

Virtual Reality Alleviates Post-Stroke Depression by Regulating FGF21

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Research

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Abstract

Background: Post-stroke depression(PSD) lacks timely and effective treatment and virtual reality (VR) technology can create a lifelike experience and simulate users' physical presence in an immersive environment. It has been confirmed to have a positive effect on stroke and depression. Data about the efficacy VR on PSD are limited. The intensification of fibroblast growth factor 21(FGF21) can improve depression and other emotional symptoms, but there is no study on its role in PSD.

Methods: We enlisted 76 PSD patients (6 lost) and divided into the experimental group and control group randomly. The patient underwent psychological rehabilitation once a week for 50 minutes each time for a total of 12 weeks. The patients in the experimental group received psychological counseling and VR rehabilitation while patients in the control group also took the same pattern but without VR rehabilitation. The Hamilton Depression Scale (HAMD) and Hamilton Anxiety Scale (HAMA) were evaluated before rehabilitation, in the 4th week and at the end of rehabilitation respectively in two groups for the sake of observing changes in the patients' depression. Then 8 people in each group did functional near-infrared spectroscopy (fNIRS), and blood samples were taken for detection with brain-derived neurotrophic factor (BDNF), IL-6, TNF- α and FGF21 by ELISA.

Results: The result of fNIRS showed the hemodynamic activation in the prefrontal region of the experimental group was significantly increased. Both groups of FGF21 increased and compared with the control group, the experimental group has a greater upsurge and a faster increase rate.

Conclusions: VR alleviates PSD. FGF21 is closely related to PSD and it is likely to be a potential pathological mechanism of PSD. It suggests that VR is possible to improve PSD by increasing FGF21.

Trial registration: We registered in Chinese Clinical Trial Registry which is the first level registration organization of WHO international clinical trial registration platform. The registration number is ChiCTR1900027987, the date of registration December 7, 2019.

1. Background

Stroke is currently the second leading cause of death in the world.^[1] Approximately one-third of stroke survivors experience major depression.^[2] This condition can hurt cognitive function, motor functional recovery, and survival.^[3] Post-stroke depression (PSD) is the most prevalent and important neuropsychiatric sequelae of stroke, characterized by somniphobia, depression, anxiety, inferiority, and even suicide.^[4] Due to lack of consciousness in post-stroke rehabilitation and lack of rehabilitation personnel, most attention is focused on rehabilitating extremity function, while a psychological function is neglected.^[5]

Since PSD treatment is often laborious and limited, a curative effect is rarely achieved. As a result, there is an urgent need to find new psychotherapy. Virtual reality (VR) has excelled in various fields.^[6] VR uses software to generate realistic images, sounds, and other sensations, which can create a lifelike experience

and simulate users' physical presence in an immersive environment to achieve the interactive situation.^[7] VR has made remarkable achievements in various diseases. One of the latest studies revealed that VR could relieve pain in patients with burn injuries and others who suffer from toothache without huge side effects.^[8, 9] In addition, VR-based simulator training advanced operation efficiency and surgical proficiency.^[10] Extensive research has demonstrated that VR distinctly stimulates the brain, producing outstanding results in neuropsychological diseases.^[11] VR has yielded remarkable advancement for improving balance and motor skills in children and adolescents with cerebral palsy.^[12] Studies have indicated that virtual reality effects on stroke rehabilitation are positive in body function and structure.^[13] Because interaction adversities in the world are at the center of psychic health controversies,^[14] the most rewarding interventions facilitate people thinking, reacting, and behaving differently in dilemmas. Surprisingly, no thorough investigation of VR in PSD has been conducted, so we performed a randomized control trial with PSD patients using a VR psychological rehabilitation system.

Functional near-infrared spectroscopy(fNIRS)has recently emerged as a new non-invasive brain imaging technology. It investigates the changes in cerebral oxyhemoglobin (Oxy-Hb), deoxyhemoglobin (Deoxy-Hb), and total haemoglobin (Total-Hb) concentrations during tasks to detect hemodynamic activity in cerebral cortex in real-time. By observing hemodynamic changes, the brain's neural activity can be deduced through the neurovascular coupling law.^[15] The major advantage of real-time detection is the ability to capture recurring brain activity. This method applies to diverse participants at different times. It has demonstrated excellent stability, implying that fNIRS may evaluate the therapeutic effect of VR in PSD and guide related treatments.^[16]

To date, no mechanism of PSD occurrence has been established. Fundamental research has indicated that energy metabolism can affect depression.^[17] Fibroblast growth factor 21 (FGF21) is an endocrine member of FGF family, holding a potent and central role in multi-pleiotropic metabolic actions.^[18] Numerous studies indicate that low heparin-binding affinity enables FGF21 to cross the blood-brain barrier by simple diffusion.^[19] Extensive research recognizes that FGF21 exhibits a neuroprotective effect^[20] and is connected with depression. Mitochondrial dysfunctions make the brain susceptible to aerobic metabolism impairment.^[21] However, little attention has been paid to the relationship between FGF21 and PSD. In this work, we are the first to probe this correlation.

Neurotrophins and inflammatory cytokines are recognized mechanisms of PSD.^[22–23] In the early stage of stroke, the decrease of brain-derived neurotrophic factor (BDNF) may predispose patients to PSD.^[24] Inflammatory cytokines, such as IL-6 and TNF- α , play a role in stimulating acute ischemic stroke and PSD development.^[25, 26] As a result, we propose that VR can alleviate PSD by improving FGF21.

2. Materials And Methods

2.1 Participants

Seventy-six PSD patients were enrolled from The Second Affiliated Hospital of Wenzhou Medical University. We conducted a statistical analysis based on patients collected past medical history and demographic data in the two groups.

The study was authorized by the Ethics Committee of The Second Affiliated Hospital of Wenzhou Medical University, and each participant signed an informed consent form. Our research was registered in the Chinese Clinical Trial Registry (registration number: ChiCTR1900027987).

All patients conform to the following inclusion criteria: (1) Ischemic stroke was diagnosed by CT or MRI; (2) Depression occurs within three months after stroke; (3) Mild to moderate depression with a score of HAMD-17 between 8 and 24; (4) Age between 30 and 90 years; (5) Clear consciousness with no dementia, aphasia and other symptoms [MMSE score ≥ 27], and can complete psychological tests; and (6) Who can accept VR rehabilitation.

Patients who met the following criteria were excluded: (1) Patients with severe neurological deficit symptoms [NIHSS score > 24] or accompanied by consciousness disturbance; (2) Patients with severe language disorder that fail to complete the scales; (3) Patients suffering from other mental disorders like schizophrenia or severe cognitive impairment; (4) Patients with other grievous organic diseases such as heart disease, lung disease, cancer or patients with autoimmune diseases or long-term use of immunosuppressants; and (5) Who is not willing to receive VR rehabilitation.

2.2 Study Design

This study is double-blind, and all patients were diagnosed with depressive symptoms within three months [HAMD-17 is between 8 and 24]. Each patient did not know the psychological rehabilitation modality of the other group, every assessor, psychologist, and statistician either. The experiment proceeded for 12 weeks, and MMSE, NIHSS, HAMD-17, HAMA and IL-6, TNF- α , FGF21, and BDNF of blood samples were assessed for baseline at the first onset. In the 4th week and the end of the experiment, the patients' HAMD-17, HAMA, IL-6, TNF- α , FGF21, and BDNF of blood samples were obtained again. The flowchart followed is presented in Fig. 1.

2.3 Grouping

All subjects were divided into two groups by random number table method, without any restriction, intervention, or adjustment in advance or during implementation. Subjects and participants in the experiment cannot know or decide which group the patient will be assigned to receive rehabilitation before.

VR group (experimental group): The group included 39 subjects (4 of them lost and the remaining 10 are males and 25 are females) with average age of (71.01 ± 11.14) years old. In addition to psychological counsel, the patients were treated with VR psychological rehabilitation program, which endures 50 min alone at their homes or communities by a psychologist once a week, which lasted for 12 weeks.

Psychological counsel group (control group): The group included 37 subjects (2 of them lost and the remaining 11 are males and 24 are females) with average age of (68.86 ± 6.94) years old. Psychological counseling was provided to patients concurrently with the VR group at their homes or communities once a week for 12 weeks.

2.4 Demographics

We recruited 76 PSD patients (25 males and 51 females) with an average age of (63.01 ± 14.45) years. A total of 6 patients were lost during follow-up; two of them moved to other cities, and four patients were lost due to unwillingness to cooperate. The demographics of subjects are exhibited in Table 1. There is no significant difference in age ($p = 0.219$), gender ($p = 0.794$), MMSE ($p = 0.713$) and NIHSS ($p = 0.587$) between the two groups. The average score of MMSE and NIHSS illustrates that patient had clear consciousness and in the stage of mild to moderate stroke.

Table 1

Clinical characteristics of participants. Abbreviations: VR virtual reality, PC psychological counseling, Hb hemoglobin, CRP c-reactive protein, CKD chronic kidney disease, DM diabetes mellitus, CHD chronic heart disease, PAD peripheral artery disease, NIHSS national institute of health stroke scale and MMSE mini-mental state examination. Data were presented as the mean \pm SD and n (%).

Characteristics	PC + VR (n = 39)	PC(n = 37)	<i>t</i> / χ^2	<i>p</i> value
Age, years	71.01 \pm 11.14	68.86 \pm 6.94	-	0.219 ^a
Gender, n (%)			0.068	0.794 ^b
Male	14(35.90)	13(35.14)		
Female	25(64.10)	24(64.86)		
Education, n (%)	17(43.59)	17(45.95)	-	0.270
Illiteracy	14(35.90)	15(40.54)		
Primary school	8(20.51)	5(13.51)		
Middle school				
Hb g/L	129.23 \pm 15.93	132.20 \pm 12.97		
CRP, mg/L	4.22 \pm 3.60	3.81 \pm 3.47		
Comorbidities				
CKD, n (%)				
No	32(82.05)	33(89.19)		
Yes	7(17.95)	4(10.81)		
DM, n (%)				
No	22(56.41)	25(67.57)		
Yes	17(43.59)	12(32.43)		
CHD, n (%)				
No	27(69.23)	31(83.79)		
Yes	12(30.77)	6(16.22)		
PAD, n (%)				
No	27(69.23)	31(83.79)		
Yes	12(30.77)	6(16.22)		
Marital, n (%)				

Characteristics	PC + VR (n = 39)	PC(n = 37)	t/χ^2	p value
No	5(12.82)	5(13.51)		
Yes	34(87.18)	32(86.49)		
NIHSS score	5.09 ± 1.93	5.34 ± 2.01	-0.545	0.587 ^c
MMSE score	27.00 ± 2.88	27.23 ± 2.26	-0.369	0.713 ^c
Days after stroke at randomization	87	91		

2.5 VR psychological rehabilitation program

VR psychological rehabilitation program takes the family and community environment as the basic rehabilitation environment. As shown in supplementary materials, the VR program is equipped with an immersive virtual environment, music, and psychological counseling language. After wearing a VR helmet, patients can simultaneously enjoy visual and auditory stimulation with corresponding art therapy. Meanwhile, patients can stand up to follow the switch of vision and perform slight movements. Compared with psychological counseling, patients not only receive more sensory stimulation but also perform appropriate actions, and it relieves some patients from the defense state to psychologists.

2.6 Near-infrared brain functional imaging system

In Fig. 2, a 52-channel NIRS device (ETG-4000, Hitachi, Kyoto, Japan) was used to measure the three types of relative concentration changes of Oxy-Hb, Deoxy-Hb, and Total-Hb by near-infrared light of a specific wavelength. The instrument has 17 emissions and detector probes. An 11 × 3 mode was utilized to arrange the probes. We selected the block task to investigate concentration changes of cerebral oxyhemoglobin (Oxy-Hb), deoxyhemoglobin (Deoxy-Hb), and total haemoglobin (Total-Hb) during cognitive tests. Each block contains a 10-second (s) pre-task rest, a 20-s VR and psychological counseling or psychological counseling alone, and a 10-s post-task rest.

2.7 Tests methods and data acquisition

HAMD-17, HAMA, MMSE, and NIHSS were executed to assess depressive, anxious symptoms, cognitive function, and stroke severity. Mini-mental state examination (MMSE) contains seven cognitive domains: time orientation, place orientation, immediate memory, attention and calculation, delayed memory, language, and visual space, reflecting the intelligence state and horizontal cognitive impairment of the subjects comprehensively, accurately, and rapidly. A score greater than or equal to 27 points is considered a normal cognitive function. It provides a basis for clinical psychological diagnosis, treatment, and neuropsychological research.^[27] Hamilton developed Hamilton Depression Scale (HAMD-17) and Hamilton Anxiety Scale (HAMA) in 1960, which is the most commonly used scale in clinical evaluation of depression and anxiety which can evaluate the severity of disease and curative effect. The score of HAMA-17 between 8 and 24 can be diagnosed as depression, and the score between 8 and 21 is

considered anxious.^[28] National Institute of Health stroke scale (NIHSS) is a practical scale model, with high reproducibility between trained, different examiners, focused on posterior circulation strokes. A baseline score less than 6 may recover well.^[29] Experienced psychiatrists assessed all patients.

Blood samples were drawn from the anterior cubital vein of each subject after admission, then placed in the anticoagulant tube and sent to the laboratory in The Second Affiliated Hospital of Wenzhou Medical University. After that, all samples were placed under low temperature and centrifuged to be examined. The main measurement method was ELISA (purchased from SHANGHAI WESTANG BIO-TECH CO., LTD), and the target indexes were IL-6, TNF- α , FGF21 and BDNF.

2.8 Statistical Analysis

Statistical analysis was calculated utilizing SPSS 25.0 (SPSS Inc.). Categorical variables were expressed as numbers and percentages, and continuous variables as means \pm SDs unless otherwise stated. Data of the two groups were compared at baseline (before the experiment), the fourth week, and the end of the experiment. Chi-square test was employed for categorical variables, and continuous variables were assessed utilizing t-tests and repeated measures ANOVAs, and the correlation analysis was performed using Pearson's correlation analysis. The level of significance was set at 0.05.

3. Results

3.1 Hemodynamic changes during the task

As Fig. 3 showed, compared with the control group, the hemodynamic activation in the prefrontal region of the experimental group was significantly increased, the activation degree in ROI region was significantly higher, and OxyHb concentration was significantly higher than that of the control group. Deoxy Hb concentration was also significantly lower than that of the control group.

3.2 Differences in depressive status

The purpose of HAMD-17 and HAMA was to estimate the depression status of PSD patients and evaluate the rehabilitation efficacy of the two groups of patients. The lower the score, the better the advancement of the depression state, and the faster the score decreases, the more convincing the competence. There was no significant difference between experimental and control groups in HMAD-17 and HAMA at the baseline ($p = 0.255$ and $p = 0.137$, respectively), whereas in the fourth and twelfth weeks, the experimental group scores were substantially lower than those of the control group ($p = 0.001$, $p < 0.001$ respectively). Besides, it is apparent from the figure that both groups were lower than the baseline level in the fourth week, and the twelfth week was substantially lower than the fourth week, but the decline rate of the experimental group was faster than that of the control group. The scale scores of the three evaluations of the two groups are exposed in Fig. 4.

3.3 Differences in neurotrophic factor

We selected BDNF as the detection factor; lower BDNF portends more severe depressive symptoms. Therefore, BDNF increase can predict the recovery of depressive symptoms. As demonstrated in Fig. 5, BDNF is enhanced in both groups. The BDNF in the experimental group increased promptly, while the control group was relatively feebly ($p = 0.011$ and $p < 0.001$, respectively), and the lifting speed of the fourth week of the two groups is far less than that of the twelfth week. These results indicated that VR and psychological counseling affect improving BDNF, and VR can enhance BDNF rapidly and advantageously. Accordingly, it can be inferred that the rehabilitation effect of VR is better than psychological counseling.

3.4 Differences in inflammatory cytokines

Inflammatory factors, such as IL-6 and TNF- α , can predict PSD prognosis like BDNF. The results obtained from the preliminary analysis of Fig. 6 illustrated that IL-6 and TNF- α of the experimental group decreased expeditiously, especially after the fourth week, compared with the control group, and the ultimate stage was much lower than those in the control group ($p = 0.013$ and $p < 0.001$, respectively). No significant differences of IL-6 and TNF- α were observed between baseline and the fourth week in both groups. Further statistical tests revealed that the difference between the fourth week and the twelfth week was astonishing, and the accomplishment of the experimental group is particularly prominent. All the above results can be speculated that the two groups effectively alleviate PSD in the later stage. Compared with psychological counseling, VR can reduce inflammatory cytokines and has a better curative consequence on PSD.

3.5 Differences in FGF21

The single most striking observation to emerge from data comparison was FGF21 changes. FGF21 in both groups demonstrated an ascending trend, confirming that FGF21 may have the same development and impact in PSD as in depression. Additionally, it could be found that FGF21 in the experimental group heightened fleetly than that in the control group. Interestingly, FGF21 in the 4th week of the control group was not significantly different from the baseline level and FGF21 in the 12th week was not greatly different from the 4th week. This demonstrated that while the increase in FGF21 aided in the improvement of PSD, the effect was stagnant in the absence of VR. Nonetheless, FGF21 of the experimental group was significantly different from that of the control group, and the consequence was more advanced in the twelfth week ($p < 0.001$). As the comparison within the group demonstrates, there is an upward trend in the subsequent period when compared to the previous period. The specific chart is displayed in Fig. 7. FGF21 levels in both groups increased, suggesting that FGF21 augmentation can mitigate the depressive state of PSD patients. Together these results provide important insights that FGF21 may be a potential pathological mechanism underlying PSD, by which VR can more effectively alleviate symptoms.

4. Discussion

In this study, we unitized HAMD-17 and HAMA to assess depression and anxiety of two groups of PSD patients before and after rehabilitation. The most important clinically relevant finding was that VR could effectively alleviate depression and anxiety in PSD patients. Apart from that, as known, BDNF has been implicated in PSD pathology and treatment.^[30] Substantial evidence indicates a decisive aspect of BDNF promoter methylation in patients with depression^[31, 32] and anxiety^[33]. BDNF analysis results presented the most conclusive evidence yet that VR is inextricably linked to the excellent prognosis of PSD.

Furthermore, as an objective measure of brain function, functional near-infrared imaging also reveals that VR has a beneficial impact on PSD. The increased oxyhemoglobin concentration in the brain indicates that neurons in this region are more active, and the decreased concentration of deoxyhemoglobin can indirectly explain this fact. Given that the prefrontal region is closely related to depression symptoms^[34], VR can help PSD patients relax more than psychological counseling alone and has a better curative effect on PSD.

Another source of strong evidence is that as inflammatory factors, such as interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) decreased considerably, the decline rate was accelerated and declined more under VR intervention. Prior research has indicated that IL-6 and TNF- α elevate inflammatory immune response, resulting in neurotransmitter secretion disorder and neural plasticity reduction, holding an important role in PSD occurrence.^[35] The ratio of TNF- α and IL-6 in PSD subjects enlarged considerably.^[36] Accordingly, the decline of these two indicators also demonstrates that VR exhibits a miraculous effect on PSD. These results further support the assumption that VR can treat PSD.

The most important clinically relevant finding was FGF21 advancement. Until now, little attention has been paid to the relationship between FGF21 and PSD. Much literature has proved that FGF21 can alleviate depression symptoms; FGF21 is considered a common regulator of mood response. It upregulated pro-inflammatory cytokines by NF- κ B suppression, inhibited microglial expression in the hippocampus, and mobilized the inflammatory response in primary microglia to markedly improved depression-like behavior deficits in LPS induced depressive-like behaviors in the mouse.^[37] Another research indicates that FGF21 was recently found to exhibit a robust neuroprotective role and act as a mediator of the effects of mood stabilizers.^[38] Since FGF21 advancement can ameliorate patients' depressive states, we assume that FGF21 is a potential key marker in PSD. The difference in FGF21 levels indicated that the diversity of FGF21 in the control group was limited, and the change of FGF21 in the experimental group was extraordinarily significant. In addition, the comparison of FGF21 levels between the two groups at the end of the experiment revealed that the experimental group had significantly higher levels than the control group. Increased FGF21 levels in the experimental group corroborate previous findings that FGF21 has a beneficial impact on depression. Furthermore, the correlation analysis reveals that HAMD-17 score is intimately related to FGF21. We further suggest that FGF21 also exhibits a progressive impact on PSD. VR likely increases FGF21, which could act as a mechanism of PSD mitigation. However, ameliorating depression impact of VR on PSD patients is gradual. There are several possible explanations for this result; a possible explanation is that FGF21 alleviates depression through

metabolism. Because FGF21 can modulate emotion by mitochondrial metabolism, we devise some motion in VR compared with psychological counseling. Another possible explanation is that VR stimulates FGF21 to downregulate inflammatory factors, thus alleviating depression in PSD patients. Nonetheless, this study did not go further to delve into the mechanism of VR on PSD; thus, we cannot provide the exact mechanism. It is also conceivable through other mechanisms, which require further exploration.

Virtual reality has recently been a hot topic in post-stroke rehabilitation. VR studies have largely focused on physical rehabilitation, and few scholars investigated post-stroke psychological rehabilitation. Numerous studies demonstrate that psychological therapies could recover the disposition of PSD patients; however, numerous patients are resistant to therapy due to the disorder's tedious pattern and sluggish response. In addition, the staff time and expertise are costly for most families.^[39] VR psychological rehabilitation program features rich scenes, immersive music, and pictures and can move with screen movement; its low cost and engaging nature encourage patients to collaborate effectively.

Although this study's findings will undoubtedly be scrutinized extensively, there are some immediately dependable conclusions for this experiment that VR is progressive on PSD. The most astonishing advantage of VR is that it causes individuals to act as though they are in a real-world, allowing people to confront problems more peacefully in VR than in real life and experiment with new therapeutic methods to solve obstacles. For PSD, it could be possible to eradicate the need for any therapist input, thus significantly reducing the time required by skilled therapists. As a result, VR could assist in increasing the access to the most impressive psychological prescriptions. It may become a forward-looking option for psychological operation. We introduce the first RCT double-blind experiment to contemplate virtual reality in PSD. FGF21 is also a dominant factor in depression, but there is no research on PSD. We are also the first to probe FGF21 impact on PSD. According to current literature, this study is the first double-blind RCT study in PSD patients' homes or community. It is advantageous to establish circumstances under which neither group is aware of the other group's intervention. We assigned two groups of people to scale assessment and rehabilitation in a double-blind experiment.

This study also presented the prospects of virtual reality rehabilitation in post-stroke. The most auspicious perception leads to creating a local district model for each patient according to the highest possible ecological validity. Studies have demonstrated that rehabilitating PSD patients at home or in the community is better than in hospitals.^[40] The prospect of neurology lies in the implementation of new technologies with traditional techniques. It seems to be a limitless VR utility in neurology, especially personalized medical rehabilitation programs. This kind of personalization should result in a much more tempting perspective, such as faster social health for PSD patients. Further research is needed to advance and discover the mechanism of VR in PSD.

The most important limitation is the insufficient subjects and significant lack of follow-up based on an uncontrolled factor associated with COVID-19 incidence. Further research is required to establish a multicenter clinical study of PSD. An additional disadvantage is that the study did not collect

cerebrospinal fluid (CSF) of patients, but the peripheral blood was collected. The level of evidence was not as high as that of CSF. CSF should be collected for further research if conditions permit. Another limitation of this study is that no previous research has been conducted on how VR improves FGF21, and the mechanism of FGF21 in PSD has not been explored, which is the next hot focus of research. One weakness in this study that could affect the results is that only ischemic stroke was adopted. Due to the small sample size, there was no study on hemorrhagic stroke and no subgroup analysis of patients with different stroke locations; this is also the subject of further investigation.

5. Conclusion

The most prominent finding to emerge from this study is that VR exhibits a very excellent outcome on the psychological rehabilitation of PSD patients. The current findings support the relevance of VR and PSD. One of the most significant findings is recognizing the critical role of FGF21 in PSD. Elevated FGF21 levels lead to improvement in the depressive stage of PSD patients. In addition, it may be a new pathological mechanism of PSD or a mechanism for VR to relieve PSD. Overall, these findings indicate that VR can promote PSD, suggesting that VR may be a new treatment for PSD.

6. Abbreviations

PSD Post-stroke depression, VR virtual reality, FGF21 fibroblast growth factor 21, fNIRS functional near-infrared spectroscopy, BDNF brain-derived neurotrophic factor, IL-6 interleukin- 6, TNF- α tumor necrosis factor α , Oxy-Hb oxyhemoglobin, Deoxy-Hb deoxyhemoglobin, Total-Hb total haemoglobin, HAMD-17 the Hamilton Depression Scale, HAMA Hamilton Anxiety Scale, MMSE Mini-mental State Examination, NIHSS National Institute of Health stroke scale, CSF collect cerebrospinal fluid.

7. Declarations

7.1 Ethics approval and consent to participate

The study was authorized by the Ethics Committee of The Second Affiliated Hospital of Wenzhou Medical University (Zhejiang, China), the registration number is LCKY2019-167-02, and each participant signed an informed consent form. Our research was registered in the Chinese Clinical Trial Registry (registration number: ChiCTR1900027987)

7.2 Consent for publication

All authors have been confirmed it have not been published in other magazines.

7.3 Availability of data and materials

The datasets used and analysed during the current study are available from the authors.

7.4 Competing interests

The authors declare that they have no competing interests..

7.5 Funding

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7.6 Authors' contributions

Yihui Zhang designed the whole experimental plan and wrote the manuscript. Zekun Xing and Zhanxiang Xie were responsible for the operation, while Yuzheng Zhou was responsible for fNIRS. Shengjie Wan and Yi Luo carried out psychological consultation. Kecheng Zhou and Songhe Jiang were the major contributor in technical guidance.

7.7 Acknowledgements

Not applicable

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Figures

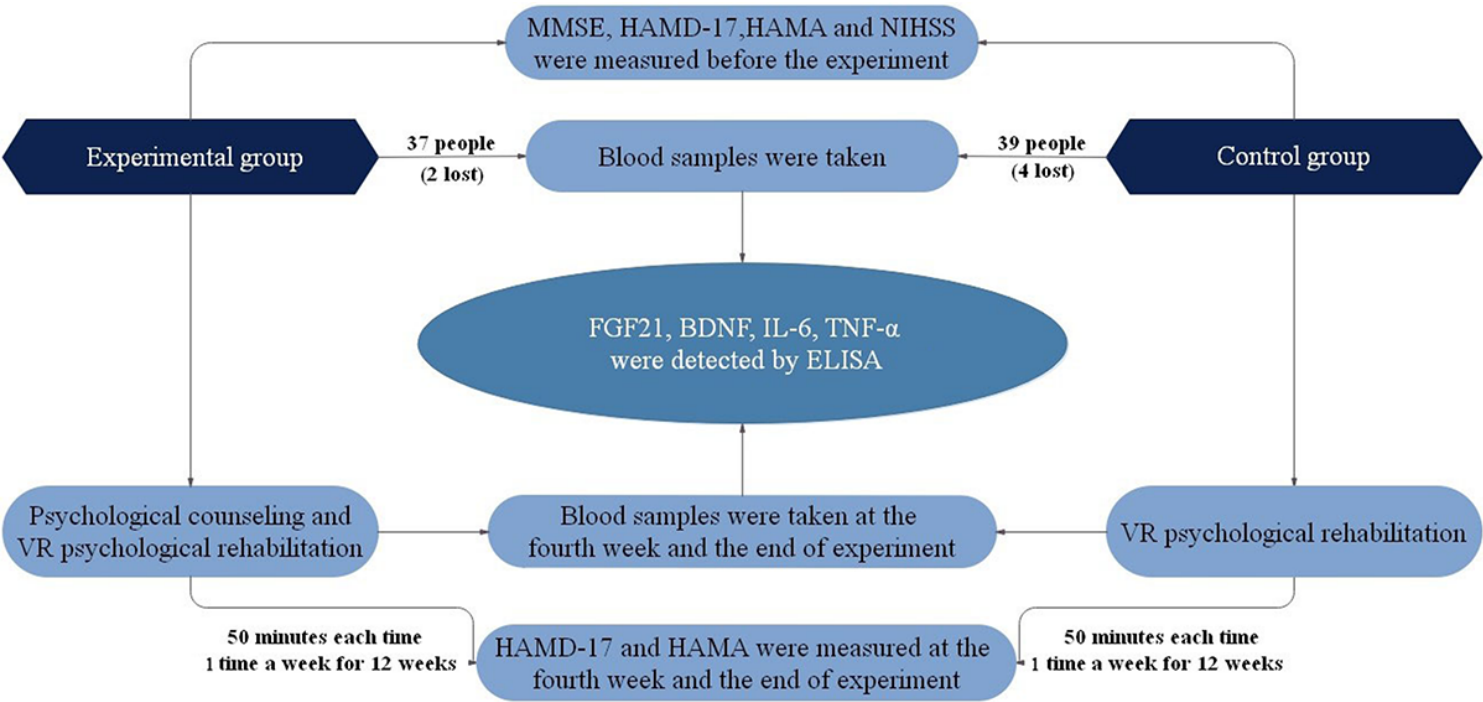


Figure 1

Study flow-chart. Abbreviations are as follows: VR, virtual Reality; MMSE, Mini-mental State Examination; HAMD-17, Hamilton Depression Scale 17; HAMA, Hamilton Anxiety Scale; NIHSS, National Institute of Health stroke scale; FGF21, fibroblast growth factor 21; BDNF, brain-derived neurotrophic factor; IL-6, Interleukin- 6; TNF- α , tumor necrosis factor alpha.

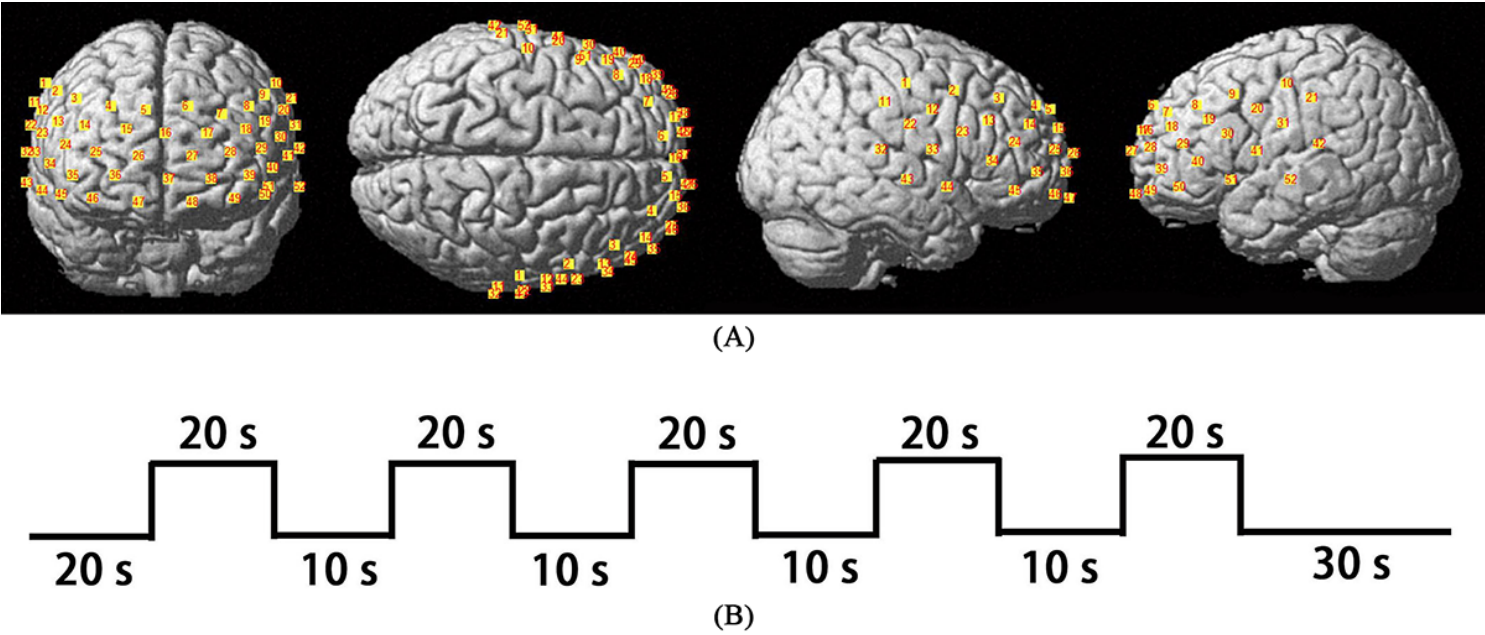


Figure 2

fNIRS and its experimental design. (A). Schematic arrangement of the fNIRS probe array. (B). Block experiment design. The first 20 seconds is the time for rest. Each 20 seconds for task time after, a total of 5 times. The interval of 10 seconds is the time for rest, the last 30 seconds is the time for rest.

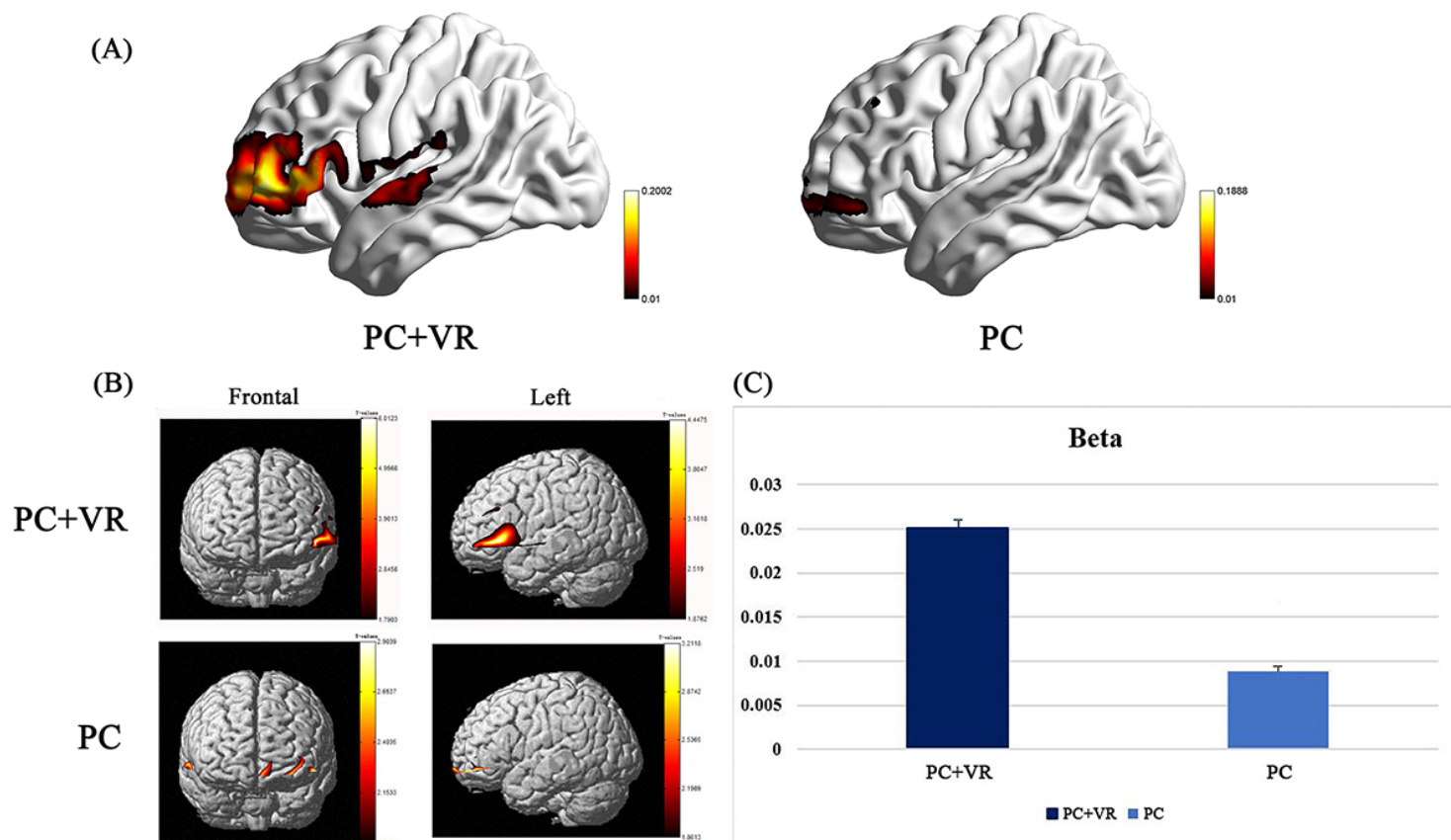


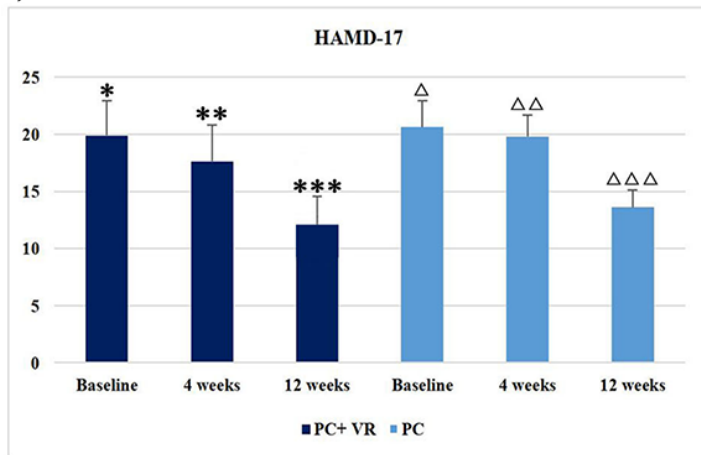
Figure 3

The results of fNIRS. (A). fNIRS activation maps for PC+VR condition and PC condition. (B). As same as (A). (C). The beta values of this two groups. $p < 0.05$.

(A)

All patients (n=70)				
	PC+ VR training, mean (SD)	PC training mean (SD)	<i>F</i>	<i>p</i> Value
HAMD-17				
Baseline	19.89 (3.07)	20.63 (2.29)	1.319	0.255
For 4 weeks	17.63 (3.17)	19.80 (1.89)	12.099	0.001
For 12 weeks	11.94 (1.94)	13.60 (1.52)	15.842	<0.001
HAMA				
Baseline	25.00 (1.96)	24.31 (1.86)	2.260	0.137
For 4 weeks	21.37 (1.96)	22.94 (1.49)	14.261	<0.001
For 12 weeks	10.66 (2.39)	13.14 (1.68)	25.339	<0.001

(B)



(C)

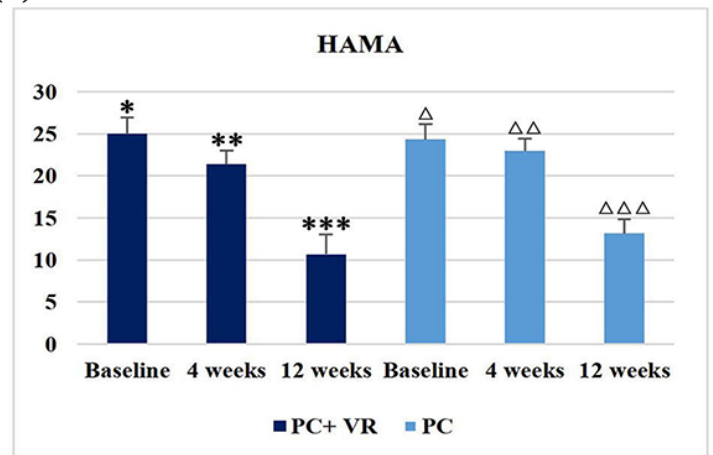


Figure 4

The histograms show HAMD-17 and HAMA scores for each group. **p* means the baseline and the 4th week comparison within the group; ***p* means the 4th week and 12th week comparison within the group; ****p* means the baseline and 12th comparisons within the group in PC+VR group. Δ*p* means the baseline and the 4th week comparison within the group; ΔΔ*p* means the second and third comparison within the group; ΔΔΔ*p* means the baseline and 12th comparisons within the group comparisons within the group in PC group. (A). The differences of HAMD-17 and HAMA between two groups. (B). HAMD 17: **p* < 0.001, ***p* < 0.001, ****p* < 0.001, Δ*p* = 0.012, ΔΔ*p* < 0.001, ΔΔΔ*p* < 0.001. (C). HAMA: **p* < 0.001, ***p* < 0.001, ****p* < 0.001, Δ*p* < 0.001, ΔΔ*p* < 0.001, ΔΔΔ*p* < 0.001. Abbreviations are as follows: HAMD-17, Hamilton Depression Scale 17; HAMA, Hamilton Anxiety Scale; VR, virtual Reality; PC, psychological counseling.

(A)

All patients (n=70)				
	PC+ VR training, mean (SD)	PC training mean (SD)	<i>F</i>	<i>p</i> Value
BDNF				
Baseline	2552.94 (426.12)	2369.04 (411.30)	3.375	0.071
For 4 weeks	2906.58 (841.31)	2416.55 (713.00)	6.911	0.011
For 12 weeks	3222.42 (564.48)	2660.45 (496.40)	19.561	<0.001

(B)

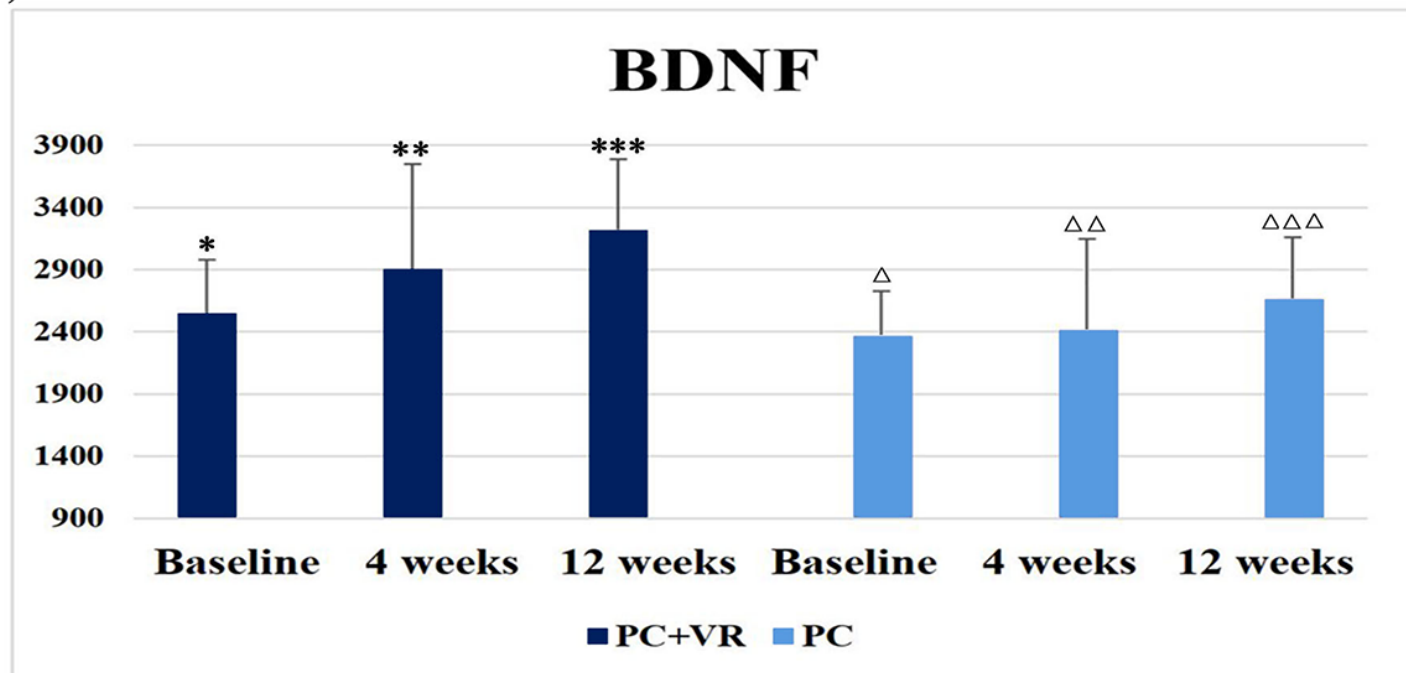


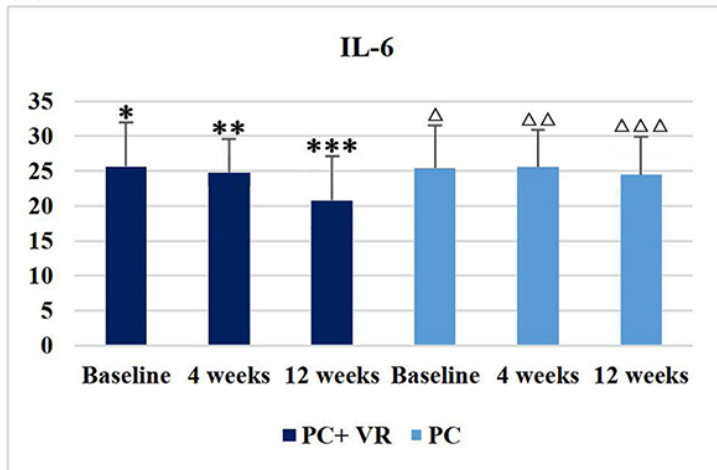
Figure 5

The histograms show BDNF level of each group. *p means the baseline and the 4th week comparison within the group; **p means the 4th week and 12th week comparison within the group; ***p means the baseline and 12th comparisons within the group in PC+VR group. Δp means the baseline and the 4th week comparison within the group; ΔΔp means the second and third comparison within the group; ΔΔΔp means the baseline and 12th comparisons within the group comparisons within the group in PC group. (A). The differences of BDNF between two groups. (B). BDNF: *p < 0.001, **p< 0.001, ***p< 0.001, Δp=0.004, ΔΔp< 0.001, ΔΔΔp< 0.001. Abbreviation is as follows: BDNF, brain-derived neurotrophic factor.

(A)

All patients (n=70)				
	PC+ VR training, mean (SD)	PC training mean (SD)	<i>F</i>	<i>p</i> Value
IL-6				
Baseline	25.64 (6.34)	25.30 (6.23)	0.050	0.824
For 4 weeks	24.96 (4.88)	25.65 (6.48)	0.250	0.619
For 12 weeks	20.90 (6.30)	24.49 (5.38)	6.558	0.013
TNF-α				
Baseline	27.58 (4.45)	27.36 (5.61)	0.035	0.852
For 4 weeks	24.70 (4.00)	27.00 (3.60)	6.397	0.014
For 12 weeks	21.41 (1.99)	24.98 (5.38)	13.613	<0.001

(B)



(C)

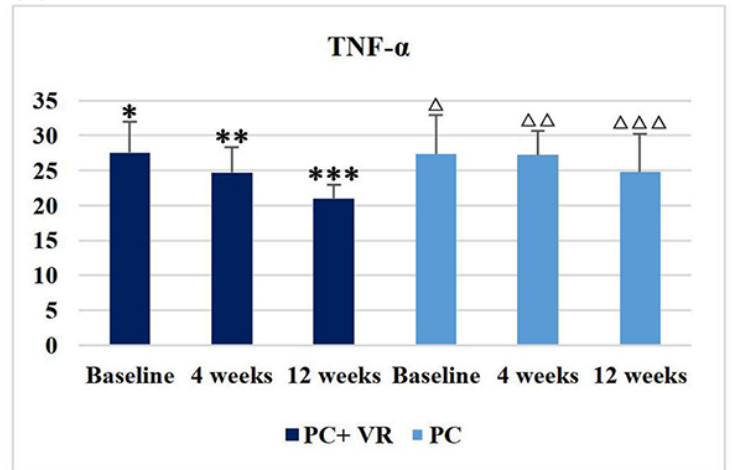


Figure 6

The histograms show IL-6 and TNF- α level of each group. **p* means the baseline and the 4th week comparison within the group; ***p* means the 4th week and 12th week comparison within the group; ****p* means the baseline and 12th comparisons within the group in PC+VR group. Δ *p* means the baseline and the 4th week comparison within the group; $\Delta\Delta$ *p* means the second and third comparison within the group; $\Delta\Delta\Delta$ *p* means the baseline and 12th comparisons within the group comparisons within the group in PC group. (A). The differences of IL-6 and TNF- α between two groups. (B). IL-6: **p* < 0.001, ***p* < 0.001, ****p* < 0.001, Δ *p*=0.001, $\Delta\Delta$ *p* < 0.001, $\Delta\Delta\Delta$ *p* < 0.001. (C). TNF- α : **p* < 0.001, ***p* < 0.001, ****p* < 0.001, Δ *p*=0.022, $\Delta\Delta$ *p* < 0.001, $\Delta\Delta\Delta$ *p* < 0.001. Abbreviations are as follows: IL-6, Interleukin- 6; TNF- α , tumor necrosis factor alpha.

(A)

All patients (n=70)				
	PC+ VR training, mean (SD)	PC training mean (SD)	<i>F</i>	<i>p</i> Value
FGF21				
Baseline	170.81 (46.44)	158.35 (42.89)	1.359	0.248
For 4 weeks	172.73 (35.96)	161.89 (33.77)	1.692	0.198
For 12 weeks	192.33 (19.25)	169.58 (30.97)	13.620	<0.001

(B)

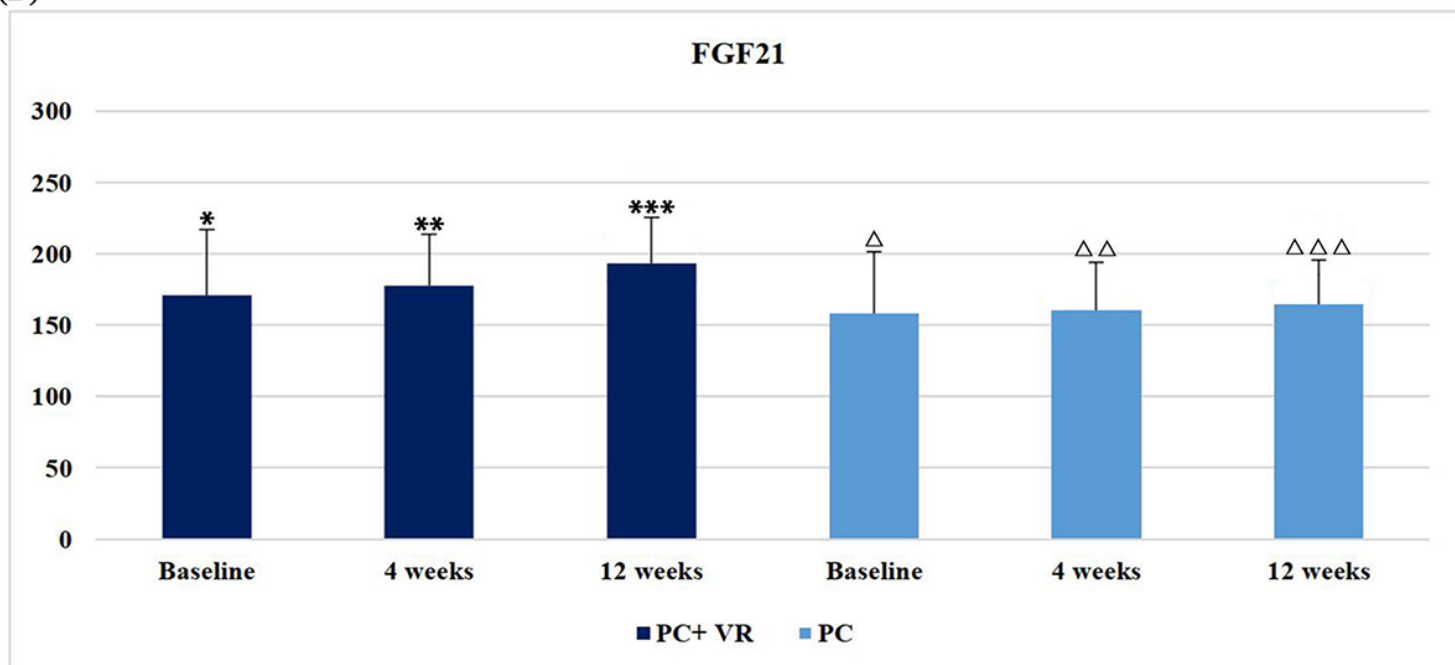


Figure 7

The histograms show FGF21 level of each group. *p means the baseline and the 4th week comparison within the group; **p means the 4th week and 12th week comparison within the group; ***p means the baseline and 12th comparisons within the group in PC+VR group. Δ p means the baseline and the 4th week comparison within the group; $\Delta\Delta$ p means the second and third comparison within the group; $\Delta\Delta\Delta$ p means the baseline and 12th comparisons within the group comparisons within the group in PC group. (A). The differences of FGF21 between two groups. (B). FGF21: *p=0.285, **p< 0.001, ***p< 0.001, Δ p=0.188, $\Delta\Delta$ p=0.001, $\Delta\Delta\Delta$ p< 0.001. Abbreviation is as follows: FGF21, fibroblast growth factor 21.

Supplementary Files

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