A 12-week physical and cognitive exercise program can improve cognitive function and neural efficiency in community-dwelling older adults: a randomized controlled trial

（１２週間の身体・認知面の複合運動プログラムにより、地域在住高齢者の認知機能と脳活動効率が改善する −無作為化比較対照試験による検討−）

西口　周

A 12-week physical and cognitive exercise program can improve cognitive function and neural efficiency in community-dwelling older adults: a randomized controlled trial

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Running head: 12-week intervention for cognitive improvement

STRUCTURED ABSTRACT

OBJECTIVES:

To investigate whether a 12-week physical and cognitive exercise program can improve cognitive function and brain activation efficiency in community-dwelling older adults.

DESIGN:

Randomized controlled trial.

SETTING:

Community in Kyoto, Japan.

PARTICIPANTS:

Community-dwelling older adults (N = 48) were randomized into an exercise group (n = 24) and a control group (n = 24).

INTERVENTION:

The exercise group participants received a weekly dual-task-based multimodal exercise class in combination with pedometer-based daily walking exercise during the 12-week intervention phase. The control group participants did not receive any intervention and were instructed to spend their time as usual during the intervention phase.

MEASUREMENTS:

The outcome measures were global cognitive function, memory function, executive function, and brain activation (measured using functional magnetic resonance imaging) associated with visual short-term memory.

RESULTS:

The exercise group participants showed significantly greater post-intervention improvements in memory and executive functions than the control group ($P < .05$). Additionally, after intervention, we found decreased activation in several brain regions associated with visual

short-term memory in the exercise group including the prefrontal cortex ($P < .001$, uncorrected).

CONCLUSION:

This study showed that a 12-week physical and cognitive exercise program can improve the efficiency of brain activation during cognitive tasks in older adults, which is associated with improvements in memory and executive function.

Keywords:

Cognitive improvement, Physical and cognitive exercise program, fMRI, Randomized controlled trial

61 **INTRODUCTION**

62 Dementia can drastically influence daily life and is currently one of the most common
63 syndromes in older adults. Dementia affects 5-8% of the population over 65 years of age [1]
64 and up to 30% of people aged 85 years and older [2]; its prevalence is also increasing.
65 Approximately 48% of people with Alzheimer's disease (AD) are estimated to live in Asia,
66 and this percentage is projected to grow to 59% by 2050 [3]. Dementia, including AD, is
67 associated with mortality [4]; therefore, approaches for preventing dementia onset are urgently
68 needed.

69 Several meta-analyses have reported that physical activity is associated with improvements
70 in cognitive performance in older adults [5-7]. Furthermore, cognitive activities effectively
71 reduce the risk of dementia [8]. A recent systematic review showed that combined cognitive
72 and exercise training, including dual-task (DT) exercises, which involve concurrent cognitive
73 and motor tasks, can improve cognitive function in older adults with and without cognitive
74 impairment [9]. This review indicated that these interventions were beneficial to various
75 components of cognitive function in older adults with healthy cognition [10], mild cognitive
76 impairments (MCI) [11], and AD [12].

77 In addition to the effect of multimodal exercise with physical and DT components on
78 cognitive performance, recent functional magnetic resonance imaging (fMRI) studies have
79 provided evidence that physical exercise intervention leads to changes in brain activation.
80 Some studies have reported decreased brain activation during memory-related [13] or conflict
81 tasks [14], which suggests that such reduced activation indicates improved neural efficiency
82 during cognitive tasks. However, few studies have tested whether neural activity, particularly
83 cortical activation, is affected by multimodal exercise. Therefore, the present study used a
84 randomized controlled trial combined with fMRI data of visual short-term memory task,
85 which require frontal lobe function [15], to investigate whether a 12-week multimodal exercise

program, including physical and DT components, can improve cognitive function and the efficiency of brain activation in community-dwelling older adults. We hypothesized that multimodal exercise would lead to decreased brain activation in the regions associated with visual short-term memory, especially the prefrontal cortex, due to the DT components of the exercise.

METHODS

Participants

Participants were recruited from the Kyoto City Silver Human Resources Center, Japan, using the following criteria: aged 60 years and older, independently community-dwelling, and willing to participate in group exercise classes for at least three months. An interview was used to exclude individuals according to the following criteria: a history of major psychiatric illness, serious neurological diagnoses, and severe cardiac, pulmonary, or musculoskeletal disorders, which were collected via self-retrospection. Participants with cognitive impairment (Mini-Mental State Examination (MMSE) score ≤ 23) [16] and participants who showed major abnormalities on brain MRI scans, such as cerebral infarction or tumor, were also excluded. The study was carried out in accordance with the guidelines of the Declaration of Helsinki, and the study protocol was reviewed and approved by the Ethics Committee of the Kyoto University Graduate School of Medicine. The trial registration number is JMA-IIA00108.

Study design and randomization

Randomization via computer-generated random numbers was performed in blocks of four participants, stratified according to MMSE. The participants were randomly assigned to the exercise intervention group (EG) or the control group (CG). Participants assigned to the EG received 90 minutes of group training sessions once per week for 12 weeks and were assigned a pedometer-based walking exercise during the 12-week intervention phase. The CG did not receive any intervention and were instructed to spend their time as usual during the intervention phase.

Required sample size

A previous study showed that two months of combined cognitive and exercise training can improve working memory in cognitively healthy older adults, with an approximate effect size of 0.9 [10]. Considering the participants' cognitive status and the intervention program used in this study, a sample size of 21 participants per group would be required to reach a power of 0.8, with an alpha set at 0.05 and beta at 0.2. Assuming a dropout rate of 15%, a final sample size of 24 per group was determined to be required.

Intervention program

The subjects assigned to the EG received 90 minutes of group training sessions once a week for 12 weeks. This group also received pedometer-based walking exercise assignments during the 12-week intervention phase that were supervised by physiotherapists.

Exercise classes followed a standardized format that included 15 minutes of stretching and moderate-intensity exercises, 15 minutes of progressive muscle strength training, and 60 minutes of DT exercise, which included three DT categories [17, 18]. The intensity of these exercises was based on the recommendation from the American College of Sports Medicine and the American Heart Association [19]. In the first category, the participants were instructed to perform a verbal fluency task during short, fast step exercises. In the second category, the supervisor assigned a number to various parts of the body (e.g., "1 = right shoulder," "2 = left shoulder," etc.). Then, the participants were instructed to perform seated or standing step exercises at a tempo of 60-120 beats per minute according to the tempo of the accompanying music. During these exercises, the supervisor periodically stated a number, at which point the participants were to touch the appropriate parts of their own body. In the third category, the participants were instructed to perform standing step exercises at the same tempo as the second category exercise and to step in one of four directions indicated verbally by the

supervisor (e.g., “right,” “forward,” “back,” and “left”). The intensity and difficulty of the three exercises were gradually increased over the 12-week period.

During the 12-week intervention phase, the EG received pedometer-based walking exercises. We used a pedometer (Yamax Power Walker EX-300, YAMASA TOKEI KEIKI CO., LTD, Tokyo, Japan) to measure participant’s daily step counts. We instructed the participants to increase the number of daily steps by 15% each month. The participants were asked to record the date on a calendar and the number of steps taken by the end of each day. At the end of every month, a sheet was given to each participant to collect brief feedback about the month’s exercises and to provide reminders to record the exercises. The feedback responses were used to assist in setting the number of daily steps assigned for the next month. The walking exercise intensity was not clearly defined. During the first month, the EG were instructed to increase their steps by approximately 15% relative to baseline (100%→115%). During the second and third months, they were also instructed to do so relative to the last month (115%→132.3%→152.1%). That is, their steps would have increased by approximately 50% relative to baseline.

Outcome measures

All participants underwent several evaluations upon entry into this study (pre-intervention) and at the end of the study (post-intervention). Evaluations included measurements of daily step counts, clinical tests (physical and cognitive functions), and MRI scans. Prior to the study, one of the authors (SN) trained all staff members to correctly obtain the measurements included in this study. The physical and cognitive function tests were administered by the physical therapists and occupational therapists, respectively, and were blinded to group allocation.

166 ***Measurement of average daily steps***

167 The participants were instructed to wear the pedometer in a clothing pocket on their
168 dominant leg for 14 consecutive days, except when bathing, sleeping, or performing
169 water-based activities. We calculated the averages of their daily step counts for 14 days.

170

171 ***Clinical tests***

172 To evaluate physical function, all of the participants underwent a 10-m walking test [20], the
173 Timed Up and Go test (TUG) [21], and the Five Chair to Stand test (5CS) [22]. In the 10-m
174 walking test, the participants walked at their usual speed over a distance of 10 m. The time
175 was recorded to yield the 10-m walking speed. In the TUG, the participants were instructed to
176 stand up from a standard chair, walk 3 m and back, and then sit down. The task was timed for
177 speed. In the 5CS, the participants were asked to stand up and sit down five times as fast as
178 possible; the time was recorded. Each of the three tests was assessed once per participant
179 using a stopwatch.

180 To evaluate global cognitive function, we administered the MMSE, a standard test in
181 cognitive aging research that is used to assess mental status [16]. Modified versions of the
182 logical memory subtest from the Wechsler Memory Scale Revised (WMS-R) were used to
183 assess memory function [23]. In the logical memory subtest, two short stories are read aloud to
184 the subjects for both immediate recall (LM-I, immediate recall; maximum score = 50) and
185 recall after 30 minutes (LM-II, delayed recall; maximum score = 50). The Trail Making Test
186 (TMT) was performed as a test of executive function, divided attention, and cognitive
187 flexibility [24]. The test is divided into two parts: Part A tested visual scanning and included a
188 numbered connect-the-dots task, and part B measured cognitive flexibility with a more
189 complex connect-the-dots task that also included alternating letters and numbers. The time
190 required to complete each task was recorded, with more time indicating worse performance.

191 We analyzed this test's data using a difference score between part A and part B, ΔTMT,
192 calculated as the difference between the times taken for each part (part B - part A) [25].
193
194 ***Image acquisition***
195 Whole-brain imaging was performed using a 3.0-Tesla Siemens Magnetom Verio MRI
196 scanner. A T2*-weighted echo planar imaging (EPI) sequence sensitive to blood oxygenation
197 level-dependent (BOLD) contrast with the following parameters was used for functional
198 imaging: repetition time (TR) = 2,000 ms, echo time (TE) = 25 ms, flip angle = 75°,
199 acquisition matrix = 64 × 64, field of view (FOV) = 224 mm, in-plane resolution = 3.5 mm ×
200 3.5 mm, and 39 axial slices with a slice thickness of 3.5 mm. A high-resolution structural
201 image was also acquired using a T1-weighted magnetization prepared rapid-acquisition
202 gradient echo (MP-RAGE) pulse sequence (voxel size = 1 × 1 × 1 mm^3). Firm padding was
203 placed around the head of each participant to restrict head motion. The visual stimuli were
204 projected onto a screen, and the participants' responses were collected using a
205 MRI-compatible response box. The EPI images were acquired during the visual sort-term
206 memory task in two consecutive rungs (one for face memory and one for location memory,
207 see below). The first five scans in each run were discarded to compensate for T1 equilibration
208 effects.
209
210 ***fMRI experimental protocol***
211 During fMRI scanning, the participants performed the n-back task (n = 1, 0) [26] for the
212 location and face stimuli created based on a previous study [27]. In the present study, we used
213 only 0- and 1-back tasks because 2- or 3-back tasks were thought to be too cognitively
214 demanding for older adults. Because the memory effort for the 1-back task is relatively low,
215 the results of the present study should be interpreted with caution. The visual short-term

memory task for face and that for location were conducted in separate fMRI runs. In the 1-back task, participants were required to monitor a series of stimuli (single dot location or faces) and to indicate whether the stimulus was the same as that presented in the previous trial. In the location 0-back task, the participants were required to monitor a stimulus and to indicate whether it was located in the center of the screen. In the face 0-back task, the participants were required to indicate the gender of a face stimulus. In the rest phase, the participants were required to gaze at a fixation cross located in the center of the screen. The location stimuli were made up of a single black dot, which was presented in a randomly designated location. The face stimuli were made up of neutral faces of young Japanese people (university students), with an equal number of male and female faces. The stimulus duration and the inter-stimulus interval for each task were both two seconds. Each of the three conditions (1-, 0-back tasks, and rest) was conducted in separate blocks. Each block, which had a duration of 32 s (i.e., 8 trials for 1- and 0-back tasks), was presented four times (a total of 12 blocks), and there was an equal number of each condition within the block. For both the face and location tasks, the order of the 12 blocks was counterbalanced across participants.

Statistical analysis for behavioral data

Baseline characteristics were compared between the EG and CG groups using Student's t-test and the chi-square test. The intervention effects on all outcome measures, except for brain activation, were determined using two-way repeated measures ANOVAs with group (EG, CG) as a between-subjects factor and time (pre-, post-intervention) as a within-subjects factor. The data were entered and analyzed using SPSS (Windows version 20.0; SPSS Inc., Chicago, IL). For all analyses, $P < .05$ was considered statistically significant.

Image preprocessing and statistical analysis for MRI data

The MRI data were analyzed using Statistical Parametric Mapping 8 (SPM8; Wellcome Department of Imaging Neuroscience, London, UK). All of the functional images were spatially realigned to the first functional image to correct for head motion. The resulting volumes were normalized to a standard EPI template based on the Montreal Neurological Institute (MNI) reference brain (re-sampled voxel size 2 mm × 2 mm × 2 mm). The normalized images were smoothed using an isotropic 8 mm full width at half maximum Gaussian kernel. A high-pass filter of 1/128 Hz was used to remove low-frequency noise, and an AR (1) model was used to correct temporal autocorrelation.

The fMRI data were analyzed using the blocked design. Activated voxels in each experimental condition were identified using a statistical model containing a boxcar function convolved with a canonical hemodynamic response function. The experimental conditions consisted of the following: (1) 1-back task, (2) 0-back task, and (3) rest. In addition to analyzing the face and location conditions, we also analyzed the fMRI data by combining two tasks to maximize the statistical power. Linear contrasts were used to obtain participant-specific estimates for each effect. The brain activation associated with visual short-term memory was analyzed using the contrast of the 1-back vs. 0-back task. These estimates were then entered into a second-level analysis that treated the participant as a random effect. To identify regions in which brain activation associated with visual short-term memory increased or decreased after the 12-week intervention, we compared brain activation prior to intervention with that after intervention in EG using two-sample t-tests. The statistical threshold was set at $P < .001$ (uncorrected for multiple comparisons, cluster size > 10 voxels).

We also used the MarsBaR [28] software to extract the signal changes of regions identified in the analysis described above. The signal changes were averaged across all voxels in a given cluster. The group × time interactions in the signal changes were determined using two-way

266 repeated measures ANOVAs using SPSS.

267

RESULTS

Overall, 70 participants were screened, 52 (74.3%) of whom met the inclusion criteria, agreed to participate, and were enrolled in the study. Of the 52 participants, four were removed on the basis of the exclusion criteria; two had an MMSE score < 24, one showed apparent brain damage on structural MRI, and the other showed missing fMRI signals. Therefore, 48 participants completed the 12-week intervention phase and the post-intervention assessment: 24 in the EG and 24 in the CG (Figure 1).

The baseline characteristics of both groups were well matched, and there were no significant differences in any variables between the groups at baseline, with the exception of reaction time in the 0-back tasks (Table 1). During the intervention phase, 12 exercise sessions were scheduled, and all were performed. The median adherence was 91.7% (25th - 75th percentile: 83.3 - 100%) in the EG over the 12 weeks. Physiotherapists monitored any adverse events; there were none.

Change in average daily steps

The average daily steps increased in the EG by 54.1% (from 7,266 ± 3,001 to 11,189 ± 5,823) during the study period; this did not occur in the CG (from 6,269 ± 1,885 to 5,692 ± 1,654). There was a significant group × time interaction (F = 30.2, $P < .001$; Table 1). The median adherence for recording the step counts was 100% (25th - 75th percentile: 99.0 - 100%) in the EG over the 12 weeks.

Effect of intervention on physical and cognitive functions

Regarding physical function, there were significant group × time interactions, and the participants in the EG showed greater improvements for walking speed (F = 9.37, $P = .004$) and 5CS time (F = 11.2, $P = .002$) but not for TUG time (Table 1).

Regarding cognitive function, there were significant group × time interactions, and the participants in the EG showed greater improvements for memory function (WMS-LM I: F = 7.44, *P* = .009; WMS-LM II: F = 7.80, *P* = .008) and executive function (ΔTMT: F = 6.05, *P* = .018). There was no group × time interaction for MMSE scores (Figure 2, Table 1).

Effect of intervention on brain activation associated with visual short-term memory

There was no significant group × time interaction for visual short-term memory performance (i.e., face, location, and face + location) after the intervention phase (Table 1), perhaps due to a ceiling effect.

In the fMRI analysis, we observed that decreased brain activation was associated with each of the face and location tasks in several brain regions in the EG (Table 2). Although these results indicate that the exercise intervention might affect different neural networks (depending on the type of stimuli), these results were not a priori hypothesized and we therefore do not discuss these results further in the present study. After the intervention phase in the EG group, we found that none of the regions showed significantly increased brain activation in association with the face and location tasks.

When combining the data from the two tasks, we found that decreased brain activation was associated with visual short-term memory in several brain regions, including the bilateral prefrontal cortex in the EG after intervention (Figure 3, Table 2), whereas we found that no region showed significantly increased brain activation. The effects observed in the prefrontal cortex did not survive correction for multiple comparisons ($P < .001$ uncorrected, k > 10 voxels) and should therefore be interpreted with caution. Nevertheless, the fact that these effects are bilateral and consistent with a strong *a priori* hypothesis reduces the likelihood that they are due to chance. The region of interest (ROI) analysis revealed that there were significant group × time interactions in the signal changes both in the right superior frontal

gyrus (F = 10.8, *P* = .002) and in the left superior frontal gyrus (F = 7.71, *P* = .008) (Figure 3). Although the interaction effect observed in the right superior frontal gyrus aligns with our prediction, the interaction in the left superior frontal gyrus was driven by greater activation during the 0-back task after the intervention phase. Therefore, the findings in the left superior frontal gyrus prevent us from drawing firm conclusions and should be interpreted cautiously. In the right superior frontal gyrus, the interaction was also observed for the face condition (F = 7.71, *P* = .008) but not for the location condition (F = 0.77, *P* = .385). In the left superior frontal gyrus, the interactions were also observed for the face (F = 3.52, *P* = .048) and location (F = 3.81, *P* = .047) conditions. Note that our ROI analyses to test a group × time interaction were performed independently of the whole brain SPM subtraction analysis (post- vs. pre-intervention) for the EG. Thus, our analysis successfully avoided the issues associated with the phenomenon called 'double dipping' [29].

DISCUSSION

The results of this study showed that a 12-week multimodal exercise program with DT and walking exercises can improve memory and executive function and can lead to decreased brain activation associated with short-term memory. These findings suggest that physical and cognitive exercise may improve the efficiency of brain function and thereby cognitive performance.

Participants in the EG showed significant improvements in memory and executive function as well as physical performance. Physical activity alone [5-7] and combined cognitive and exercise training [9] can improve cognitive function in older adults. The results of this study support and expand these previous results. Our physical and cognitive exercise program was performed for 12 weeks and involved changes in cognitive load using DT stimulation. Among previous studies that have used physical and cognitive exercise interventions for 12 or fewer weeks [10, 30, 31], only one study whose participants exhibited normal cognition [10] showed positive effects on working memory and memory function. Short-term multimodal exercise with DT training could lead to cognitive improvement only in cognitively healthy elderly individuals. In this study, the participants in the EG also received daily walking exercise in addition to DT training; they also significantly increased their daily steps over the 12 weeks. Furthermore, there were significant correlations between the percentage change in daily steps and the percentage change in memory function among the EG in this study (WMS-LM II: $r = 0.622$, $P = .001$). A previous study also indicated that physical activity and behavioral intervention improved memory and global cognitive function in older adults [32]. As few studies have indicated cognitive improvements induced by short-term aerobic exercise alone [5-7], the positive results in the present study may be attributed to the addition of walking assignments to everyday life and DT training.

Despite similar pre- and post-intervention task performance on the 0- and 1-back task (possibly due to a ceiling effect), we found (via fMRI) that decreased brain activation was associated with short-term memory in the prefrontal cortex post-intervention, regardless of the type of stimuli. This finding can be interpreted as a marker of improved neural efficiency, given that a "smaller" amount of energy (i.e., prefrontal activity) was needed to perform the "same" amount of work (i.e., n-back task) after the intervention. The logic of neural efficiency (i.e., decreased activation at comparable performance levels) has been used in several previous studies in which performance is similar among groups but activation decreases in the experimental group [33, 34]. This study hypothesized that multimodal exercise (DT training) would affect the efficiency of neural circuitry during the short-term memory task. The higher cognitive loads required by the DT exercise possibly resulted in reduced effort and improved brain activation during the short-term memory task.

Elderly with MCI or elderly at risk of dementia tend to show greater brain activation than cognitively healthy elderly during interference [35, 36] and memory tasks [37], likely due to more extensive and stronger cortical recruitment in task-related regions [38]. The compensation-related utilization of neural circuits hypothesis (CRUNCH) by Reuter-Lorenz [39] assumes more recruitment of neural resources at low levels of cognitive load in older adults than in younger adults, with a loss or reversal in age-related differences in compensatory mechanisms at higher levels of load. A similar difficulty-related reversal would also be observed in cognitively high-risk and low-risk older adults. The effect of physical exercise or cognitive training on task-related brain activation in cognitively healthy elderly has varied results [40, 41]. Erickson et al. reported that DT training led to decreased activation in the bilateral dorsolateral prefrontal cortex and the right ventrolateral prefrontal cortex, as well as increased activation in the left ventrolateral prefrontal cortex [42]. Although our results supported the finding of decreased activation in the bilateral dorsolateral prefrontal cortex, it

380 may be likely that the exercise training affects the asymmetric change of brain activation
381 depending on the brain regions. Carlson et al. also reported that a multimodal type of
382 intervention led to increased brain activation associated with interference tasks in cognitively
383 high-risk older adults [43], which may indicate that the effects of the exercise on brain
384 activation differ according to the subject's cognitive level and the type of cognitive task. In the
385 present study, the cognitive health of participants and the low cognitive load of the fMRI task
386 following the multimodal exercise are likely important factors in the decreased brain
387 activation associated with improved cognitive performance. Further studies are necessary to
388 investigate the effect of similar exercise on brain activation in elderly individuals with MCI
389 or AD.

390 There were several limitations to this study. First, this trial was not double-blinded. Second,
391 we did not arrange a follow-up after the intervention; thus, any longitudinal effects of the
392 intervention remain unknown. Third, we did not arrange the control groups to have only one
393 component (physical or cognitive exercise) of the multimodal treatment. We do not know if
394 one or both components were necessary for the observed changes. Fourth, we did not control
395 for the increased social contact of the EG. Social engagement is known to impact cognitive
396 functioning, and the exercise group may be partially affected by the social engagement in
397 addition to physical activity.

CONCLUSION

This study showed that a 12-week physical and cognitive exercise program can improve the efficiency of brain activation in older adults; this result is consistent with improvements observed in memory and executive function. Future studies are needed to examine the longitudinal effect of the intervention and whether this program can be used to prevent the onset of dementia.

ACKNOWLEDGMENTS

This work was supported by Grants-in-aid (25245068) for Scientific Research from the Japan Society for the Promotion of Science and the Ministry of Education, Culture, Sports, Science and Technology. Nobuhito Abe was supported by the Uehiro Foundation on Ethics and Education. The authors thank Dr. Mamoru Hashimoto, who diagnosed major abnormalities in brain MRI scans, and students at Kyoto University, who helped with the measurements. This study was conducted using the MRI scanner and related facilities of Kokoro Research Center, Kyoto University.

Conflicts of Interest

The authors have no financial or any other personal conflicts to report.

Author Contributions

Nishiguchi and Yamada substantially contributed to the conception of the methods used, participant recruitment, analysis, and writing the manuscript. Sekiyama and Abe made substantial contributions to the conception and design, participant recruitment, and the writing of the manuscript. Tanigawa and Kawagoe were involved in the acquisition, analysis, and interpretation of data. Suzuki, Otsuka, and Nakai contributed to the acquisition of data. Yoshikawa, Aoyama, and Tsuboyama made substantial contributions to writing the manuscript. All authors read and approved the final manuscript.

Sponsor's Role

None.

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539

Table 1. Participant baseline characteristics and outcome measures pre- and post-intervention (mean ± SD)

		Exercise group (n = 24)		Control group (n = 24)		Baseline difference *P*-value	Group × Time interaction *F*-value	Group × Time interaction *P*-value
Age (y)		73.0	± 4.8	73.5	± 5.6	.760		-
Female (n)		11	(45.8%)	11	(45.8%)	1.000		-
BMI (kg/m^2)		21.0	± 2.4	21.2	± 2.9	.813		-
Education (y)		12.2	± 2.2	13.0	± 2.5	.249		-
Medications taken (n)		2.08	± 1.91	2.13	± 2.2	.945		-
Physical function								
Walking speed (m/s)	Pre	1.33	± 0.20	1.28	± 0.14	.320		
	Post	1.40	± 0.19	1.27	± 0.13		9.37	.004**
TUG (s)	Pre	6.79	± 1.10	6.47	± 1.23	.343		
	Post	6.54	± 1.02	6.32	± 1.17		0.15	.698
5CS (s)	Pre	7.46	± 1.50	7.55	± 2.06	.868		
	Post	6.88	± 1.26	7.85	± 2.14		11.2	.002**
Cognitive function								
MMSE	Pre	27.4	± 1.8	27.9	± 2.0	.360		
	Post	28.2	± 1.6	27.7	± 2.3		1.90	.174
WMS-LM I	Pre	17.3	± 4.5	20.0	± 7.7	.144		
	Post	22.0	± 5.9	21.3	± 7.8		7.44	.009**
WMS-LM II	Pre	12.8	± 5.3	14.9	± 7.9	.281		
	Post	18.0	± 6.3	16.3	± 8.0		7.80	.008**
ΔTMT (s)	Pre	43.6	± 26.1	37.9	± 20.7	.413		
	Post	30.4	± 16.1	41.5	± 30.7		6.05	.018*
Others								
Daily steps (steps)	Pre	7,266	± 3,001	6,269	± 1,885	.181		
	Post	11,189	± 5,823	5,692	± 1,654		30.2	< .001**
Correct responses								
0-back (face + location)	Pre	96.9	± 3.0	97.5	± 2.0	.423		

(%)								
	Post	97.5	± 3.8	98.7	± 2.8		0.31	.578
1-back (face + location) (%)	Pre	90.2	± 9.8	92.9	± 5.1	.230		
	Post	94.3	± 4.8	95.9	± 3.3		0.29	.596
0-back (face) (%)	Pre	97.0	± 2.5	97.3	± 3.2	.759	0.16	.690
	Post	97.4	± 2.2	97.3	± 2.8			
1-back (face) (%)	Pre	87.8	± 11.4	90.0	± 7.0	.418	0.44	.510
	Post	94.3	± 5.8	94.8	± 4.5			
0-back (location) (%)	Pre	96.9	± 4.2	97.8	± 2.5	.366	0.05	.833
	Post	97.5	± 3.8	98.7	± 2.8			
1-back (location) (%)	Pre	92.6	± 9.8	95.8	± 4.7	.148	0.04	.844
	Post	94.2	± 7.3	97.0	± 3.4			
Reaction time								
0-back (face + location) (ms)	Pre	1,025	± 109	1,122	± 132	.009**	0.68	.414
	Post	942	± 148	1,014	± 126			
1-back (face + location) (ms)	Pre	1,181	± 213	1,224	± 179	.445	0.25	.620
	Post	1,118	± 184	1,148	± 157			
0-back (face) (ms)	Pre	1026	± 93	1120	± 140	.009**	0.90	.348
	Post	978	± 142	1037	± 130			
1-back (face) (ms)	Pre	1207	± 235	1290	± 211	.208	1.13	.293
	Post	1155	± 187	1191	± 175			
0-back (location) (ms)	Pre	1028	± 164	1125	± 151	.039*	0.16	.694
	Post	908	± 166	991	± 140			
1-back (location) (ms)	Pre	1154	± 220	1159	± 189	.933	0.34	.565
	Post	1081	± 203	1106	± 163			

Note:

BMI = body mass index, TUG = Timed Up and Go test, 5CS = 5 Chair Stand Test, MMSE = Mini-Mental State Examination, WMS-LM I/II = Wechsler Memory Scale Logical Memory subtest, TMT = Trail Making Test.

* $P < .05$, ** $P < .01$

Table 2. Regions showing decreased activation associated with visual short-term memory after the intervention.

	Region (Brodmann's Area)	MNI coordinates			Z value	Cluster size
		x	y	z		
1-0 back (face + location)						
	Left superior frontal gyrus (9)	-20	48	34	3.84	108
	Right thalamus	6	-20	-2	3.52	51
	Right superior frontal gyrus (10)	24	60	14	3.46	17
1-0 back (face)						
	Right thalamus	2	-16	-4	3.84	35
1-0 back (location)						
	Left superior temporal gyrus (22)	-50	10	-8	3.61	29
	Left parahippocampal gyrus (36)	-38	-32	-16	3.57	23
	Right superior temporal gyrus (38)	42	6	-22	3.42	13

Note:

$P < .001$ uncorrected, Cluster size > 10 voxels.

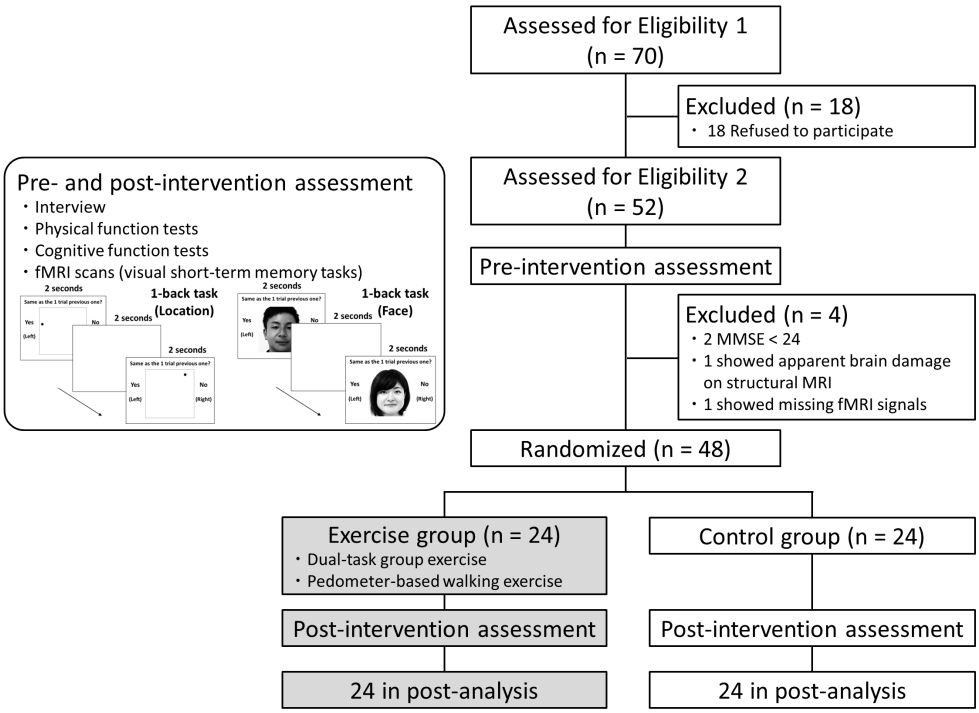
541

Figure legends

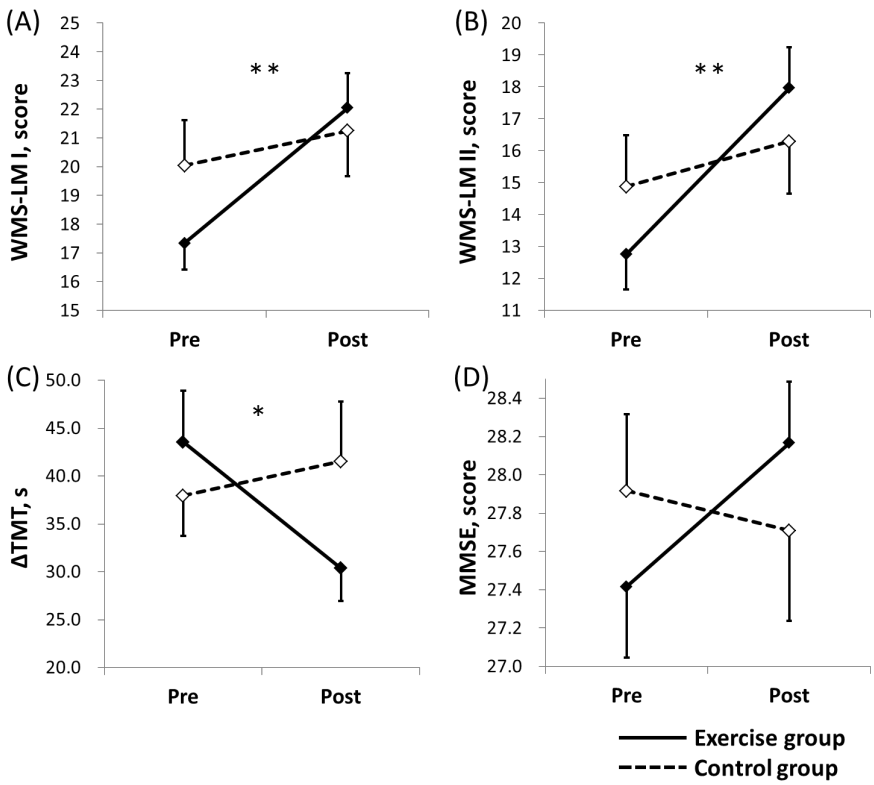
Figure 1. A flow chart showing the distribution of participants throughout the trial.

Figure 2. Group × time interactions in the cognitive functions at pre- and post-intervention. Solid and dashed lines indicate the exercise and control groups, respectively. Group mean differences and standard errors for WMS-LM I, II, ΔTMT, and MMSE are shown in panels A, B, C, and D, respectively. * $P < .05$, ** $P < .01$.

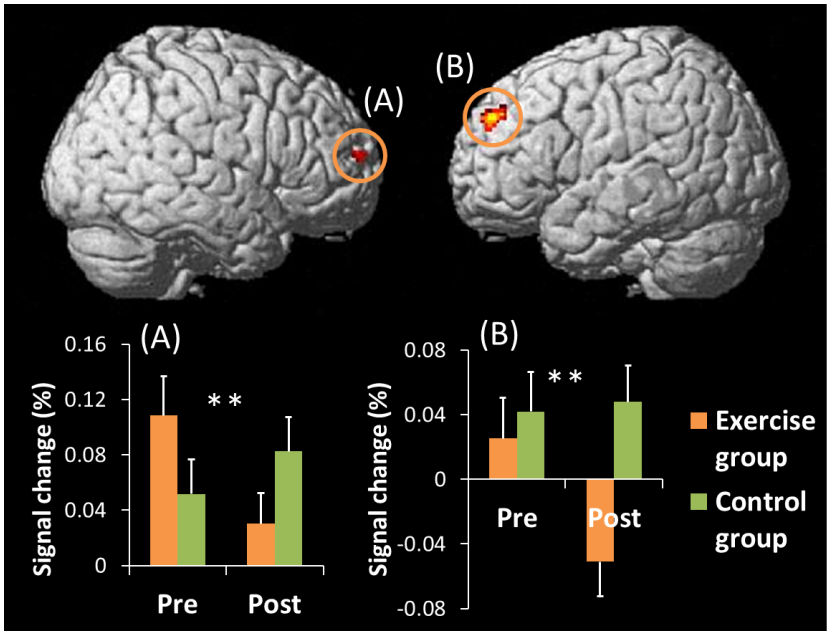
Figure 3. Bilateral prefrontal cortex showing decreased activation associated with visual short-term memory after intervention. The signal changes in these regions showed significant group × time interactions. (A) Right superior frontal gyrus and (B) Left superior frontal gyrus. * $P < .05$, ** $P < .01$.


Assessed for Eligibility 1
(n = 70)
Excluded (n = 18)
・18 Refused to participate
Assessed for Eligibility 2
(n = 52)
Pre-intervention assessment
Excluded (n = 4)
・2 MMSE < 24
・1 showed apparent brain damage on structural MRI
・1 showed missing fMRI signals
Randomized (n = 48)
Exercise group (n = 24)
・Dual-task group exercise
・Pedometer-based walking exercise
Control group (n = 24)
Post-intervention assessment
Post-intervention assessment
24 in post-analysis
24 in post-analysis
Pre- and post-intervention assessment
・Interview
・Physical function tests
・Cognitive function tests
・fMRI scans (visual short-term memory tasks)
1-back task (Location)
1-back task (Face)
2 seconds
Same as the 1 trial previous one?
Yes
(Left)
No
(Right)

555


(A)
WMS-LM I, score
25
24
23
22
21
20
19
18
17
16
15
* *
Pre
Post
(B)
WMS-LM II, score
20
19
18
17
16
15
14
13
12
11
* *
Pre
Post
(C)
ΔTMT, s
50.0
45.0
40.0
35.0
30.0
25.0
20.0
*
Pre
Post
(D)
MMSE, score
28.4
28.2
28.0
27.8
27.6
27.4
27.2
27.0
Pre
Post
Exercise group
Control group

556


(A)
(B)
(A)
0.16
0.12
0.08
0.04
0
Signal change (%)
* *
Pre
Post
(B)
0.08
0.04
0
-0.04
-0.08
Signal change (%)
* *
Pre
Post
Exercise group
Control group

557