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Hemodynamic evoked response of the sensorimotor cortex measured noninvasively with near-infrared optical imaging

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Abstract

We have performed a noninvasive bilateral optical imaging study of the hemodynamic evoked response to unilateral finger opposition task, finger tactile, and electrical median nerve stimulation in the human sensorimotor cortex. This optical study shows the hemoglobin-evoked response to voluntary and nonvoluntary stimuli. We performed measurements on 10 healthy volunteers using block paradigms for motor, sensory, and electrical stimulations of the right and left hands separately. We analyzed the spatial/temporal features and the amplitude of the optical signal induced by cerebral activation during these three paradigms. We consistently found an increase (decrease) in the cerebral concentration of oxy-hemoglobin (deoxy-hemoglobin) at the cortical side contralateral to the stimulated side. We observed an optical response to activation that was larger in size and amplitude during voluntary motor task compared to the other two stimulations. The ipsilateral response was consistently smaller than the contralateral response, and even reversed (i.e., a decrease in oxy-hemoglobin, and an increase in deoxy-hemoglobin) in the case of the electrical stimulation. We observed a systemic contribution to the optical signal from the increase in the heart rate increase during stimulation, and we made a first attempt to subtract it from the evoked hemoglobin signal. Our findings based on optical imaging are in agreement with results in the literature obtained with positron emission tomography and functional magnetic resonance imaging.

Descriptors

Diffuse optical imaging; Hemodynamic evoked response; Sensorimotor cortex

Studying neural activity in the human brain is possible with electroencephalography (EEG), magneto encephalography (MEG), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI). EEG and MEG measure the electromagnetic signals directly associated with neuronal activity and feature an excellent temporal resolution, on the order of milliseconds. With imaging techniques such as PET and fMRI, one can localize (to within a few millimeters) and characterize brain activity on the basis of enhanced neuronal metabolic demands. As a new emerging technique, near-infrared spectroscopy (NIRS) has been demonstrated to be an effective tool to monitor local changes in cerebral oxygenation and hemodynamics during functional brain activation. With NIRS, cortical hemodynamics can be monitored noninvasively, continuously, in real time, and with

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compact and inexpensive instrumentation compared to PET and fMRI. NIRS employs safe levels of optical radiation in the wavelength region 650–950 nm, where the relatively low attenuation of light accounts for an optical penetration through several centimeters of tissue. As a result, it is possible to noninvasively probe the human brain cortex using near-infrared light, and to monitor the cerebral concentration of hemoglobin, which is the dominant near-infrared absorbing species in the brain. Furthermore, the difference in the near-infrared absorption spectra of oxy-hemoglobin and deoxy-hemoglobin allows for the separate measurement of the concentrations of these two species. To this goal, it is sufficient to perform NIRS measurements at two wavelengths. The sum of the concentrations of oxy- and deoxy-hemoglobin provides a measure of the cerebral blood volume (CBV), whereas the individual concentrations of the two forms of hemoglobin are the result of the interplay between physiological parameters such as regional blood volume, blood flow, and metabolic rate of oxygen.

Here, we have investigated the contralateral and ipsilateral hemodynamic response of the primary sensorimotor cortex (SMI) to unilateral voluntary, passive, and electrical stimulation. The SMI includes the primary motor cortex (MI) and the primary sensory cortex (SI), and is located anterior and posterior to the central sulcus. Increased activity in both ipsilateral and contralateral SMI cortex during voluntary finger movements has been demonstrated by MEG, PET (Kawashima et al., 1998; Roland & Seitz, 1991) and fMRI (Cramer, Finklestein, Schaechter, Bush, & Rosen, 1999; Gelnar, Krauss, Szeverenyi, & Apkarian, 1998; Kim et al., 1993; Kwong et al., 1992; Rao et al., 1995). Several cortical regions adjacent to the SMI also show increased activity induced by voluntary motor tasks; for instance: (1) the supplementary motor area (SMA), (2) the premotor cortex (PMC), anterior to MI, (3) the posterior parietal cortex (POC), and (4) the secondary somatosensory cortex (SII), which lies deep within the parietal operculum (Sylvian fissure) lateral and posterior to the face representation in SI and anterior and medial to the primary auditory areas (for topography references see Burton, 1986; Powell & Montcastle, 1959). The activated areas during passive stimulation are smaller than during voluntary movement (Mima et al., 1999; Spiegel, Tintera, Gawehn, Stoeter, & Treede, 1999). Somatosensory stimulation elicits evoked hemodynamic response in the contralateral primary SI and bilateral secondary SII somatosensory cortex, as reported by MEG (Forss et al., 1994; Gallen et al., 1994; Suk, Ribary, Cappell, Yamamoto, & Llinas, 1991), PET (Burton, Videen, & Raichle, 1993; Fox & Raichle, 1986; Meyer et al., 1991; Seitz & Roland, 1992), and fMRI (Hammeke et al., 1994; Lin, Kuppusamy, Haacke, & Burton, 1996; Maldjian, Gottschalk, Patel, Detre, & Alsop, 1999; Maldjian, Gottschalk, Patel, Pincus, et al., 1999; Yetkin, Mueller, Hammeke, Moris, & Haughton, 1995). The same result occurs for the electric stimulation of the median nerve, which elicits activity mainly in the contralateral SI and bilateral SII, as reported by MEG (Hari, Hamalainen, Kaukoranta, Reinikainen, & Teszner, 1983; Hari et al., 1984, 1993; Karhu & Tesche, 1999; Okada, Tanenbaum, Williamson, & Kaufman, 1984; Wegner, Forss, & Salenius, 2000), PET (Ibanez et al., 1995), and fMRI (Boakye, Huckins, Szeverenyi, Taskey, & Hodge, 2000; Del Gratta et al., 2000; Kampe, Jones, & Auer, 2000; Puce, 1995).

The nature of the response in the ipsilateral SMI is still unclear. A few fMRI, EEG, and MEG studies report a small ipsilateral SI activation during tactile stimulation (Hansson & Brismar, 1999; Li, Yetkin, Cox, & Haughton, 1996; Maldjian, Gottschalk, Patel, Detre, et al., 1999; Polonara, Fabri, Manzoni, & Slavolini, 1999), and during median nerve stimulation (Korvenoja et al., 1995; Kurth et al., 1998; Noachtar, Luders, Dinner, & Klem, 1997; Spiegel et al., 1999). In contrast, others have shown deactivation of the ipsilateral SMI during voluntary finger movement (Allison, Meador, Loring, Figueroa, & Wright, 2000; Nirkko et al., 2001).

Several noninvasive NIRS studies have shown a local increase in the oxy-hemoglobin concentration (HbO_2) and a decrease in the deoxy-hemoglobin concentration (Hb) in the motor cortex during voluntary motor stimulation (Benaron et al., 2000; Colier, Quaresima, Oeseburg, & Ferrari, 1999; Gratton et al., 1995; Hirth et al., 1996; Maki, Yamashita, Watanabe, & Koizumi, 1996; Obrig, Hirth, et al., 1996). Previously, Obrig compared hemoglobin-evoked responses caused by finger tapping, vibratory, and electrical median nerve stimulation (Obrig, Wolf, et al., 1996). Although the authors found similar responses for active motor and vibratory stimuli (in both cases, HbO increases and Hb decreases), they found decreases in both oxy- and deoxy-hemoglobin concentrations in response to either ipsilateral or contralateral electrical median nerve stimulation. The limitations of Obrig's results stem from the single-point measurements on the head and the slow rate of data acquisition (1 point per second). Recent technical advances have reduced these limitations, making it possible to acquire data at multiple sites with faster data acquisition rates. Such technical advances in the number of sources and detectors, image acquisition rate, and image reconstruction algorithms have allowed the transition from spectroscopic measurements at a single location to imaging measurements over larger cortex areas (Franceschini, Toronov, Filiaci, Gratton, & Fantini, 2000; Maki et al., 1995). The system employed in this study allows for measurements over two 5.6×6.0 cm^2 areas on the left and right brain hemispheres centered on the motor cortex. Fourteen source-detector pairs are employed in each hemisphere, with an acquisition time as short as 20 ms per image (image acquisition rate: 50 Hz). With this relatively large imaged area and sparse source-detector arrangement, the spatial resolution of the image does not allow a distinction of the primary motor cortex from the somatosensory cortex posteriorly, and the premotor cortex anteriorly. The purpose of this investigation is to compare the spatial extent, temporal dynamics, and the magnitude of the oxy- and deoxy-hemoglobin responses evoked by different sensorimotor stimulations (or conditions). The goals of this study are to demonstrate the ability of diffuse optical tomography (DOT) to measure and differentiate activation due to sensory stimuli weaker than voluntary movement, and to validate the optical results through comparison with the results obtained with other techniques, such as PET and fMRI.

Methods

Participants

Ten healthy volunteers aged 22-39 years (mean age: 30 years; standard deviation: 6 years; six men, four women) participated in the study. Seven participants reported they were right-handed, 2 were left-handed, and 1 had mixed-handedness [handedness determined using Briggs and Nebes (1975) inventory]. Subjects 1 and 2 repeated all the protocols two times during three separate sessions, Subject 3 repeated the finger opposition task and finger tactile stimulation protocols two times, Subject 9 did only the finger opposition task and finger tactile stimulation protocols, and Subject 10 did only the electrical median nerve stimulation protocol. This study was approved by the Institutional Review Board of the Massachusetts General Hospital, and all participants gave their written informed consent.

DOT Instrument

We used a multichannel continuous wave (CW) optical imager (CW4 system, developed at the NMR Center, Massachusetts General Hospital), which employs 16 laser diodes and 16 avalanche photodiode detectors (Hamamatsu C5460-01). The 16 laser diodes (8 emitting light at 690 nm, and 8 at 830 nm) were frequency encoded by steps of approximately 200 Hz between 4.0 kHz and 7.4 kHz, so that their signals could be acquired simultaneously by the 16 parallel detectors. Each detector's output was digitized at $\sim$ 40 kHz. The individual source signals were filtered off-line by using an infinite-impulse-response filter with a 20-Hz bandpass frequency. Light sources and optical detectors were coupled to optical fibers

that were arranged on a probe, which was placed on the head of each participant according to the arrangement shown in Figure 1. The minimum source-detector separation was 3.0 cm. The area imaged on each hemisphere was 5.6×6.0 cm^2.

Protocols

The source and detector fibers were inserted into a flexible plastic array and secured to the head with Velcro and foam material. Participants lay flat on foam bedding and both arms were secured with straps to minimize intentional and extraneous movements. For the finger opposition task condition, participants were instructed to touch their thumb with the index and middle finger following a 4–5 Hz metronome beep (externally paced finger opposition). In the passive condition, tactile stimulation was delivered manually by an investigator by touching the first three fingers of the participant at the same rate as in the finger opposition task. The block conditions alternated stimulation periods (20 s long) and rest periods (20 s long) according to auditory cues followed by the participant (finger opposition task protocol) or the investigator (tactile stimulation protocol). To avoid introducing a difference between the auditory stimuli during the motor stimulation and rest periods, the metronome beeps were produced continuously during all measurements. A complete session consisted of an initial reference rest period followed by a blocked design of 10 task/rest sequences without any interruption. As a result, a single stimulation paradigm lasted 420 s.

Electrical stimulation of the median nerve was obtained by applying 0.2-ms-long current pulses either to the right or left wrist (Grass stimulator, Astro-Med, Inc., Mod. S88K). The pulses were delivered in trains of 10 s at a frequency of 4–5 Hz followed by 18 s of rest. For each participant, we adjusted the current to the level of motor threshold, defined as the lowest current that caused a visible contraction. The range of current values among participants was 5–10 mA. The stimulation paradigm consisted of an initial baseline followed by 20 alternating periods of stimulation (10 s) and rest (18 s). Before starting the measurement sessions, the participants were trained to follow all these instructions. A pulse oximeter (Nellcor, N-200) continuously recorded the arterial saturation and the heart rate at the participant's toe. A strain gauge belt (Sleepmate/Newlife Technologies, Resp-EZ) was placed around the participant's upper abdomen to monitor the respiratory effort. We used the analog outputs of the pulse oximeter and strain gauge for the continuous coregistration of the physiological data and optical data. Contact sensors attached to the fingers of the participants during finger tapping sent a low voltage signal to the auxiliary data board every time the thumb touched the other fingers. During tactile stimulation, the same contact sensors were attached to the fingers of the participant and of the investigator performing the task. The synchronization of the median nerve stimulation with the optical data was achieved by collecting the analog output from the back panel of the Grass stimulator.

Data Analysis

The optical raw data were processed off-line using in-house software implemented in MatLab (Mathworks Inc., Sherborn, MA). First the data were low-pass filtered and downsampled from 50 to 10 Hz, then bandpass filtered within the range 0.02–0.50 Hz to eliminate slow drifts and the arterial pulse oscillations. Finally, the data were block averaged to obtain an average response to stimulation with an improved signal-to-noise ratio with respect to single-block response. The first rest/task period was discarded to limit our analysis only to the data obtained under steady-state stimulation conditions. We translated the temporal changes in the intensity into temporal changes in the absorption coefficient ($\Delta\mu_a$) using the differential-pathlength-factor (DPF) method (Delpy et al., 1988). We used literature values of 6.51 and 5.86 for the DPF at 690 and 830 nm, respectively (Duncan et al., 1996). From the values of $\Delta\mu_a$ at two wavelengths, we determined the changes in oxy-hemoglobin (ΔHbO) and deoxy-hemoglobin (ΔHb) concentrations. From these quantities we

derived total hemoglobin concentration (ΔTHC = ΔHbO+ΔHb) and oxy/deoxy ratio (ΔHbO/ΔHb).

Hemoglobin maps were obtained using a back-projection approach (Franceschini, Toronov, et al., 2000). The two-dimensional optical maps were computed by back-projecting the hemoglobin changes measured at the nearest neighbor source-detector pairs (3 cm source-detector distance). The map in each hemisphere comprised 14 source-detector couples, and covered an area of 5.6 × 6.0 cm^2 (= 33.6 cm^2). The pixel size was 0.4 cm^2 for a total number of 84 pixels. The individual pixel values were linearly interpolated to produce the final optical maps. Similar to the DPF method, this back-projection scheme is not expected to accurately quantify nonuniform absorption changes. Consequently, the micromolar values of ΔHbO_2 and ΔHb obtained with this DPF/back-projection approach are not quantitatively accurate in the presence of localized absorption changes (Boas et al., 2001). More rigorous DOT reconstruction methods did not provide a significant improvement because of the sparse source-detector grid used in this study. Individual images were generated for every run for each participant. Group images were not considered, since spatial normalization produces a loss of effective spatial resolution because the images for different participants are not precisely aligned.

For each participant, we estimated the size of the cortical area associated with the hemodynamic response by analyzing the hemoglobin maps obtained 10 s after onset of the stimulus. Our analysis consisted of labeling an image pixel as “activated” if the hemoglobin (oxy- or deoxy-) concentration change at that pixel exceeded one half of the maximal concentration change observed in the image. The area of the collection of activated pixels was our estimate of the size of the oxy-hemoglobin or deoxy-hemoglobin response to activation.

On the data from the pixel of maximal activation we performed both individual-subject analyses and a multisubject analysis (grand average across participants). For each participant, we used the contralateral pixels that showed the maximal response during median nerve stimulation (the stimulus that produced the smallest spatial activation) for a comparison of the amplitudes of the hemoglobin response across stimuli. We considered the average amplitude of the hemoglobin response between 5 and 10 s after the onset of each stimulus because the duration of the on-period for the electrical stimulation (10 s) was shorter than the one for the finger opposition task and tactile tasks (20 s). For the significance of the activation, we set a threshold p value of .05. For the calculation of the p value, we used the mean of the standard error of the data over the 5-to-10 second period.

To estimate and correct for the effect of systemic hemodynamics, we repeated the same analysis on a pixel outside the activated area. In particular, we chose the “inactivated” pixels more posterior and further from the sagittal sinus to avoid SI and artifacts due to the proximity to a large vessel such as the sagittal sinus. When the contralateral and ipsilateral inactivated pixels showed a different amplitude in the hemoglobin change, we considered the smaller of the two hemoglobin changes. The hemoglobin concentration changes at that pixel were assigned to systemic hemodynamics and were subtracted from the hemoglobin concentration changes measured at all other pixels.

Results

Most of our measurements on the 10 subjects allowed us to record a reliable optical signal in response to brain activation. One exception was Participant 8, in whom the signal-to-noise ratio was low and we were not able to record any reliable hemoglobin response to brain activation in any of the three protocols. We attribute the low signal-to-noise ratio for

Participant 8 to thick hair and bad optical coupling. For Participant 4, we lost the data relative to the right hand finger opposition task due to technical reasons. Data from the right and left electrical stimulations on Subject 6 were discarded because of motion artifacts. After discarding the above cases that were affected by technical problems, we were able to analyze the block-averaged oxy-hemoglobin and deoxy-hemoglobin concentration changes induced by the right and left hand stimulation protocols at the contralateral and ipsilateral cortical side (a total of 252 hemoglobin changes for the 9 participants analyzed). We consider a concurrent increase in HbO and a decrease in Hb (equivalent to a positive BOLD signal in fMRI) to be indicative of a hemoglobin response to brain activation. We observed a significant (i.e., above threshold) hemoglobin response to brain activation in 57 out of 63 (90%) measurements. Specifically, there was contralateral hemoglobin response in 10/10 (100%) cases during the right hand finger opposition task, 11/11 (100%) during the left hand finger opposition task, 10/11 (91%) during the right and left hand tactile, 8/9 (89%) during the right and left wrist electrical stimulation. We identified a bilateral hemoglobin response to SMI activation in 9/11 (82%) left hand and 8/10 (80%) right hand finger opposition task measurements. During tactile stimulation, we observed ipsilateral activation above threshold ($p < .05$) in 3/11 (27%) right hand and 7/11 (64%) left hand tactile measurements. In 8/18 (40%) measurements during median nerve stimulation, we observed a concurrent decrease of HbO and increase of Hb at the ipsilateral SMI, which is indicative of brain deactivation, and in only 1/18 cases (6%) we observed an increase of HbO and decrease in Hb at the ipsilateral SMI. Table 1 summarizes all the results for the contralateral and ipsilateral oxy-hemoglobin and deoxy-hemoglobin changes induced by the three protocols for the right and left side stimulations.

The spatial maps of the block-averaged oxy-hemoglobin and deoxy-hemoglobin-evoked responses measured on Subject 2,10 s after the onset of stimulation, are reported in Figure 2. Figure 2(a), (b) refers to right hand tasks, Figure 2(c), (d) to left hand tasks. The left images are the block-average images measured during finger opposition, the middle images during tactile stimulation, and the right images during median nerve stimulation. Figure 2(a), (c) report the oxy-hemoglobin maps, whereas Figures 2(b), (d) report the deoxy-hemoglobin maps. In the color scales, green indicates no change from baseline, red represents a concentration increase, blue a decrease. The activated area is generally red (increase) for HbO, and blue (decrease) for Hb for the cortex side contralateral to the hand performing the task. During electrical stimulation there is a small decrease of HbO and increase of Hb in the ipsilateral cortex side. This ipsilateral deactivation is more evident in Figure 3.

Figure 3 shows the spatial maps of the block averaged deoxy-hemoglobin evoked responses for Subject 10, measured 10 s after the onset of the electrical stimulation.

Figure 4 shows the temporal traces of the block-averaged oxy-hemoglobin and deoxy-hemoglobin evoked responses for Subject 2 at the pixel of maximal response during electrical stimulation for both contralateral and ipsilateral SMI. The top graphs (a) refer to the right hand stimulation, and the bottom graphs (b) to left hand stimulation. The left graphs represent the block averages during finger opposition, the middle graphs during tactile stimulation, and the right graphs during median nerve stimulation. A green horizontal bar indicates the duration of each stimulus.

In all the stimuli, the typical hemodynamic response pattern in the contralateral SMI is evident, with a task-related increase in HbO concentration and a decrease in the relative concentration of Hb. Again, a smaller change of hemoglobin is visible on the ipsilateral SMI with an opposite behavior for the electrical stimulation (increase of Hb and decrease of HbO).

The grand average across subjects of the temporal traces of the evoked hemoglobin responses on the contralateral and ipsilateral SMI are reported in Figure 5. Figure 5(a) reports the results for right hand stimulation; Figure 5(b) reports the results for the left hand stimulation. The error bars represent the standard errors. For each subject we considered the pixel of maximal activation during electrical stimulation. The same hemodynamic response pattern found in a single subject (Figure 4) is also found in the grand average of all the subjects.

In Figure 6 we expand the display of the first 10 s of the hemodynamic response reported in Figure 5. In these graphs we also add the contralateral and ipsilateral total hemoglobin concentration (THC) traces. The evoked change in HbO and THC starts 1.0 ± 0.2 s after the onset of stimulation for finger opposition and finger tactile stimulation. The onset of the rise in HbO and THC precedes that of the decrease in Hb by 1.0 ± 0.3 s. THC peaks at 5.0 ± 0.6 s, HbO peaks at 6.0 ± 0.5 s, and Hb peaks at 7.0 ± 0.4 s. Contralateral and ipsilateral cortices behave similarly. To estimate the significance of the rise time and peak time differences observed for HbO, THC, and Hb, we measured the times at 10% and 90% of the maximum for each subject and for each stimulation condition. These times are representative of the time of response and the time to reach maximum, respectively. The time values reported above are the average and the standard error measured for all subjects during the finger opposition and tactile stimulation. For the median nerve stimulation, the onset of HbO and THC change occurs 2.1 ± 0.4 s after the onset of stimulation, whereas the onset of the Hb change occurs 2.7 ± 0.5 s after the onset of stimulation. The times to reach peak values are the same as for the previous two stimuli to within ± 0.8 s.

Figure 7 shows the bar graphs of the average across subjects of [HbO] and [Hb] changes for the three stimuli performed with left and right hands. For each subject, the hemoglobin changes are calculated on the position of maximum contralateral activation during median nerve stimulation (a), and on the same pixels during the ipsilateral tasks (b). The HbO and Hb amplitudes correspond to the difference between the baseline reading and the average reading 5 to 10 s after the onset of the stimulus. The error bars represent the average value of the standard deviations of the data over the 5–10 s period for all subjects. For the ipsilateral SMI, hemoglobin changes under threshold ($p > 0.05$) are included in the calculation of the average.

To estimate systemic contributions to the oxy-hemoglobin and deoxy-hemoglobin concentration changes, we considered cortical areas that are far from the pixel of maximal hemoglobin response to activation, as described in the data analysis section. Figure 8 shows bar graphs of the grand average across subjects of HbO and Hb changes on a pixel outside the SMI obtained in the same way as in Figure 7. For each subject, we considered the pixel more posterior and further from the sagittal sinus either on the right or left hemisphere. We discarded the data from 2 subjects (Subjects 2b and 7) because the positioning of the probe on the head for these subjects was more frontal and the maximal activation was too close to the posterior optodes. Left and right hand stimuli were averaged together. In Figure 8 we also show the bar graph of the average heart rate change across subjects (graph on the right). The heart rate change was calculated in the same way as were HbO and Hb, from the block average of the heart rate in each subject.

We attribute the increase of HbO and decrease of Hb in an area outside the SMI to the heart rate increase during stimulation. We assumed this systemic hemoglobin change to be the same in the whole imaged area, and we subtracted it from the data at each pixel. Figure 9 shows bar graphs of the average across subjects of [HbO] and [Hb] changes at the (a) contralateral and (b) ipsilateral SMI region before and after subtracting the contribution to the signal due to systemic hemoglobin changes. Left and right hand stimuli were averaged

together. The bar graph to the right reports the ratio between the average oxy-hemoglobin and deoxy-hemoglobin concentrations with and without subtraction of systemic contributions.

We also subtracted the systemic contribution in the images, and compared the size (full width half maximum) of the activated area for HbO, Hb, and THC with and without subtraction (see Figure 10).

Discussion

Table 1 shows the robustness and the reproducibility of the optical measurements of hemoglobin changes in the sensorimotor area during active and passive motor stimuli. Our results also show the consistency of the measurement across individuals, and from these consistent findings we can deduct physiological behaviors in response to the different stimuli. Before doing so, however, we need to explicitly consider the limitations of the optical methods used by us, and take into account the possible artifacts that can derive from these limitations.

Quantitative Accuracy

Our simplified approaches to separating oxy- and deoxy-hemoglobin concentration changes and to generating optical maps have a number of advantages, but are based on assumptions that may lead to artifacts in our results if they are not fulfilled. These potential artifacts are discussed in detail below.

Cross talk between oxy- and deoxy-hemoglobin—The application of the DPF method to a medium that is not homogeneous, and in which scattering or nonhemoglobin absorption changes may contribute to the optical signal, can lead to cross talk between the derived Hb and HbO concentration changes. We minimized the cross talk in our instrument by using optimal wavelengths identified by previous studies (Strangman, Fran-ceschini, & Boas, in press; Uludag, Kohl, Steinbrink, Obrig, & Villringer, 2002; Yamashita, Maki, & Koizumi, 2001). Moreover, by imaging a large area of the cortex, we were able to identify the pixel corresponding to the maximal optical response. The data at this pixel, which were used in our analysis, should be less prone to oxy/deoxy cross talk, as observed in previous studies (Strangman et al., in press).

Depth of activation—The median nerve stimulation activates primarily the cortex relative to the thumb, which is deeper than the representation of the other fingers. With our model, deeper areas in the cortex were weighted less than shallower areas because of the so-called partial volume effect (the weaker sensitivity of optical data to changes occurring deeper in the tissue). This lack of uniformity in the sensitivity to cortical activation at different depths can be addressed only with a more rigorous image reconstruction approach, which would require a larger number of source and detector locations with more overlapping measurements. As a result, our estimates of the magnitude of the hemoglobin response evoked by electrical stimulation and of its spatial size at the cortex may be underestimated.

Quantitative changes of oxy- and deoxy-hemoglobin—With our CW system, we could not measure the DPF for each subject, so that we opted to use brain DPF values reported in the literature (Duncan et al., 1996). The difference between our assumed DPF value and the actual DPF value for each subject, in addition to the partial volume effect, does affect the absolute values of our measured HbO and Hb concentration changes. We believe that these effects are the major reasons for the observed intersubject amplitude variability in the HbO and Hb changes.

Systemic changes—In most subjects, during the finger opposition task (and to a lesser extent during tactile stimulation), we observed an increase in the heart rate that is synchronous with the stimulus [see Figure 8(c)]. The systemic change of heart rate is reflected into optical data (Franceschini, Fantini, et al., 2000), possibly as a result of contributions from extracerebral tissue. Heart rate changes cause modulations in the volume of arterial compartment. Because oxy-hemoglobin concentration is mostly representative of the arterial compartment, it is more affected by these changes compared to deoxy-hemoglobin concentration, which comes mostly from the venous compartment. As a result of this systemic contribution of heart rate increase during stimulation, oxy-hemoglobin maps present a less localized activation than deoxy-hemoglobin maps (see Figure 2). This was observed in all subjects on the contralateral hemisphere to the stimulated hand. The filled bars in Figure 10 further indicate the proposal that the oxy-hemoglobin maps show more activated pixels than the deoxy-hemoglobin maps (15 pixels corresponding to about 6 cm^2 for finger opposition, and 14 pixels corresponding to about 6 cm^2 for tactile stimulation). We attempted to correct for the systemic contribution to cerebral hemoglobin changes by subtracting the hemoglobin changes on an area outside the SMI from the full image. By doing this subtraction, we assumed the hemoglobin systemic changes to be spatially homogeneous. This assumption is a first approximation, which needs to be further investigated. By subtracting the systemic hemoglobin contributions, the size of activation for oxy-hemoglobin maps significantly decreased in all the stimuli, while the activated area in the deoxy-hemoglobin maps remained the same, making the size of activation for HbO comparable to the size for Hb. The area of HbO activation during median nerve stimulation did not change significantly by subtracting the systemic HbO contributions. The systemic contribution of the heart rate increase also affected the amplitude of HbO during activation [see Figure 7(a)]. The decrease of deoxy was 32% of the increase of oxy for finger opposition and 53% for finger tactile. After the systemic contribution subtraction, the difference between oxy and deoxy amplitudes was reduced. In fact the decrease of deoxy became 44% of the increase of oxy for finger opposition, and 61% for finger tactile (see Figure 9). Again, no relevant changes were seen for median nerve stimulation. The temporal behavior of oxy- and deoxy-hemoglobin changes during the three stimuli was not affected by the systemic increase of heart rate.

Spatial Size of the Evoked Optical Response

As we stated in the introduction, the limited spatial resolution provided by our optical imaging setup does not allow us to distinguish the motor cortex from the sensory cortices. As a result, the activated brain areas in the sensory and motor tasks overlapped in this study.

During finger opposition, the activated cortical area in the contralateral oxy-hemoglobin and deoxy-hemoglobin maps were not highly localized (see Figure 10). The deoxy-hemoglobin maps showed about 34 pixels (corresponding to an area of ~14 cm^2) where Hb decreased significantly during stimulation with respect to the resting value. The size of the activated brain area in the optical images was smallest for the electrical stimulation (~7 cm^2 in the deoxy-hemoglobin maps). Lack of activation at the weakest stimulus may depend on the level of baseline signal-to-noise ratio (SNR), and, in our case, can be due to activation of deeper areas than the first two stimuli. Nevertheless, the fact that for sensory stimulation the activated area is relatively smaller than during voluntary motion generally agrees with previous reports (Maldjian, Gottschalk, Patel, Detre, et al., 1999). Spiegel et al. (1999) performed a comparative study of the median nerve and finger opposition tasks. They found activation in the same location of the MI and SI for the two stimuli, but different sizes of activation; in particular they reported an MI-activated area twice as large as the SI-activated area in the motor task, and both activated areas were larger than during electrical stimulation.

In Figure 10 we also report the size of total hemoglobin concentration. It has been reported that total hemoglobin concentration is the parameter that better localizes the activation area with optical imaging (Culver et al., 2002). We verified that also in our case THC maps are smaller in size with respect to Hb and HbO maps. THC is the sum of the two hemoglobin species, and because one increases while the other decreases, the size of activation on the total hemoglobin maps should be smaller.

In two cases (Subjects 6 RH and 7 LH), the area of increase of oxy did not overlap with the area of decrease of deoxy. In general, the oxy-hemoglobin-activated area overlapped with about 61% of the deoxy-hemoglobin-activated area during finger opposition, 66% during tactile stimulation, and 40% during electrical stimulation.

Amplitude Differences across Stimuli

Our results showed not only that voluntary movement activated a larger area, but also that it caused a higher hemoglobin change. From Figures 4, 5, and 7, the amplitudes of the changes in HbO and Hb in the contralateral side are larger during finger opposition task with respect to finger tactile and electrical stimulation. From the grand average across subjects, we observed a consistently higher change of hemoglobin on the right hemisphere due to left hand stimulation than on the left hemisphere (due to right hand stimulation). The decrease of Hb was approximately one-half of the increase of HbO for the three stimuli. The ratio of oxy/deoxy was −2.3 for finger opposition, and −1.7 for tactile and electrical stimulation. These results are consistent with findings of previous noninvasive NIRS studies (Obrig, Hirth, et al., 1996). The amplitude of oxy and deoxy-hemoglobin changes during tactile stimulation was 43% and 70% smaller, respectively, than during finger opposition. They were even smaller comparing electrical stimulation with finger opposition (26% HbO, 45% Hb). These results agree with previous PET studies, which showed that passive (median nerve) movement elicited a weak brain activation compared with active movement (Mima et al., 1999).

Ipsilateral Activation and Deactivation

In the ipsilateral cortex, the activation was significantly greater for the motor task than for the sensory tasks, again both spatially and in amplitude. These findings are in agreement with some fMRI findings (Li et al., 1996). Some other fMRI studies report a deactivation of the ipsilateral primary sensorimotor cortex during finger opposition (Allison et al., 2000). Nirkko et al. (2001) suggest that the deactivation of ipsilateral SMI during finger opposition possibly reflects the suppression of mirror movements. In this study, for right-handed subjects, right hand movements show higher deactivation in agreement with the report that right hand movements lead to fewer mirror movements than do left hand movements. Also, PET studies have found a decrease of rCBV in parts of the brain either ipsilateral to the location of the stimulus or in cortex surrounding the activated area (Brandt, Bartenstein, Janek, & Dietrich, 1998; Drevets et al., 1995; Ghatan et al., 1995; Haxby et al., 1994; Shulman et al., 1997; Wenzel et al., 1996). Such a decrease of blood volume (and blood flow) may indicate inhibition or a decrease in activity of certain brain areas that do not pertain to the attended process, and can be detected with fMRI when calculating negative BOLD signal changes (Allison et al., 2000; Bense, Stephan, Yousry, Brandt, & Dietrich, 2001; Carlsson, Petrovic, Skare, Petersson, & Ingvar, 2000; Fransson, Kruger, Merboldt, & Frahm, 1999; Rauch et al., 1998). For motor and tactile stimulation, we did not observe deactivation in the ipsilateral side of the brain, whereas during electrical stimulation, we observed the peculiar feature of ipsilateral decrease in blood flow—blood volume that is indicative of deactivation (see Figures 4, 5, 7, and 9). A possible reason why we do not observe deactivation in the ipsilateral side during finger opposition and tactile stimulation is the insufficient subtraction of systemic hemoglobin changes due to the increase of heart rate.

These changes in hemoglobin are opposite in sign to the hemoglobin changes caused by deactivation and can cancel out the deactivation effect. During electrical stimulation, the heart rate increase is negligible and the ipsilateral deactivation does not cancel out. Another possible explanation is that motor and tactile stimuli activate and deactivate neighboring ipsilateral areas. Because of our poor spatial resolution, the effect of deactivation on small areas can be canceled by the activation on areas in close proximity. During electrical median nerve stimulation there are no activated areas in the ipsilateral side of the cortex, so the deactivated areas are not masked. In fact, MEG and fMRI studies have shown that during median nerve stimulation only the contralateral primary sensorimotor cortex is activated (Simoes & Hari, 1999; Spiegel et al., 1999). No reports of ipsilateral activation with this stimulus have been published.

Temporal Differences across Stimuli

From Figure 6, we observe that the evoked change in HbO and THC starts approximately 1 s after the onset of stimulation for finger opposition and finger tactile. The onset of the rise in HbO and THC precedes that of the decrease in Hb by ~1 s. This temporal offset between the evoked responses of HbO, Hb, and THC has been observed before in similar optical studies of the brain (Wolf et al., 2002). THC peaks at ~5 s, whereas HbO peaks at ~6 s, and Hb peaks at ~8 s. Contralateral and ipsilateral cortexes behave similarly. For the median nerve stimulation, the onset of HbO and THC change is delayed by 2 s from the onset of stimulation, and coincides with the onset of the Hb change, whereas the timings of the peaks are the same as for the previous two stimuli. If we consider that the HbO signal comes predominantly from the arterial compartment whereas Hb comes from the venous compartment, the delayed response of Hb relative to THC and HbO is consistent with washout of deoxy-hemoglobin from the venous compartment delayed by the vascular transit time from arteries to veins (Buxton, Wong, & Frank, 1998; Mandeville et al., 1999).

In summary, this study demonstrates the capability of diffuse optical imaging to detect the hemodynamic-evoked responses to voluntary and nonvoluntary stimuli in the sensorimotor cortex. This study also shows the robustness and intersubject reproducibility of the optical measurements in detecting activation in the SMI cortex with different sensorimotor stimuli. In fact, we consistently found an increase (decrease) in the cerebral concentration of oxy-hemoglobin (deoxy-hemoglobin) at the cortical side contralateral to the stimulated hand. We also found that the hemodynamic response is stronger for the voluntary task of finger opposition, as opposed to the passive tasks of tactile and electrical stimulations. Further research in this direction may contribute to investigation of mechanisms related to agency (Ruby & Decety, 2001). Our findings, which are in agreement with results in the literature obtained with PET and functional fMRI, confirm the potential of diffuse optical imaging to become a valuable technology for noninvasive functional imaging of the brain.

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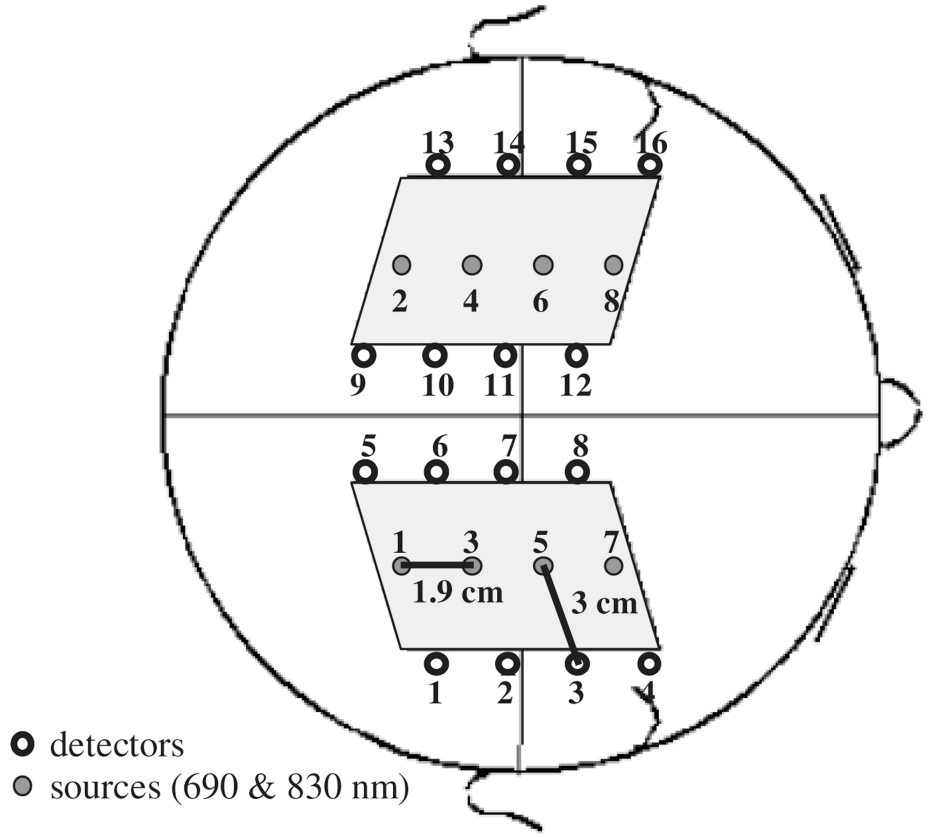

Figure 1.
Geometrical arrangement of the source and detector fibers on the head.

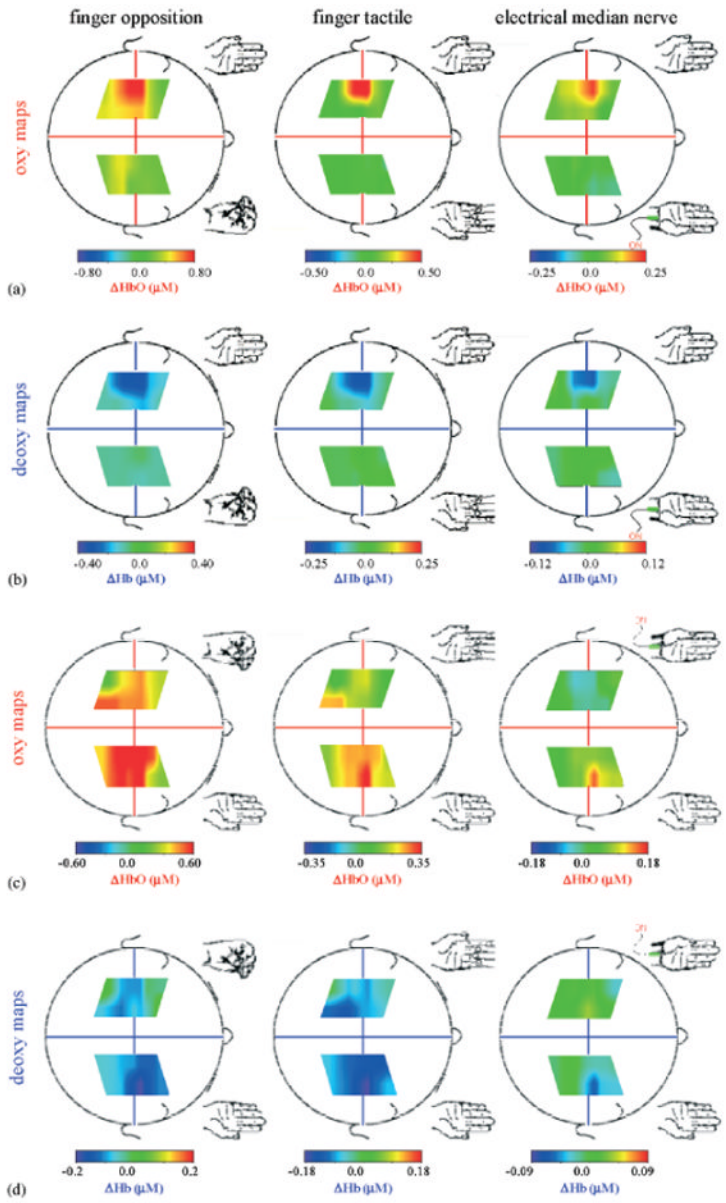

Figure 2.

Block-averaged hemoglobin maps on Subject 2, 10s after the onset of the stimulation during (a) and (b) right and (c) and (d) left hand stimulation. Top panels (a) and (b): oxy hemoglobin changes. Bottom panels (c) and (d): deoxy-hemoglobin changes. Left column: finger opposition. Center column: finger tactile. Right column: median nerve stimulation.

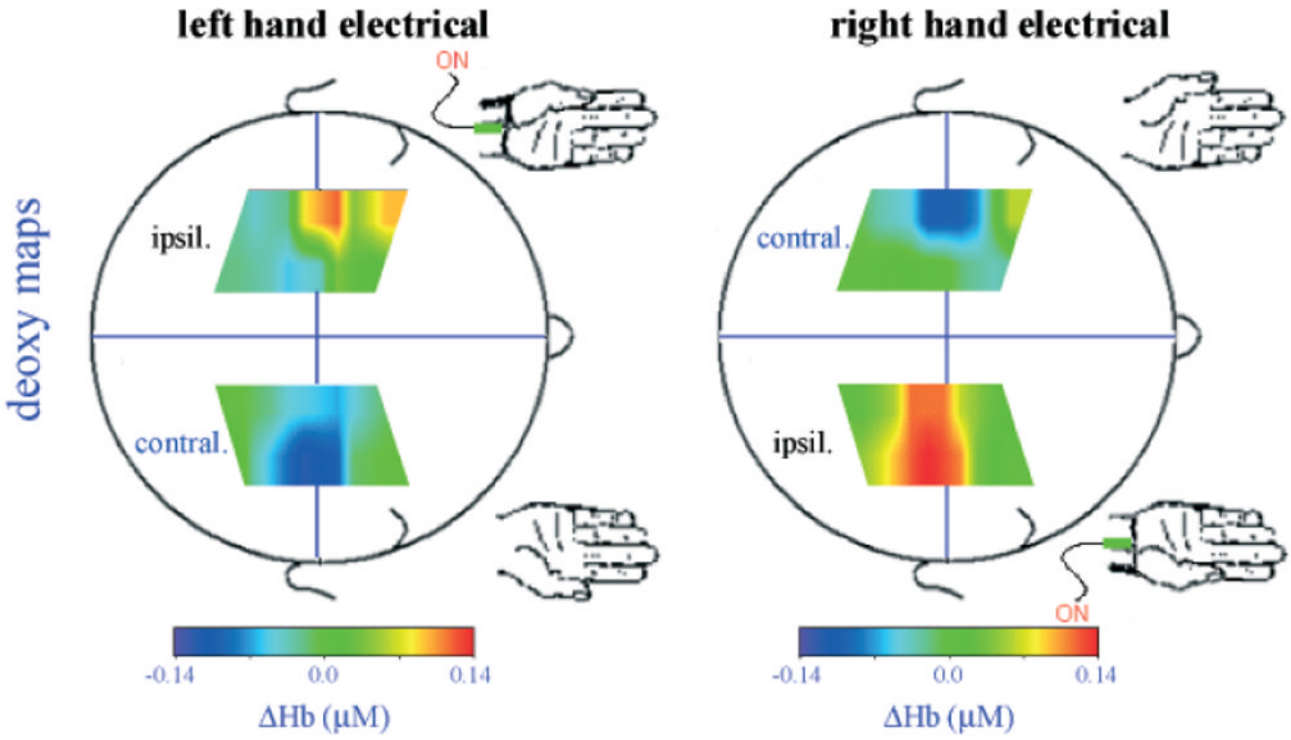

Figure 3.
Block-averaged deoxy-hemoglobin maps on Subject 10, 10s after the onset of the stimulation during right and left wrist electrical stimulation.

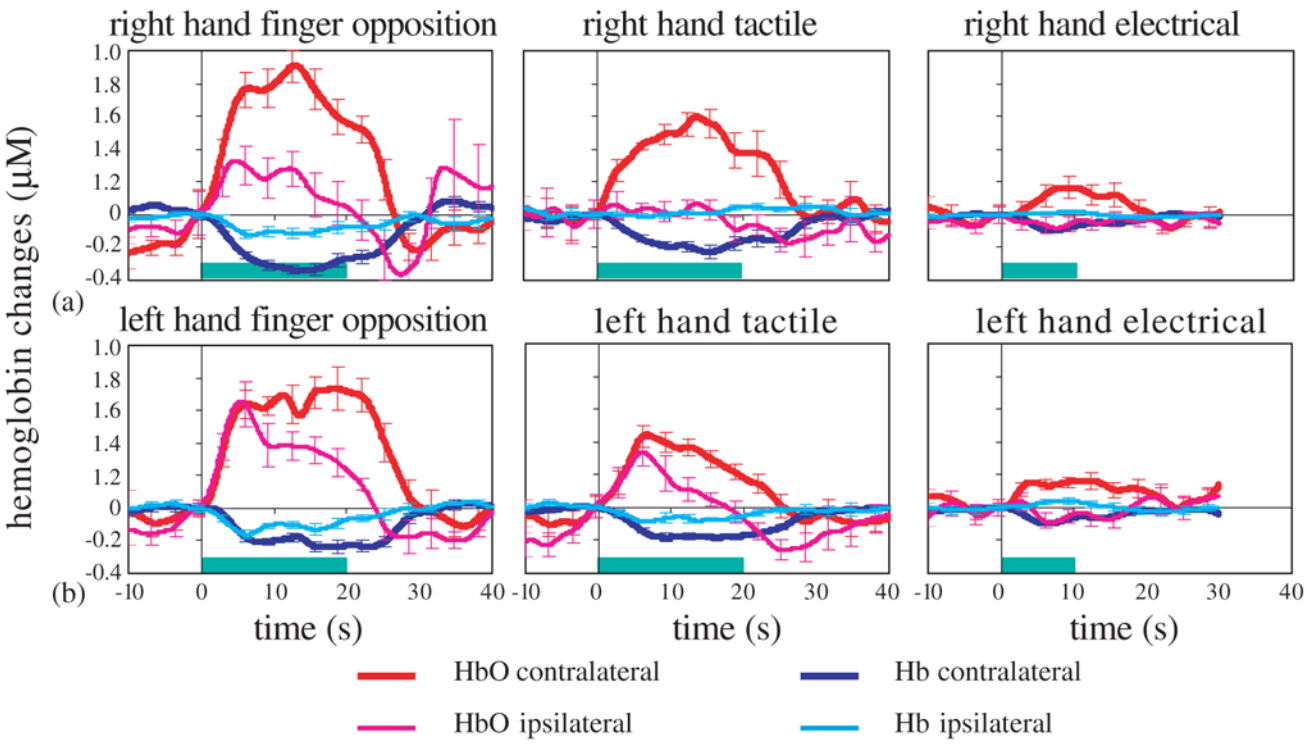

Figure 4.
Temporal traces of the block average hemoglobin responses on the contralateral (red and blue) and ipsilateral (pink and light blue) SMI of Subject 2. Red and pink: oxy-hemoglobin changes; blue and light blue: deoxy-hemoglobin changes. The error bars are the standard errors over the number of averaged blocks.

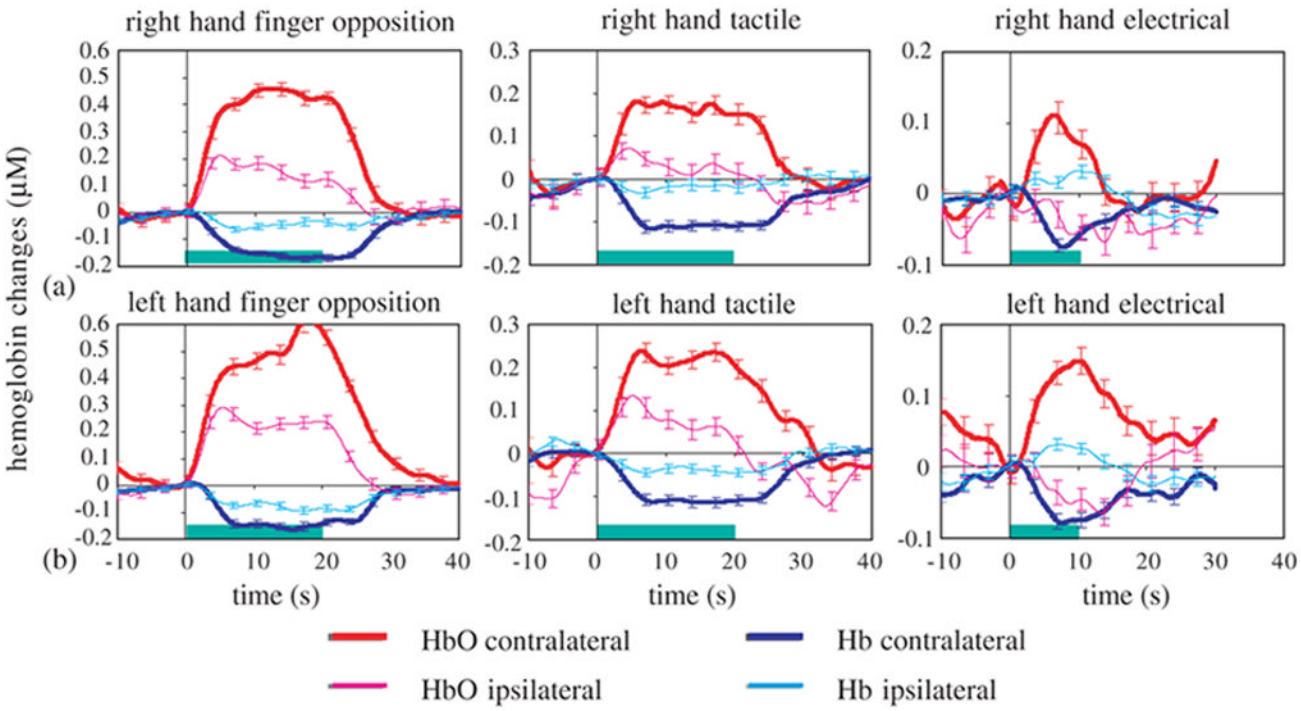

Figure 5.

Grand average of the temporal traces of the evoked hemoglobin responses on the contralateral (red and blue) and ipsilateral (pink and light blue) SMI. Red and pink: oxy-hemoglobin changes; blue and light blue: deoxy-hemoglobin changes. Notice different *y*-axis for different stimuli.

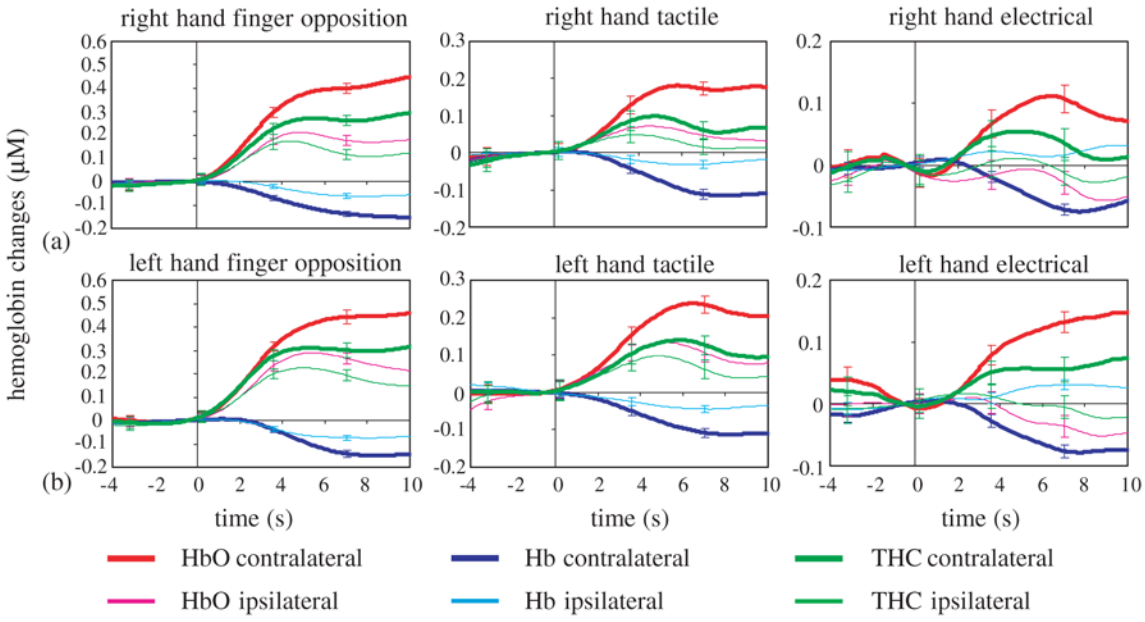

Figure 6.

Initial contralateral and ipsilateral hemodynamic response to the three tasks for right hand (a) and left hand (b) stimulation. Red and pink: oxy-hemoglobin changes; blue and light blue: deoxy-hemoglobin changes; dark and light green: total hemoglobin changes.

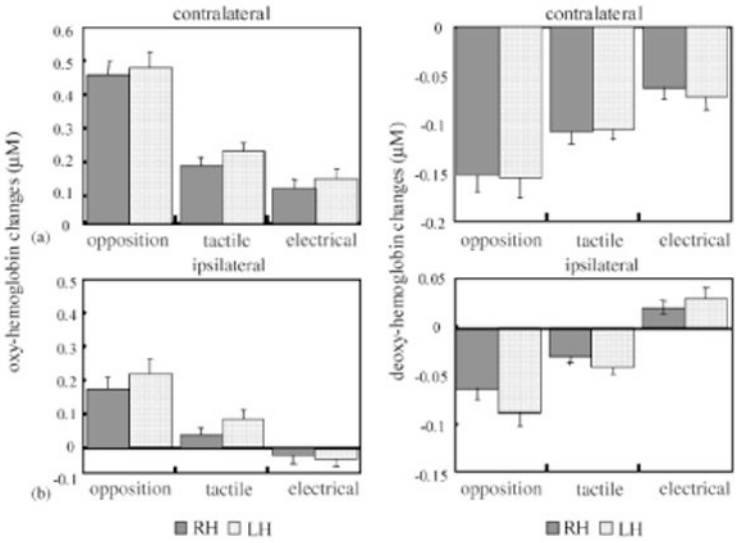

Figure 7.

Changes in oxy-hemoglobin (left) and deoxy-hemoglobin (right) at the pixel of maximal contralateral response to stimulation averaged across subjects. The filled bars correspond to right hand stimulations (left SMI); the dotted bars correspond to left hand stimulation (right SMI).

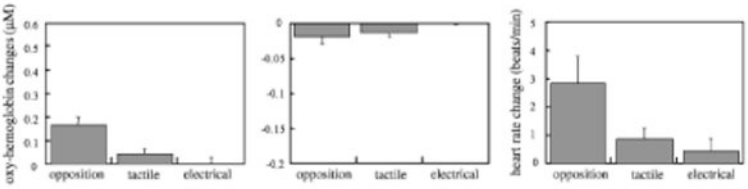

Figure 8.

Oxy-hemoglobin (left), deoxy-hemoglobin (middle), and heart rate (right) changes during stimulation averaged across subjects. Oxy- and deoxy-hemoglobin are measured in the contralateral brain hemisphere outside the SMI cortex at a posterior-medial image pixel. The heart rate is measured on a toe of each subject with a pulse oximeter.

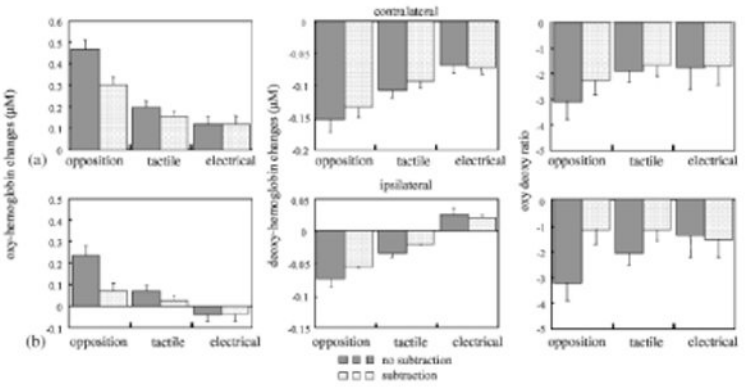

Figure 9.

Oxy-hemoglobin (left), deoxy-hemoglobin (middle), and ratio oxy- and deoxy-hemoglobin (right) changes during stimulation. The filled bars correspond to no subtraction of systemic contribution; the dotted bars correspond to the changes after correction by subtracting systemic hemoglobin changes.

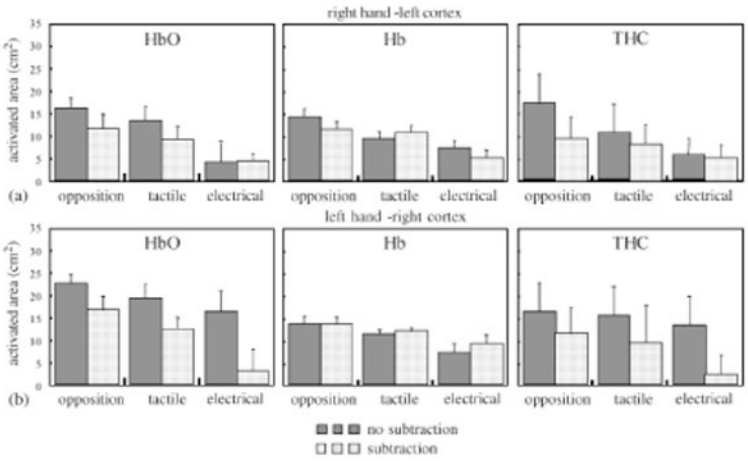

Figure 10.

Oxy-hemoglobin (left), deoxy-hemoglobin (middle), and total hemoglobin (right) activated area during stimulation. The filled bars correspond to no subtraction of systemic hemoglobin contributions; the dotted bars correspond to the activated area after correction by subtracting systemic hemoglobin contributions. (a) right hand stimulation; (b) left hand stimulation.

Table 1

Summary of All the Results for the Contralateral and Ipsilateral Oxy-Hemoglobin and Deoxy-Hemoglobin Changes Induced by the Three Protocols for the Right and Left Side Stimulations

		Contralateral												Ipsilateral									
		Opposition				Tactile				Electrical				Opposition				Tactile				Electrical			
		Oxy		Deoxy		Oxy		Deoxy		Oxy		Deoxy		Oxy		Deoxy		Oxy		Deoxy		Oxy		Deoxy	
Subject #	Handedness	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L
1	R	+	+	−	−	+	+	−	−	+	+	−	−	+	+	−	0	+	0	0	0	−	+	+	0
1b		+	+	−	−	+	+	−	−	+	+	−	−	+	+	−	−	+	+	−	−	−	−	+	+
2	M	+	+	−	−	+	+	−	−	+	+	−	−	+	+	−	−	0	+	0	−	0	−	+	+
2b		+	+	−	−	+	+	−	−	+	+	−	−	+	+	−	−	+	+	−	0	−	−	+	+
3	R	+	+	−	−	+	+	−	−	+	+	−	−	+	+	−	−	+	+	−	−	+	+	0	0
3b		+	+	−	−	+	+	−	−					+	+	−	−	+	+	0	−				
4	R	D	+	D	−	+	+	−	−	+	+	−	−	D	+	D	−	+	+	0	−	+	+	0	0
5	L	+	+	−	−	+	+	−	−	0	0	0	0	+	+	0	−	−	+	0	−	0	−	0	0
6	L	+	+	−	−	+	+	−	−	D	D	D	D	+	+	−	0	−	0	0	0	D	D	D	D
7	R	+	+	−	−	0	0	0	−	+	+	−	−	0	+	0	−	+	−	0	0	+	+	+	−
8	R	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D
9	R	+	+	−	−	+	+	−	−					+	+	−	−	+	+	0	−				
10	R									+	+	−	−									−		+	+

Notes: The first column indicates the subject number. The second column indicates the handiness of each subject: R = right-handed, L = left-handed, M = mixed handedness. The next columns report the signs of the oxy- and deoxy-hemoglobin changes during activation in the contralateral and ipsilateral sides of the brain during the three stimulation protocols. R and L indicate the hand performing the task. The + signs indicate an increase of hemoglobin concentration, the − signs indicate a decrease of hemoglobin concentration, and 0 indicates a change under the .05 threshold for *p*. The Ds in the row for Subjects 6 and 8 indicate discarded cases because either motion artifacts or low signal-to-noise ratio made the measurement unreliable. The D in the right hand finger opposition column for Subject 4 indicates that we lost the data file due to technical problems. Finally blank areas mean that the subject did not perform the specific task. Notice that for normal activation we expect to see an increase of oxy-hemoglobin (+) and a decrease of deoxy-hemoglobin (−) concentration. The gray areas indicate a deactivation (increase of deoxy-hemoglobin and decrease of oxy-hemoglobin concentration).