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Inter-subject Variability of LTD-like Plasticity in Human Motor Cortex: A Matter of Preceding Motor Activation

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ABSTRACT

Background: Continuous theta burst stimulation (cTBS) of the human primary motor cortex (M1) induces long-term depression (LTD)-like plastic changes in corticospinal excitability, but several studies have reported high inter-subject variability of this effect. Most studies use a tonic voluntary contraction of the target muscle before cTBS to set stimulation intensity; however, it is unclear how this might affect response variability.
Objective: To examine the influence of pre-activation of the target hand muscle on inter-subject response variability to cTBS of the human M1.
Methods: The response to cTBS was assessed by changes in motor evoked potential (MEP) amplitude in the right first dorsal interosseous (FDI) muscle. For Study 1, ten healthy subjects attended two sessions. They were instructed in one session to keep their FDI relaxed for the entire testing period (pre-relax), and in the other to perform a 2-min 10% of maximal voluntary tonic contraction 15 min before cTBS (pre-active). For Study 2, data from our previous study were re-analyzed to extend the pre-relax condition to an additional 26 subjects (total $n = 36$).
Results: cTBS-induced highly consistent LTD-like MEP depression in the pre-relax condition, but not in the pre-active condition. Inter-subject response variability increased in the pre-active condition.
Conclusions: cTBS induces consistent LTD-like plasticity with low inter-subject variability if pre-activation of the stimulated motor cortex is avoided. This affirms a translational potential of cTBS in clinical applications that aim at reducing cortical excitability.

Introduction

The strength of synaptic transmission in the human cortex is adaptable, undergoing constant change in an activity-dependent manner. This plasticity is important for learning and memory, as well as recovery from neurological damage, and has been the focus of considerable research. Numerous non-invasive brain stimulation (NIBS) techniques [1] have been developed that are capable of inducing short-term plasticity in the human cortex that can interact with and modify behavior [2,3]. This raises the possibility that such techniques may be useful as therapeutic tools for neurological and psychiatric disorders [4].

One NIBS technique that has gained much recent interest is theta burst stimulation (TBS), a patterned repetitive transcranial magnetic stimulation (rTMS) paradigm consisting of repeated bursts of high-frequency, sub-threshold magnetic stimuli. When applied to the human primary motor cortex (M1), TBS induces changes in corticospinal excitability that are either facilitatory when applied as intermittent TBS (iTBS), or inhibitory when applied as continuous TBS (cTBS) [2]. There is evidence that these after-effects are NMDA receptor-dependent [5,6] and occur at the level of the cortex [7,8], and are therefore likely to reflect long-term potentiation (LTP) and long-term depression (LTD)-like plastic changes in M1.

The short application times and low stimulation intensity requirements of TBS make it more suitable for patient populations than other currently available options. However, a major limitation

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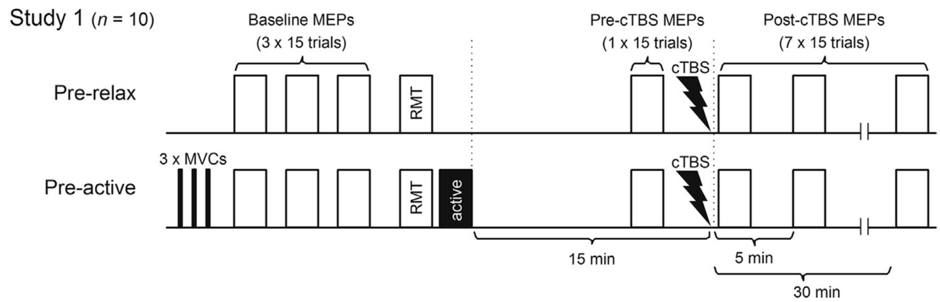

Figure 1. Experimental design of Study 1. Open rectangles designate blocks of 15 MEP recordings, measured using single-pulse TMS. 15 min prior to cTBS application in the pre-active condition, subjects performed a 2-min contraction of their right FDI (black filled rectangle) at 10% of maximal voluntary contraction (MVC). RMT, determination of resting motor threshold.

of TBS is the high inter-subject response variability [9]. There are likely many factors that lead to this variability, one of which being the history of synaptic activity in the targeted cortical region [10]. In animal experiments, prior synaptic activity can interact with subsequent LTP/LTD induction [11,12]. Similarly, in humans, NIBS-induced plasticity in M1 is modulated when the motor regions are voluntarily engaged prior to stimulation, either by phasic [13] or tonic [14,15] contraction of the targeted hand muscle. Despite this, few studies using NIBS have controlled the activation history of the target muscle. Indeed, in many studies a tonic voluntary contraction of variable duration is employed prior to TBS to establish active motor threshold (AMT), which is then subsequently used to set stimulation intensity [2,8,9].

The present investigation examined the influence that pre-activation of the target hand muscle has on the inter-subject variability of plastic responses to cTBS of the human M1. We also present a meta-analysis incorporating data collected as part of our previous study [16] to demonstrate, in a relatively large sample, the consistency of subject responses to cTBS in the absence of pre-activation.

Material and methods

Subjects

A total of 36 healthy subjects (33 right-handed and three left-handed; 15 females) aged 19–49 [24.0 ± 5.6 years (mean ± SD)] were included in this study. All subjects were screened for contraindications to TMS [17] and gave informed written consent prior to enrollment. All experiments were performed in accordance with the 2008 Declaration of Helsinki, and were approved by the University of Adelaide Human Research Ethics Committee and the ethics committee of the medical faculty of the Goethe-University of Frankfurt am Main.

Experimental design

This research consisted of two studies. Study 1 was performed in a subset of 10 subjects (five females; 22.8 ± 4.4 years) to test the impact that pre-activation of the target hand muscle [i.e., the right first dorsal interosseous (FDI) muscle] has on the response to cTBS (Fig. 1). Subjects participated in two sessions separated by at least one week. In one session, subjects were instructed to keep their right FDI relaxed for the entire testing period (i.e., pre-relax condition), whereas in the other session, they performed a 2-min 10% of maximal voluntary tonic contraction (MVC) of their right FDI prior to cTBS (i.e., pre-active condition) (see Voluntary contraction section below). The interval between the contraction and cTBS was 15 min, consistent with the interval used in a recent study demonstrating large inter-subject response variability to cTBS [9]. The order of sessions was randomized between subjects, with six subjects tested with pre-relax first, and four tested with pre-active first.

Study 2 was a meta-analysis combining the pre-relax condition of Study 1 with data collected as part of a previous investigation in 26 subjects [16]. For all 36 subjects, the response to cTBS was tested in the absence of prior motor activity, and was measured using a standardized protocol (see Quantification of cTBS effects section). All experiments were performed in the afternoon to control for possible time-of-day effects on plasticity induction [18].

Stimulation and recording procedures

Subjects were seated in a comfortable chair at the beginning of each session, and were asked to relax their right arm and hand. Surface electromyography was recorded from the right FDI using two Ag/AgCl electrodes arranged in a belly-tendon montage and sampled at 5 kHz (Cambridge Electrical Design 1401, Cambridge, UK). Signals were amplified (×1000) and band-pass filtered between 20 and 1000 Hz (Cambridge Electrical Design 1902 amplifier, Cambridge, UK) or 2000 Hz (Counterpoint Mk2 electromyograph, Dantec, Denmark), before being stored on a computer for offline analysis. Background surface electromyography was monitored throughout the entire testing period to ensure complete relaxation of subjects' right FDI.

Single-pulse TMS with monophasic waveform was applied to the left M1 to elicit motor evoked potentials (MEPs) in the right FDI. Stimuli were applied using a figure-of-eight magnetic coil (external wing diameter, 90 mm) connected to a Magstim 200 magnetic stimulator (Magstim, Whitland, UK). The coil was positioned tangentially to the skull, with the handle pointing posterolaterally at a 45° angle to the sagittal plane (i.e., posterior–anterior current flow across M1). The hand representations of the left M1 were identified using a marginally supra-threshold stimulus intensity, and the optimal position for activating the right FDI was marked on the subject's scalp using a felt marker. TMS intensity was adjusted to evoke baseline MEPs with peak-to-peak amplitudes around 1 mV; this intensity (SI_{1mV}) was used for all subsequent MEP recordings. MEPs were recorded in blocks of 15 trials, with an inter-trial interval of 7 s (±10%). Trials contaminated with background muscle activation during the 100 ms prior to TMS were excluded from analysis (less than 5% of all trials).

Continuous theta burst stimulation (cTBS)

cTBS was applied with biphasic waveform (posterior–anterior/anterior–posterior current flow) using either Magstim Super Rapid (Magstim) (Experiments 1 and 2) or MagPro X100 (MagVenture, Farum, Denmark) (Experiment 2 only) magnetic stimulators. The