High and low frequency repetitive transcranial magnetic stimulation (rTMS) are both used to treat major depressive disorder (MDD). However, the physiological mechanisms underlying the therapeutic benefit and the effect of the stimulation frequency are unclear. Twelve healthy participants received 1Hz, 2Hz, and 5Hz active rTMS. Twenty 5 second trains were delivered at left dorsolateral prefrontal cortex at 110% of resting motor threshold with a 25 second inter-train interval. Blood oxygenation (HbO) was significantly reduced following the 1Hz trains compared to the HbO increases observed in both the 2Hz and 5Hz conditions. There was no significant inter-hemispheric difference in response. These results suggest that short trains of high and low frequency rTMS delivered to prefrontal cortex evoke a differential HbO response and provide additional evidence that high frequency trains result in increased neural activity. The findings may provide further explanation for the improved symptoms observed in MDD patients treated with high frequency rTMS.

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Introduction

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation technique that can modulate localized cortical activity. It has been extensively used to study normal brain function and applied therapeutically to treat a variety of neuropsychiatric disorders such as major depressive disorder (MDD). rTMS stimulation parameters can be varied in numerous ways, such as altering the duration, intensity or frequency of stimulation.

Modulation of rTMS frequency has been the focus of considerable attention, and variations in the frequency of TMS pulses have been shown to influence antidepressant response to rTMS [1,2]. Previous research has investigated the physiological mechanisms of rTMS [3–5] see Ref. [6], employing several neuroimaging techniques [2,7,8]. One such line of research has focused on brain metabolic changes as indexed by a vascular/hemodynamic proxy [2,4,5,8–11].

Previous studies have shown that low frequency rTMS results in reduced neural activation and cerebral blood flow compared with high frequency rTMS [9,12,13]. However, most of these studies have analyzed response to motor cortex stimulation and it is not clear if responses are the same in brain regions such as the dorsolateral prefrontal cortex (DLPFC) where rTMS is commonly applied clinically. Near infra-red spectroscopy (NIRS) which can be used to measure cerebral blood hemoglobin oxygenation (HbO) levels, may be applied to do this [14,15]. In contrast with other techniques (e.g., functional MRI), NIRS provides an index of HbO predominantly from larger vessels (rather than capillary beds) at the cortical surface level [16]. This method is portable, non-invasive, and compatible with the large magnetic fields associated with TMS [1,4,14,17].

The aim of the current study was to examine the effects of both high and low frequency rTMS on changes in blood oxygenation in DLPFC. It was hypothesized that, in line with previous motor cortex

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studies, low frequency rTMS would result in a reduction and high frequency rTMS an increase in HbO levels. Based on previous observations in TMS/NIRS studies [4,17], it was also expected that contralateral response would be similar in magnitude and profile. This is the first study to examine changes in HbO at frontal regions modulated by suprathreshold short duration high and low frequency rTMS using NIRS.

Methods

Subjects

Twelve healthy volunteers (3 female), one left handed (self report) with a mean age of 22.17 (SD: ±2.62; age range: 19–28) participated in this study. All volunteers provided written informed consent prior to study participation and the experimental procedures conformed to the declaration of Helsinki.

rTMS was delivered using a figure-of-eight coil connected to a MagVenture (Copenhagen, Denmark) stimulator R30/X100. The following parameters were used: 20 trains of 5 s duration at 1 Hz, 2 Hz, and 5 Hz with 25 s inter-train interval counterbalanced [5] at 110% of resting motor threshold (RMT) [18] via the technique described in detail previously [4].

Near infra-red spectroscopy (NIRS)

An Oximeter Model 96108 (OxiTS; ISS Inc., Champaign, IL, USA) was used to measure changes in HbO via a technique described in detail previously [4]. Mean HbO was measured over a 5 s interval (post-stim) centered around the period of maximum change [5] (10 s post-stim), baseline corrected, and averaged. rTMS was applied over the left DLPFC (between F3 and AF3 in the 10−20 EEG system) just posterior to the hairline and the location of the NIRS probe [19]. An additional NIRS probe was located on the contralateral DLPFC.

Statistical analysis

A 3 × 2 repeated measures ANOVA was used comparing mean change in HbO with frequency and hemisphere as the 2 variables. Multiple comparisons were controlled by Tukey HSD and data normality was verified using Shapiro–Wilk.

Results

There was a main effect of frequency, F(2, 66) = 8.8, P < 0.005 with a large effect size (partial eta squared = 0.21). Post-hoc comparisons indicated that mean HbO in the 1 Hz condition (M = −3.9, SD = 7.0) was significantly lower than both 2 Hz (M = 3.2, SD = 5.6) and 5 Hz (M = 4.3, SD = 8.6). There was no main effect of hemisphere or interaction between frequency condition and hemisphere (Fig. 1).

Discussion

To our knowledge, this is the first study to examine changes in HbO at bilateral DLPFC in response to suprathreshold short duration high and low frequency rTMS using NIRS. The present study revealed three main findings: first, consistent with previous research studies, HbO decreased during 1 Hz rTMS with a subsequent gradual return to baseline at around 5–10 s post-stimulation. In contrast, 5 Hz produced an increase in HbO which remained above baseline for beyond 20 s and 2 Hz stimulation resulted in a lesser increase than 5 Hz. Furthermore there were comparable changes in the contralateral cortex in line with previous findings in NIRS, fMRI & EEG studies [17,20,21]. Similarly, Tupak et al. [22] also found bilaterally decreased prefrontal oxygenation following continuous theta burst stimulation applied to left DLPFC.

A previous H215O PET study by Siebner and colleagues [9] investigated the modulation of neural activity by rTMS frequencies ranging from 1 to 5 Hz by using cerebral blood flow (CBF) as a proxy for neural activity. They reported a linear increase in CBF with increasing frequency of stimulation. Although the TMS parameters used differ from those in the current study (subthreshold rTMS delivered to sensorimotor area), the pattern of modulation is similar. While PET measurements are relative to an arbitrary global average, the NIRS signal in the current study is relative to a pre-TMS baseline, revealing a differential effect of low frequency (1 Hz). This resulted in reduced HbO in contrast with the higher frequencies (2 Hz and 5 Hz) that demonstrated increases in HbO following rTMS. Reduced HbO may be indicative of an inhibitory response following the low frequency TMS consistent with a large number of previous studies of rTMS delivered to primary motor cortex demonstrating reduced excitability and increased intracortical inhibition (see Ref. [23]). This is also consistent with previous low frequency NIRS/TMS studies that employed both short [1,14,17] and long rTMS trains [4].

Figure 1. Average change in oxygenated hemoglobin (HbO) across subjects after TMS was applied to left DLPFC at three frequencies (1 Hz, 2 Hz, and 5 Hz). (A) and (B) show the HbO response for left and right DLPFC respectively. There was a main effect of frequency with significantly reduced HbO at 1 Hz.
Interhemispheric differences were more prominent at 1 Hz than at the higher frequencies, possibly indicating that increasing dose results in a greater cross-hemispheric effect, although it appears that there was a tendency for 2 Hz to have a greater cross-hemispheric effect than 5 Hz.

A limitation of this study is that there was no sham TMS condition, however we have repeatedly included sham controls in previous TMS/NIRS studies and these have only demonstrated minor non-significant fluctuations from baseline HbO levels [5,11]. It would be beneficial to also investigate the effects of varying the dose of TMS by controlling the number of pulses and by varying the TMS intensity. Further research into higher frequencies of stimulation is required, however potential complications associated with tetanic contraction and movement artifact need to be addressed. Another factor that was not investigated was the effect of inter-train interval upon the HbO response and the response at other cortical sites that could be achieved with more modern functional NIRS systems. Additionally, given that rTMS is extensively used therapeutically in mood disorders, the use of behavioral measures in future studies may provide valuable insights.

This study has demonstrated a marked differential response in HbO response between low and high frequency rTMS, and provides further evidence that high frequency rTMS is associated with increased neural activity. Furthermore, this study has demonstrated that increasing rTMS frequency results in similar changes in HbO at increased neural activity. Further research into higher frequencies of stimulation is required, however potential complications associated with tetanic contraction and movement artifact need to be addressed. Another factor that was not investigated was the effect of inter-train interval upon the HbO response and the response at other cortical sites that could be achieved with more modern functional NIRS systems. Additionally, given that rTMS is extensively used therapeutically in mood disorders, the use of behavioral measures in future studies may provide valuable insights.

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