

Hemoglobin concentration changes in the contralateral hemisphere during and after theta burst stimulation of the human sensorimotor cortices

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Abstract Using near infrared spectroscopy and repetitive transcranial magnetic stimulation (rTMS), we studied interhemispheric interactions between bilateral motor and sensory cortices in humans. RTMS consisted of a triple-pulse burst (50 Hz) repeated every 200 ms for 2 s (10 bursts, 30 pulses); one kind of theta burst TMS (TBS) (Huang et al. in *Neuron* 45:201–206, 2005). The hemoglobin concentration changes were recorded at the right prefrontal cortex, premotor area (PM), primary hand motor area (M1) and primary sensory area (S1) during and after TBS over the left PM, M1 and S1 or sham stimulation in eight normal volunteers. In addition, motor evoked potentials (MEPs) to TMS over the right M1 were recorded from the left first dorsal interosseous muscle after the conditioning TBS over left S1. TBS over PM induced a significant oxy-Hb decrease at the contralateral PM. TBS over M1 elicited a significant oxy-Hb decrease at the contralateral S1, and TBS over S1 significant oxy-Hb decreases at the contralateral M1 and S1. MEPs to TMS of the right M1 were significantly suppressed by the conditioning TBS over the left S1. These results suggest that there are mainly inhibitory interactions between bilateral

PMs and bilateral sensorimotor cortices in humans. Those are partly compatible with the previous findings. In addition to between the primary motor cortices, bilateral connection is requisite for smooth bimanual coordination between the sensory cortices or premotor cortices.

Keywords Interhemispheric interaction · Transcranial magnetic stimulation · Near-infrared spectroscopy · Motor cortex

Introduction

To investigate the interactions between two distant cortical areas in humans, several non-invasive methods have been used. They are neuroimaging methods, electrophysiological methods including transcranial magnetic stimulation (TMS) over two sites (paired stimulation method) and their combinations. Paired TMS techniques were first applied to see the connections, such as between bilateral motor cortices (Ferbert et al. 1992), cerebello-motor cortical (Ugawa et al. 1995) connections. The inhibitory interaction between bilateral primary motor cortices (M1) was demonstrated by paired TMS over the bilateral M1s (Ferbert et al. 1992). Similar paired TMS also showed interactions between premotor areas (PMs) and bilateral M1s (Civardi et al. 2001; Mochizuki et al. 2004a) and between motor related areas and the contralateral primary sensory cortex (S1) (Mochizuki et al. 2004b). These physiological studies can evaluate interactions between the sensorimotor area and other areas, but can hardly evaluate interactions between other areas (e.g., between bilateral PMs) because we have no good

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physiological measures to evaluate the excitability of areas other than the sensorimotor cortex.

Recent neuroimaging studies could show some functional connections between two distant cortical areas other than sensorimotor cortices. Positron emission tomography (PET) revealed regional cerebral blood flow (rCBF) changes at bilateral motor related areas including the supplementary motor area, PM and cerebellum elicited by repetitive TMS over M1 or PM (Siebner et al. 2000; Chouinard et al. 2003). These results suggest some tight connections between the stimulated area and areas showing rCBF changes. However, one major limitation of PET study is due to the irradiation of the subjects. Near-infrared spectroscopy (NIRS) is one of alternative noninvasive methods to see cerebral functional changes. It has four distinct advantages over preexisting techniques: high signal-to-noise ratios for single events, noninterference with magnetic field changes elicited by TMS, higher time resolution than PET and the lack of irradiation. This technique estimates hemoglobin (Hb) concentration changes by measuring reflected light, based on the differences in absorption spectra between oxy- and deoxy-Hb (Jöbsis 1977; Chance et al. 1988; Villringer et al. 1993). In previous studies we successfully recorded Hb concentration changes by a single pulse TMS (Noguchi et al. 2003; Mochizuki et al. 2006). In the present paper, using combination of NIRS and TMS, we studied the interhemispheric interactions between bilateral motor and sensory cortical areas in humans.

Subjects and methods

Subjects

Eight healthy volunteers (two women and six men, 28–53 years old) participated in this study. All subjects were right handed based on the Edinburgh Handedness Inventory (Oldfield 1971) and they all gave written informed consent to participate in the study. The experimental procedures used here were approved by the Ethics Committee of the University of Tokyo and were carried out in accordance with the Declaration of Helsinki.

Electromyographic recordings

Surface electromyograms (EMGs) were recorded from the bilateral first dorsal interosseous muscles (FDIs) with 9 mm diameter, Ag–AgCl surface cup electrodes. The active electrode was placed over the muscle belly and the reference electrode over the

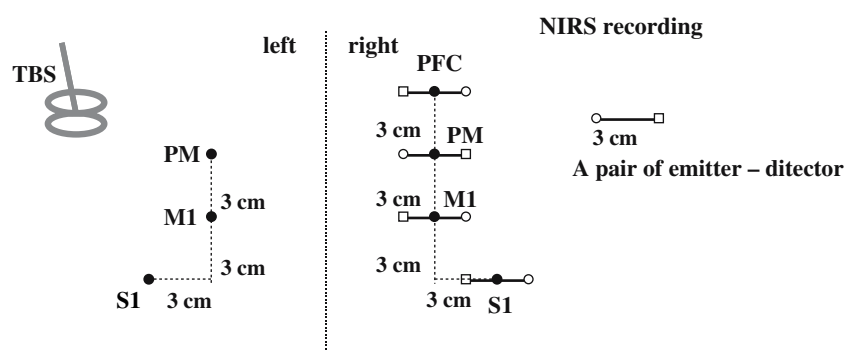
metacarpophalangeal joint of the index finger. Responses were amplified with an amplifier (Biotop, NEC Medical Systems, Japan) through filters set at 100 Hz and 3 kHz, then recorded with a sampling rate of 10 kHz and stored by a computer (Signal Processor DP-1200, NEC Medical Systems, Japan) for later off-line analysis of the data.

TMS

TMS was delivered with a figure-of-eight-shaped coil (outer diameter of each wing was 7 cm) connected to a Magstim 200 magnetic stimulator or a Magstim Super Rapid Package (The Magstim Co. Ltd, Whitland, UK). The coil was positioned over the left PM, M1 or S1. M1 was defined as the “hot spot” where stimulation evoked the largest MEP in the right FDI. In two of the subjects, that position was confirmed to be over the primary motor cortex by the neuronavigation system (Spetzger et al. 1995; Boroojerdi et al. 1999). PM is proved to be located 2–3 cm anterior site from M1 by PET study (Fink et al. 1997). To minimize stimulation effect spreading by TMS, we kept the distance between two stimulation sites as long as possible, and defined PM at a 3 cm anterior site from M1. In our previous paper (Enomoto et al. 2001), the S1 demonstrated by functional magnetic resonance images was located at 2 cm posterior to C3 of the International 10–20 system, the recording site for SEP. We selected a parietal lobe at a 3 cm posterior, 3 cm lateral site from M1. It was a bit posterior to the recording site for SEP. However, we have confirmed it to be a posterior part of somatosensory cortex, and we defined it as S1 (Fig. 1). At 2 cm away from the coil, the magnetic field elicited by single pulse TMS decreased to the half of that provoked just underneath the coil (Bohning et al. 1997). So, 3 cm apart from the coil may be long enough for excluding the stimulation spread. In fact, repetitive TMS (rTMS) at an intensity of 90% AMT could activate PM (2.5 cm anterior from M1) and M1 separately (Gerschlagher et al. 2001).

The coil was oriented to induce medially directed currents in the brain when monophasic TMS was delivered, and medially directed currents at the first phase when delivering biphasic TMS. The intensity was adjusted to be 80 and 100% of the active motor threshold (AMT) at M1 for biphasic conditioning TMS. We defined the AMT as the lowest intensity that evoked five small responses (about 100 μ V) in a series of ten stimuli when the subject made a 5% maximal voluntary contraction (about 50 μ V). Sham stimulation was performed with two coils. One non-discharging coil was positioned at the midpoint between left M1 and PM,

Fig. 1 Locations of TBS and NIRS recording sites. TBS was applied over left PM, M1 or S1. NIRS recordings were made at four measurement points. Each measurement pair of emitter (*open circle*) and detector (*open square*) was located on medio-lateral line at a distance of 3 cm. Measurement points (mid-points) were arranged on right



and the other was positioned 10 cm above the head and the same currents as real stimulation were induced in it to make sound. The holder of the first coil was touched to the edge of the other one for delivering vibration to the subject when giving a stimulus. As the conditioning stimulus, theta burst TMS (TBS) was used since it has good modulation effects on the stimulated site (Huang et al. 2005).

One train of TBS consisted of triple-pulse bursts (50 Hz) repeated every 200 ms for 2 s (10 bursts, 30 pulses). TBS over three sites and sham stimulation were applied at an intensity of 80 or 100% AMT. Eight different stimulation conditions (four sites of stimulation \times two intensities) were done in all the subjects. Each stimulation condition consisted of two sessions. Then, in total, 16 sessions (two sessions \times eight conditions) were done in one subject. Each session consisted of ten trains of TBS (total 100 bursts, 300 pulses). Each train was given at random inter-train intervals of 34–36 s. We cannot completely exclude the possibility of some accumulative effects even at this interval of 34–36 s. But continuous NIRS recording showed that in most subjects Hb concentration changes by TBS returned to the baseline before the next TBS. In addition, since all experiments were done in the same manner and compared the results between different stimulation conditions, we can safely say that some difference should be present between different stimulation conditions. The interval between the end of a session and the onset of next session was 15 min, which was long enough for the Hb concentration changes to return to the baseline. The order of sessions was counterbalanced within and across subjects. At most, six sessions were done on one experimental day (1,800 pulses at most). In one subject, all the experiments were performed on 3 days separated by a week or more.

To see some adverse effect and cope with it immediately, we recorded electroencephalograms continuously and one doctor observed the subject carefully during whole the experiments. We also sometimes

talked with the subject in the experiments to check their condition.

NIRS measurement

We used a NIRS system (ETG-A1; Hitachi Medical Corporation, Tokyo, Japan) having four emitters and four detectors, and the four measurement points (mid-points between emitters and detectors) were placed on the right PM, M1, S1 and a site at 3 cm anterior from PM [which is corresponding to prefrontal cortex (PFC)] (Fig. 1). The homologous positions in the contralateral hemisphere were also marked as the stimulated sites. Near-infrared laser diodes with two wavelengths, 790 and 830 nm, were used as the light sources, and transmittance data of the light beams were obtained every 500 ms. We calculated concentrations of oxy-hemoglobin (oxy-Hb) and deoxy-hemoglobin (deoxy-Hb) from the transmittance data. In this study, each event period ranged from 5 s before the TBS onset to 30 s after the end of TBS. Under each condition, the average Hb concentration changes were obtained from the results of two sessions and they were used in statistical analyses.

Additional physiological experiment

In the main experiments, we observed a large oxy-Hb decrease and small deoxy-Hb increase at the right M1 after TBS over the left S1 (see “Results”, third column in Figs. 3, 5). To confirm this finding electrophysiologically, we examined the excitability of the right M1 after TBS over the left S1 using a randomized conditioning-test design reported previously (Hanajima et al. 2001).

In this experiment, the test stimulus was a single pulse, monophasic TMS over the right M1 with a figure-of-eight-shaped coil (outer diameter of each wing was 7 cm). The coil was oriented to induce anteriorly directed currents in the brain. The intensity of the test stimulus was adjusted to evoke an MEP of approximately 0.2–0.5 mV peak to peak in the relaxed left

FDI. The conditioning stimulus was TBS over the left S1. TBS was composed of triple-pulse bursts repeated every 200 ms for 2 s (10 bursts, 30 pulses) at an intensity of 80% AMT. Three conditions [the test stimulus (15 trials) or conditioning TBS given alone (5 trials), and the test stimulus preceded by the conditioning TBS by an interval of 200 m from the onset of the last burst (15 trials)] were intermixed randomly in one block. Data were analyzed off-line after the experiments.

The amplitude of each single MEP from the left FDI in each condition was measured in order to compare amplitudes of the control and conditioned MEPs in the same block. We calculated the ratio of the mean amplitude of the conditioned MEP to that of the control MEP in each subject. The order of two blocks (TBS over S1 and sham stimulation) was counterbalanced across subjects. This additional experiment was performed 1 week or longer interval after the last day of the main experiments.

Statistical analysis

In the main experiments, the 95% confidence interval was calculated for each time point of oxy- and deoxy-Hb changes in each condition. We obtained the mean Hb concentration changes by averaging Hb data from 5 to 20 s after a TBS pulse in each condition, and used these values in statistical comparisons. In each NIRS recording point, two-way analysis of variance (ANOVA) [with factors of stimulation type (three sites and sham stimulation) and INTENSITY (80 and 100%)] was

performed on the mean Hb concentration changes. When an ANOVA test showed significant effects, we further performed post-hoc analyses with Scheffe's method for the significant effects. In the additional experiment, we used a paired *t*-test for comparison. The statistical significance was set at $P = 0.05$.

Results

Neither abnormal electroencephalograms nor any adverse effects were noted during or after the experiments in any subjects.

Figures 2, 3, 4 and 5 show averaged relative Hb-concentration changes and the 95% confidence intervals at right PFC (Fig. 2), PM (Fig. 3), M1 (Fig. 4) or S1 (Fig. 5) when TBS was applied over left PM, M1 or S1 or when sham stimulation was given.

No significant changes in oxy-Hb concentration (longer than 15 s) were observed at right PFC (Fig. 2). At right PM, significant oxy-Hb decreases were observed in the left PM stimulation condition (80 and 100% AMT) (Fig. 3). At an intensity of 80% AMT, oxy-Hb began to decrease after the TBS onset and returned to the baseline around 25 s later at the right PM (Fig. 3a, first column). The oxy-Hb significantly decreased as compared to the baseline 4–25 s after the TBS onset, as shown by the 95% confidence lines (the upper thin line was lower than zero), but the deoxy-Hb did not change significantly. No significant changes were seen when TBS was applied over the other sites.

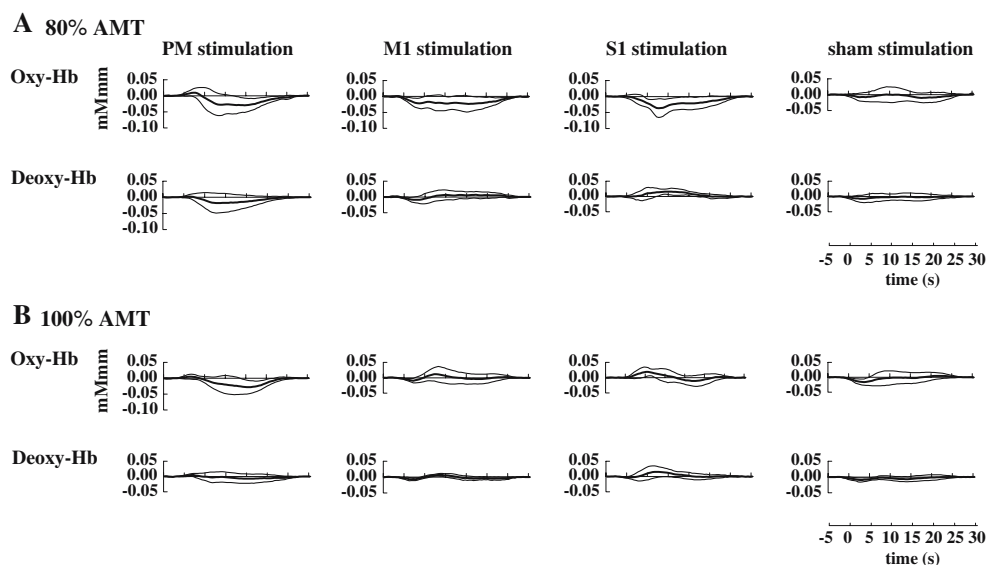


Fig. 2 NIRS recordings at right PFC. TBS was applied over left PM (first column), M1 (second column), S1 (third column) or sham stimulation (fourth column) at 80% AMT **a** or 100% AMT **b**. The first and third rows show oxy-Hb concentration changes, and the

second and fourth rows show deoxy-Hb. The ground averaged data ($n = 8$) for the four stimulation conditions are separately shown. The averages are depicted by thick lines and the 95% confidence intervals thin lines. No significant changes were evoked by any stimulation

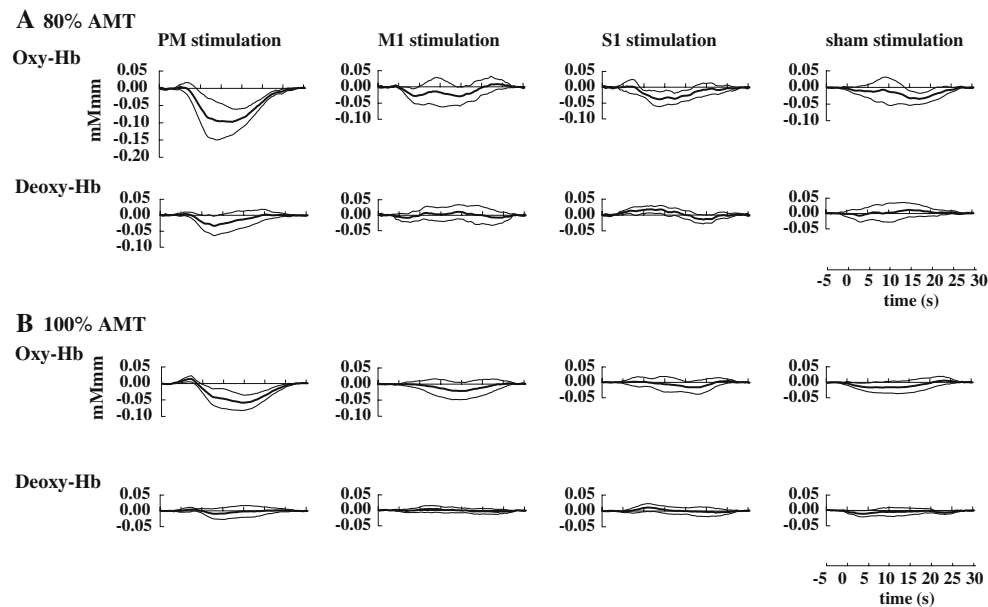


Fig. 3 NIRS recordings at right PM. Figure settings are all the same as Fig. 2. The PM stimulation evoked significant reduction of oxy Hb whereas no other stimulations elicited any changes

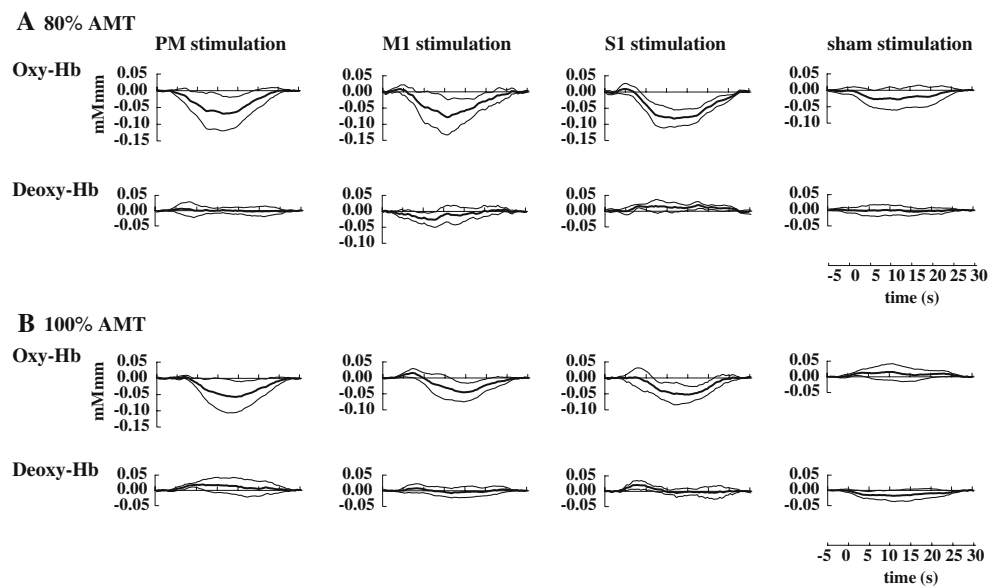


Fig. 4 NIRS recordings at right M1. Figure settings are all the same as Fig. 2. Significant oxy-Hb decrease was observed in the left PM (80% AMT) and S1 (80 and 100% AMT) stimulation conditions

At right M1, significant oxy-Hb decreases were observed in the left PM (80% AMT) and S1 (80 and 100% AMT) stimulation conditions (Fig. 4). At the right S1, significant decreases were observed in the left M1 (80 and 100% AMT) and S1 (80 and 100% AMT) stimulation conditions (Fig. 5). Sham stimulation induced no significant changes in oxy-Hb. No significant changes were observed in deoxy-Hb in any conditions.

Comparisons of mean oxy-Hb concentration changes between four sites of stimulation (stimulation SITE) or TBS intensities (INTENSITY) at each recording site showed some significant effects (SITE effects of 80% AMT TBS were summarized in Fig. 6). At the right PM, two-way ANOVA showed a significant stimulation SITE effect [SITE, $F(3, 56) = 7.38$, $P < 0.001$; INTENSITY, $F(1, 56) = 3.59$, $P = 0.06$] without any significant SITE \times INTENSITY interaction

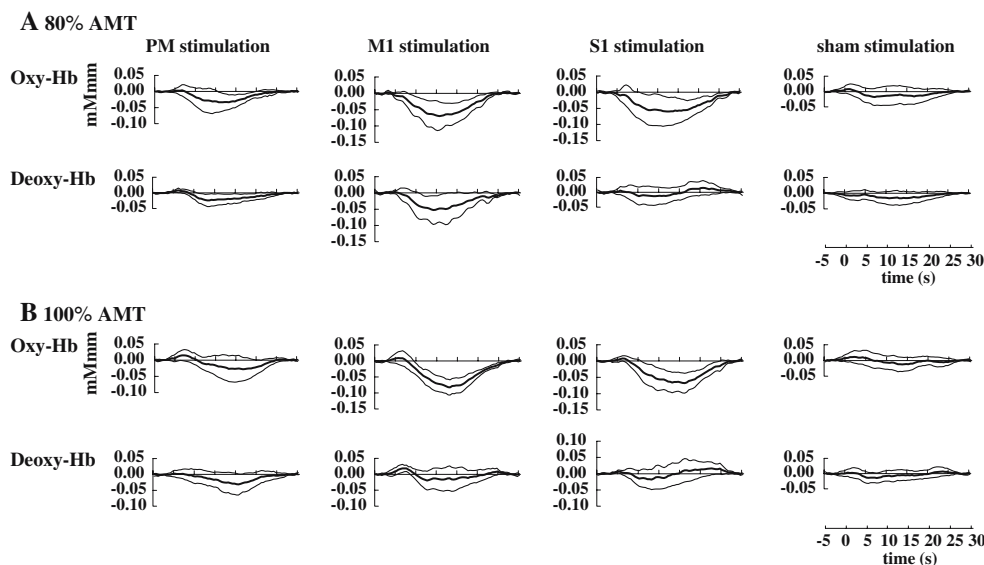


Fig. 5 NIRS recordings at right S1. Figure settings are all the same as Fig. 2. Significant oxy-Hb decreases were evoked by the left M1 (80 and 100% AMT) and S1 (80 and 100% AMT) stimulations

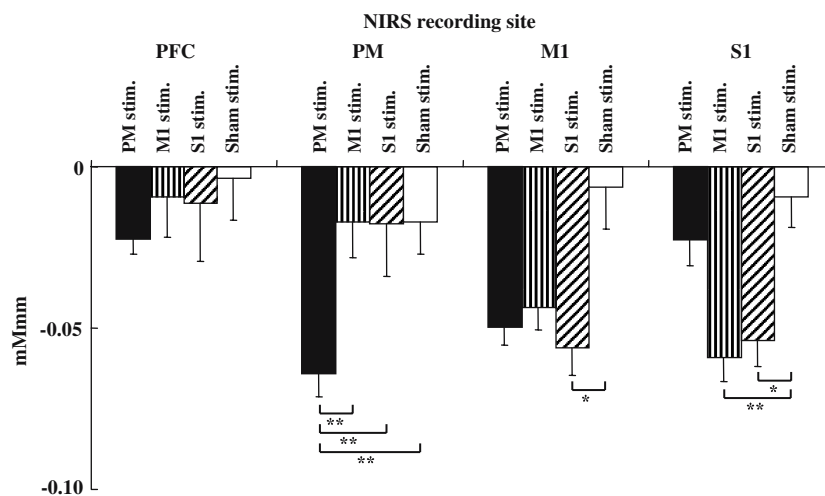


Fig. 6 Mean changes of relative oxy-Hb concentrations (averages of Hb concentration values from 5 to 20 s after the onset of TBS at 80% AMT) at right PFC, PM, M1 and S1. Concentration changes elicited by TBS over left PM are denoted by filled columns, M1 by longitudinal stripe columns, S1 by oblique stripe columns, and sham stimulation by non-filled columns. At PM, the contralateral PM stimulation induced a significant oxy-Hb

decrease. At M1, the contralateral S1 stimulation induced a significant oxy-Hb decrease; the contralateral M1 or S1 stimulation evoked a significant oxy-Hb decrease at S1. *Error bars* indicate standard errors. *Asterisks* indicate statistically significant changes ($*P < 0.05$, $**P < 0.01$, one-way ANOVA and post-hoc analysis with Scheffe's method)

[$F(3, 56) = 0.62$, $P = 0.61$] and post-hoc analysis revealed that TBS over left PM induced stronger oxy-Hb decrease than the other three stimulation sites ($P < 0.05$). At the right M1, there were significant SITE and INTENSITY effects [SITE, $F(3, 56) = 3.95$, $P = 0.01$; INTENSITY, $F(1, 56) = 4.79$, $P = 0.03$] without any significant SITE \times INTENSITY interaction [$F(3, 56) = 0.23$, $P = 0.88$]. Post-hoc analysis disclosed that TBS over left S1 induced deeper oxy-Hb reduction than sham stimulation ($P = 0.03$) whereas its effect did

not significantly differ from those evoked by TBS over left PM ($P = 0.07$) or M1 ($P = 0.15$). The significant INTENSITY effect meant that TBS effect at an intensity of 80% AMT was larger than that at 100% AMT. At the right S1, there was a significant SITE effect [SITE, $F(3, 56) = 5.98$, $P = 0.001$; INTENSITY, $F(1, 56) = 0.03$, $P = 0.86$] without any significant SITE \times INTENSITY interaction [$F(3, 56) = 0.14$, $P = 0.94$]. TBS over the left M1 or S1 induced more prominent oxy-Hb decrease than sham stimulation. At the right

PFC, there were no significant effects or interactions [SITE, $F(3, 56) = 1.34$, $P = 0.34$; INTENSITY, $F(1, 56) = 3.30$, $P = 0.08$; SITE \times INTENSITY, $F(3, 56) = 1.47$, $P = 0.23$].

The result of the additional physiological experiment was shown in Fig. 7. The MEP inhibition by TBS over S1 (28%) was significantly larger than that by sham stimulation (1%) (paired t -test: $P = 0.01$). This indicates that the right M1 was functionally suppressed after TBS over the left S1 in parallel with its oxy-Hb concentration reduction.

Discussion

The results of our present study can be summarized as follows. (1) TBS over PM induced a significant oxy-Hb decrease at the contralateral PM. (2) TBS over M1 induced significant oxy-Hb decrease at the contralateral S1 and TBS over S1 significant oxy-Hb decrease at the contralateral M1 and S1. (3) 80% AMT TBS over S1 induced larger oxy-Hb decrease at the contralateral hemisphere than that by 100% AMT TBS. (4) MEPs were also suppressed by conditioning TBS over the contralateral S1.

Oxy-Hb decrease

Three different patterns of NIRS changes have been reported in natural brain activation and TMS stimulation. First, large oxy-Hb increase and small deoxy-Hb decrease were observed in natural brain activation (Chance et al. 1988; Villringer et al. 1993; Kleinschmidt et al. 1996) or after low frequency rTMS (0.25 Hz; 30 stimuli) over the NIRS probes at an intensity of 100% of the maximal stimulator output, which was above the

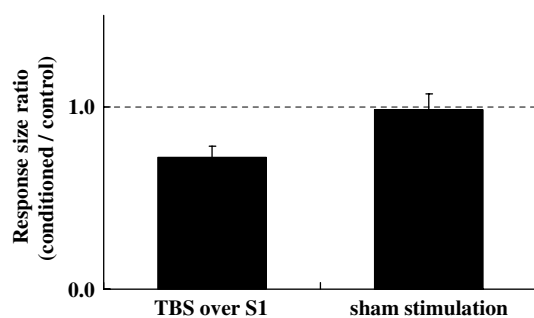


Fig. 7 Comparisons of the effects on MEPs from the left FDI evoked by TMS over right M1 between the conditioning TBS over left S1 and sham stimulation. The ratios were the average values of conditioned MEP/control MEP. TBS over left S1 induced a significant MEP decrease even though sham stimulation did not induce significant MEP changes. Error bars indicate standard errors

resting motor threshold (Oliviero et al. 1999). This pattern is usually called as activation. Another is large oxy-Hb decrease and small deoxy-Hb increase (Wenzel et al. 2000; Fabbri et al. 2003). This pattern is usually called as deactivation. The other one is small oxy-Hb change and large deoxy-Hb decrease. This pattern is observed only after a single pulse TMS under the center of the coil (Mochizuki et al. 2006). The pattern observed in the present study, large oxy-Hb decrease and small deoxy-Hb increase, is almost the same as that seen in natural deactivation among the above three patterns. Deoxy-Hb concentration, however, did not show any significant changes in the present results. This discrepancy might be due to the lower sensitivity of deoxy-Hb changes than oxy-Hb changes in NIRS measurement (Madsen and Secher 1999). We conclude that some deactivation must occur at the sensori-motor cortices after TBS over the contralateral sensori-motor cortices.

Some Hb concentration changes seemed to start a bit before the stimulation (e.g., in Fig. 4). Similar results are sometimes seen in some experiments. In the study of NIRS recording before and during gait (Miyai et al. 2001), oxy-Hb increase at supplementary motor areas started before gait. One explanation for this phenomenon is that Hb concentration changes begin when subjects can expect the start of the experiments. In our experiments, even the start of stimulation was randomized in time, randomization was not much enough to escape the expectation. It may partly explain the early start of Hb changes.

Interhemispheric connection

In animal studies, motor related areas and sensory cortex have direct connections with the contralateral homotopic and non-homotopic areas through the corpus callosum (Karol and Pandya 1971; Jenny 1979; Marconi et al. 2003). In humans, direct homotopic or non-homotopic connections have also been suggested to be present between bilateral primary motor and sensory cortices (Ferbert et al. 1992; Hanajima et al. 2001; Mochizuki et al. 2004a, b). The interhemispheric connections between other areas (e.g., PM to the contralateral PM) have not been studied physiologically because of the lack of detection methods for the function of those areas. Using a combination of NIRS and TMS, this study has physiologically proved that PM has a functional connection with the contralateral PM (directly or indirectly) in humans and that motor and sensory cortices interacted densely with the contralateral motor and sensory cortices.

The excitability changes underneath the coil most probably explain the inhibition of the contralateral

hemisphere after a short train of TMS through some interhemispheric interactions. The contralateral changes may be evoked without any changes under the coil. However, it is not plausible because we showed some changes under the coil in a previous paper (Mochizuki et al. 2006).

Intensity of TBS

The effect of 80% AMT TBS over S1 was larger than that of 100% AMT TBS. Münchau et al. (2002) reported that slow repetitive TMS over PM at an intensity of 80% AMT evoked intercortical facilitatory effects on the ipsilateral M1, but repetitive TMS at an intensity of 90% AMT had no effects. They speculated that these two areas have mutual facilitatory and inhibitory connections and stimulation at a higher intensity might evoke a mixture of effects that cancel out each other at 80% AMT. In another paired pulse TMS study (Civardi et al. 2001), single pulse TMS over PM at 90% AMT induced an inhibitory effect on ipsilateral M1, but when TMS was 110% AMT this inhibitory effect was changed to facilitatory one. In our study, 100% AMT TBS might have also evoked a mixture of facilitatory and inhibitory effects on the contralateral side and masked the inhibitory effect observed at 80% AMT TBS.

Physiological meaning

Between bilateral M1s the predominant connection is inhibitory. When one M1 is active, the contralateral M1 must be deactivated (Ferber et al. 1992; Schambra et al. 2003; Plewnia et al. 2003). This connection plays critical roles in bimanual movements. Our study has shown the physiological inhibitory connection between bilateral PMs in humans for the first time. This connection must much contribute to the interactions between both hemispheres in bimanual and one-hand movements. Our results also demonstrated dense inhibitory connections between bilateral M1s and S1s. S1 was strongly influenced by the ipsilateral M1 (Enomoto et al. 2001). Even though we cannot conclude whether the bilateral sensori-motor cortical connections are direct one or indirect one from the present results, our findings indicate dense interactions between bilateral primary motor and sensory cortices. Smooth, fine and coordinated bimanual movements must be guaranteed by combination of powerful bilateral PM connection and dense bilateral sensori-motor cortical connections.

In conclusion we found the interhemispheric inhibitory connections between bilateral PM, M1 and S1 using TBS and NIRS in humans, and these connections

would be requisite for bimanual coordinated movements in humans.

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