Huo et al. Journal of NeuroEngineering and Rehabilitation (2024) 21:213
https://doi.org/10.1186/s12984-024-01493-9

Journal of NeuroEngineering and Rehabilitation

RESEARCH **Open Access**

Effectiveness of unilateral lower-limb exoskeleton robot on balance and gait recovery and neuroplasticity in patients with subacute stroke: a randomized controlled trial

Congcong Huo[1,3], Guangjian Shao[1], Tiandi Chen[1], Wenhao Li[2], Jue Wang[1,3], Hui Xie[1,3], Yan Wang[4], Zengyong Li[1,3*], Pengyuan Zheng[5], Liguo Li[6] and Luya Li[5]

Abstract

Background Impaired balance and gait in stroke survivors are associated with decreased functional independence. This study aimed to evaluate the effectiveness of unilateral lower-limb exoskeleton robot-assisted overground gait training compared with conventional treatment and to explore the relationship between neuroplastic changes and motor function recovery in subacute stroke patients.

Methods In this randomized, single-blind clinical trial, 40 patients with subacute stroke were recruited and randomly assigned to either a robot-assisted training (RT) group or a conventional training (CT) group. All outcome measures were assessed at the enrollment baseline (T0), 2nd week (T1) and 4th week (T2) of the treatment. The primary outcome was the between-group difference in the change in the Berg balance scale (BBS) score from baseline to T2. The secondary measures included longitudinal changes in the Fugl-Meyer assessment of the lower limb (FMA-LE), modified Barthel index (mBI), functional ambulation category (FAC), and locomotion assessment with gait analysis. In addition, the cortical activation pattern related to robot-assisted training was measured before and after intervention via functional near-infrared spectroscopy.

Results A total of 30 patients with complete data were included in this study. Clinical outcomes improved after 4 weeks of training in both groups, with significantly better BBS ($F = 6.341$, $p = 0.018$, partial $\eta 2 = 0.185$), FMA-LE ($F = 5.979$, $p = 0.021$, partial $\eta 2 = 0.176$), FAC ($F = 7.692$, $p = 0.010$, partial $\eta 2 = 0.216$), and mBI scores ($F = 7.255$, $p = 0.042$, partial $\eta 2 = 0.140$) in the RT group than in the CT group. Both groups showed significant improvement in gait speed and stride cadence on the locomotion assessment. Only the RT group presented a significantly increased stride length ($F = 4.913$, $p = 0.015$, partial $\eta 2 = 0.267$), support phase ($F = 5.335$, $p = 0.011$, partial $\eta 2 = 0.283$), and toe-off angle ($F = 3.829$, $p = 0.035$, partial $\eta 2 = 0.228$) on the affected side after the intervention. The RT group also showed increased

*Correspondence:
Zengyong Li
zyongli@sdu.edu.cn
Full list of author information is available at the end of the article

neural activity response over the ipsilesional motor area and bilateral prefrontal cortex during robot-assisted weight-shift and gait training following 4 weeks of treatment.

Conclusions Overground gait training with a unilateral exoskeleton robot showed improvements in balance and gait functions, resulting in better gait patterns and increased gait stability for stroke patients. The increased cortical response related to the ipsilesional motor areas and their related functional network is crucial in the rehabilitation of lower limb gait in post-stroke patients.

Keywords Unilateral lower-limb exoskeleton robot, Stroke, Gait rehabilitation, Neuroplasticity

Introduction

Stroke is commonly associated with motor dysfunction of the lower extremities, manifested as decreased muscle strength, impaired balance, and abnormal gait. Despite professional rehabilitation attempts, 20–30% of patients still experience difficulties or loss of the ability to walk [1]. Three months after stroke, 85% of patients still have great potential to improve their walking ability, which is strongly correlated with quality of life of stroke survivors [2]. Consequently, improving walking ability is the primary focus of lower-limb rehabilitation for stroke patients.

Specific, repetitive, and high-intensity motor training is a key element in inducing functional neuroplasticity related to stroke motor rehabilitation within the 6-month post-stroke window [3, 4]. Thus, implementing gait training for stroke patients at an early stage is critical for the restoration of lower-limb function. However, traditional physical therapies are limited in providing long-term, high-quality gait training due to decreased muscle strength in early stroke patients. Robotic exoskeleton training is a promising way to deliver repetitive walking training assisted by mechanical legs, promoting the walking, balance, and daily living abilities of stroke patients [5, 6]. Achieving positive effects in gait training necessitates repetitive natural walking on the ground along with accurate proprioception and external sensory feedback [7]. Wearable robots possess the advantage of portability, enabling treatments to be performed in real-world scenarios, which have been widely applied to improve walking efficiency and enhance mobility in stroke patients [8–11]. Currently, robots for overground gait training mainly target chronic stroke survivors, with limited application in the subacute patients due to early muscle weakness. Based on the early-stage gait rehabilitation needs, the unilateral lower-limb exoskeleton robot is designed to support overground walking in real environments with active engagement of stroke patients with hemiplegia. However, there is scant evidence to support the effectiveness of overground gait training with a unilateral lower-limb exoskeleton robot for stroke patients in the literature.

Furthermore, restoring motor ability poststroke relies on brain functional reorganization. Assessment of cortical activation related to a specific task is essential for a better understanding of neural motor control. Currently, limited information is available on the cerebral mechanisms underlying locomotor recovery after stroke due to technical limitations in assessing cerebral activation during movement, particularly walking tasks. Recently, functional near-infrared spectroscopy (fNIRS) has gained attraction as a novel neuroimaging technology in stroke rehabilitation. Its low cost, portability, noninvasiveness, and motion tolerance make it a suitable for studying gait disturbances induced by stroke [12, 13]. Research has shown a bilateral increase in oxygenated hemoglobin (Δ [oxy-Hb]) in the sensorimotor cortex (SMC) and supplementary motor area (SMA) in stroke patients during gait training [14]. Additionally, increased activation in the SMC, SMA, and premotor cortex (PMC) was detected in healthy participants during exoskeleton robot walking in contrast to treadmill walking or stepping [15]. However, the effects of long-term robot-assisted overground gait training on neuroplastic reorganization have not been adequately studied in subacute patients.

This study aimed to compare the effectiveness of robot-assisted overground gait training and conventional training for the lower-limb rehabilitation of stroke patients with hemiplegia. Wearable gait analyzers combined with clinical assessment scales, including the Berg balance scale (BBS), Fugl Meyer assessment for lower extremity (FMA-LE), functional ambulation category (FAC), and modified Barthel index (mBI), were used to evaluate the motor function of the patients before and after 4 weeks of training. It was hypothesized that compared with conventional training (CT), robot-assisted training (RT) would have superior effects on both clinical outcomes and gait balance. Additionally, fNIRS was employed to monitor the cortical activation response of the patients during robot-assisted training. It was expected that the activation of ipsilesional motor-related cortices would increase following motor recovery of the lower limb. The results of this study will be used to explore the relationship between neuroplasticity and lower-limb motor recovery, thereby providing a theoretical basis for the clinical application of robot-assisted lower-limb rehabilitation.

Methods

Study population

A randomized, single-blind controlled trial was designed in this study. Among the 50 eligible patients assessed, 40 right-handed patients were recruited between March 2023 and November 2023 at the Affiliated Rehabilitation Hospital of National Research Center for Rehabilitation Technical Aids. Inclusion criteria included (1) hemiparesis due to first-ever unilateral supratentorial stroke; (2) post stroke within 6 months; (3) residual gait and balance impairment; (4) aged 18–75 years. Exclusion criteria were (1) severe general impairment or concomitant diseases; (2) arthritis, limited range of motion of joints and other severe restrictions on walking; (3) severe cognitive impairment or unable to understand and follow instruction. All participants gave written informed consent prior to their enrollments. After enrolment, the baseline characteristics of the patients were assessed (Table 1),

Table 1 Patient demographic and clinical information

Patient No./Sex/Age, y	Group	Stroke information		Functional assessment				
		Affected hemisphere	Time from stroke (d)	MMSE	NIHSS	FMA-LE	FAC	BBS
1/M/48	RT	R	65	29	4	20	2	27
2/M/74	RT	R	57	26	8	17	2	14
3/F/60	RT	L	146	27	5	16	2	18
4/M/54	RT	L	88	29	6	22	1	24
5/M/74	RT	R	65	26	5	19	3	26
6/M/54	RT	L	101	29	5	23	2	39
7/F/62	RT	L	35	26	4	26	2	34
8/F/62	RT	L	51	26	4	28	3	42
9/M/48	RT	R	50	29	6	17	0	5
10/M/57	RT	L	6	30	0	26	4	39
11/M/30	RT	R	64	30	4	21	1	10
12/M/70	RT	L	36	27	6	14	0	18
13/F/59	RT	R	74	28	8	10	1	10
14/M/59	RT	L	115	29	0	28	5	50
15/M/62	RT	L	61	23	2	19	1	23
16/M/55	RT	L	16	27	4	19	2	36
17/M/31	RT	R	114	30	3	24	1	18
18/M/69	RT	L	56	27	5	15	0	15
19/M/28	RT	R	149	27	9	12	0	1
20/M/38	RT	R	165	27	7	20	1	10
21/M/67	CT	L	94	27	5	14	1	23
22/F/53	CT	R	75	30	9	9	0	9
23/M/67	CT	L	57	27	8	13	0	12
24/F/53	CT	R	118	30	6	20	1	18
25/M/66	CT	L	50	28	3	16	1	15
26/F/62	CT	R	77	30	0	26	4	45
27/M/60	CT	R	84	30	9	9	1	6
28/F/53	CT	R	118	30	6	20	1	18
29/M/45	CT	L	63	30	5	17	4	43
30/F/59	CT	R	46	28	9	8	0	0
31/M/67	CT	L	115	27	3	19	1	25
32/M/66	CT	L	87	28	2	18	2	38
33/M/51	CT	R	37	20	9	8	0	1
34/M/35	CT	L	25	29	3	22	4	46
35/M/32	CT	L	20	29	0	25	4	46
36/M/48	CT	R	118	29	4	28	3	41
37/F/49	CT	L	158	21	3	18	1	26
38/M/52	CT	R	58	25	2	17	2	37
39/M/66	CT	R	77	27	2	19	2	38
40/M/51	CT	L	47	24	8	9	0	1

Note M: male; F: female; RT: robot-assisted training; CT: conventional training; AH: affected hemisphere; d: day; MMSE: Minimum Mental State Examination; NIHSS: National Institute of Health Stroke Scale; FMA-LE: Fugl-Meyer assessment of the lower limb; FAC: functional ambulation category; BBS: Berg balance scale including age, gender, duration from onset, lesion type and location, side of hemiparesis, Minimum Mental State Examination (MMSE), National Institutes of Health Stroke Scale (NIHSS), and motor assessments (FMA-LE, FAC, BBS). This study was approved by the Medical Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University ([2021]02-333-01) in accordance with the declaration of Helsinki. It was registered in the China Clinical Trial Registration Center (Trial registration number: ChiCTR2400081076).

Study design and treatments

Power analyses and a priori sample size estimation were conducted using G*Power (v3.1.9.2; Franz Faul, University of Kiel, Kiel, Germany). Repeated-measures mixed analysis of variance test was applied in this pilot study. An effect size of 0.25, a significance level (α) of 0.05, and a statistical power of (1 - β) 0.80 were used, indicating a minimum of 28 patients. Assuming a dropout rate of 25% and the fact that we had two groups (RT and CT), at least 18 patients per group were required. Enrolled patients were randomly allocated to RT and CT groups using a computer-generated sealed envelope method without any adjustment factors. Patients in both groups were provided with the conventional rehabilitative intervention for 5 days a week. The therapist in charge tailored therapies to each patient, which included passive joint activity, muscle strength, stretching, active control, transfer and balance function, and walking training. Patients in the CT group received rehabilitation training to improve lower-limb walking function, with each session lasting 30 min and occurring twice daily, 5 days a week, for a period of 4 weeks. The RT group received robot-assisted overground gait training for 30 min/day, 5 times a week, for 4 weeks, for a total of 20 sessions. The patients were longitudinally assessed before intervention (pretreatment, T0), 2 weeks after intervention (T1), and 4 weeks after intervention (T2), as shown in Fig. 1A.

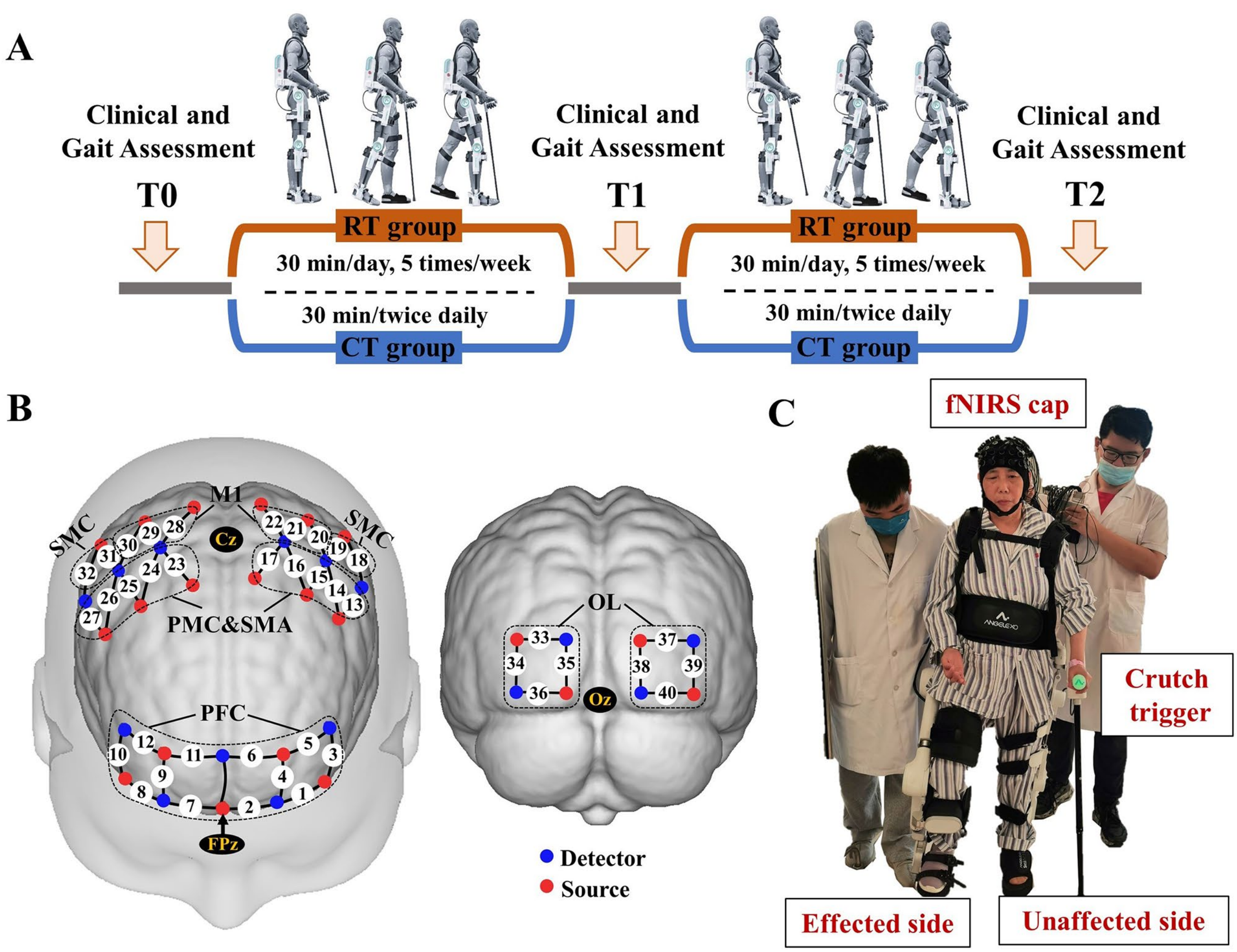

Fig. 1 Schematic of the experimental design. (**A**) Experimental design. (**B**) fNIRS optode probe set. The fNIRS system consists of 21 light sources (shown in red) and 15 detectors (shown in blue), resulting in a total of 40 channels distributed over prefrontal, motor and occipital area in accordance with the international 10–20 system. (**C**) fNIRS measurement during robot-assisted overground gait training

The robot-assisted gait training was performed using the unilateral lower-limb exoskeleton robot system (LiteStepper®, manufactured by Angelexo Scientific Co., Ltd, China). The system host backpack is attached to the patient's trunk to keep the two modules in place on the unaffected and affected lower limbs. The module attached to the affected side is a powered exoskeleton with an inner hip joint and a knee joint. Another module on the unaffected side is equipped with angle and torque sensors at the hip and knee joints to collect gait information of the healthy lower limb during voluntary movement. Furthermore, the healthy side is outfitted with a foot sole pressure sensor array and an assistive elbow crutch, which is equipped with a pressure sensor at the lower end and a trigger button on the handle. By activating the trigger button on the crutch handle, movement on the affected side with the exoskeleton can be initiated. Additionally, the assistive elbow crutch plays a crucial role in stabilizing body balance. By analyzing and learning gait characteristics and shoe pressure feedback information from the healthy side, the paralyzed lower limb receives targeted assistance from the powered exoskeleton to perform coordinated movements with the unaffected side, thereby enabling individualized rehabilitation training for patients. This feature assists the affected lower limb in performing essential movements, including hip joint adduction, abduction, extension, and flexion; knee joint extension and flexion; and ankle joint plantar flexion and dorsiflexion, even if the paralyzed side does not move at all. During gait training, a physical therapist was available to provide guidance and necessary assistance as needed.

Study outcomes

For efficacy analyses, the primary clinical outcomes were changes in the BBS score for the functional assessment of balance and gait at T1 and T2 from T0, respectively. The secondary outcomes were the changes in FMA-LE, mBI, FAC, and gait parameters assessed with gait analysis at T1 and T2 from T0. Canes or orthoses were permissible for patients during FAC evaluation.

Gait analysis

Locomotion assessment was performed with gait analysis using the intelligent wearable gait analysis system (JiBuEn, manufactured by Qianhan Technology Co., Ltd, China) [16]. All patients were instructed to perform the instrumented stand and walk test at self-preferred speed while wearing comfortable shoes, with the gait data being transmitted to a computer server at a rate of 20 Hz. The spatiotemporal gait parameters, including the total number of steps, speed, stride length, stride time, cadence, swing percentage, foot strike angle, and toe-off angle, were collected. Assessments were conducted by a trained therapist who was not responsible for treatment and was blinded to the group allocation of the patients.

fNIRS data acquisition and cortical activity analyses

For the RT group, the intervention-related cortical activation responses were evaluated using fNIRS at T0, T1, and T2 in the robot-assisted intervention sessions. Concentration changes in oxy-Hb were measured by a multichannel continuous-wave fNIRS device (Nirsmart, manufactured by Danyang Huichuang Medical Equipment Co., Ltd., China) at 10 Hz. The optodes were positioned in customized caps, resulting in 40 separate channels with an interoptode distance of 30 mm (Fig. 1B). Cz was determined according to the 10–20 electrode system relative to the nasion, inion, left preauricular point, and right preauricular point. Statistical parametric mapping NIRS-SPM software was used for spatial registration of the acquired fNIRS channels on the Montreal Neurological Institute brain. The motor-related regions of interest (ROIs), including the bilateral prefrontal cortex (PFC), primary cortex (M1), SMC, PMC and SMA (PMC&SMA), and occipital lobe (OL), were covered by fNIRS channels. The fNIRS experiment included three sessions: resting state, robot-assisted weight-shift training and gait training, each lasting for 6 min. Robot-assisted weight-shift training consists of standing with the feet apart and executing a center of gravity transfer motion between the affected and unaffected sides, sustaining the center of gravity on either side for a period of 3 s. Robot-assisted gait training involves overground walking along a walkway at a self-selected gait speed.

The analysis was conducted for longitudinal data collected from patients in the RT group at T0, T1 and T2. As patients with both right- and left-sided lesions were included, all fNIRS data from patients with a left-sided lesion were flipped horizontally before data analysis, so the affected hemisphere formed the right side of the image. For data preprocessing, the absorbance signals recorded by fNIRS were first bandpass filtered at 0.0095–2 Hz with a Butterworth filter to decrease the uncorrelated noise components and low-frequency baseline drift. The filtered signals were then converted to Δ[oxy-Hb] concentrations using the modified Beer-Lambert law [17]. The Δ[oxy-Hb] data were subsequently visually inspected and preprocessed by calculating the coefficient of variation ($CV = \sigma/\mu \times 100\%$, where μ is the signal mean and σ is the signal standard deviation) to estimate the signal-to-noise ratio of the channel data. This step was taken to ensure the quality of the data and to identify any channels with high levels of noise or artifacts. Any channels with a CV greater than 15% were excluded from further analysis. If more than one-third of the channels in a dataset were classified as bad quality, the individual's data was excluded. In this study, four participants with excessive motion artifacts in RT group were excluded from subsequent analyses. Subsequently, principal and independent component analyses were applied to diminish physiological interferences, which encompass cardiac pulsations, respiratory signals, and fluctuations in blood pressure [18–20]. The Δ[oxy-Hb] concentrations were further corrected for motion artifacts and obvious outliers by moving standard deviation and cubic spline interpolation along with the moving average method [21, 22]. Finally, based on spectral information, a prominent low-frequency (0.01 to 0.08 Hz) signal reflecting the functional hemodynamic response in the brain was identified as the component of interest [23].

The spectral wavelet amplitude (WA) based on the Morlet wavelet was extracted for the frequency interval 0.01–0.08 Hz and averaged over a time window to describe cortical activation. Additionally, to examine the interhemispheric balance of the cortical response, the lateralization index (LI) was calculated for each condition with the definition LI = (WA_{ipsi} - WA_{contra}) / (WA_{ipsi} + WA_{contra}). WA_{ipsi} and WA_{contra} denote the WA index values of the ipsilesional and contralesional sides, respectively. The LI value varies from −1 to 1, with −1 indicating only contralesional activation and 1 signifying only ipsilesional activation.

Statistical analysis

The Kolmogorov-Smirnov test was used to confirm that all variables were normally distributed. The baseline differences of all variables between the RT and CT groups were analyzed using the independent *t*-test or the χ^2 test. Clinical scales (BBS, FAC, FMA-LE, and mBI) were separately analyzed with a repeated-measures mixed analysis of variance (RM-ANOVA) through a between-individual factor of "group" (RT and CT) and a within-individual factor of "time" (T0, T1, and T2). Gait analyses of step length, step width, speed, stance, and swing percentages for the affected and unaffected legs were also performed separately by RM-ANOVA. The results are expressed as the means ± standard deviations. The *p* values were corrected for sphericity using the Greenhouse–Geisser correction, when necessary. When a significant interaction term was observed, within-group post hoc t tests were conducted to compare T1 vs. T0 and T2 vs. T0.

The one-sample t-test was used to test the significant cortical activation response to specific training sessions at T0, T1, and T2. *p* values lower than 0.05 (false discovery rate, FDR, corrected for multiple comparisons) were considered significant. Paired *t* tests were used to compare pre-test and post-test cortical activity variables in the RT group. For the channels revealed to be significant, a Pearson correlation analysis was performed between cortical activation changes and clinical improvement in lower-limb function, taking into account age, sex, and stroke time as covariates. *P*-values lower than 0.05 were significant.

Results

Study population

No adverse effects were reported. Two participants from both the RT and CT groups withdrew due to discharge. Two participants were excluded from CT group due to gait data disconnection. Four participants from RT group were excluded from the fNIRS data analysis due to excessive artifacts. A total of 30 patients ($n=14$ for the RT group and $n=16$ for the CT group) were included in the data analyses (Fig. 2). The RT and CT groups did not differ at baseline in age, sex, time since stroke, severity of stroke assessed by the NIHSS, and motor and balance functions assessed by the BBS, FMA-LE, and FAC (Table 2).

Primary outcome measure

The clinical measures for balance, gait, lower limb motor function, and activities of daily living are summarized in Fig. 3; Table 3. For primary outcome measure, RM-ANOVA revealed a significant effect of time ($F=47.025$, $p<0.001$, partial $\eta2=0.627$), with a significant group × time interaction ($F=10.874$, $p=0.001$, partial $\eta2=0.280$) for the BBS with the Greenhouse-Geisser correction. Within-group post hoc analysis revealed a significant increase in BBS between baseline and T1 ($p<0.001$, 95% CI: 7.083 − 13.917) and between baseline and T2 ($p<0.001$, 95% CI: 11.286 − 19.856) in the RT group. There was also a significant increase in the BBS score between baseline and T1 ($p=0.043$, 95% CI: 0.116 − 6.509) and between baseline and T2 ($p=0.008$, 95% CI: 1.554 − 9.571) in the CT group. Moreover, post hoc t tests revealed a significant difference between the RT and CT groups at T2 post-intervention, with higher BBS scores in the RT group ($p=0.018$, partial $\eta2=0.185$, 95% CI: 2.110 − 20.515).

Secondary outcome measures

Compared with those at baseline, motor function and daily living significantly improved post-intervention, per RM-ANOVA results. The analysis revealed a significant effect of time ($F=44.060$, $p<0.001$, partial $\eta2=0.611$), as well as a significant group × time interaction ($F=10.813$, $p<0.001$, partial $\eta2=0.279$) for the FAC with the Greenhouse-Geisser correction. Within-group post hoc analysis revealed that FAC significantly increased from baseline to T1 ($p<0.001$, 95% CI: 0.530 − 1.041) and T2 ($p<0.001$, 95% CI: 1.049 − 1.808) in the RT group. Post hoc t tests revealed that FAC scores were significantly greater in the RT group than in the CT group

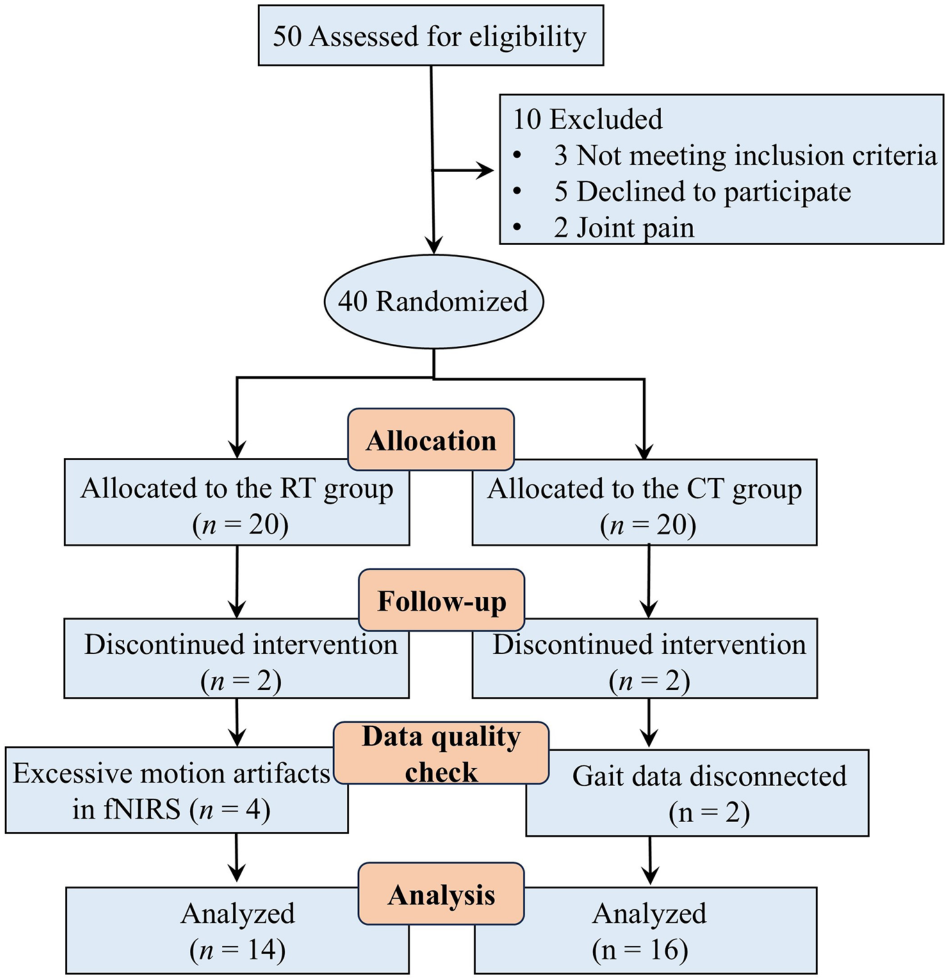

Fig. 2 Flow diagram of the study

Table 2 Comparison of the baseline characteristics of the study participants

Parameters*	RT (*n* = 14)	CT (*n* = 16)	Statistics	*p*
Gender (male/female)	10/4	11/5	χ^2=0.873	0.596
Age	57.93 ± 11.47	55.25 ± 11.16	T = 0.646	0.524
Post-stroke time (day)	68.07 ± 35.67	74.00 ± 33.29	T =-0.468	0.643
Type (haemorrhage/infarct)	6/8	3/13	χ^2=2.000	0.157
MMSE	22.93 ± 1.54	27.94 ± 3.64	T =-0.009	0.993
NIHSS	4.64 ± 2.37	5.06 ± 3.13	T =-0.417	0.680
BBS	25.43 ± 13.75	24.12 ± 16.75	T = 0.234	0.817
FMA-LE	20.50 ± 5.42	17.00 ± 6.48	T = 1.611	0.118
FAC	2.00 ± 1.41	1.68 ± 1.58	T = 0.572	0.572

Note RT: robot-assisted training, CT: conventional training. MMSE: Minimum Mental State Examination; NIHSS: National Institute of Health stroke scale; FMA-LE: Fugl-Meyer assessment scale of lower-limb; FAC: functional ambulation category; BBS: Berg balance scale

at T2 post-intervention (p=0.010, partial η2=0.216, 95% CI: 0.324 − 2.158). RM-ANOVA revealed significant main effects of time for FMA-LE (F=43.875, p<0.001, partial η2=0.610) and mBI (F=45.867, p<0.001, partial η2=0.621), as well as a significant main effect of group for FMA-LE (F=4.397, p=0.045, partial η2=0.136), with the Greenhouse-Geisser correction. Post hoc t tests revealed significant between-group differences at T2 post-intervention, showing FMA-LE (p=0.021, partial η2=0.176, 95% CI: 0.764 − 8.647) and mBI (p=0.042, partial η2=0.140, 95% CI: 0.629 − 30.353) scores significantly higher in the RT group than in the CT group.

Table 4 shows gait parameters for the RT and CT groups at T0, T1, and T2. RM-ANCOVA revealed

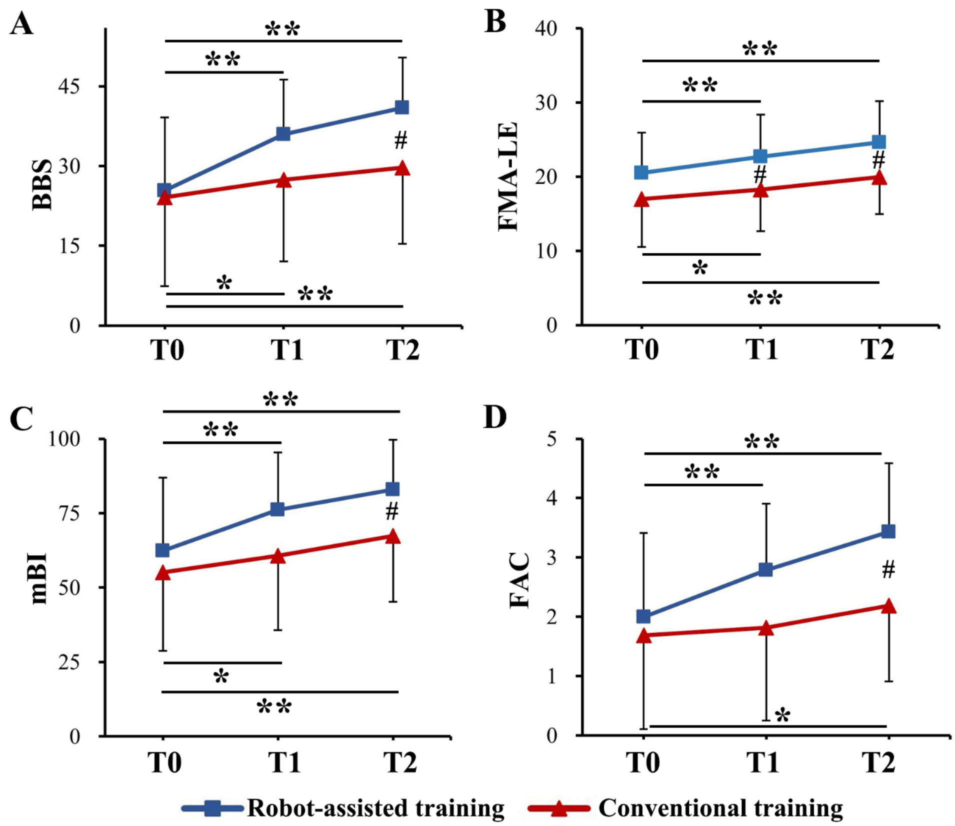

Fig. 3 Comparison of longitudinal clinical scores between the RT and CT groups. Significant within-group differences are marked with (* $p<0.05$, ** $p<0.001$). Significant between-group differences are marked with (# $p<0.05$)

significant main effects of time on stride length (F=7.141, $p=0.002$, partial η2=0.203), cadence (F=12.572, $p<0.001$, partial η2=0.310), gait speed (F=12.294, $p<0.001$, partial η2=0.305), support phase (F=4.516, $p=0.024$, partial η2=0.139), toe-off angle of the affected side (F=5.153, $p=0.013$, partial η2=0.160), foot strike angle of the affected side (F=8.033, $p=0.001$, partial η2=0.229), and stride length of the unaffected side (F=8.626, $p=0.001$, partial η2=0.236) with Greenhouse-Geisser correction. For the foot strike angle at the heel strike of the affected side, there was a significant main effect of group (F=5.523; $p=0.026$, partial η2=0.170) with the Greenhouse-Geisser correction. Significant within-group differences were found in the stride length of the unaffected side, cadence, and gait speed between the two groups. The stride length of the affected side (F=4.913, $p=0.015$, partial η2=0.267), support phase of the affected side ($p=0.011$, partial η2=0.283), angle at the toe-off angle of the affected side ($p=0.035$, partial η2=0.228), and angle at the foot strike angle of the affected side ($p=0.006$, partial η2=0.324) significantly improved after the intervention only in the RT group.

Longitudinal changes in cortical activation patterns related to specific tasks

Cortical activation maps are shown in Fig. 4A for the RT group during weight-shift training compared with the resting state, and the results are based on significant WA values tested with FDR-corrected t tests. The results revealed that no significant cortical activation response to weight-shift training survived FDR correction in stroke patients at T0. At T1, significant cortical activations were observed in the bilateral motor and occipital areas and in the contralesional prefrontal cortex. The cortical activation response was more lateral to the contralesional side. At T2, significant cortical activations were observed in the bilateral prefrontal, motor and occipital areas, with more activation lateral to the ipsilesional side. Paired t test revealed increased motor activation in the ipsilesional hemisphere following 4 weeks of training (Fig. 4B). Figure 4C shows a statistically significant increase in the LI of the PMC&SMA at T2 compared with T0 (t=2.260, $p=0.042$) and T1 (t=2.688, $p=0.019$).

Cortical activation maps are shown in Fig. 5A for the RT group during robot-assisted walking compared with the resting state, based on significant WA values tested with FDR-corrected t tests. The results revealed an increasing trend in the significant cortical activation

Table 3 Longitudinal changes in BBS, FAC, FMA-LE, and mBI scores in the RT and CT groups

Measurement Group	T0	T1	T2	within-group difference	
				T1 vs. T0 (*p*/ 95% CI)	T2 vs. T0 (*p*/ 95% CI)
BBS					
RT	25.43 ± 13.75	35.93 ± 10.30	41.00 ± 9.40	**< 0.001*/(7.08 to 13.92)**	**< 0.001*/(11.29 to 19.86)**
CT	24.13 ± 16.75	27.44 ± 15.35	29.69 ± 14.31	**0.043*/(0.12 to 6.51)**	**0.008*/(1.55 to 9.57)**
Between-group difference (*p*/ 95% CI)	0.091/(-1.44 to 18.42)	**0.018*/(2.11 to 20.52)**	0.091/(-1.44 to 18.42)		
FAC					
RT	2.00 ± 1.41	2.79 ± 1.12	3.43 ± 1.16	**< 0.001*/(0.53 to 1.04)**	**< 0.001*/(1.05 to 1.81)**
CT	1.69 ± 1.58	1.81 ± 1.56	2.19 ± 1.28	0.293/(-0.11 to 0.36)	**0.007*/(0.15 to 0.86)**
Between-group difference (*p*/ 95% CI)	0.575/(-0.82 to 1.44)	0.063/(-0.06 to 2.00)	**0.010*/(0.32 to 2.16)**		
FMA-LE					
RT	20.50 ± 5.42	22.71 ± 5.62	24.64 ± 5.54	**< 0.001*/(1.25 to 3.18)**	**< 0.001*/(2.75 to 5.54)**
CT	17.00 ± 6.48	18.25 ± 5.58	19.94 ± 5.00	**< 0.001*/(0.35 to 2.16)**	**< 0.001*/(1.63 to 4.25)**
Between-group difference (*p*/ 95% CI)	0.123/(-1.01 to 8.01)	**0.038*/(0.27 to 8.66)**	**0.021*/(0.76 to 8.65)**		
mBI					
RT	62.43 ± 24.49	76.07 ± 19.35	82.93 ± 16.73	**< 0.001*/(8.85 to 18.44)**	**< 0.001*/(13.70 to 27.30)**
CT	55.13 ± 26.30	60.69 ± 24.98	67.44 ± 22.16	**0.017*/(1.08 to 10.05)**	**< 0.001*/(5.95 to 18.67)**
Between-group difference (*p*/ 95% CI)	0.440/(-11.80 to 26.40)	0.073/(-1.52 to 32.28)	**0.042*/(0.63 to 30.35)**		

Note RT: robot-assisted training; CT: conventional training; BBS: Berg balance scale; FAC: functional ambulation category; FMA-LE: Fugl-Meyer assessment scale of lower-limb; mBI: modified Barthel Index. * $p < 0.05$

pattern related to the robot-assisted walking in the ROIs distributed in the bilateral hemispheres following rehabilitation for stroke patients. Compared with T0 (Fig. 5B), the results of the paired t test revealed significantly increased activation of the contralateral prefrontal area in response to the overground walking task after 2 weeks of gait training. The activation responses of the contralesional prefrontal and motor regions, as well as the ipsilesional sensorimotor and occipital cortices, were significantly increased during overground walking after 4 weeks of treatment, with the most significant increases being observed in the contralesional motor cortex and the affected occipital cortex.

Correlations between motor improvement and neurophysiological measures

Pearson correlations were conducted to examine the relationship between changes in motor scores and changes in cortical activation response in the RT group from T0 to T2. For the cortical response in weight-shift training (Fig. 6A), a greater increase in ipsilesional PFC was associated with a greater increase in FMA-LE score from T0 to T2 (CH3: r=0.807, p=0.003; CH8: r=0.668, p=0.025). Significant negative correlations were found between the change in BBS score and increased cortical activation in contralesional SMC (CH3: r = -0.769, p=0.009). For the cortical response in walking training (Fig. 6B), significant negative correlations were found between motor recovery (delta FMA-LE) and the cortical response changes at CH25 (r = -0.666, p=0.025), CH29 (r = -0.808, p=0.003), and CH34 (r = -0.730, p=0.011) distributed in the contralesional PMC&SMA, M1, and ipsilesional OL from T0 to T2.

Discussion

The present study investigated the effectiveness of robot-assisted overground gait training for stroke patients in a randomly controlled trial and captured cortical activity related to gait training tasks. The main findings were that both the RT and CT groups showed improvements

Table 4 Longitudinal changes in gait parameters in the RT and CT groups

Group	T0	T1	T2	Within-group *p*-value	Post-hoc *p*-value			ANOVA *p*-value		
					T0 vs. T1	T1 vs. T2	T0 vs. T2	Group	Time	Interaction
Stride length of affected side (m)										
Robot	0.43 ± 0.32	0.56 ± 0.14	0.64 ± 0.16	**0.015***	**0.030***	0.096	**0.003***	0.292	**0.002***	0.198
Control	0.42 ± 0.32	0.42 ± 0.33	0.50 ± 0.33	0.218	0.935	0.087	0.181			
Stride length of unaffected side (m)										
Robot	0.48 ± 0.37	0.56 ± 0.14	0.71 ± 0.14	**0.008***	0.320	**0.014***	**0.005***	0.311	**0.001***	0.394
Control	0.47 ± 0.32	0.42 ± 0.33	0.59 ± 0.29	**0.010***	0.505	**0.003***	0.075			
Cadence (steps/min)										
Robot	44.68 ± 31.38	59.67 ± 12.98	64.44 ± 15.47	**0.008***	**0.004***	0.213	**0.002***	0.527	**< 0.001**	0.167
Control	45.44 ± 30.59	47.42 ± 31.04	59.07 ± 27.05	**0.010***	0.659	**0.002***	**0.019***			
Gait speed (m/s)										
Robot	0.24 ± 0.21	0.31 ± 0.13	0.37 ± 0.13	**0.016***	**0.034***	**0.044***	**0.004***	0.510	**< 0.001**	0.409
Control	0.23 ± 0.20	0.24 ± 0.20	0.32 ± 0.24	**0.010***	0.768	**0.002***	**0.017***			
Support phase of the affected side (%)										
Robot	53.28 ± 34.73	76.21 ± 5.92	72.42 ± 4.19	**0.011***	**0.003***	0.464	**0.029***	0.231	**0.024***	0.067
Control	55.38 ± 30.01	54.76 ± 32.66	62.73 ± 24.93	0.277	0.925	0.106	0.353			
Toe-off angle of the affected side (°)										
Robot	12.59 ± 9.54	17.63 ± 7.29	17.11 ± 8.08	**0.035***	**0.009***	0.729	**0.045***	0.080	**0.013***	0.144
Control	9.13 ± 8.20	9.28 ± 8.52	12.65 ± 11.31	0.082	0.931	**0.026***	0.101			
Foot strike angle of the affected side (°)										
Robot	8.33 ± 6.46	12.33 ± 5.16	17.11 ± 8.08	**0.006***	**0.002***	0.510	**0.004***	**0.026***	**0.001***	0.079
Control	6.16 ± 5.00	6.03 ± 5.14	12.65 ± 11.31	0.095	0.908	0.107	**0.029***			

Note The table displays the mean ± SD alongside the corresponding statistical p value. The bold font marked with * indicates statistical significance

in lower-limb balance and gait functions, with greater outcomes in the RT group. Following rehabilitation, individuals with subacute stroke displayed a cortical activation pattern featuring ipsilesional lateral migration from T1 to T2, with enhanced responses in the ipsilesional SMC, M1, and PMC&SMA, accompanied by improved locomotor functions. These results suggest that the application of unilateral lower-limb exoskeleton rehabilitation robot for overground gait training is a more effective way to promote neuroplasticity and clinical improvements in individuals with subacute stroke.

Positive effects of robot-assisted intervention on clinical assessments and gait parameters

The statistical analyses revealed significant improvements in lower-limb function for all patients treated with RT and CT, with increased BBS, FAC, FMA-LE, and mBI scores after 4 weeks. Treatment-associated differences were noted in BBS, FAC, mBI, and FMA-LE at T2, with the RT group showing greater improvement than the CT group after 4 weeks. Specifically, for the primary outcome, post hoc analysis revealed a significant increase in the BBS score in the RT group at T1 ($p<0.001$) and T2 ($p<0.001$) compared with that at T0, with mean scores and standard deviations of T0: 25.43 [13.75], T1: 35.93 [10.30], and T2: 41.00 [9.40]. The effectiveness analysis revealed that the BBS score increased by 18.8% (T1) and 27.8% (T2) in the RT group, whereas it improved by only 5.91% (T1) and 9.92% (T2) in the CT group (mean [SD], T0: 24.13 [16.75]; T1: 27.44 [15.35]; T2: 29.69 [14.31]). The results further revealed that participants who received robot training coupled with physical therapy presented an increase in the BBS score from 25 to 41 points, getting the minimal detectable change (MDC) at the end of the training, whereas those in the CT group did not obtain the MDC for the BBS [24]. Notably, from a clinical point of view, this increase in the BBS score also indicates a significant increase in functional mobility and gait, with a lower risk of falling after robot-assisted training. Additionally, for the FMA-LE and mBI scores, the results revealed a significant increase in the 2 groups after 4 weeks of treatment. Compared with those in the baseline group, the FMA-LE scores improved by 6.5% (T1) and 12.2% (T2) in the RT group and improved by 3.7% (T1) and 8.6% (T2) in the CT group. Additionally, compared with those at baseline, mBI scores improved by 13.6% (T1) and 20.5% (T2) in the RT group and by 5.6% (T1) and 12.3% (T2) in the CT group. The RT group presented an increase in the mBI reaching the MDC at the 2-week training point, reflecting that robots can improve the efficiency of stroke rehabilitation.

Post-stroke hemiplegic gait usually manifests with a reduced gait velocity and asymmetry of bilateral kinetic, kinematic, and spatiotemporal parameters, resulting in increased energy expenditure and decreased walking stability [25]. In this study, significant improvements were

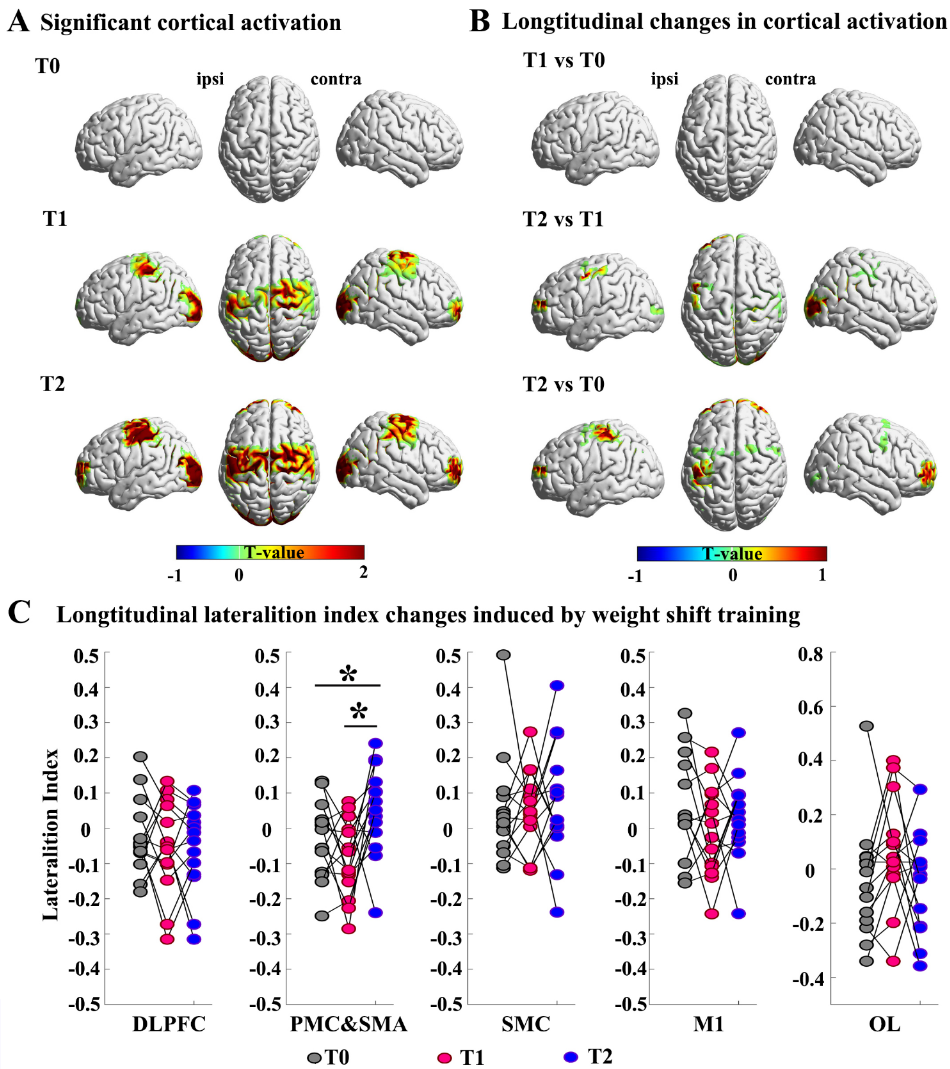

Fig. 4 Longitudinal cortical activation pattern in response to robot-assisted weight-shift training in the RT group. (**A**) Significant cortical activation maps in weight-shift training relative to rest tested by one sample t test with FDR correction. (**B**) Changes in the cortical activation response across the 4 weeks of training according to one-sample t tests with FDR correction. (**C**) Comparison of the LI for each cortex at each test with FDR correction

found in the stride length of the unaffected side, cadence, and gait speed for both groups from T0 to T2. Only the RT group showed a significant improvement in the stride length, support phase, toe-off angle, and foot strike angle of the affected side, indicating that the robot-assisted intervention had a more positive effect on promoting gait recovery. In the stroke population, the minimal clinically important difference (MCID) for gait speed ranges from 10 cm/s [26] to 16 cm/s [27]. In this study, patients in the RT group showed an increase in gait speed from 0.24 m/s to 0.37 m/s after 4 weeks of training, reaching the MCID at the end of the training. Despite an improvement in walking speed, participants in the CT group did not achieve the MCID. These findings are in agreement with previous studies showing improved gait speed after 4 weeks of robot-assisted lower-limb rehabilitation in subacute stroke patients compared with that of conventional training methods [2]. Improvements in gait speed after a stroke have been proven to have a direct effect on the quality of life of stroke patients [28]. Additionally, patients who received robot-assisted training experienced notable increases in stride length, toe-off angle and foot strike angle on the affected side. The increased angle of toe-off and foot strike might be related to improved interlimb ankle-knee-hip coordination during the walk cycle in the RT group, demonstrating that robot-assisted training can facilitate a more coordinated and efficient gait pattern for stroke patients [29]. Furthermore, the current study revealed that robot-assisted intervention had a positive effect on the support phase of the affected side, which could be correlated with the increased gait stability of stroke patients. Previous studies have

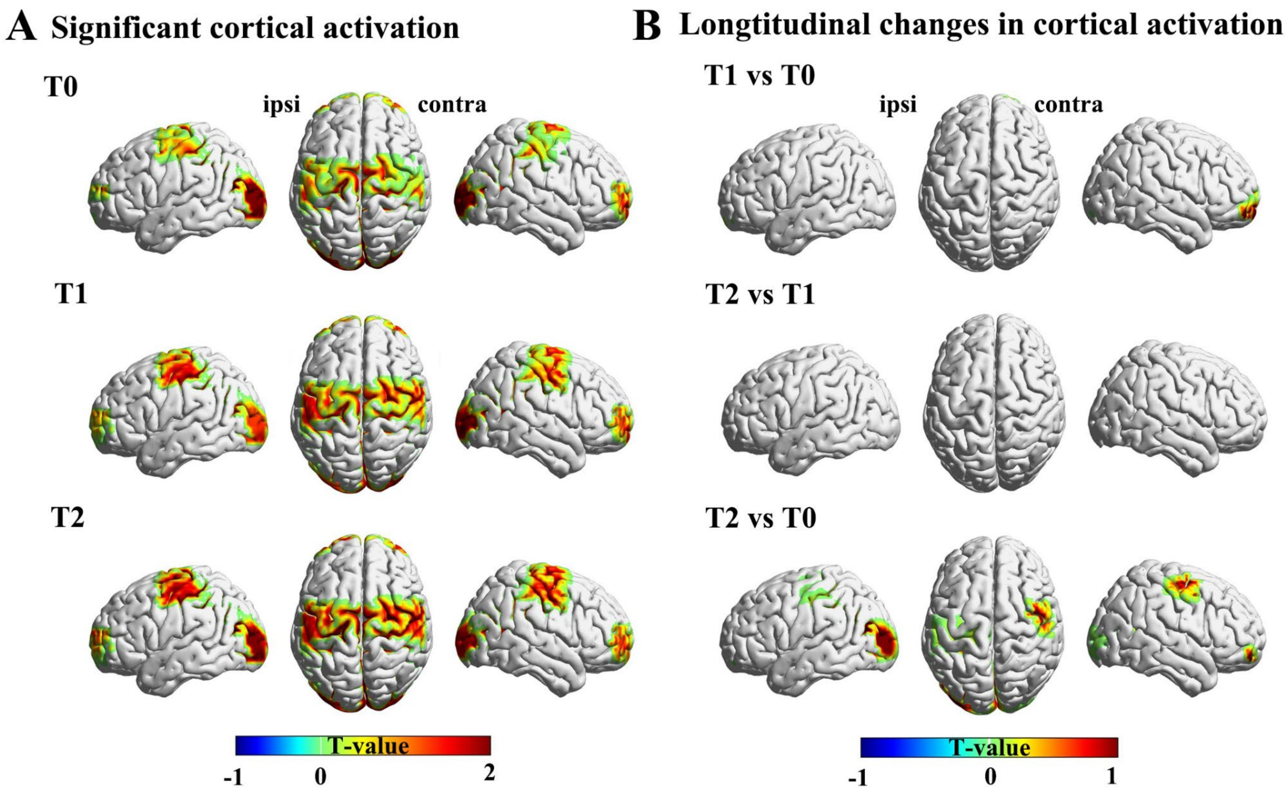

Fig. 5 Longitudinal cortical activation pattern in response to robot-assisted walking training in the RT group. (**A**) Significant cortical activation maps relative to the remaining maps were tested by one sample t test with FDR correction. (**B**) Changes in the cortical activation response following rehabilitation with FDR correction

indicated that only patients with stroke who are able to walk benefit most from gait training with body weight support [30–32]. The integration of clinical assessment scales and gait analysis in this study confirms that robot-assisted training, as opposed to conventional rehabilitation, not only enhances walking ability but also significantly reduces fall risk by improving gait parameters, including gait pattern, step length, walking speed and endurance, balance and coordination, thereby effectively enhancing functional ambulation outcomes.

Research has shown that robot-assisted training with bodyweight support can improve lower limb motor function in subacute stroke patients but may not be superior to conventional rehabilitation in restoring walking ability [7, 33]. Achieving desirable outcomes in gait training necessitates repetitive natural walking gait overground, as well as accurate proprioception and external sensory feedback. The wearable exoskeleton robot utilized in this study for gait training offers a key advantage by facilitating overground walking in natural settings and requiring the active engagement of patients in the subacute stage. With the natural gait pattern of the healthy lower limb as a reference, the robotic exoskeleton is able to drive the movements of the affected side in a coordinated and synchronized manner with the healthy side in a real-world scenario. It enables individuals with hemiplegia to relearn and regain the necessary muscle control and coordination required for walking, thereby enhancing the balance and walking stability of stroke patients during training. All these related improvements could ultimately lead to increased independence in activities of daily living, which is of great clinical importance in stroke rehabilitation [34].

Cortical changes underlying motor recovery in patients with hemiplegic stroke

Functional reorganization of the neural network is essential for gait and balance recovery after stroke [35]. In this study, the longitudinal fNIRS measurement revealed a substantial increase in the cortical activation response in the bilateral PFC, OL, and motor-related areas during robot-assisted weight-shift training. Additionally, a cortical activation pattern exhibiting ipsilesional lateral migration from T1 to T2 with an increased cortical response in the ipsilesional SMC, M1, and PMC&SMA was observed, accompanied by an increase in locomotor function after 4 weeks of rehabilitation in patients with subacute stroke. The vital role of the SMA and its descending projections has been emphasized for locomotion [36, 37]. Following a stroke, the recovery of

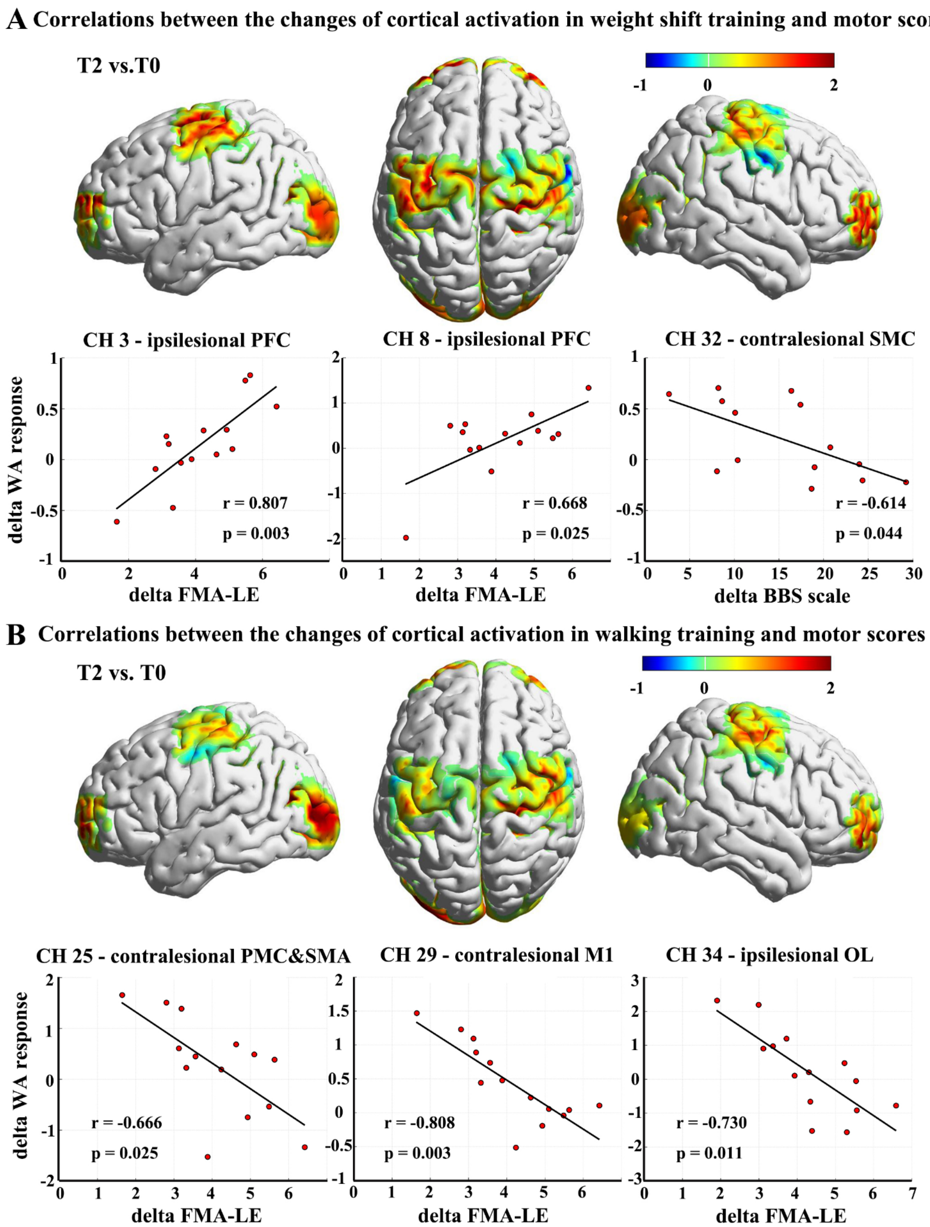

Fig. 6 Relationships between motor recovery and cortical response changes related to robot-assisted weight-shift training (**A**) and robot-assisted walking training (**B**) from T0 to T1

unilateral brain damage largely depends on reshaping the interhemispheric balance between the affected and unaffected hemispheres mediated by transcallosal inhibition [38]. Notably, the process of locomotor recovery in hemiparetic stroke involves a shift in cortical activity, beginning with the contralesional motor area being activated to compensate for the impairment and then progressing to the ipsilesional motor area with successful intervention [39]. This finding suggests that a more symmetrical motor activation pattern with greater activation in the affected hemisphere might be beneficial in restoring gait function in patients with stroke [40, 41]. The increased PFC neuronal activity involved in the weight-shift task might be related to increased motor control of balance function [40]. Further analysis demonstrated that the increased ipsilateral PFC activation response during weight-shift was positively correlated with improved lower-limb motor improvement (delta FMA-LE). This finding indicates the critical involvement of the PFC in the clinical gain of balance function [35, 40, 42]. Additionally, results revealed that a greater SMC activation response in the contralesional hemisphere was negatively correlated with improved motor function (delta FMA-LE). The brain-behavior associations analysis suggests that the activation response of the ipsilesional motor cortex could be advantageous for motor function recovery. These findings suggest that the application of a unilateral lower-limb exoskeleton rehabilitation robot may be beneficial for promoting the functional reorganization of the ipsilesional neural network underlying gait and balance control.

For the robot-assisted overground gait training, the results revealed an increasing trend toward a significant cortical activation response in the bilateral hemispheres following the 4 weeks of treatment. Compared with those at baseline, the contralesional prefrontal and motor regions, as well as the ipsilesional sensorimotor and occipital cortices, presented a significant increase in the activation response after 4 weeks, with the most remarkable increases being observed in the contralesional motor cortex and the ipsilesional occipital cortex. An fMRI study revealed that the involvement of bilateral SMC activation is essential for improving walking ability after 4 weeks [43]. Following rehabilitation, the cortex, including both the ipsilesional and the contralateral SMC-PMC-SMA motor control network, becomes more involved in postural responses during walking tasks in hemiparetic stroke patients [44]. In particular, the PMC and SMA are involved in purposeful adjustment and control during locomotion through connections with the basal ganglia, brainstem, cerebellum, and spinal cord [45]. The unilateral lower-limb exoskeleton rehabilitation robot offers overground gait training that incorporates weight bearing, walking, and balance, allowing patients to perform upright walking training with a combination of proprioceptive feedback and motor control training in the early stages of stroke. Proprioception is essential for motor learning and control in the central nervous system [46, 47]. Correct visual and proprioceptive feedback are important sensory inputs in cortical motor learning that help to predict and adjust locomotor outcomes [48, 49]. These findings indicate that through standardized, intensive, and repetitive gait training, specialized neural pathways can be stimulated and then facilitate brain functional reorganization, thereby promoting the recovery of motor function [50].

Limitations

There are some limitations should be acknowledged. First, our sample consisted of stroke patients involving both hemispheres and was limited in size. Therefore, we cannot consider the influence of laterality. Furthermore, the lack of long-term follow-up evaluation limited our understanding of the long-term effectiveness of exoskeleton gait training in stroke patients. Moreover, only one imaging modality (fNIRS) was utilized. Although fNIRS offers advantages, it is restricted by limitations, particularly its shallow penetration depth, which hinders the detection of deep brain activity. Future research should include an increased sample size with long-term follow-up evaluation, as well as the integration of multiple imaging modalities such as fMRI and neurophysiology. This will allow for a more comprehensive investigation of the effectiveness and modulating effects on cortical-subcortical activities following training with lower-limb exoskeleton robots.

Conclusion

The present study provides evidence of the effectiveness of a unilateral lower-limb exoskeleton rehabilitation robot in promoting balance and gait recovery in individuals with subacute stroke. Robot-assisted overground gait training allows for a more coordinated and efficient gait pattern and promotes the reorganization of the bilateral motor-related network related to balance and gait recovery post-stroke. This study also suggests the feasibility and efficacy of fNIRS assessment for patients with stroke with gait and balance impairments. Our findings may have clinical implications and provide insight for clinicians who are interested in locomotor neurorehabilitation in individuals with hemiparetic stroke.

Author contributions

CC.H performed the conceptualization, investigation, drafted and wrote the main manuscript text. GJ.S., TD.C, WH.L, J.W, and X.H performed the experimental data acquisition and statistical analysis. Y.W prepared the result visualization. ZY.L is involved in project administration, as well as supervision and funding acquisition. PY.Z, LG.L, and LY.L were responsible for validation, reviewing, and editing the original work. All authors read and approved the final manuscript.

Funding

This work was supported by the National Key Research and Development Project (2023YFC3603703), National Natural Science Foundation of China (Grant No. 32271370), Henan Province Medical Key Technologies Research and Development Major Joint Construction Program (Grant No. SBGJ202001009), The Key Research and Development plan of Zhejiang (Grant No. 2021C03109), Fundamental Research Funds for Central Public Welfare Research Institutes (118009001000160001), and National Natural Science Foundation of Hebei (F2022203079).

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Medical Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University ([2021]02-333-01) in accordance with the declaration of Helsinki. All participants gave written informed consent prior to their enrollments.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details
[1]Beijing Key Laboratory of Rehabilitation Technical Aids for Old-Age Disability, National Research Center for Rehabilitation Technical Aids, Beijing 100176, P.R. China
[2]School of Rehabilitation Engineering, China Civil Affairs University, Beijing 102600, China
[3]Key Laboratory of Neuro-Functional Information and Rehabilitation Engineering of the Ministry of Civil Affairs, Beijing 100176, P.R. China
[4]Department of Biomedical Engineering, Faculty of Engineering, The Hong Kong Polytechnic University, Hong Kong 999077, China
[5]The Fifth Affiliated Hospital of Zhengzhou University, Henan 450052, P.R. China
[6]Zhengzhou Health Vocational College, Henan 450052, P.R. China

Received: 28 March 2024 / Accepted: 15 October 2024
Published online: 05 December 2024

References

1. Jang SH. The recovery of walking in stroke patients: a review. Int J Rehabilitation Res Int Z fur Rehabilitationsforschung Revue Int De recherches de Readaptation. 2010;33(4):285–9.
2. Bang DH, Shin WS. Effects of robot-assisted gait training on spatiotemporal gait parameters and balance in patients with chronic stroke: a randomized controlled pilot trial. NeuroRehabilitation. 2016;38(4):343–9.
3. Gordon T. Nerve regeneration in the peripheral and central nervous systems. J Physiol. 2016;594(13):3517–20.
4. Stinear CM, Barber PA, Petoe M, Anwar S, Byblow WD. The PREP algorithm predicts potential for upper limb recovery after stroke. Brain. 2012;135(Pt 8):2527–35.
5. Jayaraman A, O'Brien MK, Madhavan S, Mummidisetty CK, Roth HR, Hohl K, Tapp A, Brennan K, Kocherginsky M, Williams KJ, et al. Stride management assist exoskeleton vs functional gait training in stroke: a randomized trial. Neurology. 2019;92(3):e263–73.
6. Tomida K, Sonoda S, Hirano S, Suzuki A, Tanino G, Kawakami K, Saitoh E, Kagaya H. Randomized Controlled Trial of Gait Training using Gait Exercise assist Robot (GEAR) in stroke patients with Hemiplegia. J Stroke Cerebrovasc Diseases: Official J Natl Stroke Association. 2019;28(9):2421–8.
7. Schwartz I, Sajin A, Fisher I, Neeb M, Shochina M, Katz-Leurer M, Meiner Z. The effectiveness of locomotor therapy using robotic-assisted gait training in subacute stroke patients: a randomized controlled trial. PM R: J Injury Function Rehabilitation. 2009;1(6):516–23.
8. Lee SH, Lee HJ, Shim Y, Chang WH, Choi BO, Ryu GH, Kim YH. Wearable hip-assist robot modulates cortical activation during gait in stroke patients: a functional near-infrared spectroscopy study. J Neuroeng Rehabil. 2020;17(1):145.
9. Lee HJ, Lee SH, Seo K, Lee M, Chang WH, Choi BO, Ryu GH, Kim YH. Training for walking Efficiency with a wearable hip-assist Robot in patients with stroke: a pilot randomized controlled trial. Stroke. 2019;50(12):3545–52.
10. Calabrò RS, Naro A, Russo M, Bramanti P, Carioti L, Balletta T, Buda A, Manuli A, Filoni S, Bramanti A. Shaping neuroplasticity by using powered exoskeletons in patients with stroke: a randomized clinical trial. J Neuroeng Rehabil. 2018;15(1):35.
11. Buesing C, Fisch G, O'Donnell M, Shahidi I, Thomas L, Mummidisetty CK, Williams KJ, Takahashi H, Rymer WZ, Jayaraman A. Effects of a wearable exoskeleton stride management assist system (SMA®) on spatiotemporal gait characteristics in individuals after stroke: a randomized controlled trial. J Neuroeng Rehabil. 2015;12:69.
12. Gramigna V, Pellegrino G, Cerasa A, Cutini S, Vasta R, Olivadese G, Martino I, Quattrone A. Near-Infrared Spectroscopy in Gait disorders: is it Time to begin? Neurorehabil Neural Repair. 2017;31(5):402–12.
13. Quaresima V, Ferrari M. Functional Near-Infrared Spectroscopy (fNIRS) for assessing cerebral cortex function during human behavior in Natural/Social situations: a concise review. Organizational Research Methods. 2019,22(1):46–68.
14. Miyai I, Yagura H, Oda I, Konishi I, Eda H, Suzuki T, Kubota K. Premotor cortex is involved in restoration of gait in stroke. Ann Neurol. 2002;52(2):188–94.
15. Miyai I, Tanabe HC, Sase I, Eda H, Oda I, Konishi I, Tsunazawa Y, Suzuki T, Yanagida T, Kubota K. Cortical mapping of gait in humans: a near-infrared spectroscopic topography study. NeuroImage. 2001;14(5):1186–92.
16. Tao S, Zhang X, Cai H, Lv Z, Hu C, Xie H. Gait based biometric personal authentication by using MEMS inertial sensors. J Ambient Intell Humaniz Comput. 2018;9(5):1705–12.
17. Cope M, Delpy DT. System for long-term measurement of cerebral blood and tissue oxygenation on newborn infants by near infra-red transillumination. Med Biol Eng Comput. 1988;26(3):289–94.
18. Virtanen J, Noponen T, Meriläinen P. Comparison of principal and independent component analysis in removing extracerebral interference from near-infrared spectroscopy signals. J Biomed Opt. 2009;14(5):054032.
19. Santosa H, Hong MJ, Kim SP, Hong KS. Noise reduction in functional near-infrared spectroscopy signals by independent component analysis. Rev Sci Instrum. 2013;84(7):411–1600.
20. Han Z, Zhang YJ, Lu CM, Ma SY, Zang YF, Zhu CZ. Functional connectivity as revealed by independent component analysis of resting-state fNIRS measurements. NeuroImage. 2010;51(3):1150–61.
21. Scholkmann F, Spichtig S, Muehlemann T, Wolf M. How to detect and reduce movement artifacts in near-infrared imaging using moving standard deviation and spline interpolation. Physiol Meas. 2010;31(5):649.
22. Huo C, Xu G, Li W, Xie H, Li Z. A review on functional near-infrared spectroscopy and application in stroke rehabilitation. Med Novel Technol Devices. 2021;11:100064.
23. Huo C, Li X, Jing J, Ma Y, Wenhao L, Wang Y, Liu W, Fan Y, Yue S, Wang Y, et al. Median nerve electrical stimulation–induced changes in effective connectivity in patients with stroke as assessed with functional near-infrared spectroscopy. Neurorehabilit Neural Repair. 2019;33:154596831987595.
24. Stevenson TJ. Detecting change in patients with stroke using the Berg Balance Scale. Aust J Physiother. 2001;47(1):29–38.
25. Sheffler LR, Chae J. Hemiparetic Gait. Phys Med Rehabil Clin North Am. 2015;26(4):611–23.
26. Perera S, Mody SH, Woodman RC, Studenski SA. Meaningful change and responsiveness in common physical performance measures in older adults. J Am Geriatr Soc. 2006;54(5):743–9.
27. Tilson JK, Sullivan KJ, Cen SY, Rose DK, Koradia CH, Azen SP, Duncan PW. Meaningful gait speed improvement during the first 60 days poststroke: minimal clinically important difference. Phys Ther. 2010;90(2):196–208.
28. Schmid A, Duncan PW, Studenski S, Lai SM, Richards L, Perera S, Wu SS. Improvements in speed-based gait classifications are meaningful. Stroke. 2007;38(7):2096–100.
29. Gait Analysis. Normal and pathological function. J Sports Sci Med. 2010;9(2):353. eCollection 2010 Jun.
30. Belda-Lois JM, Mena-del Horno S, Bermejo-Bosch I, Moreno JC, Pons JL, Farina D, Iosa M, Molinari M, Tamburella F, Ramos A, et al. Rehabilitation of gait after stroke: a review towards a top-down approach. J Neuroeng Rehabil. 2011;8:66.
31. States RA, Pappas E, Salem Y. Overground physical therapy gait training for chronic stroke patients with mobility deficits. Cochrane Database Syst Rev. 2009;2009(3):Cd006075.
32. Mehrholz J, Thomas S, Elsner B. Treadmill training and body weight support for walking after stroke. Cochrane Database Syst Rev. 2017;8(8):Cd002840.
33. van Nunen MP, Gerrits KH, Konijnenbelt M, Janssen TW, de Haan A. Recovery of walking ability using a robotic device in subacute stroke patients: a randomized controlled study. Disabil Rehabil Assist Technol. 2015;10(2):141–8.
34. Mehrholz J, Thomas S, Kugler J, Pohl M, Elsner B. Electromechanical-assisted training for walking after stroke. Cochrane Database Syst Rev. 2020;10(10):Cd006185.
35. Takakusaki K. Neurophysiology of gait: from the spinal cord to the frontal lobe. Mov Disord. 2013;28(11):1483–91.
36. Jang SH, Chang CH, Lee J, Kim CS, Seo JP, Yeo SS. Functional role of the corticoreticular pathway in chronic stroke patients. Stroke. 2013;44(4):1099–104.
37. Fujimoto H, Mihara M, Hattori N, Hatakenaka M, Kawano T, Yagura H, Miyai I, Mochizuki H. Cortical changes underlying balance recovery in patients with hemiplegic stroke. NeuroImage. 2014;85(Pt 1):547–54.
38. Grefkes C, Eickhoff SB, Nowak DA, Dafotakis M, Fink GR. Dynamic intra- and interhemispheric interactions during unilateral and bilateral hand movements assessed with fMRI and DCM. *NeuroImage* 2008, 41(4):1382–1394.
39. Jang SH. A review of motor recovery mechanisms in patients with stroke. NeuroRehabilitation. 2007;22(4):253–9.
40. Mihara M, Fujimoto H, Hattori N, Otomune H, Kajiyama Y, Konaka K, Watanabe Y, Hiramatsu Y, Sunada Y, Miyai I, et al. Effect of Neurofeedback Facilitation on Poststroke Gait and Balance Recovery: a Randomized Controlled Trial. Neurology. 2021;96(21):e2587–98.

41. Lim SB, Louie DR, Peters S, Liu-Ambrose T, Boyd LA, Eng JJ. Brain activity during real-time walking and with walking interventions after stroke: a systematic review. J Neuroeng Rehabil. 2021;18(1):8.
42. Mihara M, Miyai I, Hatakenaka M, Kubota K, Sakoda S. Role of the prefrontal cortex in human balance control. NeuroImage. 2008;43(2):329–36.
43. Enzinger C, Dawes H, Johansen-Berg H, Wade D, Bogdanovic M, Collett J, Guy C, Kischka U, Ropele S, Fazekas F, et al. Brain activity changes associated with treadmill training after stroke. Stroke. 2009;40(7):2460–7.
44. Kim HY, Yang SP, Park GL, Kim EJ, You JS. Best facilitated cortical activation during different stepping, treadmill, and robot-assisted walking training paradigms and speeds: a functional near-infrared spectroscopy neuroimaging study. NeuroRehabilitation. 2016;38(2):171–8.
45. Nutt JG, Marsden CD, Thompson PD. Human walking and higher-level gait disorders, particularly in the elderly. Neurology. 1993;43(2):268–79.
46. Wolpert DM, Diedrichsen J, Flanagan JR. Principles of sensorimotor learning. Nat Rev Neurosci. 2011;12(12):739–51.
47. Ingemanson ML, Rowe JR, Chan V, Wolbrecht ET, Reinkensmeyer DJ, Cramer SC. Somatosensory system integrity explains differences in treatment response after stroke. Neurology. 2019;92(10):e1098–108.
48. Blakemore SJ, Goodbody SJ, Wolpert DM. Predicting the consequences of our own actions: the role of sensorimotor context estimation. J Neuroscience: Official J Soc Neurosci. 1998;18(18):7511–8.
49. Rossini PM, Dal Forno G. Neuronal post-stroke plasticity in the adult. Restor Neurol Neurosci. 2004;22(3–5):193–206.
50. Tombari D, Loubinoux I, Pariente J, Gerdelat A, Albucher JF, Tardy J, Cassol E, Chollet F. A longitudinal fMRI study: in recovering and then in clinically stable sub-cortical stroke patients. NeuroImage. 2004;23(3):827–39.

Publisher's note