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Transcranial magnetic stimulation regulates brain functional network dynamics in stroke patients: a randomised controlled trial

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Abstract

Background Repetitive transcranial magnetic stimulation (rTMS) is an effective treatment for stroke patients, but its underlying neural mechanisms remain largely unknown. This study aimed to investigate changes in brain functional connectome dynamics in stroke patients whose were treated with rTMS as well as to explore their relationship with treatment outcomes.

Methods Sixty-four stroke patients were randomly divided into rTMS ($n=34$) or no-rTMS ($n=30$) groups. Resting-state functional MRI data and clinical behavioral variables were collected before and after intervention. A multi-layer network model was used to quantify functional network switching rate, followed by performance of comparison and correlation analyses to examine group differences in the treatment-induced changes in the network dynamics as well as their relation to clinical improvement. Moreover, multivariate linear regression analyses were pursued to test whether the functional connectome dynamic changes could predict rTMS treatment outcome.

Results Network switching rate changes in the rTMS group were greater than those in the no-rTMS group. Specifically, at the whole-brain level, the rTMS group had a higher network switching rate change than no-rTMS group ($p=0.014$); at the sub-network level, the network switching rate changes of the sensorimotor, default-mode, and fronto-parietal networks in the rTMS group were higher than those of the no-rTMS group ($p<0.05$); and at the nodal level, the rTMS group had higher network switching rate changes than the no-rTMS group in the prefrontal cortex, cingulate gyrus, and inferior parietal lobule ($p<0.05$), but the network switching rate change of the precentral gyrus in the rTMS group was lower than that in the no-rTMS group ($p=0.038$). Additionally, network switching rate change in the subparietal lobule was positively correlated with the improvement degree of motor function in the rTMS group ($p=0.016$). Moreover, Multivariate linear regression analyses showed that baseline connectome dynamics could predict symptom improvement in the rTMS group to a certain extent.

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Conclusions Our findings may improve the understanding of the neural mechanism of rTMS treatment for stroke from the perspective of network dynamics, and may have clinical implications for offering potential predictor for monitoring rTMS treatment efficacy in stroke patients to some extent.

Trial registration This trial was registered at https://www.chictr.org.cn/ (ChiCTR1800019452).

Keywords Stroke, Multi-layer network, Repetitive transcranial magnetic stimulation, Network switching rate, Network dynamics

Introduction

Stroke remains the leading cause of severe long-term disability among the elderly [1]. The most prevalent clinical symptom after stroke is motor dysfunction. More than half of stroke patients experience upper limb motor dysfunction, and approximately two-thirds of stroke survivors exhibit persistent motor deficits that extend into the chronic phase [2, 3]. Repetitive transcranial magnetic stimulation (rTMS) is an emerging non-invasive electrophysiological stimulation that can be used to facilitate accelerated rehabilitation of upper limb motor dysfunction after stroke [4]. Despite the wide clinical utility of rTMS, its therapeutic efficacy varies substantially and the underlying brain mechanisms remain largely unknown. This lack of knowledge is one of the major challenges in accurately predicting the treatment response to rTMS.

Over the past decades, a wide range of plausible neural mechanisms have been proposed to account for rTMS modulation of motor function recovery after stroke. The prevailing view is that rTMS exerts its effect not only locally at the site of stimulation, but also through a large-scale and widely distributed network of brain regions involved in anatomical and functional connections for motor control. For example, it is evident that rTMS increases functional connectivity in bilateral hemispheric motor areas [5, 6] and cortical-subcortical pathways [7]. In addition, changes in inter- and intra-network connectivity of multiple networks after stroke, including the default mode network (DMN) [8], can be gradually normalized by rTMS [5, 9]. These results jointly work to confirm that the therapeutic effects of rTMS on stroke can be mediated by stimulus-induced modulation of large-scale brain network activity.

However, the functional magnetic resonance imaging (fMRI) methods used in previous studies have primarily focused on conventional static functional connectivity patterns, ignoring the temporal dynamics of brain functional networks. It is increasingly recognized that the human brain is an efficient and dynamic information processing system with a complex spatio-temporal organization. Discrete alterations in brain dynamics may be associated with specific behavioral or cognitive traits associated with diseases [10, 11]. Prior research has indicated that alterations in network dynamics after stroke, such as time fractions and dwell times between dynamic functional states, correlate with the severity of motor deficits [12, 13]. Moreover, partial recovery of functional network connectivity states can be facilitated by rTMS modulation [14]. However, the exact dynamic brain network mechanisms whereby rTMS affects functional reorganization after stroke are still unknown, and whether the dynamic brain network biomarkers can be used for predicting rTMS treatment efficacy is unclear.

Multi-layer network analysis is a newly proposed network graphical model for capturing connection profiles across time and space [15]. In comparison with other time-resolved functional MRI analytic approaches, it provides a "time link" between neighbouring time points, allowing researchers to track and quantify temporal changes at each node, as well as the timing of switching between different modules or network allocation [16–18]. The multi-layer network analysis can reveal the trade-off between specialization of functional brain regions and flexible integration between networks, deepening the understanding of brain function from a dynamic perspective. There is evidence that behavioral training and learning processes affect brain network switching. For instance, Bassett et al. demonstrated that exercise training was correlated with greater brain network switching, particularly in associative cortices involving higher-order cognition [19]. A follow-up study found that individual differences in motor learning rates were associated with brain network switching on the first day of training [20]. The other study demonstrated that individuals who received six months of music training had increased brain network switching relative to those who did not [21]. Earlier work also provides evidence for neural modulation of intracranial stimulation in epilepsy patients by using brain network switching [22]. Collectively, the previous literature suggests that multilayer brain network changes have potential in accurately and reliably tracking changes in brain function, which could advance our understanding of the neural basis underlying individual differences in human cognition and behavior, and may possibly serve as an effective method for monitoring treatment responses to brain stimulation and stratifying patients for brain stimulation interventions.

In the current study, we adopted multi-layer network modeling to explore the dynamic changes of brain functional connectome derived from resting-state fMRI

(rs-fMRI). The effects of rTMS on network dynamic switching in stroke patients were comprehensively examined at the whole-brain, sub-network and nodal levels. Subsequently, potential correlations between network switching rate changes and the improvement degree of upper limb motor function were further investigated. Moreover, multivariate linear regression analyses were pursued to examine whether dynamic network switching could predict rTMS treatment response. Building on the previous evidence, we hypothesized that (i) rTMS intervention could modulate functional connectome dynamics in stroke patients and the effects on the primary motor cortex and higher-order cortical circuits would differ; (ii) the pre-treatment dynamic connectome profile could predict rTMS therapeutic outcome.

Methods and materials

Study design

A schematic overview of the study design is illustrated in Fig. 1. The framework has six main procedures: (A) stroke patients randomly assigned to rTMS or control groups; (B) extracting regional mean BOLD signals of the 160 brain regions based on the Dosenbach et al. Atlas [23]; (C) constructing a dynamic functional connectivity matrix for each subject; (D) creating the multi-layer network model; (E) calculating network switching rate at the whole brain, sub-network and nodal levels; (F) correlation with and prediction of clinical variables.

Participants

A total of 70 patients with upper limb motor dysfunction after ischaemic stroke were randomly assigned into rTMS group ($n = 35$) or no-rTMS group ($n = 35$). Inclusion criteria included: (1) first onset of disease; (2) lesions confined to a single hemisphere, primarily involving the basal ganglia and their adjacent areas; (3) an age range of 40–75 years; (4) disease duration of 2 weeks-3 months; (5) right-handedness with unilateral upper limb hemiparesis, and Brunnstrom's rating of stage II-IV. Exclusion criteria included: (1) motor dysfunction of the upper limbs prior to the onset of the disease; (2) A history of psychiatric disorders and other organic diseases of the nervous system; (3) contraindications to MRI and rTMS treatment; (4) modified Fazekas classification > 1; (5) severe cognitive dysfunction or unstable vital signs, which made it unable to complete the examination and treatment. Six patients with excessive head movement were excluded. Eventually, 64 subjects were enrolled in this study, including rTMS group ($n = 34$) and no-rTMS group ($n = 30$). The recruitment process is detailed in Figure S1. 900th Hospital's Ethics Committee approved the ethical review (NO. 2015011, ChiCTR1800019452).

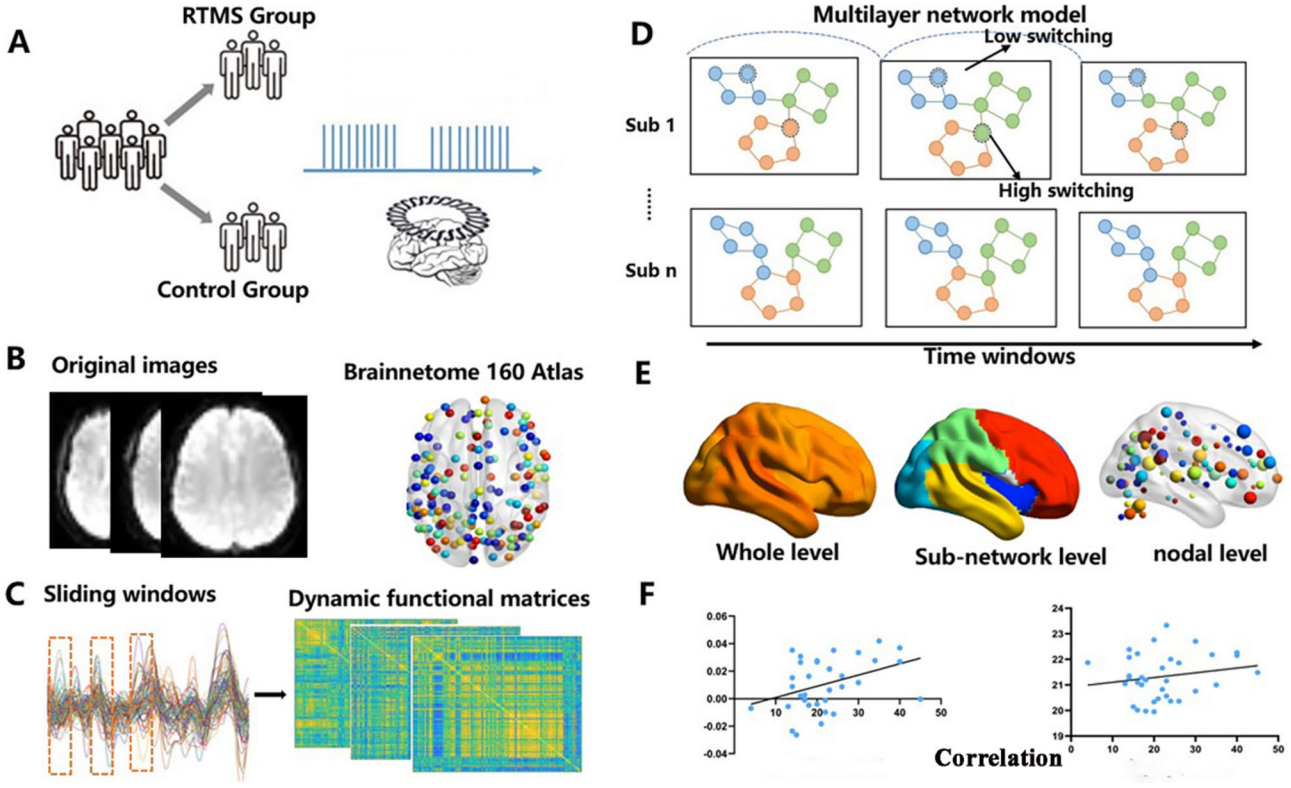


Fig. 1 Study flow chart

Written-informed consent was acquired from all subjects after a full explanation of the study.

Blinding

The patients were randomly assigned to either rTMS group or no-rTMS group in a 1:1 ratio. Randomization was generated by independent statisticians using a randomization procedure and was not disclosed to any other participants in the study. Stroke patients were enrolled by a rehabilitation physician who was unaware of the treatment allocation. Motor function assessments were performed by experienced rehabilitation therapists who were unaware of treatment allocation. rTMS treatment was performed by specialized technicians. Imaging data scanning and analysis were performed by radiologists who were unaware of the treatment assignment.

rTMS intervention

The no-rTMS group received routine ischaemic stroke basic drug treatment along with rehabilitation training, mainly including muscle stretching training, joint activity training, good limb placement, passive joint movement and neurodevelopmental treatment. The rehabilitation training lasted 8 weeks (each time 40 min, 1 time/day, 5 times/week).

The rTMS group received LF-rTMS in addition to the control group. A Magstim Rapid2 transcranial magnetic stimulation device from the UK was used, with a maximum output intensity of 2.5 T and a 70 mm figure-of-eight coil. The stimulation site was selected using the EEG 10/20 system's fiber cap positioning, targeting the primary motor cortex (M1) of the non-lesioned hemisphere, typically around the C3 or C4 position of the fiber cap. The motor threshold (rMT) was determined by inducing and recording the maximum motor evoked potential (MEP) of the abductor pollicis brevis muscle in the hand through single-pulse stimulation of the M1 area on the healthy side. The minimum stimulation intensity required to record an MEP amplitude greater than 50 μV in at least 5 out of 10 stimulations on the electromyogram was defined as the rMT. The stimulation parameters were set in accordance with the safety recommendations of the International Federation of Clinical Neurophysiology guidelines: stimulation intensity at 90% rMT, stimulation frequency at 1 Hz, 10 pulses per stimulation train, 2-second interval between stimulation trains, 120 stimulation trains, totaling 1200 pulses. The treatment was administered once a day, 5 times a week, for a total of 8 weeks.

Clinical assessment

Upper limb motor ability was assessed using the Fugl-Meyer Upper Extremity Assessment (FMA-UE) scale, and self-care ability in daily life was assessed using the Modified Barthel Index (MBI) scale.

MRI data acquisition and preprocessing

A Siemens Tim Trio 3.0 Tesla scanner equipped with a 12-channel head coil was used for MRI data acquisition. T1-weighted images were acquired using a magnetized intensity-prepared rapid acquisition gradient echo sequence. The parameters were as follows: repetition time (TR)/echo time (TE) = 1900 ms/2.52 ms, matrix = 256 × 256, field of view (FOV) = 240 × 240 mm^2, slice thickness = 1 mm, no gap, 176slices. The rs-fMRI data were obtained using a single excitation plane echo imaging sequence. The parameters were as follows: TR/TE = 2000 ms/21 ms, matrix = 64 × 64, FOV = 240 × 240 mm^2, slice thickness = 4 mm, gap = 0.8 mm, 33slices, and acquisition time 6 min.

Preprocessing of fMRI data was performed using Data Processing Assistant for Resting-State fMRI (DPARSF) and Statistical Parametric Mapping (SPM12). Before data preprocessing, we flipped the MRI data of patients with left-sided lesions from left to right along the midsagittal line. The specific steps for data preprocessing were as follows: (1) removal of the first 10 points; 2) slice-timing correction; 3) head movement correction, excluding participants with translation > 2.5 mm, rotation > 2.5°, or mean FD > 0.5 mm; 4) transforming functional images to MNI space using DARTEL anatomical alignment method and resampling voxel sizes to 3 × 3 × 3 mm^3; 5) spatial smoothing of the images using a Gaussian kernel of 6 mm full width at half maximum; 6) denormalization of trends; 7) temporal bandpass filtering (0.01–0.1 Hz), and regression of interfering signals including Friston's 24 motor parameters, white matter, cerebrospinal fluid, and global brain signals (Table S1). The preprocessed data were subsequently employed to construct a dynamic functional connectome.

Dynamic functional network construction

DynamicBC was used to construct dynamic brain functional networks. Initially, 160 network nodes were defined according to the atlas of Dosenbach et al. [23]. The BOLD time series was divided into multiple consecutive time windows by the common sliding window method. Previous studies have shown that the minimum window length in sliding window analysis should not be less than 1/fmin, as shorter window lengths may increase the risk of spurious fluctuations [24]. Following the previous recommendations [25, 26], a window length of 100 s and a step size of 1TR were used in our main analysis, generating a total of 121 time windows. For these 121 time windows, the functional connectivity strength between nodes was estimated by Pearson correlation and further converted into Fisher's z-score in order to improve normality. This procedure produced a 160 × 160 symmetric functional connectivity matrix for each

window. In accordance with previous studies, negative correlations were set to zero [27].

Constructing and analyzing multi-layer network dynamics

A generalised multi-layer network model was created using the GenLouvain software package [28]. This model assumed that the temporal modular architecture was time-varying and temporally continuous, incorporating connectivity information between neighbouring time layers. The time-varying multilayer network modular structure was identified using optimizing the modularity index Qmod. The degree of segregation between network modules was measured by Modular optimization using Lewin's algorithm [11]. The ω and γ parameters were set to ω = γ = 1 according to previous studies [28, 29]. We repeated the above analysis of brain module dynamics 50 times for each participant and the average was considered the outcome measure [30, 31].

To explore the reconstruction profile of the network modules with time, the network switching rate was used to evaluate the module participation changes of each node across the time windows. The higher the network switching rate, the more flexible a brain node switches across modules. The whole-brain level network switching rate was estimated by the average network switching rate of all nodes. To further study the network switching rate of the sub-network system, we assigned all ROIs in the Dosenbach 160 atlas to 6 sub-network systems, including sensorimotor (SMN), default-mode (DMN), frontoparietal (FPN), cingulate-orbital, occipital, and cerebellar systems (Table S2).

Statistical analysis

Two-sample *t*-tests (normally distributed data) and Mann-Whitney *U*-tests (non-normally distributed data) were used to compare the two groups in age, education and clinical characteristics where appropriate. Chi-square test was used to test for gender differences between the two groups. Inter-group two-sample *t*-test and intra-group paired *t*-test were used to analyze differences in the changes of clinical variables with treatment between the two groups. Repeated measurement covariance analysis (ANCOVA) was used to examine group differences in the changes of whole-brain, sub-network, and node-level network switching rates from pre- to post-treatment. Age, educational level, lesion volume, and mean FD were used as nuisance covariates in ANCOVA. We reported group differences, effect sizes, means, and 95% confidence intervals (CIs). Multiple comparisons were corrected using the False Discovery Rate (FDR) method, and a corrected *p*-value of less than 0.05 was deemed statistically significant.

Pearson correlation was used to assess the relationship between brain functional network dynamic and clinical changes induced by rTMS in stroke patients. Specifically, we examined the association between longitudinal changes in nodal network switching rates (post-rTMS - pre-rTMS) and changes in clinical variables (i.e., FMA-UE and MBI scores). Significance was set at p-value < 0.05.

Finally, multiple linear regression analysis was used to evaluate whether the baseline node network handover value could predict motor function improvement along with rTMS treatment. In the regression model, the FMA-UE changes induced by rTMS was considered the dependent variable, the baseline node network switching value as the independent variable, and age, lesion volume, and baseline FMA-UE score as nuisance covariates. The Durbin-Watson test was applied to evaluate the independence of the data.

Table 1 Demographic and clinical information of the stroke patients

	rTMS group ($n=34$)	no-rTMS group ($n=30$)	T/Z/X2	*P*-value
Age (years)	59.12 ± 10.86	56.73 ± 9.72	0.920	0.361
Sex (m/f)	24/10	28/10	0.114	0.736
Education (years)	6 (6, 9)	6 (3, 9)	-0.127	0.899
Duration of illness (days)	30 (18.75, 40)	30 (19.25, 48)	-0.655	0.512
Lesion location (left/right)	13/21	14/16	0.465	0.496
Lesion volume (cc)	1.77(0.23,2.67)	1.26(0.16,1.34)	-1.585	0.113
FMA-UE	32.09 ± 10.66	3 3.97 ± 9.85	-0.729	0.469
MBI	58.88 ± 17.74	59.33 ± 17.37	-0.102	0.919

Validation analysis

To examine the robustness of our results, we explored whether our main results were significantly affected by sliding window parameters (window size) or multi-layer network model parameters (γ and ω). Therefore, we used a combination of window length of 60 TR and 1TR step size, as well as ω = 0.75, γ = 1 and ω = 1, γ = 0.9 to repeat our analysis.

Results

Demographics and clinical characteristics

No significant differences were found between the two groups in terms of gender, age, education level, duration of illness, lesion location, and lesion volume (all $p > 0.05$, Table 1). In terms of clinical data, no significant differences were found between the rTMS and no-rTMS groups prior to treatment. However, the FMA-UE ($p = 0.036$) and MBI ($p = 0.023$) scores showed significant improvement after treatment in the the rTMS relative to the no-rTMS group (Table 2).

Table 2 Comparisons of between- and within-group effects on behavioral scores

	rTMS group($n=34$)	no-rTMS group ($n=30$)	T	*P*-value
FMA-UE				
Pre-treatment	32.09 ± 10.66	33.97 ± 9.85	-0.729	0.469
Post-treatment	54.03 ± 11.12*	48.50 ± 9.206*	2.150	0.036
MBI				
Pre-treatment	58.88 ± 17.74	59.33 ± 17.37	-0.102	0.919
Post-treatment	90.00 ± 8.25*	84.57 ± 10.38*	2.331	0.023

Measured data conforming to normal distribution are denoted by $\bar{X} \pm s$ indicated by two-sample t-test; not conforming to normal distribution was indicated by median (Q1, Q3), Mann-Whitney U test. Count data were tested by χ^2 test.FMA-UE, Fugl-Meyer upper extremity assessment; MBI, modified Barthel Index.

Continuous data were expressed as means ± SDs. FMA-UE, upper extremity Fugl-Meyer Assessment; MBI, modified Barthel Index test. * represents the significant difference before and after intervention.

Effects of rTMS on multi-layer network dynamics

The spatial patterns of network dynamic switching of the two groups before and after intervention are shown in Fig. 2. At the whole-brain level, the rTMS group exhibited a greater change in network switching rate compared to the no-rTMS group ($F=6.418$, $p=0.014$, $\eta_p^2 = 0.100$, mean difference (MD) [95% CI]: 0.005 [0.001–0.010]) (Fig. 3).

At the sub-network level, the intervention-induced switching rate changes of the SMN ($F=5.437$, $P=0.023$, $\eta_p^2 = 0.086$, MD [95% CI]: 0.006 [0.001–0.011]), FPN ($F=4.459$, $P=0.039$, $\eta_p^2 = 0.070$, MD [95% CI]: 0.004 [0.002–0.009]), and DMN ($F=6.214$, $P=0.016$, $\eta_p^2 = 0.097$, MD [95% CI]: 0.007[0.001–0.012]) in the rTMS group were higher than those in the no-rTMS group. No significant differences were observed in the cingulate-orbital, occipital, and cerebellar networks ($p>0.05$) (Fig. 3).

At the nodal level, longitudinal changes in network switching rates of the right prefrontal cortex, left posterior cingulate gyrus(PCC), right angular gyrus, right intraparietal sulcus (IPS_R), and left parietal lobe in the rTMS group were larger than those in the no-rTMS group (all $F \geq 4.973$, $p<0.05$, FDR-corrected). Notably, network switching rate changes of left inferior parietal lobule(IPL_L) in the rTMS group was significantly higher than those in the no-rTMS group ($F=12.757$, $p=0.001$, FDR-corrected). By contrast, network switching rate change in the right precentral gyrus was lower in the rTMS group than that in the no-rTMS group ($F=4.513$, $p=0.038$, FDR-corrected) (Fig. 3).

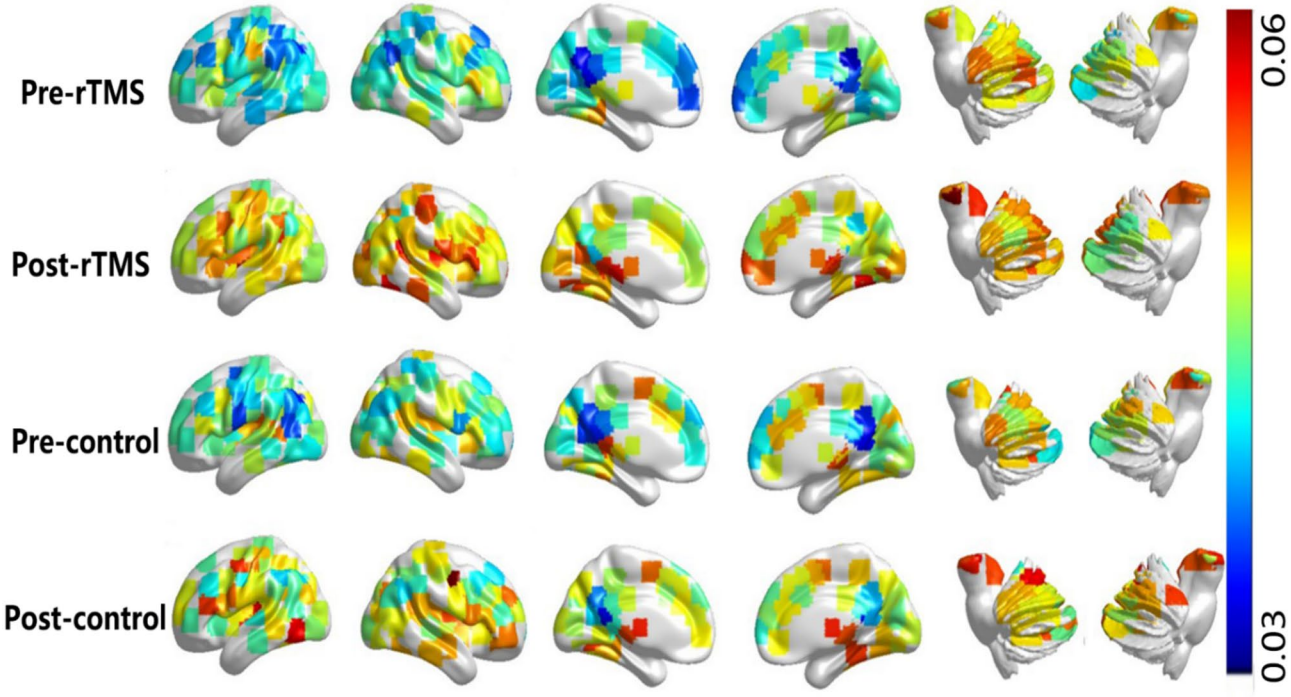


Fig. 2 Spatial patterns of network switching before and after intervention in both groups. control, no-rTMS

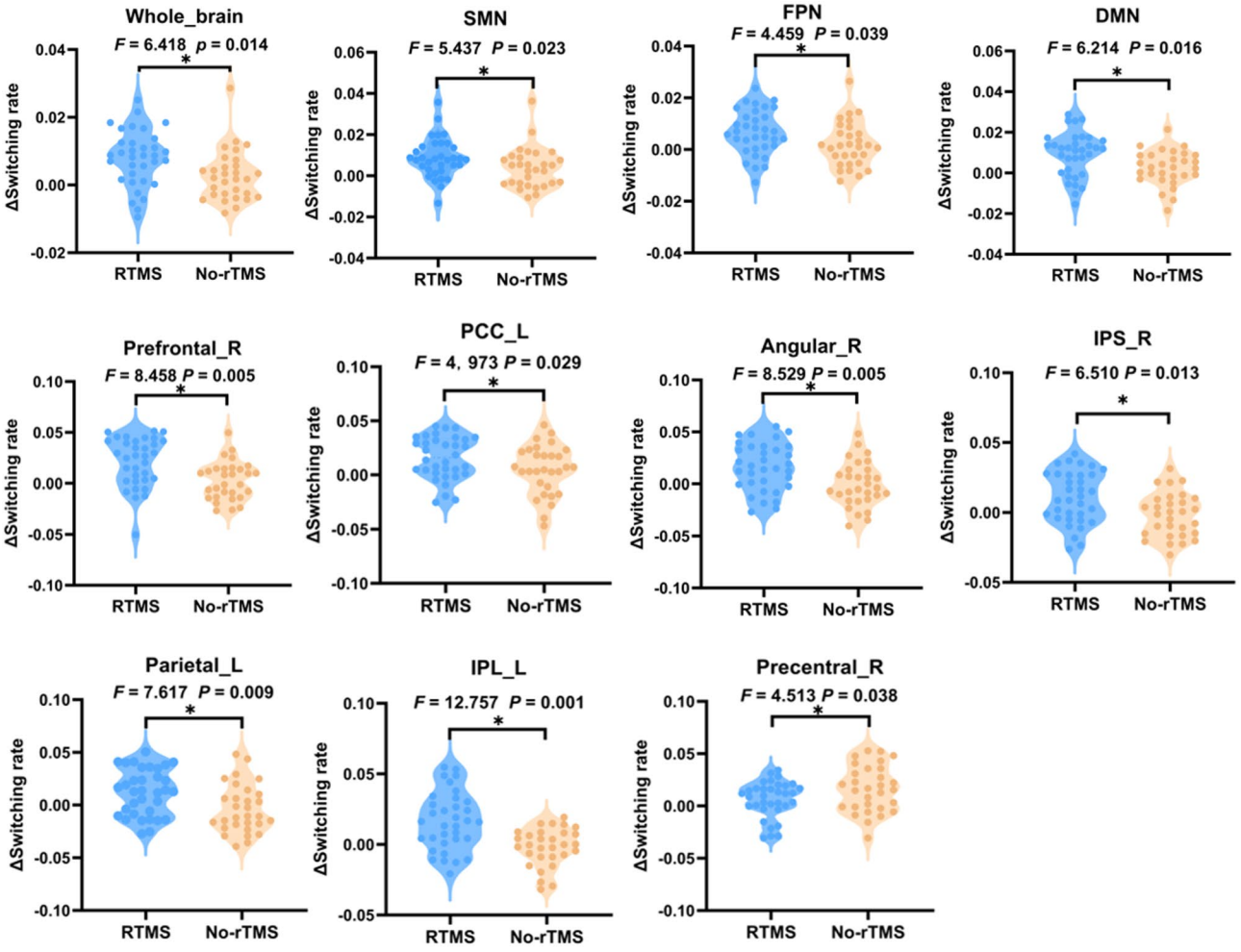


Fig. 3 Differences of changes in network switching rates between rTMS and no-rTMS groups. SMN, sensorimotor; DMN, default-mode; FPN, frontoparietal; PCC, posterior cingulate gyrus; IPS, intraparietal sulcus; IPL, inferior parietal lobule. L, left; R,right

Association between changes of clinical symptoms and network switching

Correlation analysis showed that increased network switching in the IPL_L was significantly associated with the improvement degree of FMA-UE scores in stroke patients after rTMS treatment ($r = 0.409$, $p = 0.016$) (Fig. 4).

Multivariate linear regression analyses

Exploratory multivariate linear regression analyses revealed that functional dynamics in the intraparietal sulcus and inferior parietal lobule had an effect on rTMS treatment response. The results showed that the tolerance of each variable was > 0.2, variance inflation factor (VIF) was < 5, and Durbin-Watson statistic was 2.093. β coefficient for IPL_L was 0.391 ($p = 0.014$), and β coefficient for IPS_R was 0.369 ($p = 0.020$). The model had overall $F = 6.744$, $p = 0.004$, adjusted $R^2 = 0.258$ (Table 3).

Validation analyses

To examine the robustness of our results, the effects of analysis parameter choices on our results were tested. As a consequence, our findings were largely consistent across different analytical strategies (supplementary results, Figures S2–S4).

Discussion

This study investigated rTMS-induced changes in brain functional connectome dynamics in stroke patients and established a link between brain network dynamics and clinical outcomes. The results showed that stroke patients presented with muti-scale network switching rate changes after rTMS treatment. Specifically, changes in the switching rate of the SMN, FPN, DMN, prefrontal cortex, PCC, IPL and IPS in the rTMS group were higher than those in no-rTMS group, whereas the change of network switching rate in the precentral gyrus was lower in the rTMS group than that in no-rTMS group. The change of the switching rate of the IPL was positively correlated

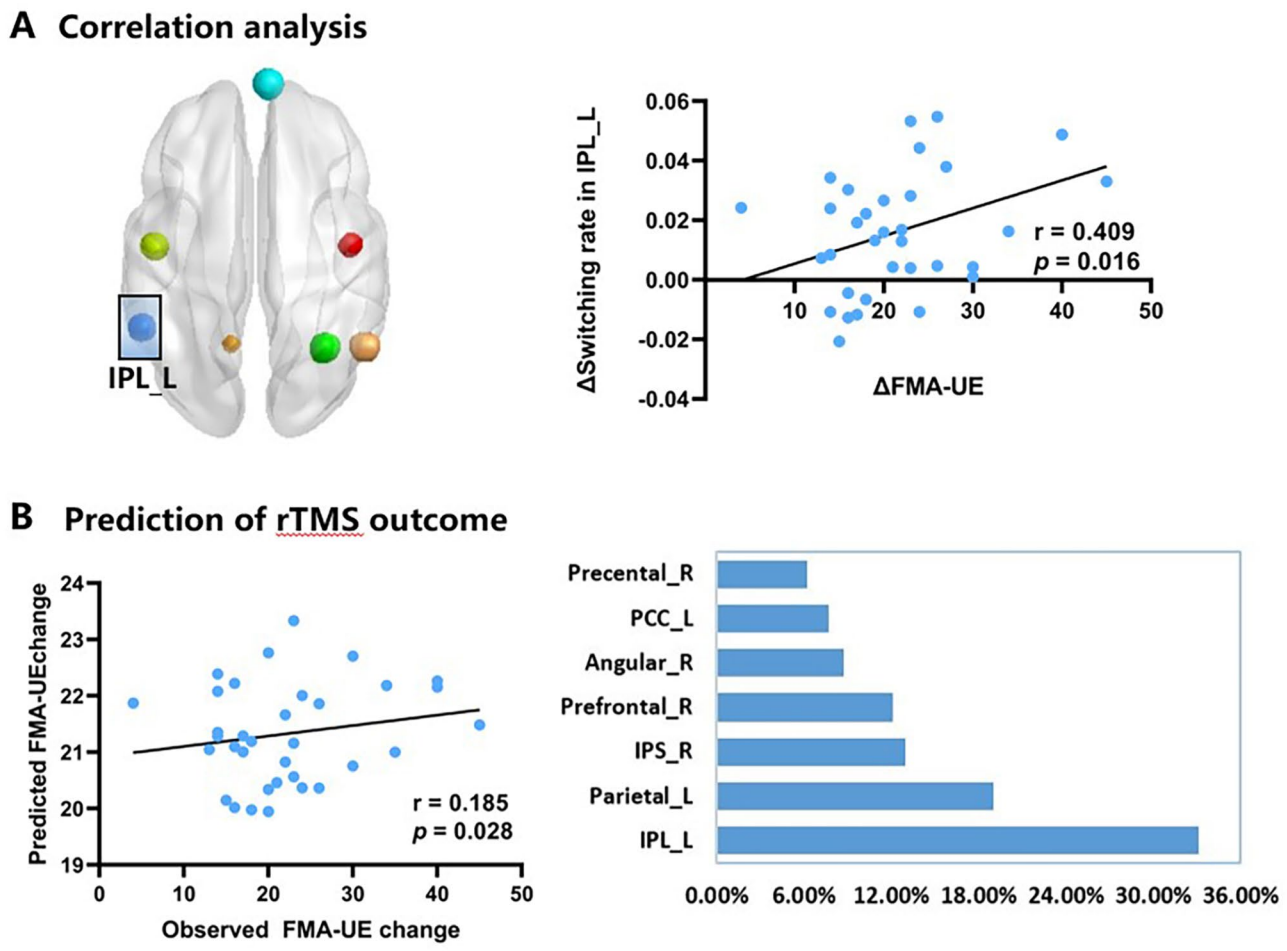


Fig. 4 Relationship between clinical symptoms improvement and change in network switching rate after rTMS treatment. IPL, inferior parietal lobule

Table 3 Results of the regression analyses

Variables	B	β	t	*p*	VIF	Tolerance
constant	17.494	-	9.544	<0.001	-	-
IPL_L	168.587	0.391	2.604	0.014	1.003	0.997
IPS_R	175.530	0.369	2.456	0.020	1.003	0.997
R^2			0.303			
adjusted R^2			0.258			
F			6.744			
D-W			2.093			

D-W Durbin-Watson

with the improvement degree of motor function. In addition, the baseline network switching rate may also predict rTMS-induced improvement of clinical symptoms in the rTMS group.

Modular organization and network flexibility play a crucial role in maintaining a balance of functional specialization and coordinated integration in the brain [32]. Network flexibility reflects the brain's ability to switch between different network configurations, which may be related to individual cognitive and behavioral abilities [33–35]. Previous studies have found that flexibility of network activities in stroke patients is insufficient, making it difficult to adapt from one neural network configuration to another to meet changing environmental conditions [36–38]. The present study found that rTMS intervention appeared to enhance the overall network switching rate, indicating that rTMS treatment may facilitate the overall regulation of brain dysfunction in stroke patients, and can contribute to the normalization of abnormal network patterns after stroke. It has been well established that rTMS may lead to changes at the large-scale network level, affecting large-scale network

connectivity within specific networks and across different networks, and promoting gradual recovery of abnormal network patterns [39, 40]. For example, Hartwigsen et al. reported that rTMS evoked the rapid reorganization of large-scale networks, improving the flexibility of the brain and thus achieving adaptive network plasticity [41]. Khanna et al. found that low-frequency electrical stimulation enhanced the propagation of neural activity across networks with impaired connectivity, restoring the neural processing in the abnormal networks and improving the network flexibility [42]. These past studies partially support our current observations.

At the sub-network level, our data showed that rTMS could increase the network switching rate of the SMN, DMN and FPN in stroke patients. The SMN has been proved to be strongly associated with poststroke motor function outcomes. Previous studies have shown that the reorganization of the sensorimotor system plays a crucial role in the recovery of motor function after brain damage [43, 44], and may underlie the continued development of motor skills [32]. In addition to the SMN, the FPN and DMN also play a major role in functional recovery after stroke. The FPN is typically considered to have a top-down influence on the primary motor network to control motor outputs [45]. It is generally accepted that communication between nodes in the FPN is crucial for goal-directed movements [46, 47] and prospective action decisions [48]. The DMN participates in the integration of primary perception and advanced cognitive processing [49, 50], thereby playing an important mediating role in the rehabilitation of stroke [51]. Our current finding of the critical involvement of the FPN and DMN extends the current knowledge by demonstrating that motor function recovery after stroke involves the dynamic reconstruction of brain activity patterns across single-modal and cross-modal networks.

At the nodal level, we found that the changes of network switching rate in the IPL, IPS, prefrontal cortex, and PCC were higher in the rTMS group than those in the no-rTMS group. The parietal cortex, including the IPL and IPS, is involved in high-level motor control and hand-object interactions [52, 53]. These functions affect the visual-motor integration of hand tasks and goal-directed attention redistribution [54], especially in goal-directed movements [55, 56]. In addition, the prefrontal cortex is engaged in attention, working memory, and decision making, enabling the execution of meaningful actions [57]. The cingulate gyrus is a key component of the DMN, which is responsible for receiving and integrating information from multiple functional networks [58, 59]. The functions of these affected brain areas are critical for upper limb rehabilitation after stroke. Their increased network switching can be partially explained by the compensatory and plastic mechanisms pertaining to the learning and execution of motor functions during the recovery process. It is noteworthy that the change of network switching rate in the precentral gyrus was lower in the rTMS group than that in the no-rTMS group. It is well known that the precentral gyrus belongs to the primary motor cortex and is an important element in the sensorimotor network. This region is responsible for regulating limb movements via connecting the inferior motor centers located in the brainstem and spinal cord [60]. The rTMS-induced network switching decrease indicates a greater bias toward temporal stability in the primary motor cortex. This might be explained by the fact that the primary motor cortex, located at the lower end of the sensory-motor associative axis, has a lower baseline level of network dynamics and relatively fixed structural connections, while the higher-order associative cortex (such as the prefrontal cortex) lies at the top of the functional hierarchy, responsible for integrating multimodal information, and has richer long-distance connections and higher synaptic plasticity [61]. The hierarchical structure differences may render them to have different network flexibility in responding to the effect of rTMS on post-stroke functional recovery.

Using multiple linear regression analysis, we found that baseline functional connectivity dynamics could predict rTMS treatment outcomes to a certain extent. Recent research on TMS modeling has demonstrated that the impact of regional stimulation on functional connectivity is largely contingent upon the brain state during stimulation [62–64]. The individual's residual local or global brain network may serve as a crucial determinant of both local and remote rTMS effects. Our findings indicated that baseline fronto-parietal network switching rates were effective in predicting the effects of rTMS interventions. One possible explanation for this observation is that the fronto-parietal regions possess a greater capacity for flexible reconfiguration in response to varying demands, thereby enhancing the establishment of the rTMS stimulus-response relationship and supporting behavioral improvements in stroke patients. However, it is important to note that this study was limited by its small sample size, necessitating future research with an expanded cohort to further investigate the clinically translational potential of the identified neuroimaging predictors.

Limitations

Although valuable insights were gained from this study, some limitations should be considered when interpreting the findings. Firstly, the small sample size and single-center study design may limit the generalizability of the results and reduce the statistical efficacy of the study. Secondly, the control group design of this study was imperfect, and sham stimuli should be added to improve

the study protocol in the future. In addition, this study focused on the multilayer network switching rate and did not explore the parameter points where the results may be reduced. Future studies could examine other aspects of dynamic brain networks such as Kalman filtering, HMM. Furthermore, the present study used multiple linear regression analysis to analyze brain connectome dynamics for exploratory analysis of rTMS treatment response prediction. Future studies could incorporate multimodal individual data including brain structure, function, and clinical phenotype to improve prediction performance. Finally, differences in lesion locations, disease duration, and degree of motor impairment in stroke patients make our patient group highly heterogeneous, which may influence our interpretation.

Conclusion

Our data provide empirical evidence that transcranial magnetic stimulation can modulate the functional connectome dynamic changes in stroke patients.Notably, rTMS may exert differential effects on network flexibility within the primary motor cortex compared to higher-order cortical circuits. Furthermore, baseline functional connectivity dynamics may serve as a positive predictor for rTMS treatment outcomes to some extent. This study may improve the understanding of the neural mechanism of rTMS treatment for stroke from the perspective of network dynamics, and may have clinical implications for offering potential predictive biomarkers for monitoring rTMS treatment efficacy in stroke patients.

Abbreviations

rs-fMR	Resting-state functional magnetic resonance imaging
rTMS	Repetitive transcranial magnetic stimulation
MBI	Modified Barthel index
FMA-UE	Fugl-Meyer upper limb assessment
SMN	Sensorimotor
DMN	Default-mode
FPN	Fronto-parietal
PCC	Posterior cingulate gyrus
IPS	Intraparietal sulcus
IPL	Inferior parietal lobule

Supplementary Information

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Supplementary Material 1.

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Author contributions

Research design: YQ and XL; Writing original draft: YQ, XL and XW; Data collection and analysis: XL, XW, XZ, SQ and YT; Funding acquisition: YQ. All authors read and approved the final manuscript.

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Data availability

The corresponding author will provide the raw data supporting the study's conclusions upon reasonable request.

Declarations

Ethics approval and consent to participate

The 900th Hospital's Ethics Committee approved the ethical review(NO. 2015011). Written-informed consent was acquired from all subjects after a full description of the study was given to them.

Consent for publication

All the authors approved the publication of the article.

Competing interests

The authors declare no competing interests.

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