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# Priming sensorimotor cortex to enhance task-specific training after subcortical stroke

Suzanne J. Ackerley [a,c], Cathy M. Stinear [b,c], P. Alan Barber [c,d], Winston D. Byblow [a,c,*]

[a] Movement Neuroscience Laboratory, Department of Sport and Exercise Science, The University of Auckland, Auckland, New Zealand
[b] Clinical Neuroscience Laboratory, Department of Medicine, The University of Auckland, Auckland, New Zealand
[c] Centre for Brain Research, The University of Auckland, Auckland, New Zealand
[d] Neurology Department, Auckland City Hospital, Auckland, New Zealand

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HIGHLIGHTS

- The effects of Theta Burst Stimulation (TBS)-primed dexterity training on sensorimotor integration, corticomotor excitability, sensation and grip-lift kinetics were examined in chronic subcortical stroke patients.
- Intermittent TBS (iTBS) of ipsilesional primary motor cortex (M1) modulated corticomotor excitability and increased M1 receptiveness to sensory input.
- Priming ipsilesional M1 with iTBS prior to upper limb therapy may facilitate sensorimotor integration and serve as a useful adjunct to improve the quality of sensorimotor training during rehabilitation after subcortical stroke.

ABSTRACT

*Objective:* This double-blind sham-controlled crossover study investigated the interactions between primary sensory and motor cortex after stroke and their response to Theta Burst Stimulation (TBS).
*Methods:* Thirteen chronic subcortical stroke patients with upper limb impairment performed standardised dexterity training primed with ipsilesional M1 intermittent TBS ($iTBS_{iM1}$), contralesional M1 continuous TBS ($cTBS_{cM1}$) or sham TBS. The effects on sensorimotor integration, corticomotor excitability, sensation and grip-lift kinetics were examined.
*Results:* After $iTBS_{iM1}$, improvements in paretic grip-lift performance were accompanied by an immediate facilitation of ipsilesional M1 excitability and a subsequent increase in ipsilesional short latency afferent inhibition (SAI) during training. Precision grip-lift performance improved after $cTBS_{cM1}$ and training, alongside increased ipsilesional M1 excitability with no effect on ipsilesional SAI. There were no effects on sensory performance.
*Conclusion:* Primary motor cortex iTBS not only modulates M1 corticospinal excitability but also increases M1 receptiveness to sensory input.
*Significance:* Priming with $iTBS_{iM1}$ may enhance ipsilesional sensorimotor integration and facilitate better quality sensorimotor training after subcortical stroke.


## 1. Introduction

Paretic upper limb impairment after subcortical stroke may be compounded by a cycle of asymmetric primary motor cortex (M1) excitability and interhemispheric inhibition, which in turn exacerbates ipsilesional M1 hypoexcitability and contralesional M1 hyperexcitability (Heald et al., 1993; Traversa et al., 1998; Shimizu et al., 2002; Murase et al., 2004; Duque et al., 2005). Repetitive transcranial magnetic stimulation (rTMS) has been used to rebalance M1 excitability in stroke patients (Takeuchi et al., 2005; Fregni et al., 2006; Talelli et al., 2007a; Di Lazzaro et al., 2008) and has been associated with better motor outcomes (for a review see Hsu et al., 2012).

Intermittent and continuous theta burst stimulation (iTBS, cTBS) are protocols of patterned rTMS (Huang et al., 2005) that

* Corresponding author. Address: Movement Neuroscience Laboratory, Centre for Brain Research, The University of Auckland, Private Bag 92019, Auckland, New Zealand. Tel.: +64 9 373 7599x86844; fax: +64 9 373 7043.
*E-mail address:* w.byblow@auckland.ac.nz (W.D. Byblow).

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can be applied to increase ipsilesional M1 excitability (Talelli et al., 2007a; Di Lazzaro et al., 2008, 2010; Ackerley et al., 2010) or decrease contralesional M1 excitability (Talelli et al., 2007a; Di Lazzaro et al., 2008), respectively. Suppressive rTMS of contralesional M1 may facilitate ipsilesional M1 excitability by reducing transcallosal inhibition from contralesional to ipsilesional M1 (Kobayashi et al., 2004; Takeuchi et al., 2005). However it is becoming evident that cTBS effects on M1 excitability are more variable than iTBS effects (Ackerley et al., 2010; Martin et al., 2006; Gentner et al., 2008). Despite this, in patients with upper limb impairment at the chronic stage after subcortical stroke, both ipsilesional M1 iTBS and contralesional M1 cTBS can improve grip-lift performance when combined with dexterity training with the paretic hand (Ackerley et al., 2010).

During rehabilitation after stroke, sensorimotor training produces afferent input to M1, which shapes and focuses descending commands (Kaelin-Lang et al., 2005). Impairments in sensorimotor integration during prehension have been observed after subcortical stroke (McDonnell et al., 2006). These impairments arise through deficient motor control and somatosensory deficits (Johansson and Westling, 1984; Nowak et al., 2001; Smania et al., 2003; Blennerhassett et al., 2007). Abnormal sensorimotor integration is common in patients with lesions involving sensorimotor cortex, basal ganglia or the cerebellum (Wiesendanger and Serrien, 2001; Sailer et al., 2003; Oliviero et al., 2005; McDonnell et al., 2006; Di Lazzaro et al., 2012). Here we investigated whether TBS makes M1 more receptive to sensory input during sensorimotor training by measuring TBS after effects on short latency afferent inhibition (SAI) (Tokimura et al., 2000).

The aim of this study was to elucidate the neurophysiological mechanisms that contribute to improvements in prehension after TBS-primed dexterity training. We applied iTBS to ipsilesional M1 ($iTBS_{iM1}$), cTBS to contralesional M1 ($cTBS_{cM1}$) or sham TBS in separate sessions. Based on previous findings (Ackerley et al., 2010), we expected that real but not sham TBS combined with dexterity training with the paretic hand would improve grip-lift kinetics. We hypothesised that ipsilesional M1 excitability would be directly facilitated by $iTBS_{iM1}$, but that the $iTBS_{iM1}$ and $cTBS_{cM1}$ protocols would have differential effects on ipsilesional sensorimotor integration evident in SAI.

## 2. Methods

### 2.1. Participants

Thirteen adults with persistent upper limb impairment after first-ever subcortical stroke at least 6 months previously participated in this double-blind, sham-controlled, cross-over study. Volunteers were excluded if they had contraindications to TMS, were on medications that interfered with the interpretation of the neurophysiological results, had motor evoked potential (MEP) amplitudes less than 0.05 mV in the paretic first dorsal interosseous muscle (FDI), or had moderate or severe sensory loss of the paretic arm (National Institutes of Health Stroke Scale (NIHSS) sensory subscale > 1). Written informed consent was provided by all participants and the study was approved by the regional ethics committee in accordance with the Declaration of Helsinki (1964).

Participants attended an introductory session where clinical assessments were performed (Table 1), and sensory and precision grip assessments, and the Action Research Arm Test (ARAT, maximum 57) (Lyle 1981) of the nonparetic upper limb were completed. FDI MEPs were examined to determine the interstimulus interval (ISI; 25, 30, or 40 ms) that produced the most SAI in the contralesional M1 (i.e. optimal ISI), using the paired pulse methods described below.

### 2.2. Experimental sessions

The three experimental sessions were randomised, counterbalanced and separated by at least 1 week (see Fig. 1 for a flowchart of the experimental procedures). Each session consisted of a TBS

**Table 1**
Participant Characteristics.

| No. | Sex | Age (years) | Time since stroke (months) | NIHSS (max 42) | NIHSS sensory subscale | FM (max 66) | mRS | ASH | Hand | 9HT (sec/peg) | Hemi | Type | Affected structures | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | BG | Capsule | Other |
| 1 | M | 61 | 34 | 4 | 1 | 53 | 2 | ⩽1 | L | 1.92 | L | I | | Cr | |
| 2[a] | M | 83 | 17 | 2 | 0 | 44 | 4 | 0 | R | >60 | L | I | | Int | |
| 3 | M | 58 | 22 | 2 | 0 | 37 | 2 | ⩽3 | R | 20.0 | R | H | Ca, Pu | Int | |
| 4 | F | 68 | 7 | 2 | 0 | 51 | 1 | 0 | R | 1.69 | R | I | Th | Cr | |
| 5 | M | 70 | 6 | 5 | 0 | 28 | 3 | ⩽3 | R | >60 | R | I | | | Pontine |
| 6 | F | 71 | 41 | 4 | 1 | 27 | 2 | ⩽3 | R | >60 | R | H | | Int | |
| 7[b] | F | 78 | 54 | 6 | 1 | 55 | 3 | 0 | R | >60 | R | I | | | |
| 8 | M | 56 | 32 | 3 | 0 | 53 | 2 | 0 | R | 2.40 | L | I | | Cr | |
| 9 | F | 65 | 36 | 4 | 1 | 42 | 2 | ⩽2 | R | 7.50 | R | I | | | MCA territory |
| 10 | F | 69 | 11 | 5 | 1 | 25 | 4 | ⩽3 | R | >60 | R | I | | | MCA territory |
| 11 | F | 79 | 6 | 4 | 0 | 46 | 2 | 0 | R | >60 | R | I | | Cr | SCWM |
| 12[c] | M | 68 | 32 | 3 | 0 | 31 | 1 | ⩽1 | L | 30.0 | L | H | | | |
| 13[b] | M | 31 | 7 | 3 | 0 | 54 | 2 | 0 | R | 1.90 | R | I | | | SCWM |
| Mean | | **69** | **23** | **4** | | **41** | **2** | | | | | | | | |
| SD | | **8** | **16** | **1** | | **11** | **1** | | | | | | | | |
| Max | | **83** | **54** | **6** | | **55** | **4** | | | | | | | | |
| Min | | **56** | **6** | **2** | | **25** | **1** | | | | | | | | |

NIHSS sensory subscale (normal = 0, mild/moderate sensory loss = 1). FM = Fugl-Meyer upper limb score. mRS = modified Rankin Score. ASH = Modified Ashworth Scale tested in paretic biceps brachii, wrist and finger flexors. 9HT = Nine hole peg test. Hand = handedness prior to stroke. Hemi = hemisphere affected by the stroke. Type (Ischaemic/Haemorrhagic). Affected Structures: BG = basal ganglia; Pu = putamen; Th = thalamus; Ca = caudate; Cr = Corona radiata; Int = internal capsule. MCA territory = Middle cerebral artery territory; SCWM = Subcortical white matter.

[a] This patient had a longstanding arthritic condition affecting both hands.
[b] Unable to access CT scans.
[c] Patient did not complete all sessions, data not included in summary statistics.