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A spatial and temporal comparison of hemodynamic signals measured using optical and functional magnetic resonance imaging during activation in the human primary visual cortex

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Abstract

Functional near infrared spectro-imaging (fNIRSI) is potentially a very useful technique for obtaining information about the underlying physiology of the blood oxygenation level dependent (BOLD) signal used in functional magnetic resonance imaging (fMRI). In this paper the temporal and spatial statistical characteristics of fNIRSI data are compared to those of simultaneously acquired fMRI data in the human visual cortex during a variable-frequency reversing checkerboard activation paradigm. Changes in the size of activated volume caused by changes in checkerboard reversal frequency allowed a comparison of the behavior of the spatial responses measured by the two imaging methods. fNIRSI and fMRI data were each analyzed using standard correlation and fixed-effect group analyses of variance pathways. The statistical significance of fNIRSI data was found to be much lower than that of the fMRI data, due mainly to the low signal-to-noise of the measurements. Reconstructed images also showed that, while the time-course of changes in the oxy-, deoxy-, and total hemoglobin concentrations all exhibit high correlation with that of the BOLD response, the changes in the volume of tissue measured as “activated” by the BOLD response demonstrate a closer similarity to the corresponding changes in the oxy- and total hemoglobin concentrations than to that of the deoxyhemoglobin.

Keywords

Human brain; Functional activity; Near infrared imaging; fMRI

Introduction

Near-infrared spectroscopy provides a unique tool to study neurovascular coupling, with the ability to measure changes in both oxy- and deoxyhemoglobin concentrations. These measures can be related to changes in physiological parameters such as cerebral blood flow (CBF), cerebral blood volume (CBV) and the cerebral metabolic rate of oxygen (CMRO₂). A current search of scientific reference engines using the keywords “near infrared” and “brain” returns more than 600 references, including about 70 review papers (for the most recent reviews see Gibson et al., 2005; Gratton et al., 2005). However, the majority of these works use near infrared spectroscopy (NIRS) to study the human brain with little spatial resolution beyond the location of the optical probe (Strangman et al., 2003; Toronov et al., 2003b). A relatively small number

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of papers have performed surface mapping of the functional cerebral hemodynamics, i.e., the locations of the hemodynamic or neuronal changes are projected onto the surface of the head, again with a significant loss of spatial information (Franceschini et al., 2000; Sato et al., 2005; Schroeter et al., 2004; Seiyama et al., 2004).

It was realized quite early on (Arridge et al., 1986) that NIRS measurements at multiple locations combined with image reconstruction algorithms can, in principle, be used for near infrared imaging, so that cerebral hemodynamic changes could be mapped in three dimensions. However, in spite of a significant amount of theoretical work (Boas et al., 2004a,b; Boas and Dale, 2005; Guven et al., 2005; Li et al., 2005; Xu et al., 2005), the literature on practical three dimensional fNIRSI of the human brain is limited to a few papers (Bluestone et al., 2001; Boas et al., 2004b; Hintz et al., 2001; Hoshi et al., 2000; Zhang et al., 2005a,b). The reason for the modest progress in full three-dimensional fNIRS is the combination of the extremely high scattering of light in biological tissue, together with the optical heterogeneity of the human head. Improvements in image reconstruction algorithms based on the solution of the inverse problem for light transport in highly scattering media continue to attract a significant effort from many groups (Arridge, 1999; Li et al., 2005; Xu et al., 2005). It has also been shown that the problem of tissue heterogeneity can be eased somewhat by utilizing structural information provided by MRI (Boas et al., 2004a,b; Guven et al., 2005; Zhang et al., 2005a,b). Another benefit of the combination of fNIRSI with MRI is the possibility of simultaneous recording of fMRI and optical data. This allows comparisons of the spatial and temporal characteristics of the fMRI signals with optically-derived hemodynamic changes to clarify the contributions of different physiological parameters to the fMRI signals. Several studies of functional activations have been performed in the human motor cortex by simultaneous fMRI and NIRS (Toronov et al., 2000, 2001b, 2003a,b). In particular it was found that, in the human motor cortex, the temporal dependence of the deoxyhemoglobin concentration was the factor most closely related to the BOLD fMRI signal. In order to extend the capability to study cerebral hemodynamics to three-dimensional tomography, our group has recently developed a methodology for integrating fNIRSI with MRI (Zhang et al., 2005a), enabling simultaneous fMRI and fNIRSI data recording. Simultaneous data acquisition allows robust incorporation of spatial MRI information into the optical data reconstruction algorithm and accurate co-registration of fNIRSI and fMRI results. A similar methodology has been developed by the Photon Migration Group at Massachusetts General Hospital (Hoge et al., 2005).

Simultaneously acquired spatiotemporal fNIRSI and fMRI data should ideally be analyzed using similar statistical methods. The standard pathway for fMRI data analysis typically comprises two stages: preparatory single-subject analysis followed by combined group analysis. The only paper which has applied group analysis to fNIRSI data was a study of the left-hand side of the human visual cortex by NIR topography (Schroeter et al., 2004). However, since no MRI data were acquired in that study, the optical data could not be spatially transformed to standard stereotactic space (Talairach and Tournoux, 1988). The primary goal of this paper is to present the results of a full fixed-effect group analysis of four-dimensional (space+time) fNIRSI data for different activation conditions in the human visual cortex, and to compare the statistical properties of fNIRSI with fMRI data. This study required designing an optical probe for simultaneous fMRI and fNIRSI recording from the human primary visual cortex, which was particularly difficult to implement because the subject's head must rest directly on the optical probe within the tight confines of the MRI scanner. A parallel aim was to compare fMRI and fNIRSI data for different activation conditions in the human visual cortex. In order to achieve these goals fNIRSI and fMRI data were acquired simultaneously during the presentation of a reversing checkerboard paradigm with different reversal frequencies, and analyzed by the standard group analysis of variance pathway (Cox, 1996; Friston et al., 1995a).

Materials and methods

Subjects

Nine healthy, right-handed subjects, seven males and two females, between the ages of 21 and 40 (median age 26), signed the Informed Consent form approved by the Institutional Review Board at the University of Illinois at Urbana-Champaign.

fNIRS instrument

The optical signals were recorded using a near infrared spectrometer (Imagent, ISS, Champaign, IL). The optical sources were laser diodes (690 and 830 nm) which were amplitude modulated at 150 MHz and time-multiplexed. Light reaching the detectors was amplified by photomultiplier tubes and consequently converted into AC, DC, and phase signals for each of the source-detector combinations (channels) at each wavelength of light. Data acquisition was synchronized with the fMRI measurements using the TTL-trigger signal from the MR scanner, which also triggered the beginning of the visual stimulation paradigm.

Optical probe

The optical probe was designed with 16 pairs of 400- μ m-diameter core plastic-clad multimode silica source fibers and 4 detector fiber bundles. The physical size of the MR scanner mandated the use of prisms with dielectric reflective layers for the fiber bundles (metal reflecting surfaces were found to produce significant artifacts in MR images). The optical fibers were “ferruled” using plastic tubing, and the frame of the optical probe was constructed from polyurethane which has appropriate mechanical properties and produces insignificant artifacts in the MR images. The topology of the probe was designed so that the optical channels overlapped and the distribution of source-detector distances covered the optimal range (Toronov et al., 2003a), between approximately 20 and 30 mm, as shown in Fig. 1. An MRI visible marker was attached adjacent to each of the 16 optical source fiber pairs and four detector fiber bundles so that accurate source and detector positions could be estimated from MR images (Zhang et al., 2005a,b). The thickness of the probe was less than 20 mm to ensure that it could be placed comfortably between the back of the head and the bottom of the MRI birdcage head coil. The probe was carefully tested on a tissue-mimicking phantom with homogeneous optical properties to ensure that all source-detector channels provided very similar signal amplitudes. For the experiment, the center of the optical probe was placed as close as possible to the primary visual cortex. This was achieved by initial positioning the center of the optical probe approximately 2 cm above theinion, followed by a rapid MR scan to locate the visual cortex: if necessary, the optical probe was then moved by the requisite distance.

In order to minimize the influence of hair on the optical contact between fibers and the skin, we have designed a special fabric mask with holes directly underneath the locations of the sources and detectors of the optical probe. The mask was attached to the back of the subject’s head using Velcro straps overlapped on the forehead. After attaching the mask, an operator cleared the hair within the holes by pushing the hair under the mask using a cotton-tipped stick. This technique worked very well, allowing consistent signal intensities to be recorded even on subjects with dark hair.

MRI setup

For MRI data acquisition a 3 T head-only MR scanner (Allegra, Siemens) was used. The MRI protocol started with a rapid T_1 -weighted spin-echo (240×240 mm field-of-view, 512×512 data matrix, 16 slices, 4 mm slice thickness, 0.4 mm inter-slice gap, and aligned along the anterior/posterior commissure). These images were used for initial co-registration of the functional scans, which were acquired using an echo planar imaging (EPI) sequence (slice orientation and

dimensions as above, 64×64 data matrix, tip angle 60°, TE 25 ms, TR 2000 ms). After the functional data were collected, high-resolution (0.5×0.5×1.0 mm³) T₁-weighted spin-echo images, termed “probe localizers”, were acquired over a small volume containing the optical probe to enable automatic recovery of the positions of the optodes. Finally, a magnetization-prepared rapid gradient-echo (MPRAGE) 3-D image (spatial resolution 0.94×0.94×1.2 mm³) of the full-head was acquired for co-registration of the optical and fMRI signals.

Visual stimulation protocol

A pair of non-magnetic goggles (Resonance Technology) with LCD screens was placed in front of the subject's eyes inside the birdcage head coil. These goggles provided vision correction for subjects when required. The block-designed visual stimulation paradigm consisted of four blocks each with 20 s fixation followed by 20 s of a black-and-white checkerboard pattern reversing at a given frequency (1, 2, or 6 Hz). The pattern subtended a visual angle of 17° horizontally and 15° vertically. Subjects were instructed to focus on a small cross, which was present during both activation and fixation periods, in the center of the field-of-view. Each block ended with a 20 s relaxation period when the subject was presented with a black screen. For each frequency of the checkerboard reversal four separate stimulation/rest blocks were used. A number of fMRI studies have investigated the effect of visual stimulation frequency on neural activation, and we were interested to determine which optical measurements were dependent upon the stimulation frequency.

Data analysis

Registration of the optode positions to the structural MR image—In order to account for subject-specific deformations of the flexible optical probe automatic estimation of source- and detector-positions from the MR images was performed using custom-developed image processing algorithms implemented in a MATLAB (Mathworks, Natick, NJ) script. The process can be summarized as computing the rotation and translation of the reference coordinate systems of the MPRAGE image with respect to the probe-localizer, determination of the angular position of the cylindrical markers by computing the rotation of the coordinate system due to rotation of the optical probe, and finally correcting for any misalignment from deformation of the probe. The accuracy of the optode localization was comparable to the resolution of the structural MR images (~1 mm).

Optical image reconstruction—Optical images were reconstructed using the AC measurements and the algorithm described in detail in Zhang et al. (2005a). The key features of the algorithm are: (i) computation of the sensitivity point spread function using Monte Carlo simulations of light transport in the digital head model derived from segmented structural (MPRAGE) MRI images, and (ii) solution of the linearized inverse problem for the local variations of the absorption coefficient using a simultaneous iterative reconstruction technique (SIRT) algorithm. Image reconstruction was restricted to brain tissue within the effective optical sensitivity region (SR), which totaled about 600 voxels, each 4×4×4 mm. Using Lambert–Beer's law (Severinghaus and Astrup, 1986), for each voxel in the reconstructed images, the temporal changes in absorption coefficient were converted into changes in the oxy-, deoxy-, and total hemoglobin concentrations.

Single subject analysis—All four-dimensional (three spatial, one temporal) fMRI and fNIRSI data sets were analyzed in the same way. After linear detrending, the correlation coefficient between the image intensity and a stimulation boxcar function, delayed by 5 s, was calculated for each voxel. Images of the mean change between activation and rest conditions were computed and thresholded so that only voxels with correlation coefficient greater than 0.7 were retained.

Group analysis—The mean-change images were converted to ANALYZE format and the AFNI software package was used to analyze further both fMRI and fNIRSI datasets. All the functional images were spatially smoothed with an isotropic 4 mm full-width-half-maximum Gaussian kernel, registered to the full head MPRAGE structural images, and transformed to the Talairach coordinate system (Talairach and Tournoux, 1988).

Fig. 2 shows central sagittal slices of all subjects in Talairach space. The filled-circles indicate the cortical locations nearest to the center of the optical probe. Although every attempt was made to center the probe as close as possible to the primary visual cortex, one can see that the position of the probe in the superior–inferior direction varied significantly among subjects. Two subjects, with extreme superior and inferior positions of the probe, shown in Figs. 2(c) and (i) were excluded from the data analysis.

In order to create group maps for the seven remaining subjects (five males and two females), a one-way ANOVA (Cox, 1996; Friston et al., 1995a,b) was performed on each voxel in Talairach space. Mean-response images, along with corresponding *t*-statistics maps were calculated for each checkerboard reversal frequency. A contrast-in-factor level was calculated to evaluate the BOLD amplitude changes across the different reversal frequencies (Cox, 1996). In all the axial images shown, left and right correspond to actual left and right of the head, respectively, and the bottom of the image corresponds to the posterior of the head. In figures showing multiple axial slices, the sequence of slices from the top to the bottom of the column corresponds to an inferior-to-superior sequence in the head. Since [HHb] usually decreases during functional activation, values in the Δ [HHb] maps are inverted.

Results

Single-subject analysis

Figs. 3(a) and (b) show BOLD maps from a single subject (subject b in Fig. 2) at a stimulation frequency of 1 Hz. Figs. 3(c) and (d) show the corresponding Δ [HHb] maps (with no spatial smoothing). From Figs. 2 and 3 one can see that the optical probe is well-centered with respect to the center of the activated region. Both the BOLD map in Fig. 3(b) and the Δ [HHb] map in Fig. 3(d) show left-sided lateralization. Fig. 3(b) shows that there is a stronger BOLD response in the superficial cortical layer in the left portion of the cortex than in the right: the maximum BOLD amplitude change occurs slightly deeper on the right portion of the brain.

Our single-subject and group average structural MRI images show a slight protrusion in the left side of the visual cortex. A similar effect can be also seen in the 152-subject averaged anatomical image provided as a sample image with the FSL software package. These observations also agree with previous morphological studies (Charles et al., 1994; Kertesz et al., 1986; Koff et al., 1986; Lemay, 1977). Fig. 4 shows representative block-averaged single-subject time traces of BOLD, $-\Delta$ [HHb], and Δ [tHb] signals for the 1-Hz stimulation experiment. The signals are averaged over all voxels defined as being “activated” by the correlation analysis. For better comparison of the time courses, all changes are normalized to their mean values during the activation period, shown by the gray rectangle. One can see that, within the experimental noise level, all three curves exhibit very similar temporal changes, indicating a high temporal correlation between changes in the BOLD, $-\Delta$ [HHb], and Δ [tHb] signals. This was confirmed by group correlation analysis.

Group analyses results

A greater BOLD contrast change in the left side of the superficial cortex was found in five out of the seven subjects, and therefore can be also seen in the cross-subject averaged maps of the BOLD response shown in Fig. 5. The data in Figs. 5(a), (b), and (c) correspond to checkerboard

reversal frequencies of 1, 2, and 6 Hz, respectively. In Fig. 5 one can see that, although the largest magnitude of the BOLD signal occurs in the right hemisphere, area of the strong BOLD signal change in the left hemisphere protrudes towards the surface of the head. In the BOLD images, the most prominent changes due to the increase in the checkerboard reversing frequency was a noticeably larger number of activated voxels at 2 Hz and 6 Hz compared to 1 Hz, listed in Table 1. Although there is an apparent increase in the magnitudes of the BOLD response averaged across subjects and over the activated region, as shown in Table 2, this increase is not statistically significant.

Figs. 6, 7 and 8 show the cross-subject maps of the mean values of $\Delta[\text{HHb}]$, $\Delta[\text{HbO}_2]$ and $\Delta[\text{tHb}]$, respectively. Panels (a)–(c) in each of these figures correspond to checkerboard reversal frequencies of 1, 2, and 6 Hz, respectively. All of the reconstructed optical images show more prominent hemodynamic changes on the left side of the visual cortex, in accordance with observations of the more superficial BOLD-detected activation discussed previously. Figs. 6 (d), 7(d) and 8(d) show the corresponding t -statistics maps (averaged over all frequencies). One can see that, in all cases, the t -values on the right side of the visual cortex are much smaller than on the left, indicating much lower statistical significance of the data. All voxels of the fNIRSI maps had significantly lower statistical significance than the corresponding BOLD maps, due to the lower signal-to-noise ratio of the measurements. Fig. 9 shows the regions of the brain which produced activation in both the fMRI and fNIRSI reconstructed images.

The p -values of the majority of voxels shown in Figs. 6–8(a–c) were between 0.1 and 0.01, much less than the corresponding voxels for the fMRI maps. The statistical quality of the functional data is illustrated in Fig. 10, which shows histograms of the voxel t -value distribution for (a) BOLD, (b) $\Delta[\text{HHb}]$, and (c) $\Delta[\text{HbO}_2]$ averaged over all subjects and stimulation frequencies. The voxels included belong to the sensitivity region of the optical probe. One can see that while many of the activated voxels in the BOLD images have a value greater than 3 ($p < 0.001$), the majority of the $\Delta[\text{HHb}]$ and $\Delta[\text{HbO}_2]$ maps have much lower significance.

Individual time traces of $-\Delta[\text{HHb}]$, $\Delta[\text{tHb}]$ and $\Delta[\text{HbO}_2]$ for all stimulation conditions were cross-correlated with the corresponding BOLD traces, as in the example shown in Fig. 4. The values of $\Delta[\text{HHb}]$, $\Delta[\text{HbO}_2]$, and $\Delta[\text{tHb}]$, shown in Table 2 were calculated by averaging over the regions in the corresponding maps having t -values higher than 2. The group mean correlation coefficient values for $-\Delta[\text{HHb}]$, $\Delta[\text{HbO}_2]$, and $\Delta[\text{tHb}]$ with the BOLD signal were found to be 0.82 ± 0.05 , 0.82 ± 0.09 , and 0.71 ± 0.1 , respectively. One can conclude from these data, that the BOLD signal is temporally correlated equally well with the $\Delta[\text{HHb}]$ and $\Delta[\text{HbO}_2]$. The $\Delta[\text{tHb}]$ signal has a slightly lower correlation coefficient with the BOLD signal; however, given that $\Delta[\text{tHb}]$ is simply the sum of $\Delta[\text{HHb}]$ and $\Delta[\text{HbO}_2]$, and that the standard deviation of the mean correlation coefficient between $\Delta[\text{tHb}]$ and BOLD is close to the difference between this value and that for $\Delta[\text{HbO}_2]$ and $-\Delta[\text{HHb}]$, one can conclude that this difference is due to the higher noise in the $\Delta[\text{tHb}]$. It should be noted that, although the changes in $\Delta[\text{HHb}]$, $\Delta[\text{HbO}_2]$, and $\Delta[\text{tHb}]$ shown in Table 2 are expressed in μM , absolute values of $[\text{HHb}]$, $[\text{HbO}_2]$ or $[\text{tHb}]$ are not given because of the uncertainty in the absolute value of the background optical properties of the head.

In terms of spatial correlation of the fMRI and optical signals, from Figs. 6 and 7 one can see that both the $\Delta[\text{HHb}]$ and $\Delta[\text{HbO}_2]$ maps show extended regions of activation at 2 and 6 Hz compared to 1 Hz. However, the size of the activated area in the $\Delta[\text{HHb}]$ images changes with frequency in a non-monotonic fashion: the activated area at 2 Hz is larger than at 1 Hz, but also larger than at 6 Hz. The behavior of the $\Delta[\text{HbO}_2]$ response maps is more consistent with the BOLD maps: the smallest activated area and magnitude occur at 1 Hz, and the largest occur at 6 Hz. From Table 2 one can also see that the magnitude of $\Delta[\text{HHb}]$ remains approximately

constant at all frequencies, while the magnitudes of $\Delta[\text{HbO}_2]$ and $\Delta[\text{tHb}]$ exhibit slight elevations with an increase in stimulation frequency.

Finally, it should be noted that all the reconstructed optical images shown in Figs. 6(a–c), 7(a–c), and 8(a–c) contain areas (shown in blue) which show an increase in $[\text{HHb}]$ and decreases in $[\text{HbO}_2]$ and $[\text{tHb}]$ during the stimulation, i.e., signal changes opposite to those one would normally expect. From Figs. 6(d), 7(d), and 8(d) one can see, however, that these areas have a much lower t -value than the voxels showing the “expected” signal changes, and occur in the parts of the brain situated far away from the center of the optical probe. These abnormalities, which are easily recognized but shown here for completeness, very probably arise from the well-documented response of algebraic reconstruction techniques to low signal-to-noise data.

Discussion

Studies of functional brain activity acquired simultaneously by fMRI and near-infrared techniques have increased significantly in recent years (Boas et al., 2004a,b; Hoge et al., 2005; Horowitz and Gore, 2004; Kennan et al., 2002; Mehagnoul-Schipper et al., 2002; Okamoto et al., 2004; Seiyama et al., 2003, 2004; Strangman et al., 2002; Toronov et al., 2001a,b). In order to be able to compare the results of both techniques, it is helpful to apply the same analysis techniques to the data from both modalities. In fMRI, group statistical analysis of data is standard. In the human fNIRSI literature, information on the statistical properties of optical data is very sparse, except for one NIR topography study (Schroeter et al., 2004). In that work NIR measurements were performed only on the left side of the visual cortex; the probe was positioned using fiducial landmarks on the subject heads without MRI control, and the group analysis was performed without transforming single-subject images to the standard stereotactic space. The work presented here represents the first time that the same statistical group analysis approach has been applied to both three-dimensional fNIRSI and fMRI data: fNIRSI images were transformed to Talairach space, converted to ANALYZE format, and analyzed using the same software tools as the BOLD data.

Considering first the BOLD data in this study, the dependence of the spatial distribution and magnitude on the visual stimulus frequency in this study is in reasonable agreement with those reported in Kaufmann et al. (2001). Kaufmann found that a frequency-graded visual (dartboard) stimulus activated both striate and extrastriate visual areas with a right hemispheric dominance in both men and women. Our results, shown in Fig. 4, also show a higher BOLD response on the right side of the visual cortex. Kaufmann also showed, however, that there were large inter-subject differences in BOLD amplitudes at 1.5 T, approximately a factor-of-four between the maximum and minimum values. In extrastriate cortex, BOLD amplitudes increased from a stimulation frequency of 0.5 Hz to 1 Hz, but then showed similar amplitudes at higher frequencies. In striate cortex there was an approximately linear increase of activation up to 8 Hz, with a plateau at higher frequencies. In this study, no differentiation was made between striate and extrastriate areas; the BOLD signal increased from 1 to 2 to 6 Hz, but this increase was not statistically significant.

In terms of the optical data, many of the characteristics of the hemodynamic changes in the visual cortex observed in this work are similar to those noted by Sato et al. (2005) in their assessment of the inter-subject variability on NIR topography data obtained during sensorimotor activation in humans. These features include the high inter-subject variability of the amplitudes of changes, and changes opposite to “normal” in some subjects, i.e., decreases in $[\text{HbO}_2]$ and increases in $[\text{HHb}]$ during activation. Statistical analysis shows that the group-mean fNIRSI images have much lower statistical significance than using fMRI. Possible reasons are the lower SNR of NIR data and the spatial variations in the optical probe locations among different subjects. The lower SNR of NIR data originates from the fact that light is

injected and collected through the surface of the head. Only a very small fraction of the photons penetrates deep into brain and re-emerges, whereas all the detected photons sample systemic signals such as respiration, heartbeat, and blood pressure variations. There is the possibility that this problem can be helped by recording systemic signals and filtering them using adaptive filtering. Another promising spatial filtering method proposed by (Zhang et al., 2005b) may also be very useful in this regards. The results obtained in this study suggest that the low statistical significance of signals in the right side of the visual cortex are at least partly due to the larger distance between this part of the brain and the surface of the head. Previous morphological studies have found the left occipital lobe to be wider and longer than the right lobe (Charles et al., 1994; Kertesz et al., 1986; Koff et al., 1986; Lemay, 1977). It is notable that a similar left-sided lateralization of hemodynamic responses was noticed by Seiyama et al. in their study of human visual cortex activation by NIR topography (Seiyama et al., 2004). In their spectroscopic study Colier et al. (2001) obtained statistically significant responses in both sides of the visual cortex: however, the magnitudes of the changes in both $[\text{HbO}_2]$ and $[\text{HHb}]$ were significantly larger on the left side than on the right. Studying relationships between language dominance and asymmetries in the human brain using structural MR, Charles et al. (1994) found that the asymmetry of the occipital lobe length was related to language dominance. It is possible that, in addition to the anatomical asymmetry, there is also a related asymmetry in the amplitude of functional hemodynamic responses to visual stimulation, which can be also related to the subject's ocular dominance (Toosy et al., 2001). In future work we will try to address these issues by testing subject's language and ocular dominance, improving optical sensor design (Boas et al., 2004b; Yamamoto et al., 2002) and incorporating other image reconstruction algorithms (Boverman et al., 2005; Xu et al., 2005). For the 1.8 Hz checkerboard reversing activation, Schroeter et al. (2004) report maximal t -values of 3.05 and 2.53 for the left-hemispheric $\Delta[\text{HbO}_2]$ and $-\Delta[\text{HHb}]$, respectively (note that although Schroeter et al. call these values the "z-values", actually they are t -values, because the actual population variance is unknown, and only the sample variance can be used when computing the statistics). One can see in Figs. 10(b) and (c) that these values are in a good qualitative agreement with the corresponding highest t -values in this present study. The slightly better statistics of our data probably result from lower inter-subject variability in the probe positioning due to input from MRI data, and from the fact that the single-subject images were transformed into Talairach coordinates. However, the similar maximum t -values obtained by Shroeter et al. and in this study indicate that the inter-subject variability in the location of imaged area was not the main reason for the lower statistical significance of the fNIRSI data compared to fMRI.

In order to interpret the comparative temporal and spatial features of the fMRI and optical data we apply a mathematical model (Buxton et al., 1998), which explicitly relates changes in the BOLD signal to changes in the deoxyhemoglobin concentration and blood volume:

$$\frac{S - S_0}{S_0} = V_0 \left[k_1(1 - q) - k_2 v \left(\frac{q}{v} - 1 \right) + k_3(1 - v) \right] \quad (1)$$

in which S is the fMRI signal intensity from a particular voxel, $q = Q / Q_0$ (where Q is the deoxyhemoglobin content when stimulated and Q_0 is the deoxyhemoglobin content at rest), and $v = V / V_0$ (where V is the CBV when stimulated and V_0 is the CBV at rest). The dimensionless parameters k_1 , k_2 , and k_3 are positive and depend on the echo time TE, the oxygen extraction factor at rest E_0 , the susceptibility difference between intravascular and extravascular medium at rest, and the ratio of intravascular and extravascular signals. The model implies that an increase in the BOLD signal can be caused by a decrease in deoxyhemoglobin content and/or by an increase in CBV. In the present study, we find that in the visual cortex the $-\Delta[\text{HHb}]$ and $\Delta[\text{HbO}_2]$ time courses have statistically equal temporal correlations with the BOLD signal.

This means that it is impossible to separate the contributions of $\Delta[\text{HHb}]$ and $\Delta[\text{HbO}_2]$, as we were able to do in a previous study in the human motor cortex using temporal correlation analysis (Toronov et al., 2003a,b). Some insight, however, can be gained by considering changes in the spatial patterns of the BOLD, $\Delta[\text{HHb}]$, and $\Delta[\text{HbO}_2]$ responses at different checkerboard reversal frequencies. Our fNIRSI data suggest that the spatial behavior of the $\Delta[\text{HbO}_2]$ and $\Delta[\text{tHb}]$ responses are more consistent with the BOLD response than that of the $\Delta[\text{HHb}]$ response, although we recognize that due to the small number of frequencies considered and the relatively low SNR of the optical data, this must be considered as a working hypothesis that needs further study. Considering the similar temporal correlation of the values of $-\Delta[\text{HHb}]$ and $\Delta[\text{HbO}_2]$ with the BOLD signal, this behavior can be explained if one assumes that, when the reversal frequency increases, new voxels in the visual cortex contribute to BOLD signal changes, in which blood volume changes occur without corresponding changes in blood oxygenation. This scenario is consistent with the balloon model if the time courses of $-\Delta[\text{HHb}]$ and $\Delta[\text{HbO}_2]$ are highly correlated. This, however, does not change significantly the *mean* BOLD response because the number of newly recruited voxels is relatively small compared to the number of voxels activated at lower stimulation frequencies. It should be also noted that, when comparing BOLD fMRI and fNIRSI responses to functional activation one must bear in mind that these responses can have slightly different vascular origins. At 3 Tesla there are contributions to the BOLD signals originating from small and large veins as well as the capillary network, while fNIRSI signals are believed to be related mostly to the capillary bed. The latter hypothesis, however, has not been rigorously shown experimentally, and is based on simulations (Firbank et al., 1998) and phantom studies (Liu et al., 1995).

In the context of prior studies, our group found previously that the time-course of the BOLD response in motor cortex (Toronov et al., 2003b) was much better correlated with the time-course of the $\Delta[\text{HHb}]$ signal than with that of the $\Delta[\text{HbO}_2]$ response. This difference in correlation can be explained by the results of Wolf et al. (2002) who, using NIR spectroscopy, found that the temporal responses of $\Delta[\text{HHb}]$ and $\Delta[\text{HbO}_2]$ in the motor cortex were asymmetric, with the $\Delta[\text{HbO}_2]$ reached its maximum value faster than the $\Delta[\text{HHb}]$ reached its minimum. The fact that in the present study in the visual cortex we find that the $-\Delta[\text{HHb}]$ and $\Delta[\text{HbO}_2]$ time courses have statistically equal correlation coefficients with the BOLD signal is also consistent with the results of Wolf, which showed that in the visual cortex there was a high correlation between the temporal increases in $\Delta[\text{HbO}_2]$ and decreases in $\Delta[\text{HHb}]$. Thus the correlation between the BOLD signal and the $\Delta[\text{HHb}]$ appears to be independent of the particular cortical brain area involved, and the correlation between the BOLD signal and $\Delta[\text{HbO}_2]$ depends on the degree of symmetry of the $\Delta[\text{HHb}]$ and $\Delta[\text{HbO}_2]$ responses. These results support previous studies in suggesting, but not having proven, that there are differences in the functional coupling unit between visual and motor cortex.

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Fig. 1. Schematic of the optical probe. The probe has 16 pairs of source fibers and 4 detector fiber bundles.

Fig. 2. Central sagittal slices of all subjects in the Talairach space. The small circle represents the cortical locations nearest to the center of the optical probe.

Fig. 3.

(a) and (b): Single subject BOLD activation maps for a visual stimulation frequency of 1 Hz. The maps show the percentage change for voxels with a correlation coefficient of 0.7 or greater. There is a lower threshold of 0.7% for the signal change, which is represented by the color bar. (c) and (d): $-\Delta[\text{HHb}]$ maps for the same subject, representing voxels with a correlation coefficient of 0.5 or higher. The color bar shows the changes in concentration in units of micromolar.

Fig. 4. Block-averaged single-subject time traces of BOLD, $-\Delta[\text{HHb}]$, and $\Delta[\text{tHb}]$ signals for the 1-Hz stimulation experiment. The unit of time is seconds.

Fig. 5.
 (a)–(c): Cross-subject mean maps of the normalized BOLD signal at checkerboard reversing frequencies 1, 2 and 6 Hz, respectively. The color map shows the percentage change in the BOLD signal. All voxels correspond to $p < 0.001$.

Fig. 6. (a)–(c): Maps of the cross-subject mean negative value of Δ [HHb] at checkerboard reversing frequencies 1, 2 and 6 Hz, respectively. As indicated by the color bar, the yellow color shows a decrease in Δ [HHb], while the blue color shows an increase in Δ [HHb]. (d): A t -statistic map for $-\Delta$ [HHb] averaged over all frequencies: the t -scores are represented as absolute values.

Fig. 7.
 (a)–(c): Maps of the cross-subject mean $\Delta[\text{HbO}_2]$ at checkerboard reversing frequencies 1, 2 and 6 Hz, respectively. As indicated by the color bar, yellow color shows an increase in $\Delta[\text{HbO}_2]$, while a blue color shows decrease in $\Delta[\text{HbO}_2]$. (d): A t -statistic map for $\Delta[\text{HbO}_2]$ averaged over all frequencies.

Fig. 8. (a)–(c): Maps of the cross-subject mean $\Delta[tHb]$ response magnitude at checkerboard reversing frequencies 1, 2 and 6 Hz, respectively. As indicated by the color bar, a red/yellow color shows an increase in $\Delta[tHb]$, while a blue color shows decrease in $\Delta[tHb]$. (d): A t -statistic map for $\Delta[tHb]$ averaged over all frequencies.

Fig. 9.

Maps of the degree of overlap between the fMRI and fNIRSI activation maps: yellow represents the highest degree of overlap. (a) BOLD and $\Delta[\text{HHb}]$, (b) BOLD and $\Delta[\text{HbO}_2]$, and (c) BOLD and $\Delta[\text{tHb}]$.

Fig. 10.

Histograms of the voxel t -value distribution for (a) BOLD, (b) $\Delta[\text{HHb}]$, and (c) $\Delta[\text{HbO}_2]$ maps averaged cross-subject and cross-stimulation frequency. Note that t -values 1.7, 2.7, and 3.5 correspond to p -values of 0.1, 0.01, and 0.001, respectively.

Table 1

Spatial characteristics of the fMRI and NIR measurements

Frequency	Number of BOLD activated voxels	Number of voxels with $t > 2$ for $\Delta[\text{HbO}_2]$	Number of voxels with $t > 2$ for $\Delta[\text{HHb}]$	Number of voxels with $t > 2$ for $\Delta[\text{tHb}]$
1 Hz	14,880	4031	15,416	1087
2 Hz	22,701	10,713	27,021	3353
6 Hz	26,466	16,857	12,306	6311

Table 2

Amplitudes of temporal changes in fMRI and fNIRSI measurements

Frequency	Δ BOLD signal (%)	Δ [HbO ₂] (μM)	$-\Delta$ [HHb] (μM)	Δ [tHb] (μM)
1 Hz	1.06±0.11	0.75±0.13	0.57±0.05	0.59±0.14
2 Hz	1.08±0.11	0.84±0.09	0.59±0.07	0.68±0.12
6 Hz	1.14±0.11	0.92±0.08	0.59±0.05	0.73±0.09