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Probing changes in corticospinal excitability following theta burst stimulation of the human primary motor cortex

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HIGHLIGHTS

- Plasticity responses to continuous and intermittent theta burst stimulation (cTBS, iTBS) were assessed using MEP input/output curves.
- Long-term depression-like response to cTBS was greatest when probed using high stimulus intensities.
- Long-term potentiation-like response to iTBS was greatest when probed using low stimulus intensities.

ABSTRACT

Objective: To determine whether the intensity of transcranial magnetic stimulation (TMS) used to probe changes in corticospinal excitability influences the measured plasticity response to theta burst stimulation (TBS) of the human primary motor cortex.
Methods: Motor evoked potential (MEP) input/output (I/O) curves were recorded before and following continuous TBS (cTBS) (Experiment 1; $n = 18$) and intermittent TBS (iTBS) (Experiment 2; $n = 18$).
Results: The magnitude and consistency of MEP depression induced by cTBS was greatest when probed using stimulus intensities at or above 150% of resting motor threshold (RMT). In contrast, facilitation of MEPs following iTBS was strongest and most consistent at 110% of RMT.
Conclusions: The plasticity response to both cTBS and iTBS is influenced by the stimulus intensity used to probe the induced changes in corticospinal excitability.
Significance: The results highlight the importance of the test stimulus intensity used to assess TBS-induced changes in corticospinal excitability when interpreting neuroplasticity data, and suggest that a number of test intensities may be required to reliably probe the plasticity response.

1. Introduction

A number of non-invasive brain stimulation (NIBS) techniques have been developed that provide significant opportunities to gain novel insights into human brain function. In particular, techniques such as transcranial magnetic stimulation (TMS) can be used not only to test the excitability of cortical networks, but also to modulate excitability in a bidirectional and reversible manner when applied in trains of repetitive stimuli (i.e., repetitive TMS; rTMS) (Vallence and Ridding, 2014). The changes in excitability induced by rTMS are likely due to processes similar to the long-term potentiation (LTP) and long-term depression (LTD) described in animal models (Huang et al., 2007; Teo et al., 2007), which are key neural mechanisms involved in learning and memory (Cooke and Bliss, 2006). As a result, rTMS is useful for probing human cortical plasticity and may be of potential therapeutic benefit in a range of different neurological and psychiatric disorders (Ridding and Rothwell, 2007).

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Conventional rTMS approaches involve a constant rate of stimulation, with low frequencies (⩽1 Hz) reducing cortical excitability (Chen et al., 1997) and high frequencies (⩾5 Hz) increasing cortical excitability (Berardelli et al., 1998). More recently, however, patterned protocols such as theta burst stimulation (TBS) have been developed which require less stimulation time and lower stimulation intensities than conventional rTMS protocols. Consisting of repeated bursts of high-frequency subthreshold magnetic stimuli, TBS can either depress (when applied as continuous TBS; i.e., cTBS) or increase (when applied as intermittent TBS; i.e., iTBS) cortical excitability (Huang et al., 2005). Although the initial report of TBS demonstrated long-lasting and robust changes, emerging evidence suggests these effects can vary considerably between individuals (for example, Hamada et al., 2013).

When applied to the human primary motor cortex (M1), the plasticity induced by TBS is usually quantified by recording a change in the electromyographic (EMG) response to single-pulse TMS (i.e., the motor evoked potential; MEP) from peripheral muscles. Most studies measure MEPs from a single TMS intensity to probe the plasticity response to TBS, typically using an intensity sufficient to evoke MEPs at baseline with peak-to-peak amplitudes of ~1 mV (SI_{1mV}) (Gentner et al., 2008; Hamada et al., 2013; Huang et al., 2007). However, given that MEP amplitudes are highly variable between subjects, using this arbitrary value potentially results in test MEPs being used that fall on different parts of the input/output (I/O) curve (Burke and Pierrot-Deseilligny, 2010; Pitcher et al., 2015). Therefore, this approach may potentially add to the inter-subject variability of the TBS response. To date, the potential importance of the stimulus intensity used to probe changes in MEPs following TBS has not been investigated systematically.

Generating I/O curves by applying TMS at a range of stimulus intensities can provide a sensitive measure of corticospinal excitability (Devanne et al., 1997; Ridding and Rothwell, 1997; Vallence et al., 2012). Here, we constructed I/O curves before and following cTBS and iTBS (assessed on separate occasions), to determine the range of test stimulus intensities that provide the most sensitive and reliable measure of TBS-induced plasticity.

2. Methods

2.1. Subjects

A total of 27 right-handed subjects (16 females) aged from 18 to 32 years (mean ± SEM: 22.1 ± 0.7 years) participated in this study, which consisted of two experiments: Experiment 1 examined the response to cTBS (18 subjects, including 11 females; mean age 22.7 ± 1.0 years), and Experiment 2 examined the response to iTBS (18 subjects, including 10 females; mean age 22.1 ± 1.0 years). Nine subjects participated in both experiments. This study was performed in accordance with the Declaration of Helsinki and approved by the University of Adelaide Human Research Ethics Committee. All subjects gave informed written consent prior to testing and were screened for any contraindications to TMS (Rossi et al., 2009).

2.2. Stimulation and recording

Surface EMG was recorded from the relaxed right first dorsal interosseous (FDI) using two Ag/AgCl electrodes arranged in a belly-tendon configuration. EMG activity was amplified with a gain of 1000, band-pass filtered between 20 and 1000 Hz (Cambridge Electrical Design 1902 amplifier, Cambridge, UK), and digitised at a sampling rate of 5 kHz (Cambridge Electrical Design 1401, Cambridge, UK).

Single-pulse TMS was applied with monophasic waveform using a figure-of-eight coil (90 mm external wing diameter) connected to a Magstim 200 magnetic stimulator (Magstim, Whitland, UK). The coil was positioned over the left M1 tangential to the scalp, with the handle pointing posterolaterally at a 45° angle to the sagittal plane (i.e., posterior–anterior current flow across M1). Stimuli were applied systematically to different scalp locations using a suprathreshold stimulus intensity to identify the optimal site for consistently evoking MEPs in the relaxed FDI. Once located, this site was marked on the scalp using a felt marker, and resting motor threshold (RMT) was determined. RMT was defined as the minimum stimulus intensity (expressed as percentage of maximum stimulator output; MSO) required to elicit an MEP in the relaxed FDI with peak-to-peak amplitude >50 μV in at least 5 out of 10 consecutive trials.

2.3. Theta burst stimulation

TBS was applied with biphasic waveform (posterior–anterior/anterior–posterior current flow) using an air-cooled figure-of-eight coil connected to a Magstim Super Rapid magnetic stimulator (Magstim, Whitland, UK). The pattern consisted of short bursts of three stimuli at 50 Hz, repeated at a frequency of 5 Hz. For cTBS (Experiment 1), this pattern of stimuli was applied as a continuous 40-s train, whereas for iTBS (Experiment 2), bursts of stimuli were applied for 2 s at 10-s intervals for a total duration of 190 s (Huang et al., 2005). Stimulation intensity was set to 70% of RMT (Gentner et al., 2008; Goldsworthy et al., 2014a, 2012a), which was assessed just prior to TBS application using the same coil and biphasic pulse waveform.

2.4. Input/output curves

I/O curves were constructed using monophasic single TMS pulses applied at 10 different stimulus intensities between 90% and 180% RMT (inclusive), with increments of 10% RMT. Stimulus intensities were determined at baseline for each experiment and remained constant for all I/O curve measurements. For each I/O curve, eight stimuli were delivered at each intensity in a pseudo-randomised order, using an interstimulus interval of 5 s (±10% variance). The time taken to obtain each curve was ~7 min. Curves were measured at five time periods during each experiment: twice at baseline (B1 and B2), and during the periods 0–7, 15–22, and 30–37 min post-TBS (P1, P2, and P3, respectively) (Fig. 1). EMG activity was monitored at all times post-TBS in both experiments to ensure complete relaxation of the right FDI and minimise the influence of voluntary contraction on the TBS response (Goldsworthy et al., 2014b; Huang et al., 2008).

2.5. Data analysis

Statistical analyses were performed with IBM SPSS Statistics 20 (IBM SPSS, Armonk, NY, USA). Identical analyses were performed in parallel for cTBS (Experiment 1) and iTBS (Experiment 2) data.

Peak-to-peak MEP amplitudes were calculated for each trial; those contaminated with background EMG activity during the 200 ms prior to TMS were excluded from analysis. Mean MEP amplitudes were calculated for each stimulus intensity at each time period. To test for differences between the two I/O curves obtained at baseline, two-way repeated measures ANOVA (RM-ANOVA) with within-subject factors TIME (2 levels: B1 and B2) and INTENSITY (10 levels: 90, 100, 110, 120, 130, 140, 150, 160, 170, 180% RMT) were performed on raw MEP amplitudes. Since there were no significant differences between baseline curves in either Experiment (see Section 3), the two baseline I/O curves were averaged. The maximum mean MEP amplitude

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