

Introduction

Alzheimer’s disease (AD) is a neurodegenerative disease that causes a decline in cognitive functions, considerably affecting a patient’s life. Recently, virtual reality (VR) technology has emerged as a new tool used in the cognitive training of patients with AD. Regular and continuous cognitive training(CT) enhances cognitive reserve, which means resilience to neuropathological damage of the brain, and promotes neuroplasticity in relevant brain networks.

In particular, cognitive training using digital devices, such as computerized cognitive training (CCT) or virtual reality cognitive training (VRCT) offers a more cost-effective, accessible, flexible, and comprehensive intervention. These approaches can also provide individualized intervention such as increasing task difficulty incrementally to ensure that the intervention remains sufficiently challenging. However, it is often accompanied by cybersickness, which is similar to motion sickness such as eye fatigue, headache, and nausea. Furthermore, it cannot be easily used by elderly people or patients who have cognitive impairment and are not familiar with operating electronic devices or virtual spaces.

Therefore, the adverse effects of VR should be reduced to use VR more widely in AD treatment, and an intuitive and easy-to-use interface should be developed. In the present study, we aimed to determine whether patients with mild to moderate AD could tolerate VR-based cognitive training by using the MentiTree software without experiencing side effects; we also aimed to elucidate the clinical efficacy of the program

Method

A. Participants

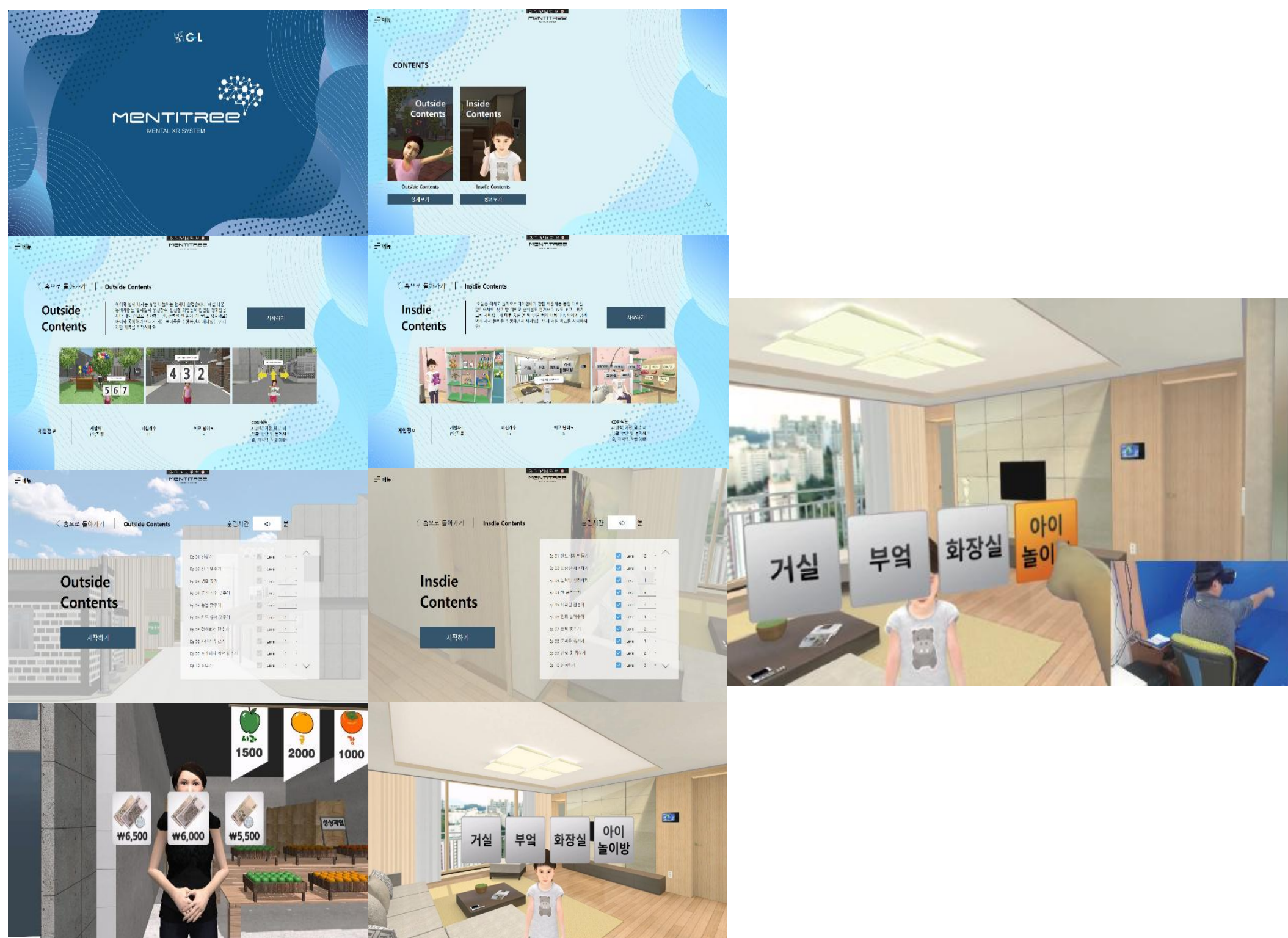
The subjects were adults aged 50–90 years and diagnosed with mild to moderate AD. The inclusion criteria were as follows:

- (1) Subjects with a history of more than 24 weeks with the National Institute on Aging-Alzheimer’s Association clinical stage ≥ 4 as of the screening date and a Clinical Dementia Rating (CDR) Global score of 0.5–2
- (2) Subjects receiving a drug or non-drug treatment to improve or alleviate the cognitive function of Alzheimer’s disease
- (3) Subjects receiving a stable treatment for more than 12 weeks as of the screening date.

B. Intervention



The participants underwent VR training using MentiTree, twice a week for 30 min at a time for 9 weeks. Cognitive functions were assessed before and after the intervention.



- In the MentiTree program, Head-mounted display (HMD, Oculus Rift S, 2560×1440 resolution, 115-degree field of view) and received a game-style 3D VR content to perform cognitive function training.
- Interact with objects in the VR by using a hand tracking technology, which recognizes the user’s hand movements through sensors and projects them onto virtual hand movements on the screen.

- MentiTree Contents :
 - Alternately provides an indoor background content (randomly provided) and an outdoor background content (sequentially provided)
 - Difficulty level(outdoor background content: 1–3 levels; indoor background content: 1–5 levels) automatically changes depending on the subject’s ability to perform the content.

C. Neuropsychological Assessment

The cognitive function of the participants was assessed using the Korean version of the Mini-Mental State Examination-2 (K-MMSE-2), Clinical Dementia Rating (CDR), Global Deterioration Scale (GDS), and Literacy Independent Cognitive Assessment (LICA) before and after the intervention.

D. Statistical Analysis

- Analyzed using the SciPy library in Python.
- The normality of the change in scores before and after each test was examined using the Shapiro–Wilk test.
- Paired sample test and the Wilcoxon signed-rank test was conducted to compare the test scores before and after the intervention.
- The test scores were expressed as mean±standard deviation, and their significance level was set at 0.05.
- The Bonferroni correction was applied to adjust for multiple comparisons.

Result

Demographic & Clinical Characteristic Data

Table 1. General characteristics of the subjects		
Variable	Mean±SD	N (%)
Demographic Data		
Female	N/A	10 (83.3)
Male	N/A	2(16.7)
Age (years)	74±10.56 (55–87)	N/A
Education (years)	6.83±4.33 (0–15)	N/A
Pre-Intervention Neuropsychological Assessment		
K-MMSE-2	17.25±6.11	N/A
CDR	1.17±0.54	N/A
GDS	4.42±0.79	N/A

A total of 13 people participated in the experiment and received VR training at least once. One of them dropped out, and the remaining patients completed the test.

- 12 of the 13 participants completed all 18 training sessions; one participant attended only two sessions. Therefore, the mean adherence rate to the VR intervention was 93% (SD = 24.65).
- Only one participant experienced dizziness during training. However, before consenting to participate, this participant had a history of dizziness and earache for several years.

Engagement of contents

12 participants who completed all 18 training sessions, showed an increase in difficulty level on the final session compared to the first session. The average difficulty level increased from an initial level of 1 to a final level of 2.85 for outdoor contents, and 3.9 for indoor contents.

Neuropsychological Assessment Results

The scores of the LICA stick recognition test(visual recognition memory) increased statistically significantly($p=0.034$). However, after Bonferroni adjustment (adjusted $p<0.003$), none of the result remained significant.

Table 2. Comparisons of neuropsychological assessment results before and after 9 weeks of VR training.					
Variable	Baseline	9 weeks	Test type	Effect size(95%CI)	p-Value
K-MMSE-2	17.25±6.11	16.92±6.04	Paired t-test	$d=-0.20[-1.39,0.73]$	0.4333
CDR	1.17±0.51	1.25±0.56	Wilcoxon	$r=-1.00[-1.00,-1.00]$	0.3173
GDS	4.42±0.79	4.58±0.79	Wilcoxon	$r=-1.34[-0.95,-0.95]$	0.1573
Total LICA	138.09±38.03	141.11±49.01	Wilcoxon	$r=-1.26[-0.82,-0.02]$	0.2334
Story immediate recall	4.08±2.01	3.08±2.02	Wilcoxon	$r=-1.75[-0.89,-0.07]$	0.0782
Story delayed recall	0.25±0.89	0.33±0.89	Wilcoxon	$r=-1.00[-1.00,-1.00]$	0.3173
Story recognition	4±1.91	3.75±2.05	Paired t-test	$d=-0.13[-1.47,0.97]$	0.5839
Stick construction	7.17±3.66	6.75±4.02	Wilcoxon	$r=-0.18[-0.64,-0.03]$	0.7150
Stick recognition	11.58±3.29	14.00±3.30	Paired t-test	$d=0.64[0.08,1.74]$	0.0342
Word immediate recall	9.83±4.20	10.33±4.89	Paired t-test	$d=0.14[-1.47,0.97]$	0.6881
Word delayed recall	0.25±0.87	0.25±0.62	Wilcoxon	$r=0.00[-0.95,0.00]$	1.00
Word recognition	12.50±3.15	12.83±3.81	Paired t-test	$d=0.12[-1.39,2.05]$	0.6338
VSS forward	3.67±2.02	3.33±2.02	Paired t-test	$d=-0.34[-0.96,0.29]$	0.2342
VSS backward	2.33±1.67	2.83±1.70	Paired t-test	$d=-0.40[-1.29,0.29]$	0.1962
Digit Stroop test	12.17±8.74	11.83±8.03	Paired t-test	$d=-0.06[-3.85,3.18]$	0.8228
Calculation	14.75±8.43	15.25±9.10	Paired t-test	$d=0.17[-1.35,2.35]$	0.6746
Animal fluency	7.08±3.90	7.75±5.67	Paired t-test	$d=0.21[-1.40,2.74]$	0.7202
CORT	10.42±2.75	10.92±3.87	Paired t-test	$d=0.23[-0.87,1.87]$	0.4924
Naming	11.00±3.36	10.83±3.59	Paired t-test	$d=-0.13[-1.02,0.68]$	0.6707

Values are mean±standard deviation (SD). CI: Confidence intervals; K-MMSE-2: Korean version of Mini-Mental State Examination, 2nd edition; CDR: Clinical Dementia Rating Scale; GDS: Global Deterioration Scale; LICA: Literacy Independent Cognitive Assessment; VSS: Visuospatial Span; CORT: Color and Object Recognition Test

Discussion

This study aimed to investigate the feasibility and changes in the cognitive function of patients with mild to moderate AD after 9 weeks of cognitive training using the MentiTree VR program. The average adherence rate to the training was high, at 93%(SD=24.65). The safety of the program was also high, and no adverse effects other than a single episode of dizziness were observed. Therefore, more caution should be taken when applying it to subjects with a history of vestibular -related disorders or vestibular hypersensitivities.

Given the small sample size and exploratory nature of this pilot study, further validation with a larger cohort is warranted to determine whether this effect is robust and clinically meaningful. Next studies should include a larger sample size, administer long-term interventions, and set a randomized control group.