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Original Articles

Inter- and Intra-individual Variability Following Intermittent Theta Burst Stimulation: Implications for Rehabilitation and Recovery

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ABSTRACT

Background: The continued refinement of non-invasive brain stimulation (NBS) techniques is indicative of promising clinical and rehabilitative interventions that are able to modulate cortical excitability. Intermittent theta burst stimulation (iTBS) is one such technique that can increase cortical excitability, purportedly via LTP-like mechanisms. While iTBS may have the capacity to promote recovery after neurological injury, and to combat cognitive and motor decline, recent reports observed highly variable effects across individuals, questioning the efficacy of iTBS as a clinical tool.
Objective: The aim of this study was to examine intra-individual reliability and inter-individual variability in responses to iTBS.
Methods: Thirty healthy participants completed two experimental sessions of the iTBS protocol 1–3 weeks apart. Motor evoked potentials in response to single pulse TMS were used to assess corticospinal excitability prior to, and up to 36 min following, iTBS.
Results: At the group level, iTBS evoked statistically significant increases in motor cortical excitability across both sessions ($P < 0.001$), with 22 out of 30 participants exhibiting increases in excitability in both sessions. A strong intraclass correlation demonstrated that both the direction, and magnitude of the plastic changes were reliable at the individual level.
Conclusions: Overall, our results suggest that iTBS is capable of inducing relatively robust and consistent effects within and between young individuals. As such, the capacity for iTBS to be exploited in clinical and rehabilitative interventions should continue to be explored.

Introduction

The human brain has the capacity to undergo adaptive modification to external environmental change and to reorganize itself in response to physiological degeneration or damage [1,2]. The development of techniques that are capable of augmenting cortical plasticity therefore have the potential to help combat motor and cognitive decline associated with normal aging [3]. Furthermore, such techniques may play a critical role in promoting recovery of function after brain injury [4]. Accordingly, the number of studies utilizing non-invasive brain stimulation (NBS) techniques to induce cortical plasticity within the human motor cortex has dramatically increased [5,6].

One type of NBS that has been purported to result in robust changes in cortical excitability is theta burst stimulation (TBS) [5]. TBS is a variant of repetitive transcranial magnetic stimulation (rTMS) that uses high frequency, sub-threshold bursts of stimulation. TBS is an appealing technique for application in clinical populations as it requires less stimulation time and lower stimulation intensity than traditional rTMS protocols [5]. Huang et al. [5] reported that intermittent TBS (iTBS) elicited an increase in the amplitude of motor evoked potentials (MEPs) – indicative of increases in cortical excitability – that persisted beyond the period of stimulation, while continuous TBS (cTBS) was found to significantly

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depress MEP size following stimulation. The authors described the effects, observed in a group of nine healthy individuals, as controllable, consistent, long-lasting and powerful. As the effects of TBS appeared to be larger, and somewhat less variable, than standard rTMS protocols [7], it was inferred that TBS may be a promising alternative for eliciting plastic change within the corticospinal network. A number of studies have since replicated Huang and colleague's results by demonstrating that, averaged across a group of participants, iTBS results in long-term potentiation (LTP)-like plasticity and increases MEP amplitude, while cTBS causes long-term depression (LTD)-like plasticity [6,8–12].

However the belief that such techniques are able to induce consistent, robust and relatively long-lasting changes in cortical excitability has recently been brought into question by a number of studies that have failed to observe the anticipated plasticity-inducing effects (across a group of participants) for both cTBS [13,14] and iTBS [14]. Furthermore, in the first of the experiments reported within Todd et al. [15] cTBS was observed to have a modulatory effect on excitability; however in another series of experiments within the same paper cTBS and iTBS did not significantly modulate excitability.

It seems plausible that the relatively small sample sizes (generally $n < 15$) common across the TMS literature, combined with an emphasis on statistical significance [16–18], rather than interpretation of the magnitude of effects, has contributed to these somewhat disparate reports. Cumming [19] noted that interpretation of confidence intervals, rather than *P*-values, appears to be a better way of interpreting results across studies. Indeed, with small sample sizes confidence intervals are generally wide (low precision) such that two studies can have substantially different *P*-values, one 'significant' and the other 'non-significant,' yet their results may be entirely consistent as reflected by a large overlap of 95% confidence intervals [19]. From this perspective apparent discrepancies among studies may be more illusory than real. Another possibility, not mutually exclusive from the above scenario, is that intrinsic variability within the technique for assessing change in plasticity (i.e., single pulse TMS) may result in some disparity between different studies' conclusions with regard to the efficacy of TBS for inducing plastic changes.

Alongside the aforementioned inconsistency of TBS group effects, recent studies have also reported highly variable responses within groups of participants to both TBS [14,15] and other NBS protocols (e.g. paired-associative stimulation, PAS [20]). Hamada et al. [14] reported that responses to both iTBS and cTBS were highly variable across a group of 52 individuals and, at the group level, neither form of stimulation elicited significant changes in corticospinal excitability. Moreover, a high proportion of the individuals exhibited excitability changes in the opposite direction to those that would be expected according to our current understanding of LTP- and LTD-like plasticity inducing protocols of iTBS and cTBS, respectively [5].

Such variability between individuals can be seen as problematic in regard to the potential efficacy of a TBS paradigm for inducing plastic changes, e.g. as an intervention to improve motor or cognitive function across a population of stroke survivors or those recovering from traumatic injury that has resulted in loss of muscle strength or coordination. Nevertheless, if the TBS-induced changes are reliable within an individual, one could predict after a single session whether an individual is likely to benefit from that particular (plasticity-inducing) intervention. In this case, TBS may still prove beneficial for individuals who exhibit a substantial response to the intervention. Thus, the issues of inter- and intra-individual variability in TBS appear to be intrinsically linked, with inadequate information existing in regard to both types of variability (for further discussion on inter- and intra-individual variability of NBS, particularly in regard to potential clinical applications, see Hinder et al. [21]).

Vernet et al. [22] made a first step in assessing intra-individual reliability in responses to cTBS, thought to induce LTD-like plasticity. They reported some degree of reliability of responses across two sessions (conducted an average of 100 days apart), but only tested ten participants with a very large age range. Given that age can affect plastic responses to non-invasive brain stimulation [23] it is difficult to ascertain the degree to which the relatively small sample of participants with vastly varying ages may have affected their findings.

To date there is no literature that systematically investigates whether individual responses to iTBS are robust and reliable such that someone who exhibits a large response to iTBS on one day would also exhibit similar changes in a subsequent session. The present study was therefore conducted on thirty individuals (18–44 years) who received iTBS in two sessions one to three weeks apart. While cTBS has been reported to induce more robust and reliable aftereffects than iTBS [24] (but also see Ref. [22]) the current study focused on iTBS due to its potential in rehabilitation via the induction or promotion of LTP-like effects (e.g. increasing the excitability of pathways that have been down-regulated following injury). Our analyses focused on inter- and intra-individual variability of iTBS-induced changes in corticospinal excitability.

Materials and methods

Participants

Thirty healthy volunteers (11 males) aged between 18 and 44 years (Mean (M) = 25.3, standard deviation (SD) = 8.7) participated in this study which was approved by the Tasmanian Human Research Ethics Committee Network and followed the international safety guidelines and recommendations for TMS [25]. All participants gave written informed consent, and completed a medical history questionnaire which confirmed the absence of any known neurological and neuromuscular dysfunction and any contraindications to TMS. Twenty-seven participants were right handed (laterality quotient, LQ, = 86.7, SD = 12.6, Range = 65–100), two were left handed (LQ = −42.5, SD = 3.5, Range = −45 to −40), and one was within the mid range (LQ = −25) [26]. All participants completed two separate sessions of the iTBS protocol (see TBS technique section, below, for details), at least one week apart (Range = 7–21 days). For each participant, both sessions were conducted at the same time of day to account for any diurnal effects on corticospinal plasticity [27].

Experimental procedure

The study was designed to assess intra- and inter-individual variability in responses to iTBS. Corticospinal excitability of projections from the left motor cortex was assessed by recording evoked potentials in the right index finger in response to single pulse TMS (see Electromyography and Transcranial magnetic stimulation sections below). Baseline corticospinal excitability was assessed in two separate blocks of TMS stimulations 3 min apart, after which iTBS was administered (see TBS technique section). Following iTBS, excitability was reassessed every 3 min for 36 min (i.e., 13 post-iTBS time points: post0, post3…, post36).

Electromyography

Participants were seated in a comfortable chair with both forearms quiescent. Electromyographic (EMG) activity was recorded