

Cognitive training in fully immersive virtual reality improves visuospatial function and fronto-occipital functional connectivity in a pre-dementia state: A randomized controlled trial

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Research

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Abstract

Background

Cognitive training has potential in staving off cognitive decline. Recent studies using semi-immersive virtual reality (VR)-assisted cognitive training have shown inconsistent results. We aimed to test the hypothesis that cognitive training using fully immersive VR, which may facilitate visuospatial process, would improve visuospatial function, comprehensive neuropsychological functions, psychiatric symptoms, and functional connectivity (FC) of the visual network in the resting brain in pre-dementia state.

Methods

Participants with subjective cognitive decline (SCD) or mild cognitive impairment (MCI) were randomly assigned to a VR (n = 23) or a control group (n = 18). VR group participants received multi-domain cognitive training in a fully immersive VR environment twice a week for one month. Both groups were evaluated for cognitive function using comprehensive neuropsychological tests including the Rey-Osterrieth Complex Figure Test (RCFT) copy task, for psychiatric symptoms using the Geriatric Depression Scale, Positive and Negative Affect Schedule-positive affect (PANAS), Apathy Evaluation Scale (AES), and Quality of Life-Alzheimer's disease, as well as resting-state functional magnetic resonance imaging (rsfMRI) at baseline and post-training. Repeated measures analyses of variance were used to compare the effect of the cognitive training between the groups. Seed-to-voxel based analyses were used to find the cognitive improvement-related FC in the visual network of the brain.

Results

After VR cognitive training, the VR group showed improvements in the RCFT copy task ($F = 15.44$, $p < 0.001$), the PANAS-positive ($F = 8.28$, $p < 0.001$), and the AES ($F = 21.28$, $p = 0.006$) compared to the control group. rsfMRI revealed that improvement in the RCFT copy task was associated with frontal-occipital FC increase in the VR group compared to the control group.

Conclusions and relevance

Fully immersive VR cognitive training had positive effects on visuospatial function, positive affect, apathy, and frontal-occipital FC in older adults at pre-dementia state. Future trials using VR cognitive training with larger sample sizes and more sophisticated design over a longer duration may observe greater improvements in cognition, psychiatric symptoms, and brain FC.

Trial registration

Clinical Research Information Service, conforming to the World Health Organization International Clinical Trials Registry Platform (WHO-ICTRP), KCT0005243. Registered 22 July 2020 – retrospectively registered, https://cris.nih.go.kr/cris/search/search_result_st01_en.jsp?seq=17055<ype=&rtype=

Background

Dementia is one of the major neurodegenerative diseases, affecting approximately 10% of elderly people [1]. It manifests as cognitive, psychological, and behavioural deterioration, ultimately resulting in functional impairments and disability [2]. The individual and societal burden of dementia is accelerating more quickly than that of any other disease [1, 3], but the unclear mechanisms and multifactorial pathology underlying the development and progression of dementia have ensured that only symptomatic treatments are available [4].

To date, many researchers have believed that prevention is crucial, and they have identified risk and protective factors associated with dementia, as well as preventive strategies [5]. A recent large study suggested that a third of Alzheimer's disease (AD) cases are attributable to potentially modifiable risk factors such as educational attainment, vascular factors, and depression [6]. Additionally, lifelong exposure to cognitively and mentally engaging activities is known to protect against cognitive decline [7], and the performance of cognitively stimulating activities in old age has been found to lead to better cognitive function [8]. Accordingly, recent cognitive training studies have shown that repeated practice of cognitive exercises to restore brain and cognitive reserves resulted in small to moderate positive improvements in cognition in patients with mild to moderate dementia [9].

Advances in computer sciences and information and communication technology (ICT) have resulted in the increased availability and accessibility of computerized cognitive training. Although conclusive results have yet to be found, preliminary studies have reported improvements in trained and non-trained cognition and enhanced brain activity in related regions after computerized cognitive training in those with mild cognitive impairment (MCI) [10–12]. Working memory training was effective in improving verbal memory and hippocampal activation in MCI patients [11], and exposure to a driving video game resulted in an increased ability to control the vehicle that was related to midline frontal theta power in older adults [12]. Moreover, emerging ICT applications using virtual reality (VR) have resulted in evolutions in healthcare, including cognitive and behavioural therapy [13]. VR can offer interventions in flexible and real-world-like environments, facilitating visuospatial function through learning and transference outcomes [14], and highlighting a role for cognitive training in a virtual environment in basic research and clinical practice. Still, there is lack of knowledge and a dearth of experiments on cognitive training using VR, especially the fully immersive type [15, 16], so further studies are needed to ascertain its potential therapeutic efficacy.

There has been a recent increase in neuroimaging studies attempting to reveal the underlying neural mechanisms associated with cognitive decline [17, 18]. More recently, owing to software improvements, functional connectivity (FC) studies using resting state functional magnetic resonance imaging (rsfMRI) have allowed for whole-brain analyses to identify networks temporally coinciding with spatially distant neurophysiological events that are intrinsically coherent during a resting state, such as the default-mode network [19]. We considered that FC studies using rsfMRI may be able to reveal the neural mechanism, especially in the visual network, responsible for the observed cognitive improvements following VR

cognitive training, as such training is based on the cognitive reserve hypothesis associated with functional neural networks [20].

To determine the efficacy and mechanisms of VR cognitive training in a pre-dementia state, we conducted a randomized, controlled trial comparing a VR training and a usual care control group. We aimed to determine the effects of VR multidomain cognitive training on visuospatial function, comprehensive neuropsychological function, and psychiatric symptoms in a pre-dementia state. In addition, we aimed to test the hypothesis that cognitive improvement would be related to increased FC in the visual network of the brain.

Materials And Methods

Participants

Participants over 60 years of age who were in a pre-dementia state (ranging from subjective cognitive decline [SCD] to MCI) were prospectively recruited from May 2019 to December 2019 from the memory clinic at Gachon University Gil Medical Center, Republic of Korea. Among 58 participants who were assessed for eligibility through the use of structured clinical interviews and brain MRI, four participants were excluded due to cerebral infarction on MRI (n = 2), severe white matter hyperintensity on MRI (n = 1), and history of a recent dental implant surgery (n = 1). Nine participants voluntarily withdrew from the study due to acute medical condition (n = 2), hospitalisation of a spouse (n = 1), scheduling conflict (n = 1), and unknown personal reasons (n = 5). A total of 45 participants were randomly assigned to either a VR group or a control group.

All participants had subjective cognitive complaints, including memory decline, but did not meet the criteria for diagnosis of a major neurocognitive disorder based on the Diagnostic and Statistical Manual of Mental Disorders (5th edition) [2]. Participants were classified as having SCD according to the research criteria for SCD and a stage 2 or lower based on the Global Deterioration Scale (GDS) [21, 22]. Participants were classified as having MCI according to Petersen's criteria for MCI [23]. Participants were interviewed by a board-certified psychiatrist (JM Kang) with over five years of experience in geriatric psychiatry and treatment of dementia, and the diagnoses were confirmed.

The exclusion criteria for participants were as follows: (i) Korean version of Mini-Mental State Examination (MMSE) score < 20; (ii) comorbidity of severe medical or surgical conditions; (iii) major psychiatric disorders; (iv) history of any kind of dementia; (v) history of neurodegenerative disorders including Creutzfeldt-Jakob disease, Pick's disease, Huntington's disease, Parkinson's disease, inflammation associated with human immunodeficiency viruses, and syphilis; (vi) structural abnormalities in MRI such as intracranial haemorrhage, cerebral, cerebellar, or brainstem infarction, hydrocephalus, traumatic brain injury, severe white matter hyperintensity, tumours, multiple sclerosis, or vasculitis.

All participants provided written informed consent, and the Institutional Review Board of Gachon University Gil Medical Center, Republic of Korea approved this study.

Study design

This study was an open-label, randomized, controlled trial (KCT0005243) investigating the efficacy of fully immersive VR cognitive training program on visuospatial function in old individuals over 60 years of age who were at risk for dementia. Participants were randomly assigned to one of two groups: a VR group and a control group. The unblinded randomization was conducted by drawing lots. Over the total six-week study period, participants in both groups were evaluated for visuospatial function, comprehensive neuropsychological function, and psychiatric symptoms, and rsfMRI in the first and the sixth weeks. From the second to the fifth week, participants in the VR group underwent VR cognitive training two times per week, for a total of eight sessions and participants in the control group received usual care.

VR Cognitive training

The VR cognitive training program was developed as multidomain cognitive training program by authors who are board-certified geriatric neuropsychiatrists and clinical neuropsychologists with expertise. The VR cognitive training program consisted of multiple games involving multidomain cognitive tasks to assess: (i) attention (to find differences); (ii) executive function and memory (to select items needed to perform certain tasks); (iii) working memory and ability to perform mathematical calculations (to prepare an exact amount of money); (iv) visuospatial orientation (to find a path using a memorized map); (v) visuoconstruction (to spatially place furniture exactly based on a memorized drawing); (vi) verbal memory (to remember certain words); (vii) visual memory (to remember specific flags and symbols); and (viii) processing speed and working memory (to catch animals in a certain order). All virtual environments were fully immersive 3D settings allowing for feelings of increased presence and visuospatial stimulation, and training was accompanied by game elements to increase the interest and motivation of the participants. Representative images of the VR training program are presented in Fig S1.

Each session was approximately 20–30 minutes in duration. The VR training was administered through a head-mounted Oculus Rift CV1 display, with Oculus Touch controllers in both the participants' hands. Each training session was conducted with the participant in a seated position, and the difficulty level increased throughout the study period from easy to difficult (levels 1–4), with two sessions at each difficulty level. Participants in the control group did not receive VR cognitive training. All procedures during VR cognitive training were guided by certified clinical neuropsychologist (SY Lee) in addition to automatic verbal and visual messages from the program.

Procedures and outcome measures

All participants underwent comprehensive neuropsychological tests and psychiatric scales, as well as rsfMRI at baseline and after the VR cognitive training period. Baseline evaluations of diagnostic criteria included global and functional scales such as the Korean version of the MMSE, the Clinical Dementia

Rating (CDR), CDR Sum of Boxes (CDR-SOB), GDS, and instrumental activities of daily living (IADL) scales.

The primary outcome measure was the effect on visuospatial function of the VR cognitive training as measure by the Rey-Osterrieth Complex Figure Test (RCFT) copy task, which has been validated in a Korean population [24, 25].

The secondary outcomes assessed the effect on global cognition, comprehensive neuropsychological function, depression, apathy, affect, quality of life (QoL), and FC in the visual network of the brain.

The neuropsychological tests consisted of MMSE and subtests from the comprehensive neuropsychological test battery [25]. Verbal memory was assessed by measuring performance on three tasks of the Seoul Verbal Learning Test (SVLT): immediate recall, delayed recall after 20 minutes, and recognition [25]. The Korean version of the Boston Naming Test (K-BNT) was used to assess language ability [25, 26]. Frontal executive function was assessed by phonemic word fluency testing, the Trail Making Test parts A and B (TMT-A and B), and the Stroop Color Test [25]. All neuropsychological test results were adjusted for age and years of education, and presented as standardized z-scores.

Non-cognitive psychiatric symptoms that typically start to decline in the early stage of dementia were also assessed [27]. Depressive symptoms were evaluated by the validated 30-item Geriatric Depression Scale (GDepS), including questions pertaining to mood, anxiety, energy, satisfaction, hopefulness, inattention, and sleep quality [28, 29]. GDepS asks a series of binary yes/no questions (scored as 1 or 0, respectively), with higher scores being indicative of severe depression. Apathy was evaluated by the validated 18-item Apathy Evaluation Scale (AES), including items pertaining to emotional affect, behaviour, and cognitive apathy [30, 31]. Items of the AES are rated on a 4-point Likert scale, with a low score being indicative of severe apathy. Affect was evaluated by the Positive and Negative Affect Schedule (PANAS), which consists of ten items to assess positive affect (PANAS-P) measures such as alertness and enthusiasm, and ten items to assess negative affect (PANAS-N) such as lethargy and feelings of sadness [32, 33]. Each of the items of the PANAS is rated from 1 (not at all) to 5 (very much), with higher scores being indicative of higher affect. Participants' QoL was evaluated by the QoL-Alzheimer's disease (QoL-AD) scale, which has been validated for use in people with dementia, with 13 subjective rating items to assess physical health, living situation, relationships with friends, and the ability to engage in leisure activities [34, 35]. Items of the QoL-AD are assessed on a 4-point Likert scale, with higher scores being indicative of a better quality of life.

MRI acquisition

A 3-Tesla whole-body Siemens scanner (TrioTim syngo; Siemens, Erlangen, Germany) was used for functional image acquisition with an interleaved T2*-weighted echo-planar imaging (EPI) gradient echo sequence (repetition time/ echo time (TR/TE) = 2500 ms/25 ms, flip angle = 90°; slice thickness = 3.5 mm; in-plane resolution = 3.5 × 3.5 mm; matrix size = 64 × 64) with a 12-channel birdcage head coil. For each participant, 160 functional volumes were acquired at the pre-training and post-training

timepoints. After fMRI, an anatomical image was acquired using a high, T1-weighted, 3D gradient echo pulse sequence with magnetization prepared rapid gradient-echo (TR/TE/TI = 1900 ms / 3.3 ms / 900 ms; flip angle = 9°; slice thickness = 1.0 mm, in-plane resolution = 0.5 × 0.5 mm, matrix size = 416 × 512). T1-weighted images were acquired only at the pre-training timepoint.

rsfMRI FC analyses

Pre-processing of the rsfMRI data was done using Statistical Parametric Mapping software version 12 (SPM12; Wellcome Trust Centre for Neuroimaging; London, UK). First, a slice-timing correction was applied and the centre of each image was relocated near the anterior commissure, then rsfMRI and T1-weighted images were imported into the CONN FC toolbox v19c (<http://www.nitrc.org/projects/conn>) [36] for further preprocessing. To correct for between-scan rigid body motion, the functional images were realigned to the first image in the time series. The functional images were co-registered with anatomical images, then spatially normalized to the Montreal Neurological Institute (MNI) space using a transformation matrix derived from the T1-weighted anatomical image segmentation. The functional images were then resliced to 2 × 2 × 2 mm and spatially smoothed using an 8 mm full width at half maximum Gaussian kernel.

All preprocessed fMRI images were band-pass filtered (0.008–0.09 Hz), and physiological and other spurious noise sources in the blood oxygenation level-dependent (BOLD) signal were removed using the anatomical component-based noise correction (CompCor) strategy implemented in CONN [37]. Outliers were calculated using the Artifact Detection Tools (ART) toolbox [38] and six motion correction parameters obtained from realignment were also modelled as nuisance covariates. The seed-to-voxel analyses were performed in the visual network with four cortical seed regions (right visual lateral, left visual lateral, visual medial, and visual occipital cortices) with predefined regions of interest (ROIs) based on the Harvard-Oxford atlas (fMRIB Software Library, Oxford, UK) [39]. The mean time series for each seed region was calculated and then correlated with the time courses of all other voxels in the brain for each participant.

Sample calculation and statistical analyses

Sample calculation was based on a recent meta-analysis on the effectiveness of VR for people with MCI or dementia that produced small-to-medium effect sizes using random-effects model (effect size = 0.29) from a total of 11 studies [15]. Assuming an attrition rate of 20%, a total sample size of 32 patients (16 per treatment arm) would provide 0.8 power and at two-sided alpha error of 0.05. Power analysis was conducted with G*Power software version 3.1.9.2.

Comparisons of demographic and clinical variables between the two groups were conducted using independent t-tests or chi-square tests. In order to compare the effects of the VR cognitive training on neuropsychological function and psychiatric symptom scales between the two groups, repeated measures analyses of variance (ANOVAs) were used. All statistical analyses were conducted with Statistical Package for Social Sciences (SPSS) software version 23 (SPSS Inc, Chicago, IL, USA), with a significance level of $p < 0.05$ (two-tailed).

For rsfMRI data, Pearson's correlation coefficients were converted to normally distributed scores using the Fisher's r-to-z transformation. Group-level comparisons between the VR and control groups were carried out using a general linear model in which improved cognitive task score was used as an explanatory variable and the post-training minus pre-training Z-transformation value as a dependent variable after adjusting age, sex, years of education, and IADL. The statistical thresholds for significance were set at voxel-wise uncorrected $P < 0.001$ and cluster-wise corrected $q < 0.05$ to correct for false positive rates.

Results

Participants

Of 45 participants who were randomly allocated to VR ($n = 25$) or control group ($n = 20$), 41 participants completed the study. After allocation, two participants of the VR group were dropped out from the study due to dizziness during the first session ($n = 1$) and unfamiliarity to the VR machine during the first session ($n = 1$). Two participants of the control group were dropped out because of hospitalisation due to a traffic accident ($n = 1$) and an unknown personal reason ($n = 1$). Ultimately, 41 participants were included in the analyses. Trial flow chart is presented at Fig. 1.

Demographic and clinical characteristics

Table 1 presents the detailed demographic and clinical characteristics of the study participants. Among the 41 participants, 23 (56%) were assigned to the VR group and 18 (44%) were assigned to the control group. Participants were 74.51 ± 5.81 years of age and were predominantly female (70.7%). No group differences were found in the baseline diagnostic evaluation.

Table 1
Demographic and clinical information of all study participants

	Total (n = 41)	VR (n = 23)	Control (n = 18)	U or χ^2	P
Age (years)	74.51 ± 5.81	75.48 ± 4.67	73.28 ± 6.96	-1.13	0.258
Sex (female; n)	29 (70.7%)	17 (73.9%)	12 (66.7%)	0.26	0.613
Education (years)	8.07 ± 4.39	7.70 ± 4.10	8.56 ± 4.83	-0.01	0.989
MMSE	26.24 ± 2.85	26.22 ± 2.91	26.28 ± 2.87	0.09	0.926
CDR	0.41 ± 0.22	0.41 ± 0.19	0.42 ± 0.26	-0.02	0.985
CDR-SOB	0.92 ± 1.00	0.98 ± 0.85	0.83 ± 1.19	-1.24	0.213
GDS	2.20 ± 0.78	2.26 ± 0.75	2.11 ± 0.83	-0.78	0.438
IADL	0.13 ± 0.24	0.14 ± 0.21	0.11 ± 0.28	-1.09	0.274

Data are presented as means ± standard deviations or numbers (%).

Mann-Whitney U tests were used for all group comparisons, except for sex, which was compared using the Pearson's chi-square test. ^a $P < 0.05$.

VR = virtual reality; MMSE = Mini-Mental State Examination; CDR = Clinical Dementia Rating; CDR-SOB = CDR–Sum of Boxes; GDS = Global Deterioration Scale; IADL = Instrumental activities of daily living

Time and group differences of neuropsychological test results

Table 2 shows the comparisons between the pre- and post-training neuropsychological test results within groups, as well as group differences in the effects of VR cognitive training. VR training resulted in improvements in the RCFT copy task ($t = -3.50$, $p = 0.002$), the K-BNT ($t = -4.08$, $p < 0.001$), the SVLT immediate recall ($t = -3.10$, $p = 0.005$) and delayed recall ($t = -4.59$, $p < 0.001$) tasks, and the TMT-B ($t = -2.30$, $p = 0.031$). In the control group, there was a decline in performance on the RCFT copy task ($t = 2.15$, $p = 0.046$) and improvements in SVLT immediate recall ($t = -2.29$, $p = 0.035$) and delayed recall ($t = -3.21$, $p = 0.005$) tasks. A difference between the VR and control group was found only for the RCFT copy task ($F = 15.44$, $p < 0.001$).

Table 2
Group comparisons of neuropsychological test results pre- and post-VR cognitive training.

	Group	Pre-training	Post-training	Within groups Pre- vs Post-		Between groups interaction		
				t	P	F	P	η^2
Visuospatial function								
RCFT copy	VR (n = 23)	-0.31 ± 1.09	0.22 ± 0.78	-3.50	0.002 ^a	15.44	< 0.001 ^a	0.284
	Control (n = 18)	-0.07 ± 1.14	-0.47 ± 1.22	2.15	0.046 ^a			
Global cognition								
MMSE	VR	26.22 ± 2.91	25.87 ± 3.36	0.97	0.343	1.73	0.196	0.042
	Control	26.28 ± 2.87	26.67 ± 3.09	-0.89	0.385			
Attention								
Digit span, Forward	VR	-0.11 ± 1.21	-0.24 ± 0.87	0.57	0.574	1.44	0.237	0.036
	Control	-0.08 ± 1.08	0.15 ± 1.03	-1.42	0.175			
Digit span, Backward	VR	-0.09 ± 0.99	-0.15 ± 0.92	0.23	0.821	0.01	0.916	< 0.001
	Control	-0.23 ± 1.26	-0.25 ± 0.82	0.08	0.941			
Language and related functions								
K-BNT	VR	-0.23 ± 1.08	0.19 ± 1.02	-4.08	< 0.001 ^a	1.77	0.191	0.044
	Control	-0.15 ± 1.00	-0.01 ± 1.37	-0.72	0.483			
Verbal memory								
SVLT, Immediate Recall	VR	0.23 ± 0.10	0.67 ± 1.24	-3.10	0.005 ^a	1.43	0.239	0.035
	Control	0.30 ± 0.83	0.52 ± 0.89	-2.29	0.035 ^a			
SVLT, Delayed	VR	-0.10 ± 1.40	0.66 ± 1.37	-4.59	< 0.001 ^a	1.71	0.199	0.042

Recall	Group	Pre-training	Post-training	Within groups		Between groups interaction		
				Pre- vs Post-		F	P	η^2
				t	P			
	Control	0.12 ± 0.97	0.58 ± 0.94	-3.21	0.005 ^a			
SVLT,	VR	0.29 ± 1.39	0.48 ± 1.30	-0.93	0.363	0.88	0.354	0.022
Recognition	Control	0.37 ± 1.01	0.29 ± 1.07	0.41	0.688			
Frontal executive function								
COWAT,	VR	-0.25 ± 0.99	-0.44 ± 1.17	1.01	0.324	0.00	0.956	< 0.001
Semantic Fluency	Control	-0.41 ± 1.00	-0.58 ± 0.88	1.09	0.290			
COWAT,	VR	-0.35 ± 0.88	-0.41 ± 0.78	0.39	0.703	3.16	0.083	0.075
Phonemic Fluency	Control	-0.09 ± 0.82	0.27 ± 1.01	-1.89	0.076			
Stroop Test	VR	-0.01 ± 1.12	0.32 ± 1.04	-1.99	0.059	0.30	0.588	0.008
Colour reading	Control	-0.01 ± 0.85	0.16 ± 1.21	-0.64	0.533			
TMT-A	VR	0.13 ± 0.58	0.12 ± 0.64	0.10	0.925	1.26	0.269	0.031
	Control	-0.87 ± 4.19	-0.38 ± 3.53	-1.00	0.331			
TMT-B	VR	-1.43 ± 2.04	-0.64 ± 1.74	-2.30	0.031 ^a	3.23	0.080	0.077
	Control	-0.55 ± 1.52	-0.55 ± 1.62	0.01	0.996			
<p>Data are presented as means ± standard deviations. All data are represented as age- and years of education-adjusted z-scores. Repeated measures ANOVAs were used for statistical comparisons. ^a $P < 0.05$.</p> <p>VR = virtual reality; MMSE = Mini-Mental State Examination; K-BNT = Korean version of the Boston Naming Test; RCFT = Rey-Osterrieth Complex Figure Test; SVLT = Seoul Verbal Learning Test; COWAT = Controlled Oral Word Association Test; TMT-A = Trail Making Test type A; TMT-B = Trail Making Test type B.</p>								

Time and group differences of psychiatric symptoms

Table 3 shows the comparisons between the pre- and post-training measures based on psychiatric symptoms within groups, as well as group differences in the effects of VR cognitive training. There were significant improvements in GDepS ($t = 2.46$, $p = 0.022$), AES ($t = -3.04$, $p = 0.006$), and PANAS-P ($t = -2.71$, $p = 0.013$) scores in the VR group after training. In the control group, there was a significant decline in

PANAS-P ($t = 4.63, p < 0.001$) scores compared to baseline. Group differences were found in the AES ($F = 8.28, p = 0.006$) and PANAS-P ($F = 21.28, p < 0.001$) measures.

Table 3

Group comparisons of depressive symptoms, apathy, affect, and QoL pre- and post-VR cognitive training.

	Group	Pre-training	Post-training	Within groups Pre- vs Post-		Between groups interaction		
				t	P	F	P	η^2
GDepS	VR (n = 23)	15.00 ± 6.08	13.26 ± 6.49	2.46	0.022 ^a	1.24	0.272	0.031
	Control (n = 18)	12.17 ± 6.85	11.72 ± 7.18	0.47	0.647			
AES	VR	47.43 ± 10.20	54.35 ± 9.41	-3.04	0.006 ^a	8.28	0.006 ^a	0.175
	Control	52.83 ± 9.38	51.22 ± 8.72	0.98	0.343			
PANAS-P	VR	17.00 ± 6.28	21.43 ± 7.27	-2.71	0.013 ^a	21.28	< 0.001 ^a	0.353
	Control	21.83 ± 7.48	16.50 ± 6.51	4.63	< 0.001 ^a			
PANAS-N	VR	18.22 ± 7.09	16.30 ± 6.35	0.97	0.341	1.89	0.177	0.046
	Control	18.89 ± 5.31	20.44 ± 8.42	-1.16	0.262			
QoL-AD	VR	31.04 ± 4.69	32.26 ± 4.96	-1.23	0.234	3.02	0.090	0.072
	Control	34.94 ± 9.43	32.72 ± 6.54	1.21	0.245			

Data are presented as means ± standard deviations.

Repeated measures ANOVAs were used for statistical comparisons. ^a $P < 0.05$

QoL = quality of life; VR = virtual reality; GDepS = Geriatric Depression Scale; AES = Apathy Evaluation Scale; PANAS-P = Positive and Negative Affect Schedule-positive affect; PANAS-N = Positive and Negative Affect Schedule-negative affect; QoL-AD = QoL-Alzheimer's disease

Increased functional connectivity in fMRI

We investigated brain FC in the visual network associated with performing the RCFT copy take using CONN software's the FC toolbox (<http://www.nitrc.org/projects/conn>). The areas with significantly increased connectivity in the seed-to-voxel visual networks are presented in Table 4: a. from the right

visual lateral cortices to the (i) left paracingulate gyrus, (ii) left frontal pole, (iii) right paracingulate gyrus, (iv) anterior cingulate gyrus, and white matter; b. from the visual medial cortices to the (i) right insular cortex, (ii) right frontal pole, (iii) right frontal operculum cortex, (iv) right caudate, (v) right putamen, and white matter.

Table 4
Functional visual network connectivity related to improved RCFT copy task scores post-VR cognitive training.

Seed	Connected regions (voxels)	Clusters		
		MNI coordinates (x, y, z)	Voxel size (2*2*2)	P- FDR corrected
a. Visual lateral, R	Paracingulate gyrus, L	-10 + 64 + 12	124	0.0080
	Frontal pole, L		55	
	Paracingulate gyrus, R		48	
	Anterior cingulate gyrus		19	
	White matter		19	
b. Visual medial	Insular cortex, R	+ 22 + 32 + 06	20	0.0004
	Frontal pole, R		18	
	Frontal operculum cortex, R		18	
	Caudate, R		10	
	Putamen, R		2	
	White matter		379	
	White matter	-26 + 32 + 10	239	
c. Visual lateral, L	None			
d. Visual occipital	None			
<p>Group-level analyses between the VR and control groups were carried out using a general linear model with RCFT copy task improvement as an explanatory variable and the post – pre training z transformation value as a dependent variable. Voxel-wise uncorrected P < 0.001 and cluster-wise corrected q < 0.05.</p> <p>RCFT = Rey-Osterrieth Complex Figure Test; VR = virtual reality; MNI = Montreal Neurological Institute; FDR = false discovery rate; L = left side; R = right side</p>				

Figure 2 and Fig. S2 depict the increased regional FC in the brain cortices and the white matter, respectively, that are related to improvements in the RCFT copy task in the VR group compared to the

control group.

Discussion

The present study found that a month of multidomain cognitive training using fully immersive VR was effective in improving visuospatial function and frontal-occipital FC, as well as apathy and positive affect in older adults in a pre-dementia cognitive state.

The first major finding of this study was that VR cognitive training resulted in improvements in the RCFT copy task. Despite the inconsistent results reported in the literature, training-related changes in cognition in older adults with cognitive disorders have been repeatedly found [9, 10]. Neuropsychological test score improvements after traditional pen-and-paper or computerized cognitive training have been found in measures of global composite cognition [40–42], verbal memory [11, 40, 43, 44], verbal letter fluency [40, 41], verbal fluency, [45, 46], and visuospatial function in the clock-drawing test [40, 47]. It has also been reported that VR cognitive training was effective in improving frontal executive function in those with MCI [48], as well as attention and visual memory in older adults [49, 50]. In line with these previous studies, our results also showed that multidomain cognitive training in a virtual environment was effective in improving language, visuospatial function, memory (immediate/delayed recall), and frontal executive function compared to pre-training baseline values, but a group difference was found only for visuospatial function. It is possible that the relatively short training period of one month might have resulted in the lack of group difference because a learning effect may have impacted the post-training neuropsychological test results in the control group. However, the improvement in visuospatial function in the VR group even after the short period of cognitive training might be attributed to the ecological nature of the fully immersive VR environment. In the enriched auditorily and visually stimulating environment, processing of visual orientation, visuospatial construction, and visual selective attention likely occurred [51, 52]. In recent studies with VR evaluation, investigators were able to effectively differentiate between the navigational [53] and visuospatial deficits seen in MCI patients from healthy older adults [54, 55]. In studies with VR intervention, authors have found that VR cognitive training was effective [49, 56] or ineffective [50, 57] in improving visuospatial function in older adults or those in the early stage of dementia. We believe that the cognitive training performed in the maximally immersive environment with the head-mounted display, headphones, and hand movement trackers in our study might have increased visuospatial functioning in those in the pre-stage of dementia [58]. The immersion methods utilized in previous studies investigating VR cognitive training in older adults employed desktop-based systems [49, 50], screen and sensors [56], screen and glasses [59, 60], and head-mounted display and fixed joystick set-ups [57]. Although heterogeneity in study populations and methodological differences between prior studies have resulted in inconsistent findings, the present study provides further evidence to support the benefits of VR cognitive training in eliciting improvements in visuospatial processing through the repeated presentation of real-world, dynamic, multisensory, and interactive environments.

Another novel finding was that we observed increased FC in the frontal-occipital cortical network after VR cognitive training, which was associated with improved performance in the RCFT copy task, consistent

with the associations between cognitive improvements and neuronal plasticity that have been observed previously [61]. In patients with MCI, significant associations have been observed between verbal memory improvement and left hippocampal activation in task-related fMRI after eight weeks of training to improve auditory processing speed and accuracy [11]. Others have shown that six weeks of episodic memory training in MCI patients resulted in the manifestation of new associations between improved delayed word recall test performance and brain activation in the right inferior parietal lobule in fMRI during memory encoding [62]. In healthy older adults, eight weeks of exposure to a cognitive control training program led to increased frontoparietal network related to cognitive control ability [63], and another study found that verbal recall was associated with increased left hippocampal volume in healthy older adults after eight weekly verbal recall memory training sessions [64]. Thus, in the present study, repetitive cognitive training in a novel fully immersive environment might have increased the frontal-occipital activation in accordance with improved visuospatial function. We also observed increased FC in white matter areas, which are known to exhibit a lower hemodynamic response than grey matter. Although fMRI studies have focused on grey matter until recently, the increased FC in the white matter we observed supports the growing neural evidence of fMRI white matter changes induced by VR cognitive training [65, 66].

This evident link between visuospatial construction and frontal-occipital FC might be explained by the acquired cognitive system engagement induced by the RCFT copy task, which requires the participant to copy a complex geometric figure [67]. Visuoconstructive ability is based on the Van Sommers' model of drawing [68]; based on this cognitive model, the RCFT copy task consists of (i) visual recognition of a 2D Rey-Osterrieth complex figure; (ii) visual representation of the figure in long-term or temporary memory; (iii) graphical output processes such as those related to depiction decisions (e.g., context, orientation, viewpoint, details, and boundary) or reproduction strategies (e.g., copying orders, dimensions, shapes, diagonals, crosses, line sets, etc.); (iv) graphical planning (e.g., routine or contingent planning); and (v) articulation and economic constraints during motor output. Through these steps, multiple brain regions have been found to be associated with RCFT copy task performance, including the temporal, parietal, occipital, and frontal cortices in both hemispheres or the right hemisphere alone [69–71]. Although we observed increased activity only in the primary visual cortices (visual medial) and the right associative visual cortices (right visual lateral) connecting to the areas in the middle frontal cortices, these regions are known to be involved in visual recognition and graphic output planning processes required to complete the RCFT copy task [68], and they are associated with visuo-motor transformation and multistep object use in the task [71]. A recent study reported that lesions in the right superior parietal lobe and the middle occipital gyrus were associated with poor RCFT copy performance [72], which is in accordance with our own results. In addition, there have been reports of improvements in non-trained cognitive functions, also known as transfer effects, in memory training in older adults with MCI [73, 74]. Previous studies showed that repeated memory-focused training might have enhanced the processing speed of memory retrieval and efficiency of working memory, leading them to assume that frontal executive function was the main recipient of the transfer effects [73, 74]. Although recent studies have applied cognitive training with novel computerized tools, with involvement of multiple cognitive domains,

existing programs have only applied cognitive training in a 2D environment with an emphasis on language abilities [9, 47, 73, 75]. Since frontal executive function plays a major role in all cognitive domains and higher-order cognitive controls [76], the improved performance on the RCFT copy task may be supported by increased FC in the frontal-occipital network.

The psychiatric benefit of VR cognitive training in those in a pre-dementia state should be considered. In this study, participants in the VR group showed improved apathy and positive affect scores after training compared to those in the control group. A recent review reported that computerized cognitive training resulted in long-term improvements in psychological outcome measures [16]. Although methodologies have varied across studies, 3D VR cognitive training was effective in improving depressive symptoms in those with MCI compared to an active control receiving music therapy [57]. In addition, a few feasibility studies have reported improved alertness, pleasure, apathy, and security following one-time exposure to a less immersive VR environment [59, 60]. We postulate that apathy and positive affect might be improved by the VR cognitive training, as these are some of the early symptoms of dementia [77]. Immersive virtual environments might facilitate the limited functioning of patients with cognitive disorders that affect communication, interaction, motivation, engagement, and positive attitudes toward others [78]. Thus, the importance of virtual environments should be considered in cognitive training because the feeling of presence itself in a 3D space can enhance volitional motivation, allowing one to constantly process external stimuli and cognitively adjust to changing environments [79].

Limitations

Our study had several strengths and limitations. This is one of the largest VR cognitive training studies to use a fully immersive 3D VR program. Compared to 2D or semi-immersive VR programs, our results highlight the positive effects of employing fully immersive 3D VR in cognitive training, as we found neural evidence supporting the improvement of visuospatial function. However, there were several limitations and lessons learned in the present study. First, the small sample size and short training period were the main limitations. Although sample sizes in studies investigating the effects of cognitive training are increasing [80], most VR trials still rely on small sample sizes and are conducted over a short duration of time, especially those using fully virtual environments [15]. Short clinical trial periods in previous studies investigating the effect of computerized cognitive training programs have also been a limiting factor in the field as a whole [80]. Thus, future studies should aim to increase sample sizes and extend the duration of the training period to better evaluate the effect of VR cognitive training. Second, we considered that the per protocol analysis can bias the result of the present randomized controlled trial, although the number of participants who dropped out from the study was same in both groups. Third, the lack of an active control group in the present study is another limitation. Some previous trials have included active control groups receiving psycho-education, cognitive therapy, face-to-face music therapy, or pen-and-paper cognitive training for comparisons with a VR training group [15, 57]. In the future, various active control groups should be considered to confirm the effectiveness of VR cognitive training.

Conclusion

We found that fully immersive VR cognitive training improved cognition and psychiatric symptoms in a pre-dementia state. Visuospatial function improved relative to controls and this finding was supported by increased frontal-occipital FC assessed by rsfMRI. These findings suggest that VR training can enhance visuospatial ability by exposing the patient to an enriched virtual environment, and VR can also lead to improved apathy and positive affect. Our results support the neurotherapeutic use of VR cognitive training as an effective non-pharmacological intervention for those who are at risk for dementia, though more rigorous trials should be performed to confirm the effects and to identify the associated neural mechanisms.

Abbreviations

AES, Apathy Evaluation Scale; BOLD, blood oxygenation level-dependent; CDR, Clinical Dementia Rating; CDR-SOB, Clinical Dementia Rating- Sum of Boxes; EPI, echo-planar imaging; FC, functional connectivity; fMRI, functional magnetic resonance imaging; GDepS, Geriatric Depression Scale; GDS, Global Deterioration Scale; IADL, instrumental activities of daily living; ICI, information and communication technology; K-BNT, Korean version of the Boston Naming Test; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; PNAS, Positive and Negative Affect Schedule; RCFT, Rey-Osterrieth Complex Figure Test; ROI, region of interest; SCT, Stroop Color Test; SPM, Statistical Parametric Mapping; SPSS, Statistical Package for the Social Sciences; SVLT, Seoul Verbal Learning Test; TE, echo time; TR, repetition time; TMT, Trail-Making Test; VR, virtual reality.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Gachon University Gil Medical Center (GCIRB2018-396), and informed consent was obtained from all study participants.

Consent for publication

Not applicable.

Availability of data and materials

The datasets are available from the corresponding author (sjcho@gilhospital.com, S-J Cho) upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JMK, NBK, and SYL conceived and designed the study, acquired, and analysed the data, interpreted the study findings, and drafted the manuscript. SKW, BKY, JYL, JHY, and SHR designed the study, interpreted the study findings, supervised and directed the conduct of the study, and critically reviewed the manuscript. SJC conceived and designed the study, acquired, and analysed the data, interpreted the study findings, supervised and directed the conduct of the study, and critically reviewed the manuscript.

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Figures

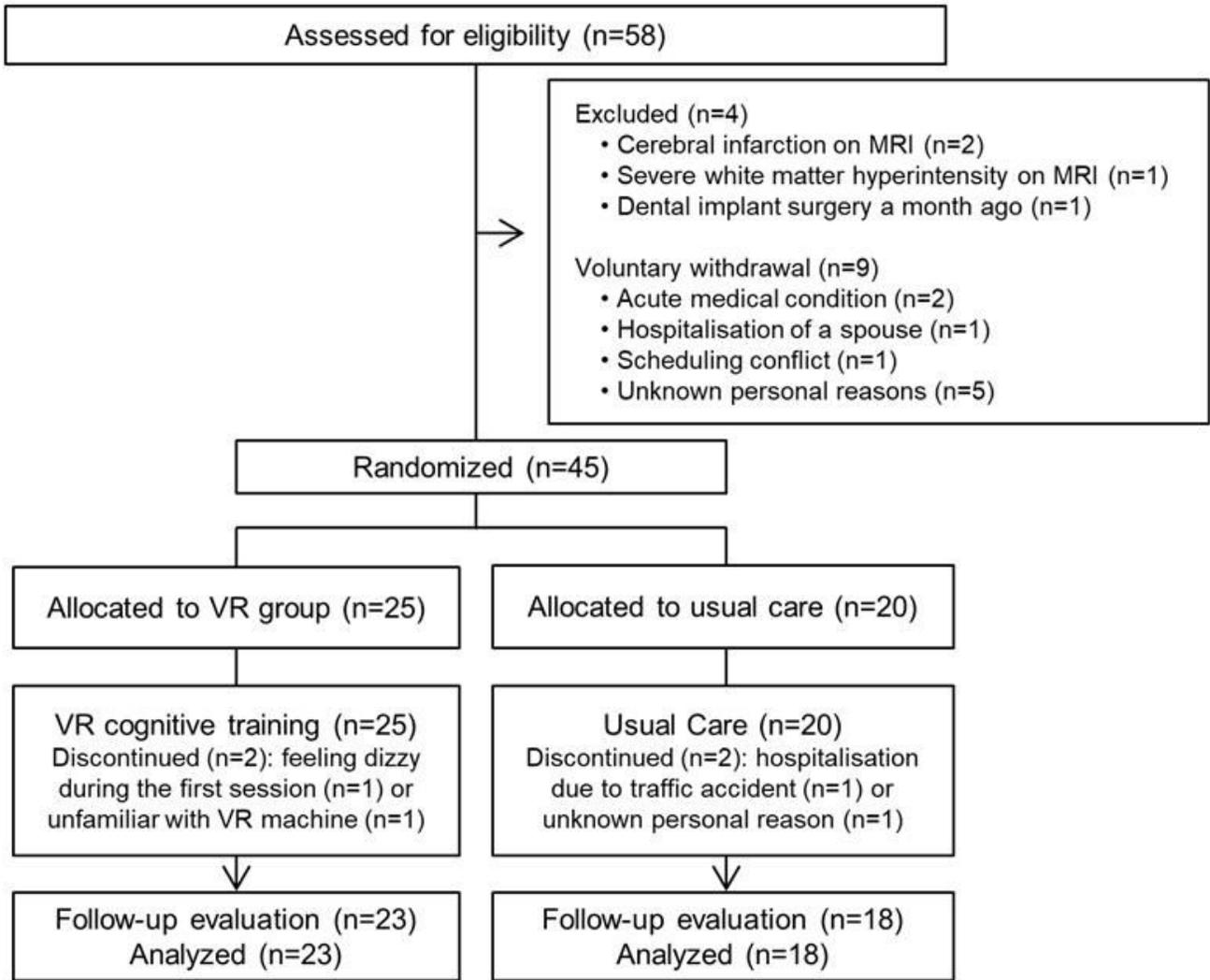


Figure 1

Trial flow chart. n = number; MRI = magnetic resonance imaging; VR = virtual reality

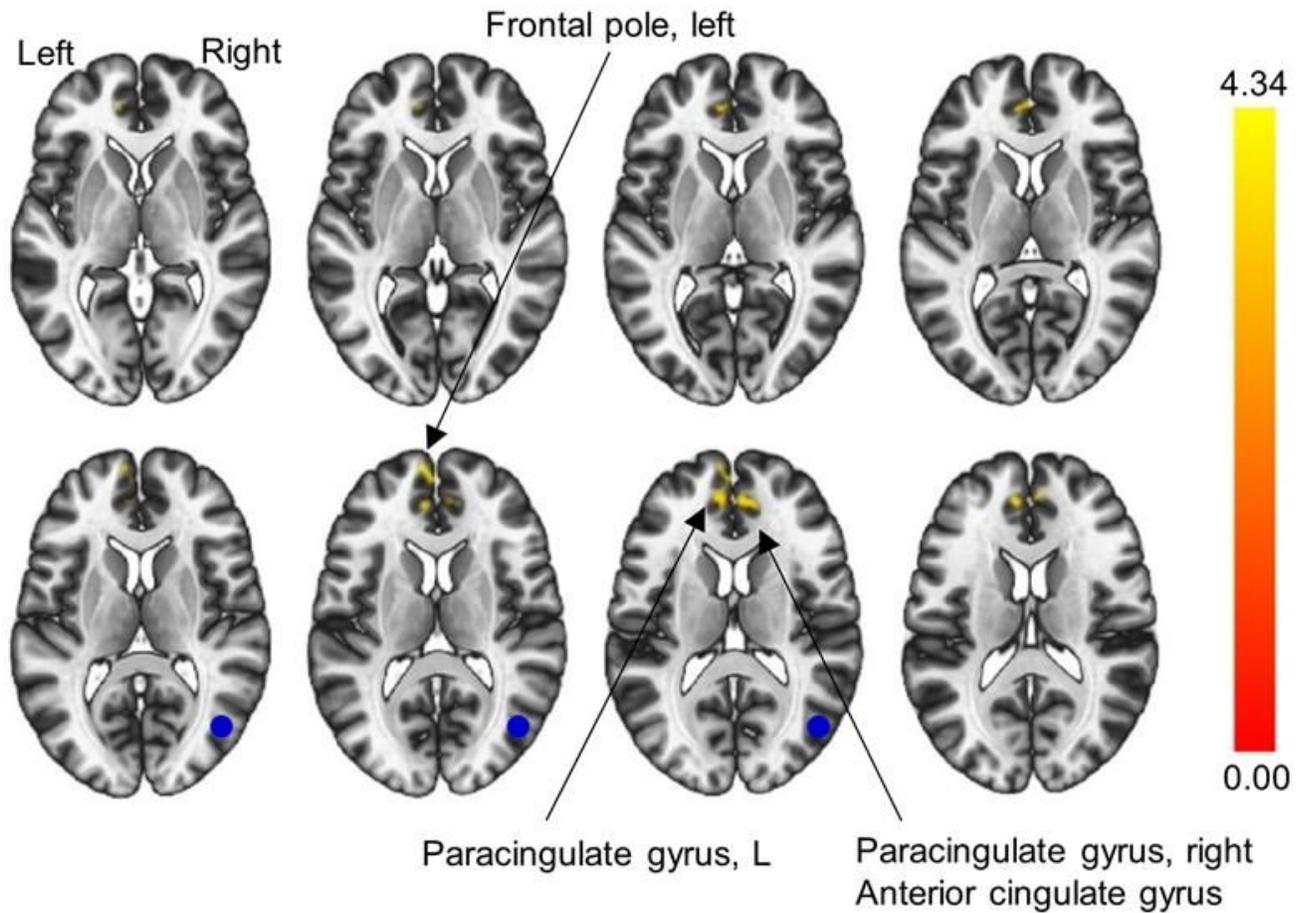


Figure 2

Increased frontal-occipital functional connectivity related to RCFT copy task improvement after VR cognitive training. Increased functional connectivity in the right and left paracingulate gyrus, the left frontal pole, and the anterior cingulate gyrus in the seed-to-voxel analysis based on the right lateral region of the visual network (blue coloured circles). RCFT = Rey-Osterrieth Complex Figure Test; VR = virtual reality

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