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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

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Table 1
Group characteristics (mean, standard deviation).

Group	Age[a]	Gender	Stroke side	Time since stroke[b]	MOCA	UE Fugl-Meyer
S1c + practice	63 (9)	3M, 1F	2L, 2R	88 (91)	29 (0.6)	51 (12.4)
Control + practice	64 (14)	2M, 2F	2L, 2R	69 (47)	27 (1.3)	54 (8.8)
M1c + practice	65 (10)	1M, 3F	2L, 2R	66 (61)	28 (1.5)	50 (15.6)

MOCA – Montreal Cognitive Assessment; UE – upper extremity.
[a] Age in years.
[b] Time since stroke in months.

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 scoreto 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 2–4 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 Rapid^2 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 $\theta = 35°$, 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^{TM} 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 Rapid^2 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

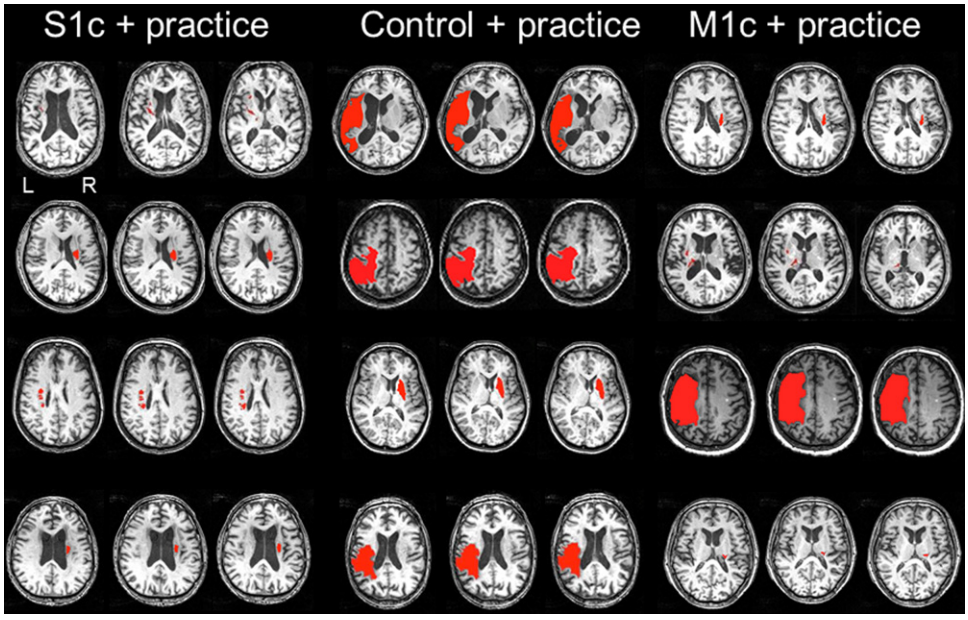

Fig. 1. Infarct location for each participant. Each row is a separate participant in each group. L – left, R – right.