Effects of Virtual Reality-Based Physical And Psychological Exercise On Depression In Stroke Patients : A Meta-Analysis

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Effects of virtual reality-based physical and psychological exercise on depression in stroke patients : a meta-analysis

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Background: Virtual Reality (VR) has been widely used in health-related fields. The aim of this study was to assess the effectiveness of virtual reality-based physical and psychological exercise on depression.

Methods: A total of 752 patients with stroke from 11 randomized controlled trial (RCT) studies were included in this meta-analysis and the studies derived from 6 electronic databases searched from database inception to August 2021. For continuous results, the standardized mean differences (SMDs) and 95% confidence intervals (CIs) were calculated to synthesize the effects.

Results: The meta-analysis showed that compared with control group, VR-based interventions significantly decreased the depression scale score (SMD = -0.71, 95% CI: -1.32, -0.10) in the subjects. The results showed that the the patient age and total intervention time had a significant impact on the outcome of depression. The smaller the age and longer the intervention duration, the greater the impact on the outcome of depression.

Conclusions: The current meta-analysis indicated the virtual reality-based physical and psychological exercise has a significant effect on depression in stroke patients compared to controls. The study showed an outstanding reduction in depression for aged under 60 participants and intervention longer than 8 weeks. At the same time, clinical studies of different ages and different intervention time also need further in-depth study.

Keywords: Virtual reality; Meta-analysis; Depression; Stroke

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1.Introduction

Stroke, as one of the most common neurological diseases resulting in permanent disability in adults^[1], has become a widespread health problem that affects people's daily independent living^[2-4]. For the patients with stroke, the risk of impaired psychological health and depression increases^[5]. About a third of stroke survivors experience post-stroke depression^[6]. The patients with depression can lead to loss of interest and happiness, and produce anxiety and fear and hostility and sadness and anger^[7]. For the stroke patients, post-stroke depression not only delays the recovery of neurological deficits but also has a negative impact on the functional recovery and rehabilitation^[8-11], resulting in a decline in the quality of life and increases the mortality^[12]. Such psychological states may lead to reduced motivation and low adherence to rehabilitation training and increased burden of caregivers^[5].

The current intervention methods mainly include drugs and psychotherapy. Studies have shown that up to 43% of patients with major depressive disorder may discontinue antidepressants due to adverse reactions during treatment^[13]. So non-drug interventions are getting more and more attention. In recent years, virtual reality-based intervention has been found to be effective for depression^[14-16]. Virtual reality (VR) is a computer-generated high-tech simulation system which can create a sense of being there using computer electronic information simulation technology, and has three basic characteristics including immersion and interaction and imagination. VR training, as a dynamic training method in line with daily life activities, can carry out active rehabilitation training from three levels of repetitive, feedback and motivation in a computer simulation of three-dimensional space.

Therefore, this method can increase patients' initiative and subjective initiative through multi-sensory feedback.

The interventions based on VR are diverse, including virtual reality exposure therapy^[17-18], virtual reality cognitive behavioral therapy^[19-20] and virtual reality-based physical^[21] and psychological exercise^[22] etc. Compared with traditional therapy, VR is more convenient to use, flexible and changeable in treatment content, more positive in users' attitude, and more pleasant in experience^[23]. A variety of immersive games can enable patients to have a deeper interest, and thus improve their subjective initiative resulting in various rehabilitation training be actively completed by patients^[24]. As a result, a virtuous cycle can be formed, and their functional level be improved^[25].

Compared to traditional teach-based training, VR is thought to reduce learning difficulty and make training safer^[26]. We have witnessed the development of tele-medicine in the last few years, and the tele-medicine overcome the barriers caused by distance and lower the cost of healthcare and encourage continuity of care^[27]. However, the application of VR technology in the treatment of depression has not been promoted in clinical practice, and its effect is still being explored.

A meta-analysis^[28] has explored the effects of game-based digital interventions on depression in adults in 2014. The meta-analysis revealed a moderate effect size of the game interventions for depression therapy at post-treatment, but no specific analysis was made. Another meta-analysis on the effectiveness of virtual reality-based interventions for symptoms of anxiety and depression in adults was published in 2018^[29]. However, depression was a secondary outcome measure, and the literature included was incomplete with only 10 articles. In 2021, a meta-analysis^[30] has explored the effects of VR exergames for promoting older adults' cognition and ameliorating depressive symptoms. Thus, the purpose of this study was to specifically analyze the effects of virtual reality-based physical and psychological exercise on depression in stroke patients.

2.Methods

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines^[31]. A study protocol was registered at PROSPERO (CRD42020194244).

2.1 Literature inclusion and eligibility criteria

Studies were selected based on the following criteria: (a) study design must be randomized controlled trials (RCTs); (b) the participants are stroke patients; (c) interventions in the experiment group are based on VR physical or psychological exercise; (d) interventions in the control group are not based on VR. If there are both active treatment group and waiting-list group in the control group, the waiting-list group is selected; (e) depression is the primary outcome, and it must be measured. Useful data (e.g., sample size, mean and standard deviation) were clearly reported in the published paper or could be retrieved through contacting corresponding author of primary studies; (f) full-text articles published in peer-reviewed journals; (g) the number of participants including the experiment group and the control group is over 10; (h) the articles are published in Chinese or English.

2.2 Data sources and search strategy

We collected a comprehensive literature from the three English databases and three Chinese databases: Medline, PubMed, Web of Science, Chinese National Knowledge Infrastructure (CNKI), SinoMed (CBM), Wanfang databases. Six databases were conducted until August 2021. The following search items will be adopted: virtual reality, VR, virtual environment, depression, depressive symptoms, depressive disorder, stroke, randomized controlled trial. Search strategies were included as Supplementary Appendix 1.

2.3 Study selection

Duplicate papers would be removed first before undertaking the screening. Two reviewers checked independently titles and abstracts of the retrieved articles

according to the review criteria. Any disagreement was resolved by consensus and a third reviewer would arbitrate disagreements.

2.4 Data Extraction

An electronic form was established to extract substantial contents, which included the first author and publish year of the study, the sample size, nation, age, condition, pre-treatment and post-treatment score for depression, interventions in experimental group and control group, the assessment tools for outcome measures and dropouts. Data extraction was carried out independently by two authors. Any disagreement will be resolved by consensus and a third reviewer will arbitrate disagreements.

2.5 Quality Assessment

Based on the Cochrane Collaboration Risk of Bias tool^[32], the assessment of methodological quality of included studies was assessed respectively independently by two review authors to evaluate the potential bias risk. Six perspectives pertained to bias risk including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, and selective reporting, and other issues were also evaluated. Using this tool, risk of bias was judged as ‘Low’, ‘High’ or ‘Unclear’.

2.6 Data Analysis

The software Review Manager 5.2 was used to analyze the outcome indicators of the included studies. Because different scales were used to measure the same outcomes for the measures of depressive, we calculated the standardized mean difference (SMD) with 95% confidence intervals (CIs) and then combined these values for the meta-analysis. I^2 was used to evaluate the heterogeneity in this study. When $I^2 \leq 24\%$, there is no heterogeneity; $25\% \leq I^2 \leq 49\%$, low heterogeneity; $50\% \leq I^2 \leq 74\%$, mild heterogeneity; $I^2 \geq 75\%$, high heterogeneity^[32]. When $I^2 > 50\%$, the substantial heterogeneity was considered and a random effect model was selected, otherwise, a fixed effect model was selected for analysis^[25]. Publication bias was assessed through visual analysis, with roughly symmetrical funnel plots indicating a

low risk of publication bias and asymmetrical funnel plots indicating a high risk of publication bias. The sensitivity analysis was used to determine the source of heterogeneity by excluding studies one by one and presented in a summary table. We also conducted subgroup analyses based on depression status, age of the participants and duration.

3.Result

3.1 Study selection

Fig. 1 shows the study selection process. In total, 2193 records were identified by searching the databases, and 1256 potentially eligible articles were identified after removing duplicates. 62 studies were retrieved and reviewed by a more detailed assessment after screening the titles and abstract. After reviewing the full-text articles for eligibility, 11 studies were included.

Fig.1. Flow chart of the study selection process in meta-analysis.

Table 1 Characteristics of the studies included the meta-analysis

Author, year	Country	Sample size	Age	Condition	Pre-treatment score for depression	Post-treatment score for depression	Experimental group	Control group	Depression Measures	Dropouts and reasons
Adomaviciene et al., 2019	Lithuania	42	EG: 62±5.9	Stroke	EG: 8.40±4.44	EG: 8.48±4.43	(1)	(2)	HADS-D	(3)
			CG: 66±7.0		CG: 5.41±3.12	CG: 4.94±3.09	45 minutes/day, 10sessions			
Bi et al.,2020	China	120	EG: 68.3±8.3	post stroke	EG: 70.37±10.13	EG: 46.33±7.42	(4)	(5)	SDS	nr
			CG: 67.9±6.1	depression	CG: 68.13±10.83	CG: 56.73±4.81	(6)			
Kim et l.2020	Korea	24	EG: 71.92±3.23	stroke	EG: 16.00±1.04	EG: 12.16±0.71	(7)	(8)	K-GDS	nr
			CG: 72.08±4.46		CG: 17.08±1.37	CG: 12.75±0.35	(9)			
Lin et al., 2020	Taiwan	145	EG:64.5±13.5	Stroke	EG: 12.1±2.5	EG: 9.3±3.2	60 minutes/day, 5 days/week	(10)	HADS-D	EG: n=0
			CG: 66.9±13.3		CG: 10.3±4.8	CG: 10±4.5	(11)			(12)
Rogers et al.,2019	Australia	21	EG: 64.3±17.4	sub-acute	EG: 32.6±9.1	EG: 24.5±6.6	(13)	(14)	NFI	nr
			CG: 64.6 ±12.0	stroke	CG: 33.9±13.9	CG: 30.6±10.6	30-40 minutes/day, 4week	3h/day		
Rooij et al.,2021	Netherland	55	EG: 65±9.6	stroke	EG: 4.39±3.35	EG: 4.04±3.49	VR gait training (VRT)	(15)	HADS-D	EG=0
			CG: 61±13.3		CG: 3.54±2.28	CG: 2.83±2.16	(16)	(17)		(18)
Song et al., 2015	Korea	40	EG: 51.37±40.6	stroke	EG: 21.2±3.8	EG: 14.1±2.4	(19)	(20)	BDI	nr
			CG: 50.10±7.83		CG: 19.6±3.2	CG: 17.5±2.7	(21)			
Sun et al., 2018	China	64	EG: 50.5±9.6	post stroke	EG: 21.8±3.4	EG: 8.7±2.8	(22)	(23)	HAMD	nr
			CG: 53.0±8.7	depression	CG: 20.8±3.2	CG: 12.3±3	(24)			
Xu et al.,2020	China	72	EG: 52.33±5.37	post stroke	EG: 15.56±3.11	EG: 10.17±2.01	(25)	(26)	HAMD	nr
			CG: 51.67±4.61	tilting syndrome	CG: 16.72±3.23	CG: 14.26±2.95	(27)	(28)		
Yu et al.,2020	China	109	EG: 39.56±4.83	ischemic stroke	EG: 28.15±1.23	EG: 11.25±2.12	(29)	(30)	HAMD	nr
			CG: 40.24±4.83		CG: 29.23±2.24	CG: 16.24±1.64	20-30 min/time, twice/day			
Zhang et al., 2017	China	60	EG: 67.80±5.76	stroke	EG: 8.83±3.09	EG: 7.97±2.4	(31)	(32)	HADS-D	nr
			CG: 69.30±5.87	hemiplegia	CG: 8.30±2.89	CG: 7.57±2.14	(33)			

EG, Experimental group; CG, Control group; HADS-D, Hospital Anxiety and Depression Scale for Depression; SDS, Self-rating depression scale; HAMD, Hamilton Depression Scale; BDI, Beck Depression Inventory; K-GDS, Korea geriatric depression scale; VRGs, virtual reality games; VRT, virtual reality gait training; NFI, Neurobehavioral Functioning Inventory; nr, not report.

(1)virtual reality Kinect-based system training+conventional rehabilitation training: virtual games+conventional rehabilitation training. (2)conventional rehabilitation training+armeo Spring robot-assisted training. (3)High blood pressure(n=6), Heart rate problems(n=4), Intolerance of physical load(n=3), Fast fatigue(n=4), Painful shoulder syndrome(n= 3), Fever(n=5), Refusal to participate in the study(n=3). (4)VR psychological rehabilitation+conventional rehabilitation training: walking across zebra crossings, boating on the river, playing table tennis indoors and having a dialogue with the characters in the virtual scene. (5)conventional rehabilitation training. (6)40-60 minutes/day, 3-4 days/week, 8 weeks. (7)VR-based trunk-centered stabilization exercise. (8)trunk-centered stabilization exercise. (9)30 minutes/day, 3 days/week, 4 weeks. (10)conventional rehabilitation training(postural training, facilitation techniques, stretching exercise. (11)VR exercise+daily conventional occupational and physiotherapy. (12)CG: n=2(transferred intensive care unit). (13)VR exercise+daily conventional occupational and physiotherapy. (14)daily conventional occupational and physiotherapy. (15)conventional treadmill training+functional gait exercises. (16)consisted of 2 30-minute sessions per week for 6 weeks (12 sessions). (17)consisted of 2 30-minute sessions per week for 6 weeks (12 sessions). (18)CG=3(2recurrent stroke,1 reason unknown because of non-response). (19)VRGs: 10-pin bowling, skiing, golf, ground walking, walking over obstacles, climbing stairs. (20)ergometer bicycle training. (21)30 minutes/day, 5 days/week, 8 weeks. (22)VRGs+conventional rehabilitation training+psychological intervention: Racing, big fish eat small fish, trajectory flight, trajectory tracking, picture matching, wipe the table, sports watch video, catch treasure, rebound ball, etc. (23)conventional rehabilitation training+psychological intervention. (24)15 minutes/day, 6 days/week, 8 weeks. (25)VR balance function training(track tracking training, mushroom picking training and walking training). (26)conventional rehabilitation training(range of motion training, balance function training, weight transfer training). (27)50 minutes/day, 6 days/week, 4 weeks. (28)50 minutes/day, 6 days/week, 4 weeks. (29)VRGs+stroke unit comprehensive treatment: parkour, matching cards, racing cars, squeezing toothpaste, holding a water glass, twisting towel. (30)stroke unit comprehensive treatment (internal medicine treatment, rehabilitation training;Comprehensive care, psychosocial and behavioral interventions, and post-rehabilitation career planning and vocational competency training)/conventional rehabilitation training. (31)VRGs+conventional rehabilitation training: Fruit cognition, life tool cognition, fruit cutting, ski event motion sensing game, speed skateboard.. (32)conventional rehabilitation training: ①training for the maintenance of range of motion of lower limbs; ②muscle strength training; ③Bridge movement; ④training of gravity shift; ⑤sitting and standing balance training; ⑥sit-stand posture transfer training; ⑦General gait training: flat ground walking training, turn in all directions, walk sideways, cross walk, up and down stairs, etc. (33)30 minutes/day, 5 days/week, 6 weeks.

3.2 Characteristics of included studies

Table 1. shows the characteristics of included studies. In this research, the 11 included RCT papers were published between 2015 and 2021, including six English studies and five Chinese studies. The population sizes of the trials ranged from 21 to 145. The participants were post stroke depression in two studies^[12,22]. The duration of each intervention ranged from 15 to 60 minutes. The intervention period was as short as four weeks, and sometimes as long as eight weeks. Assessment tools for depression included Hospital Anxiety and Depression Scale for Depression, Beck Depression Inventory, Hamilton Depression Scale, Self-rating depression scale, Korea geriatric depression scale and Neurobehavioral Functioning Inventory.

3.3 Risk of bias

The risk-of-bias results are summarized for the included studies in Fig.2. All the studies were described as randomized. Nine studies^[5,12,23,22,33-37] described the method of randomization used. Information on concealment of treatment allocation was reported in three studies^[5,23,34]. No study described clearly blinding of the participants and personnel. Two trials^[22, 34] reported adequate blinding of the outcome assessor. There was no study at unclear risk of bias about incomplete outcome data. The risk of bias due to selection reporting was low across all the studies. No other potential bias was revealed in all studies.

3.4 The effect of VR-based interventions on depression

We included 11 studies with a total of 752 patients. The random-effects model was used to pool the SMDs and corresponding 95% CIs. As shown in Fig.3(A), the results showed that depression scores in the VR group was significantly lower than that in the control group after the intervention (SMD = -0.71, 95% CI: -1.32, -0.10). Significant heterogeneity was observed among the studies ($I^2 = 92\%$, $p < 0.00001$). The funnel plot did not show significant asymmetry in Fig.4. After sensitivity analysis included as Supplementary Appendix 2, the heterogeneity did not decrease significantly.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Adomaviciene et al., 2019	?	?	-	?	+	+	+
Bi et al.,2020	+	?	-	?	+	+	+
Kim et al.2020	+	?	-	?	+	+	+
Lin et al., 2020	+	+	-	?	+	+	+
Rogers et al.,2019	+	+	-	?	+	+	+
Rooij et al.,2021	+	+	-	+	+	+	+
Song et al., 2015	?	?	-	?	+	+	+
Sun et al., 2018	+	?	-	+	+	+	+
Xu et al.,2020	+	?	-	?	+	+	+
Yu et al.,2020	+	?	-	?	?	+	+
Zhang et al., 2017	+	?	-	?	+	+	+

Fig. 2. Summary of risk-of-bias distribution across studies.

Fig.3. (A) Forest plot of the effect of VR on depression. (B) Forest plot of the effect of VR subjects' age on depression. (C) Forest plot of the effect of VR intervention duration on depression. (D) Forest plot of the effect of VR subjects' types on depression.

Fig. 4. Funnel plot of the effect of VR on depression.

Four of the subjects are under the age of 60 and seven of the subjects are over 60 years. As shown in Fig.3(B), the results revealed that depression scores are significantly reduced in participants' ages under 60 years than controls (pooled effect size = -1.67, 95% CI: -2.26, -1.08). Significant heterogeneity was observed among the studies ($I^2 = 75\%$, $p < 0.00001$). Depression scores was not significantly decreased in

participants' ages over 60 years (pooled effect size = -0.16, 95% CI: -0.84, 0.52). Significant heterogeneity was observed among the studies ($I^2 = 91\%$, $p < 0.00001$).

For the duration of the intervention, three RCTs lasted longer than eight weeks, five RCTs were less than eight weeks, while the remaining three RCTs didn't report duration of the intervention. As shown in Fig.3(C), the results of this meta-analysis revealed that intervention longer than eight weeks of RCTs were statistically significantly reduced than controls (pooled effect size = -1.46, 95% CI: -1.75, -1.16). Significant heterogeneity was observed among the studies ($I^2 = 0\%$, $p < 0.0001$). However, intervention less than eight weeks of RCTs were not significantly decreased (pooled effect size = -0.35, 95% CI: -1.15, 0.46). Significant heterogeneity was observed among the studies ($I^2 = 88\%$, $p < 0.00001$).

For different types of participants, two RCTs included people with post stroke depression, while the remaining nine RCTs included people with different types of strokes. As shown in Fig.3(D), The results revealed that depression scores are significantly reduced in participants with post stroke depression than controls (pooled effect size = -1.47, 95% CI: -1.89, -1.06). Significant heterogeneity was not observed among the studies ($I^2 = 35\%$, $p < 0.00001$). Depression scores was not significantly decreased in participants with different types of strokes (pooled effect size = -0.54, 95% CI: -1.24, 0.15). Significant heterogeneity was observed among the studies ($I^2 = 92\%$, $p < 0.00001$).

4. Discussion

Our meta-analysis systematically reviews currently available articles and included 11 studies with 752 patients to evaluate the effect of VR-based physical and psychological exercise on depression. The research results show the VR-based physical and psychological exercise is more effective at decreasing depression scores than control group in depression.

A subgroup analysis of patients with different types of strokes shows that only patients with post stroke depression apparently benefited from VR treatment for depression. The subgroup analysis of age shows that for subjects aged under 60, VR

can effectively reduce depression scores compared with control group, and that, for people aged over 60, no difference is observed. For some older people, contacting VR technology has a challenging due to the visual and auditory changes^[38]. This may be because older people have a difficulty to adapt the new treatment regimen. The subgroup analysis of intervention duration revealed that intervention longer than eight weeks of RCTs were statistically significantly reduced than control group, and intervention less than eight weeks of RCTs not significantly decreased. The research results of Hsin-Yen et al. revealed that the total intervention duration had a significant effect on the outcome of depression.

VR as a therapeutic tool is rapidly popularized and widespread used due to its novel training methods and ability to provide personalized rehabilitation training ^[27]. At present, various professional technology platforms and treatment schemes based on VR are also under active development and research ^[29]. The research results in recent decades showed that VR technology can be used to treat phobias, stress and pain. But few has tried to develop VR anti-depressant interventions. Compared with traditional rehabilitation training, the VR technology can precisely provide more individualized rehabilitation training programs according to the disease characteristics of different patients and can upload the training data on the internet in real-time. Through the data synchronization between different devices to improve the rehabilitation effect, the VR can also promote interaction between patients and the health system^[6].

Currently, no research results show which form of VR technical training or which treatment intensity has the best effect, and there is also a lack of guidelines on the VR development process. In future studies, the same interventions for patients having the same disease can be developed to eliminate high heterogeneity^[29]. Few articles have evaluated or described feelings of immersion during treatment. The feelings of immersion should be used as an indicator for observation in future research, and the system needs to be to support improved outcomes to clarify how immersive and sophisticated. Recently, commercialized VR has developed rapidly, so,

it is important to consider the cost, feasibility and accessibility of VR equipment^[39]. Few articles report the cost of VR rehabilitation training and the economic benefits of this type's training have not been compared with the control group. In future studies, the cost of different type rehabilitation training should be used as an indicator for observation^[29]. VR may also be used to alleviate depression symptoms and prevent depression in healthy people with some clinically related depression symptoms or sub-domain depression in the future. Based on evidence-based treatment techniques, consumer-targeted VR interventions have great potential to have an impact on the public's psychological health.

There were some limitations in this study that should be noted. Although a detailed literature search had been done, it must be admitted that there is still the possibility of study omission, such as gray literature. In addition, it is also different in the VR intervention forms, training time and dosage, training intensity and outcome evaluation indexes adopted in the included studies. In addition, it is not quite the same that VR technology equipment used and the conventional physical rehabilitation mode implemented by the control group in each study.

Above different may be the reason for high heterogeneity of results. Compared with VR interventions for phobias, pain and stress, the field of anti-depressive VR applications is in its early stages, which constitutes an important limitation to the current state of research. Due to the particularity of VR technology interventions, the blind method is difficult to patients in the experimental group, which may lead to the deviation of subjective data reported by patients in the result evaluation.

Conclusions and implications

The current meta-analysis indicated the virtual reality-based physical and psychological exercise has a significant effect on depression in stroke patients compared to controls. The study showed an outstanding reduction in depression for aged under 60 participants and intervention longer than eight weeks. This rehabilitation technology, suitable for promotion in family and community, has advantages of saving manpower and low technical requirements. However, this study

also has some limitations and deficiencies. There were only 11 studies in this paper. So, further confirmation in large clinical trials is needed. At the same time, clinical studies of different ages and different intervention time also need further in-depth study.

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Declaration of Competing Interest

No conflict of interest exists in the submission of this manuscript. All the analyses were based on previously published studies. All authors were approved the manuscript for publication. I would like to declare on behalf of my co-authors that the work described was original research that has not been published previously, and not under consideration for publication elsewhere, in whole or in part. All the authors listed have approved the manuscript that is enclosed.

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Supplementary Appendix 1 and 2

Supplementary material related to this article can be found in the online version.

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