Effect of tDCS Concurrent With VR-based Robot on Hemiplegic Upper Limb Function After Ischemic Stroke: A Randomized Controlled Study

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Research Article

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Abstract

Background

Upper limb hemiplegia faces the challenge of slow and difficult recovery. A “closed-loop method” based on brain plasticity has been proposed, combining central and peripheral interventions to enhance the upper limb function. Based on the theory, we aimed to investigate the effect of transcranial direct current stimulation (tDCS) concurrent with virtual reality (VR)-based robot intervention on the enhancement of upper limb function recovery and the change of cortical excitability.

Methods

In this single-blinded, randomized, controlled clinical trial, 40 patients with subacute stroke were recruited and randomized to experimental (tDCS concurrent with VR-based robotic intervention) and control (sham tDCS concurrent with VR-based robotic intervention) groups. All patients received 15 sessions for 20 minutes per day. Outcome measures included the Fugl-Meyer Assessment Upper Limb Scale (FMA-UL), the Action Research Arm Test (ARAT), and activities of daily life (ADL).

Results

Thirty-four patients completed functional near-infrared spectroscopy (fNIRS) examinations. Both groups showed meaningful enhancements in FMA-UL, ARAT, and modified Barthel index (MBI) scores following the training. When the two groups were compared, the FMA-UL and ARAT scores showed greater improvement in the examination group compared to the control group, but the MBI difference was not statistically significant. An analysis of fNIRS results revealed that the activation of the ipsilesional primary motor cortex (iM1) and contralesional prefrontal cortex (cPFC) increased after training in the experimental group, while it decreased in the control group. The activation of iM1 and cPFC in the experimental group was significantly higher than that in the control group.

Conclusions

Compared with the control group, tDCS concurrent with VR-based robot intervention can effectively enhance upper limb function and promote activation of iM1 and cPFC in subacute patients with stroke. However, there was no obvious advantage in improving ADL.

Trial registration:

The study was registered in the Chinese Clinical Trial Registration Center (ChiCTR2100047442) on June 18, 2021.
Background

Upper limb hemiplegia is a common dysfunction after stroke[1]. Most patients are unable to use the paretic side upper limb to perform simple activities within 6 months after stroke, which may affect living quality and happiness and may cause anxiety and depression[2]. Therefore, improving upper limb function is central to rehabilitation to maximize recovery. However, limited by the fine and complex function of the upper limb and the extremely dense interconnected regulatory network of the brain[3, 4], upper limb hemiplegia still faces the challenge of a slow and difficult recovery.

Recently, new therapeutic approaches, including upper limb robots, virtual reality technology (VR), and non-invasive brain stimulation (NIBS) have been applied in clinical studies. Virtual reality (VR)-based robots combine hardware and software to achieve interaction with the simulated environment, providing patients with multiple task-oriented training through different games[5]. Simultaneously, positive feedback is given to patients through sensory stimulation including vision, hearing, and vibration[6], which enhances the confidence in performing actions and encourages patients to complete high-intensity and repetitive exercise training.

Transcranial direct current stimulation (tDCS) is a potential NIBS method which regulates cortical excitability through the application of low levels of current to the scalp[7]. Anodal and cathodal tDCS can upregulate and inhibit cortical excitability, respectively[8]. Furthermore, anodal tDCS can enhance upper limb function in stroke patients through increased activation of the ipsilesional primary motor cortex (iM1)[9]. Due to its portability, lower cost, and greater tolerability, anodal tDCS has been widely used in stroke rehabilitation[10]. A systematic review has shown that tDCS combined with different forms of upper limb rehabilitation intervention had moderate effects on upper limb function recovery, and tDCS combined with VR training was more effective[11]. Therefore, tDCS concurrent with VR-based robot intervention is expected to promote a more effective recovery of upper limb function.

tDCS concurrent with VR-based robot intervention focuses on the evaluation of clinical efficacy[12, 13], and there are few studies on cerebral cortex activation. A “closed-loop method” based on brain plasticity has been proposed, which applies peripheral interventions to increase feedback and input from sensory and motor systems to the center. This induces specific long-term plasticity changes through central intervention, restores brain network connections, and promotes the remodeling of brain function[14–16].

We aimed to explore the impact of brain-limb coordination-based regulation on cerebral cortex activation. Commonly used brain imaging techniques include functional magnetic resonance imaging (fMRI) and functional near-infrared spectroscopy (fNIRS), both based on the spatial localization of neurovascular signals, reflecting the metabolic conditions of neurons and exploring cortical activation[17]. fMRI is the most accurate brain imaging technology available, but limited head and body movement, disturbing noise, and small testing spaces during fMRI imaging limit its use[18, 19]. Although fNIRS does not have the same spatial resolution as fMRI, it has the added advantage of being highly resistant to interference, more portable, less noisy, and more acceptable to patients in the resting mode. During motor tasks, fNIRS can also monitor cortical activation in real time[20–22]. We, therefore, selected fNIRS to observe the
cortical activation of tDCS concurrent with VR-based robot intervention to enhance upper limb function in subacute stroke patients.

**Methods**

**Participants**

Between June 2021 and June 2022, patients suffering from upper limb hemiplegia following an ischemic stroke were recruited from the Rehabilitation Medicine Center in Changzhou De’an Hospital, Changzhou, Jiangsu, China. We included patients with a head computed tomography or magnetic resonance imaging examination used to confirm the diagnosis of ischemic stroke, which was made in accordance with the Chinese Stroke Association’s guidelines for the clinical management of cerebrovascular disorders[23]: first-ever unilateral ischemic stroke with upper limb hemiplegia, subcortical lesion, post-stroke time between 2 weeks and 6 months, and patient age range of 30 to 80 years. We excluded patients with any other neurological condition or mental illness, severe cognitive impairments (Mini-Mental State Examination score < 20)[12], skull abnormalities, high muscle tone of the hemiplegic upper limb (modified Ashworth scale > 2)[24], and a poor signal when wearing an fNIRS detector that could not be improved. The study protocol was approved by The Changzhou Dean Hospital Human Ethics Committee (CZDALL-2021-001) and was registered with the China Clinical Trial Registration Center (ChiCTR2100047442).

**Interventions**

The study was a single-blind, randomized, controlled clinical trial. Patients were randomly divided into experimental and control groups by the group randomized method. The demographic information of all patients was collected by the same rehabilitation therapist, including name, age, gender, duration of disease, and paretic side.

Both groups received basic drug and conventional rehabilitation therapy, including exercise therapy and occupational therapy. On this basis, the experimental group was treated with tDCS concurrent with VR-based robot intervention. The control group was treated with sham tDCS concurrent with VR-based robot intervention. Both treatment programs include 15 sessions (20 minutes per day, 5 sessions per week, for 3 weeks) (Fig. 1A).

For tDCS, we used a VC-8000C type therapy instrument by Nanjing Wogao Medical Technology Co., Ltd. in Jiangsu, China. Before treatment, the electrodes (5 × 7 cm) were inserted into the isosmolar saline gelatin sponge, respectively, and fixed with an elastic bandage. Based on the international electroencephalogram (EEG) 10/20 system[25], the anodal tDCS was applied to iM1, 2.5 cm above C3/C4 on the scalp[26, 27], and the cathodal tDCS was applied to the contralesional superior orbital margin[28]. The tDCS intensity of the experimental group was set at 1.5–2.0 mA, and the intensity was adjusted according to the tolerance of the patients. In the control group, the two electrodes of the tDCS were applied in the same position as the experimental group, and the intensity of sham tDCS continued to reach 1.5–2 mA in the first 30 s, and then dropped to 0 mA in 30 s.
The device for the VR-based robot was made by ESTUN Medical Technology Co., Ltd. in Nanjing, Jiangsu, China. It includes a three-dimensional robotic arm and a screen to provide VR environments. At the end of the robotic arm, there is a sensory sensor that can provide vibration feedback. The device has been designed with multiple movement modes (passive, assistive, active, and resistive modes) and game types, such as ocean exploration, shooting, calligraphy, boxing, primarily to assist patients with movement control training, effectively making boring and challenging training interesting. For each patient, the appropriate training modes and exercise items were selected by the specific therapist according to the patient's upper limb function.

**Outcome measures**

Before and 3 weeks after treatment, upper limb function was evaluated using the Fugl-Meyer Assessment Upper Limb Scale (FMA-UL), and the Action Research Arm Test (ARAT). Activities of daily life (ADL) were evaluated by the modified Barthel index (MBI). Functional near-infrared spectroscopy (fNIRS) was applied to monitor cortical excitability while patients flexed and extended the elbow. The rehabilitation assessment was performed by the same trained rehabilitation therapist.

FMA-UL was the main outcome, measuring upper limb motor function in patients with hemiplegia. The FMA-UL assesses reflexes, synergies, range of motion, and fine and gross hand movements and includes 33 items with a maximum score of 2 for each item, giving 66 points. This scale is reliable and valid. The ARAT is divided into grasping, gripping, pinching, and gross movements, with 19 items, and 57 points, and has shown good validity and sensitivity. The MBI assesses bowel and bladder care, feeding, grooming, bathing, dressing, toileting, walking, transferring, and climbing stairs, with 10 items in total and 100 points, and is a valid and reliable tool in assessing ADL improvement.

Since the VR-based robot used in this study has shown good training for elbow flexion and extension of the upper limb, and referring to a similar research design, we chose the motions of elbow flexion and extension with hemiplegic upper limbs as our fNIRS experiment task. We set the block design as 15 s movement plus 15 s rest, repeated three times. Patients were guided by a therapist to make sure that the procedure was understood before the experiment. The patient applied the fNIRS test cap and sat in a chair, keeping quiet, with the head stable and the stimulator on a table in front of them. Then, patients were instructed by audio cues from the stimulator to repetitively try to flex and extend the elbow for 15 s, and then rest for 15 s (Fig. 1B).

We used a multi-channel fNIRS system (NirScan-6000C, Danyang Huichuang Medical Equipment Co., Ltd., Zhenjiang, China) with an 11 Hz sampling rate for data acquisition, with three wavelengths of 730 nm, 808 nm, and 850 nm, and a channel number of 35. The bilateral prefrontal cortex (PFC), primary motor cortex (M1), and primary sensory cortex (S1) were targeted with 14 sources and 14 detectors based on the 10/20 system (Fig. 1C).

Raw data were analyzed using Nirspark (NirScan-6000C, Danyang Huichuang Medical Equipment Co., Ltd., Zhenjiang, China). First, the raw near-infrared (NIR) intensities were converted to an optical density.
signal. Second, irrelevant motion artifacts from the experiment were removed. Third, 0.01 ~ 0.1 Hz was used to remove baseline noise as well as possible respiratory and heart rate signals\[38\]. Fourth, the differential path length factor was set to 6. Fifth, the filtered optical density data were converted to oxy-Hb and deoxy-Hb using the modified Beer–Lambert law\[39\]. Sixth, the block averaging module of the Nirspark software (with −2 to 0 s as the baseline and 0 to 30 s as the time paradigm for individual blocks) was used to calculate the total average HbO₂ concentration in different blocks. Finally, the mean oxygen concentrations of the three blocks were superimposed to obtain the mean value of the blocks. Since the patients in this study had different sides of brain damage, the brain images of patients with right hemisphere injury were flipped to the contralateral hemisphere along the central axis.

**Statistical analysis**

The data was analyzed using the statistical program SPSS 25.0. First, the data were subjected to the Shapiro–Wilk normality test. The mean ± standard deviation (\(\bar{x} \pm s\)) was used to express measures that followed a normal distribution, while the median and quartile distance (M [P25, P75]) were used to indicate values that did not. Within and between group comparisons were made between the experimental and control groups. For measurement data fitting into a normal distribution, a paired t-test was used for within group comparisons and an independent-sample t-test was used for between group comparisons. When comparing measurement data that deviated from the normal distribution between groups, the Mann–Whitney U test was utilized for intergroup comparisons and the Wilcoxon signed rank sum test was utilized for intragroup comparison.

**Results**

**Baseline characteristics of participants**

This study recruited 44 patients. During the experiment, four patients dropped out, including two in the experimental group (one due to hospital transfer, one due to non-compliance with treatment) and two patients in the control group (due to changes in their condition). Finally, 40 patients completed the experiment (Fig. 2). The gender, age, duration of disease, and paretic side did not differ significantly between the two groups (all \(P > 0.05\)) (Table 1).
Table 1
Demographics and characteristics of the stroke patients in the two groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Experiment group (n = 20)</th>
<th>Control group (n = 20)</th>
<th>statistical test value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61.10 ± 10.62</td>
<td>62.35 ± 12.12</td>
<td>-0.35&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.73</td>
</tr>
<tr>
<td>Gender (Male/Female)</td>
<td>17/3</td>
<td>16/4</td>
<td>-</td>
<td>0.45</td>
</tr>
<tr>
<td>Duration of disease (day)</td>
<td>28.50(17.25, 49.25)</td>
<td>30.50(16.25, 55.00)</td>
<td>198.50&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.97</td>
</tr>
<tr>
<td>Paretic side (Left/Right, n)</td>
<td>9/14</td>
<td>11/9</td>
<td>-</td>
<td>0.75</td>
</tr>
</tbody>
</table>

<sup>a</sup> t value calculated by t test.  
<sup>b</sup> z value calculated by Mann-Whitney U test. ‘-’ Fisher’s exact test.

**Effects of the treatment**

Before training, there was no discernible difference between the two groups in FMA-UL, ARAT, and MBI. Follow training, FMA-UL, ARAT, and MBI was significantly enhanced for both groups (experimental group: FMA-UL, ARAT, MBI, P < 0.01, respectively; control group: FMA-UL, ARAT, MBI, P < 0.01, respectively). The comparison of pre-post differences between the two groups showed that the differences between FMA-UL and ARAT in the experimental group were significantly better than in the control group (both P < 0.01). The group MBI scores did not differ significantly for both groups (P > 0.05) (Table 2, Fig. 3).
Table 2
Effect of intervention on outcomes in the two groups

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Experimental Group (n = 20)</th>
<th>Control Group (n = 20)</th>
<th>statistical test value</th>
<th>P_a value</th>
<th>P_b value</th>
<th>statistical test value</th>
<th>P_b value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMA-UL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>32.30 ± 15.18</td>
<td>32.75 ± 16.99</td>
<td>-0.09^a</td>
<td>0.93</td>
<td>0.01</td>
<td>-8.15</td>
<td>0.01</td>
</tr>
<tr>
<td>Post</td>
<td>48.05 ± 15.16</td>
<td>38.05 ± 18.34</td>
<td>1.88^a</td>
<td>0.07</td>
<td></td>
<td>-4.88</td>
<td></td>
</tr>
<tr>
<td>ARAT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-3.73^b</td>
<td>0.001</td>
</tr>
<tr>
<td>Pre</td>
<td>12.50(3.25, 30.00)</td>
<td>14.00(3.25, 43.00)</td>
<td>-0.29^b</td>
<td>0.78</td>
<td>0.001</td>
<td>-3.44^b</td>
<td>0.001</td>
</tr>
<tr>
<td>Post</td>
<td>35.50(11.50, 50.00)</td>
<td>23.50(4.00, 49.75)</td>
<td>-0.95^b</td>
<td>0.34</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MBI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-5.79</td>
<td>0.001</td>
</tr>
<tr>
<td>Pre</td>
<td>71.50 ± 14.36</td>
<td>68.55 ± 23.44</td>
<td>0.48^a</td>
<td>0.63</td>
<td>0.001</td>
<td>-4.73</td>
<td>0.001</td>
</tr>
<tr>
<td>Post</td>
<td>84.05 ± 13.02</td>
<td>78.80 ± 22.12</td>
<td>0.92^a</td>
<td>0.37</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


MBI, Modified Barthel Index. ^a t value calculated by t test. ^b z value calculated by Mann-Whitney U test. P_a, the results of comparison between groups. P_b, the results of intra-group comparison.

In the experimental group, one patient could not complete the evaluation due to poor fNIRS signal quality. In the control group, one patient did not cooperate, two patients had poor fNIRS signal quality, and two patients had motion artifacts that could not be removed. In total, 34 patients were included for the
analysis (Fig. 2). Of these, 17 patients with right hemisphere damage (eight in the experimental group, nine in the control group) had their images flipped to left hemisphere damage.

Before training, there was no significant difference in the HbO$_2$ concentration of each region of interest in the elbow flexion and extension tasks of the hemiplegic upper limb between the two groups (P > 0.05). After training, a comparison of the difference in HbO$_2$ concentration ($\Delta$HbO$_2$) between the two groups revealed significant differences in iM1 (P = 0.024) and cPFC (P = 0.005). The activation of iM1 and cPFC of the experimental group was increased after treatment, while the activation of iM1 and cPFC of the control group was decreased after treatment (Table 3, Fig. 4).
Table 3
Changes of elbow flexion task HbO$_2$ in two groups

<table>
<thead>
<tr>
<th>ROI</th>
<th>Experimental Group (n = 19)</th>
<th>Control Group (n = 15)</th>
<th>statistical test value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Change</td>
<td></td>
</tr>
<tr>
<td>ipsilesional PFC</td>
<td>-0.036 ± 0.046</td>
<td>0.051 ± 0.058</td>
<td>-0.836$^a$</td>
<td>0.409</td>
</tr>
<tr>
<td></td>
<td>0.039 ± 0.044</td>
<td>0.037 ± 0.040</td>
<td>0.144$^a$</td>
<td>0.886</td>
</tr>
<tr>
<td></td>
<td>0.003 ± 0.030</td>
<td>-0.014 ± 0.045</td>
<td>1.309$^a$</td>
<td>0.200</td>
</tr>
<tr>
<td>contralesional PFC</td>
<td>0.039 ± 0.040</td>
<td>0.062 ± 0.046</td>
<td>-1.562$^a$</td>
<td>0.128</td>
</tr>
<tr>
<td></td>
<td>0.053 ± 0.044</td>
<td>0.039 ± 0.044</td>
<td>0.933$^a$</td>
<td>0.358</td>
</tr>
<tr>
<td></td>
<td>0.014 ± 0.037</td>
<td>-0.023 ± 0.026</td>
<td>3.299$^a$</td>
<td>0.002</td>
</tr>
<tr>
<td>ipsilesional M1</td>
<td>0.041 ± 0.032</td>
<td>0.052 ± 0.041</td>
<td>-</td>
<td>0.537</td>
</tr>
<tr>
<td></td>
<td>0.058 ± 0.053</td>
<td>0.040 ± 0.046</td>
<td>-</td>
<td>0.083</td>
</tr>
<tr>
<td></td>
<td>0.017 ± 0.049</td>
<td>0.012 ± 0.018</td>
<td>2.393$^a$</td>
<td>0.025</td>
</tr>
<tr>
<td>contralesional M1</td>
<td>0.043 ± 0.045</td>
<td>0.049 ± 0.046</td>
<td>-0.430$^a$</td>
<td>0.670</td>
</tr>
<tr>
<td></td>
<td>0.050 ± 0.043</td>
<td>0.048 ± 0.046</td>
<td>0.121$^a$</td>
<td>0.904</td>
</tr>
<tr>
<td></td>
<td>0.008 ± 0.056</td>
<td>-0.001 ± 0.038</td>
<td>0.509$^a$</td>
<td>0.614</td>
</tr>
<tr>
<td>ipsilesional S1</td>
<td>0.064 ± 0.044</td>
<td>0.051 ± 0.042</td>
<td>0.935$^a$</td>
<td>0.357</td>
</tr>
<tr>
<td></td>
<td>0.069 ± 0.064</td>
<td>0.054 ± 0.040</td>
<td>0.793$^a$</td>
<td>0.434</td>
</tr>
<tr>
<td></td>
<td>0.005 ± 0.064</td>
<td>0.004 ± 0.026</td>
<td>-</td>
<td>0.732</td>
</tr>
<tr>
<td>contralesional S1</td>
<td>0.062 ± 0.047</td>
<td>0.046 ± 0.039</td>
<td>1.085$^a$</td>
<td>0.286</td>
</tr>
<tr>
<td></td>
<td>0.046 ± 0.046</td>
<td>0.049 ± 0.042</td>
<td>-0.184$^a$</td>
<td>0.855</td>
</tr>
</tbody>
</table>
### Discussion

We found that, after 3 weeks of tDCS concurrent with VR-based robot intervention, there was a significantly different pattern in the enhancement of upper limb function between the groups. Simultaneously, fNIRS data demonstrated a significant increase in iM1 and cPFC activation in the experimental group relative to the control group. In comparison to VR-based robot intervention alone, this suggests that tDCS concurrent with VR-based robot intervention can effectively promote the change of cortical excitability and enhance upper limb function in subacute stroke patients.

Anodal tDCS was applied to stimulate iM1. After the current flowed through the brain, membrane polarization was caused, the permeability inside and outside the membrane was reduced, the concentration of Ca\(^{2+}\) and Mg\(^{2+}\) was increased, excitatory stimulation was generated, and the activation of M1 on the affected side was increased\[40\]. After anodal tDCS, cortical facilitation is enhanced and local inhibition is weakened, which may initiate neuroplasticity and motor learning effects, thus promoting the recovery of motor function\[9, 41\]. A meta-analysis and systematic review evaluating the effect of tDCS combined rehabilitation on arm and hand function after stroke showed that the effect of tDCS combined with intervention was greatly improved, and the effect was also better than that of sham tDCS combined with intervention or tDCS alone\[11\].

VR-based robots can provide patients with two important conditions to induce neuroplasticity: a rich virtual environment and repeated reinforcement of virtual actions\[42\]. The VR-based robot training system in this study allowed patients to perform multi-dimensional training of the shoulder and elbow joints, such as those involved in cooking and playing basketball, through goal orientation in a common environment of daily life. At the same time, combined with vision, hearing, and vibration, and other sensory feedback, the system encourages patients to complete the task, and promotes the restoration of upper limb function\[43, 44\]. Sensory feedback provided to patients in VR-based robot training can increase the activation of the ipsilesional hemisphere, promote the plasticity and reorganization of M1, and help better learning of motor tasks\[45\].

Stroke destroys the balance of the bilateral cerebral hemisphere, and activates the dynamic plasticity of the brain\[12\], thus promoting the treatment of neural plasticity seems to be the future of stroke rehabilitation. On the basis of the “closed-loop method”\[14, 15\], we combined tDCS and a VR-based robot to observe whether synchronous intervention can better enhance the restoration of upper limb function and change cortical excitability. Yao et al. randomly assigned 40 subacute stroke patients to two groups: an experimental group received tDCS concurrent with VR intervention, and a control group received sham...
tDCS concurrent with VR intervention. The pre-post difference between the two groups demonstrated that the experimental group's FMA-UL, ARAT, and BI scores improved significantly compared to the control group. It is suggested that tDCS concurrent with VR can effectively enhance the upper limb function and ADL of subacute stroke patients, which is more effective than VR alone[12]. Our investigation yielded similar results; however, the pre-post MBI difference was not statistically significant, which could be explained by the brief intervention period. However, the items using the MBI score in this study were more detailed than the BI score, and it was easier to reflect the improvement of ADL[46]. Straudi et al. found that, when compared to before an intervention, the FMA-UL score of tDCS concurrent with upper limb robot intervention (experimental group) and sham tDCS concurrent with upper limb robot intervention (control group) improved after the intervention, but the difference between groups was not statistically significant[47]. The main difference between this study and ours is that the disease course and lesion location of the included patients are inconsistent, and there is heterogeneity. Our patients were those with subacute subcortical strokes who may have had greater functional recovery. This also suggests that the course of the disease and the location of the lesion may be important factors affecting the therapeutic effect.

Studies have used anodal tDCS to stimulate the iM1 to boost M1 excitability and promote neuroplasticity, thereby contributing to the recovery of upper limb function[7, 11]. Jamil et al. studied the influence of tDCS on cerebral blood flow through fMRI, and found that tDCS not only stimulated M1, but also other areas such as the premotor and somatosensory cortex, and speculated that tDCS might affect the excitability of interconnected brain networks and cerebral blood flow activities[48]. Hordacre et al. confirmed that functional connectivity of brain networks was related to the response of stroke patients to anodal tDCS by EEG measurement. They also found that, after anodal tDCS, the functional connectivity of the iM1 and contralesional frontotemporal area was enhanced, which was strongly associated with increased cortical excitability[49]. We found similar results: the activation of iM1 and cPFC increased after anodal tDCS concurrent with VR-based robot intervention. Since M1 is responsible for controlling and performing motor tasks, and PFC connects visual information to motor responses, we speculate that there are two reasons for their excitability changes[50, 51]. Firstly, this study adopts VR-based robot training, which requires patients to understand, judge, select, and execute the information and tasks on the screen on time. PFC plays a vital role in making decisions and executing motor behaviors that require sensory cooperation[52, 53]. Therefore, when completing VR-based robot tasks, the cognitive load of patients will be increased, which may lead to enhanced activation of M1 and PFC. Secondly, anodal tDCS is thought to induce activation and enhancement of task-related brain networks, thereby inducing recovery of motor function[54]. In the experimental group, anodal tDCS was used to stimulate iM1, which increased activation in iM1 and may also cause enhanced activation in task-related brain regions such as the PFC. However, we also found that the activation of iM1 and cPFC was decreased after the treatment in the control group. This may be due to the functional stabilization after compensatory reorganization of cortical function. We will further verify this phenomenon in future studies. Therefore, we suggest that anodal tDCS enhances the efficacy of VR-based robot at the central level, causing stronger cortical reorganization and improving neural plasticity.
The strength of this study is that it provides objective evidence for tDCS concurrent with VR-based robot intervention from the aspect of brain imaging and complements the clinical scale, which helps to more accurately reflect the effectiveness of rehabilitation treatment on the restoration of upper limb function in stroke patients. However, the study also has several limitations. First, the size of the sample is small. Second, the effects of timing the application of the two methods on upper limb function and cortical excitability were not examined. Third, the NIR task acquisition task only selected elbow flexion and extension, aiming to match the VR-based robot training action. Our research group aims to enlarge the sample size in the future to further study the cerebral cortex changes of tDCS concurrent with VR-based robot interventions in different upper limb movement tasks.

Conclusions

Compared with the VR-based robot intervention, there was a significant enhancement in upper limb function after tDCS concurrent with VR-based robot intervention; however, there was no obvious advantage in improving ADL. Compared with the VR-based robot intervention, the activation of the iM1 and the cPFC were significantly changed after the tDCS concurrent with VR-based robot intervention.

List of abbreviations

tDCS Transcranial Direct Current Stimulation
VR Virtual Reality
FMA-UL Fugl-Meyer Assessment Upper Limb Scale
ARAT Action Research Arm Test
MBI Modified Barthel Index
fNIRS Functional Near-Infrared Spectroscopy

Declarations

Ethics approval and consent to participate

The study involving human patients was reviewed and approved by the Changzhou Dean Hospital Human Ethics Committee. The patients provided written informed consent to participate in this research.

Consent for publication

Not applicable.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Competing interests**

The authors declare that they have no competing interests.

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**Authors' contributions**

Ying Shen and Tong Wang conceived and designed the study. Chuan Guo, Ayan Geng, Youxin Sui, Shizhe Zhu, Qinglei Wang, Chaojie Kan, Sheng Xu, and Ren Zhuang performed the study and collected raw data. Chuan Guo, Ayan Geng, and Youxin Sui analyzed the data. Chuan Guo, Ayan Geng, and Youxin Sui wrote the manuscript. Ying Shen and Tong Wang helped coordinate the study and reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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**References**


Figures

Figure 1

**Study design and methods.** a. Study intervention. b. fNIRS experimental paradigm. c. fNIRS channel setup. The red dots depict detectors, while the blue dots signify light sources. A total of 14 sources and detectors were used, resulting in 35 channels covering seven major regions of interest, namely the left prefrontal cortex, right prefrontal cortex, left primary motor cortex (LM1), right primary motor cortex (RM1), left primary sensory cortex (LS1), and right primary sensory cortex (RS1).
Figure 2

Flowchart of the study.
Figure 3

Score changes of experimental and control groups. **P < 0.01: Examination of group differences.

Figure 4

Scatter plots of HbO₂ in the two groups. The groups were compared pre- and post-intervention in ipsilesional M1 (a) and contralesional PFC (b) during flexion tasks (mmol/L).