ARTICLE CLASS OF EVIDENCE

Effects of home-based telerehabilitation in patients with stroke

A randomized controlled trial

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Abstract

Objective

To determine the effects of a 12-week home-based motor training telerehabilitation program in patients with subcortical stroke by combining motor function assessments and multimodality MRI analysis methods.

Methods

Fifty-two patients with stroke and hemiplegia were randomly assigned to either a home-based motor training telerehabilitation (TR) group or a conventional rehabilitation (CR) group for 12 weeks. The Fugl-Meyer assessment (FMA) for upper and lower extremities and the modified Barthel Index were used as primary outcomes. The secondary outcomes included resting-state functional connectivity (rsFC) between the bilateral M1 areas, gray matter volumes of the primary motor cortex (M1) areas, and white matter integrity of the corticospinal tract. Analysis of covariance was applied to examine the effects of the home-based motor training TR program on neural function recovery and brain plasticity.

Results

Compared with the CR group, the TR group showed significant improvement in the FMA (p = 0.011) and significantly increased M1-M1 rsFC (p = 0.031) at the end of the rehabilitation. The M1-M1 rsFC change was significantly positively correlated with the FMA change in the TR group (p = 0.018).

Conclusion

This study showed a beneficial effect of the home-based motor training telerehabilitation program on motor function in patients with stroke, which was accompanied by enhanced interhemispheric functional connectivity of the M1 areas. We inferred that it is feasible, safe, and efficacious for patients with stroke to receive professional rehabilitation training at home. The combined use of imaging biomarkers should be encouraged in motor training clinical studies in patients with stroke.

Classification of evidence

This study provides Class II evidence that for patients with stroke with hemiplegia, home-based telerehabilitation compared to conventional rehabilitation significantly improves some motor function tests.

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Glossary

ADL = activities of daily living; **AFQ** = automated fiber quantification; **CI** = confidence interval; **CONSORT** = Consolidated Standards of Reporting Trials; **CR** = conventional rehabilitation; **CST** = corticospinal tract; **CSTL** = left corticospinal tract; **CSTR** = right corticospinal tract; **DTI** = diffusion tensor imaging; **EPI** = echoplanar imaging; **ETNS** = EMG-triggered neuromuscular stimulation; **FA** = fractional anisotropy; **FMA** = Fugl-Meyer assessment; **FOV** = field of view; **GMV** = gray matter volume; **M1** = primary motor cortex; **MBI** = modified Barthel index; **MD** = mean diffusivity; **NIHSS** = NIH Stroke Scale; **OT** = occupational therapy; **PT** = physical therapy; **RCT** = randomized controlled trial; **RD** = radial diffusivity; **rsFC** = resting-state functional connectivity; **sMRI** = structural MRI; **SPM** = statistical parametric mapping; **TE** = echo time; **TR** = telerehabilitation; **TRS** = Telemedicine Rehabilitation System; **VBM** = voxel-based morphometry; **WM** = white matter.

Motor dysfunction is the most prominent symptom of stroke-induced disability and has led to a heavy social and economic burden.[1,2] Moreover, the lack of hospital rehabilitation resources has resulted in rehabilitation being unavailable to patients with stroke. Approved methods of rehabilitation are needed.

Home-based telerehabilitation (TR) is defined as a rehabilitation procedure in which rehabilitation physicians offer rehabilitation approaches to patients by telecommunication devices.[3] It has been indicated that TR approaches can be as efficacious as conventional rehabilitation (CR) in improving activities of daily living (ADL) and enhanced compliance with rehabilitation training.[4,5] Structural MRI (sMRI) and fMRI studies have provided information about the structural neuroplastic alterations underlying the rehabilitation process in patients with stroke,[6] and motor recovery after stroke has been associated with the structural brain reorganization of the primary motor cortex (M1), repair of the corticospinal tracts (CSTs), and functional reorganization of interhemispheric M1 areas.[7–12]

Based on the findings from prior clinical trials and our preliminary study, this trial was conducted to determine the effects of a 12-week home-based motor training TR procedure in patients with subcortical stroke with motor dysfunction by the combined use of motor function assessments and multimodality MRI analysis methods. We made the joint hypothesis that the home-based TR approach would be noninferior to CR training on both limb motor function and ADL and superior on at least one of them. Secondary hypotheses explored whether the observed improvement of neural functions could be accounted for by changes to structural and functional brain plasticity, including increased gray matter volume (GMV) in bilateral M1 areas, improved integrity of the CST, and enhanced M1 M1 resting-state functional connectivity (rsFC).

Methods

Participants

A consecutive series of patients with a diagnosis of stroke who were admitted to the neurology department of Shanghai Fifth People's Hospital affiliated with Fudan University between July 2017 and January 2019 were screened for inclusion by a consensus panel of 2 senior neurologists and 1 radiologist. The inclusion criteria were as follows: (1) aged 30 85 years; (2) right-handed before stroke; (3) screening within 1 3 weeks after stroke symptom onset and in a stable condition; (4) first-onset stroke with a single subcortical lesion involving the motor pathway; (5) clinical evidence of hemiplegia based on neurologic examination, and the corresponding responsible lesions evident on CT or MRI; (6) NIH Stroke Scale (NIHSS) score 2 20; and (7) not receiving regular rehabilitation training but who have a strong need for rehabilitation and good family support.

The exclusion criteria included the following: (1) unconsciousness, cognitive impairment, or cooperation difficulties; (2) cerebellar or pontine lesions; (3) other brain abnormalities or psychiatric disorders, or clinically significant or unstable medical diseases; (4) use of medications that might affect motor examinations, such as antipsychotics and antiepileptics; (5) contraindications for MRI scanning; and (6) claustrophobia.

Randomization and blinding

Participants who met the eligibility criteria were randomly assigned in a 1:1 ratio to the TR group or CR group using a stratified block allocation scheme (variable block size). The randomization procedure was performed by a neurologist who was not involved in the rehabilitation training, study measurements, or data analysis. The enrolled patients were aware of the differences in the rehabilitative interventions. Although they were not informed specifically to know which rehabilitation training program was the experimental or control group as neither the consent forms nor the verbal explanations referred to that specific information, given the nature of the rehabilitation intervention, it was impossible to blind the patients, caregivers, and therapists about allocation and intervention; only MRI data acquisition staff, outcome assessors, and data analysts were blinded.

Rehabilitation procedures

All the patients were required to receive the rehabilitative intervention for up to 12 weeks after inclusion with a target of 10 rehabilitation training sessions per week with 60 minutes of occupational therapy (OT) and physical therapy (PT) and 20 minutes of EMG-triggered neuromuscular stimulation (ETNS) for each session.

Patients assigned to the TR group participated in rehabilitation training at home with the Telemedicine Rehabilitation System

(TRS) under the therapists' guidance. The TRS consists of a therapist end, a network data system, and a patient end. Therapists supervise the patients to conduct OT/PT and ENTS by live video conferencing via TRS. Patients randomized to the CR group completed the rehabilitation training in the outpatient rehabilitation department and the training was conducted face-to-face with the rehabilitation therapists. The details of the rehabilitation procedures of patients in the TR group and CR group, as well as the apparatus applied in the present trial, have been described previously.[5]

The amounts of OT/PT and ETNS were registered for each patient by either the patients or the caregivers (in the TR group) and the therapists (in the CR group). All the participants were assessed at baseline (after randomization and within 72 hours before rehabilitation training), after the rehabilitative interventions (within 1 week), and at the end of the 12-week follow-up period (±1 week).

Outcomes

The primary outcomes were motor function, measured by the Fugl-Meyer assessment (FMA) for upper and lower extremities, and ADL, measured by the modified Barthel Index (MBI). The secondary outcomes included structural and functional indices: functional connectivity between the bilateral M1 areas; the GMV of the bilateral M1 areas; and white matter (WM) integrity of the bilateral CSTs measured by fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity, and radial diffusivity (RD). As a measure of directionality of the diffusion tensor, FA has been used as a substitutional parameter for microstructural WM integrity. MD is used to represent the average magnitude of molecular water translation in all directions. Axial diffusivity and RD describe the direction of diffusion and have been correlated with the constitution of axons and myelin sheaths, respectively.[13]

MRI data acquisition

The MRI data were acquired via a 3.0T Philips Achieva MRI scanner (Philips Medical Systems, Best, Netherlands) with a 32-channel head coil. Tight but comfortable foam padding was used to minimize head motion, and earplugs were used to reduce scanner noise. During scanning, all participants were instructed to remain awake, keep their eyes closed, stay motionless, and attempt to think of nothing. The imaging protocols included the following parameters: (1) resting-state fMRIs were scanned using an echoplanar imaging (EPI) sequence: repetition time 2,000 ms, echo time (TE) 30 ms, flip angle 90°, field of view (FOV) 220 × 220 mm, matrix 64 × 64, slice thickness 3 mm, gap 1 mm, interleaved transversal slices 38, voxel size 3 × 3 × 3 mm, and 180 volumes; (2) high-resolution sagittal T1-weighted images were acquired by a 3D magnetization-prepared rapid gradient echo sequence: repetition time 8.0 ms, TE 3.7 ms, flip angle 12°, FOV 256 mm × 256 mm, matrix 256 × 256, slice thickness 1 mm, voxel size 1 mm × 1 mm × 1 mm, slices 180; and (3) diffusion tensor imaging (DTI) images were obtained by a diffusion-weighted pulsed-gradients spin EPI sequence: repetition time 6,800 ms, TE 90 ms, flip angle 90°, FOV 256 × 256 mm, matrix 128 × 128, slice thickness 3 mm, voxel size 2 × 2 × 2 mm, slices 50, and 34 different diffusion directions for the diffusion-sensitizing gradients at a b value of 1,000 seconds/mm^2.

M1 definition and seed masks

The bilateral M1 areas for the GMV analysis were separately extracted from Brodmann area 4 in the Brodmann atlas. The seed masks for M1-M1 rsFC analysis of the left M1 (M1.L) and right M1 (M1.R) were defined as a sphere with a radius of 6 mm that was centered at the Montreal Neurologic Institute peak according to previous studies (M1.L: x = −12, y = −30, and z = 54; M1.R: x = 12, y = −30, and z = 54).[14]

Voxel-based morphometry (VBM) analysis

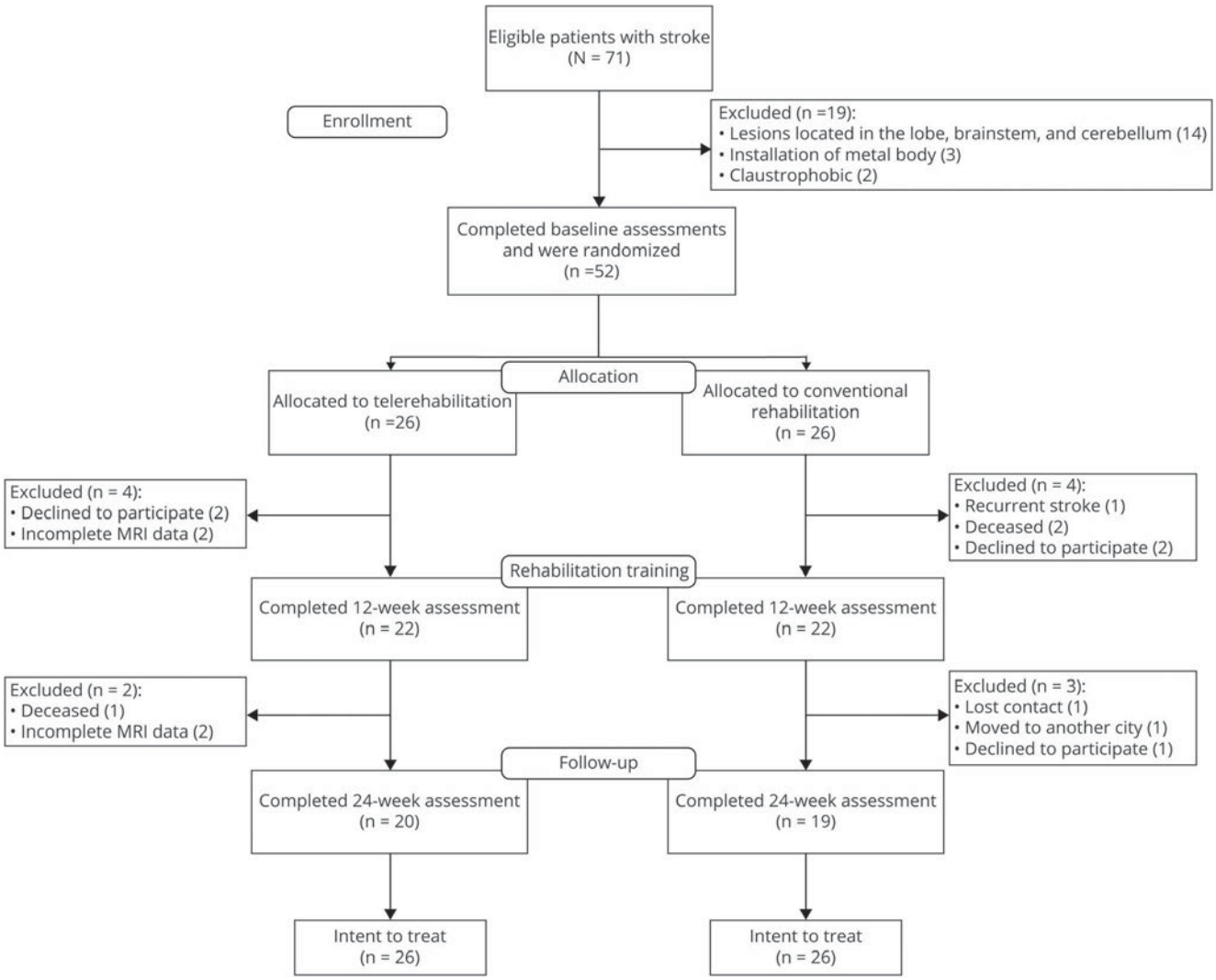
The individual 3D T1-weighted image preprocessing was conducted using the statistical parametric mapping (SPM) 8 (fil.ion.ucl.ac.uk/spm/) software packages running in MATLAB R2013a (The MathWorks Inc., Natick, MA) and the optimized VBM analysis was performed by the VBM8 toolbox (dbm.neuro.uni-jena.de/vbm). The VBM analysis procedure in the present study included a quality check, normalization, segmentation, modulation, and smoothing. The GMVs of the bilateral M1areas were calculated separately from the individual smoothed images. The GMV values of the bilateral M1 areas for each participant were extracted individually, and the GMV value between-group difference was calculated by analysis of covariance.

DTI processing and automatic tracts identification analysis

DTI data preprocessing was implemented by using FSL v5.0 software (Oxford Center for Functional MRI of the Brain; fmrib.ox.ac.uk/fsl/). Data were manually checked for excessive dropped volumes and imaging artifacts. The FMRIB's Diffusion Toolbox v3.0 (FDT) was used for correcting eddy current and head motion and calculating the diffusion measures (FA, MD, axial diffusivity, and RD).

The automated fiber quantification (AFQ) package (jasonyeatman.com/software/) was used to identify bilateral CSTs, and the diffusion measures along the tract trajectory were quantified in each participant's brain. AFQ reconstructs the whole-brain 20 major white matter tracts, and measures FA, MD, axial diffusivity, and RD along their trajectories. Each tract was sampled into 100 equidistant nodes, and the tract profile of each fiber tract was created by mapping the diffusion measures onto each tract along the central portion of the tract.[15] In the current study, to assess changes over the course of the rehabilitative intervention, the middle 80% of the CST was selected to avoid the influence from crossing fibers near cortical terminations and the potential partial volume effect at the gray matter or white matter border. Then the mean tract values of the diffusion measures for each participant for each CST were used for analysis.

Figure 1 Flowchart of the study procedures



Resting-state fMRI analysis

Resting-state fMRI data were preprocessed using the advanced data processing assistant for resting-state fMRI (DPARSF)[16] (rfmri.org/dpabi/) and SPM8 (fil.ion.ucl.ac.uk/spm/) software packages. The preprocessing included deleting the first 10 time points, slice timing, realignment, normalization, smoothing, deleting nuisance signals, detrending, and filtering. For M1-M1 rsFC analysis, Pearson correlation coefficients between the M1.L and M1.R time series were calculated and converted to z values by Fisher z transformation to improve normality.[17] The Fisher z transformation correlation coefficients were then extracted for each patient for analysis.

Sample size

On the basis of our preliminary study and according to the joint hypothesis, 42 patients were needed to have an overall 90% power at the 0.025 significance level to detect differences of 2.8 ± 2.2 on FMA and 3.3 ± 2.7 on MBI based on non-inferiority margins of 30% of change in FMA score and 50% of change in MBI in the CR group. Taking approximately 20% attrition into consideration, the recruitment of 52 patients was necessary.

Statistical analysis

The normality of all demographic, clinical, and sMRI/fMRI variables was tested by using the Kolmogorov-Smirnov method and histogram inspection. For baseline data, independent sample t tests for data with a normal distribution, nonparametric tests for data with a skewed distribution, and Pearson χ^2 tests or Fisher exact tests for categorical data were applied to assess group differences.

All outcome variables were calculated in accordance with the intention-to-treat principle, and missing data were dealt with by using the last observation carried forward method. For primary and secondary outcomes, we applied parallel gatekeeping procedures to the current study to maintaining type I error at the nominal level across all primary and secondary outcomes and assuring that secondary outcome assessment depends on primary outcome results. In parallel gatekeeping, testing proceeds to the next ordered set of hypotheses if at least one

Table 1 Demographic and clinical characteristics of patient groups

Variables	TR (n = 26)	CR (n = 26)	*p* Value
Age, y	64.19 ± 9.42	59.42 ± 10.00	0.083
Male	14 (53.8)	12 (46.2)	0.579
Education, y	10 (7.0, 13.0)	10 (7.0, 12.3)	0.818
High-risk factors			
Smoking	7 (26.9)	9 (34.6)	0.548
Hypertension	15 (57.7)	14 (53.8)	0.780
Diabetes mellitus	15 (57.7)	14 (53.8)	0.780
Dyslipidemia or obesity	10 (38.5)	7 (26.9)	0.375
Atrial fibrillation	4 (15.4)	9 (34.6)	0.109
TIA	1 (3.8)	2 (7.7)	0.548
Time from stroke onset, d	14 (13.0, 16.0)	14 (12.6, 16.0)	0.919
Hemisphere of infarction			0.402
Left-sided	10 (38.5)	13 (50.0)	
Right-sided	16 (61.5)	13 (50.0)	
Lesion location			0.674
Basal ganglia	10 (38.5)	12 (46.2)	
Corona radiate	6 (23.1)	8 (30.8)	
Internal capsule	6 (11.5)	4 (15.4)	
Thalamus	4 (15.4)	2 (7.7)	
Lesion volume, mL	4.2 (3.2, 5.4)	4.9 (3.4, 6.2)	0.176
Treatment sessions	110.0 (96.0, 116.0)	97.0 (77.5, 108.0)	0.023
Duration of OT/PT, h	109.0 (95.7, 116.0)	97.0 (77.5, 108.0)	0.031
Duration of ETNS, min	2,210.0 (1,940.0, 2,282.5)	1940.0 (1,550.0, 2,160.0)	0.019
MMSE	28 (27.0, 30.0)	28 (27.0, 29.0)	0.719
NIHSS	5 (3.0, 6.0)	5 (3.8, 8.0)	0.240
FMA	71.88 ± 10.76	71.65 ± 10.25	0.937
MBI	70.0 (58.75, 76.25)	77.5 (60.0, 85.0)	0.181

Abbreviations: CR conventional rehabilitation; ETNS EMG triggered neuromuscular stimulation; FMA Fugl Meyer assessment; MBI modified Barthel Index; MMSE Mini Mental State Examination; NIHSS NIH Stroke Scale; OT occupational therapy; PT physical therapy; TR telerehabilitation.
Data are reported as mean ± SD, n (%), or median (interquartile range).

outcome in the previous set is significant.[18] The overall type I error is protected by reducing the significant level for each sequential set of tests according to a rejection gain factor that reflects the cumulative proportion of hypotheses rejected in previous sets. The rejection gain factor for a current set is simply the product of the rejection proportions for the previously tested sets. If all previous tests have been rejected, the current set is tested at α, because the rejection gain factor would be 1.[19] We constructed ordered sets of primary and secondary outcomes: set 1 = FMA score and MBI score; set 2 = rsFC between M1.L and M1.R; set 3 = GMV of M1.L and GMV of M1.R; set 4 = FA of left CST (CSTL), FA of right CST (CSTR), MD of CSTL, MD of CSTR, axial diffusivity of CSTL, axial diffusivity of CSTR, RD of CSTL, and RD of CSTR. For primary outcomes in set 1, the α is 0.025 for both noninferiority and superiority 1-tailed testing. For secondary outcomes in set 2 4, each set tested at overall α of 0.05. Analyses of covariance for the dependent variable in outcomes comparing mean change scores from baseline to the end of the 12-week rehabilitative intervention and from baseline to the end of the follow-up period between groups were adopted, adjusting for the corresponding baseline scores, age, NIHSS score at baseline, and the number of treatment sessions, OT/PT, and ETNS durations. The relationship between significant motor function score changes and brain structural or functional changes was assessed by partial correlations (to factor out age, sex, and educational level) to investigate a potential neural mechanism for the recovery of motor function.

Classification of evidence

The primary research objective was to determine the effects of a 12-week home-based motor training TR procedure in patients with subcortical stroke with motor dysfunction by the combined use of motor function assessments and multimodality MRI analysis methods.

Standard protocol approvals, registrations, and patient consents

This randomized controlled trial (RCT) was performed according to the principles of the Consolidated *Standards* of Reporting Trials (CONSORT) statement and the CONSORT statement for nonpharmacologic interventions and approved by the local ethical committee of Shanghai Fifth People's Hospital, Fudan University (2014-ETRE-066). Patients with subcortical stroke with motor dysfunction were recruited. Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki. This trial was registered under the Chinese Clinical Trial Registry (ChiCTR-IPR-17011757) and its protocol has been published previously.[20]

Data availability

The protocol and the statistical analysis plan are available on request. Deidentified participant data are not available for legal and ethical reasons.

Results

Demographic characteristics and clinical symptoms

A total of 71 patients were screened at admission to the rehabilitation training program. Of those, 19 patients were excluded according to the exclusion criteria (figure 1). Of the 52

Table 2 Change in primary outcomes from baseline to week 12

Outcome	TR (n = 26)	CR (n = 26)	Noninferiority 1-tailed test[a]			Superiority 1-tailed test[b]	
			Mean difference (95% CI)	Delta	*p* Value	Mean difference (97.5% CI)	*p* Value
Change in FMA	11.115 ± 8.905	5.307 ± 4.593	5.807 (0.560[c] to 6.972)	0.3	0.003	5.807 (0.076[c] to 7.456)	0.011
Change in MBI	12.692 ± 9.821	7.115 ± 7.096	5.576 (0.504[c] to 10.349)	0.5	0.019	5.576 (−0.0856[c] to 11.098)	0.097

Abbreviations: CI confidence interval; CR conventional rehabilitation; FMA Fugl Meyer assessment; MBI modified Barthel Index; TR telerehabilitation. Results presented as mean (SD). Overall α is 0.025 for both noninferiority and superiority testing. Noninferiority was found on both outcomes with the given noninferiority deltas (both $p \leq 0.025$) and superiority on FMA ($p \leq 0.025/2$ 0.0125).
[a] Noninferiority: significant if lower confidence limit ([c]) is more than delta.
[b] Superiority: significant if lower confidence limit ([c]) is more than 0 for FMA and MBI.

eligible patients, 26 were randomly assigned to the home-based motor training TR group, and 26 to the CR group. Demographic characteristics, clinical characteristics, and the duration of the rehabilitation training of the patients are shown in table 1. There were no significant differences with regard to the demographic and clinical characteristics between the patients in the TR group and CR group. Significant differences were found in the number of treatment sessions and the total duration of OT/PT and ETNS between the 2 groups (table 1).

Primary outcome measures

The changes from baseline to the end of the 12-week rehabilitative intervention period for the primary outcome variables are listed in table 2 and figure 2. From the results of noninferiority testing, for change in FMA score, we observed mean (SD) of 11.115 (8.905) and 5.307 (4.593) for the TR and CR groups, respectively, for a mean difference of 5.807 with 95% confidence interval (CI) of 0.560 6.972. There was significant difference between the 2 groups in mean change in FMA score, with the lower limit of the CI, 0.560, being above the noninferiority deltas of 0.3 point ($p = 0.003$).

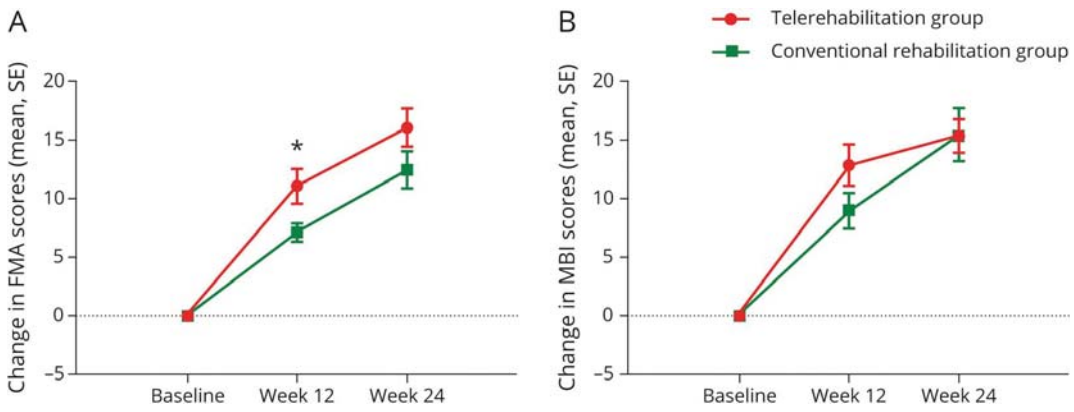
For change in MBI score, the change in mean score was 5.576 points larger in the TR group (95% CI 0.504 to 10.349; $p = 0.019$). The noninferiority margin was 0.5, which fell outside of this 95% CI, indicating that TR was noninferior to CR training on the change in MBI. From the results of superiority testing, we found significant difference for change in FMA score in a 1-tailed test ($p = 0.011$), with 97.5% CI of 0.076 7.456, and no difference was observed for change in MBI score (97.5% CI −0.0856 to 11.098; $p = 0.097$).

There were no significant differences observed in the mean change of FMA and MBI for noninferiority and superiority testing from baseline to the end of the 12-week follow-up period (figure 2, A and B).

Secondary outcome measures

As shown in table 3 and figure 3, A and B, for change in rsFC between the bilateral M1 areas from baseline to the end of the 12-week rehabilitative intervention period, we observed mean (SD) of 0.424 (0.258) and 0.219 (0.209) for the TR and CR groups, respectively, for a mean difference of 0.204 with 95% CI 0.074 0.336 adjusted by covariates. There was significant difference between the 2 groups in mean change in rsFC between the bilateral M1 areas score ($p = 0.031$). For secondary outcomes of set 3 or set 4, we found no differences between the TR and CR groups from baseline to the end of

Figure 2 Rehabilitation effect on motor function and activities of daily living



(A) Rehabilitation effect on motor function (Fugl Meyer assessment [FMA]), showing significant improvement in FMA at the end of rehabilitative intervention compared with the baseline in the TR group. (B) Rehabilitation effect on activities of daily living measured by modified Barthel Index (MBI). *Significant group by time interaction effect. The red lines and the green lines represent the telerehabilitation group and conventional rehabilitation group, respectively.

Table 3 Change in secondary outcomes from baseline to week 12

	From baseline to week 12			
Outcome	**TR (n = 26)**	**CR (n = 26)**	**Mean difference (95% CI)**	***p* Value**
Change in rsFC between M1.L and M1.R	0.424 ± 0.258	0.219 ± 0.209	0.204 (0.074 to 0.336)	0.031
Change in GMV of M1.L	0.033 ± 0.058	0.023 ± 0.052	0.009 (−0.021 to 0.040)	0.648
Change in GMV of M1.R	0.046 ± 0.076	0.026 ± 0.052	0.019 (−0.033 to 0.044)	0.706
Change in FA of CSTL	0.045 ± 0.049	0.018 ± 0.099	0.027 (−0.024 to 0.074)	0.311
Change in FA of CSTR	0.047 ± 0.063	0.038 ± 0.042	0.009 (−0.033 to 0.032)	0.971
Change in MD of CSTL	−0.015 ± 0.109	−0.012 ± 0.068	−0.003 (−0.052 to 0.059)	0.905
Change in MD of CSTR	−0.016 ± 0.078	−0.029 ± 0.178	0.014 (−0.060 to 0.106)	0.576
Change in axial diffusivity of CSTL	−0.057 ± 0.086	−0.025 ± 0.110	−0.032 (−0.072 to 0.047)	0.676
Change in axial diffusivity of CSTR	−0.021 ± 0.069	−0.042 ± 0.126	0.021 (−0.022 to 0.102)	0.197
Change in RD of CSTL	−0.135 ± 0.206	−0.105 ± 0.099	−0.029 (−0.101 to 0.930)	0.930
Change in RD of CSTR	−0.117 ± 0.142	−0.099 ± 0.135	−0.018 (−0.072 to 0.088)	0.836

Abbreviations: CI confidence interval; CR conventional rehabilitation; CSTL left corticospinal tract; CSTR right corticospinal tract; FA fractional anisotropy; GMV gray matter volume; M1.L left M1; M1.R right M1; MD mean diffusivity; RD radial diffusivity; rsFC resting state functional connectivity; TR telerehabilitation.
Results presented as mean (SD). For secondary outcomes, the overall α was set at 0.05. According to parallel gatekeeping, the joint null hypothesis for set 1 is rejected (proportion rejection is 1/1 1), so that set 2 is assessed using an α of 0.05 × (1) 0.05 for 1 outcome. Set 2 is rejected (*p* value 0.031 < 0.05), so we proceed to set 3 using an overall α of 0.05 × (1) × (1) 0.05, and we evaluate each of the 2 outcomes at 0.05/2 0.025. Because neither of the 2 outcomes is significant in set 3 (*p* value 0.648 > 0.05 and *p* value 0.706 > 0.05), the parallel gatekeeping procedure stops here, and none of the outcomes in set 4 can be deemed significant or nonsignificant.

the 12-week rehabilitative intervention period (table 3 and figures 4 and 5).

Because no significant differences were found on primary outcomes from baseline to week 24, according to parallel gatekeeping procedure, none of the secondary outcomes can be deemed significant or nonsignificant from baseline to week 24.

For the partial correlation analysis, we identified that the increased M1-M1 rsFC was positively associated with the FMA changes from baseline to week 12 in the TR group ($r = 0.537$, $p = 0.018$, uncorrected) but not in the CR group ($r = 0.203$, $p = 0.405$, uncorrected) (figure 2). However, no significant correlation was identified after adjustment for multiple comparisons.

Adverse events

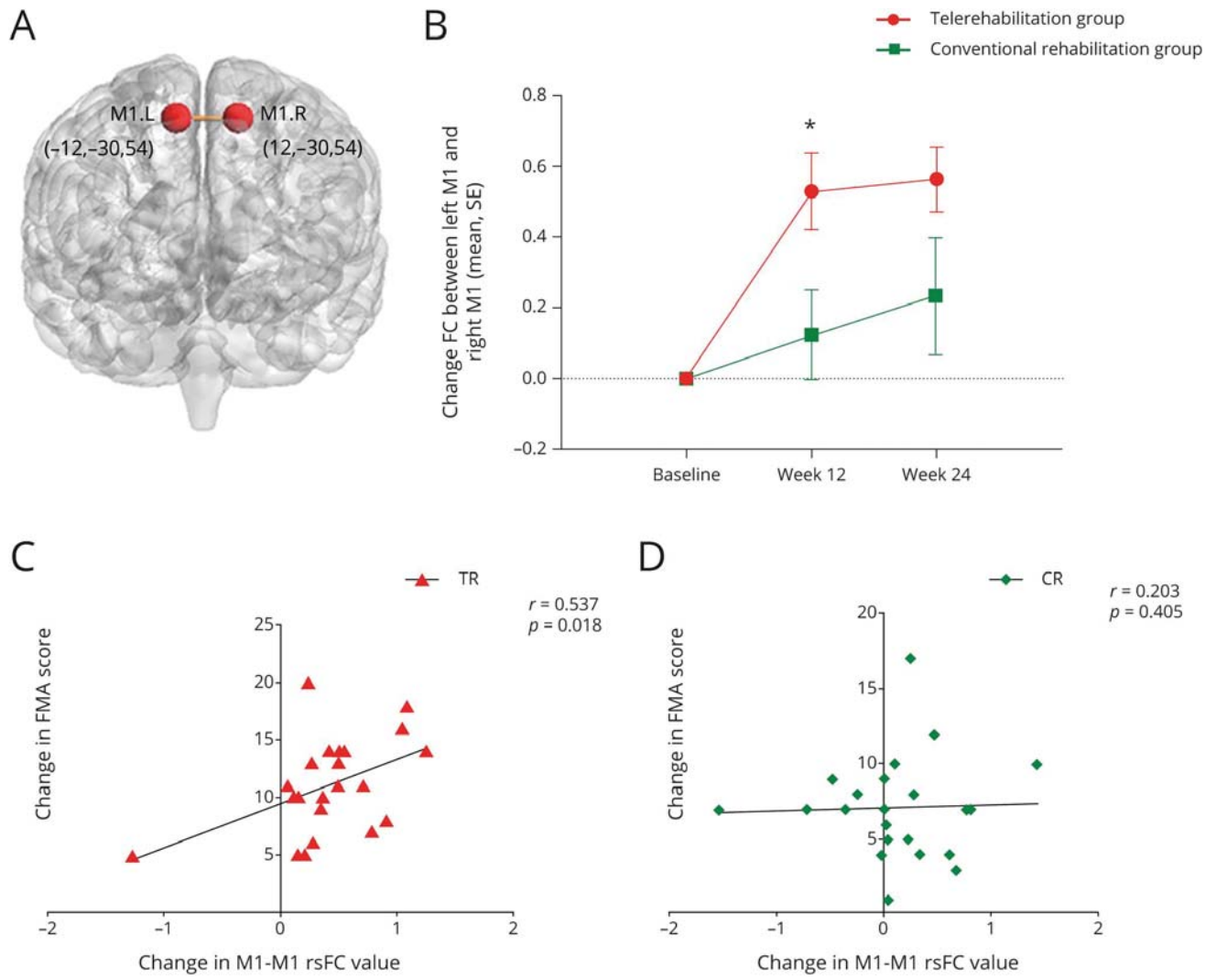
There were no study-related adverse events reported during the process of the rehabilitative intervention in either the TR or CR group.

Discussion

For the co primary outcomes, in order to protect type I error, we focused on joint hypothesis testing methods to handle the setting where TR is preferred to CR only if it is observed superior on at least one of change in FMA or MBI and noninferior (i.e., not worse) on the rest. Such a design is attractive because it ensures that "no harm" is done by the TR approach concluded to be better; it must be shown to be at least as good as CR training on each primary outcome, and better on 1 or 2 outcomes. Because both noninferiority and superiority are required, when evaluating noninferiority on all outcomes and superiority on at least one, the whole procedure is an intersection union test,[21,22] and adjustment for significant criterion is not needed.

For testing primary outcomes from baseline to week 12, first, we concluded noninferiority of TR to CR on both change score of FMA and MBI because the upper limits of the CIs are above the noninferiority of 0.3 point on the change in FMA and of 0.5 point on the change in MBI (table 2). In other words, we conclude that TR is >0.3 or 0.5 point better than CR on change in FMA or MBI score. Because noninferiority is concluded for both change in FMA and MBI, the superiority testing can be conducted to assess whether TR is superior to CR on any of the outcomes. In the current study, the smallest 1-tailed superiority *p* value for the 2 primary outcomes ($p = 0.011$ for change in FMA) was smaller than $\alpha/2 = 0.0125$, hence the TR approach is superior to CR training. Superiority is found for change in FMA because the 97.5% CI (adjusting for 2 superiority tests) is above zero (table 2). Because noninferiority is found on both primary outcomes and superiority on change in FMA (i.e., at least 1 of the 2 outcomes), the joint null hypothesis ("TR inferior to CR on ≥1 outcome" or "CR superior on none") is rejected and TR is better than CR on improved motor function.

Figure 3 Rehabilitation effect on resting-state functional connectivity (rsFC) between bilateral M1 areas



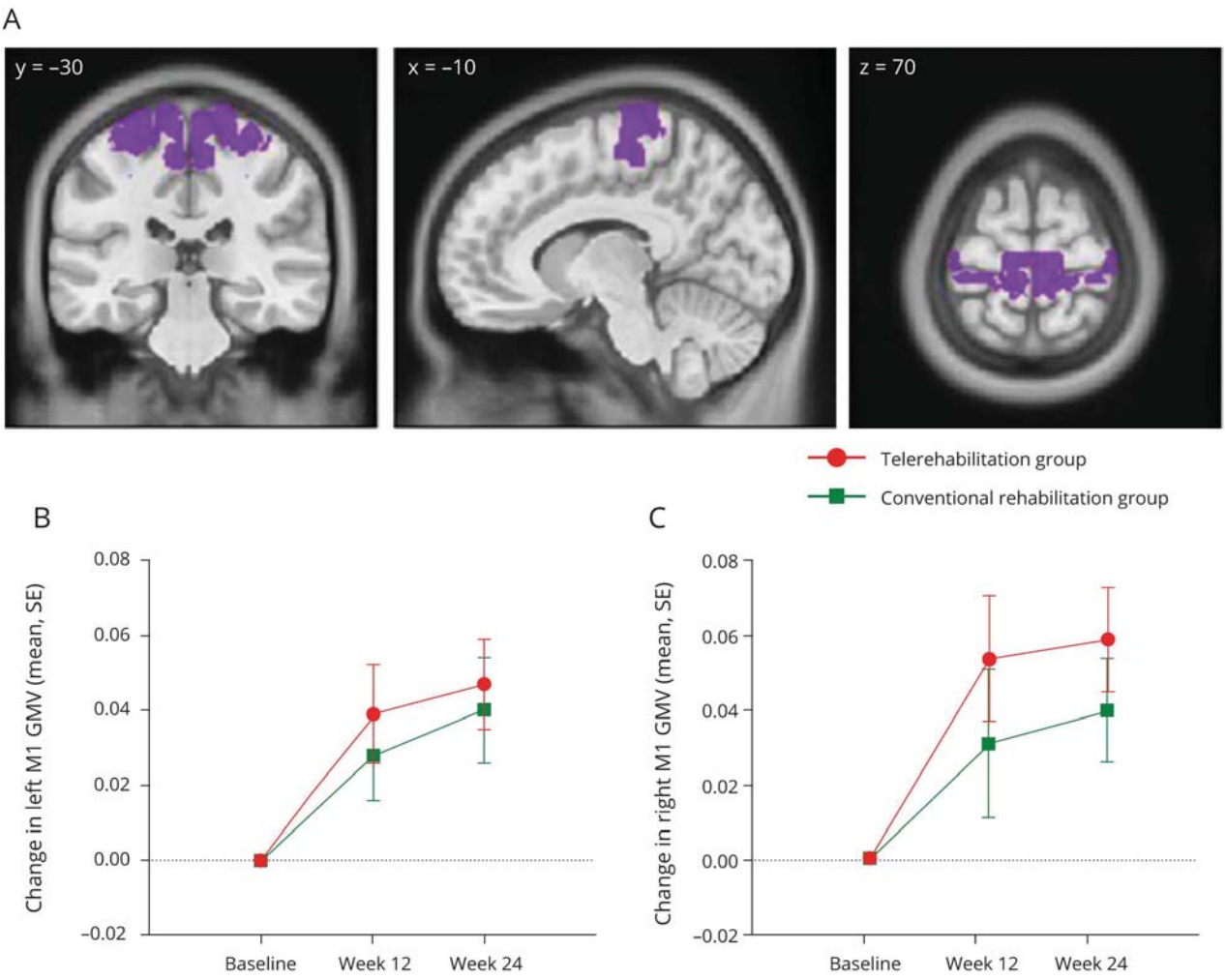
(A) The peak coordinates of M1.L and M1.R in Montreal Neurologic Institute space. (B) Significant increase in M1 M1 rsFC at the end of rehabilitative intervention relative to the baseline in the telerehabilitation (TR) group. (C) Correlation between change in M1 M1 rsFC and change in Fugl Meyer assessment (FMA) score in the TR group. (D) Correlation between change in M1 M1 rsFC and change in FMA score in the conventional rehabilitation (CR) group. *Significant group by time interaction effect. The red lines and the green lines represent the TR group and CR group, respectively. FC functional connectivity; M1.L left M1; M1.R right M1.

Parallel gatekeeping procedures were applied to maintaining type I error at the nominal level across all primary and secondary outcomes and assuring that secondary outcome assessment depends on primary outcome results. For change in outcomes from baseline to week 12, we reject the joint null hypothesis, so we can proceed to set 2 of secondary outcomes. The joint null hypothesis for set 1 is rejected (proportion rejection is $1/1 = 1$), so that set 2 is assessed using an α of $0.05 \times (1) = 0.05$ for 1 outcome. Set 2 is rejected (p value $= 0.031 < 0.05$), so we proceed to set 3 using an overall α of $0.05 \times (1) \times (1) = 0.05$, and we evaluate each of the 2 outcomes at $0.05/2 = 0.025$. Because neither of the 2 outcomes is significant in set 3 (p value $= 0.648 > 0.05$ and p value $= 0.706 > 0.05$), the parallel gatekeeping procedure stops here, and none of the outcomes in set 4 can be deemed significant or nonsignificant. For change in outcomes from baseline to week 24, we cannot reject the joint null hypothesis, so further analysis of the secondary outcomes is of meaninglessness.

Strengths of the trial include its high-compliance design and the combined use of clinical behavior measurements and sMRI/fMRI indices as outcomes. We observed that relative to CR training, the home-based motor training TR approach led to a significant improvement in motor function, as evaluated by the FMA. This result is inconsistent with the findings from a recent meta-analysis of TR approaches, which provided moderate evidence that the TR approach was as efficacious as CR training in approach for improving both ADL and motor function in patients with stroke.[23]

There are several possible explanations for this discrepancy. In the present study, all the patients were required to complete a

Figure 4 Rehabilitation effect on gray matter volume (GMV) of M1 areas

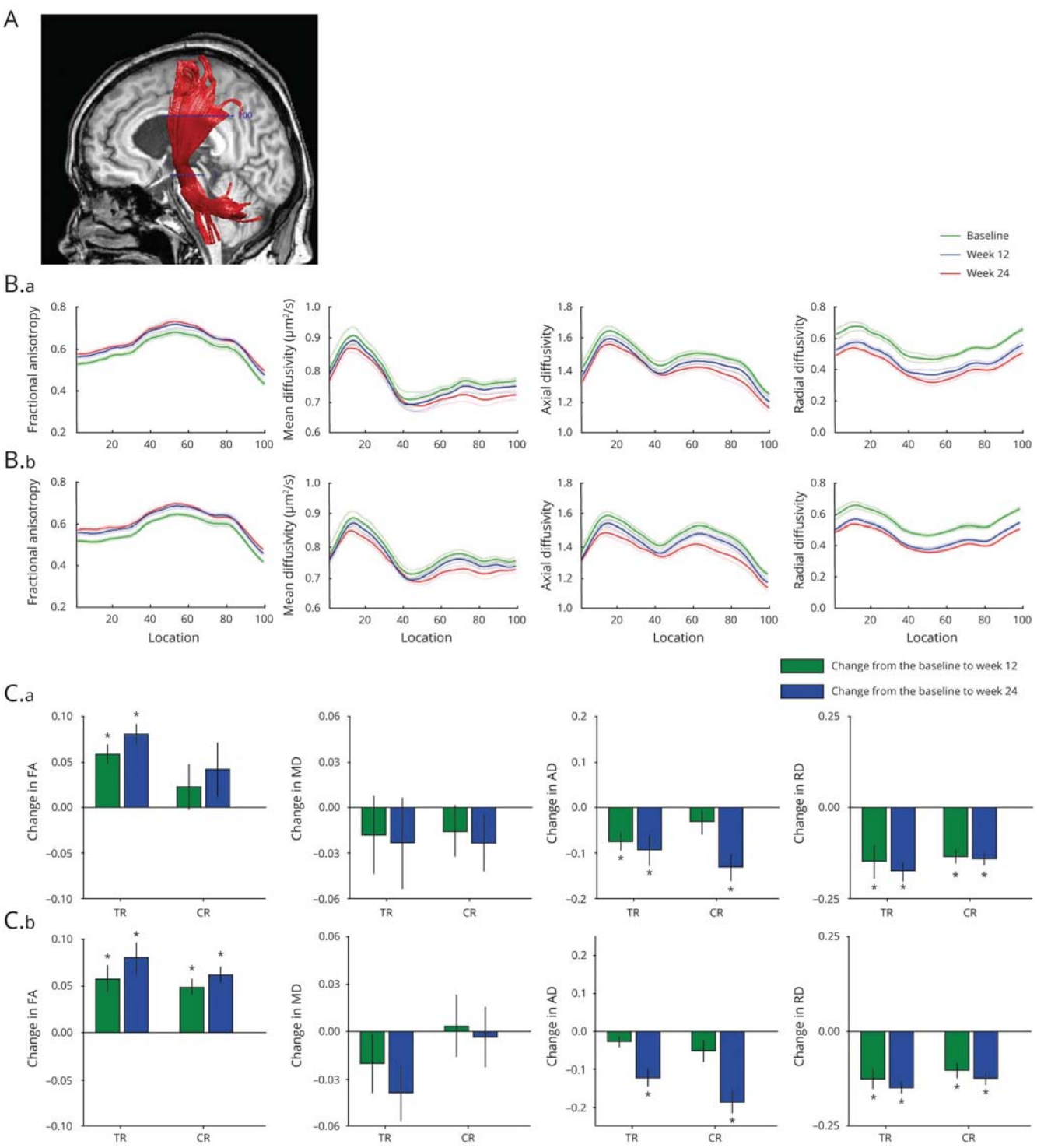


(A) The bilateral M1 areas were separately extracted from Brodmann area 4 in the Brodmann atlas, as demonstrated in Montreal Neurologic Institute space: x −10; y −30; z 70. (B, C) Rehabilitation effect on GMV of left M1 and right M1. No significant rehabilitative intervention effect on GMV of M1 was found in either hemisphere. The red lines and the green lines represent the telerehabilitation group and conventional rehabilitation group, respectively.

certain amount of rehabilitation training during the rehabilitation period, but there was no mandatory requirement for the rehabilitation training to be time matched. We found that the number of treatment sessions and the total durations of OT/PT and ETNS were significantly different between the TR and CR groups (table 1). To investigate whether the positive effects of TR on improving motor function and increasing M1-M1 rsFC were only because participants in the TR group received more rehabilitation exposure, we assessed the effects with variables for the number of treatment sessions, OT/PT, and ETNS durations entered as covariates to control the potential confounding effects. Results showed in the OT/PT and ETNS durations between the 2 groups had no effects on TR in promoting motor function or enhancing M1-M1 rsFC for patients with stroke, or the effects were not large enough to be detected (for change in FMA: treatment sessions, $F = 0.855$, $p = 0.360$, 95% CI −0.234 to 0.629; OT/PT durations, $F = 0.438$, $p = 0.512$, 95% CI −0.480 to 0.949; ETNS durations, $F = 0.079$, $p = 0.512$, 95% CI −0.041 to 0.031; for change in M1-M1 rsFC: treatment sessions, $F = 0.528$, $p = 0.471$, 95% CI −0.012 to 0.025; OT/PT durations, $F = 0.262$, $p = 0.611$, 95% CI −0.023 to 0.038; ETNS durations, $F = 0.083$, $p = 0.775$, 95% CI −0.002 to 0.001). Why was the dosage greater in the TR group than in the CR group? This may be explained by the purpose and characteristics of the TR model itself.

As previous studies have described, although it is a challenge to detect potential differences in extremity motor function in the context of spontaneous biological recovery during the subacute phase of stroke,[24] and although studies have shown that it is difficult for patients with stroke in the subacute stage to obtain effective rehabilitation training strategies that require movement tasks,[25] significant differences in extremity motor function are likely if the contrast between the rehabilitation training dosage in the intervention group and control group is remarkable.[26] Furthermore, studies have also shown that early poststroke recovery occurs as a result of possible interactions with therapies and differences in

Figure 5 Change in tract profiles during rehabilitative intervention and rehabilitation effect on diffusion parameters



(A) Tracking result of corticospinal tract (CST) in an example analyzed by the automated fiber quantification method. The blue dashed lines denote the start and termination waypoint regions of interest of CST. For each diffusion parameter, the values were mapped onto each of the 100 evenly spaced nodes from the start and termination waypoint along the CST to create a track profile (see supplementary file). (B.a) The track profiles of fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity, and radial diffusivity (RD) profiles of left CST measured at baseline, week 12, and week 24. (B.b) The track profiles of FA, MD, axial diffusivity, and RD profiles of right CST across patients, measured at baseline, week 12, and week 24. The horizontal axis indicates the location between the start and termination waypoint region of interest along CST. The solid lines represent the average diffusion parameter values and the dashed lines represent SE across patients at each node. The green, blue, and red lines represent baseline, week 12, and week 24, respectively. (C) Middle 80% nodes (nodes 10 to 90) of CST selected to avoid the partial volume effects and averaged across groups for comparison. Change in FA, MD, axial diffusivity, and RD in left CST (C.a) and right CST (C.b) from baseline to week 12 and from baseline to week 24 are shown. Bar heights stand for the magnitude of change observed at week 12 or week 24, relative to baseline. *Significant time effect of increase in FA or decrease in axial diffusivity/RD at week 12 or at week 24 relative to the baseline. The green and blue filled bars represent change from baseline to week 12 and change from baseline to week 24, respectively.

environment, suggesting that a "true" natural recovery pattern does not exist. In other words, the inability to study stroke recovery in a real naturalistic setting suggests that the observed time-dependent changes reflect progress over time (given the variability in rehabilitation intervention modality, intensity, and duration) rather than spontaneous, intrinsic recovery alone.[27] Because the current study has proven that the effects of rehabilitation intensity and duration in the improvement of motor function are not significant, we intend to consider that the TR intervention modality, including a realistic family environment, convenient rehabilitation measures, and timely rehabilitation effect feedback, plays a crucial role in the improvement of motor function and enhancement of M1-M1 rsFC.

The home-based motor training TR approaches used in the current trial were designed to make the rehabilitation training accessible for patients with stroke with movement disorders at home; they also lessen the travel burden, especially for those who found it inconvenient with regard to time and distance to receive CR in hospitals or rehabilitation centers. The TRS, which integrated ETNS treatment, the assessment of physiologic parameters, rehabilitation exercise prescriptions, rehabilitation training records, data storage, and timely rehabilitation effect feedback, provided a convenient way for patients to conduct rehabilitation, which improved patient compliance.[28] Moreover, the TR approach could afford more opportunities for patients to participate and learn from the realistic family and social environment. These unintended and individualized exercises, including daily routines and social participation activities, together with the rehabilitation prescription training, may jointly explain the positive role of the TR approach in motor recovery.[29]

The use of outcome measures that were capable of identifying recovery on an impairment and compensation level may have been important. As a primary outcome, the FMA is characterized by high reliability and validity in limb motor function with high sensitivity and specificity as its items are detailed and quantified in each part.[30] The FMA is able to assess the quality and activity level of movement; it also reflects the kinematics of various factors, such as coordinated movement, reflex activity, and joint motion.[31] Hence it is more likely that the FMA of both the upper and lower extremities would detect differences in motor function improvement for hemiplegic patients with stroke vs FMA of only the upper extremities, as was used in the abovementioned meta-analysis. Furthermore, the clinical characteristics of the patients with stroke should not be neglected in interpreting the results. In the present study, we enrolled patients with first-onset hemiplegic stroke with a single subcortical lesion involving the motor pathway, and we excluded patients who had lesions in the brainstem or cerebellar areas. Compared with the patients in the RCTs included in the above meta-analysis, the patients with stroke in our current study had less clinical heterogeneity, which may have been conducive to reducing the impact of potential confounding factors on these results.

Concerning the secondary outcomes, previous sMRI studies showed that the GMV, cortical thickness, and surface cortex of the ipsilesional sensorimotor cortex were decreased in patients with internal capsule stroke relative to healthy controls,[32] and increased cortical thickness and GMV values have been reported in motor-related areas during recovery after subcortical stroke.[33] In addition, significant changes in motor-related areas have been reported to contribute to stroke recovery.[34] In line with findings from the above studies, in our present study, patients with stroke in both the TR and CR groups exhibited significant increases in the GMV in the bilateral M1 areas after the 12-week rehabilitation training. Our finding of no significant differences between the TR and CR groups prevents us from inferring how the TR approach or CR training exerted their effects on the GMV changes.

Although the AFQ analysis used in the current study showed no significant differences in improving the WM integrity, average magnitude of molecular water translation, or constitution of the axons and myelin sheaths of the CSTL and CSTR between the TR and CR groups, we found that the mean FA increased and the mean RD decreased in the bilateral CSTs after rehabilitation training in each group. These findings indicate improvements in WM integrity and changes in myelin sheaths during the recovery. The biological mechanism underlying these changes in diffusion signals might be associated with multiple sources, such as the branching of glial cells, myelin remodeling, myelination of unmyelinated axons, or changes in vasculature.[35]

Based on the results of previous studies, our findings suggest that the M1-M1 rsFC disconnection caused by stroke could be rebuilt by rehabilitation training,[36] and it is likely that the TR approach is superior to CR training in terms of enhancing connectivity. Furthermore, the rsFC alteration was positively associated with FMA changes in the TR group but not in the CR group. The interhemispheric connectivity changes between the M1 areas may suggest that the brain functional plasticity enhancement induced by the TR approach may improve motor function recovery after stroke. After 12 weeks of follow-up, the differences in significant FMA and rsFC changes between the 2 groups disappeared, which may be due to the rehabilitation duration not being long enough to yield long-term effects on the structural plasticity changes detected by sMRI.

The neurologic function assessments applied in previous studies investigating the effects of the TR approach were not capable of yielding insights into the underlying pathophysiologic mechanisms. The incorporated use of neurologic function assessments and sMRI/fMRI in the current study was expected to explore the underlying brain structural and functional plasticity that accompanied function recovery. The finding of a positive correlation between motor function improvement and M1-M1 rsFC enhancement suggests that the

combined use of imaging biomarkers should be encouraged in motor training clinical studies in patients with stroke.

There are some limitations that need to be considered when interpreting these results. First, a design including a third group receiving no rehabilitation training would allow for the estimation of spontaneous biological recovery after stroke and would highlight the role of rehabilitative intervention in the improvement of motor function. Second, the significant improvements in motor function were diminished by the end of the 12-week follow-up, which may suggest that a longer rehabilitative intervention is required to observe potentially sustainable effects of the home-based motor TR approach. Third, though a few good studies have shown that adaptive brain plasticity in the M1 areas and repair of the CSTs were vital for motor recovery in patients with stroke with movement dysfunction,[37–40] the lack of observed changes in GMV and rsFC values in other brain areas and WM plasticity of other fiber bundles might lead to the loss of some information that would be helpful to better understand the neural mechanisms of the TR rehabilitative intervention.

The home-based motor training TR approach improved motor performances and connectivity between the bilateral M1 areas in patients with subcortical stroke with movement dysfunction. The significant correlation of improved motor function with the restored connection suggested that the imaging biomarkers of functional connectivity could be used to investigate brain plasticity mechanisms during recovery procedures in movement rehabilitation training trials. Although the efficacy and safety profile of the TR approach recommend its adoption, studies including the cost-effectiveness of the TR approach deserve further examination before it can be applied in clinical practice. TR could reduce the cost of rehabilitation delivery by reducing round trip time and travel-related expenses for stroke survivors and their caregivers.[41]

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Disclosure

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Shufan Zhang, MD	Department of Neurology, Shanghai Fifth People's Hospital, Fudan University, China	Study design, study conduct, interpretation of data, study reporting, manuscript writing and editing
Yonghui Shi, MD	Department of Neurology, Shanghai Fifth People's Hospital, Fudan University, China	Study design, study conduct, interpretation of data, study reporting, manuscript writing and editing
Fenglei Qiao, PT	Department of Rehabilitation, Shanghai Fifth People's Hospital, Fudan University, China	Study design, protocol writing, interpretation of data, revision of the manuscript
Yafei Zhou, PT	Department of Rehabilitation, Shanghai Fifth People's Hospital, Fudan University, China	Study design, protocol writing, interpretation of data, revision of the manuscript
Jun Liu, PhD	Department of Radiology, Shanghai Fifth People's Hospital, Fudan University, Shanghai, China	Interpreted data, statistical analysis
Chuancheng Ren, PhD	Department of Neurology, Shanghai Fifth People's Hospital; Department of Neurology, Shanghai East Hospital, Tongji University, China	Overall project design, reviewed the statistical analysis, interpreted data, actively contributed to the writing and reviewing of the submitted manuscript

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Effects of home-based telerehabilitation in patients with stroke: A randomized controlled trial

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