Brain Neurorehabil. 2021 Nov;14(3):e23
https://doi.org/10.12786/bn.2021.14.e23
pISSN 1976-8753·eISSN 2383-9910

Brain & NeuroRehabilitation

Original Article

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Effects of Cognitive-Physical Dual-Task Training on Executive Function and Activity in the Prefrontal Cortex of Older Adults with Mild Cognitive Impairment

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Received: May 5, 2021
Revised: Aug 13, 2021
Accepted: Aug 14, 2021

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HIGHLIGHTS

- Dual-task training is effective in improving executive function (EF).
- Improved neural efficiency in the prefrontal cortex underlies enhanced EF.
- Ecologically validated dual-task training in needed for independence daily living.

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Funding
This work was supported by 2020 Research Grant from the Korean Society for Brain & Neuro Rehabilitation and the Soonchunhyang University Research Fund.

Conflict of Interest
The authors have no potential conflicts of interest to disclose.

ABSTRACT

Effects of cognitive-physical dual-task training on prefrontal cortex (PFC)-dependent function remain unclear. This study investigated the effects of dual-task training on executive function and activity in the PFC of older adults with mild cognitive impairment (MCI). Thirty-six older adults with MCI randomly assigned to the experimental group (EG) performing cognitive-physical dual-task training requiring for simultaneous cognitive tasks and physical exercise (n = 18) or the control group (CG) receiving sing-cognitive training using the computerized cognitive training program focusing on executive function (n = 18) for 16 sessions lasting 40 minutes a session. For the primary outcomes, the Trail Making Test Part B (TMT-B) was used, and for the secondary outcome, activity in the PFC using functional near infrared spectroscopy and the Korean version of instrumental activities of daily living (K-IADL) were evaluated at pre-and post-intervention. After the intervention, the EG achieved a significantly higher improvement in the TMT-B and decreased activity in the PFC during TMT-B testing than the CG. However, there were no significant differences in the K-IADL in both groups. These findings indicate that dual-task training is more effective in improving executive process and decreasing activity in the PFC during cognitive testing than single-cognitive training with limitations of its transfer effect to daily life.

Keywords: Cognition; Cognitive Dysfunction; Prefrontal Cortex

INTRODUCTION

As the importance of early intervention in Alzheimer's disease (AD) is emphasized, interests in mild cognitive impairment (MCI), a preclinical stage of AD, are increasing [1]. Considering results of studies that 10%–30% of elderly with MCI proceed to AD, the development of effective intervention for the elderly with MCI is urgent [1].

One of hallmarks of MCI is executive dysfunction similar to AD. Executive function mainly depends on prefrontal function and it is closely related with goal-directed behavior in daily life [2]. Although there are differences in the categories of executive function, it commonly includes planning, sequencing, inhibition, flexibility of thinking, problem solving, and organization [3]. The decline in executive function causes a decrease in independence of instrumental activities of daily living (IADLs) such as financial management, calling, and home management in the elderly with MCI [4].

In prior studies, a variety of cognitive intervention have been implemented in clinical setting to improve executive function of the elderly with MCI [4-6]. Cognitive intervention for older adults with MCI could be broadly divided into two types. First, various activities requiring cognitive demands such as matching pictures by color or finding a maze, and second, computerized cognitive training by cognitive domains [5,7]. A meta-analysis study on cognitive intervention in MCI reported that traditional cognitive intervention consisting of the two types of interventions is effective in improving memory and attention, but conclude that the evidence is still insufficient for improving executive function [5]. This result is attributed by the fact that most of previous studies performed cognitive intervention using only a single cognitive training [8]. Executive function is maximally facilitated when attempting to inhibit interference effects between tasks while simultaneously implementing tasks requiring attention [8]. Indeed, this mechanism has been proven through brain imaging studies indicating that the prefrontal cortex (PFC) was activated while subjects performed cognitive tasks demanding interference inhibition [9,10] Thus, in order to conduct effective cognitive intervention for improving executive function, dual-task training that requires simultaneous attention needs to be carried out.

In most of previous studies on dual-task training, simple cognitive activity and physical exercise were performed simultaneously, for example, adding or subtracting numbers while performing walking or running [8,10,11]. It has been found that dual-task training is more effective in improving executive function than performing single cognitive training [5,11]. However, in most prior randomized controlled trials, control groups (CGs) performed a single cognitive task such as addition and subtraction that was not closely related with executive function [5,9,11]. Specifically, among dual-task conducted by experimental groups (EGs), only simple cognitive activities were selectively adopted to CGs [5,10,11]. This is not a condition that can be expected to improve executive function of CGs. In addition, given that the difficulty level of cognitive tasks has an impact on its effect, prior single cognitive tasks which is less difficult than dual-task might not be effective in improving executive function [5,10,11]. Accordingly, it is difficult to clearly elucidate effects of dual-task training on improving executive function with this CG condition. On the other hand, in most previous studies, only paper-based neuropsychological assessments were used to prove its effects, limiting in presenting objective evidence on training's effects because it cannot observe changes in the PFC [5,11].

Therefore, this study aimed to confirm the superiority of dual-task training's effect on executive function compared to computerized cognitive training focusing on executive function by using functional near infrared spectroscopy (fNIRS) as well as conventional neuropsychological assessment to confirm neural substrate of dual-task training's effects. In addition, this study also checked whether the improvement of executive function could be transferred to daily live by using the IADLs assessment.

https://doi.org/10.12786/bn.2021.14.e23

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MATERIALS AND METHODS

Design

This study was a single-blinded study, and all participants were randomly assigned to the EG or the CG by using a random numbers generated by Excel. Outcome measurements were implemented at pre-and post-intervention by a blinded assessor. Intervention was conducted for a total of 16 sessions, twice a week for 8 weeks lasting 40 minutes. This study was approved by the Institutional Review Board (202005-SB-036).

Subjects

Participants were recruited from local community welfare centers in Asan and Seoul, Korea. A total of 36 were finally selected (**Fig. 1**). The inclusion criteria are as follows: 1) over 65 years old, 2) ability to understand simple instruction, 3) Korean version of the Montreal Cognitive Assessment score lower than 23 [12], and 4) Clinical Dementia Rating score of 0.5. The exclusion criteria as follows: 1) psychiatric or neurological disorders and 2) visual or auditory impairments. All participants provided written informed consent form in accordance with the Declaration of Helsinki (2004). Sample size calculation was conducted by using G*Power 3.1.7 (Informer Technologies, Dusseldorf, Germany). According to a previous study [11], the effect size was set at 0.60, the α error at a probability of 0.05, and the power at 0.90, indicating that a minimum of 14 subjects was required in each group.

Intervention

Participants in the EG performed cognitive-physical dual-task training designated to improve executive function of the elderly with MCI according to a previous study [9]. Dual-task training involved eight programs consisted from simple dual-task to more complex dual-task tasks (**Table 1**). While verbal fluency, attention, memory, game of rock-paper-scissors, and calculation tasks were used for cognitive tasks, aerobic exercise including range of motion exercise and strengthening exercise consisting of thera-band with low intensity training and passing/throwing a ball were used for physical tasks. Detailed each content for cognitive and physical tasks were presented in **Table 1**. Eight programs were repeated twice, resulting a

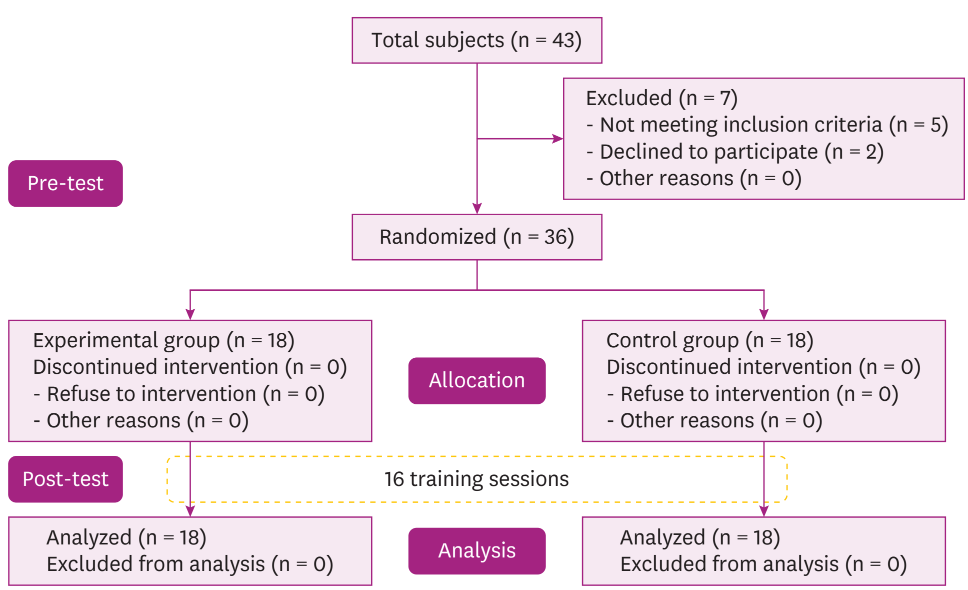

Fig. 1. Flow diagram of subjects in this study.

Table 1. The cognitive-exercise combined program

Session	Theme	Content
1, 2	Cognitive task	Naming of pictures (ex, flowers)
	Physical task	Aerobic exercise (wrist and shoulder range of motion exercise)
		Strength exercise (thera-band with low intensity exercise by hands)
3, 4	Cognitive task	Forward digit span task (3 digits)
	Physical task	Aerobic exercise (wrist and shoulder range of motion exercise)
		Strength exercise (thera-band with low intensity exercise by hands)
5, 6	Cognitive task	Backward digit span task (3 digits)
	Physical task	Aerobic exercise (wrist, elbow, and shoulder range of motion exercise)
		Strength exercise (pass the ball [0.4kg] to the side)
7, 8	Cognitive task	Answering calculation (addition, a single digit) question
	Physical task	Aerobic exercise (wrist, elbow, and shoulder range of motion exercise)
		Strength exercise (pass the ball [0.4kg] to the side)
9, 10	Cognitive task	Game of rock-paper-scissors
	Physical task	Aerobic exercise (wrist, elbow, shoulder, ankle, and knee range of motion exercise)
		Strength exercise (throw the ball [0.4kg])
11, 12	Cognitive task	Word chaining
	Physical task	Aerobic exercise (wrist, elbow, shoulder, ankle, and knee range of motion exercise)
		Strength exercise (throw the ball [0.4kg])
13, 14	Cognitive task	Remembering of shopping list
	Physical task	Aerobic exercise (wrist, elbow, shoulder, ankle, knee range of motion exercise & walking motion)
		Strength exercise (thera-band with low intensity exercise by legs)
15, 16	Cognitive task	Answering calculation (addition & subtraction, a single digit) question
	Physical task	Strength exercise (thera-band with low intensity exercise by legs)

total of 16 sessions in an ascending order. During training sessions, cognitive and physical tasks were implemented simultaneously.

In the CG, participants performed single cognitive training using RehaCom (Hasomed GmbH, Magdeburg, Germany) program, the computerized cognitive training program involving training contents for several cognitive domains consisting of attention, memory, executive function, and visual field. Among these contents, the participants in the CG performed only executive function training such as planning a vacation, logical reasoning, calculation, and shopping for 10 minutes each. The contents have different levels of difficulty which can be adjusted by participant's performance. Specifically, when the success rate of 80% or more was achieved, the level of difficulty was automatically increased. In this study, only training such shopping, planning and problem solving in executive function were carried out. Single cognitive training consists of a total of 16 sessions and each session lasted 40 minutes.

All participants in both groups performed their assigned training in community welfare centers and took five minutes for rest time to prevent their fatigue after 20 minutes of training. All sessions were implemented by an experimenter with 6 years of clinical experience.

Measurements

Primary outcomes

Executive function was evaluated by computerized version of the Trail Making Test Part B (TMT-B) and activation in the PFC with a fNIRS device. The TMT-B is a tool designed to test executive function by asking to connect 25 circle-shaped letters and numbers in alternating number-letter order. A maximum time of 300 seconds was allowed to complete the TMT-B and the time take to complete it was analyzed [13]. The TMT-B can measure executive processes of task-set inhibition, cognitive flexibility, and the ability to maintain a response set [14].

https://doi.org/10.12786/bn.2021.14.e23

Secondary outcome

Activation in the PFC was assessed by hemodynamic responses from the PFC using a fNIRS device (Octamon, Artinis, Netherlands). This device uses near infrared light transmitted two wavelengths (760 and 850nm) with eight channels to measure hemodynamic responses from the PFC. The fNIRS probe was firmly attached on participant's forehead using headband and placed in accordance with EEG 10-20 standard system [15]. During the measurement, each participant sat in a chair and they were asked to carry out the TMT-B using a computer on the desk in front of a participant. To minimize artifacts induced by participant's movement, they were instructed to minimize unnecessary movements other than mouse movement to input their responses. The hemodynamic response measurement lasted until the time a participant completed the TMT-B. In this study, 8-channel's the HbO_2 concentration in the PFC was averaged for the analyses as increases in HbO_2 can be regarded as cortical activation and are an indicator of alterations in blood volume [16]. All fNIRS data were sampled with a frequency of 10Hz with Oxysoft version 3.0.42. Primary outcomes were performed before and after the intervention by the blinded occupational therapist with 5 years of experience.

To evaluate IADLs, the Korean IADL (K-IADL) was used. It consists of 11 items in daily life such as shopping, using a transportation and housekeeping. It scores with a Likert scale ranging from 0 to 3 points, resulting a total of scores ranging from 0 to 33 points. The higher score participants get, the more independent in IADLs participants are. Its internal consistency and the test-retest reliability was 0.96 and 0.94, respectively [17]. Secondary outcome was also implemented before and after the intervention by the blinded occupational therapist with 5 years of experience.

Statistical analysis

Data analysis was conducted using SPSS for Windows version 22.0 (SPSS Inc., Chicago, IL, USA). To confirm the normality of outcome data, Kolmogorov-Smirnov test was used. Demographic characteristics of both groups were analyzed using the χ^2 test and the Mann-Whitney U test. After the intervention, differences in outcome measurements between both groups were compared using Mann-Whitney U test. Statistical significant was set at $p < 0.05$.

RESULTS

General characteristics of participants

There were no significant differences in participant's characteristics between both groups (all p's > 0.05) (**Table 2**).

Primary outcomes

After the 16 training sessions, both groups showed a shorter time to complete the TMT-B (EG: $p < 0.001$; CG: $p < 0.001$) (**Table 3**) compared to the baseline (EG: 106.50 to 101.62; CG: 107.50 to 105.00). In addition, it was found that HbO_2 in the PFC during executive function testing significantly decreases in both groups (EG: $p < 0.001$; CG: $p < 0.001$) (**Table 3**) compared to the baseline (EG: 1.14 to 1.06; CG: 1.06 to 1.03). When comparing between groups, the EG achieved a significantly higher improvement in the TMT-B (between-group differences: 3.07; $p < 0.05$) and the PFC activity (between-group differences: 0.03; $p < 0.05$) than the CG (**Table 3**).

https://doi.org/10.12786/bn.2021.14.e23

Table 2. General characteristics of both groups

Characteristics	Experimental group (n = 18)	Control group (n = 18)	χ^2/U
Sex			0.738
Male	8 (44.4%)	9 (50.0%)	
Female	10 (55.6%)	9 (50.0%)	
Age (yr)	74.00 (6.00)	74.00 (6.00)	0.521
Education period (yr)	6.00 (3.00)	7.50 (3.75)	0.542
MoCA-K (scores)	19.50 (3.00)	19.00 (3.00)	0.864
TMT-B (sec)	106.50 (8.33)	107.50 (7.75)	0.443
HbO_2 (mol)	1.14 (0.17)	1.06 (0.20)	0.265
K-IADL (scores)	16.50 (5.00)	17.00 (4.00)	0.791

Values are expressed as median (interquartile range).
MoCA-K, Korean version of Montreal Cognitive Assessment; TMT-B, Trail Making Test Part B; HbO_2, oxygenated hemoglobin; K-IADL, Korean version of instrumental activities of daily living.

Table 3. Comparison of prefrontal function and instrumental activities of daily living between both groups

Variables	Experimental group (n = 18)	Control group (n = 18)	Between-group differences
TMT-B (sec)			
Pre-intervention	106.50 (8.33)	107.50 (7.75)	
Post-intervention	101.62 (6.46)	105.00 (9.50)	
Within-group changes	4.50 (3.10)†	3.00 (2.00)†	3.07 (2.90)*
HbO_2 (mol)			
Pre-intervention	1.14 (0.17)	1.06 (0.20)	
Post-intervention	1.06 (0.11)	1.03 (0.21)	
Within-group changes	0.05 (0.08)†	0.02 (0.02)†	0.03 (0.05)*
K-IADL (scores)			
Pre-intervention	16.50 (5.00)	17.00 (4.00)	
Post-intervention	17.00 (5.00)	17.00 (4.00)	
Within-group changes	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)

Values are expressed as median (interquartile range).
TMT-B, Trail Making Test Part B; HbO2, oxygenated hemoglobin; K-IADL, Korean version of instrumental activities of daily living.
*$p < 0.05$, †$p < 0.001$.

Secondary outcome

After the 16 training sessions, within (EG: 16.50 to 17.00; CG: 17.00 to 17.00) or between both groups (between-group differences: 1.50), there were no significant differences in IADLs (all p's > 0.05) (**Table 3**).

DISCUSSION

This study aimed at investigating effects of cognitive-physical dual-task training on executive function and activity in the PFC of older adults with MCI. The dual-task training showed significant improvements in executive process and decreased activity in the PFC during cognitive testing compared to the single cognitive task. However, its effects did not transfer to IADLs of the elderly with MCI. These results indicate that cognitive-physical dual-task training could be as an effective intervention for executive process and reduce neural effort in the PFC in older adults with MCI but alternative options for improving IADLs should be considered.

Dual-task training requires to simultaneously perform two or more tasks and interference effects between tasks need to be modulated for a successful performance, which requires executive function [2]. Previous studies reported that older adults with impaired executive function showed a low performance on dual-tasks [18,19]. Thus, various dual-task trainings have been implemented and found to be beneficial to improve executive function of older adults with MCI [8,20-22], which is consistent with the findings of this study. However, this study has the difference in terms of research methodology compared to previous study [8,20-22]. The CG received single cognitive task training focusing on executive function whereas CGs in previous studies performed only single cognitive or physical tasks that are not closely related with executive function. In addition, in prior studies, a single task in CGs is relatively easier than a dual task in the EGs, which has an impact on its effects [8,20-22]. Although, the CG performed cognitive training focusing on executive function, the EG showed a higher achievement in the TMT-B than the CG, which suggests that dual-task training could be used for enhancing executive process than computerized cognitive training focusing on executive function. In addition, the EG performed physical exercise which might have a positive effect on improving executive function. Some previous studies indicated that physical exercise can increase arousal levels facilitating optimal cognitive performance, resulting in activating neurophysiological pathways into the PFC. However, majority of previous studies consistently reported that moderate to high intensive physical exercise for long-term periods can enhance executive function and induce the change in the PFC structure [23-25]. In this study, stretching and strengthening consisted of low intensive activities as they were originally intended to induce interference effects while subjects were simultaneously conducting dual-task. Therefore, physical exercise did not need to be high intensive in the EG, which suggests that physical exercise did not considerably affect executive function.

Significantly decreased HbO_2 in the PFC during executive function testing was found in both groups after the 16-session's training. Generally, more increased $Hb0_2$ in the PFC during cognitive testing could be observed in older adults with MCI than healthy older adults as the PFC compensates other medial temporal lobe structures such as the hippocampus affected by MCI, which is called compensation effect [26]. Accordingly, when performing a cognitive task, the lower brain activity than before indicates that the neural efficiency is improved [4,27,28]. Indeed, previous studies reported that decreased activation in the PFC coupled with improved performances on cognitive tasks could be regarded as an improvement in neural efficiency. Therefore, in this study, decreased $Hb0_2$ in the PFC during executive function testing after the intervention implies the neural efficiency in the PFC is increased. Executive function mainly depends on the PFC and it has been proved by several neuroimaging studies [27,29,30]. In sum, in this study, the improvement of executive function could be considered as the results of the increase in the neural efficiency in the PFC, which suggests the effects of dual-task training underlying the neural efficiency improvement. Given that most previous studies present evidence on improving executive function using only paper-based neuropsychological assessments in clinical settings, the present study has the clinical implication in terms of providing the neural evidence as well as behavioral evidence.

However, there was no significant improvement in IADLs in both groups even though executive function is closely related with IADLs [31]. This result is not consistent with that of previous studies [4,31-33] and could be attributed by the fact that training sessions were not enough to improve IADL. Indeed, previous studies reported improvements in IADL after training sessions over 3 to 6 months [4,33]. In contrast, the present study introduced the 16 training sessions, which is the considerable difference compared to previous studies showing a transfer effects of dual-task training to IADLs. This finding implies that a total number of training sessions is one of the crucial factors to expect the transfer effect to IADLs.

This study has several limitations. First, no evidence for the dual-task training's transfer effects to daily life was found. Second, since long-term effects with follow-up assessments were not found, it was not elucidated how long effect could last. Third, activity in other regions involved in MCI was not investigated due to the relative small number of channels in the fNIRS device so other potential biomarkers of functional connectivity remain unclear. Finally, to control effects of cognitive or physical task on executive function, the additional group performing conventional cognitive or physical single-task training needs to be added to control.

In conclusion, this study confirmed that the dual-task training requires more executive challenges than the single-cognitive training focusing on executive process, which is supported by changes in activity in the PFC during cognitive testing. This finding suggests that the dual-task training is more effective in improving executive process for older adults with MCI than the single-cognitive training. However, in order to increase independence of IADLs in older adults with MCI, more ecological validated contents in the dual-task training need to be considered in the future with follow-up assessments.

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