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The effect of single and repeated prefrontal intermittent theta burst stimulation on cortical reactivity and working memory

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ABSTRACT

Background: With an increasing interest in the use of theta burst stimulation (TBS) as a cognitive enhancer and a potential therapeutic tool for psychiatric disorders, there is a need to identify optimal parameters of TBS in the prefrontal cortex.
Objective/Hypothesis: This study examined the effect of two blocks of prefrontal intermittent TBS (iTBS) on cortical reactivity and working memory performance, compared to one block of iTBS and sham stimulation. We hypothesized that greater cortical effects would be obtained with two blocks of iTBS.
Methods: Eighteen healthy participants attended three experimental sessions and received either sham, one block or two blocks of iTBS with a 15-min interval. Concurrent transcranial magnetic stimulation with electroencephalography (TMS-EEG) was used to assess the change in cortical reactivity via TMS-evoked potentials. Working memory performance was assessed using the N-back task. Cluster-based permutation statistics and two-way ANOVAs were used for neurophysiological and behavioural data, respectively.
Results: Both single and two blocks of iTBS resulted in a significant increase in the amplitude of TMS-evoked N100 and P200. No significant differences were observed between active conditions in either neurophysiological changes or working memory performance, and both failed to improve working memory performance relative to sham.
Conclusions: Two blocks of iTBS did not result in stronger measured effects as compared to one block of iTBS. Future studies are needed to identify the optimal stimulation pattern in order to achieve a desired effect. It is also important to establish the best approach in quantifying neuromodulatory effects targeting the prefrontal cortex.

Introduction

Transcranial magnetic stimulation (TMS) is a non-invasive technique used to study the physiology of the human brain. Theta-burst stimulation (TBS) is one TMS paradigm, which has a major advantage over conventional repetitive TMS due to its short stimulation duration (20–192s vs > 20min). An intermittent pattern of TBS (iTBS; 2s on, 8s off, 600 pulses) increases the amplitude of motor-evoked potentials (MEPs), while a continuous pattern of TBS (cTBS, 600 pulses) results in the opposite outcome [1]. Efforts have been made to understand the mechanisms involved in the neuroplastic responses to TBS and to enhance the efficacy of TBS in the motor cortex by varying the parameters of stimulation such as intensity [2], frequency [3,4] and number of pulses [5–7]. Studies have found additive after-effects following repeated applications of cTBS [6] and iTBS [7]. However, these dose-dependent findings are not consistent, and reduced [8] or even the opposite effects [5] have been reported depending on the duration of the interval between each block. These findings suggest the

Abbreviations: Ag/AgCl, silver-silver chloride; EEG, electroencephalography; ERP, event-related potential; FDI, first dorsal interosseous; ICA, independent component analysis; LICI, long-interval intracortical inhibition; MEP, motor evoked potential; MNE, minimum norm estimates; rMT, resting motor threshold; SH, sham; SNR, signal-to-noise ratio; (c/i) TBS, (continuous/intermittent) theta burst stimulation; TEP, TMS-evoked potential; TMS, transcranial magnetic stimulation.

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after-effects of TBS may not simply be accumulative. Beyond the motor cortex, there is a paucity of information on the neurophysiological basis of the effects of TBS and the impact of different stimulation parameters on the after-effect. Studies have reported that TBS to the prefrontal cortex can affect cognitive function. For example, prefrontal iTBS has resulted in enhanced working memory performance [9], whereas cTBS has resulted in the opposite outcome [10]. However, such findings are also inconsistent with limited behavioural changes [11,12]. It remains to be determined if repeated application of TBS would promote physiological changes in a dose-dependent manner in the prefrontal cortex, and whether such changes would also result in concurrent behavioural outcomes.

TBS-induced changes in the prefrontal cortex can be probed using concurrent TMS and electroencephalography (TMS-EEG) by examining the changes in TMS-evoked potentials (TEPs) [13]. For instance, iTBS to the prefrontal cortex increases the amplitude of the TMS-evoked N100 [13].

In the present study, we examined whether there were differences in the effects of repeated iTBS stimulation blocks applied to the left prefrontal cortex on cortical reactivity and working memory performance. The experimental procedure involved comparing the effect of two blocks (600 pulses x 2, 15-min interval) of prefrontal iTBS to one block (600 pulses) and sham stimulation on TEPs. The impact of iTBS on working memory performance and task-related electrophysiology (event-related potentials (ERPs)) were also examined. We hypothesized that greater changes in these measures would be obtained with the repeated stimulation blocks/increased number of pulses, and lead to improved working memory performance compared to the application of a single iTBS block or sham stimulation.

Material and methods

Participants

Eighteen healthy subjects volunteered (25.6 ± 7.0 years, 10 female) in the study. All subjects were right-handed according to the Edinburgh Handedness Inventory [14], and average education duration was 16.5 ± 2.3 years. Prior to the experiment, volunteers provided informed consent and were screened with the mini international neuropsychiatric interview (MINI) to confirm no history of mental illness [15]. The experimental procedures were approved by the Alfred Hospital and Monash University Human Research Ethics Committees.

Procedure

Each participant attended 3 sessions with each session at least 1 week apart to avoid carry-over effect. Stimulation conditions were pseudorandomized. The experimental procedures consisted of concurrent recording of EEG during 50 single TMS pulses before (baseline; BL), 5-min post (T5) and 30-min post (T30) iTBS in the prefrontal cortex. Subjects received either sham stimulation (sham iTBS + sham iTBS; SH + SH), a single block of iTBS (sham iTBS + iTBS 600; SH + iTBS) or two blocks of iTBS (iTBS 600 + iTBS 600; iTBS + iTBS) with 15-min interval between each block of iTBS (Fig. 1A). This interval was chosen based on studies that demonstrated the additive effects of TBS when reapplied after 15 min in animals [16] and humans [7,17]. Discomfort level was assessed using 10 cm length numerical rating scale (0: No pain–10: Worst pain) before the first block of iTBS (at BL) and immediately after the second block. The N-back working memory task (2-back and 3-back) was performed before (BL), 15-min post (T15) and 40-min post (T40) iTBS while EEG was recording. Alertness was also measured using 10 cm numerical rating scale (0: Alert–10: Vague) at BL and T40 following working memory tasks to assess attention level.

Transcranial magnetic stimulation

Biphasic TMS pulses (AP-PA current direction in the underlying cortex) were delivered using a figure-of-eight MagVenture B-65 fluid-cooled coil (MagVenture A/S, Denmark) for both single-pulse TMS and iTBS. Resting motor threshold (rMT) was obtained from left motor cortex and identified as the minimum intensity needed to evoke at least 3 out of 6 motor evoked potentials (MEPs) > 0.05 mV in amplitude [18] recorded from the first dorsal interosseous muscles using Ag/AgCl electromyography electrodes. TMS was administered to the left prefrontal cortex at the F1 electrode with the coil positioned at 45° angle relative to midline. This electrode was chosen to minimize the activation of scalp muscles [19], and hence reduce the need for the amount of correction in post-processing of the TMS-EEG data. The edge of the coil was marked on the cap for reliable repositioning of the coil (~5 mm) as has been described as a suitable method when neuronavigation is unavailable [19].

50 single pulses with a 5s interval (10% jitter) were applied to the same left prefrontal region at 120% rMT before and after spaced iTBS. Studies have shown reliable TMS-evoked responses with 50 TMS pulses at supra-threshold intensities [13,20] and a high signal-to-noise ratio (SNR) was obtained particularly for latter peaks (N100 and P200) [13]. Each iTBS block consisted of a burst of 3 pulses (20 ms interval) repeated every 200 ms for 2s with an 8s break for a total of 600 pulses, given at an intensity of 75% rMT. The rMT was measured on each session, and the average intensity for each condition was as follows: SH + SH: 54.28 ± 6.5%; SH + iTBS: 54.39 ± 6.6%; and iTBS + iTBS: 54.33 ± 6.9%. The rMT for each individual at each session can be found in Supplementary Material, Table S1. The average of coefficient of variation for rMT between session was 1.14% (range: 0–3.03%). For sham iTBS, the coil was rotated 90° around the handle so that the right wing was touching the F1 electrode. In this position, the magnetic field is tangential to the scalp and does not result in cortical stimulation.

Working memory performance (N-back tasks)

Participants performed 5min of both the 2-back and 3-back task in a pseudorandomised (e.g. either 2-back followed by 3-back or vice versa) at three time points during each experimental session. A random series of white letters from A to J were presented for 500 ms every 2000 ms on a black screen in a consecutive manner. Participants were required to respond with a button press when the presented letter corresponded to the letter that appeared either 2 (Fig. 1B) or 3 trials before (Fig. 1C). Each task contained 130 trials with 25% targets. Working memory performance was assessed using *d* prime (*d*') and accurate reaction time. *d*' quantifies performance with regards to hits and false alarms (*d*' = *Z* (hit rate)–*Z* (false alarm rate)) [21].

EEG recording and data preprocessing

A detailed procedure for the recording and preprocessing of the EEG data can be found in Supplementary Material, Methods section 1 & 2. Briefly, EEG was recorded using 48 TMS-compatible Ag/AgCl electrodes on a 64-channel EEG cap, referenced to CPz and grounded to FPz. The sampling rate for TMS-EEG and N-back task were 10,000 Hz and 1000 Hz, respectively. Electrode impedance was kept below 5 kΩ and white noise was used to mask TMS click sound.