

# Magnetic stimulation and movement-related cortical activity for acute stroke with hemiparesis

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**Background and purpose:** This double-blind, randomized, placebo-controlled study investigated the beneficial effects of repetitive transcranial magnetic stimulation (rTMS) to patients with motor paresis in acute subcortical stroke on functional recovery and electrophysiological measures.

**Methods:** Twenty patients with acute stroke were randomized into real rTMS ( $n = 10$ ) or sham ( $n = 10$ ) groups. Patients received five daily sessions of rTMS with 1200 pulses at 1 Hz for 20 min or sham stimulation over the contralesional motor cortex. Movement-related cortical potential MRCP, consisting of the Bereitschaftspotential, negative slope (NS') and motor potential (MP), was recorded during self-paced wrist extension of the affected limb associated with assessment of the Fugl–Meyer assessment (FMA) of the upper extremity, the pegboard test and the grip strength before and after the rTMS session.

**Results:** Real rTMS improved the FMA and pegboard test scores compared to the sham group in the affected hand. This improvement was associated with increases in the MP and NS' over the front-central sites in the ipsilesional hemisphere, whereas the sham group did not show significant changes in MRCP components by rTMS.

**Conclusions:** Our findings suggest that low-frequency rTMS to the contralesional motor cortex facilitates functional recovery of paretic limbs in acute stroke patients through enhancing the neuronal activity of ipsilesional motor and pre-motor areas.

## Introduction

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive tool which can safely facilitate functional motor recovery. Low-frequency rTMS in the contralesional hemisphere can improve motor performance in patients with stroke in the chronic stage [1,2]. These effects might be due to cellular and molecular changes in cortical neurons in addition to the effects on cortical excitability and synaptic plasticity induced by rTMS [3]. However, the neurophysiological mechanisms for the functional improvement after rTMS are largely unknown in the clinical population, although one study reported increased peripheral

motor evoked potential (MEP) of the paretic hand after rTMS [4], which provided an indirect evidence of changes in cortical excitability.

Movement-related cortical potential (MRCP) is a gradually developed negative electrical potential recorded on the scalp [5]. A previous study showed the importance of activity of the motor area in the process of motor recovery in patients with cortical infarction within the time period of several hundred milliseconds before the movement onset [6]. Since MRCP carries excellent temporal information of neural activity related to movement execution, it provides direct evidence of temporally defined neural activity over the movement-related cortical areas associated with motor recovery modified by rTMS in stroke patients. The aim of this study was to investigate whether low-frequency rTMS to the contralesional hemisphere of patients with acute stroke-induced

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subcortical lesion could facilitate functional motor recovery, and to clarify the changes in neuronal activity of movement-related cortices associated with motor recovery after rTMS.

## Methods

### Study design and patient population

Twenty patients (11 women) aged 43–89 years (mean 73.5) with first-ever acute ischaemic stroke were studied. Patients were selected consecutively from those who were admitted to Shimane University Hospital and met the following criteria: (i) had a stroke lesion within one hemisphere as verified by magnetic resonance imaging; (ii) showed mild to moderate motor impairment in one hand with a score equal to or less than 63 for the Fugl–Meyer assessment (FMA) and could extend at least 20° at the wrist for MRCP measurement; and (iii) started the rTMS session within 30 days after stroke onset. Patients with any neuropsychiatric comorbidity other than stroke and with contraindication to rTMS, i.e. patients with metal within the brain, a cardiac pacemaker, pregnant or with a history of seizure, were excluded. All patients gave their written informed consent and the protocol was approved by the ethics committee of Shimane University.

The timing of the study entry was 9.6 days (4–21 days) after stroke onset. Following entry, patients were randomly assigned to two groups: a real rTMS group ( $n = 10$ ) and a sham rTMS group ( $n = 10$ ). Both real and sham rTMS were performed for five consecutive days. The pre- and post-rTMS assessments for motor functions and MRCP measurement were performed 24 h before and after the whole rTMS session. The long-term assessment was not performed due to hospital transfer. The examiners for assessment of motor function and MRCP were totally blind to the group assignment.

### Trial registration

This study is registered in the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (ID: UMIN000016021).

### Repetitive transcranial magnetic stimulation procedures

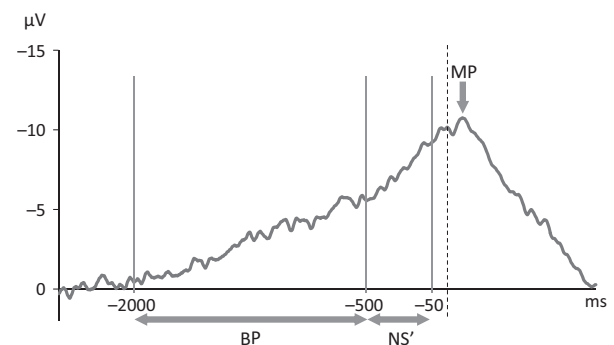
Repetitive transcranial magnetic stimulation was performed using a 70-mm figure-of-eight coil with the Magstim Rapid stimulator (Magstim Co., Whitland, UK). The coil was placed tangentially over the motor cortex of the unaffected hemisphere at the optimal loca-

tion to elicit maximal contraction of the contralateral extensor carpi radialis muscle. Motor threshold was defined as the minimum stimulus intensity that induced a reliable MEP of 50  $\mu$ V at rest in at least five out of 10 responses [7], and the threshold did not change across sessions. The stimulation was performed based on the method of Fregni *et al.* [1], at a rate of 1 Hz, and with an intensity of 100% motor threshold for 20 min (1200 pulses) per day. The mean stimulus intensity was 43.6% (30%–65%) of the maximum level for the stimulator output. Sham rTMS was performed by placing the coil perpendicularly to the scalp to reproduce the noise of a 1 Hz stimulus and tactile sensation on the scalp without cortical stimulation [8]. The head of the patient was fixed to the head-rest of a reclining chair with a belt, and the coil was fastened to the articulated metal arm attached to the chair. The head movement was also visually monitored during the session.

### Movement-related cortical potential recording and measurement

Patients were instructed to perform self-paced extension of the affected wrist at irregular intervals between 7 and 10 s. Electroencephalogram (EEG) data were measured at FC3, FCz, FC4, C3, Cz and C4 (international 10–20 system) with reference to a linked ear lobe (impedances  $<5$  k $\Omega$ , sampling frequency 1000 Hz, band-pass filter 0.016–60 Hz). The surface electromyogram (EMG) was recorded from a pair of electrodes placed over the extensor carpi radialis muscle for determining the onset of movement. The epoch of EEG data was set for 6 s, including 5 s before EMG onset and 1 s after it. A total of 80–100 EEG artifact-free epochs were collected and averaged offline for MRCP analysis.

Movement-related cortical potential was divided into three components: Bereitschaftspotential (BP), negative slope (NS') and motor potential (MP) (Fig. 1) [5]. BP was defined as a slow negative shift



**Figure 1** Components of the MRCP. The dotted vertical line shows the onset of the EMG.

lasting from 2.0 to 0.5 s before movement onset. NS' was defined as a steeper negative slope lasting from 0.5 to 0.05 s before movement onset. The first 1 s of the epoch served as baseline. Mean amplitudes for MP and NS' in the defined time window were measured. MP was defined as a negative peak around movement onset and the peak amplitude was used for statistical analysis.

**Motor function tests**

Motor impairment of the upper extremity was evaluated using the FMA, the Purdue Pegboard Test (PPT) and grip strength before and after rTMS sessions in a blinded fashion. To estimate hand dexterity, PPT measures the total number of pegs replaced in a pegboard during 30 s for each hand [9]. Grip strength was measured using a digital hand dynamometer, and two trials were averaged.

**Statistical analysis**

The MRCP data were subjected to repeated measures analysis of variance (ANOVA) using time (pre-rTMS and post-rTMS) and anterior–posterior electrode site (FC and C) and lateral electrode site (ipsilesional and contralesional) as within-subject factors and group (rTMS group and sham group) as a between-subjects

factor. The lateral electrodes were organized as a function of electrode site over the ipsilesional (i.e. FCi, Ci) or contralesional (i.e. FCc, Cc) hemisphere. Data at the midline electrodes (FCz and Cz) were excluded from statistical analysis because of no information for laterality. A level of  $P < 0.05$  was accepted as statistically significant. The Pearson correlation coefficient was used to assess associations between the MRCP and motor function data. Because bivariate correlation analysis was repeated for six electrode sites,  $P < 0.008$  was used as the statistically significant level according to the Bonferroni correction. SPSS software (version 21; IBM, Armonk, NY, USA) was used for the statistical analysis.

**Results**

**Demographic and clinical characteristics**

All patients completed their rTMS sessions and did not report any adverse effects. There were no significant differences in clinical features or demographic variables between real and sham groups (Table 1).

**Behavioral data**

The real rTMS group showed larger improvement of FMA score compared to the sham group [ $F(1, 18)$

**Table 1** Clinical characteristics of stroke patients

Patient	Age	Sex	Days post-stroke	Paretic side	Lesion site	FMA in upper limb
Real rTMS group						
1	63	F	8	Lt	Corona radiata	56
2	77	F	5	Rt	Pons	50
3	74	F	9	Lt	Corona radiata	57
4	80	M	11	Rt	Pons	61
5	66	M	5	Lt	Basal ganglia	48
6	68	M	4	Rt	Thalamus	57
7	80	F	6	Lt	Corona radiata	54
8	65	M	21	Rt	Pons	26
9	73	M	17	Lt	Corona radiata	37
10	76	M	8	Rt	Corona radiata	54
Mean ± SD	72.2 ± 6.0		9.4 ± 5.3			50.0 ± 10.7
Sham rTMS group						
11	88	F	10	Lt	Pons	56
12	80	F	11	Rt	Corona radiata	58
13	43	M	16	Lt	Pons	39
14	64	F	12	Rt	Basal ganglia	37
15	89	F	7	Lt	Corona radiata	32
16	75	M	6	Lt	Corona radiata	63
17	79	M	11	Lt	Corona radiata	58
18	73	M	8	Rt	Corona radiata	58
19	83	M	7	Rt	Basal ganglia	44
20	73	F	10	Rt	Corona radiata	63
Mean ± SD	74.7 ± 12.7		9.8 ± 2.8			50.8 ± 11.6

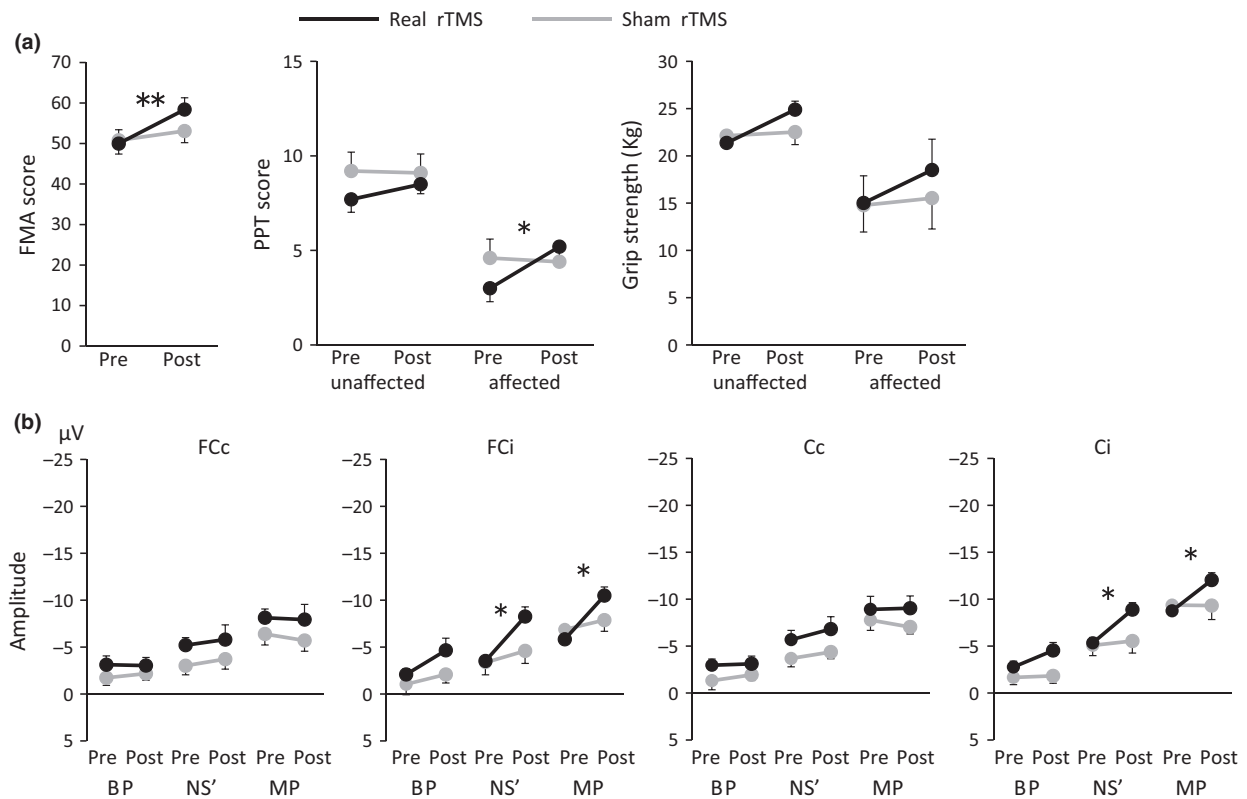
= 17.6,  $P = 0.001$ ] (Fig. 2a). The real group also showed larger improvement of PPT score compared to the sham group [ $F(1, 18) = 7.77$ ,  $P = 0.012$ ]. When the affected and unaffected limbs were compared, the PPT score of only the affected limb was improved by rTMS [affected limb,  $F(1, 18) = 6.72$ ,  $P = 0.018$ ; unaffected limb,  $F(1, 18) = 2.75$ ,  $P = 0.115$ ]. The interaction of group and time for grip strength was not significant [ $F(1, 18) = 4.21$ ,  $P = 0.055$ ]. In summary, FMA and PPT scores of the affected limb were improved by rTMS.

### Electrophysiological data

For MP, there were no main effects for group, time, lateral electrode and anterior–posterior electrode (Table 2, Fig. 3). Neither the interaction of group, time and anterior–posterior electrode nor the interaction of group, time, lateral and anterior–posterior electrode was significant. However, there was a significant interaction of group, time and lateral electrode site, which showed a larger negative increase of MP in

the real rTMS group compared to the sham group over the ipsilesional hemisphere. The interaction of group and time for each electrode site was then analyzed. There were significant interactions for MP at FCi (Fig. 2b), whereas no interactions were observed at other electrode sites. Thus, increased negativity of MP by rTMS was observed only over the ipsilesional cortex.

Negative slope amplitude showed similar changes to MP amplitude except for the main effect of time. The ANOVA showed a significant interaction of group, time and lateral electrode, indicating increased mean amplitude of ipsilesional NS' by rTMS. There were no interactions of group, time and anterior–posterior electrode, and of group, time, lateral and anterior–posterior electrode. For each electrode site, there were significant interactions for NS' at FCi (Fig. 2b), whereas no interactions were observed at other electrode sites. Thus, increased NS' by rTMS was also evident over the ipsilesional cortex. There was a significant main effect of time for NS' at FCi and Ci, although main effects of group at FCi, Ci, FCc and



**Figure 2** (a) Changes in motor function measures before and after rTMS: black circle, real stimulation; grey circle, sham stimulation; pre, pre-stimulation; post, post-stimulation. Error bars are SEM. \* $P < 0.05$ , interaction between time and group; \*\* $P < 0.01$ , interaction between time and group. (b) Changes of mean amplitudes for BP and NS' and peak amplitude of MP before and after rTMS: black circle, real stimulation; grey circle, sham stimulation; pre, pre-stimulation; post, post-stimulation. Error bars are SEM. \* $P < 0.05$ , interaction between time and group.

**Table 2** Statistical results for MRCP

	BP		NS'		MP	
	<i>F</i>	<i>P</i>	<i>F</i>	<i>P</i>	<i>F</i>	<i>P</i>
Group	2.887	0.106	3.780	0.068	1.704	0.208
Time	5.044	0.038 <sup>a</sup>	10.999	0.004 <sup>a</sup>	2.808	0.111
Time × group	0.511	0.484	3.259	0.088	3.597	0.074
Lateral electrode	0.146	0.707	1.410	0.251	2.460	0.134
Lateral electrode × group	0.505	0.487	0.061	0.807	0.312	0.583
Anterior–posterior electrode	0.008	0.930	5.977	0.025 <sup>a</sup>	13.482	0.002 <sup>a</sup>
Anterior–posterior electrode × group	0.098	0.757	0.002	0.966	0.006	0.941
Lateral electrode × time	2.894	0.106	5.360	0.033 <sup>a</sup>	15.236	0.001 <sup>a</sup>
Lateral electrode × time × group	2.515	0.130	4.538	0.047 <sup>a</sup>	4.434	0.049 <sup>a</sup>
Anterior–posterior electrode × time	1.829	0.193	1.212	0.285	1.463	0.242
Anterior–posterior electrode × time × group	0.025	0.875	0.019	0.893	0.000	0.988
Lateral electrode × anterior–posterior electrode	1.452	0.244	1.855	0.190	3.946	0.062
Lateral electrode × anterior–posterior electrode × group	0.068	0.797	0.067	0.798	0.511	0.484
Lateral electrode × anterior–posterior electrode × time	1.238	0.281	1.328	0.264	1.489	0.238
Lateral electrode × anterior–posterior electrode × time × group	0.000	0.996	0.166	0.689	0.097	0.760
FCi						
Group	1.866	0.189	1.772	0.200	0.377	0.547
Time	11.046	0.004 <sup>a</sup>	29.965	0.0001 <sup>a</sup>	25.483	0.0001 <sup>a</sup>
Time × group	1.958	0.179	10.383	0.005 <sup>a</sup>	10.609	0.004 <sup>a</sup>
FCc						
Group	1.366	0.258	2.562	0.127	1.648	0.215
Time	0.063	0.805	0.510	0.484	0.281	0.602
Time × group	0.155	0.699	0.002	0.967	0.089	0.768
Ci						
Group	3.917	0.063	2.208	0.155	0.744	0.400
Time	4.020	0.060	9.153	0.007 <sup>a</sup>	4.398	0.050
Time × group	2.777	0.113	5.903	0.026	4.676	0.044
Cc						
Group	2.064	0.168	3.007	0.100	1.146	0.298
Time	0.571	0.460	2.050	0.169	0.175	0.680
Time × group	0.212	0.651	0.140	0.713	0.339	0.568

<sup>a</sup>Statistically significant.

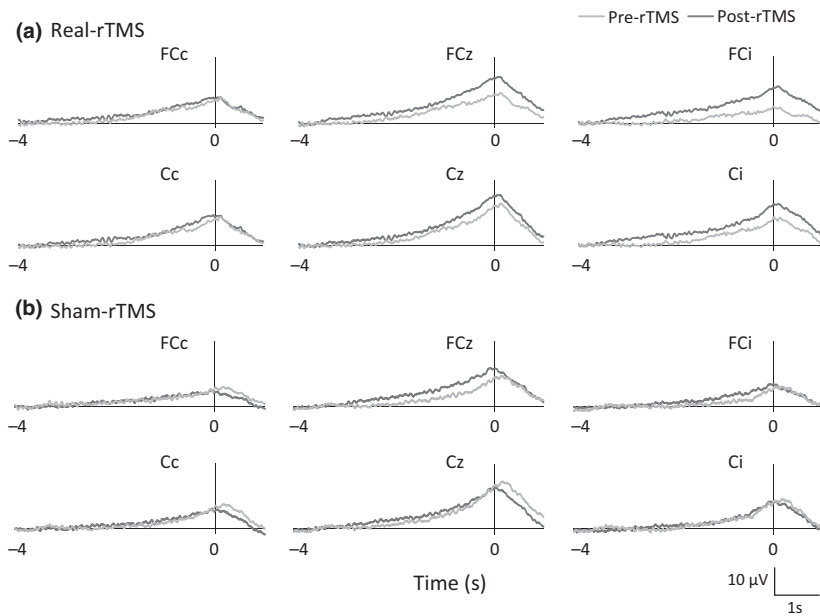
Cc site and time at FCc and Cc were not significant. Regarding BP, only the main effect of time was observed as a whole and at FCi, and the interaction of group and time for BP was not significant, indicating that BP amplitude was not modified by rTMS.

**Relationship between motor recovery and electrophysiological data**

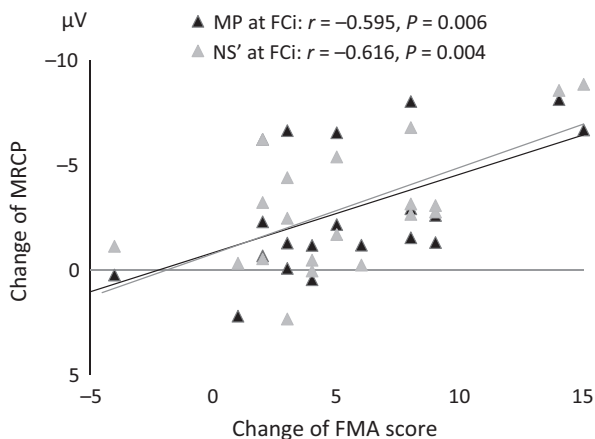
To examine the association of motor recovery with MRCP changes, a correlation analysis of the relationship between these two measures was performed (Fig. 4). The functional motor recovery was quantified by calculating the changes of FMA scores after rTMS. It was found that the increase of MP amplitude at FCi was correlated with the increase of FMA score ( $r = -0.595$ ,  $P = 0.006$  at FCi). The increase of NS' amplitude at FCi was also correlated with the increase of FMA score ( $r = -0.616$ ,  $P = 0.004$ ). There were no significant correlations of the changes of MP and NS' at other electrode sites with FMA score change.

**Discussion**

This study demonstrated that low-frequency rTMS to the contralesional motor cortex improved motor function of the affected upper limb, as assessed with FMA and PPT scores associated with increased MRCP amplitude. A meta-analysis of functional magnetic resonance imaging data in stroke patients demonstrated that good motor recovery was associated with higher activation of the contralesional motor and bilateral pre-motor areas [10]. On the other hand, it has been reported that patients with stroke have abnormally augmented interhemispheric inhibition from the contralesional to ipsilesional side during voluntary movement of the paretic hand [11], suggesting an adverse impact on persistent motor paresis by the effect from the opposite hemisphere. Functional connectivity data have also shown that inhibitory rTMS to the contralesional motor cortex can resolve pathological inhibitory influences, and the suppressed inhibition is associated with improved motor function [12].



**Figure 3** MRCP generated by affected hand movement at six electrode sites before (grey) and after (black) rTMS for (a) the real group and (b) the sham group.



**Figure 4** Relationship between changes in MP (black) and NS' (grey) amplitude and change of motor function (FMA score).

Although the validity of the interhemispheric competition model is still in dispute [13], it is plausible that low-frequency rTMS can weaken the influence of abnormal transcallosal inhibition from the contralesional motor cortex and restore the balance between the two hemispheres. To our knowledge, this is the first study providing electrophysiological evidence for this facilitated movement-related cortical activity associated with functional motor recovery.

Our results demonstrated that rTMS to the contralesional motor cortex led to an increase in MP amplitude over the ipsilesional FC electrode site. Since the MP component is generated in the motor cortex [14], it was assumed that activity of the motor cortex was primarily enhanced by contralesional inhibitory

rTMS. In addition to MP, the mean amplitude of NS' was also increased over the same region. The generator source of NS' is located in the pre-motor and motor areas [15]. Thus, activation of the pre-motor region by contralesional rTMS also seems to contribute to enhancing motor function recovery [16]. Although the spatial resolution of MRCP data was limited, this electrophysiological study provided evidence that the rTMS effect on cortical activity was clearly lateralized to the ipsilesional hemisphere and the function recovery was attributed not only to activity change of the motor cortex but also to that in the pre-motor stage of movement execution as indexed by increased NS' amplitude.

Although many rTMS studies have been conducted in patients with chronic stroke [17], there are few studies that have been conducted on patients in the acute stage. Khedr *et al.* [4] demonstrated rTMS effects on motor paresis in patients with acute stroke, where low-frequency rTMS was more effective than high-frequency rTMS. According to their MEP measures high-frequency rTMS to the ipsilesional hemisphere merely increased excitability of the stimulated hemisphere, but low-frequency rTMS to the contralesional hemisphere corrected the imbalance of cortical excitability between the two hemispheres. In contrast, Sasaki *et al.* [18] recently found that high-frequency rTMS was more effective than low-frequency rTMS. The discrepancy of these results may be due to differences in frequency or duration of stimulation.

One limitation of this study was the small number of patients included. There are a variety of parameters

that can be manipulated when applying rTMS to patients with stroke. Such parameters include frequency, intensity, location and duration of stimulation. In order to determine which parameter is the most suitable, larger numbers of patients should be recruited in the future. Alternatively, it may be possible to compare the various stimulus paradigms using MRCP to find the most appropriate rTMS parameter for the treatment of post-stroke paresis. Another limitation was that patients were not followed in terms of the durability of rTMS effects. Thus, long-term follow-up may be necessary to establish a suitable protocol for sustained effects during stroke recovery. Finally, only patients with mild to moderate motor deficit to secure MRCP measurement were recruited. Further study would be required to verify the comparable effects in patients with severe motor deficits. In conclusion, our study demonstrated that low-frequency rTMS to the contralesional motor cortex facilitates early recovery of paretic limbs in patients with acute stroke through enhancing neuronal reorganization of motor and pre-motor areas of the ipsilesional hemisphere.

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### Disclosure of conflicts of interest

The authors report no disclosures relevant to the paper.

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