Combining Theta Burst Stimulation With Training After Subcortical Stroke

Suzanne J. Ackerley, BPHTY; Cathy M. Stinear, PhD; P. Alan Barber, FRACP; Winston D. Byblow, PhD

Background and Purpose—Repetitive transcranial magnetic stimulation of the primary motor cortex (M1) may improve outcomes after stroke. The aim of this study was to determine the effects of M1 theta burst stimulation (TBS) and standardized motor training on upper-limb function of patients with chronic stroke.

Methods—Ten patients with chronic subcortical stroke and upper-limb impairment were recruited to this double-blind, crossover, sham-controlled study. Intermittent TBS of the ipsilesional M1, continuous TBS of the contralesional M1, and sham TBS were delivered in separate sessions in conjunction with standardized training of a precision grip task using the paretic upper limb.

Results—Training after real TBS improved paretic-hand grip-lift kinetics, whereas training after sham TBS resulted in deterioration of grip-lift. Ipsilesional M1 excitability increased after intermittent TBS of the ipsilesional M1 but decreased after continuous TBS of the contralesional M1. Action Research Arm Test scores deteriorated when training followed continuous TBS of the contralesional M1, and this was correlated with reduced ipsilesional corticomotor excitability.

Conclusions—Generally, TBS and training led to task-specific improvements in grip-lift. Specifically, continuous TBS of the contralesional M1 led to an overall decrement in upper-limb function, indicating that the contralesional hemisphere may play a pivotal role in recovery after stroke.

Key Words: human ▪ upper limb ▪ transcranial magnetic stimulation ▪ neurorehabilitation ▪ plasticity

After stroke, many patients are left with upper-limb impairment. Poor upper-limb recovery is associated with an imbalance in hemispheric activity, downregulated excitability in the ipsilesional primary motor cortex (M1), and upregulated excitability in the contralesional M1.1 Experimental neuromodulation techniques that “rebalance” M1 excitability have led to improved upper-limb function and may be used to prime the brain before therapy.2,3 Theta burst stimulation (TBS) is a pattern of repetitive, transcranial magnetic stimulation that can facilitate M1 excitability when delivered intermittently or suppress M1 excitability when delivered continuously.4 Intermittent TBS of the ipsilesional M1 (iTBSipsiM1) and continuous TBS of the contralesional M1 (cTBScontraM1) may be used to “rebalance” M1 excitability and may have therapeutic benefit.5,6 However, engaging in voluntary activity can block or reverse the neurophysiologic aftereffects of cTBS.7,8 Furthermore, cTBScontraM1 may have deleterious effects on the paretic upper limb if the contralesional M1 contributes to its motor control.9

In this study, iTBSipsiM1 and cTBScontraM1 were each combined with standardized upper-limb training. We hypothesized that both TBS protocols would facilitate ipsilesional M1 excitability and improve measures of upper-limb performance.

Subjects and Methods

Ten adults with persistent upper-limb impairment at least 6 months after subcortical stroke participated (the Table). Volunteers with contraindications to transcranial magnetic stimulation were excluded. Written consent was obtained, and the study was approved by the regional ethics committee.

Three experiments (iTBSipsiM1, cTBScontraM1, and sham TBS) were performed in a randomized order and separated by 1 week (see Figure 1 for a flowchart of the experimental procedures). Upper-limb motor training consisted of 4 blocks of precision grip movements, each lasting 4 minutes, and carried out 15 minutes after TBS. Grip-lift kinetics, corticomotor excitability, and upper-limb function (Action Research Arm Test [ARAT]10; maximum, 57) assessments were made before and after intervention.

TBS at 90% of the active motor threshold of the nonparetic first dorsal interosseous (FDI) was administered with a biphasic stimulator (MagStim, Dyfed, UK) by an investigator blinded to data collection and analysis. In each session, 600 stimuli were delivered,4 with a reverse coil orientation used for cTBScontraM1.11 Sham TBS was delivered to either M1 with a sham coil.
Grip-lift kinetics were acquired with an instrumented manipulandum (MLP-100, Transducer Techniques, 265 g) held between the index finger and thumb, lifted to 10 cm, and held for 3 seconds. Ten lifts were made with each hand at each grip time point. Grip force perpendicular to the contact surface and load force parallel to vertical were recorded. Preload force (PF, in newtons) was determined as the maximal downward force on the manipulandum before liftoff. Preload duration (PD, in ms) was determined as the time between grip force onset and positive load force at liftoff. PF and PD are sensitive measures of manual dexterity impairment in stroke patients.12

Corticomotor excitability was assessed with single-pulse transcranial magnetic stimulation of the M1 with a figure-of-eight coil connected to a MagStim 200 stimulator. Surface electromyography was recorded from both FDI muscles, amplified and filtered (30 to 1000 Hz), and sampled at 2 kHz for off-line analysis (LabView, National Instruments). Stimulation intensity was set to produce a maximum MEP obtainable in the resting contralateral FDI. Twelve MEPs were recorded from each FDI at each MEP time point. When no MEP was elicited from the ipsilesional M1 (both muscles at rest) the protocol was repeated (was excessive) in the paretic hand, but not the nonparetic hand (Figure 2A). Paretic-hand PF deteriorated at post26 (during training) compared with baseline and post9 (before training; both P<0.05) and remained excessive (post26 vs post9 P=0.898).

Paretic-hand PD improved when training followed real TBS compared with sham TBS. A main effect of time indicated that PD improved (shortened) during the experiment (F4,36=5.10, P=0.034). A protocol×hand interaction (F2,18=4.15, P=0.033) indicated that paretic-hand PD improved when training followed cTBScontraM1 (P=0.026) and iTBSipsiM1 (P=0.046, not significant when corrected) compared with sham TBS. Paretic-hand PD improved from baseline after cTBScontraM1 (P=0.028), with a similar trend after iTBSipsiM1 (P=0.057; Figure 2B).

Results

The protocols were well tolerated by all participants. Baseline data and stimulation intensities were stable across sessions (all P>0.1). There were differences between the paretic and nonparetic hands for all dependent variables (all P≤0.03), as expected. The amount of training was equivalent across sessions (all P>0.3). There were no significant changes in any variable for the nonparetic hand (all P>0.1).

Grip-Lift Kinetics

Paretic-hand PF deteriorated when training followed sham TBS, but not real TBS. There was a protocol×hand×time interaction (F4,36=3.42, P=0.018) and no main effects or other interactions (all P>0.1). The interaction was explored for each protocol separately with no main effects or interactions for cTBScontraM1 (all P>0.058) or iTBSipsiM1 (all P>0.54). A hand×time interaction occurred with training after sham TBS (F2,18=4.16, P=0.033) because PF deteriorated (was excessive) in the paretic hand, but not the nonparetic hand (Figure 2A). Paretic-hand PF deteriorated at post26 (during training) compared with baseline and post9 (before training; both P≤0.05) and remained excessive (post26 vs post9 P=0.898).

Paretic-hand PD improved when training followed real TBS compared with sham TBS. A main effect of time indicated that PD improved (shortened) during the experiment (F4,36=5.10, P=0.034). A protocol×hand interaction (F2,18=4.15, P=0.033) indicated that paretic-hand PD improved when training followed cTBScontraM1 (P=0.026) and iTBSipsiM1 (P=0.046, not significant when corrected) compared with sham TBS. Paretic-hand PD improved from baseline after cTBScontraM1 (P=0.028), with a similar trend after iTBSipsiM1 (P=0.057; Figure 2B).

MEP Amplitude

MEP amplitude was modulated by real TBS. For the paretic FDI, there was a protocol×time (pre, post,) interaction (F2,18=4.13, P=0.033) because MEP amplitude increased

Table. Participant Characteristics

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Age, y</th>
<th>Time Since Stroke, mo</th>
<th>NIHSS Score (Maximum=42)</th>
<th>NIHSS Sensory Subscale Score*</th>
<th>FM Score</th>
<th>mRS Score</th>
<th>Hemi</th>
<th>Type</th>
<th>Affected Structures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>74</td>
<td>19</td>
<td>2</td>
<td>0</td>
<td>22</td>
<td>2</td>
<td>R</td>
<td>I</td>
<td>Pu, Th</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>73</td>
<td>27</td>
<td>6</td>
<td>0</td>
<td>18</td>
<td>3</td>
<td>R</td>
<td>I</td>
<td>Ext</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>68</td>
<td>9</td>
<td>3</td>
<td>1</td>
<td>27</td>
<td>2</td>
<td>R</td>
<td>H</td>
<td>Th</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>44</td>
<td>51</td>
<td>4</td>
<td>0</td>
<td>21</td>
<td>2</td>
<td>R</td>
<td>I</td>
<td>Pu, GP, Ca, Int (A, G)</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>64</td>
<td>33</td>
<td>6</td>
<td>1</td>
<td>25</td>
<td>3</td>
<td>L</td>
<td>I</td>
<td>Pu, GP, Th, Int (P)</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>64</td>
<td>7</td>
<td>2</td>
<td>0</td>
<td>18</td>
<td>3</td>
<td>L</td>
<td>I</td>
<td>All</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>61</td>
<td>86</td>
<td>1</td>
<td>1</td>
<td>20</td>
<td>2</td>
<td>L</td>
<td>I</td>
<td>Ext</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>52</td>
<td>10</td>
<td>7</td>
<td>1</td>
<td>12</td>
<td>2</td>
<td>L</td>
<td>I</td>
<td>Pu, GP</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>49</td>
<td>8</td>
<td>3</td>
<td>1</td>
<td>27</td>
<td>2</td>
<td>L</td>
<td>H</td>
<td>All</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>47</td>
<td>25</td>
<td>2</td>
<td>0</td>
<td>28</td>
<td>3</td>
<td>L</td>
<td>I</td>
<td>Pu, GP, Ca, Int (A, G, P)</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>60</td>
<td>28</td>
<td>4</td>
<td>0</td>
<td>22</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td>11</td>
<td>25</td>
<td>2</td>
<td>1</td>
<td>5</td>
<td>0.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimum</td>
<td></td>
<td>44</td>
<td>7</td>
<td>1</td>
<td>0</td>
<td>12</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NIHSS indicates National Institutes of Health Stroke Scale; FM, Fugl-Meyer upper-limb score (subscale maximum=32); mRS, modified Rankin Scale; Hemi, stroke hemisphere; I, ischemic; H, hemorrhagic; BG, basal ganglia; Pu, putamen; Th, thalamus; GP, globus pallidus; Ca, caudate; Int, internal capsule (A indicates anterior limb; G, genu, P, posterior limb); Ext, external capsule; Temp, temporal cortex; and Ins, insular cortex.

*For the NIHSS Sensory Subscale, normal=0; mild/moderate sensory loss=1.
after iTBS_{ipsiM1} (P=0.029) but tended to decrease after cTBS_{contraM1} (P=0.049, not significant corrected) (Figure 2C). Sham TBS did not change paretic FDI MEP amplitude (P=0.208).

The modulation of real TBS on paretic FDI MEP amplitude did not persist. For the paretic FDI, there was a protocol\times time (post\_7, post\_13, post\_25, post\_39) interaction (F_{6,54}=2.30, P=0.048). After iTBS_{ipsiM1}, there was an effect of time (F_{3,27}=3.62, P=0.026). Although MEP amplitude was facilitated at post\_7 (before training), it did not differ from baseline at any of the other time points (during training, all P>0.1). After cTBS_{contraM1} and sham TBS, there was no effect of time on MEP amplitude during training (both P>0.1).

**Upper-Limb Function**

Paretic upper-limb function deteriorated when training followed cTBS_{contraM1}, and this was correlated with the initial reduction in paretic FDI MEP amplitude. ARAT score (median pre vs post) deteriorated after the cTBS_{contraM1} session (46 vs 41, P=0.024) but was unchanged after the iTBS_{ipsiM1} (44 vs 44, P=0.339) and sham TBS (43 vs 42, P=0.778) sessions.

Correlations were explored between ΔARAT (post−pre), Δgrip-lift kinetics, and Δparetic FDI MEP amplitude (both % change from pre) after each TBS protocol. A moderate, positive correlation was found between ΔARAT and Δparetic FDI MEP amplitude after cTBS_{contraM1} (R^2=0.47, P=0.028;
Figure 2D), indicating that a reduction in ARAT score was related to paretic FDI MEP suppression. There were no other correlations (all $P > 0.2$).

**Discussion**

This study is the first to use M1 TBS before upper-limb motor training in stroke patients, akin to its potential use in rehabilitation. Priming training with iTBSipsiM1 or cTBScontraM1 improved performance of the paretic hand, but cTBScontraM1 was associated with reduced upper-limb function.

After sham TBS, paretic-hand PF deteriorated and PD did not improve, indicating fatigue. In contrast, PF remained stable and PD improved with training after cTBScontraM1 and tended to improve after iTBSipsiM1. These improvements may have resulted from facilitated integration within the primary sensory and/or motor cortex, enabling more efficient processing of afferent feedback and shortening the preload period.14

Upper-limb function deteriorated after cTBScontraM1. Paretic upper-limb function transiently decreased after training combined with cTBScontraM1 but not with iTBSipsiM1 or sham TBS. Unlike an earlier study examining stroke patients at rest,5 cTBScontraM1 suppressed ipsilesional M1 excitability. This may have occurred because the effects of cTBS are vulnerable to motor activity or because of the reverse coil orientation.7,15 The effect of cTBScontraM1 on ipsilesional M1 is most likely mediated by transcallosal projections from the contralesional M1, but further investigation is required to elucidate specific mechanisms. Interestingly, participants in whom cTBScontraM1 had the most suppressive effect on ipsilesional corticomotor excitability had the greatest decrement in ARAT score. However, grip-lift performance was not adversely affected. Although task-specific effects of upper-limb training may be better maintained in cortical networks after real TBS, decrements in other tasks may be due to suppressive effects of cTBScontraM1. Conversely, iTBSipsiM1 produced immediate, but not persistent, facilitation of ipsilesional corticomotor excitability, consistent with previous research.5,8

These findings indicate task-specific benefits with primed training after subcortical stroke. The contralesional hemisphere may play a pivotal role in recovery after stroke, as indicated by the deterioration of functional performance after cTBScontraM1. Further research is required to ascertain the contribution of the contralesional hemisphere to stroke recovery.

**Acknowledgments**

We thank Lynley Bradnam and Denise Miller for assistance during data collection.

**Sources of Funding**

This project was funded by the Neurological Foundation of New Zealand and the Auckland Medical Research Foundation.

**Disclosures**

None.

**References**


Combining Theta Burst Stimulation With Training After Subcortical Stroke
Suzanne J. Ackerley, Cathy M. Stinear, P. Alan Barber and Winston D. Byblow

Stroke. 2010;41:1568-1572; originally published online May 20, 2010;
doi: 10.1161/STROKЕAHA.110.583278
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/41/7/1568

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/