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ORIGINAL REPORT

LONG-TERM EFFECTS OF rTMS ON MOTOR RECOVERY IN PATIENTS AFTER SUBACUTE STROKE

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Objective: **Repetitive transcranial magnetic stimulation (rTMS) has been recognized as a promising intervention for treatment of stroke patients. However, most previous reports have described the short-term effects of rTMS on motor performance. We conducted a sham-controlled trial to evaluate long-term effects of high-frequency rTMS on motor recovery in subacute stroke patients.**

Methods: **Twenty-eight patients were randomly divided into two groups, and received either real or control rTMS. Both treatments were accompanied by motor practice. A daily dose of 1000 pulses of subthreshold 10 Hz rTMS was applied over the primary motor cortex of the affected hemisphere for 10 days within one month after onset of stroke. Motor function was assessed before and after treatment, and 3 months after the stroke.**

Results: **Motor function improved in both groups after treatment; however, patients who received real rTMS experienced additional improvement in motor function of the affected upper limb. Over 3 months after the stroke, the time and type of intervention for the Motoricity Index of the affected upper extremity showed significant interaction.**

Conclusion: **Positive long-term effects on motor recovery could be achieved after 10 daily sessions of high-frequency rTMS in conjunction with motor practice during the subacute period of stroke.**

Key words: stroke; repetitive transcranial magnetic stimulation; motor recovery.

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INTRODUCTION

Repeated transcranial magnetic stimulation (rTMS) can have a beneficial effect on motor function in patients who have had a stroke (1). According to the interhemispheric competition model, there are two therapeutic strategies for improvement of motor function using rTMS; up-regulation of excitability of the primary motor cortex (M1) in the affected hemisphere with high-frequency stimulation, and down-regulation of M1 excitability in the non-lesioned hemisphere with low-frequency stimulation (1). The latter strategy has proven to be effective after a single session (2–4) and in consecutive multi-session trials (5–7) for acute (2) and chronic (5–8) stroke in children (6) and adults (2–5, 7, 8). Neural correlates of the positive behavioural effects have also been elucidated (4). On the other hand, the up-regulation strategy has rarely been applied, primarily due to safety concerns.

According to findings from recent studies of the safety of high-frequency rTMS in patients with chronic stroke, a single session of rTMS at 20 Hz at subthreshold intensity was proposed as safe and beneficial to motor function (9). In a previous study, we found that a single session of 10 Hz rTMS at subthreshold intensity facilitated practice-dependent plasticity and improved motor learning in patients with chronic stroke (10). The relatively short-term effects of rTMS could result from changes in neural excitability caused by shifts in ionic balance around populations of active neurones, or even from the electrical capacitive effect of charge storing induced by the stimulus (11). The mechanism has also been observed to involve changes in the effectiveness of synapses between cortical neurones; long-term depression and long-term potentiation of synaptic connections (12). Evidence from previous studies has shown that changes resulting from rTMS can influence natural behaviours (2, 10). With regard to the interaction model, some forms of rTMS might be ideal for promotion or enhancement of natural adaptation to injury (13).

However, no results have been reported from consecutive multi-session high-frequency rTMS trials on the long-term effects of high-frequency rTMS in stroke patients. Following onset of stroke, natural adaptations to injury occur rapidly and on a wide scale in the subacute stage (14–16). Therefore, the subacute stage would be the most appropriate time period for stroke rehabilitation. According to this point of view, rTMS in the subacute stage can produce a more powerful effect on neural plasticity, and subsequent behavioural changes last longer.

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On the basis of the above-mentioned hypothesis, we designed and implemented a single-blind, sham-controlled study to investigate immediate and long-term effects of consecutive multi-session high-frequency rTMS directed to the affected hemisphere on motor function of the affected upper extremity in subacute stroke patients.

MATERIAL AND METHODS

Subjects

Twenty-eight stroke patients with hemiparesis were included in this study. Eleven of the patients were female. The mean age (standard deviation (SD)) of all patients was 56.6 years (SD 12.2). Inclusion criteria were as follows: (*i*) first-ever cerebral infarction, (*ii*) post-onset duration of less than one month, and (*iii*) mild to severe motor deficits of the contralesional upper limb. Exclusion criteria were as follows: (*i*) any clinically significant or unstable medical disorder, (*ii*) any neuropsychiatric comorbidity other than stroke, (*iii*) direct injury to the primary motor cortex, (*iv*) complete internal carotid artery occlusion, (*v*) seizure, or (*vi*) an intracranial metallic implant. Mean post-onset duration was 13.4 days (SD 5.4) range (7–26). Written informed consent was obtained from all subjects prior to inclusion in the study, and the study protocol was approved by the local ethics committee.

Experimental design

This study was a longitudinal, pseudo-randomized, parallel-design, sham-controlled trial. Similar to the design of a previous study, subjects were divided in a 2:1 ratio and received either real or control rTMS, respectively (5). Using the table of random sampling numbers, subjects were recruited into the control rTMS group when the last number of the subjects showed a multiple of 3, and the other subjects were recruited into the real rTMS group. Eighteen and 10 subjects were included in the real and control rTMS groups, respectively. Table I lists the demographic characteristics of the subjects in this study. No significant differences with regard to age, sex, duration, and number of non-responders in motor cortex mapping and motor-evoked potentials (MEPs) amplitude since stroke were observed at baseline between the two groups. Measurements for assessment of motor function were performed prior to treatment (Pre-rTMS), immediately after rTMS (Post 1), and 3 months after onset of stroke (Post 2). Fig. 1 delineates the experimental design and time course of the experiment.

Determination of motor cortex and resting motor threshold

To determine the optimal scalp location and intensity of rTMS, single-pulse TMS was performed on each subject prior to each rTMS session. Subjects were seated comfortably in a reclining armchair with both hands pronated on a pillow. Electromyography (EMG) data were collected from the contralateral first dorsal interosseus muscle via surface electrodes placed over these muscles in a belly-tendon montage. EMG activity was amplified using the Synergy EMG/EP system (Medelec, UK), and data were band-pass filtered at 10–2000 kHz. Optimal scalp location ("hot spot") was determined using a TMS system (Magstim Rapid2® stimulator: Magstim Ltd, UK) and a 70-mm figure-of-8 coil. The handle of the coil was oriented 45° posterior to the midline, so that the electromagnetic current would flow perpendicular to the central sulcus; the stimulator was then moved over the scalp in 1-cm increments. Once a hot spot was identified, single-pulse TMS was delivered to the location for determination of resting motor threshold (RMT), which was defined as the lowest stimulus intensity necessary to produce MEPs of a ≥ 50 μV peak-to-peak amplitude in 5 of 10 subsequent trials. Muscle activity was carefully monitored by real-time EMG in order to confirm a relaxed state prior to stimulation.

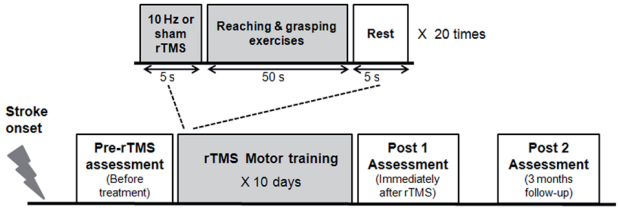

Fig. 1. Experimental design. Each motor training session consisted of 20 training blocks; each block consisted of 5 s of repetitive transcranial magnetic stimulation (rTMS) or control stimulation over the affected M1, 50 s of exercise, and 5 s of rest. Patients received 10 daily motor training sessions with rTMS or control over a period of two weeks. Measurements were performed prior to treatment (Pre-rTMS), immediately after rTMS (Post 1), and 3 months after stroke onset (Post 2).

Repetitive transcranial magnetic stimulation

Over a two-week period, patients received 10 sessions of rTMS, which were applied to the primary motor cortex of the affected hemisphere using a Magstim Rapid2® stimulator with two booster modules. Real rTMS involved 50 trains at 10 Hz for 5 s and 90% RMT applied through the coil over the target motor cortex area corresponding to the paretic hand. For subjects who showed no MEP response in the affected hemisphere, the hot spot and RMT were taken by the mirror image of the unaffected hemisphere. A total of 1000 pulses was delivered with a 55-s inter-train interval consisting of 50 s of motor training and 5 sec of rest (Fig. 1). Stimulation was applied to the motor cortex by holding the figure-of-8 coil tangentially to the skull. rTMS protocols used in the present study were in accordance with safety guidelines for rTMS applications (17). As with real rTMS, control rTMS was performed with the coil held at 90º to the scalp using the same stimulation parameters (duration, time, frequency). Motor practice consisted of 50 s of reaching and grasping exercises, which were conducted after each rTMS train by the same licensed physical therapist who did not participate in evaluation of subject function. Our motor training protocol included active and active assistive range of motion exercise of the affected extremity, grasp, move, and release of cups and cubes. Patients were instructed to give their best effort in performance of motor tasks for the designated time. All patients in both groups received the same amount of conventional, physical, and occupational therapy, including gait training, fitness training, and activities of daily living (ADL) training, etc., for 3 h each day, as scheduled.

Assessment of motor function, mobility, and functional independence

All patients underwent the following assessments. For evaluation of motor function of the affected upper limb and hand, we used the arm score in the Motricity Index (MI-A, range: 0–100) (18), the upper limb score in the Fugl-Meyer assessment (FMA-UL, range: 0–66) (19), grip strength (20), and the Box and Block test (BBT) (20). For evaluation of motor function of the affected lower limb, we used the leg score in MI (MI-L, range: 0–100) (18) and the lower limb score in FMA (FMA-LL, range: 0–34) (19). In addition, the patients' Functional Ambulatory Category (FAC, range: 0–5) (21) and modified Barthel index (MBI, range: 0–100) (22) were determined for assessment of mobility and functional independence. Differences in improvement for MI-A, FMA-UL, grip strength, and BBT were also assessed; $\Delta T1$ represents (value of the Post 1 – value of Pre-rTMS) and $\Delta T2$ represents (value of the Post 2 – value of Pre-rTMS). All assessments were performed by the same licensed occupational therapist who was blind to the grouping of each subject.

Data analysis

As indexed by the battery of assessments, our analysis focused primarily on changes in motor function of the affected hand. The Kolmogorov-Smirnov test was used to determine whether values for

Table I. *Demographic and clinical characteristics of patients*

					Baseline Motor Function								RMT (%)	
No	Gender	Age (years)	Lesion	POD (days)	MI-A	FMA-UL	GS (kg)	BBT	MI-L	FMA-LL	FAC	MBI	Affected	Unaffected
Real-rTMS group														
1	M	69	Lt. CR	10	51	35	1	12	59	30	3	73	NE	37
2	F	66	Lt. MM	12	19	15	0	0	37	8	0	20	NE	28
3	F	58	Lt. Pons	10	70	41	4	35	76	26	3	70	NE	34
4	M	56	Lt. SC	8	51	29	0	0	76	21	4	54	NE	27
5	F	55	Rt. CR	15	40	20	0	0	39	10	0	41	53	34
6	M	54	Rt. MCA	9	77	49	12	28	76	25	0	64	34	33
7	F	67	Lt. Pons	7	40	12	0	0	70	20	2	57	NE	28
8	M	52	Lt. Pons	11	39	27	0	0	51	19	2	58	NE	35
9	M	78	Rt. Pons	8	1	4	0	0	24	8	0	39	NE	22
10	M	39	Rt. Pons	13	77	48	10	22	65	25	2	81	NE	34
11	M	53	Lt. MM	25	19	5	0	0	33	7	1	32	NE	34
12	F	47	Lt. MCA	14	40	17	0	0	75	27	3	80	NE	30
13	M	55	Lt. ACA	15	36	19	0	0	28	5	1	24	35	28
14	F	36	Lt. MCA	24	38	11	0	0	70	26	3	71	NE	32
15	M	66	Rt. BG	10	40	8	0	0	76	31	2	85	NE	28
16	M	64	Rt. CR	8	27	55	10	13	76	34	2	36	NE	45
17	F	40	Lt. SC	15	27	55	0	18	47	15	2	51	49	42
18	M	60	Rt. MCA	18	23	9	0	0	48	15	0	20	NE	47
Mean (SD)		56.4 (11.2)		12.9 (5.2)	39.7 (20.2)	25.5 (17.6)	2.1 (4.1)	7.1 (11.4)	57.0 (18.8)	19.6 (9.1)	1.7 (1.3)	53.1 (21.4)	42.8 (9.7)	33.2 (6.5)
Control rTMS group														
1	M	63	Rt. CR	10	77	51	14	34	76	31	2	72	36	40
2	M	73	Lt. Pons	15	77	48	4	35	65	24	2	58	NE	42
3	M	66	Lt. MCA	21	71	41	18	12	19	12	0	25	25	23
4	F	28	Rt. MCA	9	1	5	0	0	1	5	0	36	NE	38
5	F	58	Lt. CR	10	40	10	0	0	76	26	2	47	NE	29
6	F	60	Rt. MCA	9	29	15	0	0	76	26	0	34	NE	45
7	M	52	Lt. MCA	26	61	30	0	0	70	34	2	33	40	33
8	M	38	Rt. MCA	16	60	37	12	13	59	20	2	81	35	30
9	F	58	Rt. CR	18	52	23	0	0	92	28	4	87	NE	30
10	M	74	Rt. MCA	10	19	9	0	0	24	7	0	27	NE	32
Mean (SD)		57.0 (14.5)		14.4 (5.9)	48.7 (25.8)	26.9 (16.9)	5.3 (7.3)	10.4 (14.6)	55.8 (30.2)	21.3 (10.1)	1.4 (1.4)	50.0 (23.1)	34.0 (6.4)	34.2 (6.8)

POD: post-onset duration; MI-A: arm score of Motricity Index; FMA-UL: upper limb score of Fugl-Meyer assessment; GS: grip strength; BBT: Box and Block test; MI-L: leg score of Motricity Index; FMA-LL: lower limb score of Fugl-Meyer assessment; FAC: Functional Ambulatory Category; MBI: Modified Barthel index; RMT: resting motor threshold; NE: not-evoked; Lt: left; Rt: right; CR: corona radiate; MM: medial medullar; SC: striatocapsular; MCA: middle cerebral artery; ACA: anterior cerebral artery; BG: basal ganglia; SD: standard deviation.

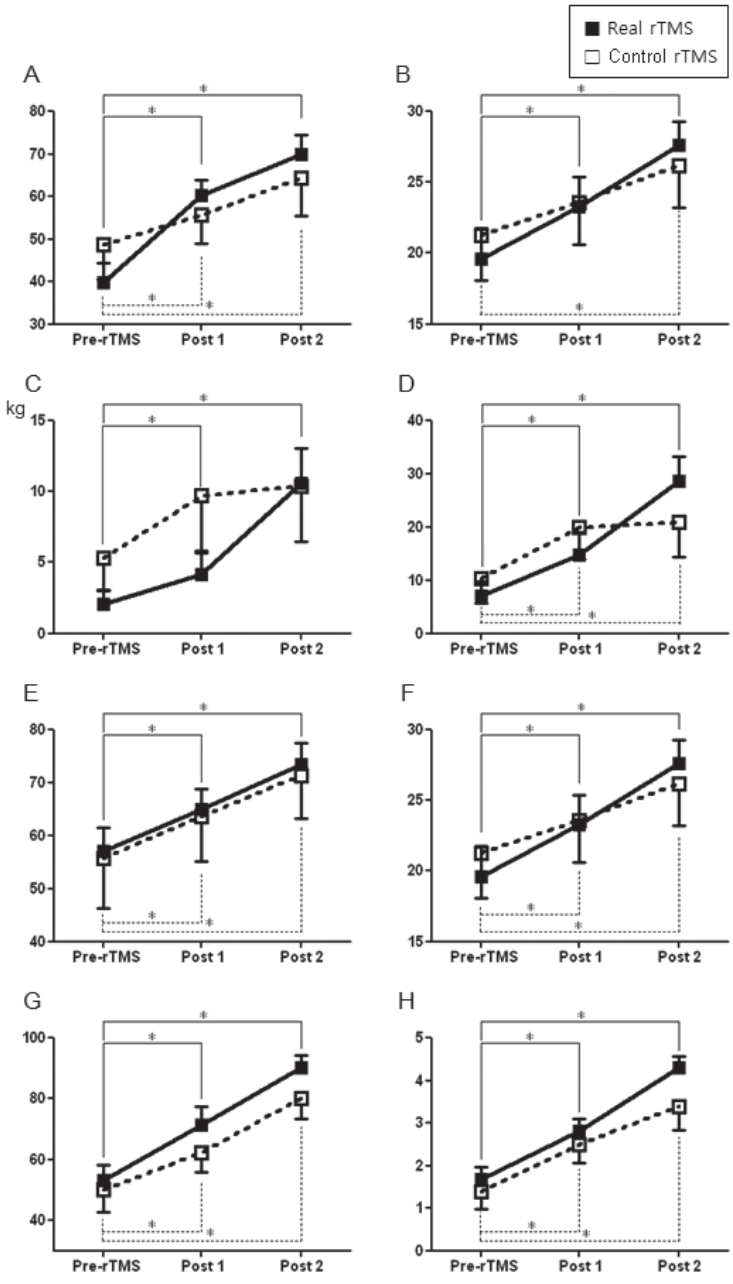

Fig. 2. Change in motor function, mobility, and functional independence in both groups. Measurements were performed prior to treatment (Pre-rTMS), immediately after repetitive transcranial magnetic stimulation (rTMS) (Post 1), and 3 months after stroke onset (Post 2). Error bars represent the standard error for each group at each time. Significance bars and stars at the top relate to the real rTMS group (solid line), and those at the bottom relate to the control rTMS group (broken line). A: arm score of Motricity Index; B: upper limb score of Fugl-Meyer assessment; C: grip strength; D: Box and Block test; E: leg score of Motricity Index; F: lower limb score of Fugl-Meyer assessment; G: Functional Ambulatory Category; H: Modified Barthel index. *$p < 0.05$.

the assessments showed a normal distribution. To test the effects of rTMS across all time-points (Pre-rTMS, Post 1, and Post 2), we used the independent *t*-test and the repeated measure analysis of variance (ANOVA) with time as the within-patient factor and group (real vs control) as the between-patient factor for parametric data with normal distribution. A Bonferroni's correction was used to correct for multiple comparisons (23). We also used the Mann-Whitney test with Bonferroni's correction and the Wilcoxon sign-rank test for non-parametric data and parametric data without a normal distribution (23). *p*-values less than 0.05 were considered statistically significant.

RESULTS

All patients completed their rTMS sessions; no adverse side-effects were reported during the course of the experiment using consecutive multi-session high-frequency rTMS with subthreshold intensity.

Motor function of the affected upper limb and hand

No significant difference in motor function of the affected upper limb and hand was observed between the two groups at Pre-rTMS. Fig. 2 (A–D) describes changes in motor function of the affected upper limb and hand after rTMS. MI-A and BBT showed significant improvement in both groups immediately following rTMS (Post 1); however, significant improvement in FMA-UL and grip strength was observed only in the real rTMS group ($p < 0.05$). Also, the difference in improvement of MI-A was significantly greater in the real rTMS group than in the

control rTMS group at Post 1 ($p < 0.05$). Significant improvement in MI-A, FMA-U, and BBT was observed in both groups at 3 months after onset of stroke (Post 2); however, improvement in grip strength was seen only in the real rTMS group ($p < 0.05$, Figs 2A–D). With regard to improvement in upper limb motor function, repetitive ANOVA showed a significant interaction effect between time (Pre rTMS vs Post 1 vs Post 2) and type of intervention (real vs control), as measured by MI-A ($F2,52 = 4.07$, $p < 0.05$); real rTMS produced greater improvement (Fig. 2A). These findings suggest that motor function of the affected upper limb improved in both groups; however, real rTMS treatment resulted in additional improvements that lasted 3 months after onset of stroke.

Motor function of the affected lower limb

No significant difference in motor function of the affected lower limb was observed between the two groups at Pre-rTMS assessment. Repeated ANOVA, as measured by MI-L ($F2,52 = 30.12$, $p < 0.0001$) and FMA-LL ($F2,52 = 37.12$, $p < 0.0001$) in both groups, showed significant improvement in motor function of the affected lower limb over time. However, no significant interaction was observed between group and time (Figs 2E and 2F). These findings suggest that motor function of the affected lower limb improved significantly in both groups and that real rTMS provided no additional definitive improvement over control rTMS.

Mobility function and functional independence

No significant difference in mobility function and functional independence was observed between the two groups at Pre-rTMS. Both groups demonstrated significant improvement in FAC and MBI over time ($p < 0.0001$); however, there was no interaction effect between group and time (Figs 2G and 2H). These findings suggest that mobility and functional independence improved significantly in both groups over time, and that real rTMS provided no additional definitive improvement over control rTMS.

DISCUSSION

Results from this study demonstrated that consecutive multi-session high-frequency rTMS with subthreshold intensity in the affected hemisphere during the subacute stage of stroke was safe, and might provide an additional beneficial effect on recovery of upper limb motor function in patients with stroke. With regard to upper limb motor function, significant interaction was observed between time and type of intervention, as measured by MI-A. Thus, real rTMS might provide additional improvement in motor function of the affected upper limb immediately following rTMS, and could also facilitate recovery of motor function up to 3 months after stroke.

Reasons for these long-term effects from consecutive multi-session, high-frequency rTMS could be described in the following manner. First, increased excitability of the affected hemisphere would improve motor function in the affected hand through facilitation of corticomotor excitability and metabolism (10, 17, 24). Although stroke itself can cause changes in MEPs during the recovery phase (25), our previous report (10) and other reports (24) have revealed increased motor cortical excitability after a single session or multiple sessions of high-frequency rTMS. Secondly, rTMS training combined with upper limb motor practice in the subacute stage of stroke might promote engagement in better quality upper limb practice from an earlier stage of stroke (10). Thirdly, multi-session cumulative rTMS treatment might provide a long-lasting effect on patients (26). Although changes in cortical excitability were not assessed after each rTMS session in this study, previous research has shown that multi-session rTMS produced a greater effect on cortical excitability (24). Other possible mechanisms of rTMS for achievement of a long-term effect may require further study. In animal experiments, transcranial magnetic field stimulation induced neurogenesis of the subventricular zone in a rat stroke model; however, no data from similar experiments in humans are available (27).

Various therapeutic strategies involving non-invasive cortical stimulation have been proposed in the last decade for enhancement of the effect of training in a neurorehabilitative setting (28). For rTMS, two different approaches have been proposed for the purpose of influencing motor function after stroke. High-frequency rTMS is used for upregulation of excitability within the affected cortices (28), whereas low frequency rTMS is used for downregulation of excitability within the unaffected cortices (8). rTMS also has an inter-hemispheric effect. Gorsler et al. (29) reported on increased left motor cortex excitability with application of high-frequency rTMS to the right motor cortex, and decreased left motor cortex excitability with application of low-frequency rTMS. Due to the risk of seizure, as well as unproven efficacy, some have suggested that high-frequency rTMS directed to the affected cortices should be better understood before implementation (30). However, recent research has already demonstrated the safety of high-frequency rTMS in normal people, adult stroke patients, and even paediatric patients (9, 10, 31). Results from this study may provide additional evidence of the safety and efficacy of high-frequency rTMS in the clinical setting.

Nevertheless, few studies have reported on treatment with consecutive multi-session high-frequency rTMS, primarily due to the safety concerns mentioned above. Therapeutic rTMS at frequencies of 20 and 25 Hz, with intensities above the motor threshold, are thought to increase the risk of seizure (32). Stimulation parameters for rTMS, which are safe for healthy subjects, may lead to a higher risk of seizure in chronic stroke patients (32). For this reason, we excluded seizure-prone patients, including a patient with a family history of seizure disorder. This experiment was designed to deliver short rTMS trains with adequate inter-train intervals. Also, intensity was delivered at a subthreshold level of 90% RMT. In this study, daily rTMS sessions were well-tolerated, and no adverse effects were reported. These findings demonstrate that, with careful design and administration, multi-session high-frequency rTMS with subthreshold intensity is safe. Vernieri et al. (33) reported that high-frequency rTMS applied to the M1 area induces a significant bilateral decrease in cerebral vaso-motor-reactivity

in healthy subjects and stroke patients. They also suggested that rTMS can interfere with brain circuits that control autonomic innervation, mainly by inducing hyper-activation of the sympathetic component. Although none of the participants in our study reported any adverse side-effects, previous observation should be taken into account when applying rTMS protocols in treatment of acute stroke patients. Therefore, careful use of high-frequency rTMS under safety guidelines for well-characterized stroke patients can be considered when establishing various concepts for enhanced improvement of motor function. However, additional study may be required for determination of the most effective rTMS parameters for improvement of motor function in stroke patients (34).

The magnitude and duration of the clinical effects of rTMS depend on the number of rTMS sessions (26). Long-term effects after several sessions of rTMS have been observed after low-frequency rTMS directed at the unaffected hemisphere (5–7). Fregni et al. (5) reported that the effects of low frequency 5-day rTMS on hand motor performance were cumulative, and lasted for at least two weeks. Mally & Dinya (7) reported that the effects of low-frequency rTMS applied for one week for improvement of upper extremity spasticity were cumulative, and lasted for 3 months. Khedr et al. (35) reported significant effects of 3 Hz 10-day rTMS, compared with sham, on disability scales, and recently reported that the effect of cumulative rTMS with suprathreshold intensity on motor function lasted for one year (24). Although some parameters of affected upper limb function did not show definite additional improvement, to the best of our knowledge, this study is the first to report on the effect of subthreshold high-frequency multi-session rTMS applied consecutively in the subacute stage of stroke.

We did not assess electrophysiological measures of intracortical and intercortical network change. In addition, we did not demonstrate excitability changes in the affected hemisphere after treatment sessions. Therefore, we were not able to reveal the different effects of rTMS on individual intracortical and intercortical excitability. The site and extension of stroke lesions, as well as the characteristics of intracortical and intercortical excitability, may affect the therapeutic effect of rTMS (36). This is a limitation of our study that requires further clarification.

We used the mirror image of the motor hot spot for patients who showed no evoked response in the MEP study on the affected side, and also used the RMT of the unaffected side. Because there was no difference in the number of MEP non-responders between the two groups, this might not influence the difference between groups. However, mirroring the stimulation side from the unaffected M1 is a much cruder method (36) because areas other than the affected M1 might have been stimulated. This could be a possible cause for our relatively small improvement in the real rTMS group compared with the control rTMS group. Neuroimaging methods, such as functional Magnetic Resonance Imaging (fMRI), would have provided better results in future.

In spite of the limitations described above, results reported in this study may serve to expand our understanding of the effects of rTMS and contribute to establishment of a new therapeutic concept for neurorehabilitation of stroke patients. Future studies will be needed for exploration of the mechanism of rTMS that is associated with long-term behavioural effects of high-frequency rTMS.

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