

ORIGINAL ARTICLE

Cognitive reserve and the effects of virtual reality-based cognitive training on elderly individuals with mild cognitive impairment and normal cognition

Hyeyoung KIM ^{1,2} Jin Pyo HONG,³ Jae Myeong KANG,⁴ Won-Hyoung KIM ¹ Seri MAENG,¹ Seo-Eun CHO,⁴ Kyoung-Sae NA,⁴ Seok Hee OH,⁵ Jung Woon PARK,⁶ Seong-Jin CHO⁴ and Jae Nam BAE¹

¹Department of Psychiatry, Inha University Hospital and ⁴Department of Psychiatry, Gachon University College of Medicine Gil Medical Center, Incheon, ²Department of Psychiatry, Seoul National University College of Medicine and ³Department of Psychiatry, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul and ⁵Department of Computer Engineering, Gachon University and ⁶Department of IT Convergence Engineering, Gachon University Graduate School, Seongnam, Republic of Korea

Correspondence: Prof Jae Nam Bae MD PhD, Department of Psychiatry, Inha University Hospital, Incheon, Republic of Korea. Email: jnbae@inha.ac.kr; Prof Seong-Jin Cho MD PhD, Department of Psychiatry, Gachon University College of Medicine Gil Medical Center, Incheon, Republic of Korea. Email: sjcho@gilhospital.com

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Abstract

Background: Cognitive reserve (CR) is a concept proposed to account for discrepancies between the extent of brain pathology and clinical manifestations of that pathology. This study aimed to explore the associations between CR and the effects of cognitive training using fully immersive virtual reality (VR).

Methods: A total of 44 older adults (22 cognitively normal, 22 with mild cognitive impairment) underwent eight cognitive training sessions using VR for a period of 4 weeks. CR was assessed using the Cognitive Reserve Index questionnaire (CRIq). To evaluate baseline cognitive function and the effects of VR training, the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological battery was administered to all participants before and after the training.

Results: Greater improvement in the total CERAD score was seen for cognitively normal participants with higher versus lower scores on the Education subdomain of the CRIq. Among patients with mild cognitive impairment, none of the CRIq subdomain scores (Education, Working Activity, Leisure Time) were related to a change in CERAD total scores. The CRIq total score did not predict the improvement of global cognition in either group.

Conclusions: This study revealed different impacts of CR on cognitive training according to the participants' cognitive status. It also suggests that employing three proxies of CR rather than using a composite score would provide a more accurate understanding of one's CR.

INTRODUCTION

Mild cognitive impairment (MCI) is an intermediate stage between the cognitive changes of normal aging and dementia.¹ MCI constitutes a high-risk state for dementia, especially for dementia due to Alzheimer's disease (AD).² Therefore, it could be a target for interventions aimed at reducing dementia risk. Currently, there are no effective pharmacological treatments for patients with MCI; non-pharmacological interventions such as cognitive training are an emerging therapeutic approach for patients with MCI.^{3,4} One recent meta-

analysis revealed that individuals with MCI who received interventions with memory-based or multi-domain forms of content were likely to display an improvement in outcome measures of cognition after intervention.⁵ Cognitive training in MCI has been associated with increased activation in the hippocampus,⁶ right inferior parietal lobe,⁷ frontoparietal network,⁸ and occipitotemporal region.⁹ It has also been suggested that training may activate pre-existing cognitive reserves¹⁰ or stimulate pre-existing neural reserves as compensatory scaffolding, prompting neuroplastic reorganisation to meet task demands.^{11,12}

Cognitive reserve (CR) is a concept proposed to account for discrepancies between the extent of brain pathology and clinical manifestations of that pathology. This suggests that greater engagement in cognitively stimulating activities during one's lifetime, such as education, occupational attainment, or leisure activities, modifies the brain so that the negative effects of brain pathology on cognition are reduced.¹³ Previous studies have demonstrated that higher levels of CR are associated with a delayed onset of cognitive symptoms; however, after clinical symptoms of the neurodegenerative disease appear, patients with high CR show accelerated cognitive decline compared to those with low CR.^{14–17} The explanation for these findings is that individuals with high CR can tolerate more pathology than those with low CR; therefore, individuals with high CR will have more advanced pathology at the onset of cognitive decline and show a more rapid rate of decline.¹⁰ Researchers further posit that the brain capacity of patients with AD and high CR to learn new information is reduced due to a more extended pathology compared to patients with low CR.¹⁸ Evidence supports this hypothesis by showing that patients with lower CR or fewer years of education benefited from a cognitive training program more than those with high CR.^{18,19}

With rapid developments in virtual reality (VR) technology, there has been a growing interest in adopting VR in cognitive interventions over the years. However, as previous research concerning VR has mainly focused on the diagnosis of dementia, there are only a handful of studies on the effects of VR-based cognitive interventions.^{20,21} According to the most recent meta-analysis by Kim *et al.*, VR interventions showed small to medium effects on cognition, larger in patients with MCI than in those with dementia.²⁰ Most of the 11 studies included in the meta-analysis adopted a semi-immersive intervention, with only two studies applying a fully immersive technology. Furthermore, none of the previous studies have looked at whether and how CR could modulate the effects of VR-based cognitive training.

Therefore, this study aimed to explore the association between CR and the effects of fully immersive VR-based cognitive training. We tested whether CR had an association with cognitive change before and after VR cognitive training in patients with MCI compared to cognitively normal individuals.

METHODS

Participants

The initial sample comprised 64 participants, 39 in the MCI group and 25 in cognitively normal group, recruited from three study sites – Gil Hospital, Samsung Medical Center, and Inha University Hospital in South Korea – between October 2018 and June 2019. A total of 56 individuals participated in cognitive training, and the complete data were obtained from 44 participants, 22 in each group (Fig. 1).

The diagnosis of patients with MCI was made based on the criteria developed by Petersen *et al.*²²: (i) memory complaint; (ii) normal activities of daily living; (iii) impairment in one or more tests in the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological assessment battery, as evidenced by scores of ≤ -1.5 SD of age- and education-appropriate norms; and (iv) no dementia. Participants were considered cognitively normal when they performed within 1.5 SD of age- and education-appropriate norms for cognitive testing. The exclusion criteria for both patients with MCI and cognitively normal individuals specified individuals with communication difficulties, cardiovascular disease, serious physical illness that may affect cognition, severe psychiatric disorders, substance use disorder, experience of severe dizziness, and/or diagnosis with major neurocognitive disorders.

All participants provided informed consent. The study was approved by the Institutional Review Board at each study site.

Cognitive training

The VR cognitive training program is designed to train memory, attention, and executive functions. The storyline of each session involves purchasing daily necessities in a supermarket. Participants were shown the list of items to buy for 10 s at the entrance of the supermarket; they could then visit seven sections by pushing a button. At each session, the list of items was evenly and randomly selected from the seven categories such as juice, dairy food, meat, fish, alcohol, processed food, and Korean side dishes. There were four difficulty levels from level 1 (number of to-buy-items: 4) to level 4 (number of to-buy-items: 7), and the practitioner chose the level according to the performance of the participant at each session. During the training, patients could use

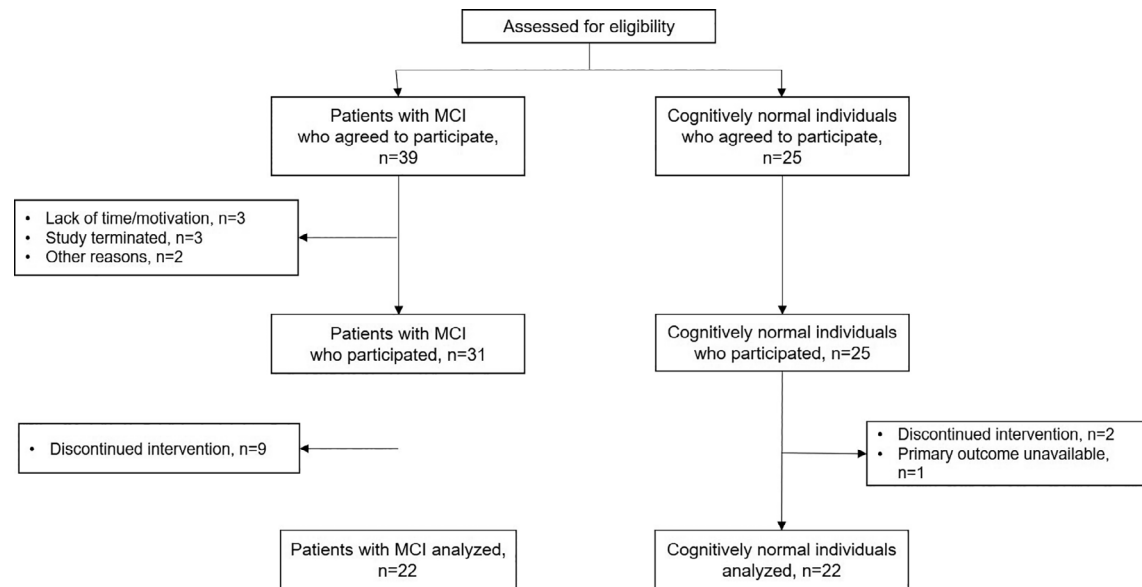


Figure 1 Recruitment and flow diagram.

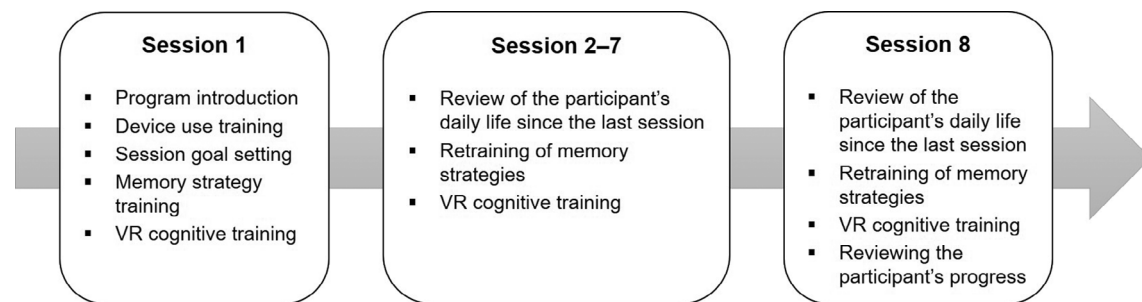


Figure 2 Overview of cognitive training sessions.

the hint button, which displayed the list of items again for 10 s. All virtual environments were 3D fully immersive virtual supermarket environments with increased visuospatial stimulation and presence. Examples of the VR training program are shown in the supplementary material (see Fig. S1 in the online Supporting Information attached to the electronic version of this paper).

Both groups underwent a total of eight cognitive training sessions using VR for a period of 4 weeks. They attended 50–60 min sessions twice a week. Figure 2 shows how each session was organised. The first session included program introduction, device use training, session goal setting, memory strategy training, and cognitive training using VR. The second session consisted of conversations about daily life since the first session, memory strategy education, and VR cognitive training. The third to

eighth sessions were conducted in the same way as the second session, including a review of the participant's daily life since the last session and retraining of memory strategies. The last session concluded by reviewing the participant's progress based on the acquisition of memory strategies and performance results. Memory strategies taught to participants during the sessions included first letter association mnemonic, rehearsal, and categorisation. Trainings were conducted with a head-mounted display Samsung Odyssey with participants in the standing position, except for one cognitively normal participant who was using an electric wheelchair.

Measures

Participants' level of CR was measured using the Cognitive Reserve Index questionnaire (CRIq).²³ The CRIq is a questionnaire designed to quantify the

amount of CR acquired during a person's lifetime. The CRIq consists of 20 items grouped into three sections: Education, Working Activity, and Leisure Time. CRI-Education considers school years and other educational/training courses. In the CRI-Working Activity section, adulthood professions and the number of years in each profession were recorded. CRI-Leisure Time includes 17 questions regarding various intellectual, social, and physical activities. The Korean version of CRIq was translated by Choi *et al.*²⁴

To evaluate baseline cognitive function and the effects of VR cognitive training, the CERAD neuropsychological assessment battery was administered to all participants before (T0) and after the training (T1). The CERAD total score was calculated by summing the scores of six tests in the CERAD battery: verbal fluency, Boston naming test, immediate recall, constructional praxis, delayed recall, and word list recognition.²⁵ According to Chandler *et al.*, the CERAD total score was highly accurate in differentiating normal controls, patients with MCI, and patients with AD. It also showed a superior discrimination ability between normal cognition and MCI to the Mini-Mental State Examination score.²⁶

Statistical analysis

All statistical analyses were conducted using SPSS, version 19.0. Group differences in demographic and clinical variables were tested using the Mann-Whitney *U*-test for continuous variables and Fisher's exact test for categorical variables. Multiple linear regression analysis was used to test the association of change in CERAD total score (T0-T1) with age, sex, and CR in each group. For each group, two

regression analyses were performed – the first with age, sex, and CRI-total score as independent variables, and the second with age, sex, CRI-Education, CRI-Working Activity, and CRI-Leisure Time as independent variables.

RESULTS

Table 1 shows the baseline characteristics of the MCI group and the cognitively normal group. There was no significant difference in age, sex, and education years between the two groups. Cognitively normal subjects had higher CERAD total scores than patients with MCI (70.41 ± 5.89 vs 49.68 ± 11.37 , $P < 0.001$). Regarding CR, CRI-total score and each subdomain score of CRIq showed no significant difference between the two groups, except for CRI-Leisure Time, which was higher in cognitively normal individuals than in patients with MCI.

After VR cognitive training, 20 out of 22 patients with MCI (90.9%) improved the CERAD total score between T0 and T1 and two (9.1%) worsened, with differences ranging from -7 to $+20$ (mean = 7.73 ; SD = 6.68). Among the cognitively normal individuals, 18 out of 22 participants (81.8%) displayed improvements in the CERAD total scores between T0 and T1 and four (18.2%) worsened, with differences ranging from -5 to $+20$ (mean = 4.95 ; SD = 6.50). There was no significant difference between the two groups for change in the CERAD total score ($P = 0.09$).

The results of multiple linear regression analysis, including age, sex, and CRI-total as independent variables, are shown in Table 2. The CRI-total score was not associated with changes in the CERAD total score (T0-T1) either in patients with MCI or

Table 1 Baseline characteristics of all participants

	Patients with MCI ($n = 22$)	Cognitively normal individuals ($n = 22$)	<i>P</i> -value
Age, mean (SD)	74.23 (7.50)	71.45 (3.95)	0.17
Sex (female), n (%)	17 (77.3)	20 (90.9)	0.41
School years completed, mean (SD)	8.68 (4.61)	8.91 (3.16)	0.71
Neurocognitive test, mean (SD)			
CERAD total score	49.68 (11.37)	70.41 (5.89)	<0.001*
CRI questionnaire, mean (SD)			
CRI-Total	86.09 (11.81)	85.09 (10.51)	0.64
CRI-Education	100.86 (14.26)	100.59 (12.6)	0.65
CRI-Working activity	89.27 (15.9)	81.45 (11.45)	0.07
CRI-Leisure time	76.95 (10.31)	84.18 (10.52)	0.03**

Abbreviations: CERAD, Consortium to Establish a Registry for Alzheimer's Disease; CRI, Cognitive Reserve Index; MCI, mild cognitive impairment; SD, Standard deviation. * $P < 0.01$. ** $P < 0.05$.

Table 2 Linear regression analysis between change in CERAD total score (T0-T1) and CRI-total score

	Patients with MCI		Cognitively normal individuals	
	Standardised coefficient (β)	P-value	Standardised coefficient (β)	P-value
Age	-0.08	0.78	-0.45	0.045*
Sex, female	0.29	0.31	0.44	0.07
CRI-total	0.29	0.31	0.28	0.22

Abbreviations: CERAD, Consortium to Establish a Registry for Alzheimer's Disease; CRI, Cognitive Reserve Index; MCI, mild cognitive impairment. * $P < 0.05$.

Table 3 Linear regression analysis between change in CERAD total score (T0-T1) and CRI subsection scores

	Patients with MCI		Cognitively normal individuals	
	Standardised coefficient (β)	P-value	Standardised coefficient (β)	P-value
Age	-0.01	0.98	-0.91	<0.001*
Sex, female	0.46	0.29	0.45	0.03**
CRI-Education	0.23	0.44	0.62	0.002*
CRI-Working activity	0.22	0.51	0.19	0.32
CRI-Leisure time	-0.03	0.92	-0.52	0.02**

Abbreviations: CERAD, Consortium to Establish a Registry for Alzheimer's Disease; CRI, Cognitive Reserve Index; MCI, mild cognitive impairment. * $P < 0.01$. ** $P < 0.05$.

cognitively normal subjects (patients with MCI, $P = 0.31$; cognitively normal individuals, $P = 0.22$). Age was negatively associated with changes in the CERAD total score only in cognitively normal individuals ($\beta = -0.45$, $P = 0.045$).

Table 3 displays the results of linear regression analysis including age, sex, and subdomain scores of CRIq as independent variables. Among cognitively normal individuals, CRI-Education was positively associated with changes in the CERAD total score ($\beta = 0.62$, $P = 0.002$), while CRI-Leisure Time had a negative association ($\beta = -0.52$, $P = 0.02$). Cognitively normal female participants showed a greater improvement in CERAD total score after VR cognitive training than cognitively normal male participants. In contrast, for the MCI group, none of the CRI subdomain scores, age, or sex, predicted changes in CERAD total scores.

DISCUSSION

In this study, both patients with MCI and cognitively normal individuals benefited from VR cognitive training. The cognitively normal individuals with higher CRI-Education showed a greater improvement in their global cognition than did those with lower CRI-Education after VR cognitive training. Among patients with MCI, none of the CRI subdomain scores were associated with a change in patients' cognitive

performance. The CRI-total score did not predict the improvement in either group.

While previous studies investigating the relationship between CR and the efficacy of cognitive training were limited to patients with MCI or dementia,^{18,19} the present investigation included cognitively normal individuals as well as patients with MCI. Our data show that the cognitively normal individuals with higher CRI-Education improved more than those with lower CRI-Education after cognitive training. This is plausible considering that those with a higher level of education were likely to have increased processing and conceptualisation abilities and utilise more efficient and flexible cognitive strategies.^{27,28} However, among patients with MCI, there was no association between CR and the outcome of cognitive training. This finding indicates that after the onset of cognitive deficits, the influence of extended underlying pathology that patients with MCI with high CR harbour counteracts the positive effect of high CR shown in cognitively normal individuals. This contradicts the studies by Mondini *et al.*¹⁸ and Olazarán *et al.*,¹⁹ suggesting that patients with lower CR benefit more from cognitive training. The discrepancy may be attributed to the different patient population; Mondini *et al.* studied patients with dementia, and Olazarán *et al.* included a patient population comprised mostly of patients with dementia and less than 20% with MCI, whereas we included only the MCI population as a patient group

whose underlying pathology is assumed to be less advanced than dementia.

In this study, the subdomain scores of CRIq contributed differently to cognitive training outcomes in cognitively normal individuals. Among the three subdomain scores of CR, CRI-Education contributed most significantly to the improvement in global cognition, which is in line with the literature considering education as a major factor in CR.^{29,30} One neuroimaging study by Foubert-Samier *et al.*³¹ revealed that among the three proxies of CR, only education is significantly associated with grey and white matter volume. The present study also demonstrated that in contrast to the impact of education on the effects of VR cognitive training, individuals with a lower CRI-Leisure Time had a greater improvement in cognition. Leisure activities encompass a broad range of activities, and prior research has shown that the relationship between leisure activity and cognitive function varies according to the activity content.^{32–34} Helzner *et al.*³⁵ categorised leisure activities into four categories (intellectual, social, physical, and other) and revealed that pre-diagnosis intellectual activity, but not social or physical activity, modifies the rates of cognitive decline in patients with AD. When applying Helzner *et al.*'s classification, the questions in the leisure activity section of CRIq adopted in this study were mostly about social and other activities with only a few questions on intellectual and physical activity. This might have hampered the proper examination of the impact of leisure activities on cognitive training effectiveness.

Another noteworthy finding of our study was that the CRI-total score did not predict the outcome of VR cognitive training, either in patients with MCI or cognitively normal individuals. This provides further evidence for the notion that using a single composite score combining three different proxies of CR (i.e., education, occupation, and leisure activities) might be doubtful.³⁴ We believe that employing subdomain scores of CR rather than a composite score would give a more accurate representation of CR.

Referring to demographic variables such as age or sex, younger age was associated with greater cognitive training effects in the cognitively normal group. Borella *et al.*³⁶ previously investigated whether individual characteristics predict the efficacy of cognitive training among healthy older adults and showed that participants who were younger and/or had higher

initial cognitive performance were more likely to improve after the training. On the other hand, other researchers have suggested that age influence on training outcomes reflects the sole effect of pre-training cognitive ability rather than a general cognitive decline over the life-span.³⁷ When we conducted additional analysis with our data, however, pre-training cognitive ability did not predict training effects in either group (MCI group, $P = 0.57$; cognitively normal group, $P = 0.37$). These findings support the independent impact of increasing age in reducing the amount of plasticity induced by cognitive training.³⁸

Meanwhile, sex showed an inconsistent impact on training gains: being female predicted higher training gains only among cognitively normal individuals in a regression model with CRI subsection scores as independent variables. The literature generally supports the hypothesis that women perform better in verbal and episodic memory tasks, whereas men show higher performance in tasks with a focus on visuospatial abilities.^{39,40}

This study has limitations. First, we did not employ an active control group. Future research to include active control participants would help to control for the possibility of a placebo effect and determine the actual benefits of VR cognitive training. Second, the sample size was small. Third, the drop-out rate was higher in the MCI group than in the cognitively normal group, although not statistically significant (29.0% vs 12.0%, $P = 0.123$). However, no significant difference was observed in demographic and clinical variables when comparing MCI patients who dropped out of the study and those who did not drop out (Supplementary Table S1), or individuals with normal cognition who dropped out and those who did not drop out (Supplementary Table S2). Fourth, the improvement in CERAD total scores between pre-training and post-training may be partially attributed to practice effects.

Nevertheless, our study shows that cognitive training that adopts fully immersive VR technology was safe and acceptable for the elderly, given that less than 20% of participants ceased the intervention. Moreover, we extended the existing research on the influence of CR in modulating the effects of cognitive training by investigating not only people with neurodegenerative diseases but also cognitively normal elderly individuals. This study design enabled us to

reveal the different impacts of CR on cognitive training according to the participants' cognitive status. A more complete understanding would be achieved by engaging a larger number of participants and broadening the study population to include patients with dementia.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's website: <http://onlinelibrary.wiley.com/doi//suppinfo>.

Figure S1 Representative images of VR cognitive training program

Table S1. Comparison between dropouts and non-dropouts among patients with MCI

Table S2. Comparison between dropouts and non-dropouts among individuals with normal cognition