Continuous theta burst stimulation over the contralesional sensory and motor cortex enhances motor learning post-stroke

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Abstract

The current study investigated the contributions of contralesional primary somatosensory cortex (S1c) to motor learning deficits post-stroke. For three days, continuous theta burst (cTBS) was delivered over the contralesional hemisphere prior to practicing a serial targeting task. cTBS was delivered over either S1c, contralesional primary motor cortex (M1c) or as control stimulation (n = 4/group). Change in motor ability was assessed from initial performance to a delayed retention test using a serial targeting task and a subset of items from the Wolf Motor Function Test. Practice preceded by cTBS over either M1c or S1c resulted in large decreases in movement time compared to practice preceded by control stimulation. M1c cTBS resulted in larger decreases in peak velocity and peak acceleration compared to control and S1c cTBS. In contrast, S1c cTBS resulted in larger reductions in time to initiate movement and time to complete the WMFT compared to control and M1c cTBS. These preliminary findings suggest that stimulation of either M1c or S1c can enhance the benefits of practice. However, changes in M1c and S1c excitability may contribute to different aspects of post-stroke motor deficits that may differentially impact rehabilitation.

A common observation after stroke is increased excitability of the contralesional and decreased excitability in ipsilesional cortex [5,22,25]. In primary motor cortex (M1) the extent of this laterality shift has been linked to the severity of the motor deficit [6]. Increasing hemiparetic arm use elevates the excitability of ipsilesional M1 [7,8] and improves function [19,33]. However, the functional gains associated with simply increasing hemiparetic arm use are limited [14], as the rate of change is low and requires a large number of repetitions [4].

One potential method to increase ipsilesional cortical excitability is transcranial magnetic stimulation (TMS). Theoretically, TMS may facilitate use-dependent neuroplasticity by decreasing the extent of cortical excitability changes that occur after stroke [29]. Studies employing this approach either directly increase the cortical excitability of ipsilesional M1 using high frequency ipsilesional stimulation, or indirectly reduce inter-hemispheric inhibition from contralesional to ipsilesional M1, using low frequency contralesional stimulation [1,7,9,12,23,26]. The latter approach is particularly appealing as it avoids stimulation of the peri-infarct region. However, results from studies investigating the benefits of contralesional stimulation vary. Inconsistencies may stem from variability in stimulation delivery site within and/or across sessions [3], use of single session experiments, failure to pair stimulation with skilled motor practice, and/or a focus upon stimulating M1.

While stimulating M1 is convenient, this area is only one part, the output, of the sensory-motor network used to guide movements. Similar to M1, the extent of contralesional S1 (S1c) activity correlates with the severity of motor deficit post-stroke [6]. Therefore, normalizing altered sensory processing appears to be as equally important to motor deficits post-stroke. Enhancing sensory representations may elicit enhanced sensory-motor processing that may be more generalizable across a range of movements.

The importance of interactions between the sensory cortices has been highlighted by observations of transient increases in functional ability of the hemiparetic limb with peripheral acute deafferentation of the non-hemiparetic limb [11,28]. Improved function after deafferentation has been associated with increased excitability in ipsilesional S1 [31] and ipsilesional M1 excitability [30]. However, the differential impact of altering excitability in M1c versus S1c to enhance functional recovery post-stroke has not been considered.

The current study tested whether continuous theta burst stimulation (cTBS) over contralesional cortex prior to practice would alter motor skill learning or functional ability of the hemiparetic limb in people with chronic stroke. Specifically, we compared the impact of cTBS over M1c versus S1c prior to motor skill practice upon
functional recovery post-stroke. It was hypothesized that cTBS over M1c or S1c would result in sustained improvement of task-specific performance, indexed by reduced movement times and kinematic measures, compared to practice alone. However, we hypothesized that only cTBS over S1c prior to practice would elicit generalized improvements in motor control, indexed by reduced times to initiate movement and time to complete selected items of the Wolf Motor Function Test (WMFT) [32].

Twelve individuals with first time, chronic (at least 12 months post-stroke onset) [17], ischemic stroke participated (Table 1 and Fig. 1). Participants’ physical impairment level was determined using the Fugl-Meyer upper extremity motor scale [13]. Participants were not enrolled if they: (1) scored <25 on the Montreal Cognitive Assessment, (2) had a Fugl-Meyer <15, (3) had any contraindications to TMS or magnetic resonance imaging (MRI), or (4) a Motor Evoked Potential (MEP) could not be elicited from ipsilesional M1.

Participants were recruited from the local community. Consent was obtained according to the Declaration of Helsinki. The research ethics board at the University of British Columbia approved all aspects of this work.

Participants were pseudo-randomly assigned to one of three groups (n=4/group) based upon Fugl-Meyer score to ensure equivalence of stroke severity among the groups. On Day 1 initial performance on a Serial Targeting Task (STT), using the hemiparetic limb, and times to complete selected items of the WMFT were assessed [32]. WMFT items included towel folding, picking up a can and picking up a paper clip. On Days 2–8 8–10 min after cTBS delivery, participants performed 4 blocks (150 trials/block) of the STT without vision of the hemiparetic arm. One group (S1c + practice) received cTBS over S1c, a second group (M1c + practice) received cTBS over M1c and a third group (control + practice) received sham cTBS that looked and sounded like active stimulation but did not induce any current in the underlying cortex. Coil position during sham stimulation was counterbalanced across the S1c and M1c sites. To assess motor learning a no-cTBS delayed retention test was performed on Day 5 [24]. This consisted of one block of the STT (with vision of the hemiparetic arm) and completion of the selected items from the WMFT.

cTBS was delivered using a Magstim Super Rapid2 stimulator and a 70 mm figure-8 air-cooled coil (Magstim Company, Ltd., Wales, U.K.) oriented tangentially to the scalp with the handle at 45° to the midline in a posterior-lateral orientation. Prior to the experiment, high-resolution anatomical MRI was acquired for each participant (TR = 12.4 ms, TE = 5.4 ms, flip angle θ = 35°, FOV = 256 mm, 170 slices, 1 mm thickness) at the UBC MRI Research Centre on a Philips Achieva 3.0 T whole body MRI scanner (Phillips Healthcare, Andover, MD) using a sensitivity encoding head coil (SENSE). These images were imported into BrainSight™ TMS neuronavigation software (BrainSight 2.0, Rogue Research Inc., Montreal, QC) to allow for stereotactic registration of the TMS coil.

Surface electromyography (EMG) over the participants’ right extensor carpi radialis (ECR) was monitored using the evoked potential unit of the Super Rapid2 control unit (Magstim Company, Ltd.). Motor Evoked Potentials (MEPs) were used to localize both the ipsilesional and contralesional ECR M1 “hotspot”. Resting motor threshold (RMT) for the contralesional M1ECR was set as the percentage of stimulator output that elicited an MEP of ≥50 μV peak to peak on 5 out of 10 trials. Active motor threshold (AMT) was determined as the percentage of stimulator output that elicited an MEP

Table 1
Group characteristics (mean, standard deviation).

<table>
<thead>
<tr>
<th>Group</th>
<th>Age*</th>
<th>Gender</th>
<th>Stroke side</th>
<th>Time since strokeb</th>
<th>MOCA</th>
<th>UE Fugl-Meyer</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1c + practice</td>
<td>63 (9)</td>
<td>3M, 1F</td>
<td>2L, 2R</td>
<td>88 (91)</td>
<td>29 (0.6)</td>
<td>51 (12.4)</td>
</tr>
<tr>
<td>Control + practice</td>
<td>64 (14)</td>
<td>2M, 2F</td>
<td>2L, 2R</td>
<td>69 (47)</td>
<td>27 (1.3)</td>
<td>54 (8.8)</td>
</tr>
<tr>
<td>M1c + practice</td>
<td>65 (10)</td>
<td>1M, 3F</td>
<td>2L, 2R</td>
<td>66 (61)</td>
<td>28 (1.5)</td>
<td>50 (15.6)</td>
</tr>
</tbody>
</table>

MOCA = Montreal Cognitive Assessment; UE = upper extremity.

* Age in years.

b Time since stroke in months.

Fig. 1. Infarct location for each participant. Each row is a separate participant in each group. L – left, R – right.
of $\geq 200 \mu V$ peak to peak on 5 out of 10 trials while participants maintained a contraction of the ECR at 20% of their maximal force. Force was monitored using a custom pressure system with a gauge upon which the target force was visually indicated.

Site of stimulation for S1c was placed 2 cm posterior to the M1c ECR “hotspot”. Single pulses were used to verify isolation of S1c from M1c.

cTBS stimulation consisted of 3 pulses presented at 50 Hz repeated every 200 ms for a total of 40 s [15]. Intensity was set to 80% AMT. Control cTBS was delivered using a custom coil (Magstim Company, Ltd.). Participants were naïve to group assignment and cTBS target location.

Participants were seated in front of a computer monitor and instructed to move a cross-hair cursor between a series of sequentially appearing targets as fast and accurately as possible while taking the most direct route. The cursor was controlled by a computer mouse (Microsoft Wheel Mouse) housed in a custom frame that was grasped with the hand pronated. To initiate the appearance of the next target, participants had to hold their cursor in the current target for 500 ms; this time was followed by an additional 500 ms inter-target interval.

Each target was 28 mm in diameter and could appear at one of nine locations. One location was central; the other eight locations formed an equidistant circular array with a radius 96 mm. The tangent distance between the azimuth locations was 75 mm. Movement between any two targets was categorized into five indices of difficulty (ID Levels: 2.85, 3.25, 3.75, 4.12 and 4.25) based upon Fitt’s Law [10]. Each block contained proportional movements in each ID level such that for every 8 movements there was one at each ID level 2.85 and 4.12 and 2 at each of the 3.25, 3.75 and 4.25 ID Levels.

Cursor position was sampled at 200 Hz according to the Cartesian pixel coordinates (Labview v8.1: National Instruments Co.). Cursor position was converted to distance offline by calculating the tangent between each subsequently sampled X, Y pixel coordinates. Pixel distance was converted to mm according to screen resolution (1280 × 1050) and display size (42.25 mm × 34.65 mm) giving a conversion factor of 3.3 pixels/mm. The resulting magnitude by time waveform was low-pass filtered at 5 Hz and used to determine: (1) time to initiate movement (time in seconds from target presentation to the first movement toward the target that exceeded 1.2 times the diameter of the target), (2) movement time (time in seconds from target appearance to the presentation of the next target, corrected for the duration of the time to initiate movement, the 500 ms stationary period and the 500 ms inter-target interval), and (3) Cumulative Distance (total distance in mm that the participant’s cursor travelled during the period of the Movement Time). All variables were extracted using custom Labview software.

Peak velocity, peak acceleration and peak deceleration of the cursor during the initial ballistic component of the movement were extracted using the same custom software. The magnitude by time waveform was differentiated once for velocity and twice for acceleration. The resulting velocity and acceleration profiles were low pass filtered at 5 Hz.

Task performance, cursor kinematics and functional ability were assessed as the change from early practice (Day 1) to the retention test (Day 5). Effect sizes were derived to determine the magnitude of change associated with preceding practice with either S1c or M1c cTBS. Effect sizes were calculated using Cohen’s d between the (1) S1c + practice vs control + practice, (2) M1c + practice vs Control and (3) S1c + practice vs M1c + practice groups and characterized as small, medium or large according to Thomas et al. [27]. Pooled sample standard deviations were used in all cases.

Mean data by group are presented in Table 2.

Effect size calculations revealed a large reduction in time to initiate movement in the S1c + practice group compared to the control + practice group ($d = 1.59$). There was also a medium sized reduction in the M1c + practice group compared to the control + practice group ($d = 0.45$). The effect was larger for the S1c + practice group compared to M1c + practice group ($d = 1.81$).

Effect size calculations for movement time reveal a different pattern of results. There was a large reduction for both the S1c + practice and M1c + practice groups compared to control + practice group ($d = 1.92$ and 1.40, respectively) but no real difference in efficacy between the S1c + practice and M1c + practice groups.

Both the S1c + practice and M1c + practice groups demonstrated a large reduction in cumulative magnitude of the distance travelled to get from one target to the next compared to the control + practice group ($d = 2.35$ and 0.95, respectively). The reduction was slightly larger for S1c + practice compared to M1c + practice ($d = 0.28$).

Effect size calculations on peak velocity revealed that both S1c + practice and M1c + practice groups demonstrated a large reduction in peak velocity from early practice to retention compared to the control + practice group ($d = 1.98$ and 2.08, respectively). This effect was slightly larger for M1c + practice compared to S1c + practice ($d = 0.26$; Table 2).

This pattern was also consistent for peak acceleration for S1c + practice and M1c + practice compared to control + practice ($d = 1.86$ and 1.69, respectively). The reduction in peak acceleration was moderately larger for M1c + practice compared to S1c + practice ($d = 0.44$).

Peak deceleration also largely decreased at retention compared to early practice in the S1c + practice and M1c + practice compared to control + practice group ($d = 1.07$ and 0.70, respectively). This effect was moderately bigger for the S1c + practice compared to the M1c + practice ($d = 0.60$).

The cumulative time to complete the selected items of the WMFT demonstrated a large decrease at retention compared to day 1 for both the S1c + practice and M1c + practice groups compared to the control + practice group ($d = 2.17$ and 0.89, respectively; Table 2). However, this effect was larger for S1c + practice compared to M1c + practice ($d = 1.47$).

In the current study, stimulation over both S1c and M1c enhanced performance of the SST compared to practice alone. However, there was dissociation in the changes driving these effects. Enhanced performance with cTBS over M1c was the result of greater changes in movement performance relating to cursor velocity and acceleration during the initial ballistic component of the movement compared to practice alone. Enhanced performance with cTBS over S1c was reflected in the time to initiate movement and cumulative magnitude of the movement compared to practice alone. Importantly, stimulation over S1c led to large changes in general functional ability, indexed by time to complete the WMFT, compared to M1c or control stimulation.

The dissociation in the effects of M1c and S1c cTBS is not surprising as M1 is generally accepted to encode aspects of movement involving force and direction [2]. Though we did not directly measure cortical excitability, theoretically cTBS over M1c may have

| Table 2 | Mean change (percent, standard error) in behavioral, kinematic and motor function. |
|---------|------------------------------|------------------------------|------------------------------|
|         | S1c + practice | Control + practice | M1c + practice |
| **Behavioral** | | | |
| Movement time | 14 (8.2) | -20 (11.8) | 14 (16.3) |
| Reaction time | 18 (3.5) | 7 (5.0) | 10 (2.0) |
| Cum. magnitude | 22 (6.7) | -8 (8.0) | 16 (18.2) |
| WMFT | 40 (18) | 5 (7.6) | 5 (2.8) |
| **Kinematic** | | | |
| Peak velocity | 17 (7.4) | -20 (14) | 21 (8.7) |
| Peak acceleration | 15 (5.7) | -26 (18.8) | 20 (6.8) |
| Peak deceleration | 10 (4.0) | -23 (25.0) | 1 (12.3) |
increased ipsilesional M1 excitability prior to practice through inter-hemispheric connections thereby enhancing control of velocity and acceleration to a greater extent than other task parameters. In contrast, initiation of movement and deceleration are likely to be reliant upon sensory processing. In particular, sensory processing relating to vision and somatosensation were also required by our experimental task to detect the target and transform the relative position into egocentric coordinates. During movement initiation and on-line error correction generating forces and assigning a movement vector are irrelevant if the relationship between current arm position/target location and/or sensory afference/motor efference is unknown or compromised. Therefore, enhancing ipsilesional somatosensory activity may benefit behavior by strengthening the connections between sensory and motor cortex directly and/or via posterior parietal-premotor pathways. In the current study, occlusion of vision of the hemiparetic arm during practice likely increased the necessity of the somatosensory system as participants could not use vision to compensate for somatosensory deficits. Visual occlusion of the hemiparetic arm may also explain why the control group demonstrated reduced performance on some parameters highlighting the benefits of cTBS over M1c and S1c in enhancing learning related gains that may be achievable in the control group given more practice.

The current results suggest that previous conflicting findings with contralesional cortical stimulation may stem in part from the focus on M1. In these studies the effects observed are likely to be task-specific and only evident if: (1) the task was dependent upon properties reflected in M1, or (2) performance was assessed using the same test employed during training. The current results suggest that changes in ipsilesional somatosensory cortical excitability may have greater potential to alter feed-forward input to multiple muscle synergies not only those directly involved in the task being practiced. In contrast, changes in ipsilesional motor cortical excitability may be more restricted to particular muscle synergies used during task practice.

The precise mechanism by which stimulation over S1c influences ipsilesional somatosensory cortex remains unclear. While the mechanism that exerts inter-hemispheric interactions between primary motor cortices is relatively well established there is limited evidence for direct transcallosal connections between the primary somatosensory cortices [16]. Combined repetitive TMS and somatosensory evoked potential studies demonstrate that there is a similar relationship between the primary somatosensory cortices in healthy individuals [20]. However, there are a number of potential mechanisms that may explain inter-hemispheric interactions between the primary somatosensory cortices. These include inter-hemispheric connections between secondary somatosensory cortices and/or cortico-thalamic projects from Layer VI to the thalamus via the thalamic reticular nucleus that may alter the properties of contralateral primary and secondary thalamic relay nuclei [18]. In addition to the inter-hemispheric mechanism, the underlying changes in ipsilesional cortex also need to be assessed. It is currently unknown whether enhanced functional ability associated with stimulation over S1c is a result of enhanced S1-M1 efficiency, SII-PMd connectivity, some combination of these two, or another as yet described inter-hemispheric interaction. Clearly, further investigation is required to elicit the exact inter-hemispheric mechanism and ipsilesional substrates by which the behavioral results associated with cTBS over S1c paired with practice may be mediated.

There are several limitations to the current study. In particular, groups were matched upon stroke severity; however, given the small sample size the control group may not be equivalent to the cTBS groups on other aspects. Further, while moderate to large effects upon task performance were observed, cause and effect need to be established. In addition, we tested individuals with both cortical and sub-cortical strokes and cannot distinguish effects associated with stroke location [1]. We also cannot characterize how stroke severity and the compensatory mechanisms employed by individuals post-stroke [21] may interact with site of stimulation. Finally, it should be noted that our measures of kinematics are based upon cursor position, not actual arm velocity. While this measure is sensitive to learning related changes in the sensorimotor control of cursor motion they may not equate directly to arm kinematics.

This preliminary report is the first to observe benefits of pairing cTBS over S1c with practice. In particular, we provide converging evidence to suggest that rehabilitation may be enhanced by interventions that seek to increase ipsilesional sensory-motor cortical excitability prior to practice to promote learning post-stroke.

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References


