Biomedical Science Letters 2024, 30(1): 1~9
https://doi.org/10.15616/BSL.2024.30.1.1
eISSN : 2288-7415

Original Article

Nature Experience-based Virtual Reality Improves Depressive Symptoms in a Young Population: A Pilot Study

Da-Been Lee[1,*], Seung-Lim Yoo[2,3,*], Sang Shin Pyo[4,], Jinkwan Kim[2,3,**], Bo-Gyu Kim[5,*], Suhng-Wook Kim[1,†,**], Byung-Jung Ko[5,†,**] and Dae Wui Yoon[2,3,†,**]**

[1]*Department of Health and Safety Convergence Science, Graduate School, Korea University, Seoul 02841, Korea*
[2]*Sleep Medicine Institute, Jungwon University, Goesan, Chungcheongbuk-do 28204, Korea*
[3]*Department of Biomedical Laboratory Science, Jungwon University, Goesan, Chungcheongbuk-do 28204, Korea*
[4]*Department of Biomedical Laboratory Science, Shinhan University, Gyeonggi-do 11644, Korea*
[5]*Department of Theater and Film, Jungwon University, Goesan, Chungcheongbuk-do 28204, Korea*

Although there have been several attempts to use virtual reality (VR) in the treatment of depression, the results have been inconsistent and existing studies have mostly relied on subjective measures to assess the effectiveness of VR in improving depression. The aim of this study was to investigate the effect of nature experience-based VR intervention on depressive symptoms in a young population using both subjective and objective measurements. The study population included 15 participants who had more than 14 identifiers of the Korean Beck Depression Inventory (K-BDI)-II. Participants received three weeks (four times per week) of VR intervention. The effectiveness of VR was assessed through changes in K-BDI-II scores and depression-related blood biomarkers. Nature experience-based VR intervention led to an approximately 50% reduction of K-BDI-II score (before 25.7±7.7 vs. after 12.5±8.3 (P<0.001)). Of these, loss of pleasure and fatigue showed the largest amount of improvement. However, levels of cortisol, brain-derived neurotrophic factor, and interleukin-6 did not differ from those at baseline. The findings of our pilot study suggest that nature experience-based VR can be a useful adjunctive treatment method for improving depressive symptoms in individuals who have difficulty accessing the real outside natural environment.

Key Words: Virtual reality, Depression, Biomarkers, Treatment

INTRODUCTION

Depression is a very common psychiatric disorder that negatively impacts daily life. It is characterized by prolonged periods of sadness or loss of pleasure or interest in activities (Willner et al., 2013). Depression can be long-lasting or recurrent, and it can have a significant impact on a person's ability to function at work or school or to cope with everyday life. This mental disorder is one of the greatest public health problems, affecting approximately 320 million people worldwide (World Health Organization, 2022). The pre-

Received: February 5, 2024 / Revised: February 19, 2024 / Accepted: March 5, 2024
*Researcher, **Professor.
†Corresponding author: Suhng-Wook Kim. Department of Health and Safety Convergence Science, Graduate School, Korea University, Seoul 02841, Korea.
Tel: +82-2-3290-5686, Fax: +82-2-921-7260, e-mail: swkimkorea@korea.ac.kr
†Corresponding author: Byung-Jung Ko. Department of Theater and Film, Jungwon University, Goesan, Chungcheongbuk-do 28204, Korea.
Tel: +82-43-830-8659, Fax: +82-43-830-8329, e-mail: filmart@jwu.ac.kr
†Corresponding author: Dae Wui Yoon. Department of Biomedical Laboratory Science, Jungwon University, Goesan, Chungcheongbuk-do 28204, Korea.
Tel: +82-43-830-8863, Fax: +82-43-830-8864, e-mail: ydw@jwu.ac.kr

valence of depression in a population varies by region, age, and gender, and the estimated number of depressed people is increasing. According to a World Health Organization (WHO) report (World Health Organization, 2022), depression is more prevalent in Southeast Asian and Western metropolitan regions, and it is more prevalent among women than men and among older people than younger people.

Several clinical studies and animal studies have been conducted to understand the pathophysiology of depression. Associations have been identified between depression and reduced levels of monoamines, increased level of blood cortisol, increased levels of inflammatory cytokines, decreased neuroplasticity and neurogenesis-regulating factor, specific gene variants, and epigenetic factors (Malhi and Mann, 2018).

Psychological treatment (e.g., behavioral activation, cognitive behavioral therapy, and problem-solving therapy), antidepressant medication (e.g., selective serotonin reuptake inhibitors), and brain stimulation therapy can be effective means of treating depression. Among them, psychotherapy is typically considered the primary treatment option (WHO, 2000; Segal et al., 2001). Recently, several studies have been conducted using virtual reality (VR) to treat depression as part of a psychological treatment plan, and the reported results were positive (Beevers et al., 2017; Dehn et al., 2018).

VR is a computer-generated simulation of life-like scenes and objects that enables users to immerse themselves in certain surroundings. Using specialized electronics equipped with a head-mounted display (HMD), computer, speakers, and headphones, the user can see, hear, and even feel in a virtual or simulated environment. Over the past few decades, VR has been employed as an effective treatment option for several medical symptoms or psychiatric diseases (Ioannou et al., 2020; Park et al., 2019). Through several case reports, clinical trials, and meta-analyses, beneficial effects of VR exposure therapy (VRET) have been reported for depression, specific phobias (Garcia-Palacios et al., 2002; Wallach and Bar-Zvi, 2007), anxiety disorders (Carl et al., 2019; Opriş al., 2012), posttraumatic distress disorders (McLay et al., 2012), and schizophrenia (Park et al., 2011).

Experience in nature has many benefits for healthy psychological functioning. Various studies have shown that exposure to natural environments (e.g., walking in outdoor nature areas or even viewing nature images or videos) can reduce stress levels while increasing positive affect (Bratman et al., 2012). Based on these promising findings, several attempts have been undertaken to use VR technology to provide nature experiences for promoting feelings of relaxation and relieving pain, anxiety, or distress in patients undergoing certain medical procedures (Furman et al., 2009; Mosso et al., 2009; Scates et al., 2020). Significant improvements in patient affect have been observed.

To the best of our knowledge, most studies have assessed the impact of VR on depressive symptoms in subjective approaches, such as questionnaires, and few have examined the positive effects of VR on depressive symptomes through blood markers. Therefore, in this study, we explored the impact of a nature experience-based VR on depressive symptoms through subjective assessments (depression questionnaire) and objective measurements (blood markers associated with depressive symptoms).

MATERIALS AND METHODS

Participants

Eighty individuals who lived in the Chungcheongbuk-do area of South Korea were initially screened between May 2023 and July 2023 for this study. All subjects completed an online questionnaire about their depressive symptoms before participating in the study. Inclusion criteria were no history of previous diagnosis, no depression treatment of any type, score higher than 14 on the Korean version of the Beck Depression Inventory (K-BDI)-II, and age between 20 and 50 years. Exclusion criteria were age under 20 years; heavy alcohol use; history of seizures or epilepsy in VR; or use of devices such as a pacemaker, hearing aids, or defibrillator. Subjects older than 50 years were excluded because they are more susceptible to VR sickness than younger users. People who have experienced undesirable symptoms, such as dizziness or headaches, when using an HMD with VR technology were also excluded. Among the 80 individuals who were assessed for eligibility, 65 were excluded because they did not meet our inclusion criteria (n=52), they declined to participate (n=4), or other reasons (n=9). After these exclusions, 15 subjects were finally included. Our study was based on previous research that evaluated the effectiveness of VR for elderly subjects with mild depression (Yang et al., 2017). The flow of participant selection for our study is shown in Fig. 1. All participants provided informed consent, and the study was approved by the Institutional Review Board of Jungwon University (No. 1044297-HR-202303-002-02). This study was registered at the Clinical Research Information Service (CRIS) of the Korea National Institute of Health (NIH), Republic of Korea (KCT0009142).

Study design and procedures

The overall study design and procedures are shown in Fig. 2. In a baseline examination, participants completed a questionnaire about their disease and medication history. Body weight and height were measured. A venous blood sample of 10 mL was obtained to measure depression-related blood markers. Following the basic instructions on operation of the VR device (Pico 4 All-in-One VR, China), participants were asked to take the HMD device home and to view the VR content in a comfortable sitting or reclining position for 10 min per day, four times per week, for three weeks. The researchers followed up with the participants by phone once a week to ensure that they were using the VR as prescribed and to check for any discomfort. Three weeks later, participants returned to Jungwon University for a follow-up examination. To minimize the impact of the non-use period, we scheduled a follow-up visit within one week of the initial use. At the follow-up visit, participants again completed the K-BDI-II questionnaire and had venous blood drawn. After centrifugation of whole blood, the serum was isolated and maintained at -80℃ before measurement. To reduce the effect of circadian rhythms, the blood draw times did not differ by more than 3 clock hours at baseline and follow-up visits.

VR device and development of nature experience-based VR content

The VR device consisted of an HMD with a speaker and a pair of haptic motion controllers. The nature experience-based VR content was developed in collaboration with Gocrates, Inc. (Seoul, Republic of Korea). The VR content included the following in video format: a view of a recreational forest in autumn, a conversation between a monk and a man at a temple, and a man walking quietly near a

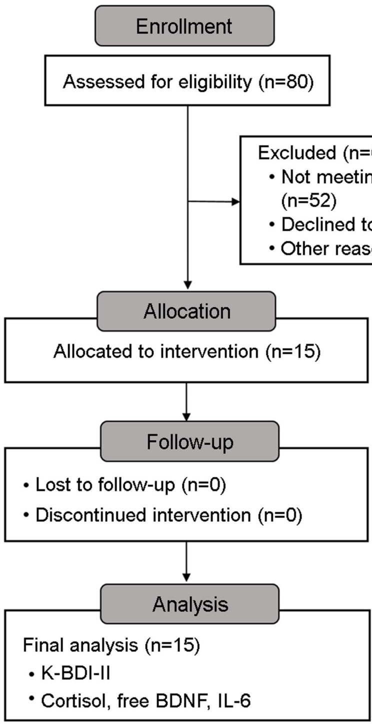

Fig. 1. Selection flow of participants.

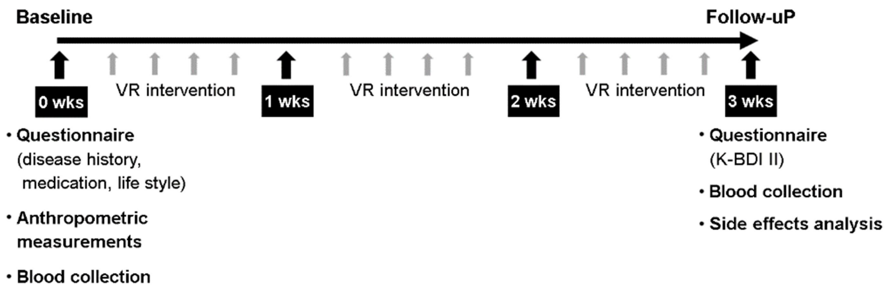

Fig. 2. Overall study design and experimental procedures.

flowing river. The VR contents were obtained with a high-quality 360-degree camera, and visual effects were added after editing to create a three-dimensional environment by experts in Dexter Studios, Inc. (Seoul, Republic of Korea).

Measurement of depressive symptoms and free BDNF, cortisol, and IL-6 levels

The level of depressive symptoms was assessed with the 21-item K-BDI-II, which is the Korean translated version of the BDI-II (Steer et al., 1999; Strunk and Lane, 2017). The reliability and validity of the K-BDI-II were demonstrated in a previous study (Sung et al., 2008). To determine the levels of free brain-derived neurotrophic factor (BDNF), cortisol, and interleukin-6 (IL-6), venous blood samples were drawn from the participants before and after VR use. The blood was centrifuged to acquire serum at 3,000 rpm and 4℃ for 10 min. Concentrations of these blood markers were determined using a commercial enzyme-linked immunosorbent assay (ELISA) kit (Quantikine ELISA, R&D systems, Minneapolis MN, USA) according to the manufacturer's instructions.

Evaluation of VR sickness symptoms

Cybersickness symptoms of nature experience-based VR were analyzed through interviews at the follow-up visit. Participants were asked to record physical and visual side effects, including general discomfort, fatigue, boredom, drowsiness, headache, dizziness, concentration problems, tired eyes, aching eyes, eyestrain, blurred vision, and difficulties focusing during the VR intervention, as in the Virtual Reality Symptom Questionnaire (VRSQ) (Ames et al., 2005). At the follow-up visits, the side effects were recorded through interviews. Multiple responses were allowed for the side-effect questions.

Statistical analysis

All data were expressed as mean (SD). The χ^2 test was used for analysis of categorical variables. To compare the values of the questionnaire-based depressive symptoms and blood markers before and after VR intervention, the paired *t*-test was performed. All statistical analyses were performed using SPSS version 20.0 (SPSS; Chicago, IL, USA), and a *P*-value less than 0.05 was considered statistically significant.

RESULTS

Baseline characteristics of the study participants

Table 1 presents the baseline characteristics of the study participants. The average age of the participants was the mid-20s. There were slightly more male subjects (60%) than female, and all subjects were current drinkers, not married, and had no history of disease. Non-smokers comprised the

Table 1. Baseline characteristics of participants

Variables	Values
Participants, *n*	15
Age (y), mean (SD)	25.7 (6.2)
Gender, *n* (%)	
Female	6 (40)
Male	9 (60)
Education, *n* (%)	
< high school	0 (0)
≥ college	15 (100)
Drinker, *n* (%)	
Past drinker	0 (0)
Current drinker	15 (100)
Smoker, *n* (%)	
Non-smoker	7 (46.7)
Past smoker	4 (26.7)
Current smoker	4 (26.7)
Marital status, *n* (%)	
Single	15 (100)
Married	0 (0)
Disease, *n* (%)	
Yes	0 (0)
No	15 (100)
Medication use, *n* (%)	
Antidepressant	0 (0)
Antipsychotic	0 (0)
Mood stabilizer	0 (0)
Benzodiazepine	0 (0)
Other psychotropic medication	0 (0)
Sleep duration (min), mean (SD)	408 (114.4)
K-BDI-II score, mean (SD)	25.7 (7.7)

Abbreviations: SD, standard deviation; K-BDI-II, Korean version of the Beck Depression Inventory-II

Table 2. Effects of nature-based VR intervention on individual depression inventory components

Depression inventory components	Before, mean (SD)	After, mean (SD)	95% CI	*P*-value
Sadness	0.9 (0.5)	0.7 (0.6)	-0.03 to 0.43	0.082
Pessimism	1.3 (0.7)	0.9 (0.9)	-0.28 to 0.95	0.265
Past failures	1.1 (0.7)	0.7 (0.8)	0.00 to 0.93	0.048
Loss of pleasure	1.7 (0.5)	0.7 (0.6)	0.53 to 1.47	<0.001
Guilt	1.4 (0.8)	0.8 (0.6)	0.10 to 1.10	0.023
Feelings of punishment	1.3 (1.0)	0.5 (0.8)	0.10 to 1.50	0.028
Self-loathing	1.4 (0.7)	0.7 (0.7)	0.34 to 1.12	0.001
Self-criticism	1.4 (0.7)	0.7 (1.0)	0.20 to 1.27	0.010
Suicidal thoughts or ideation	0.7 (0.6)	0.2 (0.4)	0.11 to 0.82	0.014
Crying	0.9 (0.9)	0.3 (0.7)	-0.09 to 1.29	0.082
Restlessness	1.2 (0.9)	0.5 (0.7)	0.20 to 0.27	0.010
Loss of interest	1.8 (0.9)	1.0 (0.8)	0.17 to 1.43	0.017
Indecisiveness	1.4 (0.9)	0.7 (0.6)	0.09 to 1.25	0.027
Feelings of worthlessness	1.4 (0.9)	0.7 (0.6)	0.09 to 1.25	0.027
Loss of energy	1.2 (0.8)	0.8 (0.7)	-0.06 to 0.86	0.082
Changes in sleep pattern	1.4 (0.9)	0.7 (0.8)	0.02 to 1.32	0.045
Irritability	1.1 (0.7)	0.4 (0.6)	0.17 to 1.16	0.120
Changes in appetite	1.2 (0.7)	0.6 (0.6)	0.19 to 1.01	0.007
Difficulty concentrating	1.3 (0.7)	0.6 (0.7)	0.24 to 1.22	0.006
Fatigue	1.3 (0.7)	0.6 (0.7)	0.40 to 1.06	<0.001
Loss of interest in sex	0.7 (0.7)	0.2 (0.4)	0.04 to 0.97	0.068

Abbreviations: VR, virtual reality; SD, standard deviation; CI, confidence interval

largest proportion (46.7%) of the study sample. None of the study subjects was using psychiatric medication. The average daily sleep duration was 6.8 h. The average K-BDI-II score was 25.7, which indicates moderate depression.

Effects of nature experience-based VR intervention on depressive symptoms

Nature experience-based VR intervention led to an approximately 50% reduction in the depressive symptom score (before 25.7±7.7 vs. after 12.5±8.3 (P<0.001)) (Fig. 3A). We further analyzed individual depression inventory component scores to investigate which aspects of depressive symptoms were improved by our VR therapy (Table 2). Fifteen of the 21 items showed significant improvement after the three-week VR intervention. Of these, loss of pleasure and fatigue experienced the largest improvement (P<0.001).

Table 3. VR sickness symptoms during nature-based VR intervention

Symptoms	Frequency of response (%)
Nausea	3 (20)
Dizziness	2 (10)
Tired eyes	2 (10)
General discomfort	1 (5)

Abbreviations: VR, virtual reality

Effects of nature experience-based VR intervention on depression-related blood markers

There were no significant differences in serum levels of cortisol (before 58.4±24.3 vs. after 56.9±15.2), free BDNF (before 3643.9±654.5 vs. after 3067.7±979.3), and IL-6 (before 0.61±2.96 vs. after 1.47±3.14) following VR intervention (Fig. 3B-3D).

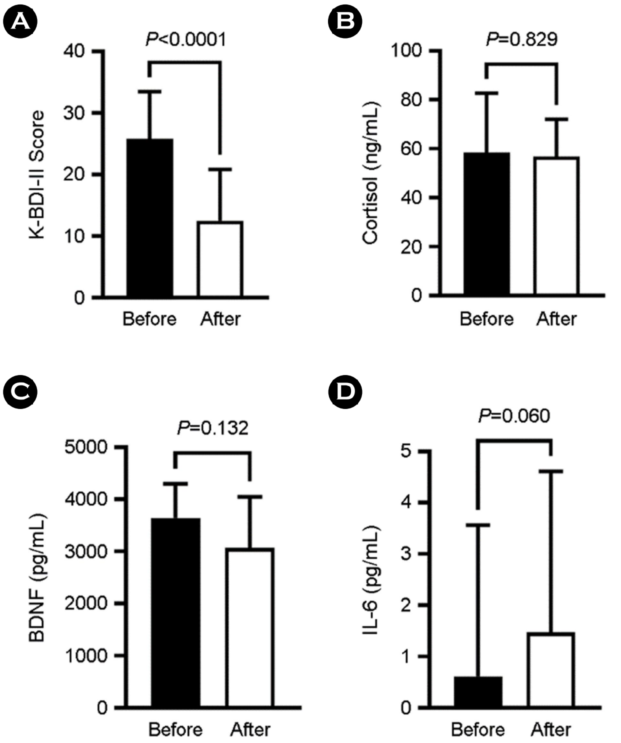

Fig. 3. Comparison of K-BDI-II scores (A) and levels of cortisol (B), BDNF (C), and IL-6 (D) before and after nature experience-based VR intervention.

VR sickness symptoms

Twenty percent of participants (*n*=3) reported VR sickness symptoms (Table 3). Nausea was the most common VR symptom after viewing nature experience-based VR content. Dizziness (10%) and tired eyes (10%) were also complaints from participants.

DISCUSSION

We found that our nature experience-based VR treatment significantly improved depressive symptoms with a low frequency of VR sickness. However, the levels of depression-related blood markers did not decrease by VR intervention, showing a discrepancy between subjective (questionnaire) and objective (blood marker measurements) outcomes. Although the restorative effects of nature can be influenced by a number of factors, including type of contact, duration of exposure, and means of nature experience delivery, the impact is broad and robust (Bratman et al., 2015). According to stress reduction theory, the possible mechanism by which nature experiences induce positive emotions is through parasympathetic nervous system (PNS) activation (Ulrich, 1981), which can reduce stress and autonomic arousal.

The pathophysiology of depression involves multiple metabolic pathways, the immune system, the nervous system, and the hypothalamic–pituitary–adrenal axis. Therefore, the biomarkers related to activation or inhibition of these pathways may be predictors of outcomes in patients with depression (Jani et al., 2015; Strawbridge et al., 2015). BDNF is a protein that plays an important role in synaptic plasticity, neurodevelopment, and maturation of neurotransmitter systems (Carvalho et al., 2008; Martinowich and Lu, 2008; Reichardt, 2006), and serum BDNF level is negatively correlated with the severity of depressive symptoms (Karege et al., 2002). Levels of pro-inflammatory cytokines, such as IL-6, IL-1β, and TNF-α, are often higher in depressed than in non-depressed subjects (Dowlati et al., 2010; Strawbridge et al., 2017), while antidepressant treatment reduces their levels (Hannestad et al., 2011; Sutcigil et al., 2007).

Contrary to expectation, however, we failed to observe significant reductions of depression-related blood markers by nature experience-based VR intervention, whereas the subjective measures of depressive symptoms were improved. Several possible reasons exist for this discrepancy. First, it may take longer for improvements in depressive symptoms by VR exposure to actually translate into improvements in blood markers. Second, the nature experience-based VR in this study may not be sufficient to induce physiological changes of multiple body systems in terms of components, duration of exposure, or mode of delivery. Third, because only three blood markers were assessed to investigate the effects of our VR system, it is possible that improvements in depressive symptoms that were not reflected by blood markers were overlooked.

Exposure to VR is known to cause various side effects in many people, such as nausea, headache, and eye fatigue (Chen et al., 2015; Ohyama et al., 2007), also known as VR sickness. Participants in our nature experience-based VR complained of several types of VR sickness. A conflict between accommodation and vergence depth cues on stereoscopic displays (Carnegie and Rhee, 2015), display overheating in enclosed spaces, and blue light exposure are important causes of discomfort in VR applications. Nausea and dizziness are the most common symptoms of motion sickness in VR, and our study found similar results. Individual differences exist in susceptibility to VR sickness (Mittelstaedt, 2020), and women are more susceptible to nausea in a VR environment than men. This is supported by the finding that all subjects in our study who complained of nausea were women.

Our study had several limitations. First, we did not include an appropriate matched control group, such as an urban experience-based VR intervention group. Therefore, the possibility of a placebo effect existed. Second, the age range of our participants was 20~50 s. Consequently, it was difficult to extrapolate these results to older people. Third, depressive symptoms were evaluated by only the K-BDI-II questionnaire. In addition to BDI-II, several instruments have been widely used to evaluate depressive symptoms in adult populations, such as the Center for Epidemiological Studies Depression Scale (CES-D) (Radloff, 1977) and the Geriatric Depressive Scale (GDS) (Yesavage et al., 1982). However, BDI-II is one of the most widely used self-rating scales for screening of depression and is used to measure the behavioral manifestations and severity of depression. Furthermore, it has many advantages, including its simplicity and rapidity of administration (via questionnaire), high validity and reliability, and applicability to a wide range of ages.

In conclusion, our nature-based VR experience is an effective adjunctive treatment for alleviating depressive symptoms in subjects who have difficulty accessing the real natural environment. Further research with a randomized controlled trial design and a larger number of subjects is needed to confirm the effectiveness of our proposed approach in alleviating depressive symptoms.

ACKNOWLEDGEMENTS

The authors thank Ms. Hee-Jeong Joo, Ji-Yoon Kwak, Da-In Kim for assisting study procedures.

This research was supported by "Regional Innovation Strategy (RIS)" through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (MOE) (2021RIS-001).

CONFLICT OF INTEREST

The authors have no potential conflicts of interest to disclose.

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https://doi.org/10.15616/BSL.2024.30.1.1

Cite this article as: Lee DB, Yoo SL, Pyo SS, Kim J, Kim BG, Kim SW, Ko BJ, Yoon DW. Nature Experience-based Virtual Reality Improves Depressive Symptoms in a Young Population: A Pilot Study. Biomedical Science Letters. 2024. 30: 1-9.