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SHORT COMMUNICATIONS

Blood oxygenation changes resulting from suprathreshold transcranial magnetic stimulation

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The hemodynamic response to low-intensity transcranial magnetic stimulation (TMS) has previously been demonstrated at motor cortex using near infrared spectroscopy (NIRS). To investigate the effect of TMS on oxy-hemoglobin (HbO) at prefrontal cortex, both subthreshold and suprathreshold TMS relative to resting motor threshold (rMT) were applied at typical intensities used in experimental settings. Although there was no significant change after 90% and 110% rMT TMS, there was a significant drop in HbO after 130% rMT TMS. This drop was maximal at approximately 8 seconds post-TMS. This study may have implications for determining appropriate TMS intensities when stimulating nonmotor areas.

Keywords transcranial magnetic stimulation; cortical blood flow; oxygenated hemoglobin; prefrontal cortex; brain stimulation

Since its conception, transcranial magnetic stimulation (TMS) has become an important tool in neurophysiology and biological psychiatry.[1] The application of repetitive stimulation (rTMS) has been shown to produce lasting changes in brain activity[2] and it is increasingly being applied in therapeutic applications,[3,4] although we lack a complete understanding of its effects. Among the previous research examining changes in hemodynamic responses resulting from single-pulse TMS and rTMS, there is considerable inconsistency between results. The modulating parameters appear to be the measurement technique used, frequency, duration, intensity, and the location of the stimulus, for example, whether stimulation is applied to M1 or prefrontal cortex (PFC).[5-14]

Near infrared spectroscopy (NIRS) is a technique that combines high- temporal resolution with a high signal to noise ratio and meets the requirements for monitoring the response to single-pulse TMS.[15] Previous studies conducted using NIRS to study the effects of single TMS pulses[16,17] have been reasonably consistent; however, they have only examined pulses delivered to the primary motor cortex (M1) and at low-moderate intensities, i.e., 70-140% of active motor threshold (aMT). At 140% of aMT, equivalent to approximately 100% of the resting motor threshold (rMT),[18] instead of the increases in oxygenated hemoglobin

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(HbO) observed at lower intensities, HbO was observed to decrease. The authors suggested that TMS at higher intensities produced an "unnatural" brain activation that results in a nonstandard hemodynamic response.[16] In practice, however, single-pulse TMS is typically delivered at suprathreshold intensities, typically 110-150% of rMT and consequently, it would be of use to understand the hemodynamic effects of this.

Therefore, the aim of the current study was to compare the effects of subthreshold with suprathreshold single-pulse TMS on changes in HbO at a clinically relevant nonmotor area, i.e., PFC. It was hypothesized that subthreshold TMS would result in an increase in HbO similar to that observed in previous studies while suprathreshold TMS would result in increasingly larger reductions in HbO.

Materials and methods

Subjects

Data were collected for 12 right-handed subjects (seven females, age 29 ± 6 years). A secondary control experiment was conducted with a further 10 participants (four females, age 27 ± 3 years). The experimental procedures conformed to the declaration of Helsinki and were approved by The Alfred Hospital Ethics Committee. All participants gave written informed consent.

Electromyography and TMS

Electromyographic (EMG) activity was recorded from Ag/AgCl surface electrodes placed over the first dorsal interosseus (FDI) muscle in a belly-tendon montage. The signal was amplified (1000×), filtered (20-2000 Hz), and sampled at 5 kHz. TMS was applied using a figure-of-eight coil over the left hemisphere at a 45° angle from the midline by a Magstim 200 (Magstim, Whitland, Dyfed, UK). The rMT was defined as the minimal TMS intensity needed to evoke an MEP in right FDI larger than 50 μV in three of five consecutive trials.[19]

The TMS was applied over the PFC, between F3 and F5 in the 10-20 system, just posterior to the hairline and the location of the NIRS probe.[20] A total of 45 pulses at three different intensities (90%, 110%, and 130% of rMT) were delivered pseudo-randomly at an interpulse interval of 25 seconds (to allow a return to hemodynamic baseline between pulses).

NIRS

An Oximeter Model 96108 (OxiTS; ISS Inc, Champaign, IL) was used to collect DC, AC, and phase data for each wavelength (687 and 830 nm) sampled at 50 Hz. The Differential Pathlength Factor (DPF) and change in absorption were calculated from the AC and phase[21] and changes in HbO were then calculated with the extinction coefficients corresponding to the selected wavelengths.[22] Quantifying these changes assumes a homogenous scattering medium, an assumption that may be nullified by the nonhomogenous layering of head tissues, hence they are expressed in arbitrary units (a.u.).[22] The signal was filtered (0.005-0.5 Hz), trials were epoched around the TMS (those that were contaminated by movement artifact were removed), baseline corrected, and individual trials separated by intensity were averaged together. The mean blood oxygenation was measured 5 seconds before (prestim) and a 5 second interval (poststim) centered around the period of maximum change[16] (10 seconds poststim). The TMS evoked hemodynamic response for each intensity was analyzed by Student *t* tests between the pre-TMS interval and the post-TMS for the three intensities. Multiple comparisons were controlled for by Holm-Bonferroni correction.[23]

To determine whether the changes observed in HbO resulted from the scalp stimulation and auditory click stimulus that accompanies TMS, an additional sham TMS study was performed. With the TMS coil 10 cm away from the head, 20 stimuli were applied while cutaneous stimuli were applied adjacent to the NIRS probe. TMS pulses were delivered with an intertrial interval of 25 seconds apart and mean levels were compared as before. The cutaneous stimulation was applied with an ML180 isolated constant current stimulator (AD Instruments, Hastings, UK) at the individual's perceptual threshold (~0.5 mA) with a duration of 0.8 milliseconds.

Results

When TMS was delivered at 130% of rMT, there was a significant reduction in HbO ($P = .01$). However, although mean levels of HbO were reduced after the TMS, the changes were not significant at 90% ($P = .38$) or at 110% ($P = .2$) of rMT. The mean rMT for all subjects was 41% of maximal stimulator output. Mean waveforms are shown in Figure 1. Compared with previous research examining motor cortex,[16] there was some baseline ripple observed; however, this is likely to be due to the PFC being more active during resting phases.[11] There was no difference between prestim and poststim levels of HbO after sham stimulation ($P = .75$).

Discussion

The current study found that single-pulse TMS delivered at 90% or 110% of rMT was not sufficient to change HbO levels, but when the intensity was increased to 130%, HbO was significantly reduced. This trough was maximal around 8-10 seconds poststimulus. To our knowledge, this is the first time that the changes in HbO evoked by these commonly used single-pulse intensities have been systematically investigated, especially in PFC.