Efficacy of Coupling Inhibitory and Facilitatory Repetitive Transcranial Magnetic Stimulation to Enhance Motor Recovery in Hemiplegic Stroke Patients

Wen-Hsu Sung, PhD; Chih-Pin Wang, MD; Chen-Liang Chou, MD; Yi-Cheng Chen, MD; Yue-Cune Chang, PhD; Po-Yi Tsai, MD

Background and Purpose—Although there has been extensive research on the effectiveness of repetitive transcranial magnetic stimulation (rTMS) to improve patients’ motor performance after experiencing chronic stroke, explicit findings on the coupling of different rTMS protocols are meager. We designed this sham-controlled randomized study to investigate the potential for a consecutive suppressive-facilitatory TMS protocol to improve motor outcomes after chronic stroke.

Methods—Fifty-four chronic hemiplegic stroke patients were allocated across 4 groups to undergo 20 daily sessions of (1) 1 Hz rTMS over the contralesional primary motor cortex (M1) and then intermittent theta burst stimulation over the ipsilesional M1 (group A); (2) contralesional sham stimulation and then ipsilesional real intermittent theta burst stimulation (group B); (3) contralesional real 1 Hz rTMS and then ipsilesional sham stimulation (group C); or (4) bilateral sham-control procedures (group D). We tested cortical excitability and motor activity assessments at the baseline, postpriming rTMS, and postconsequent rTMS periods.

Results—At post, group A showed greater muscle strength, Fugl-Meyer Assessment (FMA), Wolf Motor Function test, and reaction time improvement in comparison with group B (P<0.001=0.003) and group C (P=0.001=0.003). Correlation analyses in group A revealed a close relation between contralesional map area decrement and Wolf Motor Function test gain (P=0.005; r=−0.75), and also revealed ipsilesional map area increment and reaction time decrement (P=0.02; r=−0.87). We detected no such relations in the other 3 groups.

Conclusions—Our clinical trials established an extended timeframe during which conditioning could be safely continued and produced more favorable outcomes in facilitating motor performance and ameliorating interhemispheric imbalance than those obtained from single-course rTMS modulation alone. (Stroke. 2013;44:1375-1382.)

Key Words: facilitatory repetitive magnetic stimulation ■ inhibitory repetitive transcranial magnetic stimulation ■ motor function ■ stroke ■ treatment

Stroke is the leading cause of adult long-term disability worldwide, particularly for the domain of the motor system. Only <40% of stroke survivors have achieved complete motor recovery, even after extensive rehabilitation treatment. Recent evidence suggests that motor recovery after stroke comprises a hierarchical, dynamic framework of interacting mechanisms. Usually after the loss of interhemispheric inhibition from the ipsilesional motor cortex to the contralesional hemisphere when a stroke occurs, there is a tendency for overactivity to begin in the contralesional hemisphere soon after the stroke. In the chronic stage, the resulting transcallosal imbalance might hinder cortical reorganization within the ipsilesional hemisphere. This is considered to be a predictor for poor recovery from brain insult. Although its efficacy is still under consideration, repetitive transcranial magnetic stimulation (rTMS) has shown promise for modulating cortical excitability and harnessing neuroplasticity in stroke patients to promote their motor recovery. Inhibitory rTMS administered in the contralesional motor cortex at a frequency of <1 Hz is a strategy that has shown potential to disrupt this possible maladaptive transcallosal pathway. Under the mechanism of long-term depression (LTD), 1-Hz rTMS has been found, primarily, to reduce contralesional cortical excitability and, secondarily, to increase ipsilesional activity. Stroke patients also have experienced motor recovery after treatment with facilitatory high-frequency stimulation, including 3 Hz, 10 Hz, 20 Hz, and intermittent theta burst stimulation (iTBS), with the upregulation of cortical excitability in the affected hemisphere. iTBS-induced aftereffect consequently has been

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From the Department of Physical Therapy and Assistive Technology, National Yang-Ming University, Taipei, Taiwan (W.-H.S.); Department of Radiology, Taipei Veterans General Hospital, Taipei, Taiwan (C.-P.W.); Department of Mathematics, Tamkang University; Taipei, Taiwan (Y.-C. Chang); and Department of Physical Medicine and Rehabilitation, Taipei Veterans General Hospital, National Yang-Ming University, School of Medicine, Taipei, Taiwan (C.-L.C., Y.-C. Chen, P.-Y.T.).

Correspondence to Po-Yi Tsai, MD, Department of Physical Medicine and Rehabilitation, Taipei Veterans General Hospital, No. 201, Shih-Pai Rd, Sec 2, Taipei, 11217 Taiwan. E-mail pytsai@vghtpe.gov.tw

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proposed as a long-term potentiation (LTP)-like mechanism that may contribute to the improvement of synaptic plasticity.\textsuperscript{11}

Although conventional brain stimulation, using such strategies as exemplified, has been presented as the appropriate treatment for facilitating motor recovery, results to date nevertheless have shown only modestly beneficial effects of 10\% to 30\% improvement over sham treatment in hemiplegic stroke patients.\textsuperscript{12–14} Studies involving repetitive unilateral application of identical rTMS protocol for several days have reported no cumulative effect on the behavior gain.\textsuperscript{2,15} Previous research on combined or complex coupled stimulation protocols have produced varied results with respect to motor facilitation; (4) no history of seizure attack, dementia, cognitive impairment; (3) an MRC-strength grade of 3 to 12 months after the first-ever stroke; (2) an MRC-strength grade or hemorrhagic lesion within 1 hemisphere, as verified by MRI; (2) an MRC-strength grade or hemorrhagic lesion within 1 hemisphere, as verified by MRI; and ventral to the corpus callosum. Patients with disease duration >1 year also were not enrolled because of lower susceptibility to rTMS conditioning based on pilot study observation.

In the current randomized sham-controlled study, we applied a priming conditioning protocol with 1-Hz rTMS to the contralesional M1 and additional iTBS rTMS to the ipsilesional M1 in hemiplegic patients. We aimed to assess the efficacy of this protocol for achieving motor recovery in postacute stroke patients and to compare this effect with single-course rTMS treatment measured by upper extremity motor scales and corticomotor excitability.

**Materials and Methods**

**Subjects**

Fifty-four patients were prospectively recruited for this study comprising 13 women and 41 men aged 35 to 85 years. Each participant completed detailed clinical and neurological examinations to ascertain (1) the severity of the stroke using the National Institute of Health Stroke Scale; (2) the muscle strength of the finger flexors and wrist extensors (distal part) of the upper extremity, according to the Medical Research Council (MRC) Scale; (3) sequential motor recovery after stroke using the Brunnstrom Approach; and (4) physical and cognitive disability using the Functional Independence Measure.\textsuperscript{20} All subjects fulfilled the inclusion criteria of (1) ischemic or hemorrhagic lesion within 1 hemisphere, as verified by MRI; (2) 3 to 12 months after the first-ever stroke; (3) an MRC-strength grade of ≤3/5 in the finger flexor of the paretic upper extremity at enrollment; (4) no history of seizure attack, dementia, cognitive impairment, or other neurodegenerative diseases; and (5) absence of aphasia, spatial neglect, visual field deficit, or emotional problems. Brain lesions were classified according to whether the lesion involved the motor cortex/subcortical regions or only the subcortical regions. The subcortical regions all were areas medial to the insular cortex and ventral to the corpus callosum. Patients with disease duration >1 year also were not enrolled because of lower susceptibility to rTMS conditioning based on pilot study observation.

All patients gave their written informed consent before participating in this experiment, in accordance with the 2008 Declaration of Helsinki and with the approval of the local Institutional Review Board. Demographic data and clinical characteristics are depicted in Table 1. All 4 groups shared the same overall characteristics (P>0.05).

**Experimental Design and Protocol**

The subjects were randomly allocated to 1 of 4 groups in a sham-controlled, double-blinded parallel study design. Randomization order was computer-generated and concealed by an independent statistician in sequentially numbered opaque envelopes. The allocation was performed by a researcher blinded to assessment. Each patient received 20 daily sessions of stimulation (5 days per week for 4 weeks), consisting of 10 sessions (the first course) of either real or sham 1-Hz rTMS over the contralesional M1, followed by 10 more sessions (the second course) of either real or sham iTBS over the ipsilesional M1. Group A comprised 16 subjects who underwent a course of real 1-Hz rTMS protocol, followed by another course of real iTBS. Group B comprised 13 subjects who underwent the first course of sham 1-Hz rTMS, followed by the second course of real iTBS. Group C comprised 14 subjects who underwent the first course of real 1-Hz rTMS, followed by the second course of sham iTBS. Group D comprised 15 subjects who underwent a course of sham 1-Hz rTMS, followed by a course of sham iTBS. The iTBS and 1-Hz rTMS paradigms were selected because these are commonly used protocols with a pronounced ability to facilitate and suppress cortical excitability.\textsuperscript{18} The short trains of both stimulations can elicit long-lasting change in cortical excitability, persisting up to 30 to 60 minutes.\textsuperscript{19} Therefore, we adopted these rTMS paradigms to condition the motor cortex, subsequently but not concurrently, using what is considered to be a safe dose within 1 treatment session. The rTMS protocols used in the current study were in accordance with the safety guidelines for rTMS applications.\textsuperscript{22}

All of the subjects continued the routine of conventional physical rehabilitation and occupational therapy regardless of the group they were assigned. Daily programs included 1 hour of task-oriented training, individualized motor tasks, and activities of daily living training, which were conducted by a therapist blinded to group allocation. Before conditioning (baseline), after the first part of conditioning (mid), and after the second part of conditioning (post), all the subjects participated in motor task evaluations and TMS examinations for corticomotor excitability.

**rTMS**

Electrophysiological measures included bilateral corticomotor excitability conducted by monophasic Magstim200 through a 70-mm figure-of-eight coil, probing resting motor threshold (rMT), maximal amplitude, latency of motor-evoked potential (MEP), and motor map area.\textsuperscript{23} A Dantec Keypoint electromyography (EMG) instrument (Dantec, Skovlunde, Denmark) was connected to the stimulator to record the MEP signals. The amplified (100 μV–1 mV/div) and bandpass-filtered (20–2000 Hz) signals were digitized at a 20-kHz sampling rate.

Motor responses were recorded from the first dorsal interosseous muscle contralateral to the stimulated hemisphere with a pair of Ag-AgCl electrodes. Muscle activity was carefully monitored by real-time EMG to ensure a relaxed state before stimulation. The rMT for MEP was defined as the minimal intensity at which MEPS of at least 50-μV amplitudes could be elicited in half of 10 consecutive stimuli. We obtained maximal MEP amplitude using 100\% of maximal output by measuring peak-to-peak amplitude. Latest latency was determined within 5 consecutive stimuli with 5-second intervals. A grid of 49 positions, spaced 1 cm on the interaural and sagittal lines, was tested on each motor cortex. Applying TMS to each mapping position at 110\% of the rMT intensity obtained at baseline, we determined the positions of excitability as the point where at least 2 reproducible MEPS were induced by 3 stimuli that were separated by at least 10-second intervals. Motor-mapping area was quantified as the sum of the excitability sites. For subjects who showed no MEP response to ipsilesional stimulation, the hot spot and rMT were used by the mirror image of the contralesional hemisphere.

We performed transcranial magnetic stimulation using Magstim Rapid\textsuperscript{TM} (Magstim) with a 70-mm figure-of-eight coil; 1-Hz rTMS trains consisting of 600 pulses at 90\% of rMT were applied over the motor representation of the first dorsal interosseus in the contralesional M1. iTBS was performed at 80\% of active motor threshold over the ipsilesional M1, consisting of bursts containing 3 pulses at 50 Hz repeated at 200-ms intervals for 2 seconds (ie, at 5 Hz). A 2-second train of iTBS was repeated every 10 seconds for 190 seconds and 600 pulses.\textsuperscript{10} We used a placebo coil (Magstim) for sham stimulation,
which delivered <5% of the magnetic output with audible click-on discharge. Because all the patients had no experience with rTMS, they did not know whether they were receiving real or sham rTMS.

Assessments
The all the subjects underwent a blinded evaluation of the Wolf Motor Function Test (primary motor outcome);[23] upper extremity Fugl-Meyer Assessment (FMA),[24] finger flexor MRC Scale, simple reaction task (RT), and index finger tapping task (FT) by an independent assessor at 3 visits before and after rTMS sessions. Electrophysiological measures included bilateral corticomotor excitability, probing rMT, maximal amplitude, latency of MEP, and motor map area.

Table 1. Demographic Data and Clinical Characteristics of All Patients

<table>
<thead>
<tr>
<th></th>
<th>Group A (n=15)</th>
<th>Group B (n=12)</th>
<th>Group C (n=13)</th>
<th>Group D (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>12/3</td>
<td>9/3</td>
<td>9/4</td>
<td>11/3</td>
</tr>
<tr>
<td>Age 62.3±12.2</td>
<td>64.2±11.9</td>
<td>63.3±12.8</td>
<td>63.1±12.8</td>
<td></td>
</tr>
<tr>
<td>Ischemic/hemorrhagic</td>
<td>10/5</td>
<td>8/4</td>
<td>8/5</td>
<td>9/5</td>
</tr>
<tr>
<td>Cortical/subcortical</td>
<td>10/5</td>
<td>7/5</td>
<td>9/4</td>
<td>9/5</td>
</tr>
<tr>
<td>Months poststroke</td>
<td>7.8±1.7</td>
<td>8.1±1.5</td>
<td>7.9±2.0</td>
<td>8.2±1.6</td>
</tr>
<tr>
<td>NIHSS 13.2±4.5</td>
<td>12.1±3.6</td>
<td>12.9±3.2</td>
<td>13.5±4.8</td>
<td></td>
</tr>
<tr>
<td>Br stage, proximal</td>
<td>3.2±1.2</td>
<td>2.8±1.2</td>
<td>3.1±1.3</td>
<td>3.0±1.5</td>
</tr>
<tr>
<td>Br stage, distal</td>
<td>2.9±0.8</td>
<td>2.9±1.4</td>
<td>3.2±1.3</td>
<td>2.8±1.7</td>
</tr>
<tr>
<td>DM history, %</td>
<td>26.6</td>
<td>25</td>
<td>23</td>
<td>21.4</td>
</tr>
</tbody>
</table>

Br indicates Brunnstrom; DM, diabetes mellitus; and NIHSS, National Institutes of Health Stroke Scale. All 4 groups shared the same overall characteristics as listed without significant difference among groups (P=0.05).

Statistics
The Kolmogorov-Smirnov test was used to assess whether the data showed a normal distribution. Under our testing conditions, we used repeated-measure ANOVA with time (level 1, baseline; 2, mid; 3, post) as the within-patient factor and the groups (level 1, group A; 2, group B; 3, group C; 4, group D) as the between-patient factor. For post hoc pairwise comparisons between the groups, the Bonferroni procedure was used.

Results
All of the patients demonstrated good tolerance for the rTMS sessions, with no adverse side effects observed during the conditioning and assessments.

Table 2. Behavioral Motor Data in Affected Upper Extremity at Baseline and After rTMS Interventions

<table>
<thead>
<tr>
<th></th>
<th>Group A (1 Hz-rTMS)</th>
<th>Group B (Sham rTMS)</th>
<th>Group C (1-Hz Sham)</th>
<th>Group D (Sham Sham)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Mid</td>
<td>Post</td>
<td>Baseline</td>
</tr>
<tr>
<td>MRC 2.5±1.5</td>
<td>3.1±1.4 $\dagger$</td>
<td>3.2±1.3 $\ddagger$</td>
<td>2.3±1.7</td>
<td>2.3±2.1</td>
</tr>
<tr>
<td>FMA 28.0±12.2</td>
<td>30.1±12.5 $\dagger$</td>
<td>30.9±10.3 $\ddagger$</td>
<td>28.4±10.3</td>
<td>28.8±10.2</td>
</tr>
<tr>
<td>WMFT 31.1±11.3</td>
<td>33.3±15.1 $\dagger$</td>
<td>38.5±12.4 $\ddagger$</td>
<td>30.9±12.2</td>
<td>31.1±11.6</td>
</tr>
<tr>
<td>Finger tapping (% sound side)</td>
<td>52.4±12.4</td>
<td>60.3±16.6</td>
<td>66.5±19.7</td>
<td>56.5±21.2</td>
</tr>
<tr>
<td>Reaction 213.8±44.5</td>
<td>144.1±32.8 *</td>
<td>129.2±33.2 $\ast$</td>
<td>181.9±39.1</td>
<td>118.5±9.0</td>
</tr>
</tbody>
</table>

FMA indicates Fugl-Meyer Assessment; iTBS, intermittent theta burst stimulation; MRC, Medical Research Council Scale for hand muscles; Mid, after 10-session rTMS; Post, after 20-session rTMS; rTMS, repetitive transcranial magnetic stimulation; and WMFT, Wolf Motor Function Test. Values are mean±SD. Post hoc analyses revealed significance levels: *P<0.05, †P<0.01, and ‡P<0.001 in comparison with baseline level. §Significant difference (P<0.05) in improvement between group B and group C after 1-course real stimulations.
Motor Performance

The groups were comparable in their baseline motor scales and tasks for the affected upper extremity \((P > 0.05)\). After rTMS intervention, groups A, B, and C yielded significant improvement over sham group D in the MRC, FMA, WMFT, FT, and RT (Table 2; Figure 1). Table 3 shows comparisons of improvement between the groups. In summary, group A showed a higher MRC score compared with group B and group C \((F_{(3, 50)}=9.88; P=0.003\) and \(P=0.001\), respectively). For FMA, group A presented with higher performance relative to group B and group C \((F_{(3, 50)}=7.28; P=0.001)\). For WMFT, group A showed 68.8\% improvement and significance of \(P<0.001\) in comparison with group B \((22.6\% \text{ improvement})\) and group C \((17.1\% \text{ improvement}; F_{(3, 50)}=8.65; P<0.001)\). For RT, group A showed 83.9\% improvement in comparison with group B \((58.5\%; F_{(3, 50)}=13.41; P<0.001)\) and group C \((49\%; F_{(3, 50)}=13.40; P=0.003)\). For change in the Functional Independence Measure cognition domain, the 4 groups were comparable \((P=0.36–0.39)\), which suggests that the condition of the M1 did not exert any modulating effect on cognition or emotion. Overall, the results indicate that the subjects who received real double-course conditioning experienced improved motor performance, in clear contrast to lesser motor performance gains from real single-course stimulation.

There were also significant differences in improvement between the 1-course 1-Hz rTMS group (group C) and the 1-course iTBS group (group B), as demonstrated by the MRC score \((P=0.041)\) and FMA score \((P=0.027)\). However, the WMFT, FT, and RT tests showed equivocal results for these 2 groups (Table 2).

Cortical Excitability

Table 3 summarizes the mean group data for bihemispheric cortical excitability. The groups were comparable in their baseline rMT and MEP parameters and in motor map area. At mid, motor map area measurements in the contralesional hemisphere showed significant decrement for group A and group C \((F_{(3, 50)}=6.75; P=0.006\) and \(P=0.002\), respectively) in comparison with group D. They also presented profound decrement at post for group A \((F_{(3, 50)}=7.32; P=0.015)\), group B \((P=0.015)\), and group C \((P=0.004)\) in comparison with group D. In addition to these changes, group A showed significant change in contralesional MEP amplitude \((F_{(3, 50)}=4.90; P=0.03)\) and latency \((F_{(3, 50)}=4.11; P=0.021)\) at post in comparison with group D. In the ipsilesional hemisphere, we detected elicited MEP in 28 subjects. There was a trend of increased corticomotor excitability in the ipsilesional hemisphere and decreased corticomotor excitability in the contralesional hemisphere after the real interventions. This tendency was particularly obvious in those who showed greater WMFT improvement (Figure 2). The ipsilesional motor map area of groups A and B were enlarged significantly at post compared with group D \((F_{(3, 24)}=4.87; P=0.02\) and 0.04, respectively).
Correlation Analyses Between Motor Performance and Cortical Excitability Measures

To examine the relation between rTMS-induced cortical excitability changes and functional gain, we performed a correlation analysis for each group. For group A, the decrement of contralesional map area was negatively correlated with the increment of WMFT ($P=0.005; r=-0.75$; Figure 3), as well as the decrement of contralesional MEP amplitude with WMFT ($P=0.048; r=-0.55$). The increment of ipsilesional map area for group A was also negatively correlated with the decrement of RT ($P=0.02; r=-0.87$). However, these associations did not reach significance for group B ($P=0.56, 0.67, 1.0$, respectively) or for group C ($P=0.25, 0.24, 0.66$, respectively). These findings indicate that derived cortical excitability change in group A had a more positive impact than in groups B and C in terms of clinical consequences.

Influence of Stroke Type, Lesion Location, Poststroke Duration, and Baseline Impairments

Motor performance and cortical excitability responses to rTMS conditioning, as measured (1 Hz or iTBS), did not differ across different pathological types (ischemic or hemorrhagic), or lesion locations (cortical or subcortical; $P>0.05$). The ANCOVA revealed that the significant outcome difference between groups ($P=0.003$) was not driven by a consistent pattern across variants, nor was it an effect of baseline MRC ($P=0.992$), FMA ($P=0.690$), WMFT ($P=0.417$), or mediated by poststroke duration ($P=0.77$).

Discussion

This study investigated the effectiveness of the coupling inhibitory–facilitatory rTMS protocol to enhance the motor recovery of chronic stroke patients. Our results demonstrated the optimal effects of this approach, which has produced more profound effects than unilateral single-course modulation in facilitating motor performance and in ameliorating interhemispheric imbalance. With the aftereffects of upregulation of ipsilesional cortical excitability and downregulation of contralesional cortical excitability, this coupling protocol showed bipartite advantages for motor restoration in chronic hemiplegic patients.

Motor recovery research has illustrated the principle that a shift in interhemispheric balance toward the uninjured hemisphere signifies a distressed system. Our own rationale for targeting the ipsilesioned motor cortex with facilitatory rTMS and the contralesional motor cortex with inhibitory rTMS...
was based on functional MRI and TMS studies, which have revealed that recruitment of the ipsilesional M1, supplementary motor area, and cerebellum have correlated positively with full motor recovery, whereas contralesional M1 recruitment and the inducement of MEP from the contralesional TMS have been linked to poor motor recovery. The already-developed rTMS protocol of upregulating the affected hemisphere and downregulating the unaffected hemisphere provided us a platform from which we could remodulate these pathological transcallosal outcomes. However, the existing literature on unilateral single-course rTMS has documented only modest improvements from 10% to 30% across a variety of chronic stroke patient assessments, including MRC, FMA, and WMFT. Our own assessments revealed that the RT performance of group B benefited from real iTBS conditioning and the RT performance of group C benefited from real 1-Hz rTMS conditioning, achieving 58% and 49% improvement, respectively, relative to their baseline levels. Our approach resulted in an outranged behavior gain of 68.8% for WMFT (Figure 1A) and 83.9% for the RT test (Figure 1B). The intergroup comparisons (Table 3) indicate that the motor performance of group A achieved greater significance than conventional unilateral conditioning.

For the neural correlates underlying motor improvement, we observed a stronger association of behavioral gain with cortical excitability change in group A but not in group D (Figure 3). The upregulation of ipsilesional cortical excitability as reflected in an increase in motor map area and the downregulation of contralesional cortical excitability as reflected in a decrease in motor map area and MEP amplitude were strongly associated with motor performance improvement (as measured in FMA, WMFT, and RT testing). This fact reinforces our contention that, through the priming of the intact corticospinal tract and subsequent activation of the perilesional motor network under the mechanisms of LTD and LTP, our novel approach yields bipartite advantages (Figure 2). Having established an effective modulatory connectivity, we could then turn our attention to applying facilitatory stimulation to the ipsilesional cortex. Preconditioning the intact cortical network made it possible to break the mutual cortical imbalance and establish a foundation

Table 4. Baseline and Change of Electrophysiological Data After rTMS Intervention in Bilateral Hemispheres

<table>
<thead>
<tr>
<th></th>
<th>Group A (1-Hz iTBS)</th>
<th>Group B (Sham iTBS)</th>
<th>Group C (1-Hz Sham)</th>
<th>Group D (Sham Sham)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Mid</td>
<td>Post</td>
<td>Baseline</td>
</tr>
<tr>
<td>Contralesional Hemisphere</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rMT (% maximal)</td>
<td>70.0±10.4</td>
<td>72.4±9.7</td>
<td>74.4±9.6</td>
<td>70.8±9.7</td>
</tr>
<tr>
<td>MEP amplitude, μV</td>
<td>3.6±1.8</td>
<td>2.5±1.3</td>
<td>2.2±1.2*</td>
<td>3.2±2.1</td>
</tr>
<tr>
<td>MEP latency, ms</td>
<td>22.9±2.5</td>
<td>22.8±1.8</td>
<td>23.5±2.1*</td>
<td>23.3±2.6</td>
</tr>
<tr>
<td>Motor map area</td>
<td>12.4±3.3</td>
<td>10.3±3.7†</td>
<td>9.9±3.2†</td>
<td>14.5±3.1</td>
</tr>
<tr>
<td>Ipsilesional Hemisphere</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rMT (% maximal)</td>
<td>85.7±7.9</td>
<td>80.0±8.8</td>
<td>77.0±8.2</td>
<td>86.8±10.5</td>
</tr>
<tr>
<td>MEP amplitude, μV</td>
<td>1.3±1.2</td>
<td>2.6±1.7</td>
<td>1.5±1.1</td>
<td>1.2±1.0</td>
</tr>
<tr>
<td>MEP latency, ms</td>
<td>29.4±7.2</td>
<td>26.7±5.9</td>
<td>26.4±4.4</td>
<td>26.3±5.9</td>
</tr>
<tr>
<td>Motor map area</td>
<td>8.5±3.9</td>
<td>8.8±4.4</td>
<td>9.6±4.8*</td>
<td>7.6±3.5</td>
</tr>
</tbody>
</table>

iTBS indicates intermittent theta burst stimulation; MEP, motor-evoked potential; Mid, after 10-session rTMS; Post, after 20-session rTMS; rMT, resting motor threshold; and rTMS, repetitive transcranial magnetic stimulation. Values are mean±SD. Post hoc analyses revealed significance levels: *P<0.05 and †P<0.01 improvement in comparison with baseline level.
for a more favorable outcome. Identical to our own electrophysiological findings, previous research involving bihemispheric transcranial direct-current stimulation\textsuperscript{19} has provided functional imaging evidence that increased motor activity is associated with stimulation to the ipsilesional primary motor coupled with downregulation of excitability of the contralesional motor cortex. The laterality index from preintervention to postintervention correlated significantly with the changes in WMFT score.\textsuperscript{19}

Our own electrophysiological finding that the continuing downregulation of contralesional cortical excitability was enhanced by a second course of rTMS was somewhat different from the Bienstock-Cooper-Munro rule.\textsuperscript{26} Cortical functioning, according to this rule, can be preregulated at the target area within the same hemisphere\textsuperscript{29} or across hemispheric boundaries\textsuperscript{30} under the mechanism of homeostatic plasticity. There is a time-variable threshold for LTP/LTD induction, in which the probability of LTP induction is enhanced or LTD induction is decreased by the preconditioning suppression of neural networks. Likewise, under the same threshold, the probability of LTP induction is decreased or LTD induction is enhanced by preconditioning intensification of neural activity. An earlier study on normal subjects found that preconditioning the left M1 through administering 1-Hz rTMS to the right M1 could reverse the effect of the following iTBS by suppressing the MEP amplitude that is supposed to be enhanced.\textsuperscript{30} For our study, however, MEP amplitude, latency, and motor map area data after the coupling rTMS indicated that downregulation of cortical excitability was persisting at a significant level (Table 4) after the following iTBS in the opposite M1. Excitability decrement in the intact motor cortex through 1-Hz rTMS brought about an ≈20% decrement in motor map area, which continued by 10% after the subsequent iTBS conditioning in the opposite M1 (Figure 1C). The factors underlying this apparent discrepancy are the different study groups and the varied duration of the aftereffects sustained across individuals and experiments.\textsuperscript{31} For stroke patients experiencing interhemispheric imbalance, the modulation response may not closely follow the existing conventions of homeostatic plasticity. This is especially so for this study, in which the TMS assessment was performed after long-term multisession conditioning. At the same time, our own findings are consistent with those of the Ragert et al\textsuperscript{10} study, in which the motor performance of their subjects (tested by pinch force or FT tasks) was found to be enhanced after consecutive rTMS conditioning. This result may reinforce our rationale for establishing a coupling inhibitory–facilitatory rTMS protocol to enhance efficacy of rTMS therapy.

The MEP suppression that occurred in our study after intervention, as measured with amplitude, latency, and area in the unaffected hemisphere, were not paralleled by significant rMT elevation, although previous research has revealed that rMT increment does tend to occur after a series of interventions. Our findings do, however, concur with those of some other studies\textsuperscript{32,33} that have found that because rMT is a measure of membrane excitability, it may be influenced by both neurophysiologic substrates and by the tonic synaptic status of the corticospinal tract and, in this way, can be controlled by differing factors. Therefore, it is feasible that rMT change may have no significant association with changes to other MEP parameters, although there was a trend of decreasing ipsilesional rMT and increasing contralesional rMT after the real interventions.

In the current study, we successfully demonstrated that the coupling protocol produced more favorable results than single-course protocol under the putative mechanism of the combination of different modulation strategies, that is, the inhibitory and facilitatory rTMS montage. However, the differences in the final results derived from the rTMS treatments may have resulted from the discrepancy of conditioning dosages across the groups, after which group A experienced greater motor improvement after double-duration protocol, in comparison with groups B and C, which received only half the number of modulation sessions received by group A. To clarify the contribution of the combined protocols on rTMS-induced aftereffects, supplementary investigations devoted to control session dosage, matched for each group, would be highly beneficial for addressing this issue.

Heterogeneity within our hemiplegic sample may be a confounding factor influencing the study result. Factors such as age, time poststroke, lesion location, and pathological type must all be taken into consideration. Although there were no significant difference for these characteristics across the 4 study groups, further large-scale investigations with factor stratification are critical for expanding the evidence base. Meanwhile, it is warranted to investigate the long-term effect of this protocol in a further study. Finally, although we did not observe any abnormal behavior during or after the treatment that could indicate a complex partial or secondarily generalized seizure, future studies would be strengthened by the inclusion of electroencephalogram recording to detect ictal activity, epileptiform discharges, or notable differences before, during, or after rTMS conducted on a continuous video recording by an experienced electroencephalogram clinician.\textsuperscript{34,35} Detailed analyses of electroencephalogram band power spectrum\textsuperscript{36} or TMS-evoked electroencephalogram potentials amplitude\textsuperscript{37} could present appropriate markers for real-time monitoring to assure the safety of this paradigm, as applied in a prolonged protocol. Multichannel EMG recordings of the spreading of excitation or after-discharges to muscles not activated by single-pulse TMS also could be used for monitoring preceding TMS-induced seizures.\textsuperscript{38}

Our use in this study of a combination of different strategies is a major step toward securing an optimal motor facilitation process to chronically disabled stroke patients. This randomized, controlled, double-blinded study has contributed key explicit information to the existing literature that can serve as a sound basis for progressively fine-tuning more effective strategies. Treatment with a compound coupling rTMS protocol opens a promising era of research to underpin widespread clinical practice with greater certainty of achieving motor recovery.

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**Disclosures**

None.
References


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Wen-Hsu Sung, Chih-Pin Wang, Chen-Liang Chou, Yi-Cheng Chen, Yue-Cune Chang and Po-Yi Tsai

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