

Elevated haemoglobin levels in the motor cortex following 1 Hz transcranial magnetic stimulation: a preliminary study

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Abstract One hertz transcranial magnetic stimulation (TMS) over the motor cortex has been reported to increase activity in the motor cortex contralateral to stimulation, as evidenced by the elevated motor evoked potential on the corresponding hand muscle. Little research, however, has assessed concomitant changes in the haemoglobin level in the unstimulated motor cortex. An aim of this study was to measure the change of oxy- and deoxy-haemoglobin levels in the left motor cortex after 20 min of 1 Hz TMS over the right motor cortex. Subjects carried out a finger to thumb tapping task sequentially with six blocks of ten cycles (30 s on and 60 s off). One block was performed before TMS and five after TMS. The results show that the level of oxyhaemoglobin in the unstimulated cortex increased after TMS over the contralateral hemisphere and that the increase lasted 40 min after 1 Hz stimulation. Deoxy-haemoglobin was slightly decreased during the first 15 min after stimulation. The results identify long term physiological changes

resulting from 1 Hz stimulation and help to inform our understanding of interhemispheric interactions in TMS studies.

Keywords Haemoglobin · Oxyhaemoglobin · Blood flow · Motor cortex · Transcranial magnetic stimulation (TMS) · Near infrared spectroscopy (NIRS) · Finger tapping

Introduction

Repetitive transcranial magnetic stimulation (rTMS) can modulate cortical function by enhancing or decreasing cortical excitability depending on the parameters of stimulation. Low frequency stimulation (≤ 1 Hz), for example, has inhibitory effects (Pascual-Leone et al. 1998; Maeda et al. 2000a). Although this inhibition by 1 Hz transcranial magnetic stimulation (TMS) has been reported at the stimulation site and can outlast the stimulation by 15–30 min (Chen et al. 1997; Muellbacher et al. 2000; Fitzgerald et al. 2002; Plewnia et al. 2003; Pal et al. 2005), there is no consensus about the induced physiological changes in the unstimulated hemisphere. Some researchers have noted increased activation (Pascual-Leone et al. 1998; Gilio et al. 2003; Plewnia et al. 2003; Schambra et al. 2003; Kobayashi et al. 2004; Pal et al. 2005), but deactivation has also been observed (Wassermann et al. 1998).

The interhemispheric connections between the motor cortices have been examined in several previous TMS studies (Ferber et al. 1992; Meyer et al. 1995; Meyer et al. 1998). One proposal is that 1 Hz repetitive stimulation reduces interhemispheric inhibition resulting in an increase in activity in the contralateral motor cortex (Gilio et al. 2003; Pal et al. 2005). However, one PET imaging study showed that, at the stimulated site, regional cerebral blood

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flow (rCBF) gradually increased by up to 20% during 30 min of 1 Hz TMS, and then gradually decreased in the 10 min following stimulation. Furthermore, decreased rCBF in the opposite hemisphere was also detected during stimulation, but no data have shown how long this effect may last after stimulation (Fox et al. 1997).

Near infrared spectroscopy (NIRS), has also been used to study TMS effects. Single pulse TMS over the motor cortex increased the oxyhaemoglobin (O₂Hb) level (Noguchi et al. 2003). Applying low frequency rTMS for 2 min also increased the O₂Hb level in the stimulated area (Oliviero et al. 1999). According to the Fick principle, the increase in O₂Hb concentration can be considered an index of increased blood flow. Nevertheless, the increased O₂Hb level in these two studies (Oliviero et al. 1999; Noguchi et al. 2003) was only recorded for a maximum of 5 min after stimulation (i.e. shorter than the behavioral effects). This is an important limitation. For example, Kobayashi et al. (2004) indicated that ipsilateral finger movements were improved for at least 10 min following 1 Hz TMS. There is, therefore, a need to establish the existence of a correspondence between blood flow and behavioural changes over the time course of an experiment in order to be able to describe the physiological basis of long term cortico-cortical interactions following TMS.

Method

Design

A 2 × 6 factorial design (TMS: sham and real) × (time block: before TMS (A0) and after TMS (A1–A5)) was used in a within-subject design. The task was to move the right thumb as quickly as possible to sequentially press on the index, middle, fourth and little finger, and then reverse the sequence. The task was self-paced. A full block consisted of ten cycles of 30 s moving (on-state) and then 60 s rest (off-state). Inter-block interval was 10 min (Fig. 1). NIRS

was fixed over the hand area of the left motor cortex and TMS was delivered over the right motor cortex.

Participants

Five healthy male subjects, aged between 24 and 40 (mean 32.4, SD 8.5), participated in the experiment. All participants were right-handed and scored at least 90 in the Edinburgh Handedness Inventory (Oldfield 1971), with a mean score of 96 (SD 4.1). The experiment was reviewed and approved in advance by the Joint UCL/UCLH Committees on the ethics of human research, and subjects gave informed consent.

TMS and NIRS

TMS was applied using a 70 mm figure-of-eight coil for 20 min at 1 Hz, 115% of motor threshold (MagStim model 200, Magstim, Whitland, Dyfed, UK). The TMS coil was placed over the right motor cortex and the motor threshold was determined by the MOBS algorithm (Tyrrell and Owens 1988).

For the sham condition, two figure-of-eight coils were attached together. The inactive coil was placed on the same stimulation location, and an active coil was placed at 90°, thus no current was passed to the inactive coil. Since the active coil was away from the skull, the brain was not stimulated but subjects were exposed to the unilateral click and to the vibration of the active coil.

A NIRO-200 monitor (Hamamatsu Photonics KK, Japan) was used to measure the concentration change of O₂Hb and deoxy-haemoglobin (HHb) at 6 Hz sampling rate. Briefly, laser diode sources (750, 810 and 850 nm) emit light which is guided to the subjects' head through a fiber-optic bundle, a so-called "optode", and a similar fibre bundle carries returning light to an avalanche photodiode detector. Optodes were positioned over the left motor cortex with an interoptode distance of 3 cm. The placement of optodes was across the motor cortex and with the emitter at the posterior, which was in line with the best orientation of

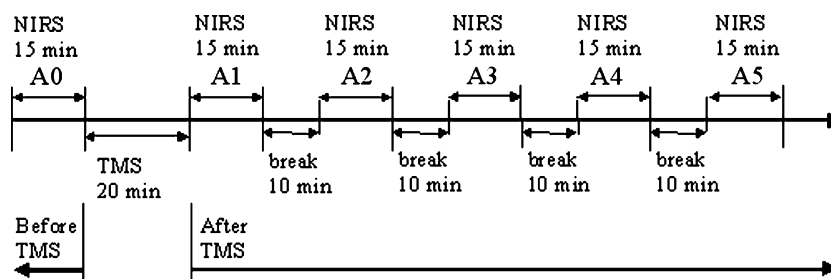


Fig. 1 Time line of NIRS measurement. NIRS was applied over the left motor cortex and blood flow changes recorded before TMS (A0) and after TMS in five different blocks (A1–A5). Every block was

15 min long, consisting of ten cycles of 30 s in the on-state and 60 s in the off-state. Inter-block interval was 10 min

the probe to obtain robust measurements of O_2Hb and HHb (Toronov et al 2001).

Procedure

The experiment began with the localization of the motor cortices with the Brainsight system (Rogue Research, Montreal, Canada). The hand area was identified by locating the superior genu of the central sulcus by TMS (Boroojerdi et al. 1999). Anatomically verified locations were checked for the best coil position for production of contralateral finger twitches (i.e. classical motor threshold (MT) determination). The locations were then fixed throughout the experiment. Participants were then instructed to do the finger tapping task. Every subject was told when to start moving fingers and when to stop. There was a total of ten cycles of 30 s moving (on-state) and then 60 s rest (off-state). After the first block of ten cycles (A0), 1 Hz TMS (or sham-TMS) was applied over the right motor cortex for 20 min. After stimulation, another five blocks (A1–A5) of ten cycles of finger tapping were recorded, with an inter-block interval of 10 min. The subject was tested on a second day with the same procedure. Three subjects were treated with 1 Hz TMS on the first day and the sham-TMS on the other day. Two subjects received the opposite order of treatments.

Data analysis

Since the NIRO-200 monitor does not allow for absolute quantification of haemoglobin concentrations, data were related to a baseline of zero calculated from the 10 s before the onset of stimulation (finger moving). To deal with the delay in the physiological response, the sampling period of the off-state was the combination of two periods: 10 s before the onset of the on-state (t_1) and 10 s starting from 20 s after the onset of the off-state (t_5). The period of activation was sampled for 20 s (t_3) starting from 5 s after the onset of the on-state (t_2). A regression line was plotted, based on the sampling data of the off-state, to eliminate any fluctuation of the baseline over time. Each data point (including on- and off states) was subtracted from the corresponding value on the regression line. The sampling period of the on and off-states and a typical response are shown in Fig. 2.

To reduce the effects of artefacts arising from sudden movement of the subject or electrical interference, the median among ten cycles was calculated as the averaged cycle of each block. The mean of each averaged cycle was calculated and the difference between the off and on-states was used for statistical analysis (two-way repeated measure ANOVA).

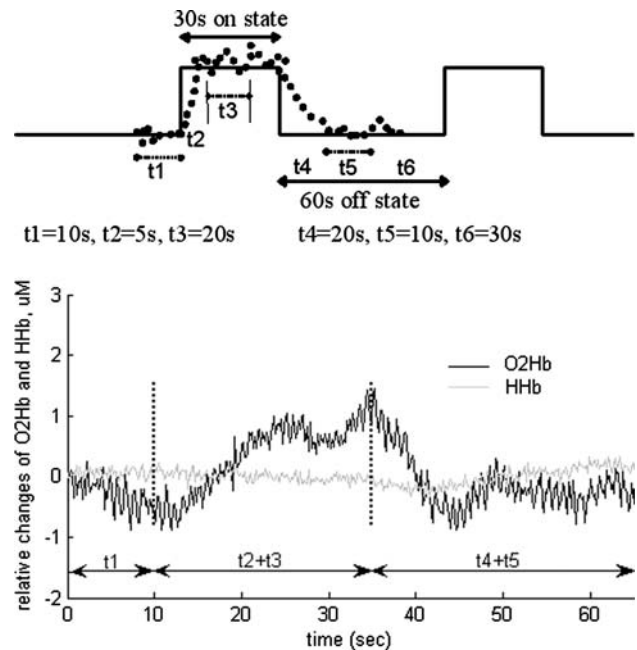


Fig. 2 The period of on- and off-states for every cycle (*top panel*) and the sampling period of responses for data analysis (one subject, *lower panel*). *Top panel*: the dotted trace represents a typical curve from the NIRS 200. In the dotted lines, t_1 marks the sampling periods (t_1) preceded the on-state by 10 s. t_2 and t_3 occupied some periods in the 30 s on-state; t_4 and t_5 were sampled in the off-state. *Lower panel*: the representative response of ΔO_2Hb and ΔHHb of one subject as a function of the sampling periods, as measured in the A1 block after 1 Hz TMS

Results

The results are plotted in Fig. 3. In general, all the ΔO_2Hb measures increased (whereby all the ΔHHb measures decreased) in both real and sham TMS in time block A0 through to A5, suggesting the motor cortex had been activated in these subjects during the finger tapping task. Depending on the time blocks and whether it was real or sham TMS, the amount of increase in the ΔO_2Hb data (or decrease in the ΔHHb data) was, however, different. In the ΔO_2Hb data (the left panel of Fig. 3), there was a significant interaction between TMS and the time blocks ($F_{(5,20)} = 4.55$, $p < 0.01$). Further analysis (simple main effects analysis) showed that, during the time block of A1 (i.e. the first 15 min after stimulation), the increase of ΔO_2Hb was higher following 1 Hz TMS ($1.10 \mu M$) than after the sham stimulation ($0.64 \mu M$), $F_{(1,20)} = 29.61$, $p < 0.01$. Similarly during the period A2, the increased ΔO_2Hb level was still higher following the 1 Hz ($0.99 \mu M$) than the sham stimulation ($0.72 \mu M$), $F_{(1,20)} = 10.58$, $p < 0.01$. There were no differences between the TMS and the sham stimulation in other time blocks (i.e. A0, A3–A5).

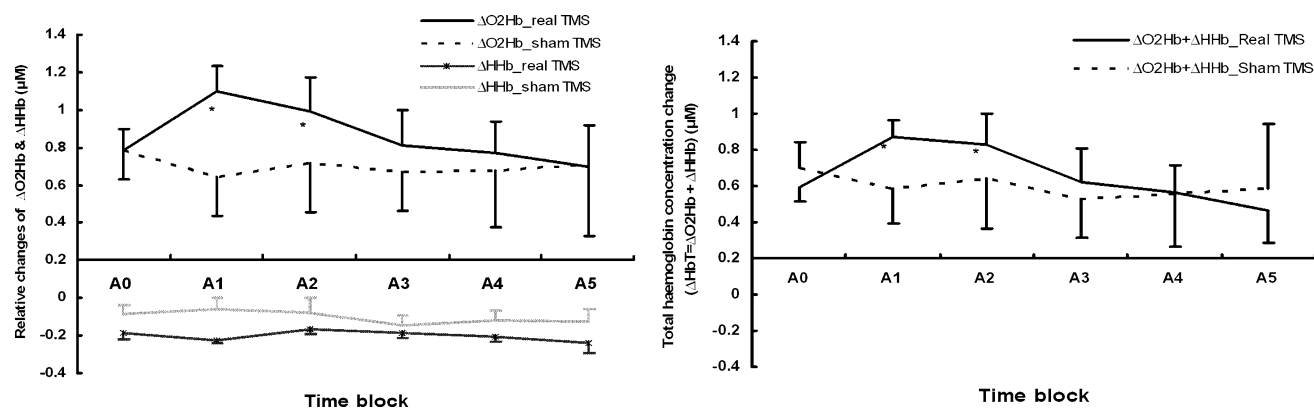


Fig. 3 The concentration of $\Delta\text{O}_2\text{Hb}$, ΔHHb (left panel) and the summation of both $\Delta\text{HHb} + \Delta\text{O}_2\text{Hb}$ (right panel), proportional to the cerebral blood volume (ΔHbT) as a function of recording time block and TMS. The symbols, A0–A5, on the X axis indicate the 15 min periods of NIRS recording, A0 marks the recording before stimulation, and A1

to A5 the recording after stimulation, with an inter-block interval of 10 min. The asterisks each show that the level of $\Delta\text{O}_2\text{Hb}$ or $\Delta\text{HHb} + \Delta\text{O}_2\text{Hb}$ is significantly higher following real stimulation than sham stimulation ($p < 0.01$ and $p < 0.05$, respectively), at the time blocks of A1 and A2. Bars show the standard error for each data point

To scrutinize the fluctuations of the sham condition, a one-way ANOVA and post-hoc paired t -tests were conducted. The result of ANOVA showed that there were no significant differences of $\Delta\text{O}_2\text{Hb}$ between different periods ($F_{(5,24)} = 0.035$, $p = 0.999$). The results of paired t -tests also showed that the changes of O_2Hb in the periods A1 and A2 were not significant against the period A0 (A1 vs. A0, $t_{(4)} = 0.940$, $p = 0.401$; A2 vs. A0, $t_{(4)} = 0.369$, $p = 0.731$).

The changes in ΔHHb data are also plotted in the left panel of Fig. 3 and revealed that there were no significant main effects (for TMS, $F_{(1,4)} = 2.09$, $p = 0.22$; for time block, $F_{(5,20)} = 0.97$, $p = 0.46$) or interactions ($F_{(5,20)} = 2.05$, $p = 0.11$) for any indices. However, in the time block of A0 (before stimulation), the levels of ΔHHb change varied between the TMS and the sham stimulation. In order to reveal the stimulation effect on the ΔHHb change, the values of ΔHHb changes in A1 to A5 were subtracted from those at A0. This showed that, in the time block of A1, ΔHHb levels decreased more following TMS ($-0.037 \mu\text{M}$), compared with the increase following the sham stimulation ($0.028 \mu\text{M}$) (but this did not reach significance t test, $t_{(4)} = -1.58 > \text{critical value, } -2.13$).

The total haemoglobin concentration change (the ΔHbT data), i.e. the sum of $\Delta\text{O}_2\text{Hb}$ and ΔHHb , plotted in the right panel of Fig. 3, is proportional to the cerebral blood volume (Delpy et al. 1988). There was a significant interaction between TMS and time block ($F_{(5,20)} = 3.49$, $p < 0.05$). Simple main effects analysis showed that, during the time block of A1 (i.e., the first 15 min after stimulation), the increase of ΔHbT was higher following 1 Hz TMS ($0.87 \mu\text{M}$) in comparison to the sham stimulation ($0.58 \mu\text{M}$), $F_{(1,20)} = 10.94$, $p < 0.01$. During the period of A2, the increased level of ΔHbT was still higher following the 1 Hz ($0.83 \mu\text{M}$) than the sham stimulation ($0.64 \mu\text{M}$), $F_{(1,20)} = 4.48$, $p < 0.05$. There were no differences between

the TMS and the sham stimulation in the other time blocks (i.e. A0, A3, A4 and A5).

Discussion

The results showed that, following 1 Hz TMS over the motor cortex, blood volume increased in the unstimulated motor cortex in the contralateral hemisphere, as evidenced by the raised level of $\Delta\text{O}_2\text{Hb}$ that lasted 40 min after the stimulation. Such change was not produced by the sham stimulation. Changes in ΔHHb level were not coupled with $\Delta\text{O}_2\text{Hb}$, but the trend revealed that, compared with the levels before stimulation (A0), a decrease in ΔHHb was observed in the A1 period (i.e. 15 min after stimulation).

The small change in ΔHHb may result from masking by the high oxygen demand for the finger tapping (Fox et al. 1988; Villringer and Dirnagl 1995). This is likely to be the case in light of evidence showing that the estimated total blood volume change (proportional to ΔHbT) increases during finger movements (Delpy et al. 1988).

The results are consistent with previous research indicating increased activation in the contralateral non-stimulated motor cortex following TMS (Pascual-Leone et al. 1998; Gilio et al. 2003; Iewnia et al. 2003; Schambra et al. 2003; Kobayashi et al. 2004; Pal et al. 2005), but also extend past imaging studies using low frequency TMS which recorded blood flow only at the stimulation site (Fox et al. 1997; Oliviero et al. 1999; Noguchi et al. 2003), by correlating physiological changes with behaviour over the same time period. The data also offer a physiological basis for behavioural effects up to 10 min following stimulation (e.g. Kobayashi et al. 2004). The longer lasting effect in the current study may be due to differences in TMS intensity. Unlike Kobayashi et al.'s (2004) experiment which used

90% of MT., the current experiment adopted 115% MT. The suprathreshold stimulation caused muscle twitches and one might argue that the twitches changed the ongoing afferent input or influenced the non-stimulated motor cortex. However, past research using suprathreshold stimulation found decreased motor excitability, and no effects on motor performance, e.g. pinch force/acceleration, finger-tapping speed, or learning ability (Chen et al. 1997; Muellbacher et al. 2000; Muellbacher et al. 2002). Further, inhibition by 1 Hz TMS at the site of stimulation has been considered a cortical effect rather than due to efferent effects (Chen et al. 1997; Maeda et al. 2000b; Touge et al. 2001). Similarly, TMS effects on the non-stimulated motor cortex have been interpreted as cortical in origin (Ferbert et al. 1992; Hanajima et al. 2001; Daskalakis et al. 2002). For example, Plewnia et al. (2003) used suprathreshold stimulation and activated the non-stimulated motor cortex through the reduction of intra-cortical inhibition, but without changes in motor evoked potential (MEP) of the hand muscles.

In their PET study, Fox et al. (1997) found increased blood flow in the stimulated motor cortex and decreased blood flow at the contralateral site, at different recorded timing from the current results; however, Fox et al. (1997) monitored blood flow change during the magnetic stimulation, rather than after stimulation. Even so, Fox et al.'s (1997) results provided evidence of inhibitory interhemispheric pathways between motor cortices (Meyer et al. 1995; Gerloff et al. 1998; Pal et al. 2005). This mutual inhibition between motor cortices may also explain the crossed decrement in excitability as reported by Wassermann et al. (1998). Additionally, the inhibitory interhemispheric connections may compromise the crossed increase effects on the non-stimulated motor cortex (Chen et al. 1997; Muellbacher et al. 2000; Plewnia et al. 2003; Schambra et al. 2003) by claiming that 1 Hz TMS reduced the excitability in the stimulated motor cortex, which would then decrease the inhibitory influence on the contralateral area (Pal et al. 2005). As a result, the raised activity occurred in the non-stimulated motor cortex.

The raised activity in the non-stimulated motor cortex was reflected only in the increased MEP of the corresponding hand muscles (Gilio et al. 2003; Schambra et al. 2003). This raised activity suggests changes in excitability, but not in the baseline activity of the non-stimulated motor cortex. Further, blood flow change of the non-stimulated motor cortex was not observed by PET after 1 Hz stimulation (Chouinard et al. 2003), therefore it is unlikely that the raised haemoglobin change ($\Delta\text{O}_2\text{Hb}$) recorded in our experiment was caused by baseline effects. The differences between TMS on- and off-periods also suggest that the raised $\Delta\text{O}_2\text{Hb}$ was a result of the increased excitability rather than baseline changes in the activity of the non-stimulated

motor cortex. Were there an elevated baseline and/or no changes of the excitability after rTMS, the increased $\Delta\text{O}_2\text{Hb}$ and ΔHbT would not have been observed and the results would resemble the pre TMS conditions: our data, however, show clear differences in $\Delta\text{O}_2\text{Hb}$ between the on- and off-periods. The increased excitability of the non-stimulated motor cortex also supports the evidence of inhibitory interhemispheric pathways between motor cortices, mentioned above (Meyer et al. 1995; Gerloff et al. 1998; Pal et al. 2005). One hertz TMS in our experiment would repress the activity of the stimulated motor cortex, which would also result in the decreased activity of inhibitory interneurons between the two cerebral hemispheres. Thus, the increased responses of $\Delta\text{O}_2\text{Hb}$ and ΔHbT occurred in the non-stimulated motor cortex following 1 Hz stimulation when subjects were doing the finger movement.

In the current study, only one NIRS monitoring channel was placed over the non-stimulated motor cortex. The use of more channels (or a complete optical topography imaging system) in further studies, e.g. on the stimulated motor cortex and adjacent areas in both hemispheres, to monitor the blood flow change over time may yield other measures of the relationship between the two hemispheres and of the effects of 1 Hz TMS on behaviour.

In summary, 1 Hz TMS inhibited the motor cortex and its inhibitory interhemispheric pathway; as a result, the motor cortex in the unstimulated hemisphere was enhanced in terms of activated blood flow by voluntary finger tapping, as evidenced by the increased O_2Hb and slightly decreased HHb. The effects lasted for 40 min after stimulation.

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