電場勾配が一定値以上となる部位であるとの報告がある[8]。また渦電流ベクトルに対する軸索の向きが活動電位の発生に関係すると考えられている[9,10]。さらに渦電流は媒質の導電率，幾何学的構造の影響を受け，不均一な脳内における電流分布を正確に予測することは非常に困難であるため[11]，末梢神経で得られた閾値をそのまま中枢神経に適用することはできない。以上のことから本研究で設計したマルチコイルが脳深部の神経興奮を生じるかどうかは議論の余地がある。

本研究の尺骨神経運動閾値には，コイル中心部の磁束密度の値を用いた。しかし前述のように，磁束密度が最大となる位置で神経興奮が生じるとは限らない。コイル中心部から測定点までの距離と磁場強度との関係から，尺骨神経の興奮は肘頭付近で生じた可能性が高い。それでも興奮部位が肘頭から僅かでも離れている場合，実際の尺骨神経運動閾値はコイル中心部での値よりも小さくなる。

一般に用いられている経頭蓋磁気刺激装置は，1～4 Tのパルス磁場を発生し[12]，コイルを被覆する樹脂面から20～30 mm離れた脳表面の神経を興奮させる。磁場強度は電流源からの距離に反比例して減衰するので，コイルの被覆樹脂厚を10 mmとすれば，刺激される大脳皮質での磁場強度はコイル樹脂面の1/3から1/4となる（減衰の仕方は電流源の形状やどの方向に距離を測るかによって異なり，たとえばコイルの中心軸上でみると，半径aのループ電流が流れる場合，コイル面から距離z離れた点における磁束密度は$(a^2+z^2)^{(-3/2)}$に比例する）。また経験的に運動野の閾値が一般的な刺激装置の最大出力の約半分から8割程度までの範囲にあることを考えると，本研究で得られた尺骨神経の運動閾値（0.1～0.2 T）は，運動野の閾値と近い値であると言える。今後本研究で設計したマルチコイルをサルに用い，刺激効果を検証する予定である。

謝　辞

本研究は，独立行政法人医薬基盤研究所の「保健医療分野における基礎研究推進事業」によるものである。

利益相反

本研究は営利的な企業・団体からの財政的支援を受けていない。

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Fabrication of multi-coil system for deep brain transcranial magnetic stimulation

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We have been developing a multi-channel coil and eight-channel pulse power supply for deep brain stimulation by transcranial magnetic stimulation (TMS), which causes negligible cortex stimulation. At the first step of the optimum coil design, we measured a distribution of synthesized high frequency magnetic field produced by several types of multi-channel coil and found an appropriate coil set that consists of an excitation lower coil, a focusing coil (short ring) and a compensation upper coil. To drive the coil set, we made an eight-channel pulse electric power supply, which generates either monophasic or biphasic pulse of 1 T at a stimulus with maximum 2000 volt. We next measured a threshold magnetic flux density for activating the ulnar nerve at the elbow then found that the threshold value ranged between 0.15 and 0.2 T with the pulse width of 0.1–0.4 ms. Based upon these results, we assembled a multi-channel coil for an animal experiment using a monkey. Magnetic flux densities of this coil assemble at a stimulus with 800 volt are 0.23 T at the central region that corresponds to the deep brain, 0.02 T at the upper portion that corresponds to the parietal cortex, and 0.19 T at the side portion that corresponds to the temporal cortex.

Key Words : transcranial magnetic stimulation, deep brain stimulation, multi-coil, threshold magnetic flux density

J Rehabil Med 2008; 40: 49–54

ORIGINAL REPORT

TRANSCRANIAL MAGNETIC STIMULATION SYNCHRONIZED WITH MAXIMAL MOVEMENT EFFORT OF THE HEMIPLEGIC HAND AFTER STROKE: A DOUBLE-BLINDED CONTROLLED PILOT STUDY

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Objective: **The aim of this study was to evaluate the effects of transcranial magnetic stimulation synchronized with maximal effort to make a target movement in patients with chronic hemiplegia involving the hand.**
Design: **Non-randomized double-blinded controlled trial.**
Subjects: **Nine chronic patients with hemiplegia who were unable to fully extend the affected fingers following stroke.**
Methods: **Patients were assigned to receive 100 pulses of active or sham transcranial magnetic stimulation of the affected hemisphere per session. Each active or sham pulse was delivered during maximal effort at thumb and finger extension as a target movement. A blinded rater assessed stroke impairments at baseline, immediately after, and one week after 4 weekly transcranial magnetic stimulation sessions. Motor evoked potential amplitudes were measured at each session.**
Results: **All sessions were completed without adverse effects. Immediately after the fourth transcranial magnetic stimulation session, 4 of 5 patients in the active transcranial magnetic stimulation group (80%) had either reduced wrist flexor spasticity or improved manual performance; no such change occurred in the sham group (Fisher's exact test, $p < 0.05$). Effects persisted one week later. In the active transcranial magnetic stimulation group, 3 patients who showed an increase in motor evoked potential amplitudes all had improvement in clinical assessments.**
Conclusion: **Transcranial magnetic stimulation synchronized with maximum effort to make a target movement improved hand motor function in patients with chronic hemiplegia.**

Key words: stroke, hemiplegia, transcranial magnetic stimulation, spasticity, therapy.

J Rehabil Med 2008; 40: 49–54

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Submitted April 2, 2007; accepted August 29, 2007.

INTRODUCTION

Maximal recovery of the upper extremity is usually attained within 6–7 months after stroke onset, although a smaller proportion of patients show some recovery from 7 months to one year (1). Therapeutic interventions for hemiplegic hands include neuromuscular facilitation (2), electromyographic (EMG) biofeedback (3), functional electrical stimulation (4) and constraint-induced movement (5). Motor recovery in patients treated with a facilitation technique did not differ significantly from recovery in patients treated with conventional therapeutic exercises (2). Treatment using EMG biofeedback or constraint-induced movement is effective in patients with chronic hemiplegia, but some preservation of voluntary movements is required (3, 5). Although electrical stimulation of wrist extensors and ankle dorsiflexors has been reported to improve movement in these muscle groups (4), the movements induced are limited to the distribution of the stimulated nerve; this is insufficient for performance of fine movements such as finger extension at all joints, or prehension. Thus, new techniques are required to enhance recovery of motor output mediating hand movements that are impaired in patients with chronic hemiplegia.

Non-invasive brain stimulation techniques, such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), have emerged as promising tools for enhancing recovery of hemiplegia (6). Up-regulation of excitability of the affected hemisphere by high-frequency rTMS or anodal tDCS over the affected motor area, or down-regulation of the unaffected motor area by low frequency rTMS or cathodal tDCS, have been reported to improve motor function in a hemiplegic hand (6). In these studies subjects were at rest during stimulation.

Use-dependent plastic changes of the motor cortex are known to occur in healthy humans (7) and in animals with damaged motor cortex (8, 9). Changes in excitability of the motor cortex depend on the direction and frequency of the movement. In addition, TMS has been reported to enhance such use-dependent plastic change when synchronized with a target movement (10).

In a previous report (11) we described results of 12 weekly sessions using the same TMS protocol examined in the present study in a 47-year-old patient who had right hemiplegia for 3 years and 4 months from a left putaminal haemorrhage. In that patient, beginning at week 3, motor evoked potentials (MEP) and voluntary electromyographic discharges of the extensor digitorum muscle appeared; Brunnstrom's recovery stage for

 doi: 10.2340/16501977-0133 ISSN 1650-1977

finger function improved from III (mass flexion) to IV (lateral prehension by thumb movement and voluntary extension of the thumb, ring, and little fingers). Thus encouraged, we implemented a double-blind study in patients with chronic stroke to investigate the effects on motor performance in the hemiplegic hand of TMS applied to the affected motor cortex during maximal movement effort. Finger extension was chosen as a target movement for patients who could not extend their fingers adequately. These patients were unlikely to be candidates for other training programs such as constraint-induced movement therapy.

MATERIALS AND METHODS

Subjects

Nine patients (7 men, 2 women; mean age 66.3 years) were recruited with informed consent after ethics committee approval, from April to December 2005. Inclusion criteria were: (*i*) adult hemiplegic patients; (*ii*) over 6 months after onset of a first-ever stroke; (*iii*) supratentorial lesion; (*iv*) inability to fully extend the affected fingers; and (*v*) ability to comprehend the task required for clinical evaluation and the intervention in this study. We excluded patients with any clinically significant or unstable medical disorder, or contraindications to TMS. All pre-existing interventions including medications, physical therapy, and occupational therapy were maintained during the study.

Experimental design

This was a longitudinal, non-randomized, parallel-design, sham-controlled, double-blinded trial. Patients were enrolled consecutively. The first 5 patients were enrolled to the active TMS group, and the following 4 patients to the sham TMS group. A rater who did not know the group to which each patient was assigned assessed the outcome. Patients did not know whether the stimulation delivered to them was active or sham.

Motor cortex mapping and motor threshold assessment

Patients were seated in a comfortable chair with the test arm supported and relaxed on the armrest in pronation. EMG data were collected from the affected extensor digitorum muscle via surface electrodes.

Recording electrodes (10-mm discs, NE102A; Nihon Kohden, Tokyo, Japan) were placed over the proximal third of the pronated forearm, midway between the radial and ulnar aspect. Reference electrodes were located 3 cm distal to the recording electrodes. Signals were sampled for 200 ms, amplified, and recorded by an EMG machine (Neuropack μ, Nihon Kohden, Tokyo, Japan) with a bandpass filter accepting frequencies between 10 and 5000 Hz. Recording of muscle activity was triggered 30 ms before stimulation.

Stimulation was delivered using a Magstim Rapid Stimulator (MRS1000/50; Magstim, Carmarthenshire, UK) equipped with a 70-mm figure-of-eight coil. Electric current travelled biphasically. Peak dB/dt was 33 kTesla/s. Active pulse duration was 250 μs. The coil was held tangentially to the scalp. The handle of the coil was oriented posteriorly, and the coil was moved over the scalp in 1-cm increments.

The motor "hot spot" of the extensor digitorum extensor digitorum muscles was determined according to the recommendations of the International Federation of Clinical Neurophysiology (12).

The resting motor threshold (MT) of the ED muscles in the affected hemisphere was measured to the nearest 5% of maximal output as the stimulus required to produce responses of at least 50 μV in at least 4 of 8 stimuli at the motor "hot spot" for the tested muscle. We did not deliver stimulation at intensities greater than 80%. When stimulation at 80% output did not reach the resting MT, the resting MT was recorded as greater than 80%.

Intervention with transcranial magnetic stimulation

Stimulation intensities were determined individually to produce a MEP of about 1 mV amplitude in response to stimulation at the motor "hot spot" during the first session, and then were kept constant throughout the trials. If this intensity exceeded 80% of the maximum stimulator output, the intensity was set at 80% to avoid heating of the coil.

If MEP were absent to stimulation of the involved hemisphere at an intensity of 80%, the motor "hot spot" was defined by symmetry with respect to the intact hemisphere, and the stimulus intensity was set at 80%.

TMS intervention was designed to restore voluntary extension and abduction of the patient's affected thumb and fingers (i.e. opening the hand). The patients were seated as for mapping and threshold determinations. They were instructed to extend the thumb and fingers at all joints and abduct the thumb, index, middle, ring, and little fingers horizontally, without contraction of the unaffected upper limb in order to prevent associated movements. For the active TMS group, 3–4 sec after instruction was given, TMS was delivered with an intensity predetermined for each patient; then the patient was instructed to relax. Patients each received 100 stimuli per session. Intervals between stimuli were 10 sec. Patients wore earplugs during TMS.

For the sham TMS group, sham stimulation was given with the coil angled at 45°, during maximum effort of hand opening. Only the edge of the coil was rested on the scalp. Stimulation frequency and intensity were set as for active TMS.

Averaged MEP were obtained for individual sets of trials. Peak-to-peak amplitudes of averaged MEP were measured.

For individual patients these procedures were carried out at essentially consistent times of the day, at weekly intervals. Four weekly repetitions of the protocol were carried out. Thus, each patient received a total of 400 active or sham stimuli.

Clinical evaluations

Main outcome measures were hand motor function evaluated by Brunnstrom's protocol (13), as well as the Stroke Impairment Assessment Set (SIAS) (14), Modified Ashworth Scale (MAS) (15) and Manual Function Test (MFT) (16). The SIAS assesses various aspects of impairment in patients with hemiplegia, including motor function, muscle tone, sensory function, range of motion, pain, trunk function, visuospatial function, speech, and intact-side function in terms of well-established psychometric properties (14). Each of the 22 items is rated from 0 (severely impaired) to 3 (normal) for muscle tone, sensory, range of motion, pain, trunk, higher cortical function, and unaffected side function; or for motor function, to 5 (normal). For the hand, 1A indicates incomplete mass flexion of the digits; 1B, incomplete mass extension of the digits; and 1C, incomplete individual finger movement. The MAS scale assessment for the wrist flexors closely followed the rater's manual to improve reliability (17). The MFT, an instrument for assessing motor function of the affected upper extremity in stroke patients according to well-established psychometric properties, is composed of 8 subtests; forward elevation of the arm, lateral elevation of the arm, touching the occiput with the palm, touching the back with the palm, grasping, pinching, carrying cubes, and peg-board manipulations. Ratings could range from 0 (severely impaired) to 32 points (full function) (16). Both affected and unaffected sides were assessed.

Secondary outcome measures were SIAS items other than hand function, and the Barthel Index (18). Handedness was assessed using the Edinburgh laterality quotient (LQ) (19).

Brunnstrom stage, SIAS, MAS, and MFT were assessed just before the first session, immediately after the fourth session, and one week after the fourth session. Barthel Index and Edinburgh LQ were assessed just before the first session.

Electroencephalography

We monitored brain activity with an online electroencephalographic (EEG) system to detect subclinical seizure activity. The recording electrode was positioned at the anterior edge of the coil, i.e. 3 cm

anterior to the "hot spot". The reference electrode was placed at the earlobe on the stimulated side.

Statistical analysis

For analysis we used StatView software (version 5.0; SAS Institute, Cary, USA). The Mann-Whitney *U* test was used to compare the active TMS and sham TMS groups concerning Brunnstrom stage, SIAS, MAS, MFT, Edinburgh LQ, and Barthel Index. Differences in distribution were evaluated using Fisher's exact test for demographic data, resting MT. Fisher's exact test also was used for comparison between active and sham groups of categorical variables immediately after session 4: MAS or MFT improved vs MAS and MFT unimproved; and SIAS or Brunnstrom stage improved vs SIAS and Brunnstrom stage both unimproved. Improvement was defined as an individual score changing at least one stage toward better function or reduction of spasticity. For comparison one week after session 4, *p*-values were calculated for individual parameters using the Mann-Whitney *U* test.

RESULTS

All subjects completed the study without showing adverse effects. No epileptiform after discharges or sharp wave potentials were observed by EEG monitoring.

No statistically significant difference was evident between active and sham TMS groups concerning demographic data or clinical assessments at baseline (Tables I and II). Cortical lesions were found in one patient (number 4) of the active TMS group and one patient (number 6) of the sham TMS group. More patients had resting MT over 80% of output in the active TMS group (4 of 5) than in the sham group (no patients; $p < 0.05$).

Improvements from baseline in clinical evaluations and in amplitudes of the averaged MEP immediately after and one week after completing the course of active or sham TMS are shown in Table III. Immediately after the fourth session, 4 of 5 patients in the active TMS group had either reduction of wrist flexor spasticity (MAS) or improvement in MFT on the affected side; this did not occur in the sham TMS group ($p < 0.05$). One week after the fourth session, improvement observed in those 4 patients in the active TMS group was found to be maintained. The difference between real and sham groups was not statistically significant because one patient in the sham group showed improvement in MFT, but a tendency

Table I. *Demographic characteristics, stroke type and stroke location*

Patient number	Gender/age (years)	Type	Location	POD
Active TMS group				
1	M/49	Infarct	Left internal capsule	783
2	M/64	Haemorrhage	Left putamen	561
3	F/77	Infarct	Right corona radiata	268
4	M/62	Infarct	Right MCA (cardioembolic)	2592
5	M/70	Infarct	Right basal ganglia and frontal lobe	941
Median	64			783
Sham TMS group				
6	M/70	Infarct	White matter and deep gray matter	3671
7	M/56	Infarct	Right corona radiata	2234
8	M/74	Haemorrhage	Right thalamus and corona radiata	1816
9	F/75	Infarct	Right basal ganglia	1963
Median	72			2099
*p**	> 0.99/0.54	> 0.99		0.086

*The Mann-Whitney *U* test was used for comparison of non-parametric variables, and Fisher's exact test for comparison of categorical variables.
TMS: transcranial magnetic stimulation; F: female; M: male; POD: days post-stroke; MCA: middle cerebral artery.

Table II. *Clinical evaluation at baseline*

	Active TMS group					Sham TMS group				
	1	2	3	4	5	6	7	8	9	*p**
Paretic side	Right	Right	Left	Left	Left	Left	Left	Left	Left	0.44
LQ	100	70	100	100	100	100	100	80	80	0.56
Brunnstrom stage (hand)	IV	III	IV	III	III	IV	III	IV	III	0.78
SIAS										
UE motor, distal	1C	1B	1C	1A	1A	1A	1A	1C	1A	0.41
UE motor, proximal	3	3	3	2	1	2	2	2	1	0.19
Touch (palm)	3	1	3	2	1	3	3	2	3	0.22
Position (digit)	3	3	3	2	2	3	2	3	3	0.65
ROM	2	2	2	2	1	2	3	2	2	0.18
Pain	3	2	3	2	3	3	3	3	3	0.18
Visuospatial	2	3	1	2	3	3	3	2	2	0.59
MFT, affected side	17	10	10	9	6	9	12	14	7	0.90
MFT, unaffected side	32	31	30	31	29	31	30	28	30	0.31
MAS (wrist flexor)	2	1+	1+	3	1+	3	1+	1	1	0.30
Barthel index	100	95	65	90	85	100	100	85	80	0.70
MEP threshold (%)	>80	>80	>80	80	>80	80	80	70	50	0.048

*The Mann-Whitney *U* test was used for comparison of non-parametric variables, and Fisher's exact test for comparison of categorical variables. MEP threshold was compared as a categorical variable, either above 80% or 80% or lower.
TMS: transcranial magnetic stimulation; LQ: laterality quotient evaluated by Edinburgh Inventory; MAS: modified Ashworth scale; MEP: motor evoked potentials; MFT: manual function test; SIAS: stroke impairment assessment set; UE: upper extremity; ROM: range of motion for the shoulder abduction.

Table III. *Improvement after transcranial magnetic stimulation*

	Active TMS group					Sham TMS group				
	1	2	3	4	5	6	7	8	9	p*
Just after fourth session										
MAS	1	0	1	0	0	0	0	0	0	
MFT	0	1	1	0	2	0	0	0	0	
MAS, MFT										0.048
SIAS	0	0	0	0	1	1	0	0	0	
Brunnstrom stage	0	0	0	0	0	0	0	0	0	
SIAS or Brunnstrom stage									> 0.99	
One week after fourth session										
MAS	2	0	1	0	0	0	0	0	0	0.18
MFT	2	1	3	0	1	1	0	0	0	0.090
SIAS	0	1	0	0	0	0	0	0	0	0.37
Brunnstrom stage	0	0	0	0	0	0	0	0	0	> 0.99
MEP amplitude ratios	9.8	1.1	4.4	0.17	7.5	n.a.	n.a.	n.a.	n.a.	

Individual numbers indicate improvements in grade compared with baseline data. MEP amplitude ratio was calculated by dividing the amplitude of the averaged MEP recorded at session 4 by that recorded at session one. In patient 2 the amplitude of the averaged MEP recorded at session 3 was divided by that from the first session, because no MEP could be recorded at session 4 due to a technical problem.

*Fisher's exact test was used for comparison between active and sham groups of categorical variables immediately after session 4: MAS or MFT improved vs MAS and MFT unimproved; SIAS or Brunnstrom stage improved vs SIAS and Brunnstrom stage both unimproved. For comparison one week after session 4, p-values were calculated for individual parameters using the Mann-Whitney U test.

TMS: transcranial magnetic stimulation; MAS: modified Ashworth scale; MEP: motor evoked potentials; MFT: manual function test; n.a.: not applicable, SIAS: stroke impairment assessment set.

toward better MFT scores in the active TMS group than the sham group was observed ($p < 0.1$). No statistically significant difference was evident between the 2 groups in improvement of voluntary hand movement as evaluated by either SIAS or Brunnstrom protocol, either immediately after or one week after the fourth session.

In the active TMS group, 3 patients who showed an increase in MEP amplitudes all had either reduction of wrist flexor spasticity (MAS) or improvement in MFT on the affected side. Another patient improved in MFT without an increase in MEP amplitude. The other patient (number 4), who showed neither improvement in the clinical assessment nor an increase in MEP amplitudes, had an embolic infarct of the middle cerebral artery territory and presented severe spasticity.

DISCUSSION

This small double-blind trial in patients with chronic hemiplegia demonstrated that TMS synchronized with maximal effort at hand opening either reduced spasticity of the forearm flexors or improved manual performance without definite enhancement of voluntary hand movement. Three of 5 patients in the active TMS group and 2 of 4 patients in the sham TMS group could not extend their affected fingers at the beginning of the trial, and accordingly were not candidates for constraint-induced movement therapy (5). Because TMS was combined with maximal effort at the target movement, we refer to the technique used here as effort-associated TMS.

In our previous single-case experience (11), the patient recovered lateral prehension by thumb movement and voluntary extension of the thumb, ring, and little fingers as well as isolated movements of the thumb and the little finger. In the present study, active and sham TMS groups did not differ in change of voluntary hand function as evaluated by Brunnstrom's protocol or SIAS, possibly reflecting fewer TMS sessions, older participants, or presence of an infarct rather than haemorrhage in most patients.

In previous reports concerning effects of rTMS or tDCS on motor function of the affected hand in chronic hemiplegic patients, these interventions improved reaction time, movement speed, or manual performance rather than voluntary hand function evaluated with clinical scales (20–24). These results were comparable with those of the present study, where effort-associated TMS enhanced manual performance (MFT) or reduced spasticity that impeded rapid, fine movements. Improvement in MFT might be explained partly by spasticity reduction undetected by the MAS.

One possible mechanism for improvement in MFT or amelioration of spasticity is use-dependent plastic change of the motor cortex (8, 9) and spinal cord (25). This explanation assumes that disuse of the hemiplegic hand had decreased motor pathway excitability, an effect that could have been reversed by excitation of the motor cortex and spinal cord induced by effort-associated TMS.

Motor imagery is known to produce facilitation of MEP in healthy subjects (26, 27) and patients after stroke (28). A cortical mechanism for such facilitation has been demonstrated in healthy subjects (27). On the other hand, training for poorly functioning patients in the chronic phase has been reported to lead to improvements, with findings suggesting reorganization of areas related to movements of the paretic limb (29). Thus, one could assume that in the present study an intact but non-functioning corticofugal pathway for finger extension might have been activated during the effort to make the target movement, even when actual finger extension could not be achieved, with further activation by TMS synchronized with the effort. Enhancement

of reciprocal inhibition could be a possible explanation for reduction of spasticity of the forearm flexors. Improvement of MFT scores observed in the sham TMS group one week after the fourth session also might have been related to the effort.

Increased excitability of spinal motor neurones for the agonist muscles also could be involved. Functional motor unit number on the hemiplegic side has been reported to decrease in stroke patients (30), although motor units have been reported to remain morphometrically unchanged in number (31).

Because stimuli at 80% of maximal stimulator output were delivered through the stimulator coil overlying the sensorimotor cortex of our patients, excitation of the sensory cortex by TMS may have contributed importantly to the effects of intervention. Afferent inputs from peripheral receptors to the motor cortex (32) following responses to TMS may also have taken part.

Improvement in MFT and MAS in the active TMS group was maintained one week after the last TMS session. In chronic stroke patients such after-effects of a single rTMS session have rarely been reported. In previous reports 600–1500 pulses of 1-Hz rTMS over the unaffected hemisphere (22, 23) or 160 pulses of 10-Hz rTMS over the affected hemisphere (24) improved function in the affected hand immediately after stimulation. Considering homeostatic control of neural activity (33), consolidation of changes in motor cortex excitability induced by rTMS would be necessary to achieve clinically significant improvement of the affected hand in chronic stroke patients. One previous report demonstrated that improvement of hand motor function induced by a 5-day course of low-frequency rTMS over the unaffected hemisphere in chronic stroke patients lasted for 2 weeks (21). In the effort-associated TMS used in our study, effort-associated activation of specific neural networks was repeated 4 times weekly, which might have been important in producing the long-term effects of the intervention, in a manner similar to use-dependent plastic change.

In the present study, MEP enhancement was also related to improvement according to a clinical scale, except in one patient in the active TMS group (patient 2), in whom no MEP could be recorded at the fourth session due to a technical problem. In previous reports any relationship between rTMS-induced change in hand function and MEP amplitude in the affected limb was equivocal (24, 34). MEP is generated mainly by activation of the corticospinal motoneuronal pathway through the rapidly conducting pyramidal tract, which does not control all types of voluntary movements. Thus, unknown pathways apart from the pyramidal tract might contribute to behavioural improvement.

Finally, in the present study, the post-stroke interval was longer in the sham TMS group (though not significantly) and MEP thresholds were higher in the active TMS group. Such discrepancies might have influenced the effects of intervention. In addition, effects of ongoing physical and occupational therapy, measurement error, or normal performance variation should be considered, given that the behavioural differences between baseline and post-treatment time points were small. Further studies, such as large randomized controlled trials with more TMS sessions and longer follow-up periods, would clarify the effectiveness and limitations of effort-associated TMS. In addition, the applicability of this intervention for patients at an earlier time-point after stroke onset should be examined as a potential way to accelerate motor recovery.

ACKNOWLEDGEMENTS

Some findings from this study were presented in June 2006 during the 43rd Annual Congress of the Japanese Association of Rehabilitation Medicine (Tokyo, Japan) and in June 2007 during the 4th World Congress of the International Society of Physical and Rehabilitation Medicine (Seoul, Korea).

We express sincere gratitude to Masayo Iibuchi, RN for co-ordination of this research. We thank Kazunori Nishijima, MD; Yoshihito Furusawa MD, PhD; Takayuki Mori, MD; Ken Sugiyama, MD; Akira Michimata, MS, OTR; Takako Itsukaichi, MS, RPT; Shinobu Okamura, MS, RPT; Kyoko Shioda, MS, RPT; Sayaka Miyamoto, MS, OTR; and Yuko Kikuchi, MS, RPT for assisting in TMS sessions.

This research was supported by a Grant-in-Aid for Scientific Research (B) from the Ministry of Education, Science, Sports and Culture of Japan (no. 15300191).

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