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RESEARCH ARTICLE

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Cortical hemoglobin-concentration changes under the coil induced by single-pulse TMS in humans: a simultaneous recording with near-infrared spectroscopy

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Abstract We measured cortical hemoglobin-concentration changes under the coil induced by single-pulse transcranial magnetic stimulation (TMS) using a technique of simultaneous recording with near-infrared spectroscopy (NIRS). Single-pulse TMS was delivered over the hand area of the left primary motor cortex at an intensity of 100, 120, or 140% of the active motor threshold (AMT). NIRS recordings were also made during sham stimulation. These four different stimulation sessions (TMS at three intensities and sham stimulation) were performed both when the subject slightly contracted the right first dorsal interosseous muscle and when relaxed it (active and resting conditions). Under the active condition with TMS at 100% AMT, we observed a transient increase in oxy-hemoglobin (oxy-Hb), which was significantly larger than sham stimulation. Under the resting conditions with TMS at 120 and 140% AMT, we observed significant decreases in both deoxy-hemoglobin (deoxyHb) and total-hemoglobin (total-Hb) as compared to sham stimulation. We suggest that the increase of oxy-Hb concentration at 100% AMT under the active condition reflects an add-on effect by TMS to the active baseline and that decrease of deoxy-Hb and total-Hb concentrations at 120 and 140% AMT under the resting condition are due to reduced baseline firings of the corticospinal tract neurons induced by a lasting inhibition provoked by a higher intensity TMS.

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

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Introduction

Transcranial magnetic stimulation (TMS) has been widely used in both clinical neurological (Currà et al. 2002) and neurophysiological examinations (Petersen et al. 2003; Chen 2004). Regional cerebral blood flow (rCBF) and cerebral metabolic changes induced by repetitive transcranial magnetic stimulation (rTMS) over the motor cortex have been studied by several researchers using positron emission computed tomography (PET), single-photon emission computed tomography (SPECT), or functional magnetic resonance imaging (fMRI) (Brandt et al. 1996; Fox et al. 1997; Wassermann et al. 1997; Paus et al. 1998; Bohning et al. 1999; Siebner et al. 2000, 2001; Baudewig et al. 2001; Bestmann et al. 2003; Okabe et al. 2003a). However, the results are inconsistent, presumably because of differences in the stimulation parameters of TMS: e.g., intensity, frequency, duration (total number of stimuli), and direction of currents in the brain. For example, at the site of stimulation (the motor cortex), rCBF or metabolic activity has been reported to increase (Brandt et al. 1996; Fox et al. 1997; Bohning et al. 1999; Paus et al. 1998; Siebner et al. 2000, 2001), decrease (Wassermann et al. 1997; Paus et al. 1998), or show no significant changes (Okabe et al. 2003a) during or after rTMS.

These previous functional imaging investigations have utilized rTMS with more than ten pulses and only a few studies have investigated rCBF changes induced by single-pulse TMS because of the following technical difficulties. First, the hemodynamic changes associated with single-pulse TMS are too small and transient to be

suitable for temporal resolution of SPECT or PET studies. Second, the large magnetic field produced by magnetic stimulation, as well as the mere presence of a TMS coil, interferes with the fMRI measurements due to low signal-to-noise ratio.

Near-infrared spectroscopy (NIRS) is one of appropriate non-invasive methods that allows visualization of the effect of single-pulse TMS. This method has three distinct advantages over the preexisting techniques: high signal-to-noise ratios for single events, non-interference with magnetic field changes, and no use of radioisotopes. This technique estimates hemoglobin (Hb) concentration changes by measuring the reflected light, based on the differences in absorption spectra between oxy-hemoglobin (oxy-Hb) and deoxy-hemoglobin (deoxy-Hb) (Jöbsis 1977; Chance et al. 1988; Villringer et al. 1993). Our previous study with NIRS has successfully detected Hb concentration changes evoked by single-pulse TMS using a novel technique to record NIRS signals just beneath the coil (Noguchi et al. 2003). Significant oxy-Hb increase was observed after single-pulse TMS when the subjects voluntarily contracted a target hand muscle.

Our previous result of oxy-Hb increase is consistent with a transient activation of the motor cortex above the active baseline by TMS. From a physiological point of view, it is known that transient, monosynaptic facilitation is almost always followed by di- or oligosynaptic inhibition in the central nervous system. In humans, such later inhibition at the motor cortex has also been known as the intracortical inhibition demonstrated by paired-pulse TMS (Kujirai et al. 1993; Ridding et al. 1995; Berardelli et al. 1996; Hanajima et al. 1998; Chen 2004) or as the silent period after motor-evoked potentials (MEPs) elicited by TMS (Inghilleri et al. 1993; Chen et al. 1999). The rCBF changes elicited by TMS may thus reflect the final outcome produced by a combination of all these short-lasting facilitation (facilitatory I-wave interaction), moderately lasting inhibition (mainly synaptic activities), and lasting inhibition of the postsynaptic neurons. According to analyses in vivo, synaptic activity causes an rCBF increase (Mathiesen et al. 1998, 2000; Strafella and Paus 2001), but it remains unknown whether the decrease of baseline activity at the postsynaptic neurons influences the rCBF or not. Such modification after TMS may be masked by voluntary activity of the motor cortex when the subjects contract the target muscle. In the present study, therefore, to study metabolic changes produced by TMS, we measured cortical Hb concentration changes induced by single-pulse TMS under active and resting conditions using a NIRS method and compared them.

Materials and methods

Subjects

Eight healthy volunteers (8 men, 28–51 years old) participated in this study. All subjects were right-handed, scoring 70–100 on the laterality quotient of the Edinburgh Handedness Inventory (Oldfield 1971). Written informed consent was obtained from all subjects after the nature and possible consequences of the studies were explained. The experimental procedures used here were approved by the Ethics Committee of the University of Tokyo, Hongo and were carried out in accordance to the Declaration of Helsinki.

Transcranial magnetic stimulation

Single-pulse 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 (The Magstim Co., Ltd, Whitland, UK). The coil was positioned over the hand area of the left primary motor cortex (M1). M1 was defined as the ''hot spot'' where a stimulation evoked the largest MEP from the right first dorsal interosseous (FDI) muscle. In two of them, that position was confirmed to be over the primary motor cortex by the neuronavigation system (Spetzger et al. 1995; Boroojerdi et al. 1999). The coil was oriented to induce medially directed currents in the brain. The intensity was adjusted to be 100, 120, and 140% of the active motor threshold (AMT) at M1. We defined the AMT as the lowest intensity that evoked five small responses (about 100 μV) in a series of ten stimulations when the subject made a 5% maximal voluntary contraction (MVC) (about 50 μV). Sham stimulation was performed as described in our previous report (Okabe et al. 2003b). During sham stimulation, the coil was positioned 10 cm above the head and discharged, while an electric stimulus was given to the skin of the head with electrodes fixed on the head to mimic skin sensation associated with real TMS. For this stimulation, we used a conventional electrical stimulator for peripheral nerves. The anode was placed over the left M1 and the cathode was over 5 cm anterior to the left M1. The duration of the electric stimulus was 0.2 ms, and the intensity was fixed at twice the sensory threshold for skin sensation. This protocol aimed to exclude non-specific effects associated with TMS, such as noise and skin sensation. TMS was tested under the eight different conditions in all the subjects. TMS pulses at three different intensities and sham stimulation were applied when the subject sustained a 10% MVC or when they maintained the relax condition. Each session consisted of 20 single TMS pulses given at random inter-trial intervals of 24–26 s. The same session was repeated two to four times to confirm the reproducibility of the results. The order of sessions was counterbalanced within and across the subjects.

NIRS measurement

We used the same NIRS system as described previously (Noguchi et al. 2003). In brief, the NIRS system (ETG-A1; Hitachi Medical Corporation, Tokyo, Japan)

consisted of two emitters and two detectors, and the four measurement points (midpoints) were placed on the center of the left-hand M1. These measurement points were aligned parallel to the medio-lateral line for minimizing the influence of the Hb-concentration change in the pre-motor and sensory cortices. 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. The combination of these wavelengths may not be the best selection because some degree of cross-talks between oxy-Hb and deoxy-Hb may occur in this combination (Uludag et al. 2002; Strangman et al. 2003) and the signal-to-noise ratio is not the highest (Yamashita et al. 2001; Sato et al. 2004). However, even using this combination of wavelengths, other groups (Watanabe et al. 1996, 1998; Isobe et al. 2001; Noguchi et al. 2003) have obtained several typical Hb-concentration changes same as those obtained by using another better combination of wavelengths. These suggest that our method could show

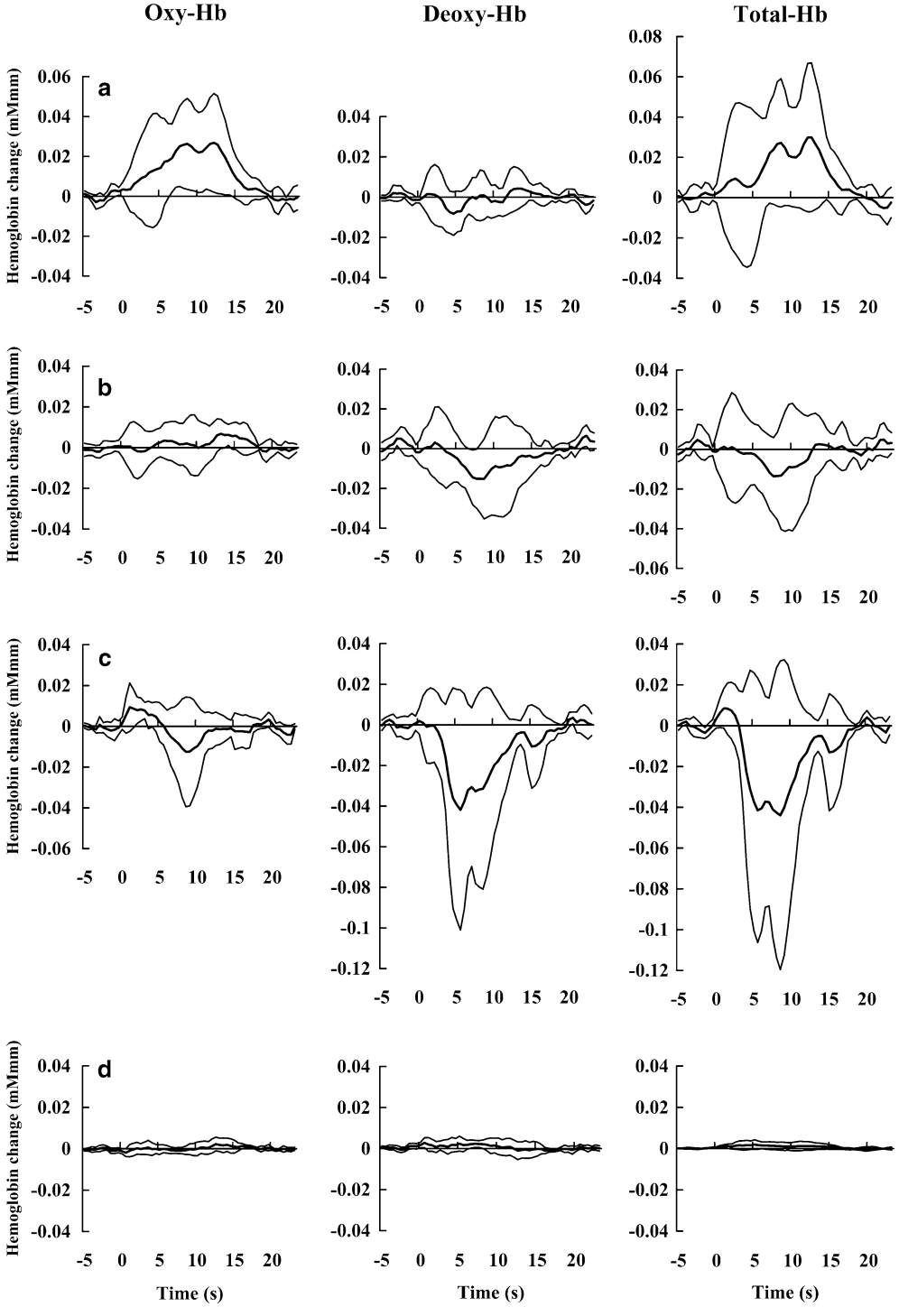

Fig. 1 Oxy-Hb (*left column*), deoxy-Hb (*middle column*), and total-Hb (*right column*) concentration changes after single-pulse TMS when the subject contracted FDI muscle (*active condition*): TMS at 100% AMT (**a**), 120% AMT (**b**), 140% AMT (**c**), and sham stimulation (**d**). Averaged data ($n=8$) obtained at three TMS intensities and sham stimulation are separately shown by *thick lines* and the 95% confidence intervals were indicated by *thin lines*

compatible results to other studies even though the wavelengths are not the best for NIRS recordings. The TMS coil was placed over the fiber probes on the scalp. The minimum distance between the coil and the scalp was 8.5 mm. We calculated concentrations of oxy-Hb, deoxy-Hb, and total hemoglobin (total-Hb) from the transmittance data with the two wavelengths. In this study, each event period ranged from 5 s before the TMS onset to 23 s thereafter. Each Hb change in each session was calculated by averaging the two data at the two measurement points. The Hb change was calculated under each condition by averaging the results of two to four sessions. The 95% confidence interval was also calculated for each time point of oxy-Hb, deoxy-Hb, and total-Hb changes. Two-way analysis of variance (ANOVA) (factors: active/resting condition and four

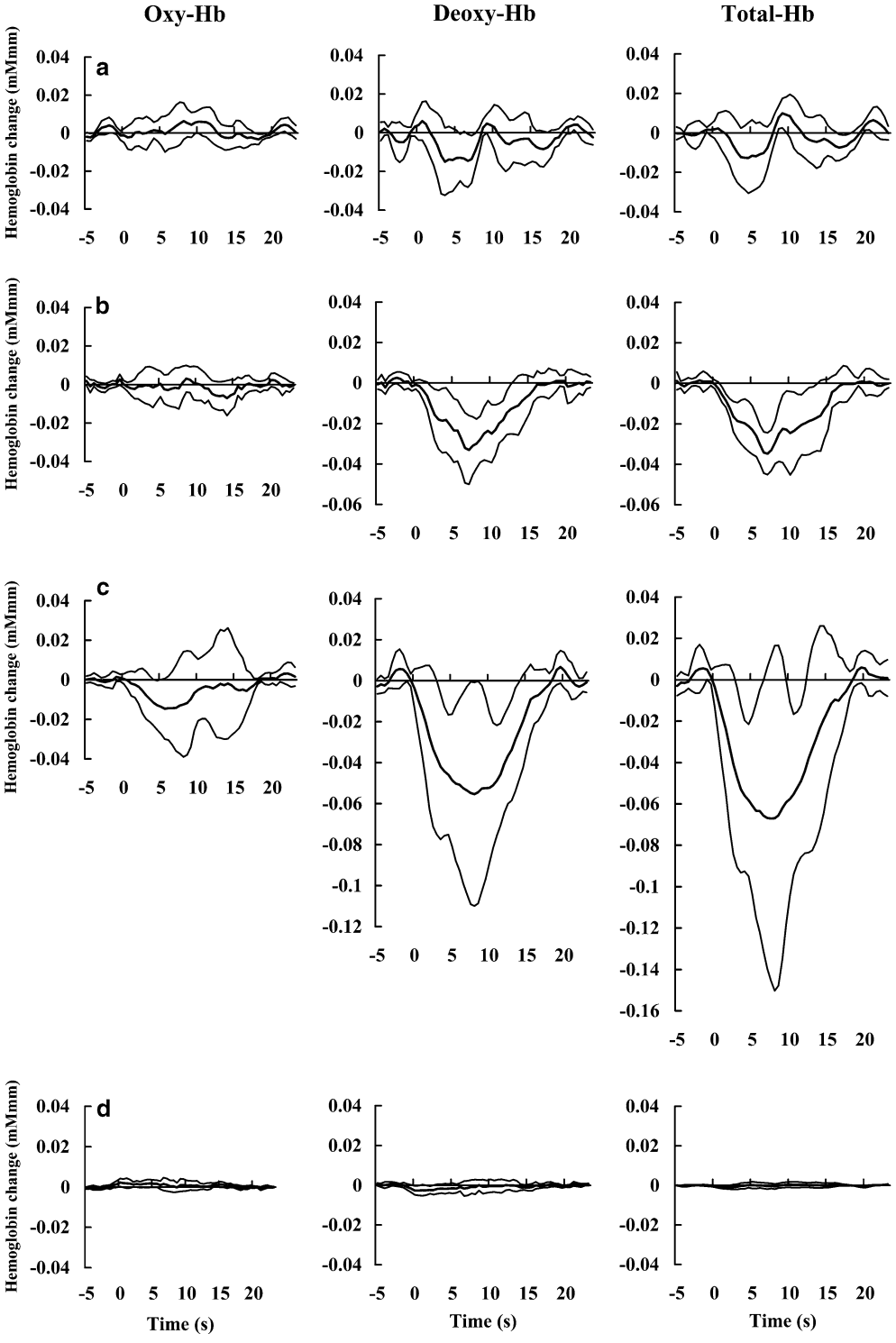

Fig. 2 Oxy-Hb (*left column*), deoxy-Hb (*middle column*), and total-Hb (*right column*) concentration changes after single-pulse TMS when the subject kept the FDI muscle relaxed (resting condition): 100% AMT (**a**), 120% AMT (**b**), 140% AMT (**c**), and sham stimulation (**d**). Averaged data ($n=8$) obtained at three TMS intensities and sham stimulation are separately shown by *thick lines* and the 95% confidence intervals are indicated by *thin lines*

types of TMS) was performed on the mean Hb changes by averaging the Hb data from 3 to 15 s after each TMS pulse.

Results

TMS under the active condition

Figure 1 shows averaged relative Hb-concentration changes and the 95% confidence intervals when the subjects made a 10% MVC (the active condition). Under the active condition with TMS at 100% AMT, oxy-Hb and total-Hb began to increase after the TMS onset, and returned to the baseline around 15 s later (Fig. 1a). The oxy-Hb significantly increased as compared to the baseline 7–14 s after the TMS onset, as shown by the 95% confidence lines (the lower dotted line was more than zero). In contrast, there were no significant changes in any Hb parameters at 120 and 140% AMT (Fig. 1b, c). We confirmed that the sham stimulation evoked no significant NIRS changes (Fig. 1d).

TMS under the resting condition

Figure 2 shows averaged relative Hb-concentration changes and the 95% confidence intervals, when the subject kept the right FDI relaxed (the resting condition). Under the resting conditions with TMS at 120 and 140% AMT, deoxy-Hb and total-Hb began to decrease 2–3 s after the TMS onset, and returned to the baseline about 15 s later (Fig. 2b, c). In contrast, neither TMS at 100% AMT nor the sham stimulation evoked significant changes in any Hb parameters. The deoxy-Hb at 120% AMT significantly decreased at 2–12 s after the TMS onset, and the total-Hb at 1–13 s. Similarly, at 140% AMT, the deoxy-Hb significantly decreased at 3–14 s after the TMS onset, and the total-Hb also decreased at 3–6 and 10–12 s.

Comparison across conditions

For comparisons between several conditions, we further calculated mean Hb changes in the oxy-Hb, deoxy-Hb, and total-Hb by averaging Hb values from 3 to 15 s after each TMS pulse (Fig. 3). Two-way ANOVA (factors: active/resting conditions and four TMS types) was performed for each parameter. It showed a significant main effect of TMS type on all the parameters (oxy-Hb, $F = 5.1$, $P = 0.003$; deoxy-Hb, $F = 6.6$, $P = 0.001$; total-Hb, $F = 6.6$, $P = 0.001$), as well as a significant main effect of conditions on oxy-Hb and total-Hb (oxy-Hb, $F = 4.7$, $P = 0.04$; deoxy-Hb, $F = 3.7$, $P = 0.06$; total-Hb, $F = 4.5$, $P = 0.04$), but without any significant interactions ($P > 0.05$). The oxy-Hb and total-Hb concentrations after the TMS pulse under the active condition were higher than those under the resting condition. Further analyses using paired t-test with corrections for multiple comparisons revealed that the oxy-Hb increase under the active condition with TMS at 100% AMT was significantly larger than the sham stimulation (Fig. 3a). Furthermore, the deoxy-Hb and total-Hb decreases under the resting condition with TMS at 120 and 140% AMT were significantly larger than the sham stimulation (Fig. 3b).

Discussion

The present study with NIRS technique has demonstrated cortical Hb-concentration changes under the coil induced by single-pulse TMS of the motor cortex. The oxy-Hb and total-Hb concentrations after TMS pulse under the active condition were higher than those under the resting condition. From the results of the 95% confidence intervals and comparisons with sham stimu-

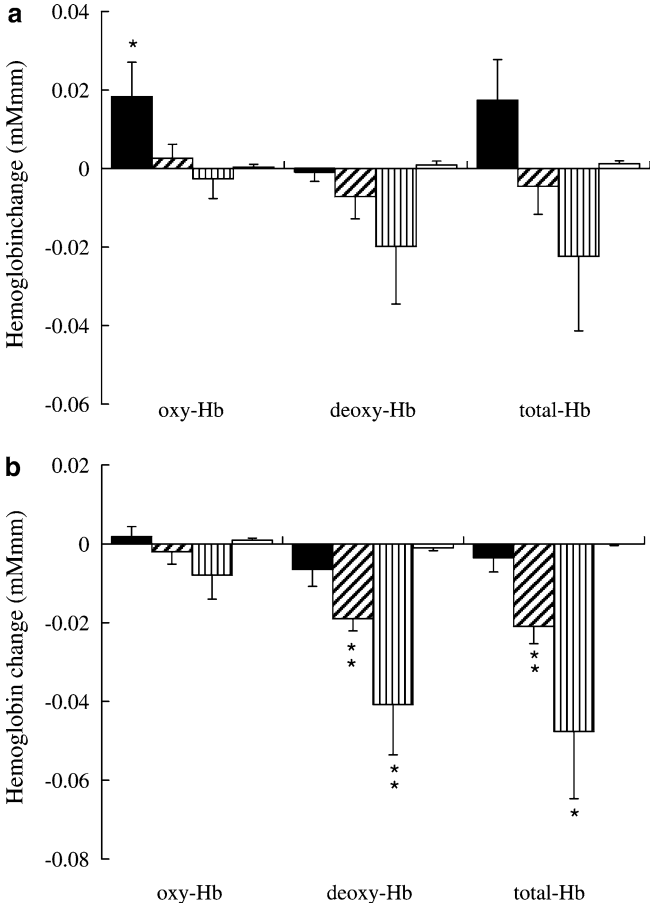

Fig. 3 Mean changes of relative oxy-Hb, deoxy-Hb, and total-Hb concentrations (averages of Hb concentration values from 3 to 15 s after TMS pulse) under the active (**a**) and resting (**b**) conditions. Concentration changes by TMS at 100% AMT are denoted by *filled columns*, 120% by *oblique stripe columns*, 140% by *longitudinal strip columns*, and sham stimulation by *non-filled columns*. *Error bars* indicate standard errors. *Asterisks* indicate the statistical significances ($^{*}P < 0.05$; $^{**}P < 0.01$, t-test corrected for multiple comparisons)

lation, TMS at 100% AMT produced a significant increase in oxy-Hb under the active condition. Under the resting condition, in contrast, TMS at 120 and 140% AMT produced significant decreases in total-Hb and deoxy-Hb.

The increment of oxy-Hb concentration under the active condition is consistent with the observation seen in other natural brain activations. It has no problems to explain what occurs in this condition. By contrast, our findings under resting condition are not consistent with any typical NIRS patterns previously reported in natural brain activation (oxy-Hb and total-Hb increases and slight deoxy-Hb decrease; Chance et al. 1988; Villringer et al. 1993; Kleinschmidt et al. 1996; Watanabe et al. 1996, 1998; Isobe et al. 2001; Mehagnoul-Schipper et al. 2002) or deactivation (oxy-Hb decrease and deoxy-Hb increase; Wenzel et al. 2000).

Two possibilities may explain our findings which have not been reported yet. One is that our findings are wrong probably because of some flaw of our method. The NIRS recording using the 790- and 830-nm wavelength combination is reported to be affected by some degree of cross-talks between oxy-Hb and deoxy-Hb (Uludag et al. 2002; Strangman et al. 2003). This may cause inconsistency of our results. However, even using this combination, we got several typical patterns of Hb-concentration changes in natural brain activations (Watanabe et al. 1996, 1998; Isobe et al. 2001; Noguchi et al. 2003). Moreover, in weak TMS (100% AMT) experiments during contraction in our present results, we got a typical pattern of Hb-concentration changes same as that already shown in natural brain activation. This may be due to the fact that weak stimulation is nearer to natural brain activation than strong TMS. These facts suggest that our combination of wavelength must give us reasonable results of Hb-concentration changes even with a small contamination of cross-talks. Based on these arguments, we conclude that our result under resting condition is not just a wrong result due to cross-talks. The other possibility is that our present new pattern of Hb-concentration changes must have some physiological meanings (see later discussion). The most important difference of our experiment from other previous studies using NIRS is that we investigated the effect of TMS, an artificial neural activation and not the natural brain activation. Weak TMS pulses at around 100% AMT may mimic a natural activation, but strong TMS pulses at more than 120% AMT must evoke unusual powerful synchronization. It should never occur in natural brain activations. Therefore, it is not surprising that our results are not the same as any other previous patterns.

We can exclude the possibility that the associated scalp movement or Hb-concentration changes in the skin cause the present results. No scalp movement was evoked even by TMS at 140%, and the higher intensity TMS evoked only slight contraction of right-hand muscles without any contraction of neck muscles. Moreover, the 32-mm distance between two NIRS probes is appropriate for detecting the Hb-concentration changes at the cortex, but it is too long to detect Hb-concentration changes at the skin (Germon et al. 1999). Electric stimulation on the skin in sham stimulation, which may elicit skin Hb-concentration changes similar to the real stimulation, evoked no detectable NIRS changes. Therefore, we conclude that the observed NIRS changes were the Hb-concentration changes at the cortex directly elicited by TMS.

Studies on exposed brain tissues of animals have demonstrated that brain activation is associated with an early decrease (initial dip) followed by a subsequent increase of oxy-Hb concentration (Malonek and Grinvald 1996). The initial dip is not always detected with conventional imaging methods because it is small and short lasting. The observable oxy-Hb concentration increase has been confirmed with the NIRS method in previous reports during voluntary muscular contraction (Kleinschmidt et al. 1996; Mehagnoul-Schipper et al. 2002). Using the same NIRS recording probes as those used in the present experiments, we also recorded oxy-Hb-concentration increase associated with a slight decrease of deoxy-Hb over the primary motor cortex during a natural self-paced voluntary contraction of the target muscle (data not shown). In those records, the oxy-Hb concentration began to increase about 4 s after the onset of contraction, gradually decrease toward the baseline and finally returned to it about 15 s after the contraction. No decrease was observed in the oxy-Hb concentration. An increase in oxy-Hb concentration observed under the active condition with TMS at 100% AMT is consistent with our previous results (Noguchi et al. 2003), and compatible with the above-mentioned brain activation during the physiological process (voluntary contraction). Under this condition, the overall contraction makes the cortex more excitable than the resting condition, and TMS further adds facilitation to this active level for a short period. Weak TMS pulses at around 100% AMT may mimic a natural activation and may not produce large inhibitory effects of TMS, because voluntary contraction usually cancels the inhibitory effect in the target muscle (Ridding et al. 1995). This cancellation of inhibition would induce the oxy-Hb and total-Hb increases under the active condition. But the deoxy-Hb concentration did not show such a significant increase. This discrepancy would be due to the lower sensitivity of deoxy-Hb changes than oxy-Hb or total-Hb changes in NIRS measurement (Madsen and Secher 1999). In the case of TMS at 140% AMT, a long-lasting inhibition after short-lasting facilitation has been reported (Inghilleri et al. 1993; Berardelli et al. 1996; Hanajima et al. 1998; Moliadze et al. 2003; Chen 2004), which would not be masked by the voluntary contraction. This may explain why TMS at 140% AMT produced a different pattern of signal changes from that observed during TMS at 100% AMT (see later discussion on mechanisms for this pattern).

Under the resting condition, decreases of total-Hb and deoxy-Hb occurred without any changes of oxy-Hb

concentration. No reports have shown this pattern of changes in Hb concentration. Reafferentation due to movements does not explain these changes because 100% RMT is about 130–140% AMT (Tergau et al. 1999; Khedr et al. 2004) and so TMS at 120% AMT usually elicited no movements in the resting condition, and because reafferentation causes an increase (not a decrease) of rCBF in the PET study (Mima et al. 1999). In this study, there was an obvious total-Hb (rCBF) decrease after TMS. Even though animal experiments have had no good explanation for rCBF decrease, many PET or SPECT studies have shown reduction of rCBF or metabolism evoked by rTMS (Wassermann et al. 1997; Paus et al. 1998; Okabe et al. 2003a; Hayashi et al. 2004). A possible explanation is vasoconstriction elicited by TMS, but this contribution may be small, because vasoconstriction should produce large decreases of total-Hb and oxy-Hb (Fantini 2002; Fabbri et al. 2003), while oxy-Hb showed no change in our results.

In animal experiments on cerebellar cortex, synaptic activity produces a rCBF increase whether it is facilitatory or inhibitory, and firings of Purkinje cells partly contribute to the rCBF changes (Mathiesen et al. 1998). Since the resting firing frequency of the corticospinal tract (CST) neurons is moderately high (Evarts 1964), the postsynaptic firing reduction must cause a CBF decrease. Furthermore, because a TMS pulse evokes synchronous suppression of many CST neurons after activation, such as known as the silent period after activation, the resting firings of CST neurons decrease dramatically after single-pulse TMS. A practical recording showed dramatic firing decrease after TMS pulse in cat visual cortex (Moliadze et al. 2003). So, the total firing number of CST neurons must be reduced after single-pulse TMS. These suppressions physiologically seen at 100–200 ms after stimulation must cause CBF changes seen at several seconds after stimulation. This lag time between the physiological event and the CBF change is always observed (Villringer et al. 1993; Malonek and Grinvald 1996; Mathiesen et al. 1998; Noguchi et al. 2003). At the site under the coil, during stimulation, both facilitatory and inhibitory synaptic activities evoke a rCBF increase and postsynaptic long-lasting reduction of firings must cause a rCBF decrease. The combination of these two opposite effects may provoke a rCBF decrease and postsynaptic neuronal suppression. These rCBF changes must be detected as Hb-concentration changes in our study. Consequently, all of oxy-Hb, deoxy-Hb, and total-Hb supplies to these regions will decrease. The oxygen consumption must also be reduced in the inhibited areas, and then the oxy-Hb is not used. The reduction of oxy-Hb supply and decrease of its consumption finally result in the unchanged oxy-Hb concentration. Therefore, these changes will finally lead to decreases in total-Hb and deoxy-Hb and absence of oxy-Hb changes.

As mentioned above, under the active condition with weak stimulation, voluntary motor command would surpass the inhibition elicited by TMS and thus only a short-latency facilitation was observed. However, under the active condition with strong intensity, powerful inhibition may become greater than the facilitatory effect produced by voluntary contraction. The NIRS pattern of TMS at 140% AMT under the active condition thus becomes very similar to that under the resting condition.

In conclusion, the present study showed cortical Hb-concentration changes induced by single-pulse TMS of the motor cortex, suggesting that the oxy-Hb increase at 100% AMT under the active condition reflects a facilitatory effect by TMS, and that the decreases of deoxy-Hb and total-Hb at 120 and 140% AMT under the resting condition are due to postsynaptic firing-frequency reduction induced by a higher intensity TMS.

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References

Baudewig J, Siebner HR, Bestmann S, Tergau F, Tings T, Paulus W, Frahm J (2001) Functional MRI of cortical activations induced by transcranial magnetic stimulation (TMS). Neuroreport 12:3543–3548

Berardelli A, Rona S, Inghilleri M, Manfredi M (1996) Cortical inhibition in Parkinson's disease. A study with paired magnetic stimulation. Brain 119:71–77

Bestmann S, Baudewig J, Siebner HR, Rothwell JC, Frahm J (2003) Subthreshold high-frequency TMS of human primary motor cortex modulates interconnected frontal motor areas as detected by interleaved fMRI-TMS. Neuroimage 20:1685–1696

Bohning DE, Shastri A, McConnell KA, Nahas Z, Lorberbaum JP, Roberts DR, Teneback C, Vincent DJ, George MS (1999) A combined TMS/fMRI study of intensity-dependent TMS over motor cortex. Biol Psychiatry 45:385–394

Boroojerdi B, Foltys H, Krings T, Spetzger U, Thron A, Töpper R (1999) Localization of the motor hand area using transcranial magnetic stimulation and functional magnetic resonance imaging. Clin Neurophysiol 110:699–704

Brandt SA, Davis TL, Obrig H, Meyer BU, Belliveau JW, Rosen BR, Villringer A (1996) Functional magnetic resonance imaging shows localized brain activation during serial transcranial stimulation in man. Neuroreport 7:734–736

Chance B, Leigh JS, Miyake H, Smith DS, Nioka S, Greenfeld R, Finander M, Kaufmann K, Levy W, Young M, Cohen P, Yoshioka H, Boretsky R (1988) Comparison of time-resolved and -unresolved measurements of deoxyhemoglobin in brain. Proc Natl Acad Sci USA 85:4971–4975

Chen R, Lozano AM, Ashby P (1999) Mechanism of the silent period following transcranial magnetic stimulation. Evidence from epidural recordings. Exp Brain Res 128:539–542

Chen R (2004) Interactions between inhibitory and excitatory circuits in the human motor cortex. Exp Brain Res 154:1–10

Currà A, Modugno N, Inghilleri M, Manfredi M, Hallett M, Berardelli A (2002) Transcranial magnetic stimulation techniques in clinical investigation. Neurology 59:1851–1859

Evarts EV (1964) Temporal patterns of discharge of pyramidal tract neurons during sleep and waking in the monkey. J Neurophysiol 27:152–171

Fabbri F, Henry ME, Renshaw PF, Nadgir S, Ehrenberg BL, Franceschini MA, Fantini S (2003) Bilateral near-infrared monitoring of the cerebral concentration and oxygen-saturation of hemoglobin during right unilateral electro-convulsive therapy. Brain Res 992:193–204

Fantini S (2002) A haemodynamic model for the physiological interpretation of in vivo measurements of the concentration and oxygen saturation of haemoglobin. Phys Med Biol 47:N249–N57

Fox P, Ingham R, George MS, Mayberg H, Ingham J, Roby J, Martin C, Jerabek P (1997) Imaging human intra-cerebral connectivity by PET during TMS. Neuroreport 8:2787–2791

Germon TJ, Evans PD, Barnett NJ, Wall P, Manara AR, Nelson RJ (1999) Cerebral near infrared spectroscopy: emitter-detector separation must be increased. Br J Anaesth 82:831–837

Hanajima R, Ugawa Y, Terao Y, Sakai K, Furubayashi T, Machii K, Kanazawa I (1998) Paired-pulse magnetic stimulation of the human motor cortex: differences among I waves. J Physiol 509:607–618

Hayashi T, Ohnishi T, Okabe S, Teramoto N, Nonaka Y, Watabe H, Imabayashi E, Ohta Y, Jino H, Ejima N, Sawada T, Iida H, Matsuda H, Ugawa Y (2004) Long-term effect of motor cortical repetitive transcranial magnetic stimulation induces. Ann Neurol 56:77–85

Inghilleri M, Berardelli A, Cruccu G, Manfredi M (1993) Silent period evoked by transcranial stimulation of the human cortex and cervicomedullary junction. J Physiol 446:521–534

Isobe K, Kusaka T, Nagano K, Okubo K, Yasuda S, Kondo M, Itoh S, Onishi S (2001) Functional imaging of the brain in sedated newborn infants using near infrared topography during passive knee movement. Neurosci Lett 299:221–224

Jöbsis FF (1997) Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. Science 198:1264–1267

Khedr EM, Gilio F, Rothwell JC (2004) Effects of low frequency and low intensity repetitive paired pulse stimulation of the primary motor cortex. Clin Neurophysiol 115:1259–1263

Kleinschmidt A, Obrig H, Requardt M, Merboldt KD, Dirnagl U, Villringer A, Frahm J (1996) Simultaneous recording of cerebral blood oxygenation changes during human brain activation by magnetic resonance imaging and near-infrared spectroscopy. J Cereb Blood Flow Metab 16:817–826

Kujirai T, Caramia MD, Rothwell JC, Day BL, Thompson PD, Ferbert A, Wroe S, Assleman P, Marsden CD (1993) Cortical inhibition in human motor cortex. J Physiol 471:501–519

Madsen PL, Secher NH (1999) Near-infrared oximetry of the brain. Prog Neurobiol 58:541–560

Malonek D, Grinvald A (1996) Interactions between electrical activity and cortical microcirculation revealed by imaging spectroscopy: implications for functional brain mapping. Science 26:551–554

Mathiesen C, Caesar K, Akgören N, Lauritzen M (1998) Modification of activity-dependent increases of cerebral blood flow by excitatory synaptic activity and spikes in rat cerebellar cortex. J Physiol 512:555–566

Mathiesen C, Caesar K, Lauritzen M (2000) Temporal coupling between neuronal activity and blood flow in rat cerebellar cortex as indicated by field potential analysis. J Physiol 523:235–246

Mehagnoul-Schipper DJ, van der Kallen BFW, Colier WNJM, van der Sluijs MC, van Erning LJTO, Thijssen HOM, Oeseburg B, Hoefnagels WHL, Jansen RWMM (2002) Simultaneous measurements of cerebral oxygenation changes during brain activation by near-infrared spectroscopy and functional magnetic resonance imaging in healthy young and elderly subjects. Hum Brain Mapp 16:14–23

Mima T, Sadato N, Yazawa S, Hanakawa T, Fukuyama H, Yonekura Y, Shibasaki H (1999) Brain structures related to active and passive finger movements in man. Brain 122:1989–1997

Moliadze V, Zhao Y, Eysel U, Funke K (2003) Effect of transcranial magnetic stimulation on single-unit activity in the cat primary visual cortex. J Physiol 553:665–679

Noguchi Y, Watanabe E, Sakai KL (2003) An event-related optical topography study of cortical activation induced by single-pulse transcranial magnetic stimulation. Neuroimage 19:156–162

Okabe S, Hanajima R, Ohnishi T, Nishikawa M, Imabayashi E, Takano H, Kawachi T, Matsuda H, Shiio Y, Iwata NK, Furubayashi T, Terao Y, Ugawa Y (2003a) Functional connectivity revealed by single-photon emission computed tomography (SPECT) during repetitive transcranial magnetic stimulation (rTMS) of the motor cortex. Clin Neurophysiol 114:450–457

Okabe S, Ugawa Y, Kanazawa I (2003b) The effectiveness of rTMS on Parkinson's disease study group 0.2-Hz repetitive transcranial magnetic stimulation has no add-on effects as compared to a realistic sham stimulation in Parkinson's disease. Mov Disord 18:382–388

Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9:97–113

Paus T, Jech R, Thompson CJ, Comeau R, Peters T, Evans AC (1998) Dose-dependent reduction of cerebral blood flow during rapid-rate transcranial magnetic stimulation of the human sensorimotor cortex. J Neurophysiol 79:1102–1107

Petersen NT, Pyndt HS, Nielsen JB (2003) Investigating human motor control by transcranial magnetic stimulation. Exp Brain Res 152:1–16

Ridding MC, Tavlor JL, Rothwell JC (1995) The effect of voluntary contraction on cortico-cortical inhibition in human motor cortex. J Physiol 487:541–548

Sato H, Kiguchi M, Kawaguchi F, Maki A (2004) Practicality of wavelength selection to improve signal-to-noise ratio in near-infrared spectroscopy. Neuroimage 21:1554–1562

Siebner HR, Peller M, Willoch F, Minoshima S, Boecker H, Auer C, Drzrezga A, Conrad B, Bartenstein P (2000) Lasting cortical activation after repetitive TMS of the motor cortex: a glucose metabolic study. Neurology 54:956–963

Siebner HR, Takano B, Peinemann A, Schwaiger M, Conrad B, Drzezga A (2001) Continuous transcranial magnetic stimulation during position emission tomography: a suitable tool for imaging regional excitability of the human cortex. Neuroimage 14:883–890

Spetzger U, Laborde G, Gilsbach JM (1995) Frameless neuronavigation in modern neurosurgery. Minim Invasive Neurosurg 38:163–166

Strangman G, Franceschini MA, Boas DA (2003) Factors affecting the accuracy of near-infrared spectroscopy concentration calculations for focal changes in oxygenation parameters. Neuroimage 18:865–879

Strafella AP, Paus T (2001) Cerebral blood-flow changes induced by paired-pulse transcranial magnetic stimulation of the primary motor cortex. J Neurophysiol 85:2624–2629

Tergau F, Wanschura V, Canelo M, Wischer S, Wassermann EM, Ziemann U, Paulus W (1999) Complete suppression of voluntary motor drive during the silent period after transcranial magnetic stimulation. Exp Brain Res 124:447–454

Uludag K, Kohl M, Steinbrink J, Obrig H, Villringer A (2002) Cross talk in the Lambert–Beer calculation for near-infrared wavelengths estimated by Monte Carlo simulations. J Biomed Opt 7:51–59

Villringer A, Planck J, Hock C, Schleinkofer L, Dirnagl U (1993) Near infrared spectroscopy (NIRS): a new tool to study hemodynamic changes during activation of brain function in human adults. Neurosci Lett 154:101–104

Wassermann EM, Kimbrell TA, George MS, Danielson AL, Herscovitch P, Hallett M, Post RM (1997) Local and distinct changes in cerebral glucose metabolism during repetitive transcranial magnetic stimulation (rTMS). Neurology 48:A107–A108

Watanabe E, Yamashita Y, Maki A, Ito Y, Koizumi H (1996) Non-invasive functional mapping with multi-channel near infrared spectroscopic topography in humans. Neurosci Lett 205:41–44

Watanabe E, Maki A, Kawaguchi F, Takashiro K, Yamashita Y, Koizumi H, Mayanagi Y (1998) Non-invasive assessment of language dominance with near-infrared spectroscopic mapping. Neurosci Lett 256:49–52

Wenzel R, Wobst P, Heekeren HH, Kwong KK, Brandt SA, Kohl M, Obrig H, Dirnagl U, Villringer A (2000) Saccadic suppression induces focal hypooxygenation in the occipital cortex. J Cereb Blood Flow Metab 20:1103–1110

Yamashita Y, Maki A, Koizumi H (2001) Wavelength dependence of the precision of noninvasive optical measurement of oxy-, deoxy-, and total-hemoglobin concentration. Med Phys 28:1108–1114