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TMS Orientation for NIRS-Functional Motor Mapping

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Summary: Functional near-infrared spectroscopic imaging (NIRS imaging) has the potential to elucidate the relationship between neuronal activity and oxygenation responses. However, its signal specificity to the functional cortex is sometimes spoiled by its rough spatial resolution. In this study we incorporated transcranial magnetic stimulation (TMS) motor mapping into an NIRS imaging study to enhance spatial specificity to the functional cortex. Distinctive biphasic responses in the cortical oxygenation status were observed in the center of the primary motor cortex during a motor task. The early response phase, occurring within 1 to 3 seconds after task initiation, represents a cortical deoxygenation which consists of a significant increase in deoxygenated hemoglobin concentration (HbR) and a nonsignificant decreasing tendency in oxygenated hemoglobin concentration (HbO_2). The delayed response phase represents an excess of incoming blood flow, which appears as an increase in HbO_2/total Hb (tHb) and a decrease in HbR following the early response. In the surrounding area, cortical oxygenation change showed a monophasic response consisting of an increase in HbO_2 /tHb and a decrease in HbR. Combining TMS mapping with NIRS imaging enabled us to specify the cortex with the strongest functional activity.

Key words: Near-infrared spectroscopy (NIRS) imaging; Cortical oxygenation; Transcranial magnetic stimulation; Initial dip.

Introduction

Functional near-infrared spectroscopic imaging (NIRS imaging) is a developing neuroimaging technique that measures oxygenated hemoglobin (HbO_2) and deoxygenated hemoglobin (HbR) independently in capillary beds of the cerebral cortex by means of near-infrared light passing through the scalp and the skull. This human noninvasive optical methodology proposed by Jobsis in 1977 (Jobsis 1977) has made progress by some investigators (Hoshi et al. 1993; Kato et al. 1993; Villringer et al. 1993), who introduced a concept of functional NIRS imaging, in which enhanced local cerebral oxygen metabolism in the functional activated cortex was differentiated from nonenhanced metabolism in the nonactivated cortex by scattering near-infrared light. Since then, NIRS imaging has been utilized as a means of bed-side functional brain monitoring for evaluating local cortical oxygenation changes during visual (Kato et al. 1993), motor (Hirth et al. 1996; Watanabe et al. 1996) and cognitive tasks (Fallgatter et al. 1997; Yamamoto et al. 2002) that can be applied even to neonates (Sakatani et al. 1999). Although NIRS imaging has been accepted as a means of bedside functional brain monitoring, some problems remain to be solved, namely, the establishment of the physiological basis for observing cortical oxygen metabolism through near-infrared light, and the improvement in the spatial accuracy of this methodology through technical progress. Both of these problems have not been discussed thoroughly to date.

Transcranial magnetic stimulation (TMS) has been widely used as a tool for functional brain mapping because of its accurate detection of activation sites from the surface of the scalp (Barker et al. 1985; Wassermann et al. 1992) and its good correlation with direct electrical cortical stimulation (Krings et al. 1997). Co-localization studies of TMS and fMRI/PET have also revealed good concordance between neural activity and both fMRI signals (Boroojerdi et al. 1999; Neggers et al. 2004) and PET activation maxima (Wassermann et al. 1996).

Because the absence of spatial specificity to the functional cortex in NIRS imaging causes mislocalization of the targeted cortex resulting from low spatial resolution and rough arrangement of the probes, we expected that the NIRS signal could be made more specific to the functional cortex with the aid of TMS mapping. The aim of this study is thus to extract dynamic oxygenation changes from the genuine functional cortex based on the results of TMS mapping. We used TMS motor mapping and a motor task in NIRS imaging as a simple

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model. In analysis, we particularly focus on the early phase deoxygenation in the functional cortex as a task-specific metabolic change

Material and Methods

Subjects

This study was performed on 10 healthy young adults (6 males and 4 females), 24 to 34 years of age (average 29.5), who gave written informed consent after receiving and understanding a full explanation of the study. All the subjects were confirmed to be right-handed.

Method

The study was conducted by using TMS and NIRS imaging.

TMS Measurement

A tightly fitting cap, with a premarked grid of 8 × 8 points, 1 cm apart, was placed on the subject's head. The grid started at 2 cm lateral from Cz towards the ear, and covered the area from 2 cm to 10 cm lateral from Cz and between 5 cm anterior and 3 cm posterior to the line passing through Cz and the preauricular crease. Focal TMS was delivered using a figure-of-eight shaped coil with loops of 7 cm in diameter. The coil was connected to a MAGSTIM 200 stimulator (The Magstim Company Ltd, UK), which delivers monophasic pulses with a maximum field strength of 2.2 Tesla. During stimulation, the coil was positioned with the handle pointing backward and approximately 45° lateral from the midline, and its center (the intersection of the coil's wings) is in contact with and tangential to the scalp at the point of stimulation. With this coil orientation, the current induced in the brain flows perpendicular to the line of the central sulcus, which leads to a predominantly transsynaptic activation of the corticospinal system (Kaneko et al. 1996).

The motor threshold was defined as follows. The site where the largest motor-evoked potentials (MEPs) could be evoked was first explored, wherein the threshold was then determined as the stimulus intensity level at which the stimulus evoked an MEP with an amplitude larger than 20 μV in at least three out of five consecutive trials. The stimulus intensity was set at a level of 120% of the motor threshold.

EMG recordings were obtained with Ag surface electrodes applied to the relaxed abductor pollicis brevis (APB) muscle of the right hand. Electromyographic activity was recorded by a Neuropack 8 (Nihon Kohden, Japan) with a bandpass filter of 2–3000 Hz and a gain of 100–500 μV per division. Data were stored on a hard disk for later off-line analysis. Muscle relaxation was confirmed by EMG monitoring before and several times during the experiment.

Peak-to-peak amplitudes of 5 MEPs obtained from each stimulation site were averaged after data acquisition. Using these amplitudes, the MEP centers of gravity (CoG) were calculated by the formula $X_{\mathrm{CoG}} = \sum_i A_i X_i / \sum_i A_i$, where A_i stands for the mean MEP amplitude at the site and X_i stands for the antero-posterior distance of the stimulation points from the vertex. The Y coordinate of the CoG (medio-lateral distance from the midline) was calculated by replacing X values in the formula by Y values. To represent intersubject averaged mapping, the relative MEPs were normalized to the largest relative response in the APB in each subject (largest MEP obtained = 100%). After the calculation of CoG, the exact position of the calculated CoG (X_{CoG}, Y_{CoG}) for the right APB was marked on the subject's head surface. In one of the subjects, anatomical MRI was performed using a T1-WI [1.5 × 1.4 × 0.5 mm resolution, TR/TE = 11.4/4.4 ms] with a fiducial marker (vitamin E capsule) placed on the calculated CoG to confirm the concordance of the anatomically defined and functionally defined motor cortex (Huppert et al. 2006).

NIRS Imaging Measurement

For the NIRS imaging measurement, we used three-wavelength (780, 805 and 830 nm) multichannel NIRS imaging equipment (OMM2001, Shimadzu, Japan), which consists of three pairs of emitting and detecting optical fibers attached to a square pad placed on the left side of the head. These optical fibers are arranged as shown in Fig. 1 to make a grid of 7 detecting points. The distance between the fibers was 30 mm, making the detecting points centered between the fibers at a depth of 15 to 20 mm (Kato et al. 1993). To record specific oxygenation changes in the strongest activation site in the primary motor cortex during motor tasks, we set the central NIRS image detecting channel on the CoG calculated from TMS for the right APB muscle.

The sampling time for the data acquisition was 130 ms. Changes in HbO_2, HbR and total Hb (tHb) were calculated by using different absorption indices at three wavelengths as shown below (Matcher et al. 1995).

$$\begin{aligned}\mathrm{HbO_2} &= -1.4887 \times \Delta\mathrm{Abs780\,nm} + 0.5970 \times \Delta\mathrm{Abs805\,nm} \\ &\quad + 1.4847 \times \Delta\mathrm{Abs830\,nm} \\ \mathrm{HbR} &= 1.8545 \times \Delta\mathrm{Abs780\,nm} - 0.2394 \times \Delta\mathrm{Abs805\,nm} \\ &\quad - 1.0947 \times \Delta\mathrm{Abs830\,nm} \\ \mathrm{tHb} &= 0.3658 \times \Delta\mathrm{Abs780\,nm} + 0.3576 \times \Delta\mathrm{Abs805\,nm} \\ &\quad + 0.39 \times \Delta\mathrm{Abs830\,nm}\end{aligned}$$

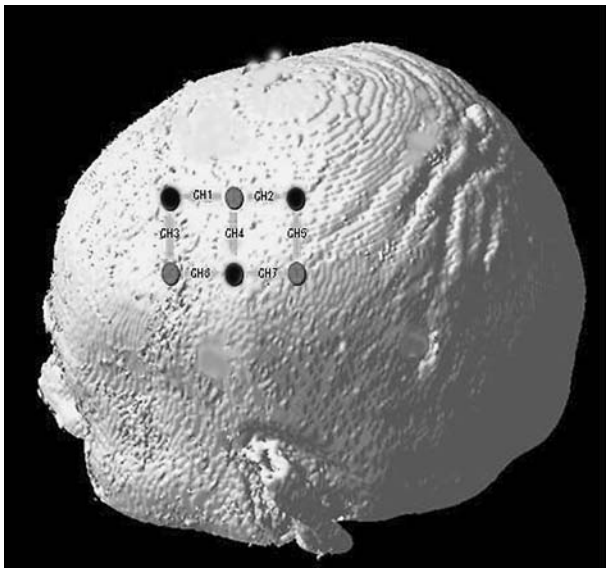


Figure 1. Arrangement of NIRS probes on the head surface. Gray circles represent the emitting probes and black circles the detecting probes. The inter-probe distances are 3 cm. This arrangement of probes creates 7 detecting channels. These channels (CH1∼7) are also superimposed on this scheme.

Each subject was instructed to repeatedly grasp his/her right hand at a pace of 1.5 Hz for a period of 10 s, and then to rest for 50 s between each trial. All subjects practiced the motor task for more than 5 min before the experiments so that everyone could perform the task fluently. During the experiment, the same examiner continuously monitored their task performance. Ten consecutive trials were conducted for each subject, and time-locked averaging was performed after eliminating trials containing inappropriate signals, such as motion artifact or incomplete task performance. Note that for convenience, the time point of task initiation will be referred to as 0 s and the lapse of time from task initiation will be expressed as a positive numeral; e.g. 3 s after task initiation will be referred to as +3 s.

Statistics

In individual analyses, the averaged baseline Hb concentration from −2 s to 0 s and the averaged peak Hb concentration after stimulus for 2 s in each session were compared by a paired *t*-test. The peak Hb concentration was determined and analyzed in both the early response phase (0 to +3 s) and the delayed response phase (+4 s and later). In group analyses, we analyzed the grand-averaged hemoglobin concentration changes for every 2 s, beginning from +1 s, comparing the averaged baseline hemoglobin concentration from −2 s to 0 s by a paired *t*-test. The significance level was set at $p<0.05$ in this study.

Results

Transcranial Magnetic Stimulation (TMS)

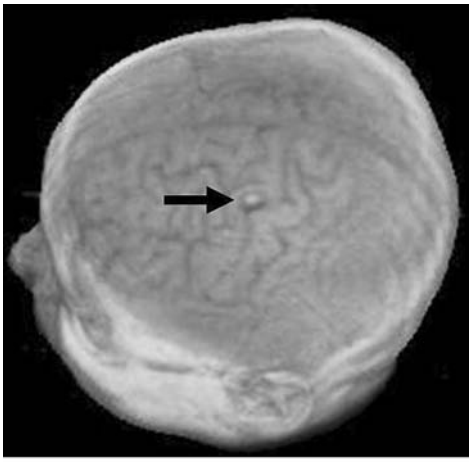
In all subjects, MEPs were recorded from the contralateral APB muscle. The area where the MEPs were recorded varied among subjects. The mean areas with relative MEP amplitudes of 33% or more and 67% or more were $7.1 \pm 2.1\,cm^2$ (mean ± s.d.) and $2.9 \pm 0.7\,cm^2$, respectively. CoGs for the APB muscle were successfully calculated in all subjects, and each point was marked on the subject's head surface to identify the site for NIRS imaging measurement. The structural MRI scanned in one subject showed that the external fiducial marker attached to the CoG was precisely located on the anatomical primary motor cortex which is characterized as a "reversed omega" sign (Fig. 2). Intersubject averaged mapping with reference to the CoG on which the NIRS imaging detecting channel is superimposed is shown in Fig. 3.

NIRS Imaging

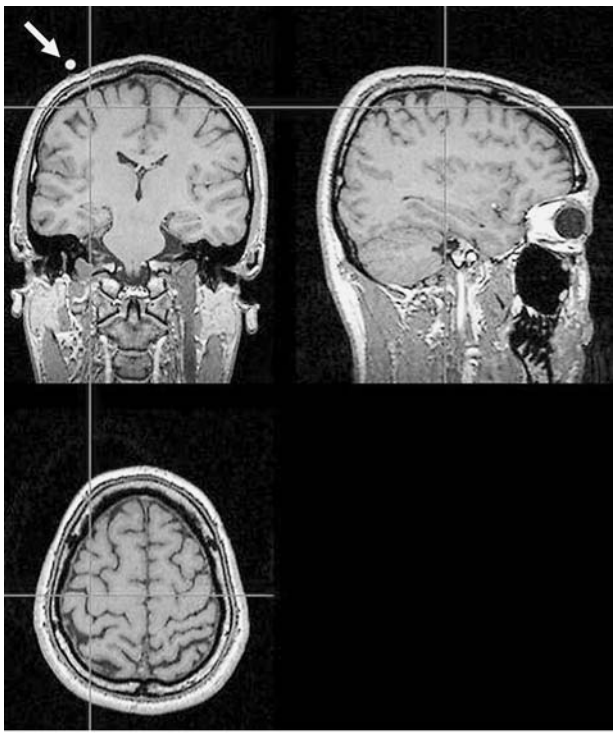
Time Course of Hb Concentration Change in the Center of the Primary Motor Cortex

The hemodynamic response to motor stimulation in the center of the primary motor cortex, as determined by TMS mapping, was divided into two phases: an early response phase, defined as from +1 to +3 s, and a delayed response phase, defined as beginning at +4 s. HbO_2 concentration decreased and HbR and tHb concentration increased in the early response phase. To visualize this response clearly, the averaged time course of the hemoglobin concentration changes is shown in Fig. 4. HbO_2 decreases immediately after task initiation, reaches trough at around +1.5 s, and then increases, peaking at around +9 s. HbR increases immediately after task initiation, peaks at around +2 s, then decreases and bottoms out at around +10.5 s. tHb shows a monophasic pattern, gradually increasing after task initiation and peaking at around +7 s after task initiation.

In individual analyses, 6 of 10 subjects showed a significant increase in HbR concentration in the early response phase. Meanwhile, HbO_2 showed a decrease in the early response phase though it was not significant. In 9 of 10 subjects, the absolute concentration change in HbR was significantly higher than the change in HbO_2 in the early response phase. On the other hand, HbO_2 and tHb concentration significantly increased and HbR concentration significantly decreased in 9 of 10 subjects during the delayed response phase.



(A)



(B)

Figure 2. (A) 3-D reconstructed MRI showing spatial relationship between a fiducial marker (vitamin E capsule: arrow mark) attached to the CoG and cortical surface in one of the subjects. (B) Coronal (upper left), sagittal (upper right) and axial (lower) section of anatomical MRI with the fiducial marker (arrow mark) on the CoG of the same subject. The intersection shows the point that is just beneath the fiducial marker perpendicular to the cortical surface. From these films, CoG (TMS-defined motor cortex) is confirmed to be precisely located on the anatomical motor cortex.

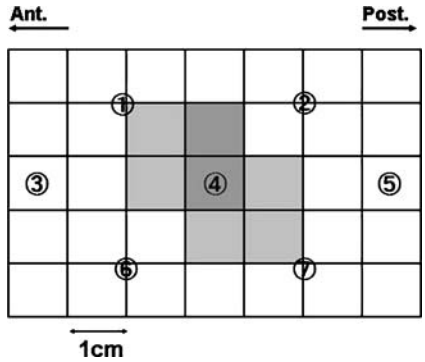


Figure 3. Relationship between averaged TMS mapping and NIRS channel position. NIRS Ch4 is located on the CoG for contralateral APB muscle. Seven channels cover all the areas where MEP for APB is recorded. Ch3 is anterior to the primary motor cortex of the APB (premotor area), and Ch5 is posterior to the central sulcus (sensory area). Black: MEP $>$ 66%; gray: MEP $>$ 33%; white: MEP $<$ 33%. Circled numbers: NIRS detecting channels.

Similarly, in group analysis, as shown in Table I, HbR showed a significant increase in the CoG for the APB during this early response phase (+1 to +3 s). Significant increases in HbO_2 and tHb were observed from +3 to +15 s and from +3 to +11 s, respectively, in the CoG for the APB. A significant decrease in HbR concentration was observed from +7 to +15 s.

Time Course of Hb Concentration in Areas Surrounding the Motor Cortex

Task-related hemoglobin concentration changes in the areas surrounding primary motor cortex, 2–3 cm from the center, are shown in Fig. 5. During the early response phase, an increasing tendency in HbR is detected in some channels, but only the center channel (the center of the motor cortex) showed significance. A decrease in HbO_2 is not detected during the early phase in channels other than the center channel. Concentration changes in the delayed response phase showed a significant increase in HbO_2 and tHb in all channels. The area covered by the 7 NIRS channels is far broader than the area of the motor cortex calculated by TMS mapping. In channels 1, 2, 4, 6, and 7, significant decreases in HbR were detected in the delayed response phase.

Discussion

Early Phase Deoxygenation Detected in the Center of the Primary Motor Cortex

One of the most important advantages of NIRS imaging is that the time course of Hb concentration

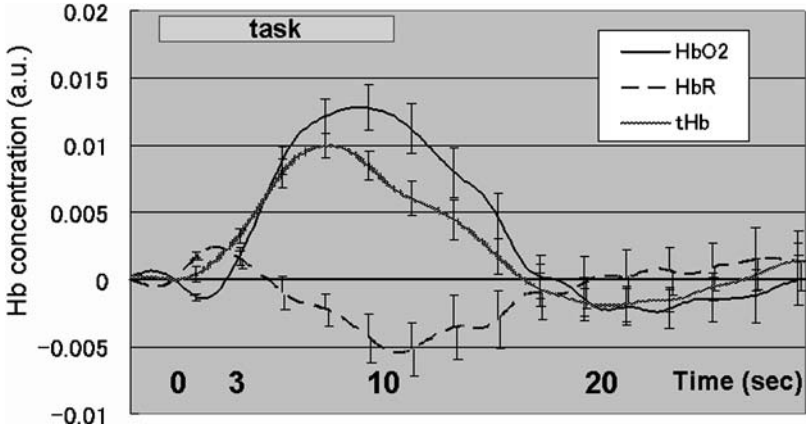


Figure 4. Time course of averaged Hb concentration changes in the center of the primary motor cortex. The error bars show the standard error of each time point from the average. The hand-grasping task is performed from 0 to +10 s. HbO_2 decreases immediately after task initiation, reaches trough at around +1.5 s, and increases, peaking at around +9 s. HbR peaks at around +2 s, then decreases and reaches trough at around +10.5 s. tHb gradually increases and peaks at around +7 s after task initiation. For better viewing, the data were smoothed by simplified least square procedures (Savitzky et al. 1964). X axis: time in seconds. Y axis: relative hemoglobin concentration in arbitrary unit.

change can be measured with the relatively high temporal resolution of 100 milliseconds which cannot be attained with PET or fMRI. A $H_2{}^{15}O$ PET study revealed the stimulus-induced focal augmentation of cerebral blood flow (29% [mean]) far exceeded the concomitant local increase in the tissue metabolic rate (5% [mean]) (Fox et al. 1986) which made the basis for the functional neuroimaging methodologies utilizing hemodynamic response to neural activity. However, this concept considers only the delayed blood flow changes following neural activity, not the subtle change of oxygen metabolism during the early phase. We assume that NIRS imaging is suitable for the elucidation of the early oxygen metabolic changes because of its high temporal resolution and specificity for cortical oxygenation status.

We aimed to provide evidence for the existence of early-phase deoxygenation in the activated cortex, which has not been previously reported in the primary motor cortex using NIRS imaging. This early phase deoxygenation, or the 'initial dip' in other word, was first reported in an optical study (Frostig et al. 1990) and has attracted much attention (Kato 2004; Malonek et al. 1996; Nemoto et al. 1999), in the sense that its presence can be a better indicator of neural activity, because signals are generated mostly from activated tissue and not contaminated by arterial or venous blood change during this phase. Although some reports have denied its existence

Table I. Averaged Hb concentration change from baseline (arbitrary units) for each 2-s period in the center of the primary motor cortex

	HbO_2		HbR		tHb	
	Average	*P*	Average	*P*	Average	*P*
1–3 s	−0.00037	0.470242	0.00243	0.016503*	0.00038	0.77212
3–5 s	0.00622	7.15E−05*	0.0009	0.209178	0.00443	0.002735*
5–7 s	0.01089	1.90E−06*	−0.0015	0.086722	0.00802	0.00049*
7–9 s	0.01209	1.48E−05*	−0.00283	0.020753*	0.00848	0.001744*
9–11 s	0.01169	0.000252*	−0.00494	0.002341*	0.00608	0.023384*
11–13 s	0.00898	0.004715*	−0.0039	0.018926*	0.00444	0.079987
13–15 s	0.00619	0.028525*	−0.00352	0.01875*	0.00225	0.313849
15–17 s	0.00066	0.740157	−0.00182	0.141776	−0.00037	0.868996
17–19 s	−0.00068	0.779347	−0.00058	0.655424	−0.00209	0.343629

Note. Grand-averaged hemoglobin concentration changes for every 2 s, beginning from +1 s, are compared with the averaged baseline hemoglobin concentration from −2 s to 0 s by a paired *t*-test.
*$P < 0.05$.

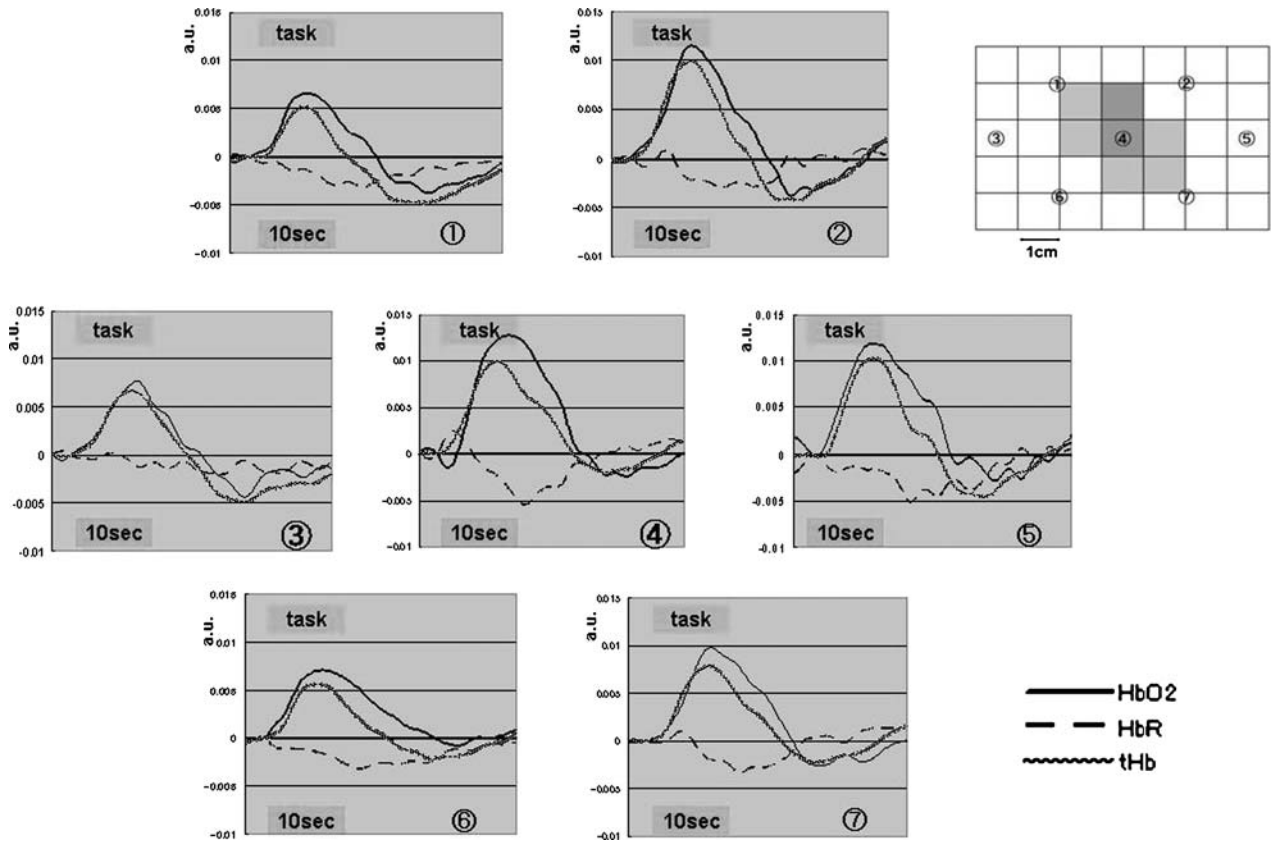


Figure 5. Averaged Hb concentration changes in and around the primary motor cortex determined by TMS mapping. The time course of hemoglobin concentration in the CH4 is identical with the result shown in Fig. 4. A lack of biphasic response of HbO_2 or HbR is observed in channels surrounding the center of the motor cortex for APB. X axis: time in seconds. Y axis: relative hemoglobin concentration in arbitrary unit.

(Lindauer et al. 2001), recent studies using hemodynamic response to stimuli such as direct measurement of cortical oxygenation (Thompson et al. 2003) and fMRI (Ernst et al. 1994; Hu et al. 1997; Menon et al. 1995) have supported the existence of an early response phase. Upon this hypothesis, task-related metabolic reactions would occur immediately after task initiation and reach a maximum in the early phase; the vascular reaction would then gradually emerge and override the degree of oxygen metabolism. We assume that the time point where the vascular response overrides the early oxygen consumption would be at around +3 s because the cerebral blood flow velocity change reaches the maximum 3.3 s after task initiation, as reported in a transcranial Doppler study (Sitzer et al. 1994). To elucidate oxygen metabolism in the microcirculation within +3 s, temporal resolution is a factor of importance, which can be sufficiently accomplished by NIRS imaging. In the present study, a significant increase in HbR and a nonsignificant trend of decrease in HbO_2 concentration were detected during the early response phase of a motor task in the center of the primary motor cortex for APB. Although the hand-grasping task might produce motor activation in a broader area than the CoG for APB stimulation, the CoG should be nearly the same as the strongest activation site for the hand-grasping movement. Averaged tHb concentration during this phase also increased, although the degree of increase was larger for HbR than for tHb, and tHb concentration does not form a peak in the early response phase. These results imply that during the early response phase (+1 to +3 s); oxygen exchange occurs between the capillaries and the activated cortical tissue, which prevails over the degree of tHb increase.

Delayed Phase Response

In the delayed response phase, the amount of incoming blood flow into the motor cortex is considered to be several times higher than what is required for oxygen metabolism, as reported in previous reports (Fox et al. 1986). Spatial specificity to the neural activation during the delayed response phase may be less specific

than during the early phase of deoxygenation, because this response reflects the anatomical vascular supply into and around the functional cortex and not the oxygen exchange in the neural cells directly (Kato 2004). Furthermore, in the studies utilizing delayed hemodynamic responses, such as BOLD-fMRI, activation signals are detected not only from the capillaries in the activated cortex, but also from the downstream veins (Frahm et al. 1992; Gati et al. 1997). So even in NIRS imaging studies, the activation signals might be detected in a broader area, and the main components of the signals are from the venous side of the cortical vascular structure (Lai et al. 1993) during the delayed response phase, compared to the activation signals during the early deoxygenation phase, which are only from capillaries and focal.

As the results of the present experiment show, the area of HbO_2/tHb increase (all channels) and the area of HbR decrease (channels 1, 2, 4, 6, and 7) are broader than both of the electrophysiologically defined motor cortex and the area where the early phase response detected. We must consider the activation of the premotor and sensory cortex as well as the wider area of the primary motor cortex employed during the hand-grasping movement as compared with the primary motor cortex which was estimated by TMS mapping. However, these two results, (1) concordance of electrophysiologically defined motor cortex and the area where an early response was detected, and (2) discrepancy of activated areas during delayed response and early response phase, may support the low specificity of the delayed oxygenation response.

Spatial Localization Using NIRS Imaging and TMS Mapping

NIRS imaging has been considered to have inferior spatial resolution because of the complex propagation of light, which sometimes results in a misidentification of the center of activation. Improper signals of cortical oxygen metabolism are sometimes obtained because of a malpositioning of the detecting probes off the center of activation, resulting in a misinterpretation of signals and thus preventing the genuine physiology of cortical oxygen metabolism. In most published NIRS studies, however, probes have been placed on the subjects' heads based on EEG electrode positions or skull surface landmarks with no reference to gyral structure or function. Although these methods can be used to roughly estimate anatomical positions, the range of their accuracy would be 10 to 20 mm. Strangman et al. (Strangman et al. 2003) reported that NIRS signal levels drop substantially when off target by more than 1 cm in either the longitudinal or transverse direction. This means that essential signals can be easily overlooked unless the target is measured accurately. In the present study, we solved this problem by combining TMS mapping with NIRS imaging. Electrophysiological information from the surface of the skull by TMS enables us to capture the center of the activation; this is evident when contrasting the signals from the true center to the signals from the surrounding channels. The loci of the elicited neural activity and the hemodynamic response to volitional activation were concordant in this study, as were fMRI or PET combined with magnetic or electric stimulation (Boroojerdi et al. 1999; Wassermann et al. 1996). Further refinement of this methodology is required in the future, however, such as a finer spatial resolution of NIRS imaging (presently 20 to 30 mm) and a simultaneous recording of NIRS and TMS (Mochizuki et al. 2006).

Conclusion

In this study, we improved the spatial specificity of NIRS imaging to the level of gyral identification by combining it with TMS mapping in addition to the high temporal resolution of NIRS imaging. Through the identification of the specific activation patterns of NIRS imaging in the functional center, we have demonstrated the precise relationship between the neural activity and the oxygen metabolism in the capillaries of the primary motor cortex in humans. Our results support a model of a tight coupling of oxygen consumption and supply between neurons and the cortical capillary beds in the early phase preceding oxygenation. The present method incorporating electrophysiology and cortical hemodynamics is therefore very practical and can be applied to a variety of studies investigating human cortical function.

Acknowledgements

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