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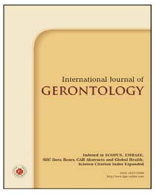

Original Article

Effects of Spatial Cognitive Training Using Virtual Reality on Hippocampal Functions and Prefrontal Cortex Activity in Older Adults with Mild Cognitive Impairment

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SUMMARY

Background: The effects of spatial cognitive training on hippocampal functions and prefrontal cortex (PFC) activity in older adults with mild cognitive impairment (MCI) are unclear yet. The purpose of this study was to investigate the effects of spatial cognitive training using virtual reality (VR) on hippocampal function and PFC activity in older adults with MCI.

Methods: Fifty older adults with MCI were randomly assigned to the experimental group (EG) performing spatial cognitive training using VR or the control group (CG) receiving computerized spatial cognitive training for a total of 24 sessions. To confirm the effects of spatial cognitive training using VR, the Weschsler Adult Intelligence Scale-Revised Block Design Test (WAIS-BDT) and the Seoul Verbal Learning Test (SVLT) were performed and oxygenated hemoglobin (HbO_2) was measured using a functional infrared spectroscopy (fNIRS) system.

Results: After 24 sessions, the EG showed significantly greater improvements in WAIS-BDT scores ($p < .001$, $\eta^2 = .495$), the SVLT scores ($p < .05$, $\eta^2 = .110$), and HbO_2 values ($p < .05$; $\varsigma^2 = 0.244$), compared to the CG.

Conclusion: Spatial cognitive training using VR could be clinically effective for improving hippocampal functions and PFC activity in older adults with MCI.

1. Introduction

To date, cognitive intervention used to delay cognitive decline or maintain cognitive function due to Alzheimer's disease (AD) has been reported to be ineffective.[1] This limitation of conventional cognitive intervention is largely explained by the fact that AD is already in progress at the time of the intervention, which limits the effectiveness of the intervention.[1]

Accordingly, as the interest in early intervention for AD has increased, management at the stage of mild cognitive impairment (MCI), which is the prodromal stage of AD, has gained a lot of attention.[2] Similar to AD, hippocampal atrophy is a hallmark of MCI, inducing declines in spatial cognition and episodic memory.[3,4] Indeed, spatial cognition and episodic memory have been found to be considerable predictors that distinguish patients with MCI from controls.[2,3] Specifically, even though hippocampal dysfunction was observed in both AD and MCI, AD showed greater volume deficits in the entorhinal cortex than in the hippocampus, which could be one point discriminating MCI from AD.[4] Therefore, cognitive training for hippocampal function in patients with MCI could be used to prevent the conversion from MCI to AD, which would reduce the enormous social costs of AD management.[5]

Recent studies have performed spatial cognitive training using virtual reality (VR) for high ecological validity.[6] Specifically, allocentric navigation strategy-based spatial cognitive training using VR was found to be more effective in improving hippocampal function since hippocampus activity corresponds to allocentric navigation compared to egocentric navigation.[3]

However, neuropsychological assessments were used to evaluate hippocampal functions as tools to investigate the effects of spatial cognitive training in patients with MCI.[3,6] Although previous studies reported improved performances on neuropsychological assessment,[2,6] they could not present changes in actual brain activity and thus, could not provide objective evidences on its effects.[7]

Among a variety of brain imaging devices, a functional near-infrared spectroscopy (fNIRS) system, which can observe brain activity via changes in hemoglobin levels, was applied to patients with MCI to investigate the effectiveness of cognitive training.[8] The fNIRS system is relatively easy to use and has superior temporal and spatial resolution compared to functional magnetic resonance imaging (fMRI), which means that the fNIRS system is a suitable method for monitoring brain changes in real-time.[8]

Neuroimaging studies indicated that the hippocampus has been identified to constitute neural circuits for hippocampal functions including spatial cognition and episodic memory with the prefrontal cortex (PFC), suggesting that PFC function could be regarded as a key factor in the effects of cognitive intervention for MCI.[9]

Thus, the primary objective of this study was to determine whether spatial cognitive training using VR could lead to enhanced hippocampal functions. The secondary objective was to confirm that spatial cognitive training using VR could decrease PFC activity during hippocampal functioning.

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2. Methods

2.1. Study design

This was a single-blind study, and the participants were randomly divided into the experimental group (EG) or the control group (CG) using random numbers generated by MATLAB (2012b, MathWorks, Inc., Natick, MA, USA). Two assessors with five years of clinical experience were blinded to the group allocation. This study was performed for eight weeks, and assessments were conducted before and after the 8-week training. This study was approved by the Institutional Review Board of Soonchunhyang University (202005-SB-040-5).

2.2. Participants

Older adults over 60 years with amnestic MCI were recruited from local community welfare centers in Seoul, South Korea. Amnestic MCI was defined according to a previous study.[10] The inclusion criteria were as follows: (a) subjective memory complaint, (b) objective memory impairment defined by a score of ≤ 7 on the Seoul Neuropsychological Screening Battery, (c) intact general cognitive function determined by a score of ≥ 24 on the Korean version of the Mini-Mental State Examination (MMSE-K), and (d) intact activities of daily living determined by a score of less than 1.5 standard deviations (16%) from norm on the Seoul instrumental activities of daily living score, considering subject's age, sex, and education levels. The exclusion criteria were as follows: (a) dementia diagnosed by a physician, (b) the presence of neurological or psychiatric disorders diagnosed by a physician, (c) moderate or severe depressive symptoms determined by a score of ≥ 18 on the Korean version of the Geriatric Depression Scale, (d) the presence of auditory or visual impairments diagnosed by a physician, and (e) participation in any programs to improve cognitive function within one month.

Sample size estimation was calculated using G*Power (Informer Technologies, Dusseldorf, Germany). Based on a previous study,[11] the effect size was set at 0.84 with the α error at a probability of 0.05 and the power at 0.90, resulting in a minimum of 25 subjects was required in each group.

2.3. Intervention

All sessions were implemented by an occupational therapist with eight years of clinical experience. All participants performed a total of 24 sessions lasted 30 minutes a session, three days a week for eight weeks.

The participants in the EG a performed three-dimensional spatial cognitive training program based on VR as the intervention and it ran on a desktop computer. They used a joystick to freely move in the VR environment and they were given an opportunity to undergo two sessions in an empty environment, allowing them to familiarize themselves with the environment and the control of the joystick until they felt sufficiently familiar before the training sessions. During the training sessions, they were immersed in one environment with boundary cues that prevented them from moving any further. No local landmarks were given during the training sessions, excluding compensatory navigation strategies. The participant's initial position was randomly located in the environment and they were instructed to look around. There was a gem at a certain point in the environment and they were asked to move toward the gem. Once they reached the gem, another gem was presented in a different location than the previous one and they were encouraged again to move toward the new gem in the same way as before. The gem would disappear after the participants reached it and the next gem in sequence would appear, resulting in participants got each gem in two different locations. After reaching the second gem, the participant was instructed to walk back to their initial location. Once they estimated that they had arrived at their initial location, they were asked to press a confirmation button on the joystick. Performance in the training sessions was recorded using the Euclidean distance between the estimated and actual initial location.

The participants in the CG performed a two-dimensional computerized spatial task. This task was implemented using a laptop with a stimulus display composed of a 5×5 grid, in which black circles were serially presented at different locations. Each circle was shown for three seconds and the circles were redistributed in each session. They were asked to memorize the locations of the circles within the grid and choose them with arrows and enter keys on the keyboard. In each session, the number of circles was determined according to the performance. Auditory and visual feedbacks on participant's performance were instantly presented during each session.

The level of difficulty of both cognitive tasks was adjusted to the participant's performance, requiring 80% task accuracy during all training sessions. The participants in both groups took a 3-minute rest to minimize their fatigue after 10 minutes of training. None of them showed adverse effects in using the computer. To maintain or facilitate the participant's adherence to each cognitive intervention, an attendance checklist was used, which contributed to ensuring that they never skipped the intervention.

2.4. Assessments

The neuropsychological assessments for assessing spatial cognition and episodic memory were performed before and after the intervention by two blinded assessors in a fixed order and they evaluated the same participants.

Spatial cognition was measured using the Wechsler Adult Intelligence Scale-Revised Block Design Test (WAIS-BDT). It involves arranging nine colored blocks to replicate 10 patterns within 120 seconds in order of ascending difficulty. The score ranges from 0 to 48, with higher scores meaning better spatial cognition.[12] The WAIS-BDT has been regarded to reflect spatial cognition,[13] heavily depending on hippocampal function. According to the cognitive map theory, the hippocampus specifically supports spatial information processing in contrast to other brain areas revealed by a study of a London taxi driver.[14]

The Seoul Verbal Learning Test (SVLT), standardized with 12 words in three semantic categories Korean people widely use in everyday life, was used to assess verbal episodic memory. The participants were asked to listen to the 12 words at 2 seconds interval and repeat them immediately three times. After 20 minutes, the participants were encouraged to recall the same words again regardless of the word order. A score of 1 was allocated for correct response with a total score of 12.[15] Since the hippocampus plays a crucial role in encoding and retrieving information, performance on verbal learning tests could be considered to reflect hippocampal function.[16]

PFC activity was measured with the OctaMon fNIRS system (Artinis, Netherlands) with near-infrared light that is transmitted at two wavelengths, 760 and 850 nm. The OctaMon uses a total of eight channels through a combination of light sources and detectors and is wirelessly connected to a computer to measure oxygenated hemoglobin (HbO_2) and deoxygenated hemoglobin (HHb) concentrations. Source and detector pairs were placed over the left (Fp1) and right (Fp2) frontal cortex regions that targeted the left and right dorsolateral PFC[17] according to the modified international EEG 10-20 system. Before applying the fNIRS system, the participants were asked to wipe their foreheads with alcohol and keep their hair from falling down. Additionally, by using a program that connected with the system, the source and detector pairs were placed in the same position. All data were sampled with a frequency of 10 Hz.[18]

In this study, while performing the WAIT-BDT and the SVLT, PFC activity was measured. Since HbO_2 concentration changes indicate the amount of hemoglobin absorbed during stimulation of the brain, it could represent brain activity.[18] The activity was analyzed using only HbO_2 as it sensitively assesses cognitive function compared to HHb.[18]

2.5. Statistical analyses

All data were analyzed using SPSS version 25.0 (SPSS Inc., Chicago, IL, USA). The mean and standard deviation of the cognitive outcomes and HbO_2 levels were calculated. The Kolmogorov-Smirnov test was conducted to identify the normal distribution of all measurements. To compare the characteristics between the two groups, independent-sample *t*-tests and chi-squared tests were used.

After the 8-week interventions, the differences between the groups were investigated using a 2 by 2 mixed model repeated-measures analysis of covariance with time (pre- and post-intervention) as the within-group variable and intervention as the between-subject variable. The effect size (ES) of each intervention group was calculated using partial η^2,[19] and statistical significance was set at $p < 0.05$.

3. Results

3.1. Subject characteristics

A total of 52 elderly people with cognitive impairment were selected from 74 elderly people in a local community welfare center. Among them, 50 were finally selected according to the inclusion and exclusion criteria as two subjects additionally expressed their refusal to participate in addition to one participant who refused to participate (Figure 1). They were randomly allocated to groups of 25. No significant differences in the general characteristics of the participants were found ($p > 0.05$) (Table 1).

3.2. Spatial cognition

Table 2 reveals that there was a significant group × time interaction for the WAIS-BDT scores ($p < 0.001$; $\eta^2 = 0.495$), suggesting that the participants in the EG gained significantly improved their spatial cognition compared to the CG (Table 2).

3.3. Episodic memory

The findings indicated a significant group × time interaction for SVLT scores ($p < 0.05$; $\eta^2 = 0.110$), which suggests that the participants in the EG achieved a moderate improvement in episodic memory compared to the CG (Table 2).

Table 1
General characteristics of subjects (N = 50).

	EG (n = 25)	CG (n = 25)	χ2/t	*p*
Gender			0.081	0.777
Male	11	12		
Female	14	13		
Age (year)	68.27 ± 3.97	70.05 ± 3.84	-1.502	0.141
Years of education	8.05 ± 3.74	6.95 ± 3.51	0.996	0.325
MMSE-K (score)	26.59 ± 1.70	26.32 ± 1.28	0.598	0.553

Values are expressed as mean ± SD.
EG, experimental group; CG, control group; MMSE-K, Korean version of mini-mental state examination.

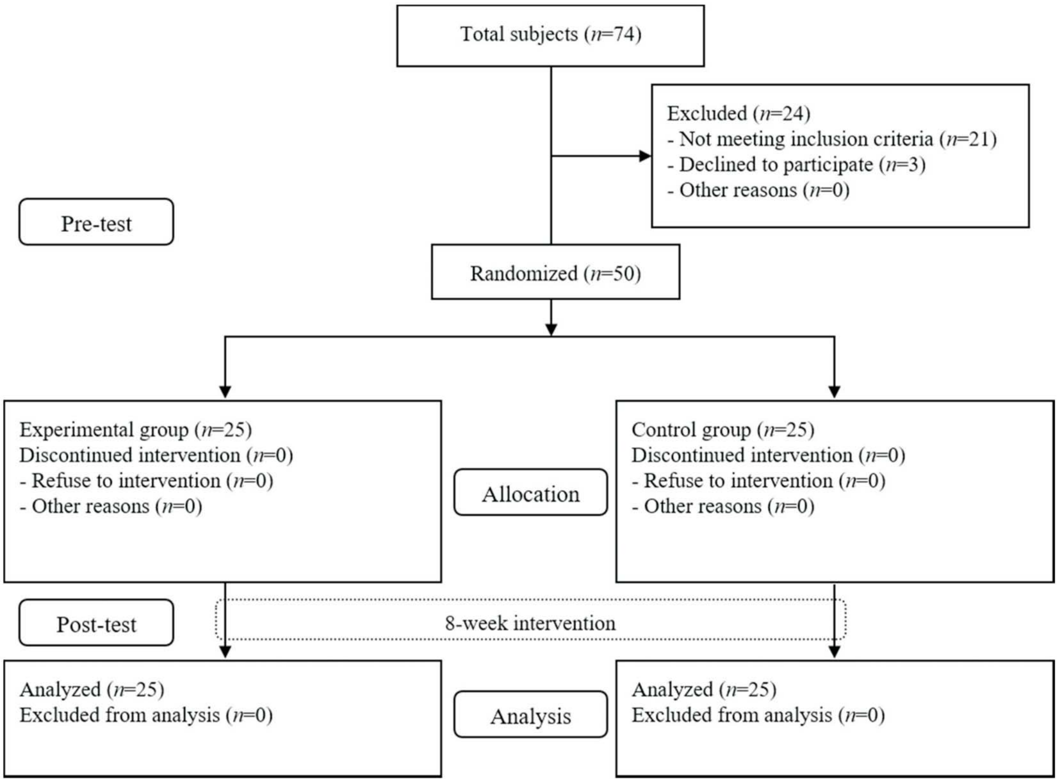

Figure 1. Flow diagram of subjects in this study.

Table 2
Changes in hippocampal function and prefrontal cortex activity (N = 50).

Variables	EG (n = 25)			CG (n = 25)			Between-group difference (95% CI)	η^2
	Pre	Post	Change value	Pre	Post	Change value		
Spatial cognition								
WAIS-BDT (score)	25.41 ± 2.70	29.09 ± 2.42	3.68 ± 1.52	25.45 ± 1.96	26.64 ± 2.19	1.18 ± 1.00	2.50 (1.71 to 3.28)***	0.495
Episodic memory								
SVLT (score)	5.68 ± 1.04	6.59 ± 1.00	0.90 ± 0.97	5.18 ± 1.29	5.45 ± 1.01	0.27 ± 0.88	0.63 (0.07 to 1.20)*	0.110
PFC activity								
During WAIS-BDT (μM)	0.375 ± 0.08	0.151 ± .021	0.222 ± 0.088	0.222 ± 0.066	0.158 ± 0.026	0.064 ± 0.067	0.159 (0.111 to 0.207)***	0.517
During SVLT (μM)	0.385 ± 0.104	0.158 ± 0.200	0.200 ± 0.102	0.248 ± 0.096	0.159 ± 0.200	0.089 ± 0.097	0.110 (0.050 to 0.171)**	0.244

Values are expressed as mean ± SD.

CG, control group; EG, experimental group; PFC, prefrontal cortex; SVLT, Seoul Verbal Learning Test; WAIS-BDT, Wechsler Adult Intelligence Scale-Block Design Test.

Significant group × time interaction (*$p < 0.05$, **$p < 0.01$, *** $p < 0.001$).

3.4. Prefrontal cortex activity

There was a significant group × time interaction for PFC activity, which indicated that HbO_2 decreased in the PFC while performing spatial cognition ($p < 0.001$; $\eta^2 = 0.517$) and episodic memory ($p < 0.01$; $\eta^2 = 0.244$). This finding indicated that the participants in the EG showed a large decrease in PFC activity during hippocampal functioning compared to the CG (Table 2).

4. Discussion

This study investigated the effects of spatial cognitive training based on VR on hippocampal function and PFC activity in older adults with MCI. The results showed that spatial cognitive training based on VR induced enhanced spatial cognition and episodic memory and decreased PFC activity during hippocampal function after 8-week of training, which is consistent with previous studies.[2,11]

In this study, both groups showed positive effects on spatial cognition. A prior study indicated that the hippocampal volume of London taxi drivers was larger than that of bus drivers, suggesting that spatial cognition depends on navigational experiences.[11,14] Thus, spatial cognitive training involving repetitive spatial experiences could be effective for improving spatial cognition, which supports the findings of this study. Indeed, a previous neuroimaging study reported that spatial cognition mainly depends on the hippocampus.[20] Accordingly, spatial navigation has been clinically used for improving spatial cognition in older adults with MCI.[6] Interestingly, in this study, episodic memory was also enhanced after the intervention. A prior study has shown that hippocampal functions involved both spatial cognition and episodic memory.[11] This finding suggests that improved hippocampal function after spatial cognitive training might positively affect episodic memory,[21] suggesting that it has an effect to transfer to episodic memory, supported by a previous study indicating that spatial cognitive training was effective in improving episodic memory, supporting the results of this study.[11]

Since most prior studies have conducted neuropsychological assessments to investigate the effects of spatial cognitive training on hippocampal functions,[22,23] they could not successfully demonstrate its neural effects. In contrast, this study confirmed decreased HbO_2 levels in the PFC during hippocampal functioning, coupled with improved performance in spatial cognition and episodic memory tasks. Decreased activity in the brain after the intervention could be considered to be training-induced increases in neural efficiency. In other words, the participants could achieve higher levels of hippocampal function with a lower amount of energy.[24] A previous study on the concept of neural efficiency reported decreased activity coupled with improved cognitive function in older adults after training, supporting the present study.[24] The increased efficiency in the PFC could be attributed to the prefrontal-hippocampal circuit, which supports the acquisition of spatial memory and episodic memory considered to be hippocampal functions.[3,9] Indeed, a growing body of evidences has indicated that PFC lesions negatively affected both spatial cognition and episodic memory.[25,26] Therefore, spatial cognitive training might improve neural efficiency in the prefrontal-hippocampal circuit and hippocampal function in older adults with MCI.

Spatial cognition strategy can be divided into allocentric and egocentric strategies. In this study, the participants in the EG performed VR-based spatial tasks using allocentric strategy depending on the processing of relationships among a goal and clues to determine the goal location, while those in the CG conducted spatial cognitive tasks using an egocentric strategy using the self as a reference for navigating a route to memorize spatial locations.[27] A previous study reported that allocentric strategy-based navigation was regulated through the hippocampus,[28] whereas egocentric strategy-based navigation relied on the striatum rather than the hippocampus.[29] Given that the EG showed a greater improvement in both spatial cognition and episodic memory than the CG, it can be said that allocentric strategy-based navigation training was appropriate for older adults with MCI characterized by atrophy of the hippocampus.

This study, however, had some limitations. First, due to the relatively small number of fNIRS device channels, PFC activity was not analyzed in the sub-regions of the PFC. Considering that the dorsolateral PFC was found to be correlated with spatial cognition and episodic memory compared to the ventromedial PFC,[30] it is necessary to compare the HbO_2 levels between both regions. Second, although the level of difficulty of both cognitive tasks was adjusted to the participant's performance, the difference in nature between both tasks could influence the effect of the cognitive interventions. Finally, even though a VR program was used to secure ecological validity, there is a difference between VR and the real world navigation with actual movement including the head and lower limbs,[6] which limits generalizing the finding of this study. In addition, actual navigation is depending on the entorhinal cortex function which could identify the very earliest state of AD prior to the hippocampus.[6] Therefore, in the future, studies on spatial navigation with actual movement with more fNIRS channels are needed to be more ecological validated findings and clarify the robustness of the current findings.

5. Conclusion

The study demonstrated that spatial cognitive training using VR is effective for improving hippocampal function and neural efficiency in the PFC. Given that the neural correlates with its effects have been rarely investigated, this finding has considerable clinical implications. This study also suggested that the application of the fNIRS system as a tool to investigate the effects of spatial cognitive training.

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Conflict of interest

The author declares that there is no conflict of interest.

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