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ORIGINAL REPORT

EFFECTS OF REPETITIVE TRASCRANIAL MAGNETIC STIMULATION ON REPETITIVE FACILITATION EXERCISES OF THE HEMIPLEGIC HAND IN CHRONIC STROKE PATIENTS

Seiji Etoh, MD, PhD[1], Tomokazu Noma, OT, BSc[2], Keiko Ikeda, PT[2], Yuiko Jonoshita, OT[2], Atsuko Ogata, MD, PhD[1], Shuji Matsumoto, MD, PhD[1], Megumi Shimodozono, MD, PhD[1] and Kazumi Kawahira, MD, PhD[1]

From the [1]Department of Rehabilitation and Physical Medicine, Graduate School of Medical and Dental Sciences, Kagoshima University and [2]Department of Rehabilitation, Kirishima Rehabilitation Center of Kagoshima University Hospital, Kagoshima, Japan

Objective: **To investigate whether multiple sessions of 1-Hz repetitive transcranial magnetic stimulation (rTMS) facilitates the effect of repetitive facilitation exercises on hemiplegic upper-limb function in chronic stroke patients.**
Design: **Randomized double-blinded crossover study.**
Patients: **Eighteen patients with hemiplegia of the upper limb.**
Methods: **Patients were assigned to 2 groups: a motor-before-sham rTMS group, which performed motor rTMS sessions for 2 weeks followed by sham rTMS sessions for 2 weeks; or a motor-following-sham rTMS group, which performed sham rTMS sessions for 2 weeks followed by motor rTMS sessions for 2 weeks. Patients received 1-Hz rTMS to the unaffected motor cortex for 4 min and performed repetitive facilitation exercises for 40 min during motor rTMS sessions. The Fugl-Meyer Assessment, Action Research Arm Test (ARAT) and Simple Test for Evaluating Hand Function were used to evaluate upper-limb function. The Modified Ashworth Scale and F-wave were measured to evaluate spasticity.**
Results: **Motor function improved significantly during the motor, but not sham, rTMS sessions. ARAT score gains were 1.5 (0–4.0) (median, interquartile range) during the motor rTMS session, and 0 (–0.8–1.8) during the sham rTMS session ($p = 0.04$). Spasticity did not significantly change during either session.**
Conclusion: **Multiple sessions of 1-Hz rTMS facilitated the effects of repetitive facilitation exercises in improving motor function of the affected upper limb, but did not change spasticity.**

Key words: functional recovery; hemiplegia; repetitive facilitation exercises; repetitive transcranial magnetic stimulation; stroke.

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Correspondence address: Seiji Etoh, Kirishima Rehabilitation Center, 3930-7 Takachiho, Makizono-cho, Kirishima-City, Kagoshima 899-6603, Japan. E-mail: ethos@m2.kufm.kagoshima-u.ac.jp

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INTRODUCTION

The contralesional motor cortex affects the ipsilesional motor cortex via abnormal transcallosal inhibition, and impairs motor performance in some stroke patients (1). Downregulation of the contralesional motor cortex by 1-Hz repetitive transcranial magnetic stimulation (rTMS) might decrease the transcallosal inhibition from the contralesional to the ipsilesional motor cortex, and thus facilitate recovery after stroke. A single session of 1-Hz rTMS was reported to improve the motor function and learning of the affected hand in stroke patients (2–6). Multiple sessions of 1-Hz rTMS were shown to improve motor function and performance in chronic-stage stroke patients (7–9). Combining multiple sessions of 1-Hz rTMS with physiotherapy could further improve the motor function of the hemiplegic upper limb. However, to our knowledge, only two studies have previously reported on this effect: one suggested that 1-Hz rTMS for 25 min over 10 days boosted the effect of physiotherapy in chronic-stage stroke patients (10); the other suggested that 1-Hz rTMS to the contralesional motor cortex for 30 min did not augment the effect of physiotherapy in subacute-stage stroke patients (11). The effect of multiple sessions of combined 1Hz rTMS and physiotherapy therefore remains unclear.

Repetitive facilitation exercises (RFEs) are effective physiotherapy for hemiplegic limbs (12, 13). RFEs for upper limbs and fingers provide sufficient physical stimulation (such as stretch or skin–muscle reflexes elicited immediately before movements) to elevate the level of excitation of corresponding, injured, descending motor tracts; this allows patients to initiate their intended movements. RFEs are considered suitable for use in combination with rTMS because the target movements can be repeated many times during a relatively short time-period (500–800 repetitions can be performed within 30 min), and 1-Hz rTMS might induce a temporary state in which motor learning is optimized.

In this study we investigated whether multiple sessions of 1-Hz rTMS to the contralesional motor cortex would facilitate the effect of RFEs on hemiplegic upper-limb function in chronic stroke patients.

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METHODS

Subjects

Eighteen stroke patients were enrolled in this crossover study (mean age 59.7 years (standard deviation; SD 11.0) and mean duration after onset 29.9 months (SD 18.8)) (Table I). Inclusion criteria were: adults (> 18 years of age) experiencing a first or second unilateral stroke, chronic stroke (> 5 months' duration); mild-to-moderate motor upper-limb deficits (Brunnstrom proximal upper-limb stage ≥ Ш); and the ability to comprehend the tasks required for the intervention. Exclusion criteria were: clinically unstable medical disorders; seizures; intracranial metallic implants; severe sensory disturbance, pain and contracture of the upper limb, and severe aphasia that made it impossible to follow the verbal instructions of the therapist. All subjects gave their written informed consent, and the study protocol was approved by the local ethics committee of the Kagoshima University Graduate School of Medicine, Japan.

Experimental design

Patients were randomly assigned to two groups: a motor-before-sham rTMS group ($n = 9$), which performed motor rTMS sessions for two weeks, followed by sham rTMS sessions for two weeks; or a motor-following-sham rTMS group ($n = 9$), which performed sham rTMS sessions for two weeks, followed by motor rTMS sessions for two weeks. During motor rTMS sessions, patients received 1-Hz rTMS to the contralesional motor cortex for 4 min. During sham rTMS sessions, patients received 1-Hz rTMS to a region 5-cm posterior to the contralesional motor cortex for 4 min. RFEs were performed for 40 min after rTMS. Patients underwent motor or sham rTMS sessions once daily for 5 days a week. Each patient also performed voluntary training without the assistance of a physical or occupational therapist for 1–2 h. Neural block and electrical treatments were not administered during the study period. The dose of muscle relaxant was not changed during the study period.

Clinical evaluation

The Fugl-Meyer Assessment (FMA) was used to evaluate motor function (14). This is a commonly used measure, and the motor score for the upper extremity includes 33 items and ranges from 0 to 66. The Action Research Arm Test (ARAT) and the Simple Test For Evaluating Hand Function (STEF) were used to assess the ability to manipulate objects. The ARAT is a commonly used, validated and reliable measure of upper-extremity function with 4 subsections: grip, grasp, pinch and gross movement (15). The maximum summed ARAT score is 57. The STEF was designed to evaluate the speed at which objects (3 types of sphere, 2 types of disk, 1 type of rectangular box and 2 types of cube) are carried to a specified area, sticks are inserted into holes and cloths are turned over (12). The maximum STEF score is 100. The Modified Ashworth Scale (MAS) score was used to evaluate spasticity in the elbow, wrist and finger flexors of the affected upper limb (16). The FMA, ARAT, STEF and MAS scores were assessed immediately before the first session, and immediately after the first and second sessions, respectively. All patients were blinded to the rTMS conditions. The RFEs were carried out by therapists blinded to the group allocation. The FMA, ARAT, STEF and MAS scores were evaluated by therapists blinded to the group allocation.

Repetitive transcranical stimultation parameters

rTMS was applied using a 70-mm figure-of-eight coil and a Magstim Rapid stimulator (Magstim Co., Dyfed, UK). rTMS was applied for 4 min, and comprised 240 pulses over the motor cortex of the unaffected hemisphere at a frequency of 1 Hz and a stimulus intensity of 90% of the resting motor threshold (rMT). When the rMT exceeded 80% of the maximum output, the stimulus intensity was adjusted to 72% of the maximum output in 3 cases in which the patients reported pain at higher levels. The coil was placed tangentially over the motor cortex at the optimal site for the unaffected abductor pollicis brevis (APB) muscle; this was defined as the location where stimulation at a slightly suprathreshold intensity elicited the largest MEPs in the APB. This position was marked on the scalp and used throughout the experiment. Electromyographic (EMG) activity was recorded using silver–silver chloride (Ag-AgCl) electrodes positioned in a belly-tendon montage on the skin overlying the APB. The signal was amplified, filtered (20–5000 Hz) for on-line analysis (Neuropack; Nihon Koden, Tokyo, Japan). The rMT was defined as the lowest stimulator output that could produce MEPs with a peak-to-peak amplitude of > 50 µV in $\geq 50\%$ of the 10 trials. The protocols were in accordance with the safety guidelines for rTMS application to the motor cortex (17).

Table I. *Clinical characteristics of post-stroke patients*

No.	Age, years/sex	Duration (months)	Paretic side	FMA	ARAT	Type	Lesion site
Motor-before-sham rTMS group							
1	48/M	5	L	31	4	Infarction	Corona radiate
2	49/M	12	R	19	3	Haemorrhage	Putamen
3	58/M	30	L	54	45	Infarction	Pons
4	61/F	26	R	36	11	Infarction	Pons
5	61/M	56	L	55	32	Haemorrhage	Thalamus
6	63/M	23	L	54	45	Infarction	Corona radiate, pons
7	69/F	8	R	30	3	Haemorrhage	Putamen
8	71/M	47	R	62	57	Infarction	Putamen
9	83/M	9	R	55	37	Infarction	Putamen
Motor-following-sham rTMS group							
1	34/M	14	R	31	4	Haemorrhage	Putamen
2	50/M	38	L	25	3	Haemorrhage	Thalamus
3	50/M	43	L	31	17	Infarction	Putamen
4	58/M	16	R	49	12	Infarction	Putamen
5	60/M	36	L	56	41	Infarction	Corona radiata, internal capsule
6	60/M	60	R	55	42	Infarction	Pons
7	61/F	10	L	31	5	Infarction	Thalamus, putamen
8	69/M	48	L	30	5	Infarction	MCA
9	69/F	57	L	51	36	Infarction	Corona radiata

M: male; F: female; L: left; R: right; FMA: Fugl-Meyer Assessment; ARAT: Action Research Arm Test; MCA: middle cerebral artery.

F-wave measurement

F-waves were measured before the first session, immediately after the first session and immediately after the second session, to evaluate neurophysiological parameters. The subjects relaxed in a supine position. A Nihon-Koden Neuropack was used with a band-pass filter of 20 Hz to 5 kHz, and with the sensitivity set at 5 mV and 500 µV/division, respectively. Compound muscle action potentials (CMAPs) and F-waves were recorded from the APB of the affected and unaffected upper limbs. Paired Ag–AgCl surface electrodes were taped to the belly and tendon of the APB. The median nerve was stimulated at 1 Hz with a rigid bar electrode at the wrist. Stimuli were 0.2 ms in duration, and ranged from 8 to 15 mA when set 20% higher than the intensity that elicited the largest CMAPs. In total, 96 F-waves were recorded following supramaximal percutaneous electrostimulation for each session. Peak-to-peak measurements were made of the M-response amplitude and the 96 averaged F-wave amplitudes for each limb. The ratio of the F-mean to the M-response amplitude (F/M ratio) was used for evaluation. The F-waves were recorded in 14 out of 18 patients by an experimenter non-blinded to the group allocation.

Data analysis

The FMA, ARAT, STEF, MAS and F/M ratio during the combined first and second two-week sessions of motor rTMS were compared with those for sham rTMS in all patients. Data analyses were performed using the Wilcoxon *t*-test. All significance tests were two-tailed, and *p*-values <0.05 were deemed statistically significant. All values are presented as median (interquartile range (IQR)) for the FMA, ARAT and STEF scores. The MAS scores are presented as the median and range. Analysis was performed using SPSS version 18.0 for Windows.

RESULTS

The subjects did not report any adverse effects during the course of the study. The characteristics of the patients in the two groups are shown in Table I. Table II presents the combined data for the 9 patients in each group. The increases in the ARAT scores significantly differed between the two types of session. The FMA, ARAT and STEF scores of the hemiplegic upper limbs increased significantly during the motor rTMS sessions, but not during the sham rTMS sessions. The FMA, ARAT and STEF scores of the hemiplegic upper limbs increased significantly during the 4 weeks of motor and sham rTMS sessions. The "Pre" scores of the motor rTMS session and sham rTMS session were higher than the corresponding "Pre" scores in the 4 weeks, because "Pre" scores for each of the motor rTMS and sham rTMS session included the "After the first session" scores. The MAS scores of the elbow, wrist and finger flexors did not show significant improvement during either type of session (Table III). The F/M ratio of the affected side did not change, whereas the F/M ratio of the unaffected side during motor rTMS decreased significantly.

Table III. *Pre- and post-treatment Modified Ashworth Scale (MAS) score*

	Pre-treatment Median (range)	Post-treatment Median (range)
MAS (elbow)		
Motor rTMS	1 (0–1.5)	1 (0–2)
Sham rTMS	1 (0–1.5)	1 (0–1.5)
4 weeks	1 (0–1.5)	1 (0–2)
MAS (wrist)		
Motor rTMS	1 (0–2)	1 (0–2)
Sham rTMS	1 (0–1.5)	1 (0–2)
4 weeks	1 (0–1.5)	1 (0–2)
MAS (fingers)		
Motor rTMS	1 (0–2)	0 (0–2)
Sham rTMS	1 (0–1.5)	0 (0–2)
4 weeks	1 (0–1.5)	0 (0–2)*

*$p<0.05$ Comparison between pre- and post-treatment values in each group according to the Wilcoxon *t*-test.
A MAS score of 1+ was treated as 1.5.

DISCUSSION

Multiple sessions of 1-Hz rTMS facilitated the effects of RFEs in improving the motor function of the affected upper limb, but did not change spasticity in chronic stroke patients. Significantly larger improvements were observed in the ARAT score compared with sham rTMS. The FMA, ARAT and STEF

Table II. *Pre- and post-treatment Fugl-Meyer Assessment (FMA), Action Research Arm Test (ARAT) and Simple Test for Evaluating Hand Function (STEF) scores*

	Pre-treatment Median (IQR)	Post-treatment Median (IQR)	Gain Median (IQR)	*p*-values[a]
FMA				
Motor rTMS	46.5 (31.3–54.0)	46.0 (33.3–55.8)*	1.0 (0 to 2.0)	0.98
Sham rTMS	43.0 (31.0–55.0)	46.5 (32.3–56.8)	1.0 (0 to 2.0)	
4 weeks	42.5 (31.0–54.8)	46.0 (33.0–56.8)**		
ARAT				
Motor rTMS	18.5 (4.3–37.8)	22.5 (5.3–40.8)**	1.5 (0 to 4.0)	0.04*
Sham rTMS	14.5 (5.0–41.0)	18.5 (5.0–37.8)	0 (–0.8 to 1.8)	
4 weeks	14.5 (4.3–40.0)	22.5 (5.0–39.5)**		
STEF				
Motor rTMS	5.0 (0–26.0)	12.5 (0–32.8)**	0.5 (0 to 7.8)	0.95
Sham rTMS	2.5 (0–28.3)	8.5 (0–36.0)	0 (0 to 10.8)	
4 weeks	2.5 (0–20.8)	9.0 (0–37.0)**		

*$p<0.05$, **$p<0.01$. Comparison between pre- and post-treatment values in each group according to the Wilcoxon *t*-test.
[a]*p*-values indicate the significance level of between-group differences in increase according to the Wilcoxon *t*-test.
rTMS: repetitive transcranial magnetic stimulation; IQR: interquartile range.

scores improved significantly during the motor rTMS sessions, but the trend did not reach statistical significance during sham rTMS sessions. The MAS score and F/M ratio of the affected side did not change significantly. These results demonstrated that priming by rTMS enhanced the improvement in the affected hand function through a motor-training effect in chronic patients after stroke. Combining 1-Hz rTMS to the unaffected motor cortex with RFEs produced significantly greater improvement than sham rTMS.

The present study extends the findings of previous studies. This study was based on the hypothesis that the application of 1-Hz rTMS to the unaffected motor cortex decreased the transcallosal inhibition (2) and increased the local excitability of the affected motor cortex, which could represent an increase in synaptic efficacy. Previous studies reported that 1-Hz rTMS to the unaffected motor cortex improved the function of affected upper limbs in chronic stroke patients. Single sessions of 1-Hz rTMS for 25 min (1,500 pulses) improved the pinch acceleration (2). Stimulation at 1 Hz (600 pulses) decreased single and choice reaction time (4). Single sessions of 1-Hz rTMS for 25 min (1,500 pulses) enhanced the effect of motor training on pinch force in stroke patients (3). Multiple sessions of 1-Hz rTMS for 25 min (1,500 pulses) for 10 days boosted the effect of physiotherapy in chronic stroke patients (10). In the present study, 1-Hz rTMS for 4 min (240 pulses) facilitated the effect of RFEs, supporting and extending the findings of previous studies.

Although high correlations have previously been documented for the FMA and ARAT (18), there was a difference in gain between sessions for FMA and ARAT in this study. STEF was designed to evaluate the speed of carrying objects, which might be difficult to differentiate among subjects with moderate impairment. The small size of the study group might prevent us from detecting a clear difference in gain between sessions for FMA, STEF and ARAT.

Short duration (4 min, 240 pulses) 1-Hz rTMS facilitated the effect of RFEs on hemiplegic upper-limb function in our study. The effects would have been greater if the period of rTMS was longer. But there were two reasons why we used 4 min 1-Hz rTMS, even though many previous studies have used 25 min. First, previous studies reported the effect of short duration of 1-Hz rTMS. MEPs were significantly reduced after 1-Hz rTMS for 4 min (240 pulses) (19). Significant inhibition continued for 5 min after 150 pulses of 1-Hz rTMS (20). Short duration 1-Hz rTMS could affect the excitability of the motor cortex. Stimulation at 1 Hz, 10 min (600 pulses) decreased single and choice reaction time in stroke patients (4). Thus, it might be possible to induce a temporary state in which motor learning was optimized even after short duration 1-Hz rTMS. Secondly, short-lasting effects of 1-Hz rTMS were considered sufficient for enhancing the effect of RFEs, because the RFEs were able to facilitate and directly repeat isolated movements in the hemiplegic upper limb over a relatively short time-period. If the minimum period of effective rTMS was known, it might be of great benefit to stroke patients. Koganemaru et al. (21) reported that combining motor training with 5-Hz rTMS could facilitate use-dependent plasticity and achieve functional recovery of motor impairments. RFEs can repeat and improve target movements, such as finger extension, thumb abduction and elbow extension. Combining rTMS and RFEs might facilitate use-dependent plasticity. Short-duration of 1-Hz rTMS to the unaffected motor cortex and RFEs could therefore be an effective rehabilitative approach for patients with hemiplegic stroke.

F-waves can be used to study long-pathway nerve conduction and motor neurone excitability. We used MAS scores and F-waves to measure spasticity. Although we expected 1-Hz rTMS to reduce spasticity and F-wave amplitudes, the MAS score and F/M ratio of the affected upper limb did not change during our study. We put forward 3 reasons why the MAS and F/M ratio of the affected upper limb did not change. First, the adequacy of MAS is not conclusive, although the MAS is often used to assess spasticity (22). Secondly, the range of MAS scores before the first session were 0–2, thus we only measured mild-to-moderate spasticity. MAS scores might change after rTMS sessions in patients with severe spasticity. Thirdly, the rTMS conditions are different from other reports. Valle et al. (23) showed that there was a significant reduction in spasticity after multiple sessions of 5-Hz rTMS, but not 1-Hz. Mally & Dinya (24) showed that multiple sessions of 1-Hz rTMS using a circular coil significantly reduced the spasticity of affected limbs in chronic stroke patients. Kondo et al. (25) reported that a single session of 1-Hz rTMS significantly decreased the F/M ratio in affected upper limbs. Reducing spasticity after rTMS in stroke patients might thus depend on the stimulated area or the duration and frequency of rTMS.

Some limitations of the current study should be noted. First, we did not measure neurophysiological data except for upper-limb F-waves. We were unable to investigate whether 1-Hz rTMS decreased excitability in the intact hemisphere and increased excitability in the affected hemisphere. Secondly, our sham rTMS may affect the sensory cortex, because the position 5 cm posterior of the motor cortex is close to the sensory cortex. Thus, the motor cortex may be influenced indirectly through the sensory cortex. Thirdly, the small size of the study group prevented us from examining the effects of differences in the severity of hemiplegia using subgroup analysis. Further research is needed to confirm the effectiveness of combining 1-Hz rTMS and RFEs.

In conclusion, this study shows that multiple sessions of 1-Hz rTMS of the unaffected motor cortex facilitates the effects of RFEs on hemiplegic upper-limb function in chronic stroke patients.

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