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RESEARCH

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Rehabilitation training robot using mirror therapy for the upper and lower limb after stroke: a prospective cohort study

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Abstract

Background This prospective cohort study was designed to investigate and compare the effectiveness of rehabilitation training robots versus conventional rehabilitation training on stroke survivors by monitoring alterations in brain network of stroke patients before and after robot intervention.

Methods Between September 2020 and November 2021, stroke patients at four grade-A tertiary hospitals underwent limb rehabilitation training. Of the total of participants, 117 patients received conventional limb rehabilitation, 93 patients participated in upper-limb robot training, and 103 patients underwent lower-limb robot training. The measured outcomes included modified Barthel Index (MBI), Fugl-Meyer assessment subscale (FMA), and manual muscle testing (MMT). Functional magnetic resonance imaging (fMRI) was conducted on 30 patients to assess changes in the brain network. Data were mainly analyzed based on the Intention-to-Treat (ITT) principle.

Results Post-interventional analysis utilizing linear mixed models in ITT analysis revealed that the robot training group had greater enhancements compared to the conventional limb rehabilitation training group. Notably, the shoulder flexor strength ($P=0.043$) was significantly higher in the upper-limb group. On the other hand, hip flexor strength ($P<0.001$), hip extensor strength ($P<0.001$), knee extensor strength ($P=0.013$), ankle dorsiflexion strength ($P<0.001$) and ankle plantarflexor strength ($P<0.001$) were significantly higher in the lower-limb group. In the upper-limb group, region-of-interest (ROI) -to-ROI analysis revealed enhanced functional connectivity between the left hemisphere's motor control region and the auditory network. ROI-to-ROI analysis primarily showed enhanced interhemispheric functional connectivity in the lower-limb group, specifically between right the hemisphere's motor control region (central opercular cortex) and left hemisphere's primary motor area in the precentral gyrus.

Conclusions According to our research findings, upper- and lower-limb rehabilitation robots demonstrated great potential in promoting motor function recovery in stroke patients. Robot-assisted training offers an alternative treatment method with comparable efficacy to traditional rehabilitation. Large-scale randomized controlled trials are needed to confirm these results.

*Trial registration***:** The study was registered on the Chinese Clinical Trial Registry (ChiCTR1800019783).

Keywords Stroke, Rehabilitation robot, Cohort study, Motor recovery

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Introduction

Stroke is the second most common cause of mortality worldwide. Recently, there has been a worrisome increase in the global incidence rate of stroke among young and middle-aged people (those under 55 years) [1]. Approximately 90% of stroke survivors have some kind of functional impairment, which imposes substantial social and economic burdens on the patients and their families [2]. Movement disorders are the most common challenge, characterized by the loss or limitation of muscle control, which often leads to limited functional capacity and reduced participation in daily activities [2–5].

Impairment of upper limb function, paralysis, poor spatiotemporal coordination and spasticity are highly prevalent among stroke survivors [6, 7] and can result in impaired reaching, grasping, and manipulation [8]. About one-third of ischemic stroke survivors experience reduced mobility and inability to walk, characterized by impaired gait and balance, which affects the patient's daily self-care, quality of life, occupational and social integration, and increasing the risk of falls [9–14].

Mirror therapy (MT) is a type of rehabilitation therapy in which a mirror is placed between the subject's arms or legs so that the patient can look at the mirror image of the healthy limb to create an illusion that the affected limb is also moving normally. This operation has the ability to stimulate different areas of the brain to produce movement, sensation and pain consciousness, resulting in promotion of motor function reconstruction and brain function remodeling of hemiplegic limbs [15, 16]. Rehabilitation training robots apply the same concept as mirror therapy.

Robotic mirror therapy (RMT) techniques are a new type of mirror therapy, that integrate robot technology [17]. RMT works by replicating the gait trajectory of the healthy side. It perceives the patient's active motion intention in real time by using the angle, angular velocity, angular acceleration, and phase information of the sampling point, and adjusting the reference trajectory in real time according to the state of the affected side to drive its movement and achieve rehabilitation [18].

Furthermore, robot training may enhance brain function by altering cortical excitability, which supports neuroplasticity and creates an environment conducive to neuronal reorganization in response to treatment [19, 20]. The effectiveness of robotic neurorehabilitation is assessed using established, standardized clinical scales, including the Functional Ambulation Scale (FAC), the Fugl-Meyer Assessment (FMA), the 10 m and 6-min walking tests [21], etc. Clinical measures are less sensitive when assessing neurobiological effects of sophisticated forms of neurotherapy. The most comprehensive and objective method for evaluating the impact and effectiveness of robotic neurorehabilitation is to use functional magnetic resonance imaging (fMRI) [22]. Initially, fMRI was employed to evaluate the occurrence and progression of motor dysfunction [23]. The blood oxygenation level-dependent (BOLD) signal provides an indirect assessment of human brain activity with a very high spatial resolution, relying on variations in deoxyhemoglobin (deoxyHb) levels [24]. Lately, the emphasis has shifted to examining the properties of the functional organization of brain networks, offering a promising way to comprehend a wide-ranging alteration brought on by strokes [23, 25], particularly the time correlation measurement between various areas of the brain blood oxygen level-dependent (BOLD) signals during a resting state of functional connection [26, 27].

Following a stroke, robot-assisted training has demonstrated the potential for enhancing activities of daily living (ADL), including motor function and muscle strength [28–35]. Studies report variability in outcomes based on patient characteristics, device utilized, length and volume of training, control group, and the outcomes measured. However, it is uncertain whether robot-assisted limb training is more beneficial than traditional therapy for the same frequency and length of time [36–39].

Given the significance of limb function for everyday activities, a prospective cohort study was conducted on stroke patients who had undergone motor dysfunction. The study investigated the clinical effects of rehabilitation training robots and whether robot training was more effective than conventional rehabilitation training. Additionally, it also investigated the changes in brain networks of stroke patients before and after robot intervention.

Methods

Study design

This was a prospective cohort study designed to evaluate the therapeutic efficacy of conventional rehabilitation training versus robotic-assisted training in stroke patients. After the pretrial, the stroke patients were initially reluctant to enter the control group and preferred to try the robot rehabilitation training. The physicians recommended the patient enrollment based on their condition, which was in line with their clinical needs. Clinical registration was originally a randomized controlled study, changed to a cohort study. All patients included gave their informed consent. The study was registered on the Chinese Clinical Trial Registry with the unique identification number ChiCTR1800019783, and it was approved by the ethics council of Nanjing Medical University's first affiliated hospital (No. 2019-SR-310).

Setting

According to their motor function and selection, patients were divided into three groups: the upper-limb robot group (Upper limb group), the lower-limb robot group (Lower limb group) and conventional training group (Control group). Enrolled participants were managed through an online system (http://47.102.217.116:8888/apoplexy/) with each center having its own account and password to log in. Patients in the upper-limb group received robot-assisted motor function training using a desktop-type upper limb rehabilitation robot developed by Southeast University (Fig. 1). Those in the lower limb robot group received robot-assisted motor function training using lower limb walking exoskeleton assistant training device Xwalk, (Fig. 2). Patients in the control group received conventional or traditional rehabilitation instruction from therapists. Both groups received two sessions every day, five days a week, for four consecutive weeks. Each session lasted for 20 min.

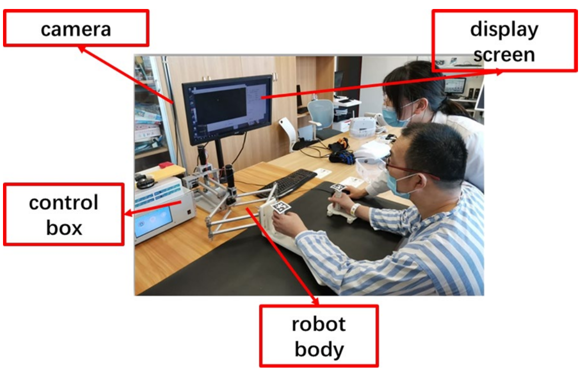

Fig. 1 Desktop type upper limb rehabilitation robot

The desktop-type upper limb rehabilitation robot included a display screen, camera, control box, robot body, and a computer host (Fig. 1), and involved four training modes: passive training, mirror training, active training, and damping training. Each training mode was equipped with various rehabilitation games. The upper limb robot system is a mirror rehabilitation robotic arm system based on a desktop force feedback device. During the rehabilitation game training, the force feedback device collects the patient's limb movement trajectory, force information, etc., which can flexibly adjust the rehabilitation training plans. The system has the characteristics of high positional accuracy, large feedback force, and large motion space. It guides rehabilitation patients to complete designated training tasks in stages according to their physical condition. By playing games, patients can improve their training enjoyment, attention, and initiative. Assist patients in promoting the formation of separation movements, stimulating residual muscle strength, enhancing muscle endurance, restoring joint coordination, and restoring joint flexibility. Specifically, when the patient is in a flaccid phase, the machine perceives the flaccid state of the affected limb and uses a passive or assisted mirror training mode where the healthy side drives the affected side. When the patient is in a spastic phase and the affected limb is in a spastic state, the

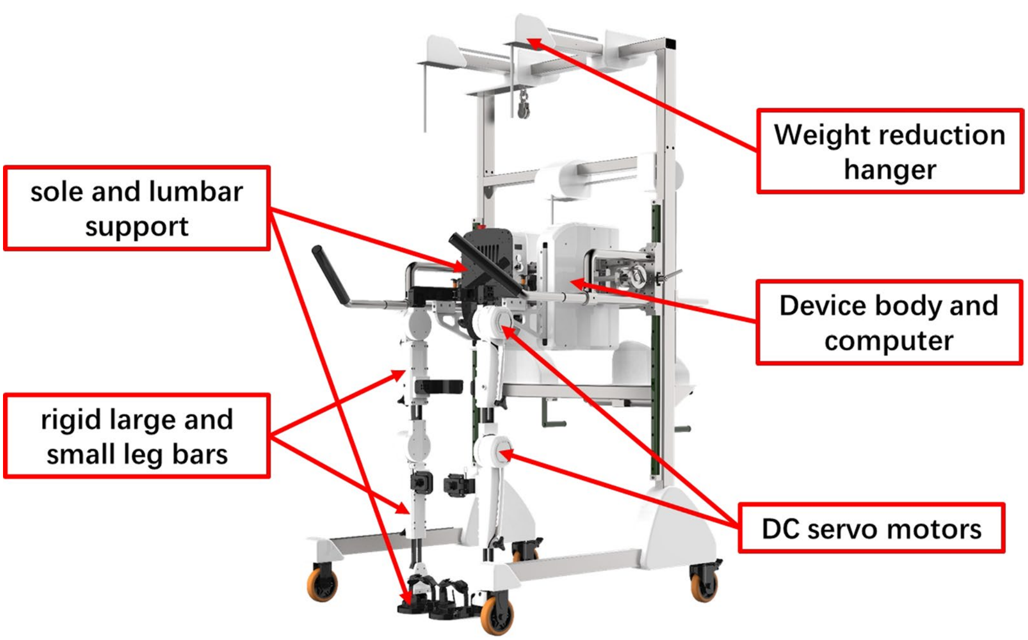

Fig. 2 Lower limb walking exoskeleton assistant training device Xwalk

machine perceives that the muscle tension on the affected side is significantly higher than normal. The machine will activate the spasticity protection mechanism, follow the limb movements, and no further training will be performed. Then, slowly stretch the spastic limb to reduce muscle tension, and when the muscle tension decreases, perform task-oriented active training on the affected limb. When the muscle tension of the affected limb decreases and enters the separation movement phase, the machine perceives that the muscle tension of the affected limb has decreased to a level close to normal, and performs task-oriented active resistance training on the affected limb. Highly repetitive and engaging upper limb exercises can enhance motor sensory input and stimulate the brain to generate motor plans, effectively improve the patient's upper limb motor function and thus motivating the patient. The robot's weight reduction system can be used to reduce the upper-limb physical and active muscle exercise demands to achieve optimal training [40].

The robot-assisted training used mirror therapy integrated training with the lower limb walking assistant training device Xwalk (Fig. 2) with rigid large and small leg bars, and sole and lumbar support to assist the patient in standing. The controller operated four DC servo motors at the hip and knee joints to assist patients with walking training. The device simulated a normal gait, providing symmetrical, high-intensity, repetitive rehabilitation to stimulate sensory input and promote the reconstruction of neural control mechanisms in patients with upper motor neuron injuries. During Xwalk training, the patients were instructed to make attempts to match the movement of the robot while receiving biofeedback on their hip and knee joint from a computer monitor in the back. The patients used the biofeedback to monitor their performance during robotic-assisted stepping, adjusting the timing and intensity of leg movements to reduce errors. The lower limb robot system can provide patients with auxiliary support and reduce the level of lower limb weight bearing. Real time motion data of both limbs of the patient can be provided, such as torque current values and real-time motion trajectories of each joint. Multiple parts can be adjusted, including waist width and leg length, to achieve precise adaptation. It has basic training modes, such as passive, assisted, and resistance. The passive training mode simulates natural gait and sets parameters such as walking cycle, step length, and step height to provide patients with correct sensory input. The assistance and resistance training modes can enhance patients' active walking ability. Provide multiple training gaits, while real-time natural gait planning can be performed based on the patient's height, weight, and training situation to correct abnormal gaits and help patients to regain walking function.

Upper and lower limb robot training focused on restoring motor function through precise, repetitive, task-specific exercises. It incorporated routine motor rehabilitation including balance and posture training, locomotion exercises, lower extremity function training, and ADL practice. The intervention was customized to each patient's functional abilities. For patients with severe impairments, early sessions concentrated on static and dynamic postural tasks, trunk alignment, increasing lower extremity range of motion enhancement, and overground walking. As patients improved or began the program with higher function, they progressed to more advanced balance and gait exercises. Training data was recorded everyday on the Case Report Form.

Patients in the control group received conventional or traditional rehabilitation instruction from therapists. Each group received two sessions every day, five days a week, for four consecutive weeks. Each session lasted for 20 min. The specific content of upper limb training for patients includes passive movements, massage, and traction for the shoulder, elbow, and wrist joints of the upper limbs. Active movement of upper limb shoulder, elbow, and wrist joints is included to enhance arm strength. Task-oriented training, such as daily life simulations such as (e.g., lifting, grasping, and dressing), as well as functional activities for specific tasks (such as writing and using utensils). The patients' lower limb training includes increasing lower limb muscle strength through resistance exercises, isokinetic exercises, and other methods. We will gradually enhance the strength of the core muscle group through movements such as turning over, moving the center of gravity forward, standing up, and maintaining sitting balance. Gradually improve balance ability through methods such as standing on one foot, standing on a balance board, and walking sideways. Correct walking posture and gait, while correcting walking posture and gait, and conducting gait training in daily life scenarios.

Participants

Four rehabilitation facilities recruited participants between September 2020 and November 2021, i.e., the First Affiliated Hospital of Nanjing Medical University, Guangzhou First People's Hospital, the Affiliated Brain Hospital of Nanjing Medical University and BENQ Medical Center. In all, 330 stroke patients took part, including 120 undergoing traditional limb rehabilitation training, 100 receiving upper-limb robot training and 110 receiving lower-limb robot training.

The functional magnetic resonance imaging (fMRI) examination was conducted on 30 patients to assess brain network alterations. However, due to limited project funding, the high cost of fMRI tests, and the need for two scans per patient (before and after intervention), the budget could not cover all patients. To ensure the data were representative of the cohort, we randomly selected 10 patients from each group, minimizing bias in image data processing.

The participation criteria for the interventional study included: (1) Cerebral infarction or cerebral hemorrhage in accordance with the 2016 edition of the Chinese Guidelines for the Diagnosis and Treatment of Cerebrovascular Diseases and consensus; (2) stable vital signs; (3) less than 75 years old; (4) significantly limited range of motion in the joints; (5) heart and lung function that is capable of completing training; (6) good cognitive function, MMSE (>24), can understand and actively participate in training programs; (7) agree and sign this informed consent for clinical research. Exclusion criteria included: (1) patient with other neurological complications or musculoskeletal diseases (e.g. Parkinson's disease, multiple sclerosis, severe joint contracture, osteoporosis, fracture, etc.); (2) cardiac and circulatory diseases such as heart failure, unstable angina pectoris, poorly controlled hypertension, etc.; (3) weight > 120 kg; (4) Previous psychiatric history, severe anxiety and depression, uncooperative or aggressive behavior; (5) patients were judged on whether they had poor compliance and could complete the study as required; (6) ongoing involvement in other clinical trials. Written informed permission was acquired from each participant.

The flow process and research design are displayed in Fig. 3.

MRI acquisition

A 3.0 T Verio MRI scanner (Siemens, Erlangen, Germany) with an 8-channel parallel head coil was used to scan each patient, who had to remain awake and close their eyes while lying quietly. Both structural and functional images were acquired. Echo-planar imaging (EPI) was used to obtain resting-state functional images with the following settings: repetition time (TR) = 2000 ms; echo time (TE) = 21 ms; slice thickness/gap = 4 mm/0.6 mm; acquisition matrix = 64 × 64; flip angle = 78°; voxel size = 3.5 mm × 3.5 mm × 4.0 mm; and field of view (FOV) = 224 × 224mm^2. Sagittal T1-weighted images were obtained with the following parameters: TR/TE = 1900 ms/2.19 ms; acquisition matrix = 256 × 256; flip angle = 9°; voxel size = 1.0 mm × 1.0 mm × 1.0 mm; slice thickness/gap = 1 mm/0.5 mm.

Data measurement

The demographic and scale scores of three groups of patients were recorded for comparison. Assessments were performed before treatment, and after 4 weeks of treatment.

The primary outcome was ADL measured using the Modified Barthel Index (MBI) [41], a scale that evaluates 10 fundamental elements of everyday tasks linked to mobility and self-care. Each of the 10 elements has five ranks (1–5), with higher scores denoting greater independence. Complete independence is represented by a total score of 100, whereas total reliance is represented by a score of 0.

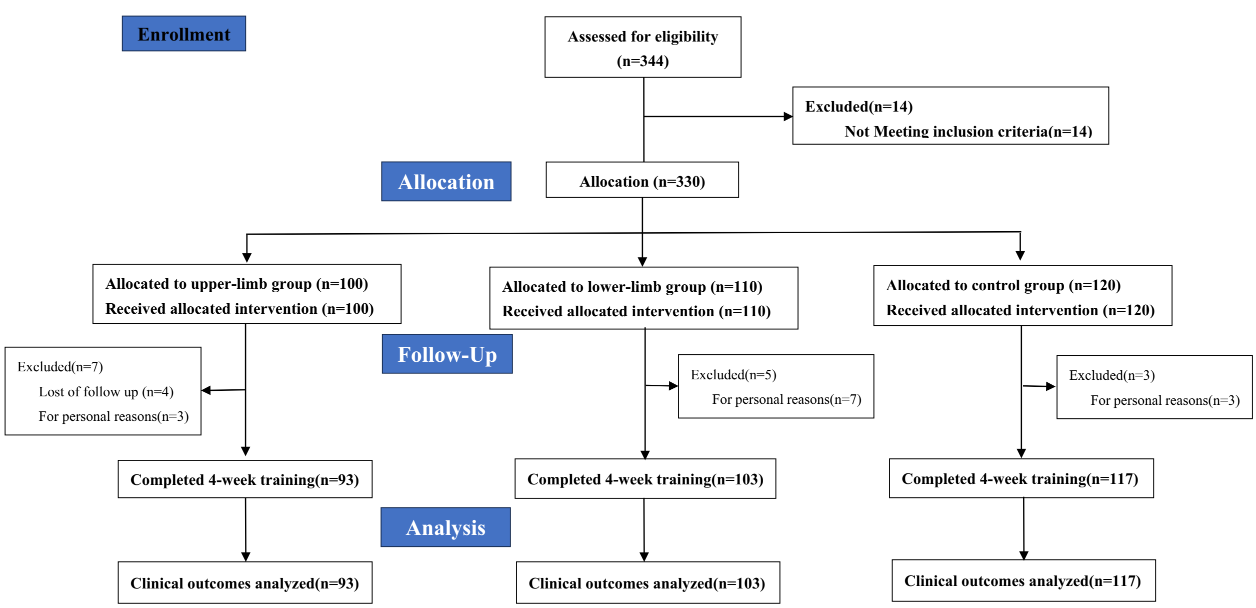

Fig. 3 Patient enrollment. The flow chart illustrating the study design and patients screened and enrolled in the study

The secondary outcome was the Fugl-Meyer assessment (FMA) [42], including FMA-UE and FMA-LE [43], which evaluates the level of motor impairment in the paretic lower and upper extremities, with higher scores indicating better performance. The Action Research Arm Test (ARAT) was used to evaluate upper-limb function by examining grasp, grip, pinch, and gross-motion exercises [44]. The test uses various equipment, including various-sized wood blocks, a sharpening stone, a cricket ball, a glass and water jar, hollow tubes with varying heights and thicknesses, ball bearings, washers, and marbles of varying diameters. Each task receives a score ranging from 0 to 3, contributing to a total score of 57, which is divided among the many tasks using the various pieces of equipment mentioned above.

Manual muscle testing (MMT), a 6-point grading standard ranging from 0 to 5, was used to assess muscular strength, with higher levels indicating higher muscle strength and level 5 representing normal strength [45, 46]. The modified Ashworth scale, also a 6-point grading scale, was employed to evaluate muscle tone, ranging from 0, 1, 1+, 2, 3, and 4 levels, with higher levels indicating higher muscle tone, and level 0 representing normal muscle tone [47].

Functional magnetic resonance imaging (fMRI), which detects changes in cortical signals in patients, was employed to localize the cortical central functional areas and to provide indepth analysis of other brain functions. Functional connectivity (FC) study offered activation analysis and additional insights into the mechanism behind the brain network-level therapy effects of robot training [48].

The indicators measured in the upper-limb group included MBI, FMA-UE, ARAT, MMT and MAS, while the lower-limb group included MBI, FMA-LE, MMT and MAS. All the above indicators were measured in the control group. Additionally, before and after the intervention fMRI data were collected from 10 participants in each group.

Sample size

To detect a minimal clinical relevant difference (MCID) of 5.34-point in MBI [49] with an SD of 25 [50], a statistically significant signal with an F-test power of 80% and an alpha error of 5% required 72 patients per arm, per earlier results. Assuming a 15% dropout rate, the recruitment target was set at 83 participants per group.

Statistical analysis

Scale data

Baseline differences between the three groups were assessed using the analysis of variance (ANOVA) for continuous variables and the chi-square test for categorical data.

Data were mainly analyzed based on the Intention-to-Treat (ITT) principle, using chain equations for multiple imputations of missing data (20 groups). All patient baseline characteristics-center, age, gender, height, weight, stroke type, stroke side, stroke duration-were used as covariate variables for data imputation. The analysis adopted a linear mixed model, treating the results of each evaluation as dependent variables, e.g., the primary outcome MBI. Fixed effects included time, group, and the interaction between time and groups, individuals were included as random intercept terms in the model to address baseline imbalance, and baseline measured variables were controlled for treatment weighted inverse probability (IPTW) [51]. IPTW involves two main steps. First, the probability—or propensity—of being exposed, given an individual's characteristics, is calculated. This is also called the propensity score. Second, weights for each individual are calculated as the inverse of the probability of receiving his/her actual exposure level. The application of these weights to the study population creates a pseudopopulation in which measured confounders are equally distributed across groups [52]. Each person is attributed to a propensity score, estimated using a logistic regression model, and assigned a conditional probability of receiving robot assisted therapy. The covariates include all baseline characteristics of the patient (center, age, gender, height, weight, stroke type, stroke side, stroke duration). Create a pseudo population by taking the reciprocal of the probability of each individual receiving actual treatment (i.e., 1/PS for individuals receiving robot assisted therapy and 1/(1-PS) for individuals in the control group). The stable weight calculated by multiplying the original weight by the unadjusted treatment probability is used to ensure accurate estimation of variance. This study reports the interaction term's β value (with the 95% confidence interval) between group and time as the therapeutic effect. Maximum likelihood was used to fit all models, and all models were checked for normality and homogeneity of variance.

Sensitivity analyses were conducted using ITT analysis without data imputation and Per-protocol (PP) analysis, applying the same analysis method as the main analysis. All statistical analyses were conducted in R 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria).

fMRI data

Preprocessing Functional and anatomical data were preprocessed using CONN (RRID:SCR 009550, version 22.a) [53, 54] and SPM [55] (RRID:SCR 007037 version 12.7771) with a flexible preprocessing pipeline [56]. Anatomical data were normalized into standard MNI space, segmented into grey matter, white matter, CSF, and lesion tissue classes. The data was then resampled to 1 mm isotropic voxels using SPM unified segmentation and normalization algorithm [57, 58] with an alternative tissue probability map (TPM) extended to include custom lesion masks.

Denoising Functional data were denoised using a standard denoising pipeline [56] that included: regression of possible confounding effects based on motion parameters and their first order derivatives (12 factors); white matter timeseries (5 CompCor noise components); and CSF timeseries (5 CompCor noise components) [59], outlier scans (below 54 factors) [60]. Bandpass frequency filtering of the BOLD timeseries [61] between 0.008 and 0.09 Hz.

First-level analysis Global Correlation maps (GCOR), representing network centrality at each voxel, were computed as the average of all short- and long-range connections between a voxel and the rest of the brain [62]. Connections were calculated using bivariate correlation coefficients between BOLD timeseries from voxel pairs, based on singular value decomposition of z-score normalized BOLD signals (subject-level SVD) with 64 components for each subject and condition [50]. Seed-based connectivity maps (SBC) and ROI-to-ROI connectivity matrices (RRC) were derived using 964 ROIs to characterize functional connectivity patterns.

Group-level analyses used a General Linear Model (GLM [53]). The differences in GCOR between follow-up and baseline measurements across groups (Upper limb or Lower limb) were tested to assess brain connectivity changes over time, controlling for age, gender, duration, and motor scores (ARAT or FMA-LE). Moreover, correlations between changes in brain connectivity and motor function improvements before and after the intervention were analyzed.

Changes within the somatomotor network of the Yeo 17 Networks (Schaefer 400 parcels) [63] before and after the intervention were analyzed using a ROI-to-ROI approach. The analysis of Functional Network Connectivity (FNC) utilized parametric multivariate statistics for cluster-level inferences [64]. The primary cluster-forming threshold was set at $P<0.05$, with cluster-level correction for multiple comparisons using the False Discovery Rate (p-FDR). An uncorrected threshold of $P<0.05$ was applied for individual connections, ensuring robust detection of significant connectivity changes while balancing the risk of Type I errors.

Results

Baseline characteristics

Between September 2020 and November 2021, 344 stroke survivors were consecutively recruited, among whom 313 were assigned to three groups, with 93 cases in the upper-limb robot group, 103 cases in the lower-limb robot group and 117 cases in the control group. A total of 313 (94.84%) received a 4-week assessment. The overall patient enrollment process is presented in Fig. 3. The baseline demographics (gender, age, height, weight) and stroke characteristics (type of stroke, or hemiplegic side) were comparable among the three groups ($P>0.05$) (Table 1). After adjusted by the IPTW, the imbalance among groups has been addressed, and the standard mean differences (SMD) are almost all <0.1 (Table 1).

Comparisons between upper limb group and control group

There was no significant difference in MBI between the control group and upper-limb group. Notably, the MMT results, revealed that shoulder flexor muscle strength ($P=0.043$) was significantly higher in upper-limb group compared with the control group (Table 2).

In the upper limb group, changes in GCOR maps between pre- and post-intervention were observed at MNI coordinates (14, −72, 46), with a cluster size of 41 and a corresponding cluster-level qFDR-corr value of 0.007. Seed-to-voxel analysis identified two clusters, with peak MNI coordinates at (58, −22, −2) and (64, −16, −24), and corresponding cluster sizes of 47 (qFDR-corr = 0.006) and 32 (qFDR-corr = 0.029), respectively. ROI-to-ROI analysis identified enhanced FC between the left hemisphere's motor control region and the auditory network (Fig. 4.).

Comparisons between lower limb group and control group

No significant difference in MBI was found between the control and lower-limb groups. However, the lower-limb group showed significantly higher strength in hip flexors ($P<0.001$), hip extensors ($P<0.001$), knee extensors ($P=0.013$), ankle dorsiflexors ($P<0.001$), and ankle plantarflexors ($P<0.001$) (Table 3).

In the lower limb group, no significant differences were found in GCOR between pre- and post-intervention. However, changes in GCOR were strongly associated with changes in the FMA-LE motor score symptom score, with a peak activation at MNI coordinates (2, −50, 34) and a cluster size of 244 (qFDR-corr < 0.001). Seed-to-voxel analysis identified two significantly activated clusters, with peak MNI coordinates at (12, −40, −2) and (54, −52, 14), and corresponding cluster sizes of 44 (qFDR-corr < 0.001) and 41 (qFDR-corr < 0.001), respectively.

Table 1 baseline characteristics of the enrolled subjects

Variable	Control (N = 117)	Upper_limb (N = 93)	Lower_limb (N = 103)	*P* Value	Unadjusted SMD	SMD after IPTW
Age, mean (SD)	60.2 (13.4)	59.7 (13.4)	61.2 (11.2)	0.686	0.076	0.001
Sex, N (%)				0.432	0.14	0.055
Male	80 (68.4%)	67 (72.0%)	80 (76.2%)			
Female	37 (31.6%)	26 (28.0%)	25 (23.8%)			
Height (cm), Mean (SD)	167.1 (8.0)	167.9 (6.6)	168.9 (6.0)	0.15	0.195	0.026
Weight (kg), Mean (SD)	67.2 (10.3)	67.3 (11.5)	66.2 (9.4)	0.696	0.078	0.035
Stroke type, N (%)				0.508	0.108	0.039
Hemorrhage	46 (39.3%)	44 (47.3%)	45 (42.9%)			
Ischemic	71 (60.7%)	49 (52.7%)	60 (57.1%)			
Stroke side, N (%)				0.602	0.154	0.122
Left	63 (53.8%)	46 (49.5%)	52 (49.5%)			
Right	54 (46.2%)	45 (48.4%)	51 (48.6%)			
Bilateral	0 (0)	2 (2.2%)	2 (1.9%)			
Duration (month), Mean (SD)	2.9 (3.3)	3.1 (2.8)	3.4 (3.1)	0.437	0.125	0.013
Center, N (%)	24 (20.5)	27 (29.0)	20 (19.4)	0.162	0.292	0.075
The First Affiliated Hospital of Nanjing Medical University	29 (24.8)	24 (25.8)	30 (29.1)			
BENQ Medical Center	10 (8.5)	15 (16.1)	13 (12.6)			
Guangzhou First People's Hospital	54 (46.2)	27 (29.0)	40 (38.8)			
The Affiliated Brain Hospital of Nanjing Medical University	24 (20.5)	27 (29.0)	20 (19.4)	0.437	0.125	0.013

Values are presented as mean (SD)

*Statistically significant ($P < 0.05$)

ROI-to-ROI analysis confirmed enhanced interhemispheric FC, specifically between the right hemisphere's motor control region (central opercular cortex) and the left hemisphere's primary motor area in the precentral gyrus (Fig. 5.).

Sensitivity analyses

The results of the sensitivity analyses are shown in Tables 4 and 5. Treatment effects remained consistent between ITT analysis with raw data and the PP analysis. Additionally, the ITT analysis with MI demonstrated robustness.

Discussion

Upper-limb

This study was conducted during the 2019 coronavirus disease (COVID-19) pandemic. It describes the clinical outcomes of robot-assisted training on stroke patients, including activities of daily living, motor functions, muscle strength, functional and anatomical data.

The MCID of FMA-UE was found to be 4.25–7.25 [65]. Before and after intervention, the mean difference for the control group was 6.02, and the mean difference for the upper limb robot group was 6.87, exceeding the MCID in the literature, indicating that both conventional treatment and upper limb robot treatment have clinical significance for the rehabilitation of stroke patients. But there was no statistical difference between the two groups, and the improvement value of the upper limb group was slightly higher than that of the control group, indicating that within the 4-week intervention, the two groups were equivalent, and the upper limb robot group was slightly better than the control group.

The MCID of the ARAT scale was 6.0 [66]. Before and after intervention, the mean difference between the control group was 3.32, and the mean difference between the upper limb robot group was 3.27, both of which did not reach the MCID, indicating that both conventional treatment and upper limb robot treatment did not produce clinical significance in fine motor function of the upper limb within 4 weeks. Because the functions of the upper limbs, especially the hands, are extremely delicate and diverse, including grasping, pinching, and other movements, which require high coordination and precise control, and require larger neural control areas in the brain. A 4-week intervention is not sufficient to bring about changes in fine motor skills in the upper limbs.

The findings showed that shoulder flexor muscle strength was significantly higher in the upper-limb group. This outcome is consistent with an earlier study on

Table 2 MBI, FMA, ARAT, MMT and MAS score at 4 weeks rehabilitation between upper limb group and control group (Mixed effects model—ITT with MI)

	Mean (SD)		β with 95% CI (unadjusted)	*P* value	β with 95% CI (after IPTW)	*P* value
	Baseline	Post-intervention				
MBI						
Control group	42.11 (27.90)	53.55 (28.93)	Ref		Ref	
Upper limb group	45.55 (23.68)	56.59 (24.13)	−0.39 (−3.93, 3.14)	0.828	−0.12 (−3.57, 3.33)	0.948
Lower limb group	44.14 (21.01)	58.21 (20.54)	2.64 (−0.79, 6.07)	0.133	3.07 (−0.38, 6.52)	0.082
FMA-UE						
Control group	18.07 (18.65)	24.09 (22.22)	Ref		Ref	
Upper limb group	19.59 (18.05)	26.46 (20.47)	0.85 (−2.03, 3.72)	0.565	1.23 (−1.46, 3.92)	0.371
ARAT						
Control group	10.59 (18.62)	13.91 (20.55)	Ref		Ref	
Upper limb group	9.32 (17.24)	12.59 (18.57)	−0.06 (−1.84, 1.73)	0.951	0.75 (−0.98, 2.48)	0.396
MMT						
sh_flex						
Control group	32.44 (31.24)	42.48 (35.18)	Ref		Ref	
Upper limb group	26.94 (25.24)	41.61 (30.32)	4.64 (0.18, 9.09)	**0.043**	4.75 (0.32, 9.19)	**0.037**
sh_ex						
Control group	31.92 (32.04)	40.60 (33.52)	Ref		Ref	
Upper limb group	25.48 (27.94)	35.86 (30.02)	1.70 (−2.85, 6.25)	0.465	3.15 (−1.39, 7.68)	0.176
sh_add						
Control group	32.78 (31.17)	41.93 (34.19)	Ref		Ref	
Upper limb group	28.71 (28.87)	41.45 (33.80)	3.59 (−1.96, 9.13)	0.206	3.80 (−1.79, 9.38)	0.184
sh_abd						
Control group	31.58 (31.87)	39.66 (34.41)	Ref		Ref	
Upper limb group	27.15 (28.80)	36.51 (31.40)	1.28 (−3.31, 5.87)	0.586	1.94 (−2.56, 6.45)	0.399
el_flex						
Control group	34.53 (34.52)	44.44 (36.92)	Ref		Ref	
Upper limb group	32.53 (30.73)	45.38 (32.53)	2.94 (−2.59, 8.46)	0.299	2.78 (−2.71, 8.26)	0.323
el_ex						
Control group	31.92 (34.86)	41.11 (37.78)	Ref		Ref	
Upper limb group	27.96 (28.74)	40.70 (34.79)	3.56 (−2.23, 9.34)	0.230	2.68 (−3.05, 8.41)	0.360
wr_flex						
Control group	24.68 (31.18)	33.25 (34.84)				
Upper limb group	19.84 (24.37)	27.37 (28.96)	−1.05 (−5.55, 3.45)	0.649	−1.70 (−6.12, 2.71)	0.451
wr_dor						
Control group	23.24 (30.85)	31.50 (35.26)				
Upper limb group	16.61 (22.13)	24.78 (28.69)	−0.08 (−4.49, 4.32)	0.970	−0.61 (−4.95, 3.73)	0.784
MAS						
sap						
Control group	0.26 (0.65)	0.23 (0.60)	Ref		Ref	
Upper limb group	0.38 (0.74)	0.35 (0.74)	0.01 (−0.09, 0.10)	0.862	0.00 (−0.09, 0.09)	0.993
semg						
Control group	0.10 (0.47)	0.09 (0.44)	Ref		Ref	
Upper limb group	0.22 (0.56)	0.21 (0.61)	0.00 (−0.08, 0.08)	0.978	−0.01 (−0.09, 0.06)	0.727
efmg						
Control group	0.43 (0.80)	0.44 (0.77)	Ref		Ref	
Upper limb group	0.55 (0.78)	0.53 (0.77)	−0.04 (−0.15, 0.09)	0.544	−0.05 (−0.16, 0.06)	0.390
fcmg						
Control group	0.27 (0.68)	0.29 (0.67)	Ref		Ref	
Upper limb group	0.40 (0.75)	0.40 (0.75)	−0.02 (−0.12, 0.08)	0.677	−0.03 (−0.13, 0.07)	0.605

Table 2 (continued)

Bold value indicates that there is a statistically significant difference compared with the control group

MBI Modified Barthel Index, *FMA-UE* Fugl-Meyer assessment of the upper extremity, *ARAT* action research arm test, *MMT* manual muscle testing, *Sh* shoulder, *Ex* extension, *Add* adduction, *Abd* abduction, *Dor* dorsiflexion, *El* elbow, *Wr* wrist, *MAS* modified Ashworth scale, *Sap* shoulder adductor muscle group, *Semg* Shoulder extensor muscle group, *Efmg*, elbow flexor muscle group, *Fcmg* flexor carpi muscle group, *Ref* reference

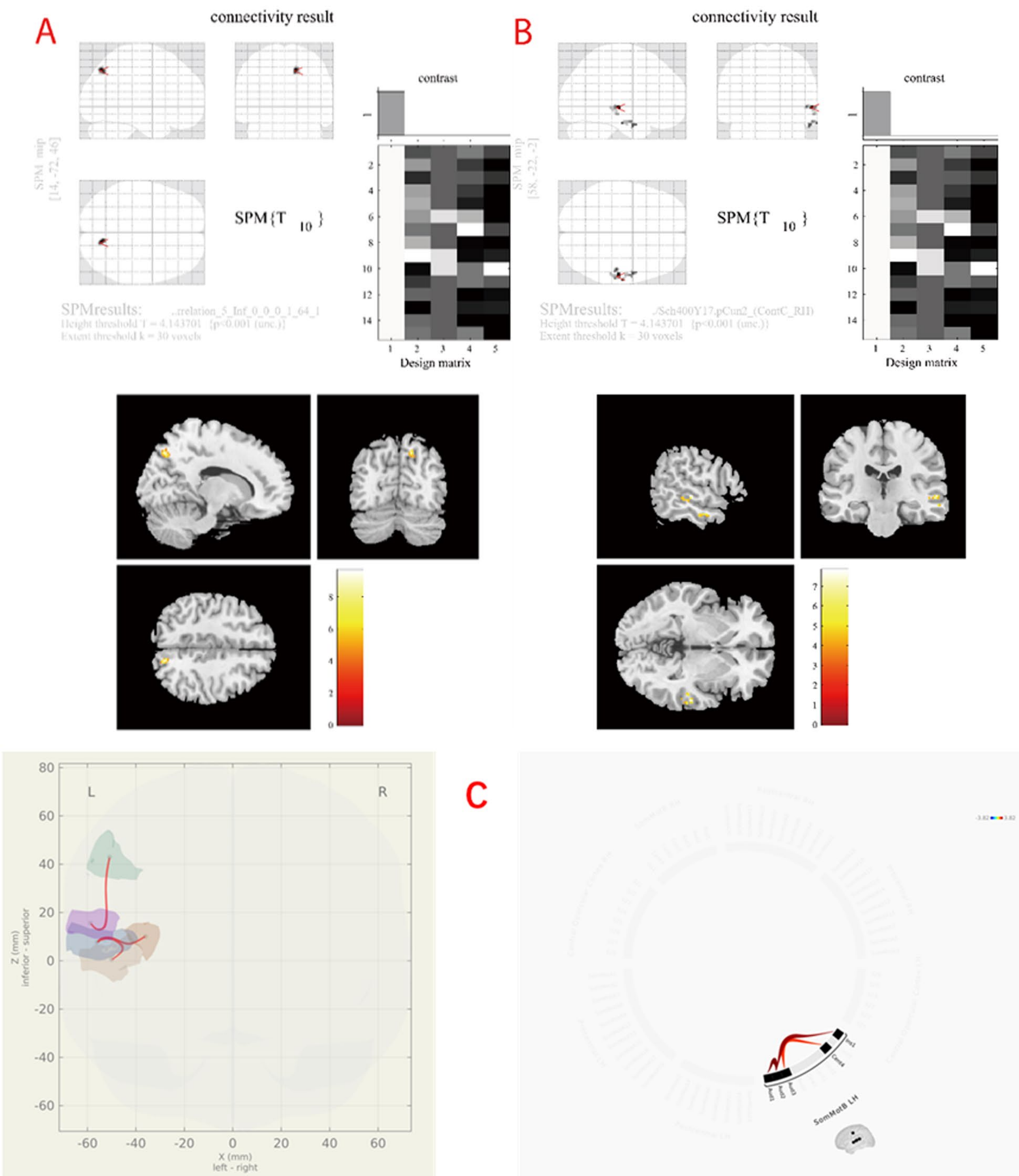

Fig. 4 Functional and anatomical data (upper limb). **A** The difference in Global Correlation maps (GCOR) between pre- and post-intervention. **B** Seed-to-voxel analysis in the upper limb group. **C** ROI-to-ROI analysis in the upper limb group

Table 3 MBI, FMA, MMT and MAS score at 4 weeks rehabilitation between lower limb group and control group (mixed effects model—ITT with MI)

	Mean (SD)		β with 95% CI	*P* value	β with 95% CI	*P* value
	Baseline	Post-intervention				
MBI						
Control group	42.11 (27.90)	53.55 (28.93)	Ref		Ref	
Upper limb group	45.55 (23.68)	56.59 (24.13)	−0.39 (−3.93, 3.14)	0.828	−0.12 (−3.57, 3.33)	0.948
Lower limb group	44.14 (21.01)	58.21 (20.54)	2.73 (−0.71, 6.18)	0.121	3.07 (−0.38, 6.52)	0.082
FMA-LE						
Control group	15.13 (9.76)	19.78 (10.03)	Ref		Ref	
Lower limb group	15.71 (8.10)	19.67 (7.41)	−0.69 (−2.32, 0.95)	0.41	−0.89 (−2.47, 0.68)	0.269
MMT						
hipfl						
Control group	122.01 (10.34)	124.06 (10.34)	Ref		Ref	
Lower limb group	115.49 (16.83)	123.01 (11.40)	5.47 (3.11, 7.83)	**<0.001**	4.93 (2.73, 7.14)	**<0.001**
hipex						
Control group	16.03 (7.81)	17.31 (8.47)	Ref		Ref	
Lower limb group	16.36 (9.27)	19.95 (9.69)	2.31 (1.23, 3.39)	**<0.001**	2.28 (1.22, 3.33)	**<0.001**
Knfl						
Control group	132.35 (7.03)	134.49 (8.37)	Ref		Ref	
Lower limb group	132.62 (9.77)	135.39 (10.09)	0.63 (−0.97, 2.23)	0.441	1.17 (−0.42, 2.76)	0.152
Knex						
Control group	2.01 (2.94)	2.56 (3.32)	Ref		Ref	
Lower limb group	2.38 (4.07)	1.80 (2.87)	−1.14 (−2.03, 0.25)	**0.013**	−1.08 (−2.03, −0.13)	**0.027**
andor						
Control group	46.58 (7.79)	47.65 (7.64)	Ref		Ref	
Lower limb group	43.06 (11.19)	46.21 (11.54)	2.09 (1.00, 3.17)	**<0.001**	1.98 (0.88, 3.07)	**<0.001**
anpl						
Control group	13.12 (5.68)	14.19 (5.98)	Ref		Ref	
Lower limb group	9.47 (7.31)	12.18 (6.67)	1.65 (0.72, 2.58)	**<0.001**	1.87 (0.91, 2.82)	**<0.001**
MAS						
hag						
Control group	0.35 (0.75)	0.37 (0.73)	Ref		Ref	
Lower limb group	0.43 (0.80)	0.47 (0.75)	0.02 (−0.07, 0.10)	0.627	0.01 (−0.08, 0.10)	0.792
kemg						
Control group	0.32 (0.75)	0.31 (0.78)	Ref		Ref	
Lower limb group	0.41 (0.83)	0.39 (0.72)	−0.01 (−0.13, 0.10)	0.853	0.00 (−0.12, 0.12)	0.965
kfg						
Control group	0.12 (0.44)	0.15 (0.46)	Ref		Ref	
Lower limb group	0.20 (0.68)	0.26 (0.63)	0.03 (−0.04, 0.10)	0.352	0.04 (−0.03, 0.10)	0.312
apfg						
Control group	0.55 (1.00)	0.66 (1.11)	Ref		Ref	
Lower limb group	0.67 (1.07)	0.72 (0.94)	−0.06 (−0.21, 0.09)	0.416	−0.04 (−0.18, 0.10)	0.593
avmg						
Control group	0.26 (0.72)	0.34 (0.82)	Ref		Ref	
Lower limb group	0.30 (0.68)	0.39 (0.61)	0.01 (−0.11, 0.14)	0.87	0.02 (−0.10, 0.14)	0.798

Bold value indicates that there is a statistically significant difference compared with the control group

FMA-LE Fugl-Meyer assessment of the lower extremity, *MMT* manual muscle testing, *Hipfl* hip flexion, *Hipex* hip extension, *Knfl* knee flexion, *Knex* knee extension, *Andor* ankle dorsiflexion, *Anpl* ankle plantflexor, *MAS* modified Ashworth scale, *Hag* hip adductor muscle group, *Kemg* knee extensor muscle group, *Kfg* knee flexor muscle group, *Apfg* ankle plantar flexor muscle group, *Avmg* Ankle varus muscle group, *Ref* reference

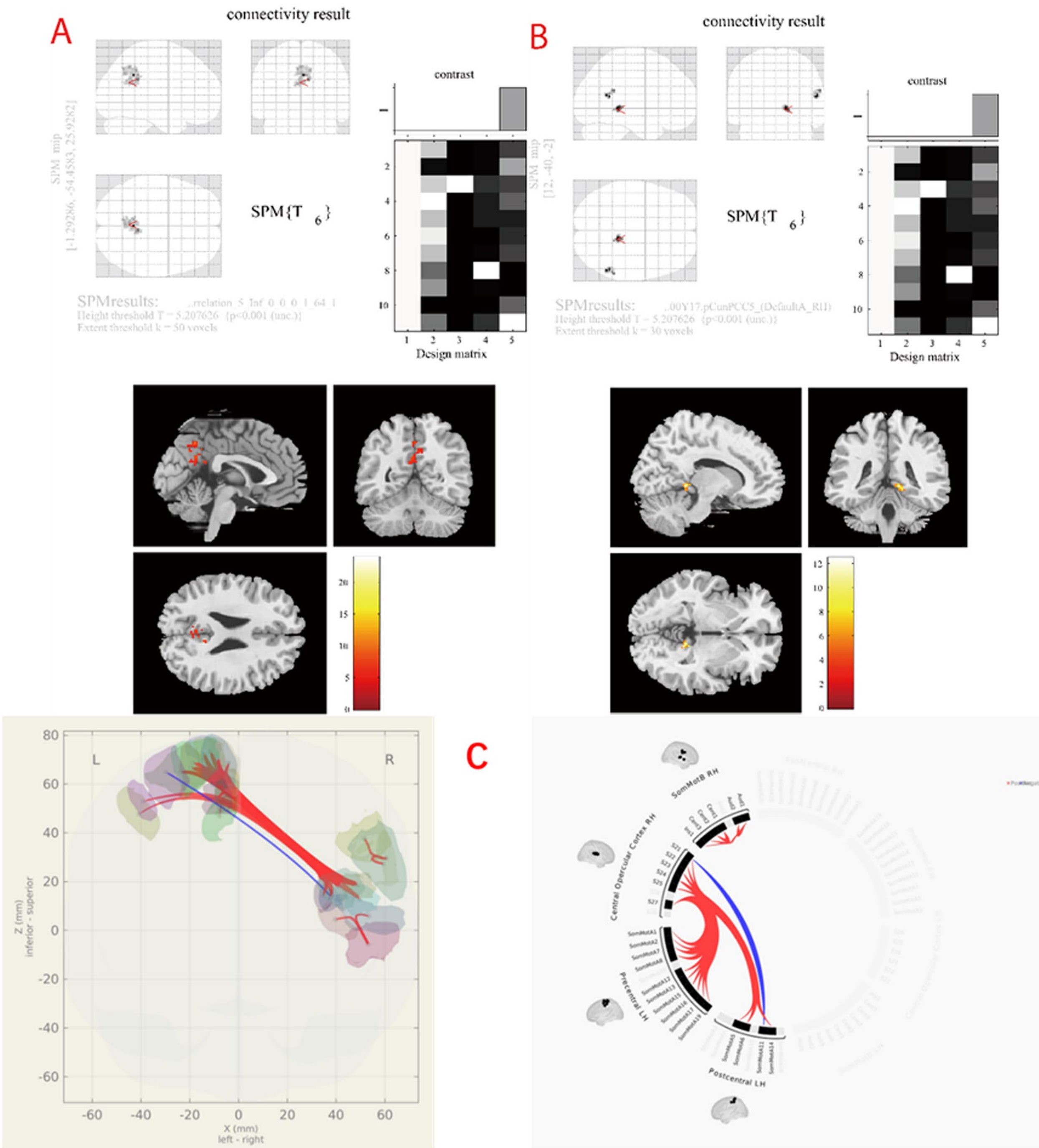

Fig. 5 Functional and anatomical data (lower limb). **A** The difference in Global Correlation maps (GCOR) between pre- and post-intervention. **B** Seed-to-voxel analysis in the lower limb group. **C** ROI-to-ROI analysis in the lower limb group

robot-assisted arm training that employed a device with an end effector for 40–105 min daily over four weeks in addition to traditional therapy [66–70].

Muscle weakness, an obvious symptom after stroke [71], is one of the main factors that slow down the recovery to normal physical fitness in patients [72]. Paralysis on the side of the body on the opposite the brain lesion is the most notable consequence [73], although a correlation between insufficient strength on the same side and walking speed has also been observed [74]. Paresis, defined as a change in the ability to generate normal levels of muscle strength [75], can lead to abnormal posture

Table 4 MBI, FMA, ARAT, MMT and MAS score at 4 weeks rehabilitation between upper limb group and control group (sensitivity analysis)

	Mixed effects model – ITT with raw data					Mixed effects model – PP analysis				
	mean (SD)					mean (SD)				
	Baseline	post-intervention	β with 95% CI	SE	P Value	Baseline	post-intervention	β with 95% CI	SE	P Value
MBI										
control group	42.11 (27.90)	53.55 (28.93)	Ref			43.15 (28.34)	54.64 (29.13)	Ref		
upper limb group	45.55 (23.68)	56.59 (24.13)	0.01 (-3.46, 3.48)	1.77	0.996	46.16 (23.54)	57.22 (23.98)	-0.1 (-3.62, 3.42)	1.79	0.956
lower limb group	43.77 (20.79)	58.21 (20.54)	3.37 (-0.10, 6.84)	1.77	0.058	44.54 (20.79)	58.43 (20.45)	3.4 (-0.11, 6.9)	1.79	0.059
FMA-UE										
control group	18.14 (18.72)	24.09 (22.22)	Ref			18.39 (18.90)	24.71 (22.35)	Ref		
upper limb group	19.59 (18.05)	26.46 (20.47)	1.14 (-1.55, 3.82)	1.37	0.408	19.72 (18.11)	26.66 (20.49)	0.92 (-1.81, 3.66)	1.39	0.508
ARAT										
control group	10.59 (18.62)	13.91 (20.55)	Ref			10.68 (18.79)	13.98 (20.59)	Ref		
upper limb group	9.32 (17.24)	12.59 (18.57)	0.75 (-0.98, 2.48)	0.88	0.396	9.42 (17.30)	12.57 (18.67)	0.62 (-1.13, 2.37)	0.89	0.490
MMT										
sh_flex										
control group	31.89 (31.46)	41.67 (35.17)	Ref			32.17 (31.45)	42.04 (35.10)	Ref		
upper limb group	26.94 (25.24)	41.61 (30.32)	4.96 (0.50, 9.42)	2.28	**0.031**	27.17 (25.27)	41.85 (30.40)	4.70 (0.20, 9.20)	2.30	**0.042**
sh_ex										
control group	31.80 (32.06)	40.09 (33.73)	Ref			31.37 (31.88)	39.73 (33.67)	Ref		
upper limb group	25.48 (27.94)	35.86 (30.02)	3.52 (-1.03, 8.06)	2.32	0.131	25.71 (28.01)	36.20 (30.01)	3.37 (-1.21, 7.95)	2.34	0.151
sh_add										
control group	32.68 (31.50)	41.46 (34.43)	Ref			32.96 (31.49)	41.82 (34.36)	Ref		
upper limb group	28.71 (28.87)	41.45 (33.80)	4.12 (-1.51, 9.75)	2.87	0.153	28.97 (28.92)	41.68 (33.91)	3.98 (-1.7, 9.67)	2.90	0.171
sh_abd										
control group	31.27 (32.20)	39.21 (34.59)	Ref			31.55 (32.20)	39.56 (34.54)	Ref		
upper limb group	27.15 (28.80)	36.51 (31.40)	2.04 (-2.52, 6.59)	2.32	0.381	27.39 (28.87)	36.68 (31.52)	1.81 (-2.79, 6.42)	2.35	0.441
el_flex										
control group	34.39 (34.88)	43.86 (36.81)	Ref			34.69 (34.89)	44.25 (36.74)	Ref		
upper limb group	32.53 (30.73)	45.38 (32.53)	3.15 (-2.36, 8.66)	2.81	0.264	32.83 (30.76)	45.65 (32.60)	2.97 (-2.61, 8.55)	2.85	0.298
el_ex										
control group	31.97 (35.25)	40.61 (37.87)	Ref			32.26 (35.27)	40.97 (37.84)	Ref		
upper limb group	27.96 (28.74)	40.70 (34.79)	3.14 (-2.59, 8.87)	2.93	0.285	28.21 (28.80)	41.09 (34.78)	3.11 (-2.71, 8.92)	2.97	0.296
wr_flex										

and stretching reflexes, as well as loss of autonomous movement [76, 77]. Restoring hand function is challenging due to its complex, precise movements. Moreover, hand function is primarily controlled by the anterior central gyrus, a larger area of the left cerebral cortex plays a key role in right-handed individuals. Stroke-induced upper limb motor dysfunction mechanisms is attributed to pathologically reduced cortical excitability and impaired limb innervation. Repetitive motor training of the affected limb stimulates the corresponding cortical

Table 4 (continued)

control group	24.45 (31.50)	33.07 (35.21)	Ref			24.66 (31.55)	33.36 (35.23)	Ref		
upper limb group	19.84 (24.37)	27.37 (28.96)	-1.76 (-6.22, 2.71)	2.28	0.442	20.00 (24.45)	27.45 (29.11)	-1.91 (-6.43, 2.61)	2.31	0.407
wr_dor										
control group	23.19 (31.10)	31.58 (35.59)	Ref			23.40 (31.17)	31.86 (35.63)	Ref		
upper limb group	16.61 (22.13)	24.78 (28.69)	-0.75 (-5.14, 3.65)	2.24	0.739	16.74 (22.22)	25.00 (28.78)	-0.83 (-5.28, 3.61)	2.27	0.714
MAS										
sap										
control group	0.26 (0.65)	0.23 (0.60)	Ref			0.24 (0.64)	0.21 (0.58)	Ref		
upper limb group	0.38 (0.74)	0.35 (0.74)	0.00 (-0.09, 0.09)	0.05	0.993	0.36 (0.72)	0.35 (0.74)	0.01 (-0.09, 0.10)	0.05	0.877
semg										
control group	0.10 (0.47)	0.09 (0.44)	Ref			0.10 (0.48)	0.10 (0.45)	Ref		
upper limb group	0.22 (0.56)	0.21 (0.61)	-0.01 (-0.09, 0.06)	0.04	0.727	0.21 (0.56)	0.20 (0.61)	-0.01 (-0.09, 0.06)	0.04	0.708
efmg										
control group	0.43 (0.80)	0.44 (0.77)	Ref			0.41 (0.79)	0.42 (0.76)	Ref		
upper limb group	0.55 (0.78)	0.53 (0.77)	-0.05 (-0.16, 0.06)	0.06	0.390	0.54 (0.77)	0.52 (0.77)	-0.04 (-0.16, 0.07)	0.06	0.431
fcmg										
control group	0.27 (0.68)	0.29 (0.67)	Ref			0.25 (0.67)	0.27 (0.65)	Ref		
upper limb group	0.38 (0.74)	0.38 (0.74)	-0.03 (-0.13-0.07)	0.05	0.606	0.38 (0.74)	0.38 (0.74)	-0.02 (-0.12, 0.08)	0.05	0.710

FMA-LE Fugl-Meyer assessment of the lower extremity, *MMT* manual muscle testing, *Hipfl* hip flexion, *Hipex* hip extension, *Knfl* knee flexion, *Knex* knee extension, *Andor* ankle dorsiflexion, *Anpl* ankle plantflexor, *MAS* modified Ashworth scale, *Hag* hip adductor muscle group, *Kemg* knee extensor muscle group, *Kfg* knee flexor muscle group, *Apfg* ankle plantar flexor muscle group, *Avmg* Ankle varus muscle group, *Ref* reference

representative area of the cortex to be enlarged and the efficiency of nerve signalling to be increased. Robotic training provides a specific context for motor relearning, emphasing on visual and auditory feedback to correct abnormal movement patterns [78, 79]. Highly repetitive and engaging upper limb exercises can enhance motor sensory input and stimulate the brain to generate motor plans, effectively improve the patient's upper limb motor function and thus motivating the patient. The rehabilitation robot's exoskeleton device and support system promote autonomous patient movement by adjusting active or passive modes. The robot's weight reduction system can be used to reduce the upper-limb physical and active muscle exercise demands to achieve optimal training [40].

In the upper-limb group, ROI-to-ROI analysis revealed enhanced functional connectivity between the left hemisphere's motor control region and the auditory network. Studies have confirmed that there are unidirectional or bidirectional direct nerve fiber projections between the auditory and somatosensory cortices, as well as between the visual and auditory cortices [78]. The interaction between the motion and auditory systems takes the form of feedforward and feedback relationships. These interactions may be related to the "auditory action" system, similar to the mirror neuron system. The auditory system primarily affects motor output in a predictive manner. For instance, musicians receive input and feedback from multisensory information by repeatedly practicing hand and upper limb movements alongside auditory and visual information, which not only activates the parietal lobe but also enhances the functional connection between the auditory and motor cortices [79]. Studies analyzing the changes in FC of the brain network in upper limb amputees (ULAs) report that both the left precentral gyrus in the auditory network and the left precuneus gyrus in the dorsal attention network showed a decrease in intra network FC [40]. These examples demonstrate that when upper limb motor function is enhanced, the connection between the motor cortex and auditory network is strengthened. Conversely, when motor function is weakened, the connection between the two functions is weakened.

Upper limb functional indicators showing significant differences in shoulder flexor strength after four weeks of rehabilitation, robotic training appears to accelerate

Table 5 MBI, FMA, MMT and MAS score at 4 weeks rehabilitation between lower limb group and control group (sensitivity analysis)

	Mixed effects model – ITT with raw data					Mixed effects model – PP analysis				
	mean (SD)					mean (SD)				
	Baseline	post-intervention	β with 95% CI	SE	P Value	Baseline	post-intervention	β with 95% CI	SE	P Value
MBI										
control group	42.11 (27.90)	53.55 (28.93)	Ref			43.15 (28.34)	54.64 (29.13)	Ref		
upper limb group	45.55 (23.68)	56.59 (24.13)	0.01 (-3.46, 3.48)	1.77	0.996	46.16 (23.54)	57.22 (23.98)	-0.1 (-3.62, 3.42)	1.79	0.956
lower limb group	43.77 (20.79)	58.21 (20.54)	3.37 (-0.10, 6.84)	1.77	0.058	44.54 (20.79)	58.43 (20.45)	3.4 (-0.11, 6.9)	1.79	0.059
FMA-LE										
control group	15.54 (9.77)	19.46 (10.02)	Ref			15.85 (9.69)	19.74 (9.93)	Ref		
lower limb group	15.71 (8.10)	19.67 (7.41)	-0.09 (-1.54, 1.36)	0.74	0.903	15.46 (8.01)	19.44 (7.33)	6.19 (1.28, 11.10)	0.75	0.891
MMT										
hipfl										
control group	122.01 (10.34)	124.06 (10.34)	Ref			121.65 (10.52)	124.17 (10.22)	Ref		
lower limb group	115.49 (16.83)	123.01 (11.40)	4.93 (2.73, 7.14)	1.13	**<0.001**	115.30 (17.01)	122.85 (11.49)	4.48 (2.29, 6.66)	1.12	**<0.001**
hipex										
control group	16.03 (7.81)	17.31 (8.47)	Ref			16.06 (7.94)	17.52 (8.57)	Ref		
lower limb group	16.36 (9.27)	19.95 (9.69)	2.28 (1.22, 3.33)	0.54	**<0.001**	16.55 (9.31)	20.20 (9.72)	2.14 (1.05, 3.24)	0.56	**<0.001**
knfl										
control group	132.35 (7.03)	134.49 (8.37)	Ref			132.34 (7.25)	134.77 (8.43)	Ref		
lower limb group	132.62 (9.77)	135.39 (10.09)	1.17 (-0.42, 2.76)	0.81	0.152	132.50 (9.83)	135.35 (10.18)	1.03 (-0.62, 2.67)	0.84	0.223
knex										
control group	2.01 (2.94)	2.56 (3.32)	Ref			1.97 (2.97)	2.57 (3.38)	Ref		
lower limb group	2.38 (4.07)	1.80 (2.87)	-1.08(-2.03, -0.13)	0.48	**0.027**	2.40 (4.11)	1.75 (2.88)	-1.19 (-2.17, -0.20)	0.50	**0.020**
andor										
control group	46.58 (7.79)	47.65 (7.64)	Ref			46.51 (7.98)	47.61 (7.86)	Ref		
lower limb group	43.06 (11.19)	46.21 (11.54)	1.98 (0.88, 3.07)	0.56	**<0.001**	43.00 (11.15)	46.05 (11.44)	1.84 (0.73, 2.95)	0.57	**0.001**
anpl										
control group	13.12 (5.68)	14.19 (5.98)	Ref			13.03 (5.73)	14.22 (5.98)	Ref		
lower limb group	9.47 (7.31)	12.18 (6.67)	1.87 (0.91, 2.82)	0.49	**<0.001**	9.60 (7.34)	12.30 (6.64)	1.74 (0.80, 2.69)	0.48	**<0.001**
MAS										
hag										
control group	0.35 (0.75)	0.37 (0.73)	Ref			0.34 (0.72)	0.36 (0.70)	Ref		
lower limb group	0.43 (0.80)	0.47 (0.75)	0.01 (-0.08, 0.10)	0.04	0.792	0.43 (0.81)	0.47 (0.76)	0.01 (-0.08, 0.10)	0.05	0.841

the process of upper limb rehabilitation. This and other data trend are an indication of better improvement compared with the control group.

Lower-limb

Gait training is not only about restoring the patient's ability to walk, but also about the patient's ability to walk and

Table 5 (continued)

kemg										
control group	0.32 (0.75)	0.31 (0.78)	Ref			0.30 (0.73)	0.30 (0.76)	Ref		
lower limb group	0.40 (0.84)	0.38 (0.72)	0.00 (-0.12, 0.12)	0.06	0.962	0.41 (0.84)	0.39 (0.72)	-0.01 (-0.13, 0.11)	0.06	0.892
kfg										
control group	0.12 (0.44)	0.15 (0.46)	Ref			0.12 (0.45)	0.15 (0.47)	Ref		
lower limb group	0.21 (0.68)	0.26 (0.63)	0.04 (-0.03, 0.11)	0.04	0.307	0.21 (0.69)	0.27 (0.63)	0.04 (-0.04, 0.11)	0.04	0.338
apfg										
control group	0.55 (1.00)	0.66 (1.11)	Ref			0.53 (0.97)	0.65 (1.08)	Ref		
lower limb group	0.67 (1.07)	0.72 (0.94)	-0.04 (-0.18, 0.10)	0.07	0.593	0.66 (1.08)	0.71 (0.95)	-0.05 (-0.20, 0.10)	0.08	0.538
avmg										
control group	0.26 (0.72)	0.34 (0.82)	Ref			0.24 (0.68)	0.30 (0.73)	Ref		
lower limb group	0.30 (0.68)	0.39 (0.61)	0.02 (-0.10, 0.14)	0.06	0.798	0.30 (0.69)	0.38 (0.60)	0.02 (-0.10, 0.14)	0.06	0.721

FMA-LE Fugl-Meyer assessment of the lower extremity, *MMT* manual muscle testing, *Hipfl* hip flexion, *Hipex* hip extension, *Knfl* knee flexion, *Knex* knee extension, *Andor* ankle dorsiflexion, *Anpl* ankle plantflexor, *MAS* modified Ashworth scale, *Hag* hip adductor muscle group, *Kemg* knee extensor muscle group, *Kfg* knee flexor muscle group, *Apfg* ankle plantar flexor muscle group, *Avmg* Ankle varus muscle group, *Ref* reference

participate in the community [80]. Routine rehabilitation of stroke patients with gait abnormalities is carried out in steps. Gait training can only begin when there is adequate supportive strength in the trunk and limbs [81]. Previous studies show that chronic stroke survivors (>6 months after stroke) have decreased muscle mass and strength in both hemiplegic and non-hemiplegic limbs [82, 83].

Robot-assisted gait training has demonstrated equivalent or even better training effects and safety standards compared to conventional rehabilitation training. It has several notable advantages, including precise and controllable training patterns, repeatability, low energy consumption, timely feedback, and objectivity [84–87].

Conventional rehabilitation therapy for post-stroke motor function recovery often requires multiple therapists to manually guide the training. The limitations of conventional rehabilitation training method are becoming more apparent due to the rising incidence of stroke and the shortage of therapists. Efficiency in personnel utilization remains low, with significant variability in the skills and experience among therapist partly impacting treatment outcomes. Furthermore, the traditional rehabilitation training method fail to accurately record the training parameters such as joint movement speed, displacement and torque, but they cannot be accurately controlled. As a result, individual patient training sessions are therefore restricted. With the increased demand in personnel in the field of rehabilitation medicine, rehabilitation robots offer a capability of assisting or replacing therapists by streamlining traditional rehabilitation training methods. The combination of robotics and medical technology has helped patients rebuild the central nervous system, restoring their activities of daily living, global motor function, limbs and trunk strength, and gait improvement with enhanced safety and efficacy compared with conventional therapy [86–90].

The MCID of FMA-LE was found to be 6.0 [91]. Before and after intervention, the mean difference for the control group was 4.65 and for the lower limb robot group was 3.96, both of which did not reach MCID. This indicates that both conventional treatment and lower limb robot treatment have clinical significance for lower limb motor function within 4 weeks. The results showed that hip flexor muscle strength, hip extensor muscle strength, knee extensor strength, ankle dorsiflexion strength and ankle plantarflexor strength were significantly higher in lower-limb group compared with conventional therapy. These results were consistent with previous research [92, 93]. The effectiveness of the robot may have been driven by the following mechanisms: the robot's bodyweight support enhanced the stroke patients' walking stability and training effectiveness, provided continuous, consistent, repetitive, and intense training, which increased its efficacy, and ameliorated the cardiopulmonary function and blood circulation within the lower limbs. Moreover, the mirror rehabilitation robot allowed monitoring of the patient's recovery status in real time and adjustment of the training mode. During the soft paralysis stage, the robot detected the affected limb's condition and activated the passive or assisted mirror training mode, enabling the healthy side to guide the movement of the affected side. In the case of muscle spasm, the robot sensed the increased muscle tension in the affected side, thereby opening the spasm protection mechanism. The robot followed the limb activities without the need for prior training and reduced the muscle tension by slowly stretching the spasm limb. If the muscle tension decreased, the task-oriented active training of the affected limb was performed. As the muscle tension of the affected limb decreased and entered the separation movement phase, the robot detected the near-normalization of muscle tension on the affected side and initiated task-oriented active resistance rehabilitation training for the affected limb.

In the lower limb group, ROI-to-ROI analysis identified enhanced interhemispheric functional connectivity, specifically between the right hemisphere's motor control region (central opercular cortex) and the left hemisphere's primary motor area in the precentral gyrus. The stroke was accompanied by extensive changes in the structure and functional connections between hemispheres [94, 95]. These changes may be associated with neurological deficits and the dynamics of functional recovery after stroke. Several studies on stroke patients measured the interhemispheric FC, which is located within the sensorimotor network. Similarly, this study found that almost all patients experienced a decrease in interhemispheric FC intensity in the early stages after stroke [96–99]. Vahdat et al. [100] and Guerra Carrillo et al. [101] demonstrated that interhemispheric FC was enhanced after motor and perceptual training. Fan et al. [102] reported that robot-assisted bilateral arm movement therapy enhanced the interhemispheric FC and improved the motor function. Another study exploring the brain-computer interface revealed that the subjects achieved significant functional recovery after a 5-week brain computer interface intervention treatment. Results of the EEG analysis indicated that the functional connectivity between the damaged hemisphere motor areas of the subjects was enhanced before and after treatment [103]. A previous study investigated how the resting-state functional connectivity (rsFC) and motor outcomes in stroke recovery were affected by the combination of EEG-based BCI intervention and functional electrical stimulation (FES). Following BCI intervention, the motor network's interhemispheric and network rsFC significantly increased at the group level [104]. Our imaging results are consistent with previous studies, indicating that the enhanced functional connectivity between hemispheres suggests the role of this lower limb robot in promoting neurological recovery in stroke patients.

The MCID of the MBI scale was 5.34 [49]. From the statistical results, the mean changes of the three groups before and after the intervention were greater than the MCID, indicating significant clinical improvement in the treatment of stroke patients. However, there was no statistical difference between the three groups before and after the intervention, and the lower limb robot group was only numerically superior to the control group, indicating that within the 4-week intervention, robot intervention and the conventional rehabilitation intervention were equivalent, but lower limb robot intervention showed certain advantages. In our study, MBI scores did not differ between the control and robot groups, likely due to several factors. While robotic training enhances muscle strength, through repetitive, precise limb movements, without a focus on functional tasks or ADL, individuals may not experience improvements in their ability to perform these tasks. After a stroke, the brain can self-reorganize, and with the formation of new neural pathways, muscle strength is initially improved [105]. However, this does not always translate into an improvement in functional abilities in daily activities. Psychological factors, such as motivation and self-efficacy, can affect the performance of daily life activities [106]. Even with increased strength, a person may lack the confidence to perform certain tasks. After a stroke, some patients may experience severe functional impairment and may not be able to recover to normal in the short term. In addition to being unable to take care of themselves in daily life, their work, economy, and other aspects will also be greatly affected, and even their status in the family and society will change. Secondly, patients often feel fear and worry about the disease and prognosis, which can lead to psychological disorders, in turn affecting the recovery of motor function. Stroke behavioral deficits refer to the behavioral changes that occur in individuals after a stroke. These changes may include sensory, motor, cognitive, and emotional disorders. Including difficulties in movement, coordination, and balance. as well as difficulty with memory, attention, and problem-solving [107]. Emotional changes such as anxiety, depression, and irritability are common. Utilizing these robots can improve various behavioral and psychological outcomes. Patients may experience reduced anxiety and depression levels, increased self-efficacy, and improved mood due to positive experiences during therapy.

Compared with traditional training, robot intervention has the following advantages. Mirror rehabilitation robots can promote motor recovery in patients with nerve injuries through precise repetitive training, thereby enhancing brain plasticity. The interactive nature of robotic systems may increase patient motivation and compliance during rehabilitation exercises [108]. These robots can be programmed to tailor exercises to individual patient needs, potentially leading to more effective rehabilitation outcomes. Robots can track progress and performance metrics, allowing therapists to adjust treatment plans based on real-time data [109].

However, there are also limitations, the high cost of mirror rehabilitation robots may limit accessibility for some patients and healthcare facilities [110]. Both patients and therapists may require training to effectively use these systems, which could be a barrier in some settings. The effectiveness of the intervention may vary among individuals due to differences in motivation, severity of disability, and other factors. Overreliance on robotic rehabilitation systems may weaken the effectiveness of traditional rehabilitation techniques, which are beneficial for stroke patients [111].

In terms of cost-effectiveness, although the initial cost of mirror rehabilitation robots may be high, including the purchase and maintenance costs of the robots, personnel training costs, and operating costs. However, in the long run, the use of rehabilitation robots can accelerate the readaptation process of stroke patients, reduce hospitalization time or rehabilitation courses, thereby offsetting initial costs [112]. Overall, although the initial cost may be high, the long-term benefits and savings often make robot intervention a cost-effective solution.

The results of this study must be interpreted in the context of certain limitations. A more trobust experimental design would include artificial mirror therapy as a control group, enabling direct comparison of changes in range of motion and strength between this group and the mirror rehabilitation robot group. Moreover, considering individual preferences, rehabilitation psychology, and economic factors would provide a more comprehensive understanding of the strengths and weaknesses of both mirror robot rehabilitation and traditional mirror therapy. Considering the evaluation of the relative benefits, limitations, cost-effectiveness, scalability, and accessibility of robot interventions make research design more comprehensive. This approach would be instrumental in tailoring personalized rehabilitation plans.

Conclusion

This study demonstrates that upper and lower limb rehabilitation robots can accelerate the recovery of motor function in stroke patients. Therefore, robot-assisted training may be an alternative treatment that provides persistent efficacy. In the future, large-scale randomized controlled studies are needed to validate our results.

Abbreviations

MBI	Modified Barthel Index
FMA	Fugl-Meyer assessment subscale
MMT	Manual muscle testing
fMRI	Functional magnetic resonance imaging
PP	Per-protocol
ITT	Intention-to-treat
ROI	Region-of-interest
MT	Mirror therapy
RMT	Robotic mirror therapy
FAC	Functional ambulation scale
BOLD	Blood oxygenation level-dependent
deoxyHb	Deoxyhemoglobin
ADL	Activities of daily living
ARAT	Action research arm test
FC	Functional connectivity
MCID	Minimal clinical relevant difference
ANOVA	Analysis of variance
TPM	Tissue probability map
STC	Slice-timing correction
FWHM	Full-width at half maximum
GCOR	Global correlation maps
SBC	Seed-based connectivity
RRC	ROI-to-ROI connectivity matrices
GLM	General linear model
FNC	Functional network connectivity
COVID-19	2019 Coronavirus disease
BCI	Brain-computer interface
FES	Functional electrical stimulation

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Author contributions
XXW, and XL were involved in the development and design of the study concept; YDX, QYY, WTA, LFX and JTL were responsible for intervention and assessment; XXW and XQ were in charge of data acquisition and analysis; XXW, XQ and XL contributed to the initial manuscript writing. All authors revised and agreed to the final version of this article. Xixi Wu, Xu Qiao, Yudi Xie and Qingyan Yang contributed equally to this work.

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

Declarations

Ethics approval and consent to participate
The study was registered on the Chinese Clinical Trial Registry with the unique identification number ChiCTR1800019783, and it was approved by the ethics council of Nanjing Medical University's First Affiliated Hospital (No. 2019-SR-310). The Ethics Committee of the first affiliated hospital of Nanjing Medical University approved all protocols. All participants provided written confirmed consent according to the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Feigin VL, Owolabi MO. Pragmatic solutions to reduce the global burden of stroke: a World Stroke Organization-Lancet Neurology Commission. Lancet Neurol. 2023;22(12):1160–206.
2. Baker KB, Plow EB, Nagel S, Rosenfeldt AB, Gopalakrishnan R, Clark C, et al. Cerebellar deep brain stimulation for chronic post-stroke motor rehabilitation: a phase I trial. Nat Med. 2023;29(9):2366–74.
3. Lieshout E, van de Port IG, Dijkhuizen RM, Visser-Meily JMA. Does upper limb strength play a prominent role in health-related quality of life in stroke patients discharged from inpatient rehabilitation? Top Stroke Rehabil. 2020;27(7):525–33.
4. Wade DT. Measurement in neurological rehabilitation. Curr Opin Neurol Neurosurg. 1992;5(5):682–6.
5. Li S, Ghuman J, Gonzalez-Buonomo J, Huang X, Malik A, Yozbatiran N, et al. Does spasticity correlate with motor impairment in the upper and lower limbs in ambulatory chronic stroke survivors? Am J Phys Med Rehabil. 2023;102(10):907–12.
6. Pollock A, Farmer SE, Brady MC, Langhorne P, Mead GE, Mehrholz J, et al. Interventions for improving upper limb function after stroke. Cochrane Database Syst Rev. 2014;2014(11):Cd010820.
7. Rathore SS, Hinn AR, Cooper LS, Tyroler HA, Rosamond WD. Characterization of incident stroke signs and symptoms: findings from the atherosclerosis risk in communities study. Stroke. 2002;33(11):2718–21.
8. Jones TA. Motor compensation and its effects on neural reorganization after stroke. Nat Rev Neurosci. 2017;18(5):267–80.
9. Veerbeek JM, van Wegen E, van Peppen R, van der Wees PJ, Hendriks E, Rietberg M, et al. What is the evidence for physical therapy poststroke? A systematic review and meta-analysis. PLoS ONE. 2014;9(2): e87987.
10. van de Port IG, Kwakkel G, Schepers VP, Lindeman E. Predicting mobility outcome one year after stroke: a prospective cohort study. J Rehabil Med. 2006;38(4):218–23.
11. Koch G, Bonnì S, Casula EP, Iosa M, Paolucci S, Pellicciari MC, et al. Effect of cerebellar stimulation on gait and balance recovery in patients with hemiparetic stroke: a randomized clinical trial. JAMA Neurol. 2019;76(2):170–8.
12. Calvo-Lobo C, Useros-Olmo AI, Almazán-Polo J, Martín-Sevilla M, Romero-Morales C, Sanz-Corbalán I, et al. Quantitative ultrasound imaging pixel analysis of the intrinsic plantar muscle tissue between hemiparesis and contralateral feet in post-stroke patients. Int J Environ Res Public Health. 2018;15(11):2519.
13. Hornby TG, Henderson CE, Plawecki A, Lucas E, Lotter J, Holthus M, et al. Contributions of stepping intensity and variability to mobility in individuals poststroke. Stroke. 2019;50(9):2492–9.
14. GBD 2016 Stroke Collaborators. Global, regional, and national burden of stroke, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2019;18(5):439–58.
15. Yavuzer G, Selles R, Sezer N, Sütbeyaz S, Bussmann JB, Köseoğlu F, et al. Mirror therapy improves hand function in subacute stroke: a randomized controlled trial. Arch Phys Med Rehabil. 2008;89(3):393–8.
16. Broderick P, Horgan F, Blake C, Ehrensberger M, Simpson D, Monaghan K. Mirror therapy for improving lower limb motor function and mobility after stroke: a systematic review and meta-analysis. Gait Posture. 2018;63:208–20.
17. Nisar H, Annamraju S, Deka SA, Horowitz A, Stipanović DM. Robotic mirror therapy for stroke rehabilitation through virtual activities of daily living. Comput Struct Biotechnol J. 2024;24:126–35.
18. Burgar CG, Lum PS, Shor PC, Machiel Van der Loos HF. Development of robots for rehabilitation therapy: the Palo Alto VA/Stanford experience. J Rehabil Res Dev. 2000;37(6):663–73.
19. Murphy TH, Corbett D. Plasticity during stroke recovery: from synapse to behaviour. Nat Rev Neurosci. 2009;10(12):861–72.
20. Sanes JN, Donoghue JP. Plasticity and primary motor cortex. Annu Rev Neurosci. 2000;23(1):393–415.
21. Bonanno L, Cannuli A, Pignolo L, Marino S, Quartarone A, Calabrò RS, et al. Neural plasticity changes induced by motor robotic rehabilitation in stroke patients: the contribution of functional neuroimaging. Bioengineering (Basel). 2023;10(8):990.
22. Wanni Arachchige PR, Ryo U, Karunarathna S, Senoo A. Evaluation of fMRI activation in hemiparetic stroke patients after rehabilitation with low-frequency repetitive transcranial magnetic stimulation and intensive occupational therapy. Int J Neurosci. 2023;133(7):705–13.
23. Tang Q, Li G, Liu T, Wang A, Feng S, Liao X, et al. Modulation of interhemispheric activation balance in motor-related areas of stroke patients with motor recovery: systematic review and meta-analysis of fMRI studies. Neurosci Biobehav Rev. 2015;57:392–400.
24. Ogawa S, Lee TM, Kay AR, Tank DW. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. Proc Natl Acad Sci U S A. 1990;87(24):9868–72.
25. Thiel A, Vahdat S. Structural and resting-state brain connectivity of motor networks after stroke. Stroke. 2015;46(1):296–301.
26. Biswal B, Yetkin FZ, Haughton VM, Hyde JS. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn Reson Med. 1995;34(4):537–41.
27. Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci. 2007;8(9):700–11.
28. Langhorne P, Coupar F, Pollock A. Motor recovery after stroke: a systematic review. Lancet Neurol. 2009;8(8):741–54.
29. French B, Thomas LH, Coupe J, McMahon NE, Connell L, Harrison J, et al. Repetitive task training for improving functional ability after stroke. Cochrane Database Syst Rev. 2016;11(11):Cd006073.
30. Wu WX, Zhou CY, Wang ZW, Chen GQ, Chen XL, Jin HM, et al. Effect of early and intensive rehabilitation after ischemic stroke on functional recovery of the lower limbs: a pilot, randomized trial. J Stroke Cerebrovasc Dis. 2020;29(5): 104649.
31. Jayaraman A, O'Brien MK, Madhavan S, Mummidisetty CK, Roth HR, Hohl K, et al. Stride management assist exoskeleton vs functional gait training in stroke: a randomized trial. Neurology. 2019;92(3):e263–73.
32. Hyun SJ, Lee J, Lee BH. The effects of sit-to-stand training combined with real-time visual feedback on strength, balance, gait ability, and quality of life in patients with stroke: a randomized controlled trial. Int J Environ Res Public Health. 2021;18(22):12229.
33. Yoshikawa K, Mizukami M, Kawamoto H, Sano A, Koseki K, Sano K, et al. Gait training with Hybrid Assistive Limb enhances the gait functions in subacute stroke patients: a pilot study. NeuroRehabilitation. 2017;40(1):87–97.
34. Zhao M, Wang G, Wang A, Cheng LJ, Lau Y. Robot-assisted distal training improves upper limb dexterity and function after stroke: a systematic review and meta-regression. Neurol Sci. 2022;43(3):1641–57.
35. Liang S, Hong ZQ, Cai Q, Gao HG, Ren YJ, Zheng HQ, et al. Effects of robot-assisted gait training on motor performance of lower limb in poststroke survivors: a systematic review with meta-analysis. Eur Rev Med Pharmacol Sci. 2024;28(3):879–98.
36. Husemann B, Müller F, Krewer C, Heller S, Koenig E. Effects of locomotion training with assistance of a robot-driven gait orthosis in hemiparetic patients after stroke: a randomized controlled pilot study. Stroke. 2007;38(2):349–54.
37. Watanabe H, Tanaka N, Inuta T, Saitou H, Yanagi H. Locomotion improvement using a hybrid assistive limb in recovery phase stroke patients: a randomized controlled pilot study. Arch Phys Med Rehabil. 2014;95(11):2006–12.
38. Nilsson A, Vreede KS, Häglund V, Kawamoto H, Sankai Y, Borg J. Gait training early after stroke with a new exoskeleton–the hybrid assistive limb: a study of safety and feasibility. J Neuroeng Rehabil. 2014;11:92.
39. Yoshimoto T, Shimizu I, Hiroi Y, Kawaki M, Sato D, Nagasawa M. Feasibility and efficacy of high-speed gait training with a voluntary driven exoskeleton robot for gait and balance dysfunction in patients with chronic stroke: nonrandomized pilot study with concurrent control. Int J Rehabil Res. 2015;38(4):338–43.
40. Bao BB, Zhu HY, Wei HF, Li J, Wang ZB, Li YH, et al. Altered intra- and inter-network brain functional connectivity in upper-limb amputees revealed through independent component analysis. Neural Regen Res. 2022;17(12):2725–9.
41. Ohura T, Hase K, Nakajima Y, Nakayama T. Validity and reliability of a performance evaluation tool based on the modified Barthel Index for stroke patients. BMC Med Res Methodol. 2017;17(1):131.
42. Rech KD, Salazar AP, Marchese RR, Schifino G, Cimolin V, Pagnussat AS. Fugl-Meyer assessment scores are related with kinematic measures in people with chronic hemiparesis after stroke. J Stroke Cerebrovasc Dis. 2020;29(1): 104463.

43. Fugl-Meyer AR, Jääskö L, Leyman I, Olsson S, Steglind S. The post-stroke hemiplegic patient. 1. A method for evaluation of physical performance. Scand J Rehabil Med. 1975;7(1):13–31.
44. Lyle RC. A performance test for assessment of upper limb function in physical rehabilitation treatment and research. Int J Rehabil Res. 1981;4(4):483–92.
45. Saygin D, Oddis CV, Moghadam-Kia S, Rockette-Wagner B, Neiman N, Koontz D, et al. Hand-held dynamometry for assessment of muscle strength in patients with inflammatory myopathies. Rheumatology (Oxford). 2021;60(5):2146–56.
46. Toigo M, Flück M, Riener R, Klamroth-Marganska V. Robot-assisted assessment of muscle strength. J Neuroeng Rehabil. 2017;14(1):103.
47. Meseguer-Henarejos AB, Sánchez-Meca J, López-Pina JA, Carles-Hernández R. Inter- and intra-rater reliability of the Modified Ashworth Scale: a systematic review and meta-analysis. Eur J Phys Rehabil Med. 2018;54(4):576–90.
48. Promjunyakul NO, Schmit BD, Schindler-Ivens SM. A novel fMRI paradigm suggests that pedaling-related brain activation is altered after stroke. Front Hum Neurosci. 2015;9:324.
49. Yang H, Jia S, Ying S, Wei W, Xialing W. A study on the minimum clinically significant difference in evaluating ischemic stroke using the modified Barthel index China Health. Statistics. 2022;2:039.
50. Cabanas-Valdés R, Bagur-Calafat C, Girabent-Farrés M, Caballero-Gómez FM, Cuchí GU. The effect of additional core stability exercises on improving dynamic sitting balance and trunk control for subacute stroke patients: a randomized controlled trial. Clin Rehabil. 2016;30(10):1024.
51. Hernan MA, Robins JM. Causal inference: what if. London: CRC Press; 2024.
52. Chesnaye NC, Stel VS, Tripepi G, Dekker FW, Fu EL, Zoccali C, Jager KJ. An introduction to inverse probability of treatment weighting in observational research. Clin Kidney J. 2022;15(1):14–20. https://doi.org/10.1093/ckj/sfab158.
53. Whitfield-Gabrieli S, Nieto-Castanon A. Conn : a functional connectivity toolbox for correlated and anticorrelated brain networks. Brain Connect. 2012;2(3):125–41.
54. Nieto-Castanon A, Whitfield-Gabrieli S. CONN functional connectivity toolbox: RRID: SCR_009550), Version 22. 2022.
55. Penny WD, Friston KJ, Ashburner JT, Kiebel SJ, Nichols TE. Statistical parametric mapping: the analysis of functional brain images. 1st ed. New York: Academic Press; 2011.
56. Nieto-Castanon A. Handbook of functional connectivity magnetic resonance imaging methods in CONN. Philadelphia: Hilbert Press; 2020.
57. Ashburner J, Friston KJ. Unified segmentation. Neuroimage. 2005;26(3):839–51.
58. Ashburner J. A fast diffeomorphic image registration algorithm. Neuroimage. 2007;38(1):95–113.
59. Friston KJ, Williams S, Howard R, Frackowiak RS, Turner R. Movement-related effects in fMRI time-series. Magn Reson Med. 1996;35(3):346–55.
60. Power JD, Mitra A, Laumann TO, Snyder AZ, Schlaggar BL, Petersen SE. Methods to detect, characterize, and remove motion artifact in resting state fMRI. Neuroimage. 2014;84:320–41.
61. Hallquist MN, Hwang K, Luna B. The nuisance of nuisance regression: spectral misspecification in a common approach to resting-state fMRI preprocessing reintroduces noise and obscures functional connectivity. Neuroimage. 2013;82:208–25.
62. Saad ZS, Reynolds RC, Jo HJ, Gotts SJ, Chen G, Martin A, et al. Correcting brain-wide correlation differences in resting-state FMRI. Brain Connect. 2013;3(4):339–52.
63. Schaefer A, Kong R, Gordon EM, Laumann TO, Zuo XN, Holmes AJ, et al. Local-global parcellation of the human cerebral cortex from intrinsic functional connectivity MRI. Cereb Cortex. 2018;28(9):3095–114.
64. Jafri MJ, Pearlson GD, Stevens M, Calhoun VD. A method for functional network connectivity among spatially independent resting-state components in schizophrenia. Neuroimage. 2008;39(4):1666–81.
65. Page J, Fulk S, Boyne GD. Clinically important differences for the upper-extremity Fugl-meyer scale in people with minimal to moderate impairment due to chronic stroke. Phys Ther. 2012;10:21.
66. Nordin A, Alt Murphy M, Danielsson A. Intra-rater and inter-rater reliability at the item level of the action research arm test for patients with stroke. J Rehabil Med. 2014;46(8):738–45.
67. Lee D, Lee G. Effect of afferent electrical stimulation with mirror therapy on motor function, balance, and gait in chronic stroke survivors: a randomized controlled trial. Eur J Phys Rehabil Med. 2019;55(4):442–9.
68. Liao WW, Wu CY, Hsieh YW, Lin KC, Chang WY. Effects of robot-assisted upper limb rehabilitation on daily function and real-world arm activity in patients with chronic stroke: a randomized controlled trial. Clin Rehabil. 2012;26(2):111.
69. Wu C, Yang C, Chuang L, Lin K, Chen H, Chen M, et al. Effect of therapist-based versus robot-assisted bilateral arm training on motor control, functional performance, and quality of life after chronic stroke: a clinical trial. Phys Ther. 2012;8:1006–16.
70. Hsu HY, Chiu HY, Kuan TS, Tsai CL, Su FC, Kuo LC. Robotic-assisted therapy with bilateral practice improves task and motor performance in the upper extremities of chronic stroke patients: a randomised controlled trial. Aust Occup Ther J. 2019;66(5):637–47.
71. Bohannon RW. Muscle strength and muscle training after stroke. J Rehabil Med. 2006;39(1):14–20.
72. Cramp MC, Greenwood RJ, Gill M, et al. Low intensity strength training for ambulatory stroke patients. Disabil Rehabil. 2006;28(13–14):883–9.
73. Pak S, Patten C. Strengthening to promote functional recovery poststroke: an evidence-based review. Top Stroke Rehabil. 2008;15(3):177–99.
74. Maria KC, Eng JJ. The relationship of lower-extremity muscle torque to locomotor performance in people with stroke. Phys Ther. 2003;83(1):49–57.
75. Flansbjer UB, Miller M, Downham D, Lexell J. Progressive resistance training after stroke: effects on muscle strength, muscle tone, gait performance and perceived participation. J Rehabil Med. 2008;40(1):42–8.
76. Mehta S, Pereira S, Viana R, Mays R, McIntyre A, Janzen S, et al. Resistance training for gait speed and total distance walked during the chronic stage of stroke: a meta-analysis. Top Stroke Rehabil. 2012;19(6):471–8.
77. Aprile I, Conte C, Cruciani A, Pecchioli C, Castelli L, Insalaco S, et al. Efficacy of robot-assisted gait training combined with robotic balance training in subacute stroke patients: a randomized clinical trial. J Clin Med. 2022;11(17):5162.
78. Kayser C. Integration of touch and sound in auditory cortex. Neuron. 2005;48(2):373–84.
79. Thaut MH, Kenyon GP. The connection between rhythmicity and brain function. Eng Med Biol Mag IEEE. 1999;18(2):101–8.
80. Wall JC, Turnbull GI. Gait asymmetries in residual hemiplegia. Arch Phys Med Rehabil. 1986;67(8):550–3.
81. Meng G, Ma X, Chen P, Xu S, Li M, Zhao Y, et al. Effect of early integrated robot-assisted gait training on motor and balance in patients with acute ischemic stroke: a single-blinded randomized controlled trial. Ther Adv Neurol Disord. 2022;15:17562864221123196.
82. English C, Mclennan H, Thoirs K, Coates A, Bernhardt J. Loss of skeletal muscle mass after stroke: a systematic review. Int J Stroke. 2010;5(5):395.
83. Hunnicutt JL, Gregory CM. Skeletal muscle changes following stroke: a systematic review and comparison to healthy individuals. Top Stroke Rehabil. 2017;24(6):1–9.
84. Cho JE, Yoo JS, Kim KE, Cho ST, Jang WS, Cho KH, et al. Systematic review of appropriate robotic intervention for gait function in subacute stroke patients. Biomed Res Int. 2018;2018:4085298.
85. Li Y, Fan T, Qi Q, Wang J, Qiu H, Zhang L, et al. Efficacy of a novel exoskeletal robot for locomotor rehabilitation in stroke patients: a multi-center, non-inferiority. Randomized controlled trial. Front Aging Neurosci. 2021;13: 706569.
86. Rodríguez-Fernández A, Lobo-Prat J, Font-Llagunes JM. Systematic review on wearable lower-limb exoskeletons for gait training in neuromuscular impairments. J Neuroeng Rehabil. 2021;18(1):22.
87. Louie DR, Mortenson WB, Durocher M, Schneeberg A, Teasell R, Yao J, et al. Efficacy of an exoskeleton-based physical therapy program for non-ambulatory patients during subacute stroke rehabilitation: a randomized controlled trial. J Neuroeng Rehabil. 2021;18(1):149.
88. Mehrholz J, Pollock A, Pohl M, Kugler J, Elsner B. Systematic review with network meta-analysis of randomized controlled trials of

robotic-assisted arm training for improving activities of daily living and upper limb function after stroke. J Neuroeng Rehabil. 2020;17(1):83.
89. Chen ZJ, He C, Guo F, Xiong CH, Huang XL. Exoskeleton-assisted anthropomorphic movement training (EAMT) for poststroke upper limb rehabilitation: a pilot randomized controlled trial. Arch Phys Med Rehabil. 2021;102(11):2074–82.
90. Frisoli A, Barsotti M, Sotgiu E, Lamola G, Procopio C, Chisari C. A randomized clinical control study on the efficacy of three-dimensional upper limb robotic exoskeleton training in chronic stroke. J Neuroeng Rehabil. 2022;19(1):14.
91. Pandian S, Arya KN, Kumar D. Minimal clinically important difference of the lower-extremity fugl-meyer assessment in chronic-stroke. Top Stroke Rehabil. 2016;23(4):233–9. https://doi.org/10.1179/1945511915Y.0000000003.
92. Zhai X, Wu Q, Li X, Xu Q, Zhang Y, Fan S, et al. Effects of robot-aided rehabilitation on the ankle joint properties and balance function in stroke survivors: a randomized controlled trial. Front Neurol. 2021;12: 719305.
93. Lee SH, Lee HJ, Kim K, Lee BH, Kim YH. Effect of exercise using an exoskeletal hip-assist robot on physical function and walking efficiency in older adults. J Pers Med. 2022;12(12):2077.
94. Wang LE, Tittgemeyer M, Imperati D, Diekhoff S, Ameli M, Fink GR, et al. Degeneration of corpus callosum and recovery of motor function after stroke: a multimodal magnetic resonance imaging study. Hum Brain Mapp. 2012;33(12):2941–56.
95. Chen JL, Schlaug G. Resting state interhemispheric motor connectivity and white matter integrity correlate with motor impairment in chronic stroke. Front Neurol. 2013;4:178.
96. Park CH, Chang WH, Ohn SH, Kim ST, Bang OY, Pascual-Leone A, et al. Longitudinal changes of resting-state functional connectivity during motor recovery after stroke. Stroke. 2011;42(5):1357–62.
97. Wang L, Yu C, Chen H, et al. Dynamic functional reorganization of the motor execution network after stroke. Brain. 2010;133(4):1224–38.
98. Lin LY, Lenny R, Metcalf NV, Jennifer R, Shulman GL, Shimony JS, et al. Stronger prediction of motor recovery and outcome post-stroke by cortico-spinal tract integrity than functional connectivity. PLoS ONE. 2018;13(8): e0202504.
99. Lu Q, Huang G, Chen L, et al. Structural and functional reorganization following unilateral internal capsule infarction contribute to neurological function recovery. Neuroradiology. 2019;61(10):1181–90.
100. Vahdat S, Darainy M, Milner TE, Ostry DJ. Functionally specific changes in resting-state sensorimotor networks after motor learning. J Neurosci. 2011;31(47):16907–15.
101. Guerra-Carrillo B, Mackey AP, Bunge SA. Resting-state fMRI: a window into human brain plasticity. Neuroscientist. 2014;20(5):522–33.
102. Fan YT, Wu CY, Liu HL, Lin KC, Wai YY, Chen YL. Neuroplastic changes in resting-state functional connectivity after stroke rehabilitation. Front Hum Neurosci. 2015;9:546.
103. Biasiucci A, Leeb R, Iturrate I, Perdikis S, Al-Khodairy A, Corbet T, et al. Brain-actuated functional electrical stimulation elicits lasting arm motor recovery after stroke. Nat Commun. 2018;9(1):2421.
104. Sinha AM, Nair VA, Prabhakaran V. Brain-computer interface training with functional electrical stimulation: facilitating changes in interhemispheric functional connectivity and motor outcomes post-stroke. Front Neurosci. 2021;15: 670953.
105. Kemlin C, Moulton E, Lamy JC, Houot M, Valabregue R, Leder S, Obadia MA, Meseguer E, Yger M, Brochard V, Corvol JC, Samson Y, Rosso C. Elucidating the structural and functional correlates of upper-limb poststroke motor impairment. Stroke. 2019;50(12):3647–9. https://doi.org/10.1161/STROKEAHA.119.027126.
106. Wan X, Chan DNS, Chau JPC, Zhang Y, Liao Y, Zhu P, Choi KC. Effects of a nurse-led peer support intervention on psychosocial outcomes of stroke survivors: a randomised controlled trial. Int J Nurs Stud. 2024;160: 104892. https://doi.org/10.1016/j.ijnurstu.2024.104892.
107. Fu V, Thompson S, Kayes N, Bright F. Supporting long-term meaningful outcomes in stroke rehabilitation. Curr Neurol Neurosci Rep. 2025;25(1):17. https://doi.org/10.1007/s11910-025-01403-z.
108. Aguirre-Ollinger G, Chua KSG, Ong PL, Kuah CWK, Plunkett TK, Ng CY, Khin LW, Goh KH, Chong WB, Low JAM, Mushtaq M, Samkharadze T, Kager S, Cheng HJ, Hussain A. Telerehabilitation using a 2-D planar arm rehabilitation robot for hemiparetic stroke: a feasibility study of clinic-to-home exergaming therapy. J Neuroeng Rehabil. 2024;21(1):207. https://doi.org/10.1186/s12984-024-01496-6.
109. Li Y, Fan T, Qi Q, Wang J, Qiu H, Zhang L, Wu X, Ye J, Chen G, Long J, Wang Y, Huang G, Li J. Efficacy of a novel exoskeletal robot for locomotor rehabilitation in stroke patients: a multi-center, non-inferiority, randomized controlled trial. Front Aging Neurosci. 2021;23(13): 706569. https://doi.org/10.3389/fnagi.2021.706569.
110. Pinto D, Garnier M, Barbas J, Chang SH, Charlifue S, Field-Fote E, Furbish C, Tefertiller C, Mummidisetty CK, Taylor H, Jayaraman A, Heinemann AW. Budget impact analysis of robotic exoskeleton use for locomotor training following spinal cord injury in four SCI Model Systems. J Neuroeng Rehabil. 2020;17(1):4. https://doi.org/10.1186/s12984-019-0639-0.
111. Huo CC, Zheng Y, Lu WW, Zhang TY, Wang DF, Xu DS, Li ZY. Prospects for intelligent rehabilitation techniques to treat motor dysfunction. Neural Regen Res. 2021;16(2):264–9. https://doi.org/10.4103/1673-5374.290884.
112. Wagner TH, Lo AC, Peduzzi P, Bravata DM, Huang GD, Krebs HI, Ringer RJ, Federman DG, Richards LG, Haselkorn JK, Wittenberg GF, Volpe BT, Bever CT, Duncan PW, Siroka A, Guarino PD. An economic analysis of robot-assisted therapy for long-term upper-limb impairment after stroke. Stroke. 2011;42(9):2630–2. https://doi.org/10.1161/STROKEAHA.110.606442.

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