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Research article

Transcranial direct current stimulation with virtual reality versus virtual reality alone for upper extremity rehabilitation in stroke: A meta-analysis

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ABSTRACT

Background: Stroke is one of the most prevalent diseases. Motor impairment in patients with stroke frequently affects the upper extremities. Several randomized clinical trials (RCTs) have tried to prove whether or not the combination of transcranial direct current stimulation (tDCS) with virtual reality (VR) is superior to VR alone for upper extremity rehabilitation.
Methods: We searched Embase, MEDLINE, the Cochrane Library database, and Clinicaltrials.gov for relevant RCTs published before June 10, 2022. The results were analyzed by using standard mean differences (SMD) and 95% confidence intervals (95% CI).
Results: We pooled 120 patients from 4 RCTs. There were no significant improvements in the Fugl-Meyer Upper Extremity scale (SMD = 0.51; 95% CI, −0.04 to 1.06), the Box and Block Test (SMD = 0.42; 95% CI, −0.02 to 0.86), and the Modified Ashworth Scale after the combined treatment of tDCS and VR. But tDCS combined with VR could enhance the Barthel Index scores in patients with stroke compared to VR alone (SMD = 0.49; 95% CI, 0.04 to 0.94).
Conclusions: The combination of tDCS and VR can improve the quality of daily living in patients with stroke. No more satisfactory efficacy has been demonstrated in terms of upper extremity function. However, we observe a distinct trend toward significance in some outcomes.

1. Introduction

Stroke is a cerebrovascular disease with high morbidity, disability, and mortality rate. Stroke has become the second common cause of death globally and in several countries stroke has become the most common cause of death, according to a study spanning nearly 40 years [1]. Even if they survive, 80% of patients have varying degrees of neurological deficits throughout their lives [2] and the loss of

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high disability-adjusted life years leaves patients suffering greatly [3]. The incidence of stroke has increased by 68% in recent decades [4]. Therefore, not only the prevention and timely treatment of stroke is extremely important, but also post-stroke rehabilitation.

One of the most common symptoms of stroke is unilateral hemiparesis [4], which particularly presents with upper and lower extremity dysfunction. Hence, rehabilitation becomes urgent and essential when aggressive and effective treatment fails to accomplish. More and more rehabilitation approaches are being used for patients with post-stroke [5]. Virtual reality (VR) can communicate the virtual world with reality, allowing people to experience the virtual world more realistically. Initially, VR was used to enhance the gaming experience. With the development of technology, VR had the characteristics of experiential learning, augmented feedback, observational learning, and goal-oriented, so it was encouraging to see that some research used VR in the medical industry with satisfactory results [6, 7, 8, 9, 10, 11, 12]. In the case of the upper extremity, only 11.6% of the patients are able to regain full function at 6 months post-stroke [13]. Combining with VR is an easier way for patients with upper extremity hemiplegia to benefit from rehabilitation compared to conventional physical rehabilitation [12]. However, some limitations occur in the use of VR [14].

Non-invasive brain stimulation can modulate cortical excitability. Transcranial direct current stimulation (tDCS) as a type of non-invasive brain stimulation is gradually applied in clinical treatment because of lower cost, easier operation, and better security [15]. A meta-analysis has demonstrated that tDCS improves motor performance in patients recovering from chronic stroke or mild to moderate stroke [16]. In addition, Kim et al. found the combined effect and a stronger short-term corticospinal facilitation of tDCS with VR [17]. Llorens et al. also proved that the combination of tDCS and VR was significantly more efficacy than conventional physical therapy [18]. These trials investigated the possibility that patients could achieve a better long-term prognosis by receiving both noninvasive brain stimulation with tDCS and guided training with VR. Some articles suggested that upper extremity function in patients with stroke could benefit more from the combination of tDCS and VR compared to VR alone [19, 20, 21]. However, no study has specifically and systematically evaluated the efficacies of the combination of tDCS and VR versus VR alone for upper extremity training until now. Therefore, we conduct this meta-analysis and systematic review to assess whether the combination of tDCS and VR is better than VR alone.

2. Methods

The meta-analysis and systematic review followed the updated PRISMA statement [22].

2.1. Search strategy

The terms used for searching were ((transcranial direct current stimulation OR tDCS) AND (virtual reality OR VR)) AND (upper limb OR upper extremity OR rehabilitation OR stroke). All the articles were systematically searched in the Embase, MEDLINE, the Cochrane Library database, and Clinicaltrials.gov until June 10, 2022. In order to avoid omissions, the authors also checked the references of any other relevant trials.

2.2. Inclusion and exclusion criteria

Inclusion criteria were as follows: (1) study type: randomized clinical trials (RCTs); (2) participants: any patient diagnosed with stroke by computed tomography, magnetic resonance imaging or clinical symptoms; (3) subtypes of stroke: ischemic stroke or hemorrhagic stroke; (4) intervention: tDCS + VR (the combined treatment of tDCS and VR) and VR; (5) outcomes: any outcome to assess upper extremity motor impairment, upper extremity motor function, and the quality of daily life; (6) language restriction: any language. Exclusion criteria were as follows: (1) study type: prospective or retrospective trials, meta-analysis, reviews, protocol, and comments; (2) control group: conventional physical therapy only.

2.3. Data extraction

For each included article, basic information (authors, year of publication, number of patients, etc.), characteristics of patients (sex ratio, age, time since stroke, stroke lesion, paretic side, stroke type, etc.), inclusion criteria, exclusion criteria, treatment procedures, tDCS procedures, VR procedures, and outcomes were extracted separately by two authors. If any disagreement occurred, it would be settled through discussion. Another author was responsible for checking the extracted data.

2.4. Outcome measures

We chose the Fugl-Meyer Upper Extremity (FM-UE) scale [23], the Modified Ashworth Scale (MAS) [24], and the Box and Block Test (BBT) [25] to evaluate the upper extremity motor impairment and motor function. To evaluate the quality of daily life, the Barthel Index (BI) [26] was used.

The FM-UE used to measure upper extremity motor function is a part of the Fugl-Meyer motor function score. The FM-UE is divided into 33 items and subjects will receive 0, 1, or 2 points depending on the degree of completion. The results judged by FM-UE have excellent consistency and accuracy [23]. The MAS is a scale used to assess muscle tension and passive motor resistance. The subjects with higher scales have increased resistance to passive motion. When the MAS is 0, the subject's muscle tension can be considered completely normal [24]. Subjects who undergo the BBT are asked to move a block from one box to another in sequence using the affected upper extremity. The number of blocks transferred by the subject in 1 min is the BBT scores [25]. The BI is an evaluation form to measure independent daily living ability. Subjects are considered to have the ability to live independently when the BI score is above 60 [26].

The manual muscle test, the manual function test, the Wolf motor function test, the Stroke Specific Quality of Life Scale, the minimal clinically important differences, the grip strength, the Action Research Arm Test, the Jebsen-Taylor Hand Function Test, the Stroop Test, and the Trail Making Test were not selected for the outcome measures of this article, because these outcomes were only used in one article.

For adverse events, only one RCT reported four cases of tingling and one case of itching [19], while the other three RCTs did not find any adverse event. In addition, a large sample size review found few serious adverse effects with tDCS [27]. Therefore, adverse events were not considered in the results of this meta-analysis.

2.5. Statistical analysis

The data in this article was analyzed using the Review Manager 5.4 software. Standard mean difference (SMD) and 95% confidence interval (95% CI) were used to analyze the outcomes. The statistical heterogeneity among the included articles was assessed using I^2 and *P*-value. When $I^2 < 30\%$, the statistical heterogeneity is low; when $I^2 > 50\%$, the statistical heterogeneity is substantial. *P*-value <0.05 was considered a statistically significant difference. All tests are two-tailed.

2.6. Risk of bias

The Cochrane collaboration uniform criteria [22] and Review Manager 5.4 software were used to assessing the risk of bias in the

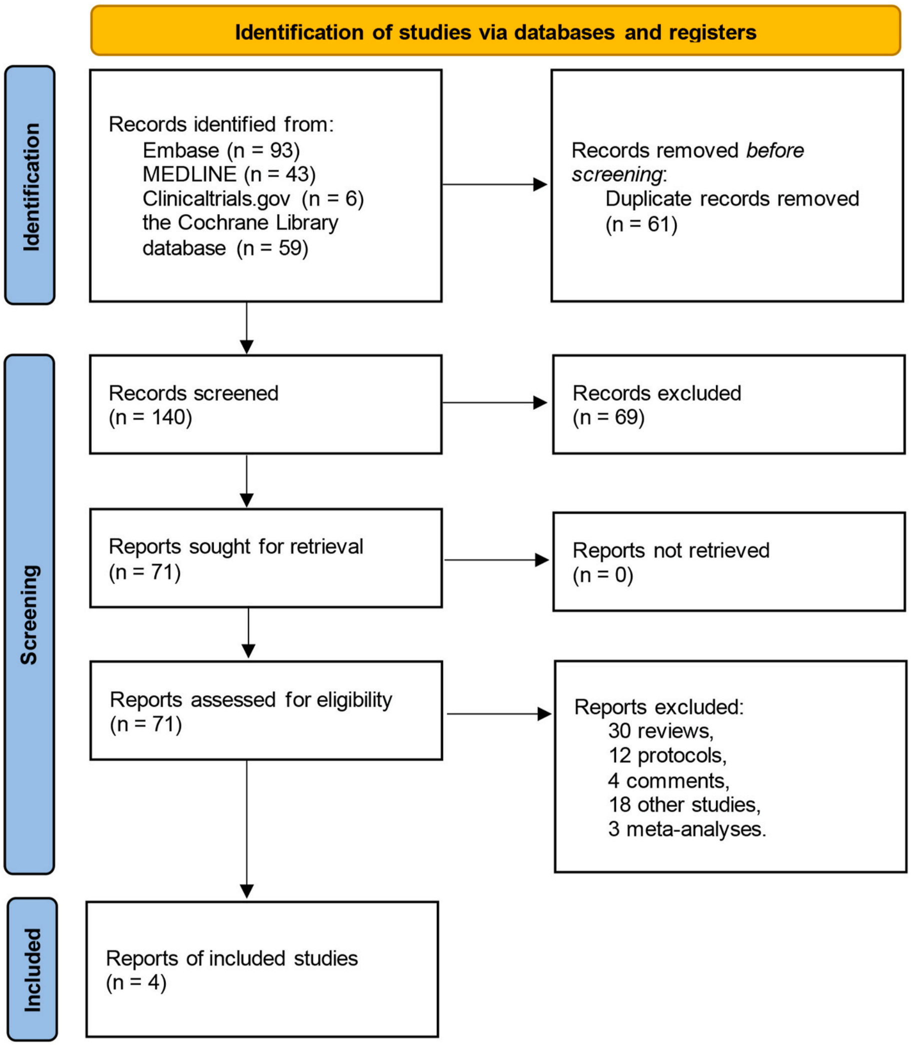

Figure 1. PRISMA flow diagram of the study inclusion process. Abbreviations: n, number of studies.

articles. The following biases were considered and included in this article, such as selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases.

3. Results

3.1. Search results

According to the search strategy of this study, we extracted 201 articles from the databases and registers published online before June 10, 2022. Specifically, 93 articles were identified from EMBASE, 43 articles were retrieved from MEDLINE, 59 of them were recorded in the Cochrane Library database, and the other 6 remaining studies were registered in Clinicaltrials.gov. Then 61 duplicate articles were excluded by automation tools (EndNote X9) and 69 irrelevant articles were removed by reading the titles. After reading the full articles and excluding non-relevant articles, four articles [19, 20, 21, 28] that met our inclusion criteria were selected for this meta-analysis. It should be noted that one relevant conference abstract [29] due to unavailability of valid data and one RCT [18] due to only comparing the combined treatment of tDCS and VR with conventional physical therapy were excluded. Figure 1 showed the complete PRISMA 2020 flow diagram.

3.2. Characteristics of the included RCTs

The number of patients, sex ratio, age of patients, time since stroke, stroke lesion, paretic side, and stroke type were listed in Table 1. Table 2 illustrated inclusion criteria, exclusion criteria, treatment procedures, tDCS procedures, and VR procedures for each RCT.

3.3. Upper extremity function

To evaluate the efficacy of the combined treatment to patients with stroke compared to VR alone, we chose the FM-UE scale, BBT, and MAS as upper extremity function outcomes. As for the FM-UE scale, three articles included a total of 100 patients with relevant reports. No differences were observed for the combination of tDCS and VR greater than VR alone (SMD = 0.51; 95% CI, −0.04 to 1.06; $P = 0.07$; $I^2 = 45$ %) (Figure 2A). Two articles chose BBT as an outcome. There was no evidence that the combined treatment of tDCS and VR was superior to VR alone in terms of BBT (SMD = 0.42; 95% CI, −0.02 to 0.86; $P = 0.06$; $I^2 = 0$ %) (Figure 2B). MAS was reported in only two articles for 60 of 120 individuals. However, in Viana's study [28] the patients with stroke did not show any difference in either mean or standard deviation (SD) before and after the treatment of VR alone. So, the SMD and 95% CI were not estimable. No significant differences were found between the experimental and control groups in both Lee's [21] (SMD = −0.43; 95% CI, −1.06 to 0.19; $P = 0.18$) and Viana's [28] research (Figure 2C).

3.4. Quality of daily living

BI is a reliable index to evaluate the quality of daily living. Two RCTs including 80 patients selected BI as an outcome. Significantly higher BI scores in patients with stroke who treated by the combination of tDCS and VR compared to the VR alone group (SMD = 0.49; 95% CI, 0.04 to 0.94; $P = 0.03$; $I^2 = 0$ %) (Figure 2D).

3.5. Risk of bias

To make the results of this study more reliable, we analyzed the risk of bias in four RCTs (Figure 3). Primarily, there was no clinical trial that had an unclear or high risk of bias in random sequence generation and allocation concealment. And we might exclude the

Table 1
Characteristics of the included studies and patients.

RCTs	Populations (n)		Sex (M/F, n)		Age (years)		Time since stroke		Paretic side (L/R, n)		Stroke type (I/H, n)	
	tDCS + VR	VR	tDCS + VR	VR	tDCS + VR	VR	tDCS + VR	VR	tDCS + VR	VR	tDCS + VR	VR
Lee 2014	20	20	12/8	9/11	63.1 ± 10.3	60.6 ± 14.1	17.8 ± 7.3 (d)	16.9 ± 5.5 (d)	9/11	7/13	12/8	14/6
Viana 2014	10	10	9/1	7/3	56.0 ± 10.2	55.0 ± 12.2	31.9 ± 18.2 (m)	35.0 ± 20.3 (m)	5/5	3/7	9/1	10/0
Yao 2020	20	20	14/6	17/3	63.0 ± 7.5	66.2 ± 6.2	60.5 ± 35.5 (d)	56.5 ± 33.3 (d)	12/8	10/10	20/0	20/0
Lee 2021	10	10	6/4	7/3	67.5 ± 6.7	65.0 ± 5.7	112.5 ± 44.4 (d)	123.6 ± 46.5 (d)	7/3	8/2	7/3	8/2

All values are mean ± SD or number. Abbreviations: RCT, randomized controlled trial; n, number of patients; M/F, male/female; L/R, left/right; I/H, ischemic/hemorrhage; tDCS, transcranial direct current stimulation; VR, virtual reality; d, days; m, months; NA, not applicable.

Table 2
The inclusion criteria, exclusion criteria, and treatment procedures of the RCTs.

RCTs	Inclusion Criteria	Exclusion Criteria	Treatment Procedures	tDCS Procedures	VR Procedures
Lee 2014	<1 month after diagnosis of first stroke; Unilateral hemiparesis caused by stroke; Motor power of the affected shoulder greater than a poor grade	Contraindications to brain stimulation; History of brain neurosurgery or seizure; Metallic implants in the brain; Severe cognitive impairments or aphasia; Poor sitting balance; Severely damaged eyesight; Hemispatial neglect	tDCS + VR: tDCS + VR + conventional rehabilitation VR only: VR + conventional rehabilitation 15 sessions (30 min/d and 5 times/wk for 3 wk)	C: over the hand area of the unaffected motor cortex A: over the contralateral orbit Intensity: 2 mA Duration: 20 min	Complete the three programs: bird and ball, conveyor, and juggler using the affected UE
Viana 2014	Aged >21 years; <6 months after diagnosis of unilateral stroke; Weakness and/or spasticity of the affected UE; Hold the Wii controller with affected UE; No cognitive deficits; Follow instructions and interact with the games	History of seizure or cerebral aneurysm; Prior surgery involving metallic implants	tDCS + VR: tDCS + VR VR only: VR + sham tDCS	C: over the contralateral orbit A: over the primary motor cortex of the affected hemisphere Intensity: 2 mA Duration: 13 min	Complete the three programs: Wii Sports resort, Wii Play Motion, and Let's Tap using the affected UE for 45 min
Yao 2020	Aged 18–80 years; First-ever ischemic stroke diagnosed by CT or MRI; >2 weeks and <1 year after diagnosis of first ischemic stroke; Using tDCS can induce MEP of contralesional FDI	Prior surgery involving metallic implants; History of seizure; History of brain neurosurgery or cerebral trauma; Aphasia; Unilateral neglect; Cognitive deficits; Refused to sign informed consent	tDCS + VR: tDCS + VR VR only: VR + sham tDCS 10 sessions (20 min/d and 5 times/wk for 2 wk)	C: over the primary motor cortex of the unaffected A: over the contralateral supraorbital region Intensity: 2 mA Duration: 20 min	Complete the different motion mode (passive, assistant, active and resistant mode) and different game forms using the affected UE for 20 min
Lee 2021	>3 months and <1 year after diagnosis of stroke; FM-UE: 26–56; MMSE-K > 24; MAS <1+; Brunnstrom stage >4	Orthopedic problems; Visual impairment or visual perception impairments; History of seizures or heated by electrical current	tDCS + VR: tDCS + VR VR only: VR + sham tDCS 20 sessions (20 min/d and 5 times/wk for 4 wk)	C: over the hand area of the unaffected motor cortex A: over the contralateral orbit Intensity: 2 mA Duration: 20 min	Complete the three programs: flipping a book, painting, and cooking for 20 min

Abbreviations: RCT, randomized controlled trial; tDCS, transcranial direct current stimulation; VR, virtual reality; min, minutes; d, days; wk, weeks; mA, milliampere; UE, upper extremity; CT, computed tomography; MRI, magnetic resonance imaging; MEP, motor evoked potential; FDI, first dorsal interossei muscle; FM-UE, Fugl-Meyer Upper Extremity; MMSE-K, Mini-Mental State Examination; MAS, Modified Ashworth Scale; C, the cathodal electrode; A, the anodal electrode.

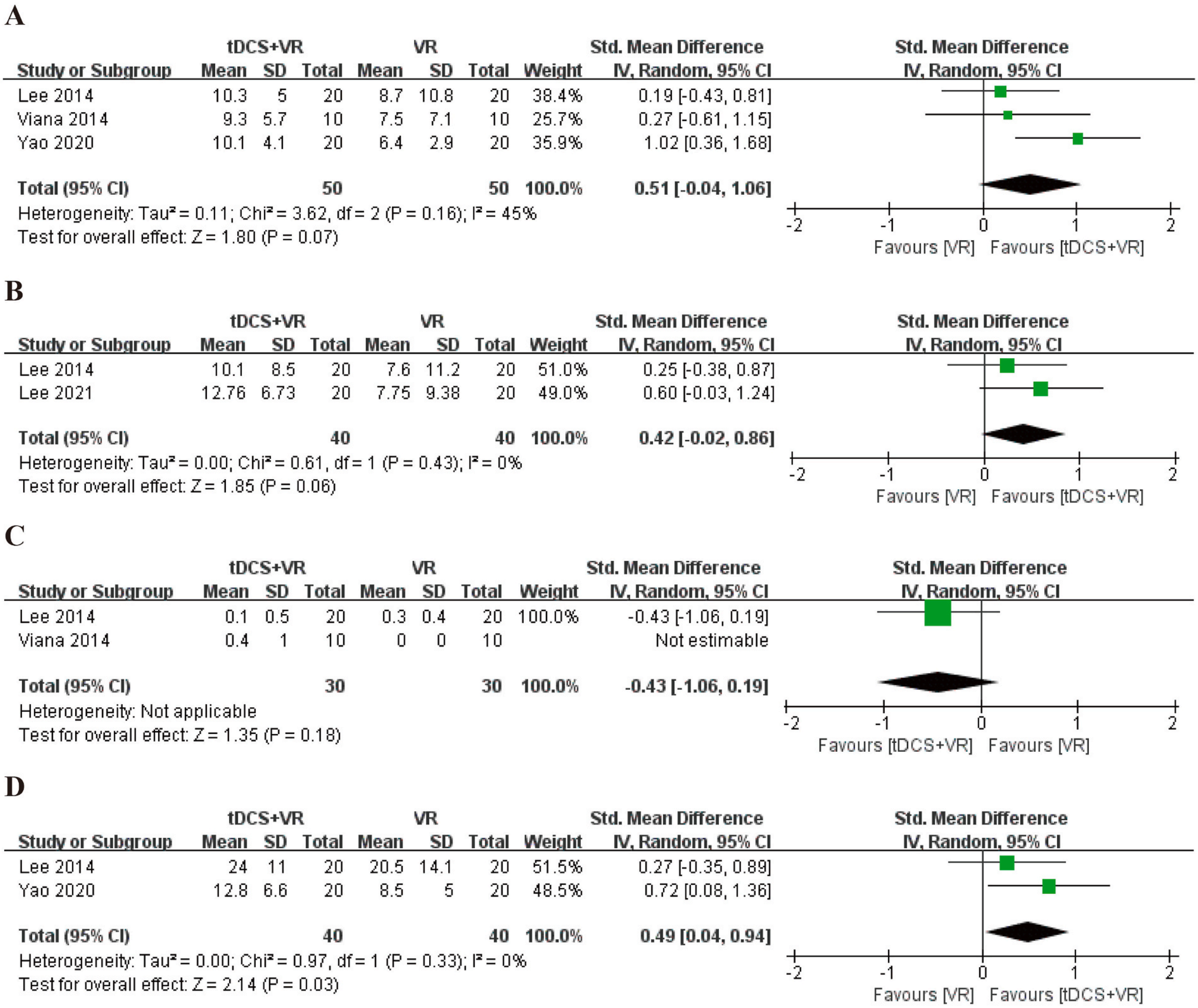

Figure 2. Efficacies for the combined treatment to patients with stroke compared to VR alone. A: FM-UE; B: BBT; C: MAS; D: BI. Abbreviations: tDCS, transcranial direct current stimulation; VR, virtual reality; SMD, standard mean differences; 95% CI, 95% confidence intervals; SD, standard deviation.

selection bias in this research. For performance bias, it was high in the studies conducted by Lee et al. in 2014 and Yao et al. in 2020 in terms of blinding of participants and personnel. The bad part was that the detection bias was unclear for most RCTs and the study conducted by Yao et al. in 2020 was even high. Moreover, the risk of biases in all studies were acceptable for incomplete outcome data and selective reporting. Generally speaking, the quality of the included RCTs in this meta-analysis was accredited.

4. Discussion

This article is the first elaborated meta-analysis and systematic review summarizing the efficacy of tDCS combined with VR versus VR alone on upper extremity rehabilitation of patients with stroke. Stroke as a common disease has a significant impact on the quality of daily living [30]. Measuring the self-care and mobility of patients with stroke determines the impact of the treatment on the quality of life. Although the BI can't evaluate patients' cognition, speech function, visual function, and pain, the BI is still an index with reliability and validity at the same time. Interestingly, the difference between tDCS combined with VR and VR alone in terms of the improvement in BI was significant. This meant that combination therapy improved the quality of life in patients with stroke better than VR alone.

The FM-UE scale was commonly used to measure upper extremity impairment and was scored based on the quality of movement. This meta-analysis revealed that the combination of tDCS and VR did not result in better improvement in the FM-UE scale compared to VR alone. For BBT, upper extremity function in various subjects could be judged by the number of blocks that the affected upper extremity could grasp and release in 1 min. We also did not find conclusive evidence that the combination therapy of tDCS and VR was superior to the VR alone group. However, it was worth to note that quantitative measures of upper extremity function in both groups

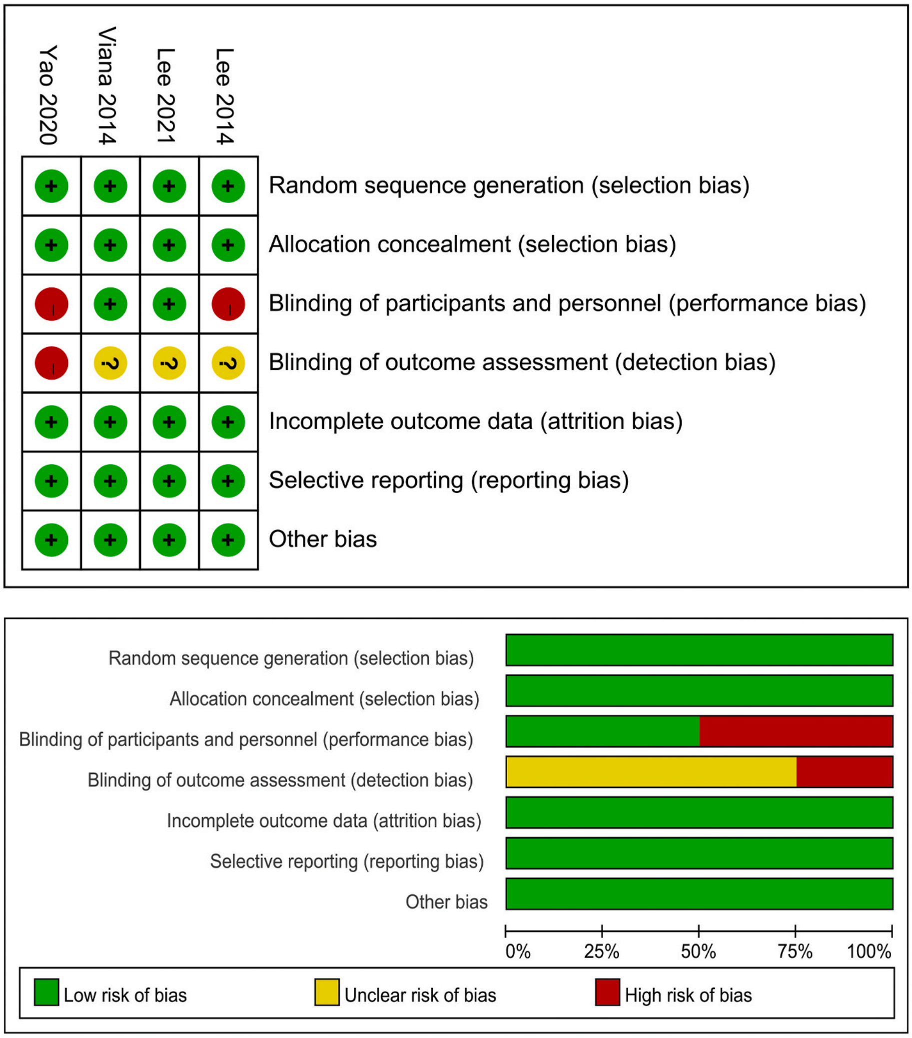

Figure 3. Risk of bias: A summary table for each risk of bias item for each study.

showed a considerable trend toward significance (FM-UE: $P = 0.07$; BBT: $P = 0.06$). This might be due to the small sample sizes of all four RCTs included in this meta-analysis and the RCT with the largest sample size had just 40 participants. If future studies can include more participants and have the same trend as the existing studies, favorable results may be observed. The excessive spasticity of the extremity is considered to limit movement and the usage of MAS is sufficient to assess the spasticity of the subject's upper extremity. Since the mean and SD of the differences within the VR alone group were zero in Viana's study, the overall effect between the two groups after treatment could not be estimated. However, there were also no significant differences in each RCT separately. Some studies suggested that recovery of limb function was not necessarily associated with improvement of spasticity [30], which explained the above results.

Motor impairment in patients with stroke occurs in the upper extremities frequently, which can have a serious negative impact on the patient's daily life [30]. The main aim of stroke treatment is to reduce brain damage as well as to facilitate the recovery of the patient. Many researchers are exploring different novel approaches of neurorehabilitation and which one is better or more applicable to different populations. Constraint-induced movement therapy used for upper extremity rehabilitation after stroke enhanced upper extremity movement and function [31]. A review of 45 studies demonstrated that robot-assisted upper extremity training could improve upper extremity function, upper extremity muscle strength, and the quality of life without increasing the additional risk [32]. Thieme et al. found that mirror therapy, a method that let the patient believe the affected extremity moved like the unaffected extremity, was able to increase upper extremity motor function and decrease the pain [33]. Recent evidence has established that neuromuscular electrical stimulation improved the Fugl-Meyer scale and MAS scores, meanwhile, the positive effects were retained for six months [34].

VR and tDCS were the two neurorehabilitation methods involved in this meta-analysis. Thomson et al. revealed that although VR was able to assist upper extremity training in patients with stroke, but the evidence could not conclude that VR was more beneficial at the time [8]. VR as an adjunct could be used not only for stroke [8, 12] but also for cerebral palsy [7], Parkinson's disease [10], schizophrenia [11], anxiety [9], and post-traumatic stress disorder [35], etc. Noninvasive brain stimulation included tDCS and transcranial magnetic stimulation was capable of modulating motor cortical excitability. The existing studies did not draw the conclusion that patients with stroke who received transcranial magnetic stimulation benefited from it [36]. Nonetheless, tDCS was already a potential method of upper extremity rehabilitation after stroke [16]. The cathodal electrode decreased the excitability of the non-lesioned motor cortex, whereas the anodal electrode increased the excitability of the lesioned motor cortex [37]. Through this potential mechanism, tDCS improved motor function in the affected extremity.

So, whether the combined treatment of tDCS and VR will have a synergistic effect? Several studies have demonstrated that combination therapy promoted recovery of upper extremity motor function [17, 18], possibly due to an increase in corticospinal facilitation [17]. Besides, stroke disrupted the balance of the bilateral cerebral hemispheres but activated the neuroplasticity at the same time [38]. VR-assisted rehabilitation benefitted rebalance of bilateral cerebral hemispheres [39] and tDCS-assisted rehabilitation helped modulation of neuroplasticity [19]. Rezaee et al. found that the combination of tDCS and VR could activate the prefrontal cortex and sensorimotor cortex by combining functional near-infrared spectroscopy with electroencephalography [40]. The combination of tDCS and VR as a potential treatment modality is applied to cerebral palsy, anxiety, post-traumatic stress disorder, neuropathic pain, and multiple sclerosis [41].

In terms of improving capacity in the activities of daily living after stroke, a network meta-analysis has proven that cathodal tDCS is the best treatment option among the different forms of tDCS and physical rehabilitation [42]. Ahmed et al. observed that transcranial vagus nerve stimulation and tDCS were more effective in various electric neurostimulation [43]. Although the combination of noninvasive brain stimulation and virtual reality was found to be promising in subacute stroke by Subramanian et al [44]. Nevertheless, the types of stimulation included varied, including tDCS as well as repetitive transcranial magnetic stimulation. Besides, the participants included healthy volunteers who were not exclusively stroke patients. However, no meta-analysis has ever directly compared the efficacy of combination treatment with VR alone for upper extremity training in patients with stroke. Is the combination treatment necessary for patients with stroke? Both clinicians and patients need further evidence.

There would be varying degrees of spontaneous rehabilitation in the short time after the stroke has occurred [45]. Spontaneous rehabilitation was highly heterogeneous from patient to patient. This process was important and facilitated by other drugs or rehabilitation measures. The time to start taking rehabilitation measures also bothered us. Kwakkel et al. suggested that FM-UE scores within four weeks post-stroke were strongly associated with long-term prognosis [13]. Most of the patients included in the trial by Yao et al. were in the subacute phase and had a significant improvement in FM-UE after the combination treatment of tDCS and VR [19]. The other study, which included only patients with chronic stroke, did not draw the same conclusion [28]. What's more, the cathodal electrode was placed over the hand area of the unaffected motor cortex in 3 RCTs, while the anodal electrode was placed over the primary motor cortex of the affected hemisphere in another RCT. Elsner et al. concluded that cathodal stimulation was the best treatment option for improving the activities of daily living in patients with stroke compared to anodal stimulation and dual stimulation [42]. Thus, the time window and stimulation type for combined therapy needed to be further defined.

There were several limitations in this meta-analysis. Firstly, the four included RCTs were entirely single-center and small samples, which led to a reduction in the credibility of the evidence. Secondly, the trials by Lee et al. and Yao et al. were single-blind studies which might bring the possibility of bias, and the bias of the patient or researcher might affect the accuracy of the results. Thirdly, inclusion criteria and treatment procedures were also variable among the different trials. The time since stroke, stroke type, treatment procedures, the placement of the electrode, devices for tDCS, and devices for VR varied from trial to trial, which could lead to different results.

5. Conclusions

The combination treatment of tDCS and VR is a slightly better treatment strategy than VR alone for patients with stroke who require upper extremity training. It is related to a significantly better quality of life in patients with stroke. As for the upper extremity motor impairment and motor function, the combined treatment isn't superior to VR alone. However, the scores of the FM-UE scale and the BBT tend to increase. The stimulation type for combined therapy needs to be further defined. In the future, multi-center studies including more patients are needed. The clear time window for tDCS and VR therapy needs to be further defined.

Declarations

Conflict of interest

The authors declare that they have no conflict of interest.

Statement of ethics

Ethical approval is not required.

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