



rTMS combined with motor training changed the inter-hemispheric lateralization

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Abstract

Repetitive transcranial magnetic stimulation combined with motor training (rTMS-MT) can be an effective method for enhancing motor function. However, the effects of rTMS-MT on inter-hemispheric lateralization remain unclear. Nineteen healthy volunteers were recruited. The volunteers were randomized to receive 2 weeks of rTMS-MT or MT to improve the motor function of the nondominant hand. Hand dexterity was tested by the Nine-Hole Peg Test. Resting motor threshold (RMT), motor evoked potentials (MEP) and electroencephalography (EEG) in the resting state with eyes closed were recorded, to calculate inter-hemispheric lateralization before and after rTMS-MT or MT. rTMS-MT and MT improved the dexterity and MEP amplitude of the nondominant hand. Furthermore, there were significant changes in the lateralization of not only power spectral density, but also information transmission efficiency between regions following rTMS-MT, especially between the central cortices of both hemispheres. However, although the lateralization change of the power spectral density between the central cortices was observed following MT, there was no such change for information transmission efficiency between any cortices. These results suggested that rTMS-MT could modulate inter-hemispheric lateralization. Changes in inter-hemispheric lateralization might be an important neural mechanism by which rTMS-MT improves motor function. These results could be helpful for understanding the brain mechanism of rTMS-MT.

Keywords Repetitive transcranial magnetic stimulation · Motor training · Corticospinal tract excitation · Electroencephalography · Lateralization

Introduction

Motor training (MT) is commonly used to improve motor function. However, the improvement in motor function induced by MT is usually limited, and functional gains can be further enhanced (Bolognini et al. 2009; Nowak et al. 2009; Mozaffarian et al. 2015). Repetitive transcranial

magnetic stimulation (rTMS) is a promising noninvasive neurophysiological brain-stimulation technique, which can be used to modulate cortical excitability for several minutes after the stimulation period (Hoffman and Cavus 2002; Hummel and Cohen 2005). rTMS can induce plastic changes within the network of sensorimotor areas of the cortex, while at the same time improving dexterity of the hand (Conforto et al. 2012; Sandrini and Cohen 2013). Recently, it has been reported that rTMS can enhance the effect of MT; thus, rTMS combined with MT (rTMS-MT) might be a better method to improve motor function than MT alone (Bolognini et al. 2009).

An increasing number of studies have shown a positive effect of rTMS-MT on aspects of motor function such as reactivity and accuracy (Podubecka et al. 2010; Chang et al. 2012; Kakuda et al. 2012; Kwon et al. 2014). Kakuda et al. (2016) recruited 1700 dyskinesia patients from multiple institutions and evaluated the motor gains induced by rTMS-MT over the course of 6 years. The results suggested that the combination protocol was a useful intervention for

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improving upper limb function. The neural substrates of rTMS-MT associated with increased motor function have gradually attracted more research attention. Takekawa et al. (2014) tested the effects of rTMS-MT on regional brain perfusion in the resting state using single-photon emission computed tomography and found significant changes in the asymmetry index of the superior and middle frontal areas. Kondo et al. (2015) evaluated the impact of rTMS-MT on motor neural excitability using an F-wave parameter. Recently, our group studied the effects of rTMS-MT on cortical function using functional connectivity and graph theoretical analysis (Jin et al. 2017). However, a deeper understanding of the neural mechanism behind the improvement of motor function is still needed to promote its application.

The two cerebral hemispheres are functionally coupled and balanced, and inter-hemispheric interaction in the human brain is closely related to the motor function of limbs (Kinsbourne 1993; Hilgetag et al. 2001). In other words, motor plasticity results from changing the interaction between the two hemispheres. For example, rTMS was shown to produce inter-hemispheric modulation, resulting in modulation of cortical excitability and motor functions (Park et al. 2014). The application of rTMS-MT is also based on inter-hemispheric interaction. Lower-frequency rTMS over the primary motor can reduce inter-hemispheric inhibition from the stimulated to the unstimulated hemisphere, thus increasing the cortical excitability of the unstimulated hemisphere (Pal et al. 2005). Higher frequency rTMS over the primary motor cortex increases the cortical excitability of the stimulated hemisphere, leading to increased inter-hemispheric inhibition from the stimulated to the unstimulated hemisphere, which could enhance the effect of MT on motor performance (Ward 2005; Carey et al. 2006). This suggests that the improvement in motor function induced by rTMS-MT might be closely related to the change in inter-hemispheric interaction. However, the effects of rTMS-MT on inter-hemispheric interaction have remained unclear.

Inter-hemispheric lateralization is a measure of inter-hemispheric interaction. In this study, we aimed to investigate the lateralization changes of brain activity induced by rTMS-MT to gain a greater understanding of how to improve motor function. A healthy person often uses their nondominant hand to assist the dominant hand to complete activities of daily living; however, its flexibility and accuracy are inferior. Thus, the nondominant hand was used as the target hand in this study. We applied 1 Hz rTMS to the dominant hemisphere to downregulate its excitability, and the nondominant hand was used to execute MT to improve its motor function. Hand performance was tested before and after rTMS-MT. Motor evoked potentials (MEP), resting motor threshold (RMT), and electroencephalography (EEG) in a resting state with eyes closed were also recorded before and after rTMS-MT. We evaluated the lateralization of hand

dexterity, excitability of the corticospinal tract, power spectral density, and information transmission characteristics.

Materials and methods

Volunteers

Nineteen healthy volunteers participated in this study. They were randomly divided into two groups. One group (10 men, age 23.4 ± 2.1 years) performed rTMS-MT, and the other group (7 men and 2 women, age 26.7 ± 2.7 years) performed MT. All volunteers were right-handed according to the Edinburgh Handedness Inventory. All volunteers were screened for any contraindications to TMS (Nyffeler and Müri 2010). Any related medical history was reviewed and approved by a physician prior to participation. This study was performed according to the Declaration of Helsinki and approved by the Ethics Committee of Institute of Biomedical Engineering, Chinese Academy of Medical Sciences and Peking Union Medical College. All subjects provided informed consent prior to inclusion in the study.

Procedure

A single-blind design was used for this study. Volunteers were not told which group they were assigned to, and, as they had never experienced rTMS, they did not know whether they were receiving real or sham rTMS. However, the experimenter had information about the group to which each volunteer belonged before the first session of real or sham rTMS.

In this study, rTMS-MT was performed based on an inter-hemispheric competition model. Participants were instructed to sit in a comfortable chair with both hands placed on the armrest in a relaxed position, and to stay awake during the procedure. Low-frequency 1 Hz rTMS was delivered to the dominant hemisphere to downregulate its excitability, and MT with the nondominant hand began immediately after rTMS. The MT group performed only the MT. All volunteers performed rTMS-MT or MT. Figure 1 shows the experimental paradigm. The nine-hole peg test was used to assess the dexterity of the bilateral hands before and after rTMS-MT or MT. Subsequently, EEG in a resting state with eyes closed, RMT, and MEP were recorded before and after rTMS-MT or MT. All volunteers performed rTMS-MT or MT for 14 days. For the rTMS-MT group, rTMS was performed over 10 sessions (one session per day, 5 days per week), and MT was performed over 14 sequential sessions (one session per day). MT was still performed on non-rTMS days. For the MT group, the procedure was same as for the rTMS-MT group, but sham rTMS was used instead of real rTMS. Figure 2 shows the intervention paradigm.

Fig. 1 Experimental paradigm: the volunteers underwent rTMS-MT or MT over 14 days. Each volunteer underwent a Nine-Hole Peg Test. At least 2.5 min resting EEG, MEP and RMT measured by single-pulse TMS were recorded before and after rTMS-MT and MT, respectively

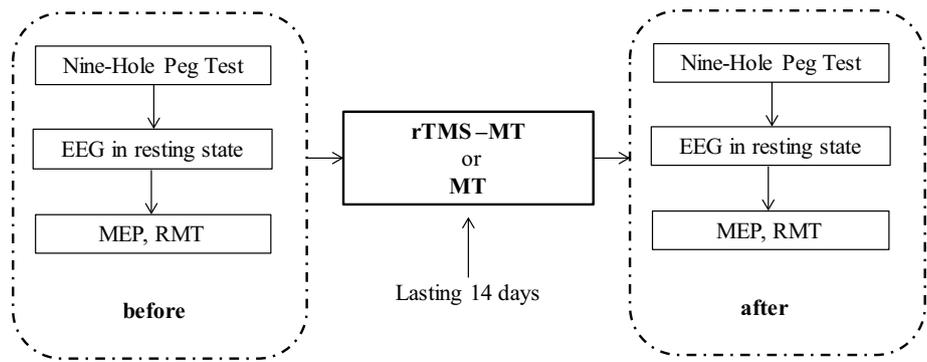


Fig. 2 Intervention paradigm. The rTMS-MT group performed rTMS (20 min) and MT (60 min) on days 1–5 of the intervention, MT (60 min) on days 6 and 7, rTMS (20 min) and MT (60 min) on days 8–12, and MT (60 min) on days 13 and 14. The MT group performed MT (60 min) on all 14 days

group	intervention (lasting 14 days)			
	1 -5 day	6-7 day	8-12 day	13 -14 day
rTMS-MT	rTMS (20min)	MT (60min)	rTMS (20min)	MT (60min)
	MT (60min)		MT (60min)	
MT	sham rTMS (20min)	MT (60min)	sham rTMS (20min)	MT (60min)
	MT (60min)		MT (60min)	

Repetitive transcranial magnetic stimulation and motor training

rTMS was carried out by a MagStim Rapid² stimulator and a 70 mm figure-of-eight coil (MagStim Co., Ltd., Carmarthen-shire, Wales, UK). RMT was defined as the lowest stimulator output intensity that elicited a MEP in the contralateral abductor pollicis brevis (APB) with a peak-to-peak amplitude of at least 50 μ V in at least 5 out of 10 trials. The motor cortex was stimulated by holding the coil tangentially over the optimal cortex site that responded to a right APB, and the coil was placed with the handle pointing backward and laterally at a 45° angle away from the midline (Brasil-Neto et al. 1992; Mills et al. 1992). The location of the stimulation was marked in the neuro-navigation system (Brainsight, Rogue Inc., UK) to maintain the accuracy and consistency among stimulation sessions. rTMS was delivered at 90% RMT and applied for 1200 pulses (1 Hz) for 20 min during each session, which was performed over 10 sequential sessions.

To control for any placebo response related to the real rTMS, and to make the rTMS-MT and MT experimental procedures more consistent in terms of session completion times, a sham stimulation was performed in the MT group using a placebo figure-of-eight coil (Magstim). This placebo coil generates a magnetic field that is more than 90% attenuated, but produces noise and vibration similar to

those of a real magnetic coil. The placebo coil was placed in the same position as the coil used for real rTMS, and the same stimulation parameters were used.

When the volunteers in the rTMS-MT group completed the rTMS each day, they were immediately asked to perform three MT tasks using their nondominant hand. The duration of MT was 60 min each day. MT was performed for 14 consecutive days. The three MT tasks were as follows: (1) to turn coins over using the index and thumb finger for 10 min each day; (2) to put a nut around a screw, with the nondominant hand holding the nut and the dominant hand holding the screw, for 10 min each day; and (3) to write letters for 40 min each day. The volunteers in the MT group performed the same MT tasks without receiving rTMS.

Nine-hole peg test

The nine-hole peg test was conducted as previously described (Mathiowetz et al. 1985). Each volunteer was instructed: “Are you ready? Go!”; the stop watch was started when the volunteer touched the first peg and stopped when the last peg hit the container. The time taken to complete the test (in seconds) was recorded. The volunteers were asked to complete the test as quickly as possible.

EEG and EMG recording

EEG was recorded for 2.5 min with the volunteers in a resting state, sitting in a comfortable chair with their eyes closed, before and after the rTMS-MT or MT. EEG recording started with a period during which the volunteers had their eyes closed. This period lasted 60 s then they were instructed to open the eyes for 30 s, and then close them again for 60 s (total 2.5 min). The reason for measuring the EEG with the eyes closed was to decrease eye movement and muscle-related artifacts. Electrode montage and placement were recording using the international 10/10 system. EEG signals were acquired through a 64-channel synamps² EEG system (SynAmps2 64, Neuroscan Compumedics, USA). The ground electrode was positioned in AFz and the FCz electrode served as the reference for all electrodes. Skin/ electrode impedance was maintained below 5 k Ω for all subjects. The activities of the vertical and horizontal electrooculogram on the right eye were recorded through two surface electrodes. EEG data were digitized at a sampling rate of 1 kHz and then processed offline.

The surface electromyography (EMG) was recorded from the APB via Ag/AgCl electrodes in a belly-tendon montage (Myoquick Matrix Line-Micromed Srl, Mogliano Veneto, Italy). The ground electrode was placed over the pisiform bone. The sampling rate of the signal was 32768 Hz. The EMG was recorded by stimulation of the motor cortex at 110% RMT. A total of 60y stimuli were delivered with an inter-stimulus interval of 5 s. EMG signals were filtered and stored in a laboratory computer for offline analysis.

Phase lag index

The functional connectivity between different brain regions was computed using the phase lag index (PLI) (Stam et al. 2007). The PLI is a measure of the asymmetry in the distribution of phase differences between two signals and reflects the consistency with which one signal is phase leading or lagging in comparison with another. If the phase differences between two time series are $\Delta\Phi(t_k)$ ($k = 1 \dots N$), the PLI can be computed by

$$\text{PLI} = \left| \langle \text{sign}[\Delta\Phi(t_k)] \rangle \right|$$

where $\langle \cdot \rangle$ is the mean value operator. The value of the PLI ranges between 0 and 1. A PLI of 0 indicates either no coupling or coupling with a phase difference centered at approximately $0 \bmod \pi$, whereas a PLI of 1 indicates perfect phase locking at a value $\Delta\Phi$ distant from $0 \bmod \pi$. The stronger the nonzero phase locking, the larger the value of the PLI.

In this study, the PLI in the alpha frequency band (8–13 Hz) was computed. The PLI results for all pairwise combinations of channels yielded an $N \times N$ synchronization

matrix ($N=60$) in which each entry $\text{PLI}_{i,j}$ contained the value of the PLI for channels i and j .

Graph analysis

Next, a brain network based on graph analysis was constructed to explore the differences in brain networks before and after rTMS-MT or MT. The nodes in the graph were represented by EEG electrodes, and the aforementioned PLI values were assigned to corresponding edges to reflect the connection strength between the two nodes. For each subject, we defined a network of 60 nodes and the corresponding edge weights mapped from the PLI matrix. The weighted graph was used directly to analyze the brain network, to avoid choosing an arbitrary threshold for binary graph analysis. The weight between two nodes in a weighted network is an indication of the strength of the connection between these two nodes. A stronger weight means faster transmission or a shorter path. The node path length is usually defined as the reciprocal of the weights. Thus, the network's characteristic path length is closely related to the communication properties of the network (Thuraisingham 2015); the smaller the characteristic path length, the greater the communication efficiency (Latora and Marchiori 2001; Sporns 2013). The node efficiency is defined as the sum of the inverse of the node length. The greater the characteristic node efficiency, the greater the communication efficiency. In this study, path length and node efficiency were used to evaluate brain network characteristics. The path length and node efficiency for the weighted graph were calculated according to the approach of Latora and Marchiori (2001).

Laterality index

To evaluate the changes in the inter-hemispheric imbalance before and after rTMS-MT or MT, we calculated the inter-hemisphere laterality index (LI) (Cramer et al. 1997; Bhatt et al. 2007). The value of the LI ranges from -1 to 1 , where 1 indicates purely left dominant and -1 indicates purely right dominant, and can be computed by the following equation:

$$\text{LI} = \frac{\text{nondominant} - \text{dominant}}{\text{nondominant} + \text{dominant}}$$

In this study, we calculated the laterality index of hand dexterity, MEP, RMT, power spectral density, path length and node efficiency. In the above equation, the nondominant and dominant indicated the nondominant hand and dominant hand, respectively, when we calculated the laterality of motor function and MEP. The nondominant and dominant indicated the non-dominant hemisphere and dominant hemisphere, respectively, when we calculated the laterality index of RMT, power spectral density, path length and node

efficiency. Especially, LI was calculated by the characteristics of EEG signal in symmetrical position of the two hemispheres with the central longitudinal fissure as the axis, for example, F3 and F4, C3 and C4. Midline channels were not used in the calculation of LI.

Data analysis

The EEG periods with closed eyes (120 s) were selected for further removal of artifacts. We used MATLAB (version 10.0) and EEGLAB Toolbox (version 13.0) to process the EMG and EEG signals. EMG trials were reviewed, and those contaminated with physiological artifacts were discarded. For each volunteer, the mean peak-to-peak amplitude of MEPs was measured. EEG data were recorded with a sampling frequency of 1000 Hz and down-sampled to 250 Hz in offline processing. All channels were referenced to the bilateral mastoid. To insure stable EEG data, 5 s EEG data from the initial record and the last record respectively was removed. The continuous EEG signal was segmented into non-overlapping 4 s epochs, and detrended. Visual inspection and independent components analysis (ICA) were used in combination to remove extra-brain artifacts from the EEG data. First, the data were visually inspected for contamination by overt activity, such as swallowing or cheek movements, and contaminated data were removed from further analysis. During this process, to keep the consistency of EEG data from different volunteers, the non-artifact EEG epochs of the same time after the recording started in all volunteers were selected. In other words, if the artifact in one epoch for one volunteer was found, this epoch was removed from all volunteers. Next, the EEG data underwent Infomax ICA decomposition (EEGLAB; Delorme and Makeig 2004). Amplitude topography of components, frequency spectra of components, and component time series were inspected to identify eye blinks, eye movements, muscle artifacts, and heart rhythms (Delorme et al. 2007), which were removed. Finally, data were transformed back to channel space, and epochs were again visually inspected to insure the absence of artifacts. A bandpass filter was used to extract the alpha frequency band (8–13 Hz). A total of 12 segments, each lasting 4 s, were chosen for data analysis.

To evaluate the effects of three factors (intervention method: rTMS-MT vs. MT; intervention time: before vs. after; hand: left vs. right) on motor performance, MEP amplitude, and RMT, three-way analysis of variance (ANOVA) was applied, along with the post hoc Bonferroni test. To evaluate the effects of two factors (intervention method: rTMS-MT vs. MT; intervention time: before vs. after) on the lateralization of hand dexterity, MEP amplitude and RMT, two-way ANOVA was applied, again with the post hoc Bonferroni test. For statistical analysis involving a single factor (such as motor performance, MEP amplitude, and RMT before and after rTMS-MT), a student's paired-sample *t* test was used. All data are expressed as mean \pm standard deviation. All analyses were performed using SPSS version 21.0. The significance level was set at 0.05 unless otherwise indicated.

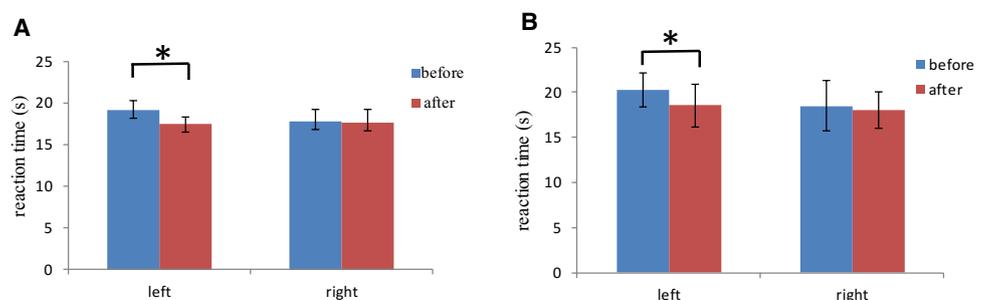
Results

Changes in hand dexterity

The time taken to complete the nine-hole peg test was recorded for each hand. The ANOVA results showed a significant difference in intervention time ($p=0.038$) and intervention method ($p=0.049$). There was a trend toward significant differences in hand factor ($p=0.082$), but no statistical significance for an interaction effect ($p>0.05$). The results of the student's paired-sample *t*-test for intervention time are shown in Fig. 3. The reaction time of the left hand (nondominant hand) decreased significantly after rTMS-MT ($p=0.001$) and MT ($p=0.01$), which suggested a significant improvement in motor performance for the left hand. However, the reaction time of the right hand (dominant hand) did not change significantly after rTMS-MT ($p=0.281$) or MT ($p=0.304$).

The LI of hand dexterity was also calculated. The ANOVA results showed a significant difference in intervention time ($p=0.028$). Intervention method had no significant influence on behavioral lateralization ($p=0.339$), and there was no statistical significance for the interaction effect ($p>0.05$). Furthermore, the student's paired-sample

Fig. 3 Changes in reaction time in the nine-hole peg test, which reflects hand dexterity, for both hands. **a** rTMS-MT. **b** MT. The reaction time of the left hand (nondominant hand) decreased significantly after rTMS-MT and MT ($*p<0.05$)



t-test was used to analyze the effects of different intervention methods on behavioral lateralization; the results are shown in Table 1. The LI of hand dexterity changed significantly after rTMS-MT ($p=0.004$), suggesting a significant improvement in motor performance for the left hand relative to the right hand. The LI also decreased after MT, but the difference was not significant ($p=0.129$).

Lateralization of MEP and RMT

The MEP amplitude of both hands was tested before and after rTMS-MT and MT. The ANOVA results showed a significant difference in intervention time ($p=0.042$). There was no significant difference between intervention methods, or between hands ($p=0.856$), and no significant interaction effect ($p>0.05$). The results of the Student's paired-sample *t*-test for intervention time are shown in Fig. 4. The MEP amplitude of the left hand increased significantly after rTMS-MT ($p=0.042$) and MT ($p=0.045$), suggesting that the excitability of the corticospinal tract in the nondominant hemisphere increased significantly. There was no significant change in MEP amplitude for the right hand after rTMS-MT ($p=0.232$) or MT ($p=0.376$). Subsequently, the LI of the MEP amplitude was calculated; the ANOVA results showed no significant difference for intervention time or interaction effect ($p>0.05$). Furthermore, the student's paired-sample *t*-test was used to analyze the effects of different intervention methods on MEP; the results are shown in Table 1. There

was no significant change in LI for MEP after rTMS-MT ($p=0.294$) or MT ($p=0.223$).

We measured RMT before and after rTMS-MT or MT. The ANOVA results showed there was no significant difference in intervention time ($p=0.861$), intervention methods ($p=0.084$) or between the right and left hemisphere ($p=0.383$), and no significant interaction effect ($p>0.05$). The student's paired-sample *t*-test for intervention time showed no significant change after rTMS-MT (left hemisphere, $p=0.153$; right hemisphere, $p=0.438$) or MT (left hemisphere, $p=0.929$; right hemisphere, $p=0.195$). The LI for RMT showed no significant changes after ($p=0.127$) or MT ($p=0.257$).

The lateralization of power spectral density

Changes in power spectral density in the alpha frequency band before and after rTMS-MT or MT were calculated. The results are shown in Fig. 5. Based on brain topography, the power spectral density in the left hemisphere (dominant hemisphere) decreased and that in the right hemisphere (nondominant hemisphere) increased after rTMS-MT, including in the central cortices, frontal cortices, and parieto-occipital cortices. However, the power spectral density in both central cortices increased after MT, more so in the nondominant hemisphere. We found no statistically significant change in power spectral density in any cortex before and after rTMS-MT or MT.

Table 1 Laterality of manual dexterity, MEP, and RMT

	Before	After	After-before	Significance
(A) rTMS-MT				
Reaction time	0.035 ± 0.037	- 0.004 ± 0.052	- 0.039 ± 0.027	0.004*
MEP	- 0.088 ± 0.236	- 0.052 ± 0.221	0.036 ± 0.202	0.294
RMT	- 0.001 ± 0.046	- 0.012 ± 0.047	- 0.011 ± 0.027	0.127
(B) MT				
Reaction time	0.049 ± 0.053	0.013 ± 0.039	- 0.036 ± 0.060	0.129
MEP	- 0.164 ± 0.218	- 0.004 ± 0.307	0.159 ± 0.433	0.223
RMT	- 0.018 ± 0.022	- 0.025 ± 0.037	- 0.007 ± 0.032	0.257

*Represents the significant difference ($p < 0.05$) of laterality before and after rTMS-MT

Fig. 4 Changes in MEP amplitude, which reflects the excitability of the corticospinal tract, for both hands. **a** rTMS-MT. **b** MT. The MEP amplitude of the left hand (nondominant hand) increased significantly after rTMS-MT and MT ($*p < 0.05$)

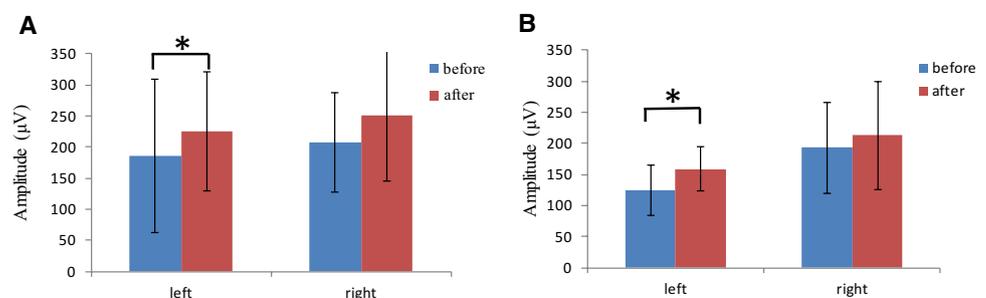
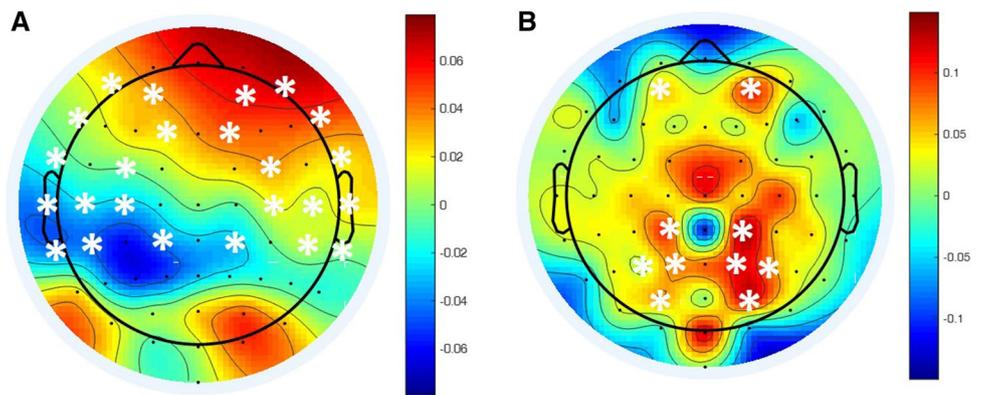


Fig. 5 Changes in power spectral density. **a** rTMS-MT. **b** MT. Significant changes in the LI of the power spectral density are designated by a white asterisk. rTMS-MT and MT did not change the power spectral density significantly ($p > 0.05$). However, rTMS and MT changed the inter-hemispheric lateralization ($p < 0.05$)



However, the LI of the power spectral density showed changes after rTMS-MT or MT. These results are also shown in Fig. 5, where significant changes in the LI are designated by a white asterisk. In the cortices, the changes in LI induced by rTMS-MT were greater than those induced by MT. The LI in the frontal cortex, central cortex, and temporal cortex increased significantly after rTMS-MT. However, only the central cortex and parietal cortex showed significant increases in LI after MT.

Changes in functional connectivity

To evaluate functional connectivity, EEG channels were grouped into four regions (frontal, temporal, central, and occipital) for each hemisphere. Inter-region connectivity involved synchronizations between two different regions, while intra-region connectivity involved synchronizations between two electrodes within one region. Midline channels were not used. The allocations of channel pairs are illustrated in Fig. 6a. A 60 × 60 channel matrix consisting of the PLI values for each electrode pair was obtained for each subject before and after rTMS-MT or MT. The means of

inter-region and intra-region PLI values were calculated, and significant changes in PLI values were assessed at a significance level of $p < 0.05$. The results are shown in Fig. 6b, c.

PLI values changed significantly during the 14 days of rTMS-MT or MT. The inter-region PLI increased, but the intra-region PLI did not change significantly. The PLI between the central region in the right (nondominant) hemisphere and frontal regions in both hemispheres, as well as the temporal region in the left (dominant) hemisphere, increased after rTMS-MT. However, only the PLI between the central region in the right hemisphere and temporal region in the left hemisphere increased after MT.

Lateralization of network characteristics

We constructed a weighted brain network using PLI values. The path length and node efficiency of the brain network were calculated before and after rTMS-MT or MT. We found that the path length and node efficiency did not change significantly after rTMS-MT or MT. Furthermore, we calculated the lateralization of network characteristics. The results are shown in Fig. 7. We found that the LI of

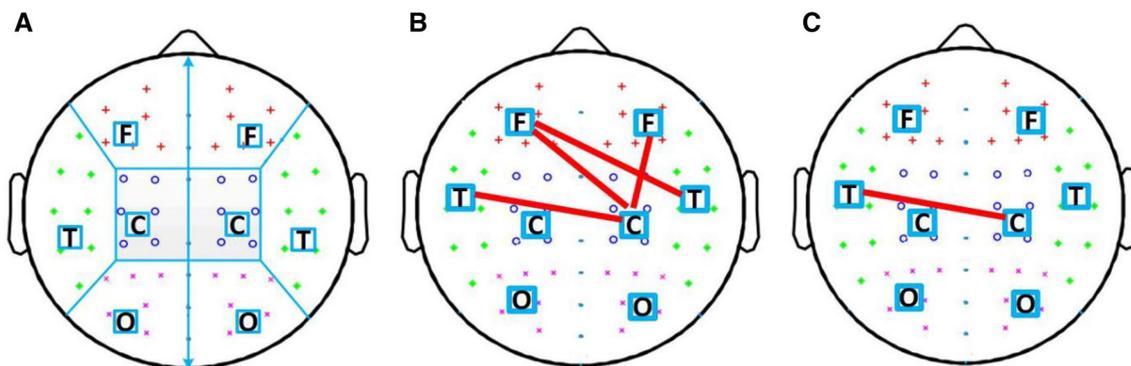
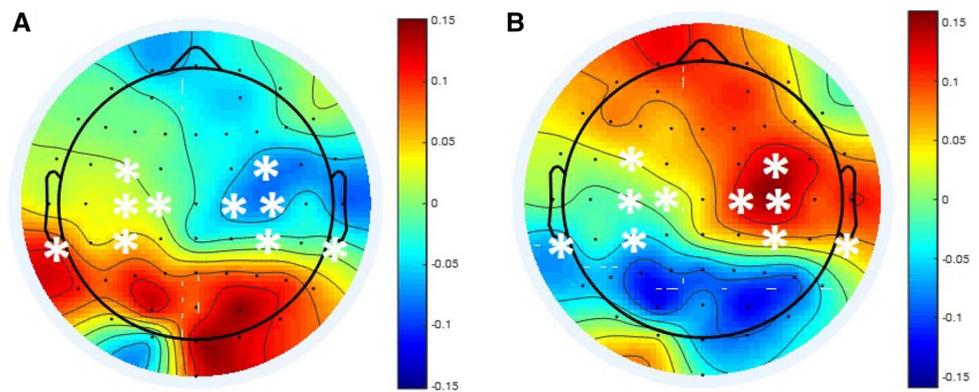


Fig. 6 Changes in inter-region and intra-region functional connectivity. **a** Allocations of channel pairs and channels are grouped into frontal (red plus sign), central (blue circle), occipital (purple cross), and

temporal (green asterisk) regions for both hemispheres. **b** rTMS-MT. **c** MT. A significant increase in functional connectivity is designated by red lines

Fig. 7 Changes in network characteristics before and after rTMS-MT. **a** Node path length. **b** Node efficiency. Significant changes in the LI of network characteristics are designated by a white asterisk. rTMS-MT changed the lateralization between the central regions



network characteristics for central regions changed significantly after rTMS-MT. Specifically, the path length of the central region in the nondominant hemisphere decreased relative to that in the dominant hemisphere. The results for node efficiency were contrary to those for path length. However, we found no significant change in the LI of network characteristics after MT.

Discussion

In this study, we focused on the effect of rTMS-MT on the lateralization of brain activity. We found that rTMS-MT could improve the hand's motor function and change the lateralization of hand dexterity. Subsequently, we evaluated the excitability changes of the corticospinal tract induced by 14 days of rTMS-MT. In the end, to observe the changes of brain activity, we recorded the EEG in a resting state with eyes closed, and calculated the power spectral density and the functional connectivity between regions in the alpha frequency band. We found that rTMS-MT changed the brain activity and inter-hemispheric lateralization.

rTMS-MT changed the lateralization of hand dexterity

In this study, the nondominant hand of healthy volunteers was regarded as the target hand because of its poor motor function. The motor function of the nondominant hand was improved after inhibiting the excitability of the dominant hemisphere with 1 Hz rTMS and enhancing the excitability of the nondominant hand with motor training (Fig. 3), which is consistent with the results of the literature (Avenanti et al. 2012; Emara et al. 2010; Kakuda et al. 2012, 2016; Lüdemann-Podubecá et al. 2015). This study's results suggest that rTMS-MT is an effective method to improve limb motor function.

In addition, the lateralization of hand dexterity changed. This means that compared with the dominant hand, the

dexterity of the nondominant hand improved more. In the literature, although 1 Hz rTMS was used to inhibit the excitability of the dominant hemisphere, the pernicious impact of rTMS on the dexterity of the dominant hand has not previously been reported. In this study, it is noteworthy that rTMS-MT improved the motor function of not only the nondominant hand but also that of the dominant hand, although there was no significant difference. It has been reported that motor function of one limb could be enhanced by motor training of this limb, and this training could also improve the motor function of the non-motor training limb, which was referred to as cross education (Farthing et al. 2011; Farthing and Zehr 2014; Pearce et al. 2013). Therefore, we could speculate that the increasing trend of dexterity in the dominant hand might be because of the cross-education of the central nervous system.

rTMS-MT did not change the lateralization of the corticospinal tract

The excitability of the corticospinal tract in the nondominant hemisphere increased significantly after rTMS-MT or MT (Fig. 4). Previous studies on motor function improvement in dyskinesia patients have shown that the corticospinal tract excitability of patients was significantly decreased compared with healthy subjects, and that it could be significantly increased by rehabilitation therapy. Further, the excitability of the corticospinal tract was related to changes in limb motor function (Fregni et al. 2006; Di Lazzaro et al. 2008; Lee et al. 2015). This indicates that increased corticospinal tract excitability might be one of the neural substrates involved in the improvement of motor function induced by rTMS-MT.

Although the excitability of the corticospinal tract in the nondominant hemisphere increased, the lateralization did not change significantly (Table 1). We also observed an increase in the amplitude of MEP in the dominant hemisphere, an unexpected finding. This might be have been due to cross-education of the central nervous system. Previous

studies showed that motor function improvement after stroke was accompanied by an increase in corticospinal tract excitability in the affected hemisphere, but no effect of rTMS-MT on the unaffected hemisphere was found (Avenanti et al. 2012), contrary to the results of our study. We speculate that the impact of rTMS-MT on the excitability of the corticospinal tract after stroke is different from that in a healthy person because of the brain injury in stroke patients. In other words, healthy people might have greater cross-education capacity than stroke patients.

rTMS-MT changed the lateralization of the power spectral density

In this study, EEG performed in a resting state with eyes closed was used to investigate the effect of rTMS-MT on brain activity. The resting state with eyes closed while awake is the baseline state of the human body. Studying the neural activity in this state is of great importance for understanding the brain's neurophysiological mechanisms and responses to external stimulation (Klimesch 1999). The main rhythm in the resting state is the alpha frequency oscillation (8–13 Hz), which is an important neural substrate for cognition and motor function. It has been reported that brain activity in the alpha frequency band can predict the efficiency of cognitive, motor, and other neural processes (Klimesch 1997; Klimesch et al. 2003; Lim et al. 2006; Babiloni et al. 2010). Therefore, in this study, the power spectral density and the characteristics of the brain network of EEG signals in the alpha frequency band were analyzed.

The inter-hemispheric lateralization of the power spectral density in the frontal and central brain cortices increased significantly after rTMS-MT (Fig. 5), indicating that the power spectral density in the nondominant hemisphere increased compared with that in the dominant hemisphere. An increase in the power spectral density in the resting alpha frequency band indicates that neurons are in a more active state of preparatory movement and have a stronger function to move the limb (Neubauer et al. 1995; Klimesch 1997; Babiloni et al. 2010). The frontal cortex is responsible for responding to the sensory signals that lead to movement, whereas the central cortex includes the pre-motor, primary motor, and somatosensory cortices, which are closely related to the generation and execution of movement. The results of this study suggest that rTMS-MT could affect brain activity in multiple brain regions related to motor function.

rTMS-MT changed the functional connectivity of the central region in the nondominant hemisphere

The results of this study showed that the functional connectivity of the central and bilateral frontal lobes in the

nondominant hemisphere increased significantly after rTMS-MT (Fig. 6). Dubovik et al. (2012) reported that a decrease in functional connectivity in the central cortex was related to a decrease in hand motor performance. Furthermore, motor learning could change the functional connectivity of the central cortex. Albert et al. (2009) found that the neural network between the frontal cortex and parietal cortex increased after a visual motor tracking task. Lewis et al. (2009) found that a shape-identification task lasting 2–9 days could regulate functional connectivity and interaction between the visual cortex and the frontal-parietal cortex. Daselaar et al. (2010) found that the activation of the parietal cortex during task training was stronger after MT. Although the methods and results of the above studies were different, they consistently found changes in functional connectivity between the frontal cortex and parietal cortex, indicating that the functional connectivity of the frontal-parietal cortex is closely related to motor function and motor learning.

We did not find any changes in intra-region functional connectivity induced by rTMS-MT. Thus, we speculate that rTMS-MT changed information transmission over long distances (inter-region) but not over short distances (intra-region). Specifically, the changes in functional connectivity in the frontal-parietal cortex might represent important neural mechanisms for the improvement of motor function. In other words, motor function might be modulated by rTMS-MT through increases in the functional connectivity of the frontal-parietal cortex.

However, no changes in functional connectivity were observed when rTMS was applied to the dominant hemisphere. Kobayashi et al. (2004) reported that 1 Hz rTMS of primary motor cortex shortened the execution time of a motor task with the ipsilateral hand, without affecting the performance of the contralateral hand, consistent with the motor performance results of our study. Thus, the absence of changes in functional connectivity in the dominant hemisphere in our study might be the explanation of brain center state for change absence of the motor performance. Furthermore, Bolognini et al. (2009) reported a study of rTMS without coupling to any specific MT; the functional benefits were often limited (10–20%) because rTMS activated neural circuits in a non-specific way. Performing MT may be more effective if the pertinent areas of the cortex are facilitated. In other words, the role of rTMS in rTMS-MT is to make the cortex excitable. In this state, if MT were immediately performed, its effects would be enhanced. Therefore, we speculated that the absence of changes in functional connectivity in the dominant hemisphere in our study might be closely related to the effects of rTMS-MT on brain mechanisms, that is, 1 Hz rTMS inhibited the excitability of the dominant hemisphere and excited the nondominant hemisphere through the corpus callosum. When the nondominant hemisphere was excited and MT of the nondominant hand was

carried out, the excitability of the nondominant hemisphere would be superimposed, affecting the motor performance of the nondominant hand. However, the changes in functional connectivity of the dominant hemisphere were not sustained.

rTMS-MT changed the lateralization of network characteristics

In this work, a weighted and undirected brain network was established using the functional connectivity in the alpha frequency band. We found that the node path length increased and the node efficiency increased in the nondominant hemisphere after rTMS-MT, with the opposite results in the dominant hemisphere, although the changes were not significant. However, the lateralization of the network changed significantly (Fig. 7). These results suggest that communication efficiency increased in the nondominant hemisphere and decreased in the dominant hemisphere. The changes in communication efficiency between the central cortices showed a significant difference. 1 Hz rTMS can inhibit cortical excitability and was performed over the dominant hemisphere. The lower communication efficiency of the dominant hemisphere might be the influence of rTMS on brain activities, while the change in transcallosal inhibition induced by rTMS and MT may have increased the communication efficiency of the nondominant hemisphere. Therefore, rTMS-MT rebalanced the information transmission between hemispheres, which might be an important neural modulation induced by rTMS-MT.

Limitations

One limitation of this study was the lack of an rTMS group, as rTMS may not be capable of inducing results similar to those of rTMS-MT. It has been reported that the effects of rTMS alone on brain activity were stronger in the stimulation target cortex (Bolognini et al. 2009; Woźniak-Kwaśniewska et al. 2014). However, in our study, the greatest changes in brain activity induced by rTMS-MT were observed in the contralateral stimulation cortex. Moreover, we conducted an additional experiment to determine the effects of rTMS alone on brain activity, in which one 20-min session of rTMS was performed. We collected the resting state EEG before and after rTMS, and calculated the functional connectivity of the alpha frequency band, using the same method as in this study. We found rTMS decreased the functional connectivity of the ipsilateral stimulation hemisphere, which was different from the results induced by rTMS-MT (increased the functional connectivity of contralateral stimulation hemisphere). Therefore, rTMS alone was not capable of inducing similar results to rTMS-MT in this case. Nevertheless, it will be important to investigate the effects of multiple sessions of rTMS alone; we will carry out such experiments at

a later stage. The other limitation of this study was the small subject sample size (ten subjects in the rTMS-MT group, nine subjects in the MT group). Future studies with more subjects would help provide greater insight into the modulation of brain activity involved in the improvement of motor function induced by rTMS-MT. Despite these limitations, the results observed in our study confirmed that rTMS-MT could change the inter-hemispheric lateralization of neural activities, and our study results could be helpful for understanding the neural mechanism of rTMS-MT.

Conclusion

In summary, our findings suggest that rTMS-MT could improve motor function and change the lateralization of hand dexterity. Furthermore, rTMS-MT changed the lateralization of power spectral density and network characteristics significantly. The improvement of motor function induced by rTMS-MT might be closely related to the change of inter-hemispheric lateralization, rather than intra-hemispheric lateralization. Inter-hemispheric lateralization might be a promising method to study the impact of rTMS-MT on neural activities. The findings in our study enhanced the understanding to the impact of rTMS-MT on brain activity. These results could be used as a reference for future research on the effects of rTMS-MT in stroke patients.

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