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An event-related optical topography study of cortical activation induced by single-pulse transcranial magnetic stimulation

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Abstract

To visualize cortical activations during transcranial magnetic stimulation (TMS), it is necessary to measure those activations at high spatiotemporal resolution while preventing interference with the magnetic property of a coil. One suitable method that satisfies these demands is optical topography (OT), which has been used in cortical activation studies. In the present study, single-pulse TMS was applied to the left primary motor area, and cortical responses at the stimulation site were measured simultaneously with event-related OT. When TMS was applied at 110% motor threshold (MT), we observed significant oxyhemoglobin increases that were both time-locked and correlated with the hemodynamic basis function. Moreover, when TMS was applied at 90% MT, significant oxyhemoglobin increases were detected even though there were no motor-evoked potentials. These results demonstrate that OT can directly measure cortical responses to subthreshold single-pulse TMS, independent of the afferent feedback from the peripheral neuromuscular activity.

Keywords: Transcranial magnetic stimulation; Optical topography; Near-infrared spectroscopy; Simultaneous measurement; Oxyhemoglobin; Motor cortex

Introduction

Transcranial magnetic stimulation (TMS) has been applied recently to the study of various cognitive functions in the human brain (Pascual-Leone et al., 2000; Hallett, 2000), allowing the examination of the causal link between cortical activity and function. Two types of TMS have been used thus far: repetitive TMS (rTMS) and single-pulse (or paired-pulse) TMS. In rTMS, multiple magnetic pulses are applied at a rapid rate ($>$ 1 Hz) to produce larger effects on cortical activity than single-pulse TMS. The effects of rTMS have been observed in recent imaging studies that combined rTMS with positron emission tomography (PET) (Fox et al., 1997; Paus et al., 1997; Mottaghy et al., 2000; Siebner et al., 2001) or functional magnetic resonance imaging (fMRI) (Bohning et al., 1999; Baudewig et al., 2001). By measuring the cortical activations induced by rTMS, these studies have revealed TMS-induced cortical responses covarying with stimulation frequency or intensity, further revealing the transcortical propagation of TMS-induced activations.

Single- or paired-pulse TMS has a maximal temporal resolution of ~20 ms (Pascual-Leone et al., 2000), which is an obvious advantage of this technique. Recent TMS studies have clarified cortical mechanisms of human cognitive functions such as motion perception (Pascual-Leone and Walsh, 2001) and syntactic processing (Sakai et al., 2002). On the other hand, only a limited number of functional imaging studies have examined cortical activations induced by single-pulse TMS, because of several technical difficulties. First, an interference with the coil-generated magnetic field is a major problem in fMRI studies. Another type of interference is caused by the mere presence of the TMS coil, whose magnetic property interferes with the magnetic field of an MR scanner. In the previous fMRI studies, where MR

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scanning and TMS pulses were temporally separated, the susceptibility-induced signal loss was reported especially in the area under the coil (Bohning et al., 1999, 2000). In PET studies, measurements were conducted with or without magnetic shielding for PET photomultipliers, and several studies have recommended the use of the shielding (Thompson et al., 1998). Second, the hemodynamic responses associated with single-pulse TMS are too transient and small to be detected by the current sensitivities of PET. To overcome low signal-to-noise ratios for TMS responses in fMRI studies, stronger TMS pulses must be applied to the cortex. However, as previous studies have indicated (Ilmoniemi et al., 1997; Bohning et al., 1999; Siebner et al., 2001; Strafella and Paus, 2001), the motor cortex activation owing to the sensory feedback from the peripheral neuromuscular activity, which is induced by TMS pulses, could conceivably confound the response observed in the above-mentioned fMRI study (Bohning et al., 2000). Therefore, it is necessary to develop new techniques, besides PET or fMRI, that can measure the cortical activations induced by single-pulse TMS while preventing interference with the magnetic property of a coil.

One suitable noninvasive method that satisfies these demands is optical imaging for measuring cortical activations, in which measurement devices can be well separated from a TMS coil, by transmitting optical signals through glass fibers. Near-infrared spectroscopy (NIRS) is one of the optical imaging techniques for measuring changes in hemoglobin concentration in brain tissues by using the difference between the light absorption spectra of oxy- and deoxyhemoglobin (Jöbsis, 1977; Chance et al., 1988; Villringer et al., 1993). Optical topography (OT), a recently developed extension of NIRS, measures light reflection and scattering from multiple measurement points (Maki et al., 1995; Yamashita et al., 1996; Koizumi et al., 1999), whereas in early NIRS studies optical signals were measured with only one pair or widely separated pairs of an emitter and a detector. In OT, measurements from closely placed pairs are achieved by independently modulating the intensity of each radiated laser beam; that is, by the frequency encoding of spatial information. Here we applied an event-related paradigm of OT, which was established in our previous study (Noguchi et al., 2002), to the measurement of each event with single-pulse TMS. In the present study, a higher and more reliable signal-to-noise ratio was achieved by measuring a single region with multiple pairs of an emitter and a detector. We examined whether or not this measurement was sensitive enough to detect cortical responses to single-pulse TMS.

Materials and methods

Subjects

Six male subjects (ages, 22–49 years) participated in the present study. They showed right-handedness (laterality quotients, 53–100) by the Edinburgh inventory (Oldfield, 1971). During the experiments, their heads were held in place with a TMS coil and a chin rest. Informed consent was obtained from each subject after the nature and possible consequences of the studies were explained. All experiments strictly followed the safety guidelines of TMS experiments (Wassermann, 1998) and those adapted by the Japan Neuroscience Society. Approval for these experiments was obtained from the institutional review board of The University of Tokyo, Komaba.

TMS methods and electromyogram measurements

Before the experiments, a 3D magnetic resonance (MR) image of the brain was taken of each subject, who wore a cap with multiple MR markers (alfacalcidol beads; diameter, 3 mm) on its surface. Using the MR image, we estimated the vertically projected position of the center of the left hand motor area (Boroojerdi et al., 1999) relative to these markers (Fig. 1A and B). This position was then transferred to the distance from Cz position in the electroencephalogram (EEG) international 10–20 system.

We applied single-pulse TMS to the left hand motor area of each subject by using a Magstim 200 stimulator (Magstim, Carmarthenshire, UK). Magnetic pulses were delivered through a figure-8-shaped coil (dual 70-mm coil), so that the induced electric current flowed in a posterior–anterior direction (Paus et al., 1998; Terao et al., 1998). As an index of TMS effects on peripheral nerves, motor-evoked potentials (MEPs) were recorded from the right first dorsal interosseous (FDI) muscle with surface electrodes. Electromyogram (EMG) signals were amplified and recorded with a 10- to 1000-Hz bandpass filter (MEG-2100; Nihon-Kohden, Tokyo, Japan).

We determined the tonically active motor threshold (MT) for each subject from the FDI muscle in 10% maximal voluntary contraction (Terao et al., 1998). The active MT was defined as the lowest TMS intensity sufficient to elicit five MEPs, each of at least 50 μV peak-to-peak amplitude, in a series of 10 stimulations. During the simultaneous OT measurement, the TMS intensity was set to each of 110, 90, and 70% MT, and EMG data were monitored online. There was no voluntary contraction during the OT measurement to ensure that no MEPs would be induced at 90% MT condition while maintaining MEPs at 110% MT condition. Each session contained 20 single TMS pulses with variable intertrial intervals (20, 22, 24, 26, and 28 s, pseudorandomized within a session). The 1-day experiment consisted of six sessions (two sessions for each intensity), and the experiment was repeated for each subject twice to four times in separate days. The order of the session sequences was counterbalanced within and across subjects.

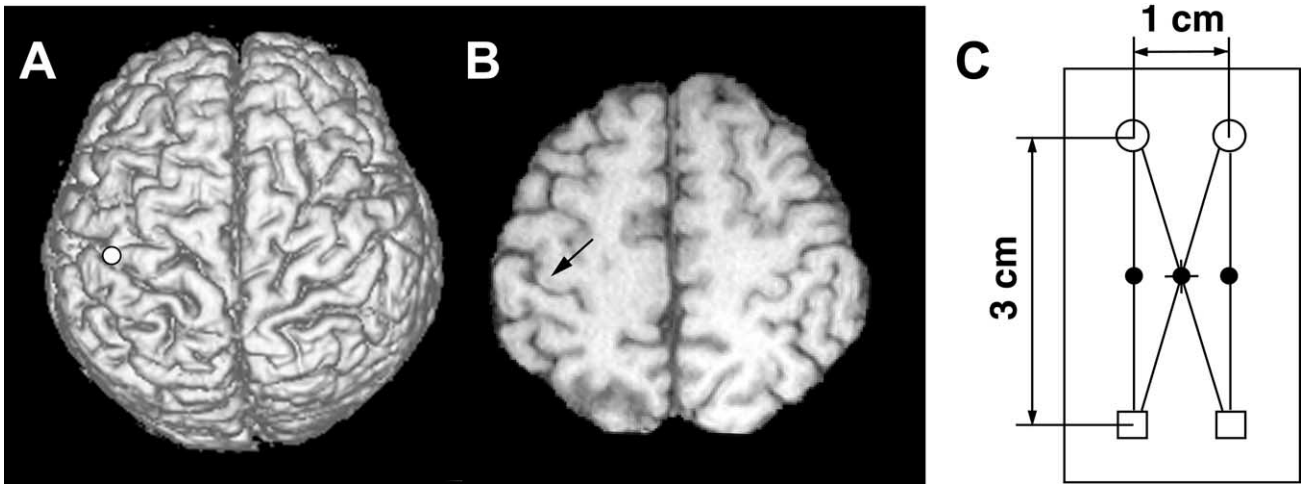

Fig. 1. A region in the motor cortex for TMS and OT measurements. MR images of the dorsal surface (A) and a horizontal slice (B) of a representative subject's brain are shown. An open circle in (A) represents the projected position of an MR marker on the left hand motor area, where magnetic pulses were applied. The horizontal slice (B) is a transection ($z = 48$, the slice 48-mm above the anterior commissure and posterior commissure line) below the level of the projected position, which includes the hand motor area (an arrow pointing to the omega-shaped precentral gyrus). (C) The configuration of four optodes over the left hand motor area. Open circles and rectangles represent the positions of emitters and detectors, respectively. This configuration formed four emitter-detector pairs around the center of a TMS coil (+). Filled circles denote the measurement points, each of which is located at the midpoint of a single emitter–detector pair.

OT measurements

We used an OT system (ETG-A1; Hitachi Medical Corporation, Tokyo, Japan) to measure the cortical responses at the stimulation site. Near-infrared laser diodes with two wavelengths (ranges, 783–793 and 823–833 nm) were used as the light sources (intensity, 1.5 mW/mm^2, modulation, 1–10 kHz), and transmittance data of the light beams were obtained every 500 ms. We used two emitters and two detectors, each of which was connected to a bundle (diameter, 1 mm) of flexible glass fibers running in parallel with the subject's scalp (Fig. 1C). The tips of the fibers were bent into an L shape and fixed to the head shell (size, 6×4 cm^2), which was placed on the scalp over the hand motor area. The midpoint of the diagonal emitter–detector pairs, which corresponded to a measurement point (Maki et al., 1996), was placed on the center of the hand motor area. The midpoints of the parallel emitter–detector pairs were located 5 mm apart from this center. The TMS coil was placed over the fibers while maintaining the vertical placement of the fiber tips on the scalp. The minimum distance between the coil and the scalp was 8.5 mm.

OT data were analyzed according to the event-related paradigm established in our previous study (Noguchi et al., 2002), in which oxyhemoglobin changes were successfully observed. Twenty event periods, each of which corresponded to a single pulse of TMS, were extracted from time-series data in each session, allowing for overlaps during the baseline. Each event period ranged from 6 s before the stimulation onset to 20 s after the onset. Excluding the activation period during the first 12 s after the stimulation onset, time points were baseline-corrected with a curve of the third degree (Sato et al., 1999). The event data of the different TMS intensities were averaged separately at each wavelength. After averaging, the relative changes in oxyhemoglobin concentration and deoxyhemoglobin concentration were calculated for each subject using the equation below (Maki et al., 1995). The relation between light absorbance changes at wavelength λ1 ($\Delta A_{(\lambda 1)}$) and oxy- and deoxyhemoglobin concentration changes (ΔC_{oxy} and $\Delta C_{\mathrm{deoxy}}$) can be expressed as

$$\Delta A_{(\lambda 1)} \approx \varepsilon_{\mathrm{oxy}(\lambda 1)} \Delta C_{\mathrm{oxy}} d + \varepsilon_{\mathrm{deoxy}(\lambda 1)} \Delta C_{\mathrm{deoxy}} d, \qquad (1)$$

where $\varepsilon_{\mathrm{oxy}(\lambda 1)}$ and $\varepsilon_{\mathrm{deoxy}(\lambda 1)}$ are the wavelength-dependent molar absorption coefficients of oxy- and deoxyhemoglobin at wavelength λ1, respectively. The effective path length d is a distance on the trajectory of light beams in the gray matter. A previous theoretical study of NIRS reported that its value is approximately 5 mm in 3-cm emitter–detector spacing (Firbank et al., 1998). By solving the simultaneous equations for two wavelengths (1), the relative hemoglobin concentration changes, $\Delta C_{\mathrm{oxy}}\, d$ and $\Delta C_{\mathrm{deoxy}}\, d$, were calculated in units of millimolar-millimeter (mMmm). We then obtained the grand average of $\Delta C_{\mathrm{oxy}}\, d$ or $\Delta C_{\mathrm{deoxy}}\, d$ across all tested subjects. To statistically examine whether TMS-induced hemodynamic changes were present in each condition, we calculated correlation coefficients (r values) between the averaged data and a basis function of the peristimulus time for hemodynamics (Friston et al., 1998), which depicts a typical hemodynamic change associated with neural activity.

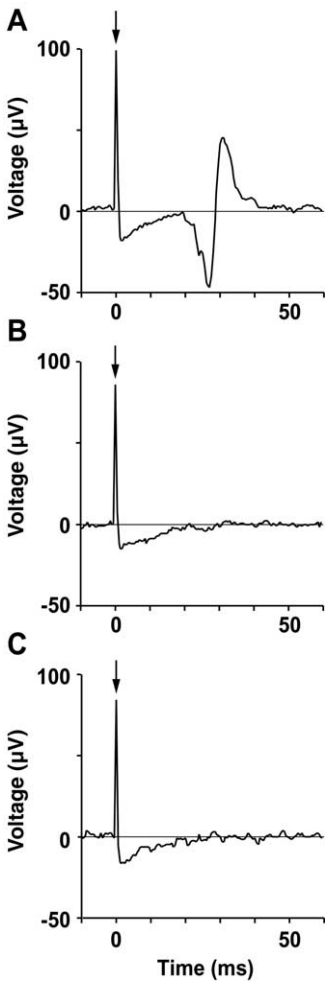

Fig. 2. MEPs induced by TMS pulses at three different intensities: 110% MT (A), 90% MT (B), and 70% MT (C). Data obtained from six subjects were averaged. An arrow in each figure indicates the artifact of TMS pulses, at which the time is set to zero. Note that MEPs were detectable only at 110% MT.

Results

The MEPs averaged across six subjects are shown in Fig. 2. At 110% MT, MEPs of 100 μV peak-to-peak amplitude were clearly observed from the FDI muscle (Fig. 2A). The latency of the MEPs was 20 ms, which is comparable to that of previous studies (Pascual-Leone et al., 1998; Strafella and Paus, 2001). In contrast, there were no MEPs at 90 or 70% MT (Fig. 2B and C). We monitored all EMG data online and confirmed that no magnetic pulses induced an MEP under these two conditions. These results confirmed that the subthreshold TMS pulses did not induce any neuromuscular activity in the FDI muscle.

Next, we present the results of OT measurements at 110% MT in Fig. 3. Averaged data ($N = 6$) obtained at each of four measurement points are separately shown. In transmittance data (Fig. 3A), decreases of light intensity time-locked to the TMS pulse were detected at all measurement points. The relative oxyhemoglobin concentration changes, which were calculated from these transmittance data (see Materials and methods), also showed time-locked patterns of signal increases at all of four measurement points (Fig. 3B). Each of the time courses was highly correlated with the basis function of hemodynamics (r values, 0.78, 0.82, 0.81, and 0.84), indicating that significant oxyhemoglobin increases were induced by the TMS pulses at all measurement points. The oxyhemoglobin increases were also observed in all subjects (Fig. 4). Therefore, we averaged the data across all measurement points and all subjects and calculated the relative oxyhemoglobin concentration changes under the three conditions of different TMS intensities (Fig. 5). Significant oxyhemoglobin increases were observed at both 110% MT (Fig. 5A) and 90% MT (Fig. 5B), but not at 70% MT (Fig. 5C). The signal changes at 110 and 90% MT were highly correlated with the hemodynamic basis function ($r =$ 0.93 and 0.87, respectively), whereas there was no significant correlation at 70% MT ($r = -0.17$). We fitted the basis function of hemodynamics to the time courses with a least square method and confirmed that the signal changes exactly followed the basis function at both 110 and 90% MT. There were significant oxyhemoglobin increases at the peak of 110 and 90% MT time series (one-group t test, $P < 0.01$). On the other hand, we confirmed that signal changes were not significant for any time points at 70% MT ($P > 0.05$, for all). We further calculated mean changes of relative oxyhemoglobin concentration, averaging temporal points from 3 to 9 s after each TMS pulse (Fig. 6). One-way ANOVA indicated a significant main effect of TMS intensity [$F(2, 15) = 9.6$, $P < 0.01$], and a t test performed for each condition showed significant oxyhemoglobin increases at both 110 and 90% MT ($P < 0.05$), but not at 70% MT ($P > 0.1$). We performed the same analyses for deoxyhemoglobin data and observed no significant concentration changes under any of the three conditions ($P > 0.1$, for all).

Discussion

To our knowledge, this is the first OT experiment to simultaneously measure the oxyhemoglobin changes at the stimulation site during TMS. The oxyhemoglobin time series measured with OT were highly correlated with the hemodynamic basis function, which reliably depicted hemodynamic changes induced by each event of single-pulse TMS. Moreover, the present study succeeded in detecting the cortical responses to subthreshold single-pulse TMS. The activation at 90% MT directly reflected the TMS effects on the motor cortex, even though it did not induce detectable responses in the FDI muscle. These results established that subthreshold single-pulse TMS activates the motor cortex, which cannot be explained by the sensory feedback from the peripheral nerves.

There has been a controversy about whether blood flow changes in the motor area induced by TMS are increases or decreases. One PET study by Fox et al. (1997) has reported

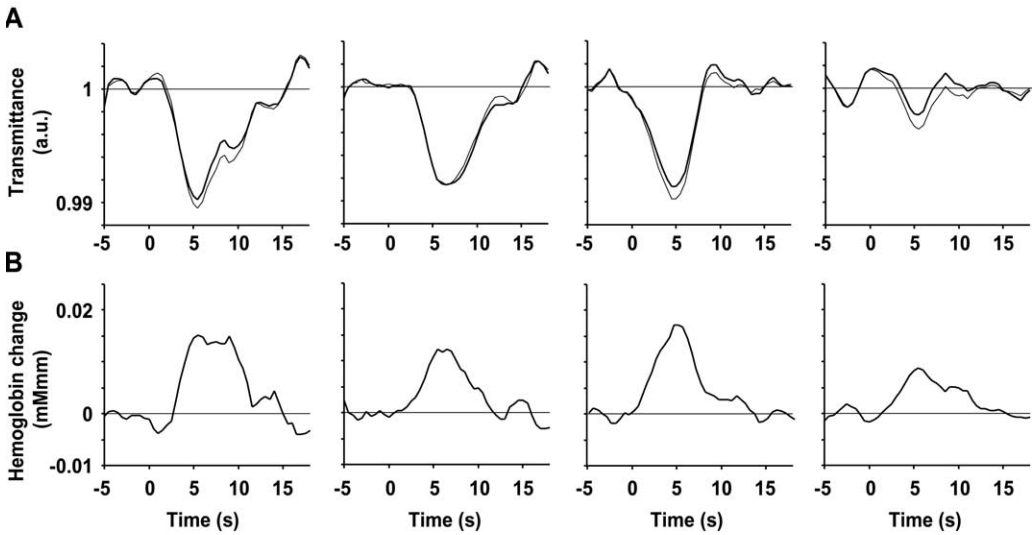

Fig. 3. Event-related changes of transmittance and relative oxyhemoglobin concentration at 110% MT. Averaged data ($N = 6$) obtained at each of four measurement points are separately calculated. The left two columns show data from diagonal emitter–detector pairs, while the right two columns show data from parallel pairs (Fig. 1C). (A) The transmittance data are shown for each wavelength in an arbitrary unit (a.u.); thick lines: 780 nm, thin lines: 830 nm. (B) The vertical axis represents relative oxyhemoglobin changes (mMmm), which were calculated from the transmittance data. In each figure, a TMS pulse was delivered at time zero. Similar patterns of signal changes were observed across all measurement points.

that rTMS applied to the motor cortex induces increases of blood flow at the stimulation site. On the other hand, another PET study by Paus et al. (1998) has reported the opposite result: the decrease of blood flow in the motor cortex. Because these studies measured the cumulative effects of magnetic pulses, the contradicting changes might result from stimulation parameters such as pulse frequency, duration of the train, and the number of trains (Pascual-Leone et al., 1998, Siebner et al., 2001). Our results with an event-related design clearly indicate that single-pulse TMS increases, rather than decreases, the regional cerebral blood flow, because oxyhemoglobin changes correlate positively with blood flow changes.

A couple of NIRS studies have measured the effects of TMS (Oliviero et al., 1999; Eschweiler et al., 2000), although they have not employed event-related designs. These studies have reported cumulative effects of a number of magnetic pulses continuously delivered for a period of 2 or 20 min. In addition, these measurements were conducted before and after the TMS period, not during TMS. By

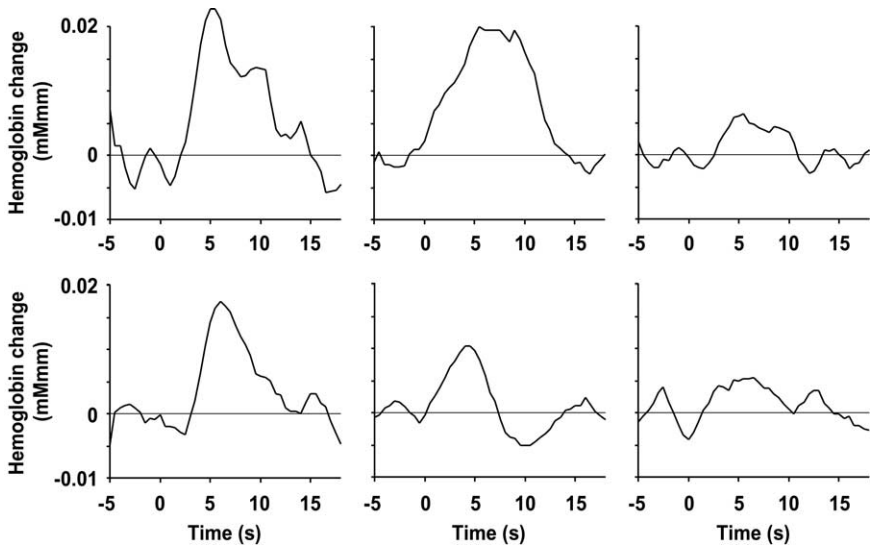

Fig. 4. Relative oxyhemoglobin concentration changes observed in individual subjects at 110% MT. The relative oxyhemoglobin concentration changes obtained from each subject were averaged across the four measurement points. The event-related oxyhemoglobin increases induced by a TMS pulse (delivered at time zero) were observed in all six subjects.

combining the event-related techniques for OT measurements with TMS, the present study demonstrates that real-time measurements of TMS effects are possible by optical imaging with a signal-to-noise ratio and temporal resolution that are both high enough to follow the cortical responses to single-pulse TMS.

Previous EEG studies have measured cortical responses to single-pulse TMS (Ilmoniemi et al., 1997; Paus et al., 2001). Although EEG techniques have a relatively higher temporal resolution, the conduction of electric signals often makes the precise estimation of the activation source difficult. The multichannel EEG system and the cortically constrained minimum-norm estimation of neural activity are necessary to overcome this problem. On the other hand, OT can measure the TMS effects without these correction techniques, thus extending the findings in previous EEG studies. According to a previous theoretical study of near-infrared imaging, the measurement area in each emitter–detector pair (spacing, 3 cm) is confined to a small region on the cortical gray matter, the spatial extent of which is approximately 1.8 cm in full width at half-maximum (FWHM) centered on the measurement point (Firbank et al., 1998). If a larger region is measured with OT, the cortical spread or remote effects of TMS may be studied with this spatial resolution. Therefore, we believe that the combination of OT with TMS is a promising approach to investigate the various effects of magnetic stimulation.

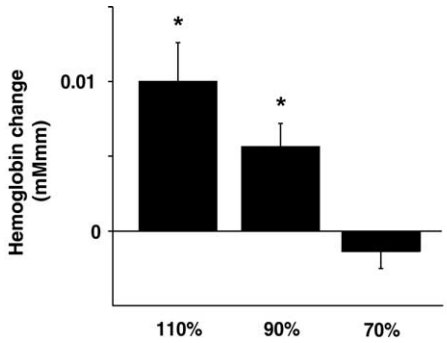

Fig. 6. Mean changes of relative oxyhemoglobin concentration (3–9 s after each TMS pulse). Error bars indicate standard errors of the mean across six subjects. $*P < 0.05$ (t test).

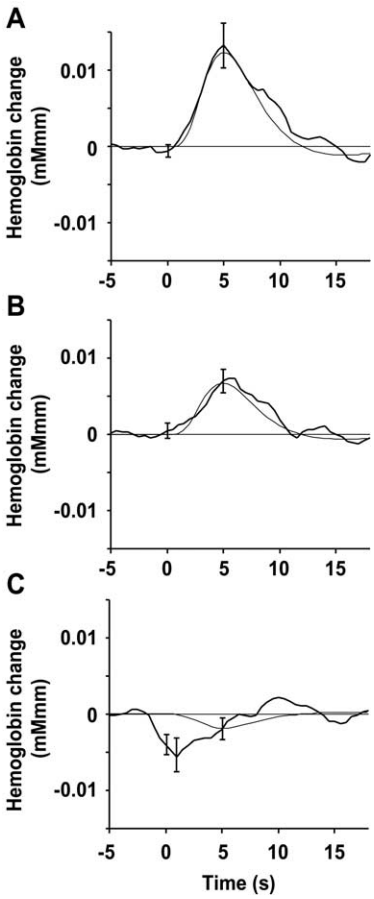

Fig. 5. Relative oxyhemoglobin concentration changes induced by TMS pulses at three different intensities: 110% MT (A), 90% MT (B), and 70% MT (C). In each figure, the basis function of hemodynamics (thin line) was fitted to the grand average data (thick line) with a least square method. Error bars indicate standard errors of the mean across six subjects.

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