Marks the significant group × time effect. Red lines represent the training group, and the blue lines represent the active control group. Abbreviations: MoCA, Montreal Cognitive Assessment; TMT B-A, Trail Making Test B-A; BNT, Boston Naming Test.

the active control group (21.23 to 21.15), with an effect size of 0.637 (95% CI 0.115–1.153) compared with the control group. This difference did not persist at the 6-month follow-up. We found no significant group × time interaction in the TMT B-A.

3.3. Secondary outcome measures

Secondary outcome measures included hippocampal GM volume, WM integrity, and functional connectivity. There was no significant group × time effect for hippocampus GM volume (Fig. 3 and Supplementary Table 1) or WM integrity (Supplementary Table 1).

Critically, at the end of the intervention, there was a significant group × time interaction for the connectivity between the DLPFC.L and medial prefrontal cortex (Fig. 4). Furthermore, we found a significant increase in connectivity from the baseline to the end of the intervention in the training group; this change was absent in the active control group. The enhanced connectivity across the intervention was positively correlated with MoCA changes ($r = 0.463$, $P = .017$) in the training group but not in the active control group ($r = 0.08$, $P = .68$). No significant group × time interaction for connectivity was found between the other pairs or at the 6-month follow-up (Supplementary Table 2).

For other neuropsychological tests, a significant group × time interaction was observed in the BNT (Fig. 2) at the end of the intervention (effect size = 0.560, 95% CI 0.042–1.074, $P = .028$); this finding had also dissipated by the 6-month follow-up. No significant group × time interaction was observed in the activities of daily living, Auditory Verbal Learning Test, Digit Span, Neuropsychiatric Inventory, or Geriatric Depression Scale.

3.4. Adverse events

No study-related adverse events were reported in either the cognitive training or active control groups.

4. Discussion

VCIND features potential as an effective point at which interventions may delay or even prevent dementia. The Cog-VACCINE study is the first registered randomized controlled trial to investigate the efficacy of computerized, multidomain, adaptive cognitive training in patients with subcortical VCIND. The strengths of the present study include its active control design and use of both neuropsychological evaluation and sMRI and fMRI as outcomes.

Concerning primary outcomes, we found that relative to the active control condition, cognitive training led to a significant improvement in global cognitive function, as measured by MoCA, but not in executive function, as measured by TMT B-A, by the end of the 7-week intervention. This result is consistent with findings from a recent meta-analysis of computerized cognitive training [5]: although computerized cognitive training affected small-to-moderate improvements in the global cognition of patients with mild cognitive impairment, the meta-analysis reported a lack of efficacy on executive function. This is further endorsed by another meta-analysis of 16 studies that showed a small but significant effect of cognitive training among MCI patients; however, 13 of them failed to find a significant effect of cognitive training on executive functions [20]. Small samples or inadequate training of executive processes may account for the nonsignificant results in previous studies. Although processing speed, inhibitory control, and reasoning were included in our multidomain training paradigm, the inclusion of more executive tasks may have yielded stronger gains in executive function. The limited ability of the elderly participants, particularly those with relatively more severe cognitive impairment, to transfer gains from trained to untrained cognitive domains provides an alternative explanation [21].

For secondary outcomes, we found a trend of hippocampal GM volume decline in the active control group,

Table 2
Estimated mean change and effect sizes in primary outcome variables and other neuropsychological assessments

	Change from the baseline to week 7 (end of intervention)						Change from the baseline to month 6 (end of follow-up)					
				Effect size						Effect size		
Variables	Training group (95% CI)	Active control group (95% CI)	*P* (group × time)	Mean difference	Cohen's d	95% CI	Training group (95% CI)	Active control group (95% CI)	*P* (group × time)	Mean difference	Cohen's d	95% CI
MoCA	3.356 (1.467–5.244)	−0.085 (−2.062 to 1.892)	**0.013**	3.441	0.637	0.115–1.153	2.224 (0.256–4.192)	1.358 (−0.899 to 3.614)	0.562	0.866	0.146	−0.361 to 0.653
TMT B-A	−5.958 (−38.558 to 26.642)	−10.702 (−45.259 to 23.856)	0.842	4.744	0.051	−0.456 to 0.556	−3.891 (−37.031 to 29.249)	−17.596 (−51.693 to 16.500)	0.564	13.705	0.146	−0.362 to 0.652
BNT	2.500 (0.595–4.405)	−0.687 (−2.845 to 1.472)	**0.028**	3.187	0.560	0.042–1.074	2.015 (−0.026 to 4.056)	−0.192 (−2.308 to 1.925)	0.135	2.207	0.380	−0.132 to 0.889
ADL	−1.333 (−2.580 to 0.086)	−0.570 (−1.850 to 0.709)	0.394	−0.763	−0.216	−0.723 to 0.292	−0.894 (−2.343 to 0.556)	−0.761 (−2.025 to 0.503)	0.890	−0.133	−0.035	−0.541 to 0.471
Digit span forward	0.078 (−0.745 to 0.900)	−0.096 (−0.762 to 0.571)	0.744	0.174	0.083	−0.423 to 0.589	−0.048 (−0.812 to 0.715)	0.020 (−0.601 to 0.642)	0.889	−0.068	−0.035	−0.541 to 0.471
Digit span backward	−0.189 (−0.842 to 0.464)	−0.135 (−0.733 to 0.462)	0.904	−0.054	−0.031	−0.537 to 0.475	0.064 (−0.723 to 0.850)	0.100 (−0.541 to 0.742)	0.942	−0.036	−0.018	−0.524 to 0.488
Immediate recall	3.433 (0.361–6.505)	1.386 (−2.591 to 5.363)	0.415	2.047	0.206	−0.302 to 0.713	0.918 (−2.604 to 4.441)	0.020 (−3.777 to 3.818)	0.728	0.898	0.088	−0.419 to 0.594
Delayed recall	1.996 (0.476–3.517)	0.428 (−1.502 to 2.357)	0.202	1.568	0.323	−0.188 to 0.831	1.518 (−0.184 to 3.220)	−0.639 (−2.602 to 1.323)	0.098	2.157	0.420	−0.093 to 0.930
Recognition	1.326 (−0.062 to 2.714)	0.032 (−1.624 to 1.687)	0.232	1.294	0.303	−0.207 to 0.811	0.703 (−0.782 to 2.188)	−0.386 (−2.133 to 1.362)	0.342	1.089	0.240	−0.269 to 0.747
NPI	−2.082 (−5.145 to 0.981)	−1.388 (−3.268 to 0.491)	0.699	−0.694	−0.098	−0.604 to 0.409	−4.467 (−9.446 to 0.512)	−1.170 (−3.894 to 1.554)	0.219	−3.297	−0.294	−0.802 to 0.216
GDS	−1.597 (−5.002 to 1.807)	0.179 (−2.882 to 3.239)	0.438	−1.776	−0.196	−0.703 to 0.312	0.042 (−3.868 to 3.953)	−0.687 (−3.888 to 2.515)	0.773	0.729	0.073	−0.434 to 0.579

Abbreviations: MoCA, Montreal Cognitive Assessment; TMT B-A, Trail Making Test B-A; BNT, Boston Naming Test; ADL, activities of daily living; WHO-UCLA AVLT, WHO-UCLA Auditory Verbal Learning Test; NPI, Neuropsychiatric Inventory; GSD, Geriatric Depression Scale. The bold values indicate $P < .05$.

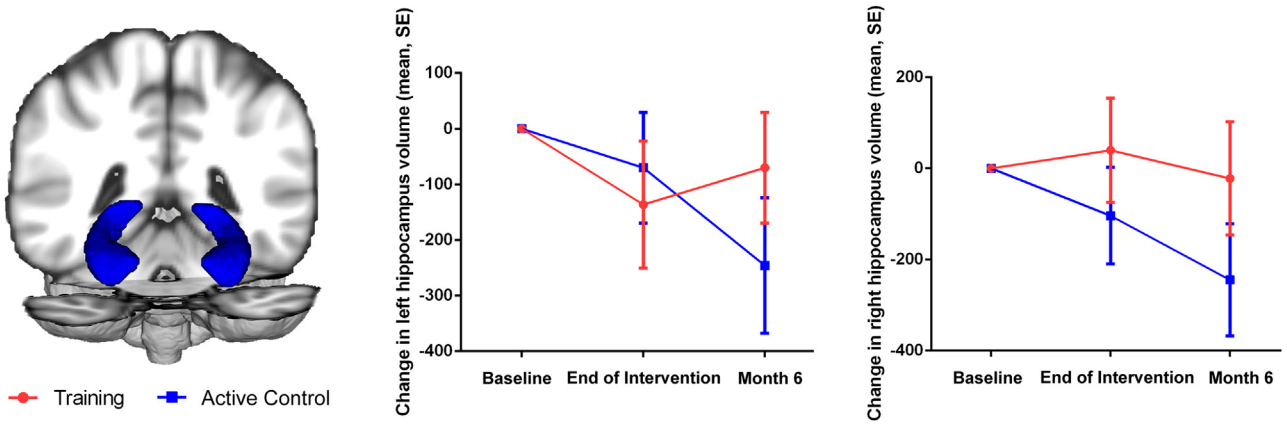

Fig. 3. Training effect on the hippocampus volume. The hippocampus was defined by FSL-integrated registration and segmentation toolbox (FIRST) following guidelines from FSL (https://fsl.fmrib.ox.ac.uk). No significant training effect on hippocampus volume was found in either hemisphere. Red lines represent the cognitive training group, and the blue lines represent the active control group.

yet no significant group × time interaction was found. Similarly, in line with a recent study showing that cognitive training in MCI induced no improvement in brain structure [22], no training effect on WM integrity was found [23]. The cognitive training group did, however, exhibit significant increases in functional connectivity between the DLPFC.L and medial prefrontal cortex by the end of intervention. Evidence from AD studies showed that the anticorrelation between the DMN and ECN found in healthy adults was diminished in MCI and AD patients [14]. In agreement with the results found in the healthy elderly [15] and AD patients [24], our results suggest that the disconnection can be rebuilt by cognitive training [25]. Moreover, the connectivity change was significantly correlated with MoCA change, that is, a stronger anticorrelation connectivity was linked with larger MoCA performance improvement in the training group but not in the active control group. This internetwork connectivity changes may suggest improvement in brain plasticity for cognitive improvement. The changes in both MoCA and functional connectivity disappeared at 6-month follow-up, possibly on account of the training duration having been too short to yield long-term effects on structural integrity markers detected via sMRI. Because these are the first data concerning VCIND collected by an explorative analysis, this finding requires replication in an independent sample.

The number of cognitive training studies has increased over the last few years [5]. Most of such studies have used neuropsychological assessments as outcomes to assess the direct clinical benefit of intervention. However, neuropsychological evaluation does not yield insights into concomitant underlying pathophysiological changes. Moreover, AD studies have shown that the incorporation of biomarkers, especially those reflecting the underlying pathophysiological mechanism of AD progression or targets of intervention, in clinical trials could help to reveal target

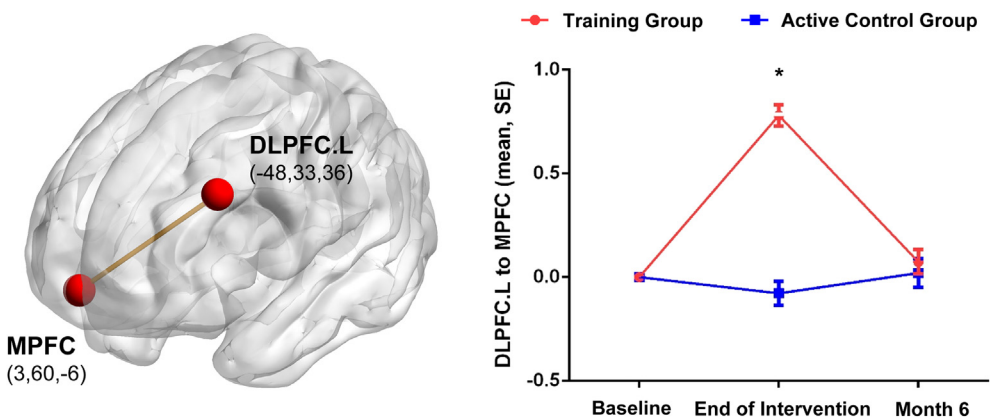

Fig. 4. Significant cognitive training effect on functional connectivity between DLPFC.L and MPFC. The anticorrelation was rebuilt in the training group by the end of the 7-week intervention. *Marks the significant group × time effect. Red lines represent the training group, and the blue lines represent the active control group. Abbreviations: DLPFC.L, left dorsolateral prefrontal cortex; MPFC, medial prefrontal cortex.

engagement and identify evidence of disease modification [26], such as CSF $A\beta_{1-42}$ and amyloid PET for antiamyloid therapeutic trials [27]. Similarly, the incorporation of biomarkers should also be encouraged in cognitive training clinical trials, as brain plastic changes are expected to underlie functional gains achieved by cognitive training [28]; the combined use of sMRI and fMRI is a potential proxy of changes in brain plasticity [29]. Recently, clinical trials on cognitive training effects in AD have begun to consider the use of fMRI findings as markers to elucidate the mechanisms underlying clinical efficacy [24]. We therefore included sMRI and fMRI indices previously found to be associated with cognitive decline in dementia conversion as secondary outcomes in the present study. We found that cognitive training increased functional connectivity between the DMN and ECN, which was significantly correlated with improvement in global cognitive function. Our study therefore suggests that fMRI indices could provide suitable biomarkers for cognitive training studies not only in AD [30] but also in VCIND.

In addition to MoCA and TMT B-A, we analyzed the effect of intervention on other cognitive domains. Our results showed that cognitive training significantly improved language function as measured by BNT. While one meta-analysis reported that cognitive training had a beneficial effect on language function [20], another meta-analysis reported null findings on language function in patients with MCI [5]. Although these two meta-analyses had different results for test statistics, they had similar effect sizes for language function (Hedges' $g = 0.511$ and 0.41, respectively). The inconsistent results are probably due to the high heterogeneity ($I^2 = 80.69\%$ for the null finding). However, in patients with cognitive impairment after stroke, computerized training improved global function as well as the BNT scores [31], which supported the present finding.

Although cognitive training affected a significant improvement on MoCA, BNT, and internetwork connectivity after the 7-week intervention, the improvement disappeared by the 6-month follow-up. Regarding the resilience of cognitive training gains, the literature is inconsistent. One previous investigation found that although cognitive training prevented memory decline of MCI patients during a 6-month intervention period, this effect had dissipated by the 18-month follow-up [32]. By contrast, the Advanced Cognitive Training for Independent and Vital Elderly trial showed that, in cognitively normal older adults, 10–14 weeks of cognitive training with booster training induced significant improvements in the trained domains that persisted up to 5–10 years [4]. Considered in the context of our findings, the maintenance of a training effect is less likely among those with some degree of cognitive impairment. For subcortical VCIND patients to sustain cognitive improvements, continuous training is recommended.

The present study is subject to several limitations. First, the significant attenuation of the improvements by the 6-month follow-up suggests that a longer intervention period is needed to observe potentially sustainable benefits of cognitive training. Second, although this study used well-defined inclusion and exclusion criteria for subcortical VCIND, we cannot rule out the possibility of mixed pathology, such as concomitant AD. By excluding individuals with indications of atrophy of the hippocampus or entorhinal cortex, we likely excluded individuals with advanced AD pathology; however, prodromal stages with increased amyloid load could not be excluded. Future studies using AD biomarkers are needed to rigorously evaluate the efficacy of cognitive training in patients with subcortical VCIND and to test whether different pathologies respond differentially to cognitive training. Third, as the first registered randomized controlled trial study to investigate the efficacy of computerized cognitive training in subcortical VCIND, except for the mostly used primary outcome-global cognitive function, we also explored the training effect on the characteristic executive dysfunction in subcortical VCIND. Therefore, both MoCA and TMT B-A were set as primary outcomes. In the interest of an unambiguous outcome of the study, it would have been preferable to declare a priori that observing a statistically significant difference in any of the two primary outcomes would provide preliminary evidence of efficacy.

5. Conclusion

In conclusion, the computerized, multidomain, adaptive cognitive training improved global cognitive function and the connection between two cognition-related networks, the DMN and ECN, in patients with subcortical VCIND. The significant correlation between the restored connection and improved global cognitive function suggested that biomarkers of functional connectivity as proxy for effects of brain plasticity should be incorporated as outcomes in cognitive training trials. Although the efficacy and good safety profile of cognitive training in patients with subcortical VCIND recommend its adoption, more clinical trials are needed for further evidence.

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Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jalz.2019.01.009.

RESEARCH IN CONTEXT

1. Systematic review: We searched ClinicalTrials.gov and WHO's International Clinical Trial Registry Platform up to August 31, 2018, to identify randomized controlled trials. Search terms were "vascular cognitive impairment no dementia OR mild vascular cognitive impairment OR mild vascular cognitive disorder" AND "cognitive training OR cognitive intervention." The present study was the only identified randomized controlled trial.
2. Interpretation: While the focus of dementia trials has shifted to presymptomatic and predementia stages, much less effort has been applied to patients with vascular cognitive impairment no dementia, which is a potential key stage to delay or prevent dementia. This approach is similar to a nonpharmacological intervention, a tractable and feasible way to improve the quality of life of patients with cognitive disorders. Except for the efficacy of computerized cognitive training in subcortical vascular cognitive impairment no dementia, the present study also provides evidence for the incorporation of brain plasticity biomarkers into cognitive training trials.
3. Future directions: Large, longer-term trials are needed for further evidence.

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