




# BMJ Open Combined robot motor assistance with neural circuit-based virtual reality (NeuCir-VR) lower extremity rehabilitation training in patients after stroke: a study protocol for a single-centre randomised controlled trial

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## ABSTRACT

**Introduction** Improving lower extremity motor function is the focus and difficulty of post-stroke rehabilitation treatment. More recently, robot-assisted and virtual reality (VR) training are commonly used in post-stroke rehabilitation and are considered feasible treatment methods. Here, we developed a rehabilitation system combining robot motor assistance with neural circuit-based VR (NeuCir-VR) rehabilitation programme involving procedural lower extremity rehabilitation with reward mechanisms, from muscle strength training, posture control and balance training to simple and complex ground walking training. The study aims to explore the effectiveness and neurological mechanisms of combining robot motor assistance and NeuCir-VR lower extremity rehabilitation training in patients after stroke.

**Methods and analysis** This is a single-centre, observer-blinded, randomised controlled trial. 40 patients with lower extremity hemiparesis after stroke will be recruited and randomly divided into a control group (combined robot assistance and VR training) and an intervention group (combined robot assistance and NeuCir-VR training) by the ratio of 1:1. Each group will receive five 30 min sessions per week for 4 weeks. The primary outcome will be Fugl-Meyer assessment of the lower extremity. Secondary outcomes will include Berg Balance Scale, Modified Ashworth Scale and functional connectivity measured by resting-state functional MRI. Outcomes will be measured at baseline (T0), post-intervention (T1) and follow-ups (T2–T4).

**Ethics, registration and dissemination** The trial was approved by the Ethics Committee of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Chinese Traditional Medicine (Grant No. 2019–014). The results will be submitted to a peer-reviewed journal or at a conference.

**Trial registration number** ChiCTR2100052133.

## INTRODUCTION

In the past decade, stroke has become the second leading cause of death worldwide

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This study describes an innovative trial protocol combining neural circuit-based virtual reality (VR) rehabilitation training with robot motor assistance, providing an effective therapy for patients after stroke with lower extremity motor dysfunction.
- ⇒ This study adopts routine two-dimensional VR rehabilitation training as the controlled intervention to minimise performance bias.
- ⇒ This study will provide insightful evidence of whether immersive multisensory stimuli and rewarding incentives can improve motor function through adaptive brain functional remodelling.
- ⇒ This study is a single-centre randomised controlled trial, which may lead to possible analytical bias.

and China's first leading cause of death.<sup>1–3</sup> The global prevalence of cerebrovascular disease was 24.9% in 2016.<sup>4</sup> More than half of 1 million stroke survivors have a disability.<sup>5</sup> However, the recovery of lower extremity motor function has always been challenging in rehabilitation. More than 50% of the patients still have difficulties walking after receiving conventional rehabilitation treatments, such as walking on uneven ground, obstacle avoidance function and long-distance walking, which limited the patients' daily life and social participation.<sup>6–8</sup>

At present, rehabilitation treatment technology is developing rapidly, and it accepts that the conventional rehabilitation treatments for post-stroke dysfunction are modest and far from satisfied.<sup>6</sup> Therefore, there is an urgent need for new rehabilitation technologies as auxiliary treatments for motor function reconstruction.<sup>9</sup> Recent researches have

increasingly focused on robot-assisted training in stroke rehabilitation, involving highly repetitive, intensive and task-specific training with feedback.<sup>10 11</sup> Although the efficacy of robot-assisted rehabilitation remains debatable, multiple studies have shown that robot-assisted lower extremity motor function training can improve the flexibility and coordination of patients after stroke and improve balance and walking ability.<sup>12–14</sup>

Recent research revealed that robot-assisted training could help accelerate motor learning for restoring mobility and play an essential role in promoting the functional reorganisation of the representative area of the motor cortex.<sup>15 16</sup> Early start of robot-assisted gait training after stroke can accelerate bi-hemispheric reorganisation of motor-related brain regions, especially the superior temporal gyrus, cingulate gyrus and posterior central gyrus.<sup>17</sup> Nevertheless, studies have also shown that the effect of robot-assisted rehabilitation on balance, walking ability or gait speed is often not better than conventional rehabilitation treatments.<sup>12 18 19</sup> Nonetheless, rehabilitation robots still have many advantages. Robot-assisted training can provide purposeful movement training<sup>20</sup> and serve as a platform to integrate other rehabilitation technologies to improve rehabilitation efficacy, such as virtual reality (VR),<sup>21</sup> neuromuscular electrical stimulation<sup>22</sup> and transcranial direct current stimulation.<sup>15</sup>

VR, a novel rehabilitation strategy regarded as an enjoyable alternative to enhance motor recovery after stroke, can provide a variety of scenes and sensory stimulation through an enriched environment and dual tasks. It can increase patients' multisensory input, fully mobilise the enthusiasm to participate in rehabilitation treatment and increase the interest in rehabilitation.<sup>23</sup> VR allows the sensory environment to be involved, rather than merely using robotics to perform the movement. A previous study found that enriched environmental training can activate brain-derived neurotrophic factor protein expression, improve neurological function and enhance resilience to cerebral ischaemia.<sup>24</sup> Besides, enriched environment treatment may provide neuroprotection<sup>25</sup> and enhance angiogenesis to promote functional recovery after stroke.<sup>26</sup> Furthermore, multiple studies have shown that reward positively affects motor adaptation,<sup>27–29</sup> influencing neural activity related to motor preparation and execution.<sup>30</sup> Actually, a previous study has found that multiple rewards can enhance motor recovery and adaptive brain plasticity.<sup>15</sup> Moreover, virtual rewards have shown to be equally effective in reward circuits.<sup>31</sup> A neuroimaging study has demonstrated that the reward processing system of the mesolimbic network is activated by VR-based rewards and may benefit motor recovery after stroke.<sup>32</sup>

According to previous studies on robot-assisted or VR lower extremity rehabilitation, only simple walking training is carried out.<sup>21 33 34</sup> The patients of these studies need to have a certain walking ability, such as functional ambulation category  $\geq 3$  points, which makes the equipment only be appropriated for patients with mild

dysfunction.<sup>35</sup> It is urgent for patients after stroke with poor walking ability to explore a lower extremity rehabilitation programme following the theory of motor relearning and neural circuit remodelling to improve lower extremity motor function.

Robot-assisted training enables patients after stroke to perform repetitive tasks in a highly consistent manner tailored to their motor abilities. Additionally, VR scene provides stimulus through vision and audio; this multi-sensory stimulus significantly improves neuroplasticity and increases movement quality and functional capacity. Here, we developed a rehabilitation system combining robot motor assistance with neural circuit-based VR (NeuCir-VR) rehabilitation programme involving procedural lower extremity rehabilitation with reward mechanisms, from muscle strength training, posture control and balance training to simple and complex ground walking training. It hypothesised to enhance motor circuit activation and improve lower extremity motor outcomes when combined with these two techniques and training according to motor learning and plasticity principles.

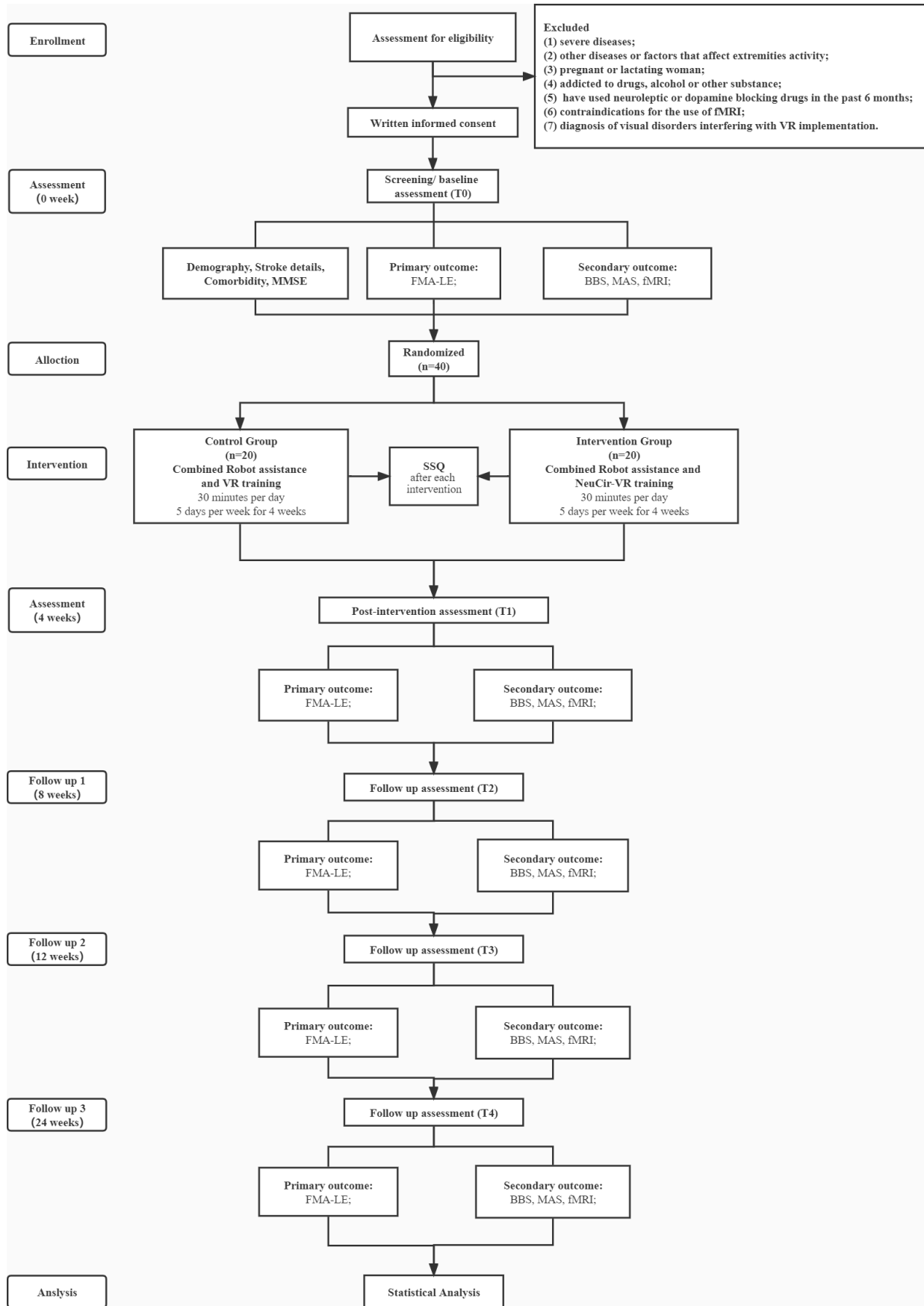
Therefore, we describe a trial protocol to observe the effect of NeuCir-VR rehabilitation training combined with robot motor assistance on the lower extremity motor function in patients after stroke and explore the neurological mechanisms of motor-related and reward-related neural circuits brain functional MRI (fMRI).

## METHODS

### Design

This study is a single-centre, observer-blinded, randomised controlled trial with two parallel groups. Patients with lower extremity hemiparesis after stroke will be recruited from Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine. All recruited patients voluntarily gave written informed consent following the Declaration of Helsinki. A total of 40 participants will be randomly divided into two groups equally: the intervention group (combined robot assistance and NeuCir-VR training) and the control group (combined robot assistance and VR training). All patients will receive 4 weeks of treatment. All assessments will be conducted at baseline (T0), post-intervention (T1), 4 weeks after the completing intervention (T2), 8 weeks after the completing intervention (T3) and 20 weeks after the completing intervention (T4) by an independent evaluator blinded to the study allocation.

The trial was approved by the Ethics Committee of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Chinese Traditional Medicine under protocol number 2019–014, and registered in China Clinical Trial Registration Center. We started recruiting patients on 18 October 2021, and data collection will likely be completed by December 2022. The flowchart of the trial is shown in [figure 1](#). The schedule of enrolment, interventions and assessments is shown in [figure 2](#).



**Figure 1** The flowchart of the trial. BBS, Berg Balance Scale; FMA-LE, Fugl-Meyer assessment of the lower extremity; fMRI, functional MRI; MAS, Modified Ashworth Scale; MMSE, Mini-Mental State Examination; NeuCir-VR, neural circuit-based virtual reality; SSQ, Simulator Sickness Questionnaire; VR, virtual reality.

		TIME POINT					
		Enrolment	Allocation	Assessment	Follow up		
		Screening	Baseline	4 weeks	8 weeks	12 weeks	24 weeks
Assessment/activity		-T0	T0	T1	T2	T3	T4
Screening assessment	Written informed consent	×					
	Contact details	×					
	Demography	×					
	Stroke details	×					
	Comorbidity	×					
	Cognitive function (MMSE)	×					
Baseline assessment	Motor impairment of lower extremities (FMA-LE)		×				
	Functional balance (BBS)		×				
	Spasticity (MAS)		×				
	fMRI scans		×				
	Current lower extremity rehabilitation treatments		×				
	Randomisation		×				
Interventions	Conventional rehabilitation		◆	◆			
	Combined robot assistance and VR training		◆	◆			
	Combined robot assistance and NeuCir-VR training		◆	◆			
Outcome assessments	Motor impairment of lower extremities (FMA-LE)			×	×	×	×
	Spasticity (MAS)			×	×	×	×
	Functional balance (BBS)			×	×	×	×
	fMRI scans			×	×	×	×
Safety assessment	SSQ		×	×			

**Figure 2** The schedule of enrolment, interventions and assessments. BBS, Berg Balance Scale; FMA-LE, Fugl-Meyer assessment of the lower extremity; fMRI, functional MRI; MAS, Modified Ashworth Scale; MMSE, Mini-Mental State Examination; NeuCir-VR, neural circuit-based virtual reality; SSQ, Simulator Sickness Questionnaire; VR, virtual reality.

### Participants

Inclusion criteria for participants were as follows: (1) stroke was diagnosed according to WHO criteria<sup>36</sup>; (2) aged between 18 and 70 years and with no gender restrictions; (3) within 6 months after stroke onset; (4) motor dysfunction confirmed by Fugl-Meyer assessment of the

lower extremity (FMA-LE); (5) Mini-Mental State Examination (MMSE) score  $\geq 27$ .<sup>37</sup> Exclusion criteria were as follows: (1) severe diseases such as severe diabetes, cardiovascular diseases and infectious diseases; (2) other diseases or conditions that result in significant impairment of the extremities activity such as severe joint contracture and

ankylosis; (3) pregnant or lactating woman; (4) addicted to drugs, alcohol or other substance; (5) have used neuroleptic or dopamine blocking drugs in the past 6 months; (6) contraindications for MRI such as a cardiac pacemaker or metal implants; (7) diagnosis of visual disorders interfering with VR implementation.

Participants who meet the inclusion criteria and have no exclusion criteria will be assigned to the study. After getting signed written informed consents, the participants are enrolled.

### Patient and public involvement

No patient or public involvement.

### Randomisation and blinding

The randomisation will be conducted by an investigator who is not involved in the recruitment, assessment, intervention or data analysis. All the enrolled participants will be randomised into two groups equally through a computer-generated random number table. Details of randomisation will be sent in an opaque sealed envelope to the researchers in sequential order. Assessments for all participants will be done by a well-trained physiotherapist blinded to the randomisation procedure and group allocation.

### Screening assessment

Once written informed consent has been obtained, a screening assessment will be conducted by the independent evaluator. The following data will be collected: demography; stroke details; comorbidity; cognitive function (MMSE). The demographic information and stroke details of the participants are shown in [box 1](#). The evaluator will proceed to the baseline assessment if the participant meets the study inclusion and exclusion criteria.

### Baseline assessment

The following data will be collected: motor impairment of lower extremities (FMA-LE), functional balance (Berg Balance Scale (BBS)), spasticity (Modified Ashworth Scale (MAS)), fMRI scans and current lower extremity rehabilitation treatments.

#### Box 1 The demographic information and stroke details

- ⇒ Age (years).
- ⇒ Gender (male/female).
- ⇒ Height (metres).
- ⇒ Weight (kg).
- ⇒ Education.
- ⇒ Time since stroke (months).
- ⇒ Hemiparetic side (right/left).
- ⇒ Type of stroke.
- ⇒ Site of stroke.
- ⇒ Use of orthoses/walking aids (yes/no).
- ⇒ Medications.

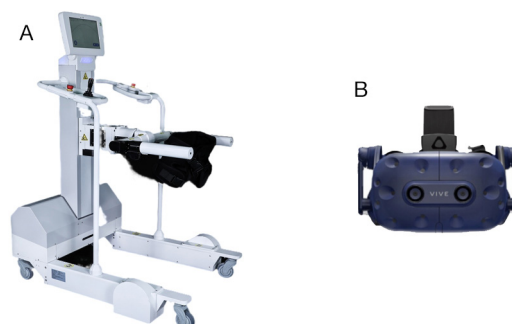
### Interventions

Each participant will receive multidisciplinary medication and conventional rehabilitation (5 days/week for 4 weeks). Their routine rehabilitation programmes mainly include physical therapy (PT) (30 min per day) and occupational therapy (OT) (30 min per day) and will be carried out by the same experienced therapist. The patient-specific treatment content will be set according to their functional levels and the particular needs. The goal of PT is increasing muscle strength, reducing spasticity, improving range of motion and improving motor control. The goal of OT is improving transfer capacity and the ability of activities of daily living.

In addition to the conventional rehabilitation, participants receive combined robot assistance and routine VR (the control group) or NeuCir-VR (the intervention group) training for 30 min per day, 5 days per week for 4 weeks. The robot-assisted training will be performed with a robot-assisted rehabilitation system called iReGo (Shanghai Jinshi Robot Technology, China), a lower extremity training robot with pelvic support programmed to move an individual's lower extremities along a predetermined trajectory on a ground walking track ([figure 3A](#)). The applications of VR will run through the Steam software application on the laptop computer connected to an HTC VIVE headset (three base stations had been set up in the room) (Pro Eye Series) ([figure 3B](#)). In the intervention group, a combination of robot assistance and NeuCir-VR training programme is conducted for 30 min simultaneously. The control group, a 20-min robot-assisted training and a 10-min VR training programme are provided separately. The therapist can customise the difficulty and intensity (duration) of each task according to the limb function of the patients. A detailed description of the training programme using the Template for Intervention Description and Replication checklist is provided in online supplemental materials 1.

#### Control group (combined robot assistance and routine VR training)

Robot-assisted training is divided into three kinds of tasks ([figure 4A–C](#)). The difficulty of each task can be divided into three modes: easy, general and difficult. The therapist



**Figure 3** (A) The iReGo, a rehabilitation robot-assisted training system; (B) an HTC VIVE headset, a virtual reality system which can provide 360-degree headset tracking, realistic graphics, directional audio and high definition haptic feedback deliver exciting action in the virtual world.

will adjust the most suitable difficulty according to the patient's specific condition. The task difficulty of each patient may or may not change throughout the course of treatment. This will be determined by the patient's condition on the training day, which will help achieve the best treatment effect.

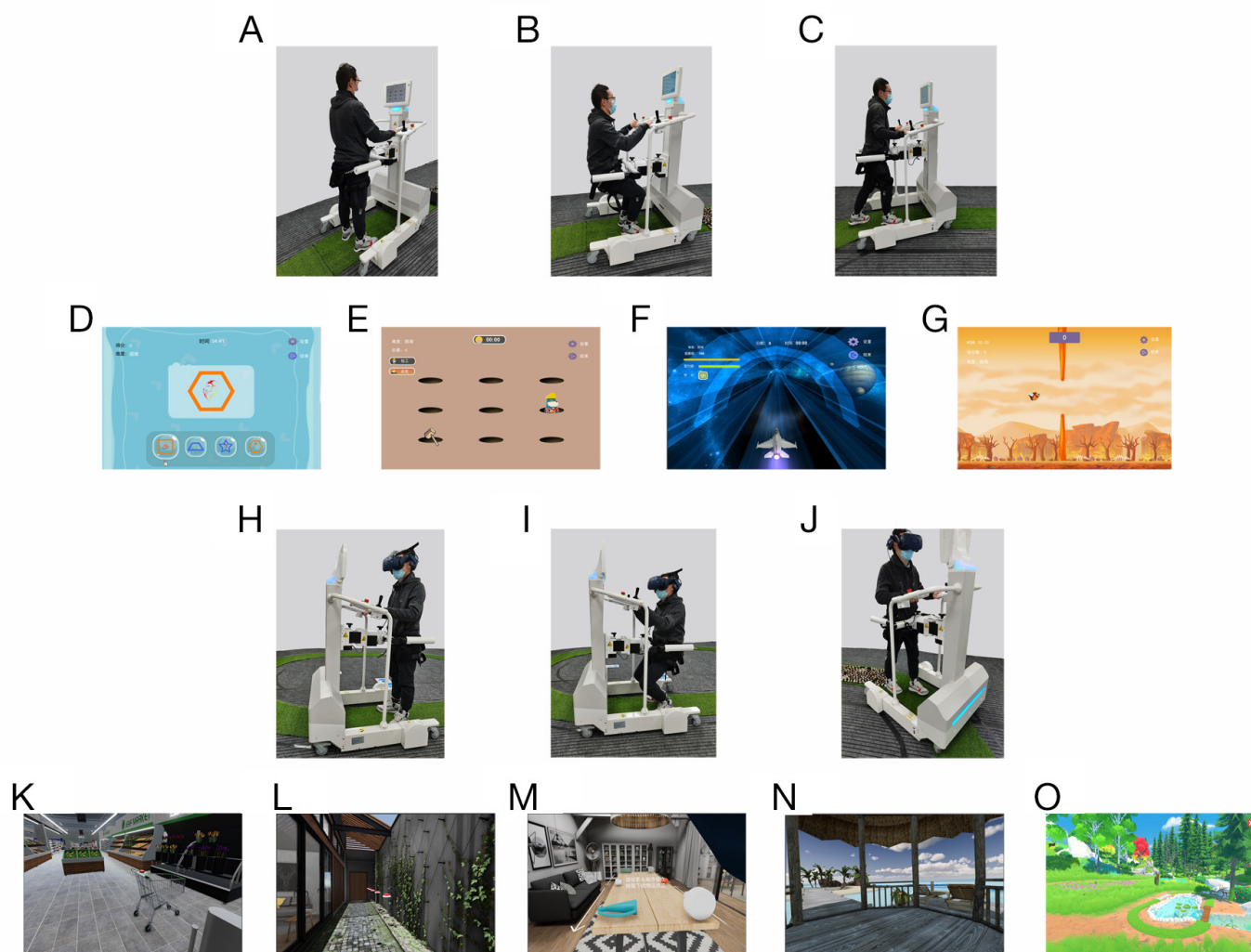
**Task 1: Standing training** lasts for 5 min. In the easy mode, patients stand with their eyes open. In the general mode, patients stand with their eyes closed. In the difficult mode, patients stand on one leg and each leg for 2.5 min.

**Task 2: Sitting training** lasts for 5 min. In the easy mode, iReGo will provide all the assistance to help patients complete sit-to-stand continuously. In the general mode, patients need to actively participate in the training, and iReGo will provide partial assistance to help patients complete sit-to-stand continuously. In the difficult mode, patients need to complete sit-to-stand by themselves

continuously, and iReGo will not provide assistance except for safety protection.

**Task 3: Walking training** lasts for 10 min. Patients are trained to walk in the treatment area after wearing iReGo belts. In the easy mode, the patients can only control the speed and direction of walking through a remote sensor and iReGo will provide all the assistance to ensure the safety. In the general mode, patients can control the walking speed and direction by themselves. The iReGo will provide partial assistance. In the difficult mode, patients can only control the walking speed and direction by themselves and iReGo will not provide assistance except for safety protection. If it is not safe for the patients to operate the remote sensor by themselves, the physiotherapist will operate it.

After 20 min of robot-assisted training, 10 min of VR training immediately followed. VR training is based on game training, which lasts for 10 min. There are four



**Figure 4** The diagram of the control group and intervention group. (A) Standing training of control group; (B) sitting training of control group; (C) walking training of control group; (D) game training of Matching Pattern; (E) game training of Whac-A-Mole; (F) game training of Obstacle Avoidance 1 (horizontal direction); (G) game training of Obstacle Avoidance 2 (vertical direction); (H) standing training of intervention group; (I) sitting training of intervention group; (J) walking training of intervention group; (K) VR training scenarios of supermarket; (L) VR training scenarios of gallery; (M) VR training scenarios of living room; (N) VR training scenarios of seaside; (O) VR training scenarios of forest. VR, virtual reality.

games: Matching Pattern, Whac-A-Mole, Obstacle Avoidance 1 (horizontal direction) and Obstacle Avoidance 2 (vertical direction) (figure 4D–G). The difficulty of each task can be divided into three modes: easy, general and difficult. Be sure to wear the iReGo safety belt and VR headset before training.

In the Matching Pattern game, patients need to find a pattern that matches the standard pattern and twist their waist and lower extremities to match the two patterns perfectly. As the difficulty mode increases, the pattern becomes more complex and more patterns need to be judged. In the Whac-A-Mole game, the patients need to quickly shoot a gopher out of a hole (there are nine holes, and the gophers come out randomly) by twisting his waist and lower extremities. As the difficulty mode increases, the gophers come out faster and faster. In Obstacle Avoidance 1 (horizontal direction) game and Obstacle Avoidance 2 (vertical direction) game, patients need to quickly move their waist and lower extremities to avoid horizontal or vertical obstacles. As the difficulty mode increases, obstacles appear faster and faster.

#### Intervention group (combined robot assistance and NeuCir-VR training)

The training is divided into four kinds of tasks (figure 4H–J). The difficulty of each task can be divided into three modes: easy, general and difficult. The therapist will adjust the most suitable difficulty according to the patient's specific condition. The task difficulty of each patient may or may not change throughout the course of treatment. This is determined by the patient's condition on the training day, which will help achieve the best treatment effect.

The basic procedures and contents of the four training tasks (standing training, sitting training, walking training and game training) are the same as those of the control group. The advantage is that there are five VR training scenarios (a supermarket, a gallery, a living room, a seaside and a forest, figure 4K–O) to choose from VR system. The VR scenarios match the real environment, such as grass, gravel paths, wood and marble floors, giving patients real stimulation during training. Patients can choose the scenario they are interested in before training.

All task instructions will be told to patients by the VR voice assistant through the headset. If patients follow the instructions to complete each task, the VR system will give them auditory feedback to induce active participation in the training. Furthermore, VR system can also provide visual feedback by displaying score or flower rewards in the virtual world on the upper left of the field of view. When the patient completes a task, the reward level is based on the speed, accuracy and completion of the task.

#### Outcome measures

The primary outcome will be the change of FMA-LE between baseline (T0) and after 4-week intervention (T1). Secondary outcomes will include BBS, MAS and fMRI, and safety outcomes. All outcomes will be measured

at the following time points: (1) baseline (before the intervention, T0), (2) post-intervention (after 4 weeks intervention, T1), (3) three follow-ups (4 weeks after the completing intervention, T2; 8 weeks after the completing intervention, T3; 20 weeks after the completing intervention, T4).

#### Primary outcome

The FMA-LE is considered the gold standard for evaluating the extent of motor impairment of lower extremities in stroke survivors.<sup>38 39</sup> It includes 17 items in reflex activity, synergic patterns and coordination. Each item is rated on a 3-point scale from 0 to 2 (0=no performance; 1=partial performance; 2=complete performance) and the maximum score is 34.<sup>40</sup> According to the FMA-LE scores, motor impairment is classified as mild (equal or more than 29), moderate (between 20 and 28) or severe (less than 19).<sup>41</sup>

#### Secondary outcomes

The BBS is a common scale to assess functional balance in clinical settings.<sup>42</sup> The BBS assesses static balance in sitting and standing positions, as well as dynamic balance in transferring positions.<sup>43</sup> It consists of 14 items, and each item is rated on a 5-point scale from 0 to 4. The total score ranges from 0 to 56.<sup>44</sup> The test will be repeated three times, and the final score obtained after three times is averaged.

The MAS is a measurement of spasticity.<sup>40</sup> It is rated on 6-grade scale from 0 to 4 and +1 according to the resistance to a fast, passive movement (0=no increase in muscle tone and 4=stiffness).<sup>45</sup> In this study, MAS is used for assessing the spasticity of the hip/knee extensors, hip/knee flexors, ankle dorsiflexors and ankle plantar flexors.

The fMRI scans of the brain are acquired on a 3-Tesla scanner (Siemens Verio, Erlangen, Germany) in the Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Chinese Traditional Medicine. In the study, the resting-state fMRI and T1-weighted image scans are collected. Participants will be asked to lay supine in the scanner with their eyes closed but remain awake, and their heads are immobilised with foam pads to minimise head motion. The resting-state fMRI are acquired using a single-pass gradient recalled echoplanar imaging sequence with the following parameters: repetition time (TR)=2000 ms, flip angle (FA)=90°, field of view (FOV)=230 mm×230 mm, matrix=64×64, slice thickness=3 mm (no gap) and number of slices=43. The three-dimensional T1-weighted images are acquired using a brain volume sequence with the following parameters: TR=1900 ms, echo time=2.93 ms, FA=9°, FOV=256 mm×256 mm, matrix=256×256, slice thickness=1 mm (no gap).

#### Safety outcomes

We also assessed the acceptability and safety of the therapy. Adverse events such as headaches, dizziness, nausea, vomit, fatigue or epileptic seizures will be considered

safety outcomes. Before and after each treatment, patients will be asked about their physical condition and whether they feel uncomfortable. For each patient, adverse events will be assessed by the Simulator Sickness Questionnaire before and after each treatment session, which is a gold standard for assessing physical condition after exposure to VR environments.<sup>46</sup>

### Sample size

The primary outcome in this study is the change of FMA-LE between baseline (T0) and after 4-week intervention (T1). We referred to the previous similar study as the basis for estimating the sample size, the changes of FMA-LE scores before and after treatment in two groups were  $3.0 \pm 1.8$  and  $3.8 \pm 2.50$ .<sup>47</sup> The standardised effect sizes were calculated using Cohen's *d* ( $d=0.37$ ). The power of the test considered was 90%, and the alpha was 0.05 (two-tailed). Considering a 20% drop-out rate, a total of 40 participants should be recruited (20 per group).<sup>48</sup>

### Statistical analysis

Data statistical analysis will be handled by statistical analysts who are blind to the study. The intention-to-treat (ITT) principle will be used in all analyses. The target of  $N=20$  per group refers to completers, and that the ITT will be carried out to any drop-outs. Multiple imputation methods will be used for missing data.<sup>49</sup>

### Clinical data analysis

Clinical data will be analysed using SPSS software V.24.0 (SPSS, Chicago, Illinois, USA). Continuous data will be presented as means and SD. Categorical data will be presented as counts and percentage changes. The  $\chi^2$  test will be used to analyse demographic data such as gender, education, hemiparetic side and so on. Clinical assessment results and demographic data such as age, height and weight will use the Shapiro-Wilk test to test the normality first. Non-normal continuous variables will be evaluated with the Mann-Whitney U test. Normally distributed variables will be evaluated with the independent sample t-test and analysis of covariances (ANCOVAs). The ANCOVAs will be used with age and the FMA-LE score at baseline as covariates. A  $p$  value  $< 0.05$  will be considered statistically significant, and all reported  $p$  values will be two-sided.

### Resting-state fMRI data analysis

Resting-state fMRI data will be processed and analysed using SPM V.12 (<https://www.fil.ion.ucl.ac.uk/spm/software/spm12/>) on MATLAB R2013b (MathWorks, Natick, Massachusetts, USA). Functional connectivity (FC), a measurement of the relationship between BOLD activity of brain regions, will be analysed considering the primary motor cortex and the supplementary motor area as the regions of interest. The FC maps were compared between two groups by two-sample t-tests (two-tailed). A  $p$  value  $< 0.05$  with AlphaSim correction is considered statistically significant.

## DISCUSSION

More than 50% of the patients still suffer from motor dysfunction after receiving conventional rehabilitation treatments, like PT and OT.<sup>6-8</sup> Therefore, more and more new rehabilitation technologies have been developed.<sup>9 15 50</sup> In recent years, robot-assisted and VR rehabilitation training have been employed in brain rehabilitation from stroke, especially for motor recovery.<sup>51</sup> In contrast, the effects of robot assistance and VR training are still largely debated. Previous studies found that robot assistance and VR rehabilitation training can improve balance and gait ability.<sup>50 52 53</sup> However, some studies have found that the effects are not significantly more beneficial than conventional rehabilitation treatments, especially for less impaired patients.<sup>54 55</sup> To date, the neural mechanisms underlying robot assistance and VR rehabilitation training are still unknown.

In a study conducted by Kayabinar *et al*<sup>56</sup> VR combined with robot-assisted training was used to perform motor and cognitive multitasks together in patients with lower extremity hemiparesis after stroke. However, the results showed that the combined training was not superior to robot-assisted only training in the efficacy of function rehabilitation of lower extremity. Moreover, these multitasks require high cognitive participation, which is a great challenge for many patients who had stroke. In addition, multitasks training may also affect motor performance, which may be one of the reasons why the combined training was not superior to robot-assisted only training.

Motor rehabilitation after stroke focuses on the principles of motor relearning and neural plasticity. Motor learning theory is fundamental to rehabilitation and supported by the reorganisation of motor circuits.<sup>57</sup> The principles of motor relearning were developed based on motor learning theory by Carr and Shepherd in 1987.<sup>56</sup> They proposed that the recovery of motor function after central nervous system injury is regarded as a process of motor relearning.<sup>58 59</sup> In addition, multisensory training, task-specific training and goal-oriented training are all based on the principle of motor relearning.<sup>60</sup> However, the key to stroke rehabilitation is the remodelling of neural circuits. It has been found that motor learning may play an essential role in activating neuroplasticity during the chronic stage after brain injury.<sup>61</sup> In animal models of rats, motor learning is associated with the functional reorganisation of the rat motor cortex.<sup>62</sup> A diffusion tensor imaging study showed that motor learning improves the ability of our brains to control behaviour by improving attention, sensorimotor, default mode and visual networks.<sup>63</sup> Rehabilitation based on motor learning may be associated with the reorganisation of cortical networks, which changes the cortical activation patterns of sensorimotor areas of the contralateral hemisphere and cerebellar. These changes contribute to the improvement of patients' motor function.<sup>64</sup>

A review of the literature revealed that only a few clinically controlled trial studies on the application of motor relearning and neural plasticity principles have been



conducted. Previous research on robot assistance and VR rehabilitation training did not follow these principles, which could lead to uncertain efficacy. However, robot assistance and VR training can perform highly repetitive, intensive and task-specific training with feedback through motor relearning and neural plasticity principles. We hypothesise that a robot-assisted rehabilitation programme designed based on motor relearning and neural plasticity principles, combined with VR multisensory stimulus feedback, can promote the remodelling of neural motor circuits and improve the efficacy of motor function rehabilitation.

This study also has some limitations. First, the samples are relatively small. Second, our sample size estimation was based on previous reports, which may overestimate effect sizes.<sup>65</sup> Third, our study is done based on a random number generator and not in a balanced way based on possible predictors, which may bias results. In addition, this study is a single-centre randomised controlled trial, which may lead to possible analytical bias.

In summary, we design a rehabilitation programme combining robot motor assistance with NeuCir-VR training based on motor learning and neural plasticity principles and observe the effect of NeuCir-VR rehabilitation training combined with robot motor assistance on the lower extremity motor function in patients after stroke. We hope to provide clear evidence of whether immersive multisensory stimuli and multiple rewards can improve motor function of the lower extremity and even promote brain function remodelling.

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**Contributors** J-GX and C-LS are co-corresponding authors of this paper. J-GX, C-LS, X-YH and J-JW designed the study. Z-QZ drafted and finalised the manuscript. X-YH and J-JW helped to revise the manuscript critically for important intellectual content. J-JX and MR collected and sorted out the related materials. All authors have reviewed the manuscript and contributed to its writing.

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#### REFERENCES

- Gan Y, Jiang H, Room R, *et al*. Prevalence and risk factors associated with stroke in China: a nationwide survey of 726,451 adults. *Eur J Prev Cardiol* 2021;28:e6–10.
- Naghavi M, Abajobir AA, Abbafati C, *et al*. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the global burden of disease study 2016. *Lancet* 2017;390:1151–210.
- Wu S, Wu B, Liu M, *et al*. Stroke in China: advances and challenges in epidemiology, prevention, and management. *Lancet Neurol* 2019;18:394–405.
- Virani SS, Alonso A, Benjamin EJ, *et al*. Heart disease and stroke Statistics—2020 update: a report from the American heart association. *Circulation* 2020;141.
- Robinson N, Ye T, Ronan P, *et al*. Acupuncture for stroke: perceptions and possibilities. *Acupunct Med* 2020;38:158–68.
- Jørgensen HS, Nakayama H, Raaschou HO, *et al*. Recovery of walking function in stroke patients: the Copenhagen stroke study. *Arch Phys Med Rehabil* 1995;76:27.
- Perry J, Garrett M, Gronley JK, *et al*. Classification of walking handicap in the stroke population. *Stroke* 1995;26:982–9.
- Mayo NE, Wood-Dauphinee S, Côté R, *et al*. Activity, participation, and quality of life 6 months poststroke. *Arch Phys Med Rehabil* 2002;83:1035–42.
- Huo C-C, Zheng Y, Lu W-W, *et al*. Prospects for intelligent rehabilitation techniques to treat motor dysfunction. *Neural Regen Res* 2021;16:264.
- Kang M-G, Yun SJ, Lee SY, *et al*. Effects of upper-extremity rehabilitation using smart glove in patients with subacute stroke: results of a prematurely terminated multicenter randomized controlled trial. *Front Neurol* 2020;11:580393.
- Duret C, Grosmaire A-G, Krebs HI. Robot-assisted therapy in upper extremity hemiparesis: overview of an evidence-based approach. *Front Neurol* 2019;10:412.
- Mayr A, Quirbach E, Picelli A, *et al*. Early robot-assisted gait retraining in non-ambulatory patients with stroke: a single blind randomized controlled trial. *Eur J Phys Rehabil Med* 2018;54:819–26.
- Tomida K, Sonoda S, Hirano S, *et al*. Randomized controlled trial of gait training using gait exercise assist robot (GEAR) in stroke patients with hemiplegia. *J Stroke Cerebrovasc Dis* 2019;28:2421–8.
- Kim HY, Shin J-H, Yang SP, *et al*. Robot-assisted gait training for balance and lower extremity function in patients with infratentorial stroke: a single-blinded randomized controlled trial. *J Neuroeng Rehabil* 2019;16:99.
- Mazzoleni S, Tran V-D, Dario P, *et al*. Effects of transcranial direct current stimulation (tDCS) combined with wrist robot-assisted rehabilitation on motor recovery in subacute stroke patients: a randomized controlled trial. *IEEE Trans Neural Syst Rehabil Eng* 2019;27:1458–66.
- Goodman RN, Rietschel JC, Roy A, *et al*. Increased reward in ankle robotics training enhances motor control and cortical efficiency in stroke. *J Rehabil Res Dev* 2014;51:213–28.
- Kim DH, Kang CS, Kyeong S. Robot-assisted gait training promotes brain reorganization after stroke: a randomized controlled pilot study. *NeuroRehabilitation* 2020;46:483–9.

- 18 Taveggia G, Borboni A, Mulé C, *et al.* Conflicting results of robot-assisted versus usual gait training during postacute rehabilitation of stroke patients: a randomized clinical trial. *Int J Rehabil Res* 2016;39:29–35.
- 19 Belas Dos Santos M, Barros de Oliveira C, Dos Santos A, *et al.* A comparative study of conventional physiotherapy versus robot-assisted gait training associated to physiotherapy in individuals with ataxia after stroke. *Behav Neurol* 2018;2018:1–6.
- 20 McPherson JG, Stienen AHA, Drogos JM, *et al.* The relationship between the flexion synergy and stretch reflexes in individuals with chronic hemiparetic stroke. *IEEE Int Conf Rehabil Robot* 2011;2011:5975516.
- 21 Bergmann J, Krewer C, Bauer P, *et al.* Virtual reality to augment robot-assisted gait training in non-ambulatory patients with a subacute stroke: a pilot randomized controlled trial. *Eur J Phys Rehabil Med* 2018;54:397–407.
- 22 Lee Y-yun, Lin K-chung, Cheng H-ju, *et al.* Effects of combining robot-assisted therapy with neuromuscular electrical stimulation on motor impairment, motor and daily function, and quality of life in patients with chronic stroke: a double-blinded randomized controlled trial. *J Neuroeng Rehabil* 2015;12:96.
- 23 Bart O, Agam T, Weiss PL, *et al.* Using video-capture virtual reality for children with acquired brain injury. *Disabil Rehabil* 2011;33:1579–86.
- 24 Yu K-W, Wang C-J, Wu Y, *et al.* An enriched environment increases the expression of fibronectin type III domain-containing protein 5 and brain-derived neurotrophic factor in the cerebral cortex of the ischemic mouse brain. *Neural Regen Res* 2020;15:1671–7.
- 25 Deng Y-H, Dong L-L, Zhang Y-J, *et al.* Enriched environment boosts the post-stroke recovery of neurological function by promoting autophagy. *Neural Regen Res* 2021;16:813.
- 26 Zhang X, Liu J-Y, Liao W-J, *et al.* Differential effects of physical and social enriched environment on angiogenesis in male rats after cerebral ischemia/reperfusion injury. *Front Hum Neurosci* 2021;15:622911.
- 27 Abe M, Schambra H, Wassermann EM, *et al.* Reward improves long-term retention of a motor memory through induction of offline memory gains. *Curr Biol* 2011;21:557–62.
- 28 Widmer M, Ziegler N, Held J, *et al.* Rewarding feedback promotes motor skill consolidation via striatal activity. *Prog Brain Res* 2016;229:303–23.
- 29 Galea JM, Mallia E, Rothwell J, *et al.* The dissociable effects of punishment and reward on motor learning. *Nat Neurosci* 2015;18:597–602.
- 30 Ramakrishnan A, Byun YW, Rand K, *et al.* Cortical neurons multiplex reward-related signals along with sensory and motor information. *Proc Natl Acad Sci U S A* 2017;114:E4841–50.
- 31 Tran DA, Pajaro-Blazquez M, Daneault J-F, *et al.* Combining dopaminergic facilitation with robot-assisted upper limb therapy in stroke survivors: a focused review. *Am J Phys Med Rehabil* 2016;95:459–74.
- 32 Marsh R, Hao X, Xu D, *et al.* A virtual reality-based fMRI study of reward-based spatial learning. *Neuropsychologia* 2010;48:2912–21.
- 33 De Keersmaecker E, Lefeber N, Geys M, *et al.* Virtual reality during gait training: does it improve gait function in persons with central nervous system movement disorders? A systematic review and meta-analysis. *NeuroRehabilitation* 2019;44:43–66.
- 34 Mehrolz J, Thomas S, Kugler J, *et al.* Electromechanical-assisted training for walking after stroke. *Cochrane Database Syst Rev* 2020;10:D6185.
- 35 Holden MK, Gill KM, Magliozzi MR. Gait assessment for neurologically impaired patients. standards for outcome assessment. *Phys Ther* 1986;66:1530–9.
- 36 Aho K, Harmsen P, Hatano S, *et al.* Cerebrovascular disease in the community: results of a WHO collaborative study. *Bull World Health Organ* 1980;58:113–30.
- 37 Pangman VC, Sloan J, Guse L. An examination of psychometric properties of the mini-mental state examination and the standardized Mini-Mental state examination: implications for clinical practice. *Appl Nurs Res* 2000;13:209–13.
- 38 Barak S, Duncan PW. Issues in selecting outcome measures to assess functional recovery after stroke. *NeuroRx* 2006;3:505–24.
- 39 Kwong PWH, Ng SSM. Cutoff score of the lower-extremity motor Subscale of Fugl-Meyer assessment in chronic stroke survivors: a cross-sectional study. *Arch Phys Med Rehabil* 2019;100:1782–7.
- 40 Rastgoo M, Naghdi S, Nakhostin Ansari N, *et al.* Effects of repetitive transcranial magnetic stimulation on lower extremity spasticity and motor function in stroke patients. *Disabil Rehabil* 2016;38:1918–26.
- 41 Rech KD, Salazar AP, Marchese RR, *et al.* Fugl-Meyer assessment scores are related with kinematic measures in people with chronic hemiparesis after stroke. *J Stroke Cerebrovasc Dis* 2020;29:104463.
- 42 Pickenbrock HM, Diel A, Zapf A. A comparison between the static balance test and the Berg balance scale: validity, reliability, and comparative resource use. *Clin Rehabil* 2016;30:288–93.
- 43 Louie DR, Eng JJ. Berg balance scale score at admission can predict walking suitable for community ambulation at discharge from inpatient stroke rehabilitation. *J Rehabil Med* 2018;50:37–44.
- 44 Saso A, Moe-Nilssen R, Gunnes M, *et al.* Responsiveness of the Berg balance scale in patients early after stroke. *Physiother Theory Pract* 2016;32:251–61.
- 45 Deveci H. Evaluation of the effectiveness of treatment with botulinum toxin on sleep quality in stroke-related spasticity. *J Stroke Cerebrovasc Dis* 2020;29:105160.
- 46 Chan CLF, Ngai EKY, Leung PKH, *et al.* Effect of the adapted virtual reality cognitive training program among Chinese older adults with chronic schizophrenia: a pilot study. *Int J Geriatr Psychiatry* 2010;25:643–9.
- 47 Mustafaoglu R, Erhan B, Yeldan I, *et al.* Does robot-assisted gait training improve mobility, activities of daily living and quality of life in stroke? A single-blinded, randomized controlled trial. *Acta Neurol Belg* 2020;120:335–44.
- 48 Weir JP, Vincent WJ. *Statistics in kinesiology*. 4th ed. Human Kinetics, 2012.
- 49 Brown CH, Wang W, Kellam SG, *et al.* Methods for testing theory and evaluating impact in randomized field trials: intent-to-treat analyses for integrating the perspectives of person, place, and time. *Drug Alcohol Depend* 2008;95 Suppl 1:S74–104.
- 50 Corbetta D, Imeri F, Gatti R. Rehabilitation that incorporates virtual reality is more effective than standard rehabilitation for improving walking speed, balance and mobility after stroke: a systematic review. *J Physiother* 2015;61:117–24.
- 51 Schache AG, Baker R, Vaughan CL. Differences in lower limb transverse plane joint moments during gait when expressed in two alternative reference frames. *J Biomech* 2007;40:9–19.
- 52 Luque-Moreno C, Ferragut-Garcías A, Rodríguez-Blanco C, *et al.* A decade of progress using virtual reality for poststroke lower extremity rehabilitation: systematic review of the intervention methods. *Biomed Res Int* 2015;2015:342529.
- 53 Darekar A, McFadyen BJ, Lamontagne A, *et al.* Efficacy of virtual reality-based intervention on balance and mobility disorders post-stroke: a scoping review. *J Neuroeng Rehabil* 2015;12:46.
- 54 Saposnik G, Cohen LG, Mamdani M, *et al.* Efficacy and safety of non-immersive virtual reality exercising in stroke rehabilitation (EVREST): a randomised, multicentre, single-blind, controlled trial. *Lancet Neurol* 2016;15:1019–27.
- 55 Schuster-Amft C, Eng K, Suica Z, *et al.* Effect of a four-week virtual reality-based training versus conventional therapy on upper limb motor function after stroke: a multicenter parallel group randomized trial. *PLoS One* 2018;13:e204455.
- 56 Kayabinar B, Alemdaroglu-Gurbuz İpek, Yilmaz Öznur. The effects of virtual reality augmented robot-assisted gait training on Dual-task performance and functional measures in chronic stroke: a randomized controlled single-blind trial. *Eur J Phys Rehabil Med* 2021;57:227–37.
- 57 Hwang EJ, Dahlen JE, Hu YY, *et al.* Disengagement of motor cortex from movement control during long-term learning. *Sci Adv* 2019;5:y1.
- 58 Shepherd RB, Carr JH. *A motor relearning programme for stroke*. 2nd ed. Oxford: Heinemann Medical Books, 1987.
- 59 Basteris A, Nijenhuis SM, Stienen AHA, *et al.* Training modalities in robot-mediated upper limb rehabilitation in stroke: a framework for classification based on a systematic review. *J Neuroeng Rehabil* 2014;11:111.
- 60 Maier M, Ballester BR, Verschure PFMJ. Principles of neurorehabilitation after stroke based on motor learning and brain plasticity mechanisms. *Front Syst Neurosci* 2019;13:74.
- 61 Kleim JA, Jones TA, Schallert T. Motor enrichment and the induction of plasticity before or after brain injury. *Neurochem Res* 2003;28:1757–69.
- 62 Kleim JA, Barbay S, Nudo RJ. Functional reorganization of the rat motor cortex following motor skill learning. *J Neurophysiol* 1998;80:3321–5.
- 63 Pi Y-L, Wu X-H, Wang F-J, *et al.* Motor skill learning induces brain network plasticity: a diffusion-tensor imaging study. *PLoS One* 2019;14:e210015.
- 64 Luft AR, McCombe-Waller S, Whittal J, *et al.* Repetitive bilateral arm training and motor cortex activation in chronic stroke: a randomized controlled trial. *JAMA* 2004;292:1853–61.
- 65 Algermissen J, Mehler DMA. May the power be with you: are there highly powered studies in neuroscience, and how can we get more of them? *J Neurophysiol* 2018;119:2114–7.