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Effects of 30 Hz Theta Burst Transcranial Magnetic Stimulation on the Primary Motor Cortex

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Abstract

Theta Burst Stimulation (TBS) is a relatively new form of repetitive Transcranial Magnetic Stimulation (TMS) used to probe neuroplasticity in the human cortex. Thirty-Hz TBS, a variation of the originally described 50 Hz TBS, has been shown to induce cortical changes in several nonmotor regions. However, its effects over the primary motor cortex have not been examined. Due to TMS device mechanical properties, 30 Hz TBS is advantageous over 50 Hz TBS in that it can be delivered at higher stimulation intensities. The goal of this pilot study is to examine the neurophysiologic effects of 30 Hz TBS on the primary motor cortex (M1) of healthy adults. Eighteen right-handed adults (33 ± 9.0 years; M:F = 8:10) completed intermittent TBS (iTBS) or continuous TBS (cTBS) over left M1. TBS was performed with Magstim® SuperRapid2 with stimulation bursts (3 pulses at 30 Hz) repeating every 200 milliseconds. For iTBS, each 2-second stimulation train was separated by 8 seconds but there was no pause between trains for cTBS. Each TBS consisted of a total of 600 pulses delivered at an intensity of 90%*Resting Motor Threshold. Motor-Evoked Potentials (MEP) in the right first dorsal interosseous muscle were measured before, and one and ten minutes after TBS. Pre/post-TBS MEP amplitudes were compared using repeated-measures ANOVA. MEP amplitudes increased after 30 Hz iTBS and decreased after 30 Hz cTBS (TBS-Type*Time effect $p=0.009$). In conclusion, 30 Hz TBS induced similar neurophysiologic effects over M1 as conventional 50 Hz TBS.

Keywords

Repetitive Transcranial Magnetic Stimulation; Theta Burst Stimulation; Neuroplasticity; Motor Cortex

1. INTRODUCTION

Huang et al. first developed Theta Burst Transcranial Magnetic Stimulation (TBS) in human as a quick noninvasive method to examine neuroplasticity (Huang et al., 2005). This original

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protocol uses high-frequency 50 Hz bursts to alter cortical excitability and produces after-effects that outlast the duration of the stimulation. The effects of TBS on the primary motor cortex have been compared with conventional Repetitive Transcranial Magnetic Stimulation (rTMS) and are found to be similar (Zafar et al., 2008). However, TBS has several advantages over rTMS. First, the stimulation duration is much shorter, with intermittent TBS (iTBS) lasting 190 seconds and continuous TBS (cTBS) lasting 40 seconds. Second, TBS uses lower intensities, which are more comfortable, heat the coils less, and may be more tolerable to sensitive individuals such as children.

Both rTMS and TBS have potential clinical applications (Ridding and Rothwell, 2007). Notably, the United States Food and Drug Administration recently cleared rTMS for treatment of refractory depression in adults. Similarly, in other diagnostic and treatment studies, rTMS has been used much more commonly in adults than children (Bloch et al., 2008; Kirton et al., 2008; Kirton et al., 2010; Kwon et al., 2011; Rotenberg et al., 2009; Sokhadze et al., 2010). One factor that may influence this is the long duration and higher stimulation intensity required for conventional rTMS. It has been suggested that shorter, lower intensity TBS protocols be considered an alternative method of neuromodulation in children (Oberman et al., 2010).

In a prior adult study (Wu and Gilbert, 2011), our laboratory reproduced findings showing excitatory changes in the primary motor cortex (M1) with conventional 50 Hz iTBS, which is delivered at 0.8 times the Active Motor Threshold using the Magstim® SuperRapid2 Device. Unfortunately, subsequent attempts to perform these studies in >40 children were unsuccessful for the following reasons (unpublished data). First, due to children's higher motor thresholds (Nezu et al., 1997), TBS needed to be performed at higher stimulation intensities. However, the Magstim® SuperRapid2 mechanical parameters (<http://www.magstim.com/transcranial-magnetic-stimulation/magstim-rapid>) require counter-balancing stimulation intensity with stimulation burst frequency. Therefore in children, the SuperRapid2 device would not permit the higher stimulation intensity and the conventional 50 Hz burst-frequency combination. In response, we lowered the stimulation intensity to a level that the Magstim® SuperRapid2 permitted. At this lower intensity, we could not evoke consistent changes in M1 excitability (unpublished data).

The present pilot study reports results of another approach – lowering the TBS burst frequency to 30 Hz. This variation of TBS has been shown to alter cortical excitability in several nonmotor cortical regions (Nyffeler et al., 2008; Nyffeler et al., 2006). However, its effects on the primary motor cortex are unknown. By lowering the burst frequency, we were able to increase the maximal stimulation intensity of Magstim® SuperRapid2 by ~50%. In this study, we examined the neurophysiologic effects of 30 Hz iTBS and cTBS on M1 in eighteen healthy adults.

2. MATERIAL AND METHODS

2.1. Participants

Healthy adults who are free of neurologic, psychiatric, serious medical conditions, substance abuse history, not pregnant and not on any neuropsychiatric medications were recruited by email and flyer advertisements. All participants were right handed. Participants gave written informed consent for the study, which was approved by the Cincinnati Children's Hospital Medical Center Institutional Review Board.

2.2. Single-pulse Transcranial Magnetic Stimulation (TMS)

Single-pulse TMS was performed with a Magstim®200 stimulator connected to a figure-8, 70mm coil (Magstim Co., Wales, UK). Surface electromyography (EMG) leads were placed

over the first dorsal interosseous (FDI) muscle on the right hand. Participants were seated comfortably, with both arms fully supported on a pillow. Full muscle relaxation was maintained through visual and EMG monitoring. The coil was placed over the left primary motor cortex at the optimal site for obtaining a motor-evoked potential (MEP) in the right FDI, and resting and active motor thresholds (RMT, AMT) were quantified using standard methods (Mills and Nithi, 1997). Once the hotspot was located on left M1, the scalp location was marked with a wax pencil to ensure that the application of single-pulse and theta-burst TMS occurred at the same cortical region. Ten consecutive TMS pulses separated by at least 5 seconds were administered at 120% of baseline RMT to obtain MEP amplitudes at 3 time points: before, and at one and ten minutes following TBS.

Each surface EMG tracing was reviewed and tracings that contained muscle movements prior to the TMS pulse were excluded from data analysis.

2.3. Theta Burst Stimulation

iTBS and cTBS were performed using Magstim® SuperRapid2 (Magstim Co., Wales, UK). All participants received TBS in the afternoon. Other than the difference in burst frequency, the 30 Hz TBS protocol is identical to the original TBS (Huang et al., 2005). Each session of iTBS and cTBS delivered a total of 600 magnetic pulses. The stimulation intensity used was 90% of RMT. Before and after TBS, a structured diagnostic interview with a detailed sixteen-question review of systems was conducted to assess for adverse events.

2.4. Statistical Analysis

The participants' age, RMT and AMT between the iTBS and cTBS groups were compared using Wilcoxon-Mann-Whitney test. The outcome of interest was the TBS-Type*Time interaction for mean MEP fold change, which is expressed as a ratio of post-TBS/pre-TBS MEP amplitudes. The Shapiro-Wilk test showed that these ratios were normally distributed ($p=0.56$, 0.92 for iTBS at 1 and 10 minutes; $p=0.47$, 0.27 for cTBS at 1 and 10 minutes) in each group for each level of the within-subjects factor (Time). Data was subsequently subjected to repeated-measures ANOVA (PROC MIXED) in SAS®v.9.2 (Cary, NC), with two tailed $p<0.05$ considered significant.

3. RESULTS

Eighteen healthy adults (33 ± 9.0 years; M:F = 8:10) completed the study. Nine participants completed iTBS and nine others completed cTBS. The two groups did not differ significantly in age ($p=0.74$), RMT ($p=0.07$) and AMT ($p=0.19$). There was no seizure or any serious adverse event following TBS identified on structured diagnostic interviews. One participant complained of a mild headache that resolved without any medical intervention.

The mean MEP fold change increased at 1 and 10 minutes after 30 Hz iTBS while cTBS had the opposite effect as shown in Figure 1 (TBS-Type*Time: $F_{2,32}=5.41$, $p=0.009$).

4. DISCUSSION

The aim of this study was to examine the neurophysiologic effects of 30 Hz TBS on left M1. We demonstrated that 30 Hz iTBS safely increased while cTBS decreased MEP amplitudes.

The development of noninvasive transcranial magnetic TBS for human research was based on *in vitro* animal studies showing that high-frequency theta burst electrical stimulations can induce LTP and LTD (Hess et al., 1996). Modeling this stimulation pattern, high frequency transcranial magnetic TBS was developed using M1, yielding similar LTP-like and LTD-like effects (Huang et al., 2005). Although the initial TBS was performed with 50 Hz

stimulation bursts, others have modified the stimulation protocol using 30 Hz bursts (Nyffeler et al., 2008; Nyffeler et al., 2006). These 30 Hz TBS studies demonstrated that cTBS had inhibitory effects on the underlying cortical regions. However, the regions examined were outside of M1 and the effects of 30 Hz TBS on the primary motor cortex are unknown. Based on other repetitive TMS studies, we hypothesized that the excitatory and inhibitory effects of 30 Hz TBS would be similar over M1 when compared to nonmotor regions. For instance, in post-stroke nonfluent aphasic patients, inhibitory 1 Hz rTMS over the right hemisphere language homologue area produces speech improvement and increased left hemispheric language activation (Naeser et al., 2012). Whereas speech improvement has also been reported by using excitatory repetitive magnetic stimulation over the residual left hemispheric Broca's area after a stroke (Szaflarski et al., 2011). Hence our pilot data confirms our hypothesis by showing that 30 Hz iTBS and cTBS have the expected neurophysiologic effects on M1 and these effects are similar to those of the conventional 50 Hz TBS (Huang et al., 2005).

There are currently several repetitive TMS methods that produce cortical excitability changes outlasting the duration of the stimulation (Hoogendam et al., 2010). Of these, TBS has the following potential advantages – lower stimulation intensity and shorter stimulation duration. Conventional rTMS at set frequencies (e.g., 1 Hz, 25 Hz) has been in use since the 1990s. Low frequency inhibitory rTMS takes longer than inhibitory cTBS (i.e., 600 pulses of cTBS takes 40 seconds while 600 pulses of 1 Hz rTMS takes 10 minutes). Compared to low frequency conventional rTMS, high frequency excitatory rTMS takes less time. However, this time is still significantly longer than iTBS (190 seconds). For example, based on the most recent safety recommendations requiring pause intervals between stimulation trains (Rossi et al., 2009), it would take at least 17 minutes to deliver 600 pulses of 25 Hz rTMS. Other forms of patterned repetitive TMS (Paired Associative Stimulation, Repetitive Paired-Pulse TMS, Quadripulse Stimulation) also requires longer stimulation time (Hoogendam et al., 2010), often lasting up to 30 minutes. In general, these non-TBS techniques usually use higher stimulation intensities when compared to TBS (Hoogendam et al., 2010). Therefore, the shorter stimulation duration of TBS makes this technique practical especially for participants who have difficulty staying still during the study (e.g., children, movement disorder patients). Furthermore, the lower stimulation intensity required for TBS also makes it useful for persons with higher motor thresholds (e.g., children, patients taking certain neuropsychiatric medications).

Although TBS may be easier to deliver compared to other forms of rTMS, it still carries the risk of inducing seizures. TBS research is much less prevalent compared to conventional rTMS. The crude risk of seizure per session of TBS is estimated to be approximately 0.02% (Oberman et al., 2011). Seizure induction rate for conventional rTMS has only been calculated in the epilepsy population, with a crude risk per participant of ~1.4% (Bae et al., 2007). To date, virtually all TBS publications are adult studies. However, we recently published our data involving 40 kids showing that TBS is relatively safe in children (Wu et al., 2012). Unfortunately, at the most recent international meeting for TMS researchers, a consensus for TBS stimulation parameters was not reached (Rossi et al., 2009). The consensus group stated that several TBS factors still need to be evaluated for safety: numbers of stimulation pulses, interval between repeated TBS sessions, number of multiple applications and stimulation intensity (Rossi et al., 2009).

There are several limitations with this study. First, we did not measure MEP beyond ten minutes after TBS. Therefore, we do not know if the duration of the after-effects is comparable to 50 Hz TBS. Second, the sample size is small ($n = 9$ for each group), although this is the same size as the initial 50 Hz TBS report (Huang et al., 2005). Third, we measured AMT before applying TBS. Different groups have shown that muscle activity

prior to TBS can change or eliminate TBS after-effects (Gentner et al., 2008; Goldsworthy et al., 2012). Finally, we did not directly compare, within the same individuals, the magnitude of the iTBS and cTBS effects at 30 Hz vs. 50 Hz. However, the 30 Hz effect size we identified (Figure 1) is comparable both to 50 Hz TBS studies in our lab as well as to those published elsewhere.

In conclusion, the modified 30 Hz TBS safely produced the expected neurophysiologic changes in left M1. These changes are similar to 50 Hz TBS. However, when delivering 30 Hz TBS with Magstim® SuperRapid2, one can use higher stimulation intensities. Therefore, 30 Hz TBS may be useful in persons with higher motor thresholds.

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Highlights

- 30 Hz theta burst stimulation (TBS) allowed for higher intensity stimulation.
- 30 Hz TBS produced similar neurophysiologic effects on primary motor cortex as 50 Hz TBS.
- 30 Hz TBS may be useful in persons with higher motor thresholds.

Figure 1.
MEP fold changes after 30 Hz TBS.
Error bars represent standard error means.
MEP = motor-evoked potentials, TBS = theta burst stimulation