Diffuse optical measurement of blood flow, blood oxygenation, and metabolism in a human brain during sensorimotor cortex activation

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We combine diffuse optical and correlation spectroscopies to simultaneously measure the oxyhemoglobin and deoxyhemoglobin concentration and blood flow in an adult human brain during sensorimotor stimulation. The observations permit calculation of the relative cerebral metabolic rate of oxygen in the human brain, for the first time to our knowledge, by use of all-optical methods. The feasibility for noninvasive optical measurement of blood flow through the skull of an adult brain is thus demonstrated, and the clinical potential of this hybrid, all-optical noninvasive, methodology can now be explored. © 2004 Optical Society of America

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Although many methods for assessment of cerebral blood flow (CBF) have been explored,[1] there remains a critical need for continuous, noninvasive instruments to measure CBF in humans through intact skull. Furthermore, estimation of the cerebral metabolic rate of oxygen ($CMRO_2$) is often of clinical importance but requires measurement of several hemodynamic parameters that are difficult to derive simultaneously. In this Letter we demonstrate a hybrid instrument that combines diffuse optical and correlation spectroscopies to measure variations of blood flow, blood oxygenation, and oxygen metabolism in an adult human brain during sensorimotor cortical activation.

Diffuse optical imaging and spectroscopy is an important subfield of biomedical optics whose aim is to investigate physiology at millimeters to centimeters below the tissue surface. Use of the diffusion model has made it possible to quantitatively separate tissue scattering from tissue absorption and to quantify the influence of scatterer motion on multiply scattered light.[2–5] Thus far, diffuse optical methods have been used in research and clinical settings for measurement of blood volume, blood oxygen saturation; and, to a lesser extent, blood flow.[6] For example, these technologies were applied for investigation of breast cancer, muscle disease, photodynamic therapy, and recently oxygen metabolism in the rat brain.[7,8]

Collectively, this research suggests it might be possible to build noninvasive all-optical devices that concurrently extract information about flow, oxygenation, and oxygen metabolism in a human brain. The human brain presents numerous challenges, however; most significantly, the physiological signals are buried beneath the skull. In this Letter we demonstrate that measurement of these signals is feasible in an adult human brain. Future advances based on our approach might be useful in the management of patients with brain injuries and will provide information on functional activation in humans.

Seven male volunteers (ages 38–73) participated in the sensorimotor cortical activation studies. Two volunteers were studied twice in intervals of two weeks to assess repeatability. One subject also participated in a 3-T functional magnetic-resonance imaging (fMRI) study[9] in which activation data based on blood-oxygen level-dependent (BOLD) and arterial spin-labeled perfusion with the same task were obtained sequentially before the optical study.

The subjects were first asked to sit while one investigator localized the hand sensorimotor cortical area contralateral to the dominant hand according to the 10–20 system.[10] The probe [Fig. 1(a)] was secured over this region. Several locations were tested, and the location with the largest activation signal was selected for the study. The subject lay comfortably on a bed with his head slightly tilted to view a monitor for stimulus presentation. The subject was instructed to tap his index and middle fingers against the thumb at 3 Hz, in time with an auditory cuing signal. A 1-min baseline was recorded before and after each stimulus, and a blocked design of 15 such stimuli was used. One subject was asked to repeat the study using the ipsilateral hand to confirm the contralateral nature of the optical response, and with another subject 30 s of stimulus were obtained, and signals were compared with those of 1-min stimulus duration. In two subjects the probe was placed slightly off the sensorimotor area, and no response was obtained.

Details of the instrument are described elsewhere.[8] Briefly, ~3 mW of light from amplitude-modulated (70 MHz) lasers operating at 690, 785, and 830 nm were fiber-coupled onto the tissue surface. Photons transmitted into the brain were detected in reflection. These wavelength-dependent data were used to determine the oxyhemoglobin and deoxyhemoglobin

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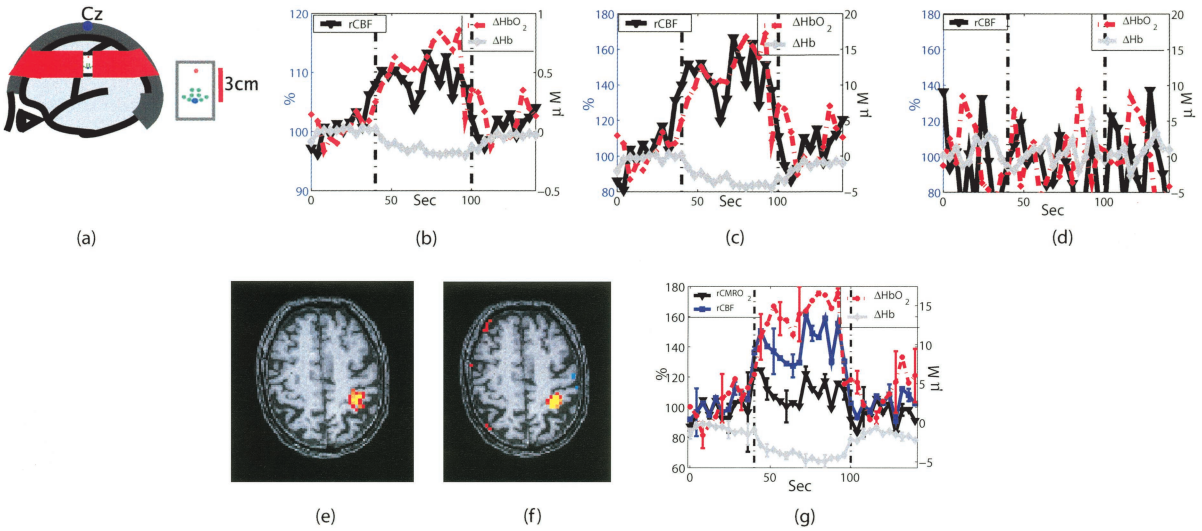

Fig. 1. (a) Placement of fibers; the source (red) is 3 cm from the diffuse optical spectroscopy detector (blue). Diffuse correlation spectroscopy detectors (green) are located 2 cm (×2), 2.5 cm (×2), and 3 cm (×4) from the source. Optical results are presented showing changes in (right) oxyhemoglobin and deoxyhemoglobin and (left) rCBF: (b) prior to partial volume correction, (c) corrected data with the probe placed on the motor cortex, (d) data with the probe displaced ~2 cm from the motor cortex. Representative MRI slices through the motor cortex show (e) perfusion and (f) BOLD activation from the same volunteer. (g) Block and group-averaged optical results.

concentrations by near-infrared (NIR) spectroscopic analysis.[11] A narrowband cw laser (800 nm, ~5 mW), eight photon-counting, fast avalanche photodiodes, and an eight-channel autocorrelator board facilitated measurements of blood flow; temporal autocorrelation functions of the reflected light were used to derive flow information.[8]

Blood oxygenation data were analyzed with the differential path-length factor (DPF) method.[11] Blood flow data were analyzed by fitting each source–detector pair to a semi-infinite diffusion model[2,8]; the flow measurements yielded relative CBF (rCBF). For quantification, all the measured data were corrected for partial volume effects as described below. Changes in the relative $CMRO_2$ ($rCMRO_2$) were derived from the measured variation in blood flow, deoxyhemoglobin concentration, and total hemoglobin concentration.[8,12] In this model a constant arteriolvenous tissue compartmentalization is assumed, and for slow variations (of the order of seconds) the $rCMRO_2$ is found to be proportional to the product of the rCBF and relative changes in the deoxyhemoglobin and total hemoglobin concentrations. The hemodynamic parameters were block averaged over repeated stimuli and further averaged over the whole group. We present the mean and standard errors.

Figure 1(b) shows the changes observed from one volunteer. Even though our hemoglobin concentration results are in agreement with other optical measurements,[13,14] the observed changes in the hemoglobin concentration and blood flow are underestimated because of partial volume effects. In essence, the diffuse optical spectroscopies probe large tissue volumes without discriminating between tissue types, e.g., bone and brain tissue. Mehagnoul-Schipper *et al.*[14] conducted a comparative study of diffuse optical tomography and magnetic-resonance imaging (MRI) and found that partial volume effects caused a significant (i.e., >2×) reduction in optical signal variation compared with MRI signal variation. Similarly, Boas and colleagues[15,16] demonstrated that diffuse optical spectroscopic methods are subject to errors due to tissue heterogeneity when measuring focal changes. Since these spectroscopic approaches have been used in the bulk of brain optical studies thus far, various methodologies have been suggested to account for these discrepancies.[17,18] We have implemented the findings of Strangman *et al.*,[15] who showed that the differential path-length analyses used in our geometry and protocol overestimate the DPF by a factor of ~20, which varies with probe placement; empirically, probe displacements of 3 mm from the signal maxima resulted in 8% DPF reduction.

We also determined a correction factor for the flow data based on numerical simulation and laboratory experiments. By approximating the layered structure of the head (scalp, skull, brain) with a two-layer model,[19] we simulated a series of diffuse-light temporal autocorrelation curves for the *in vivo* probe geometry. The top layer (skull) thickness was set at 1 cm with a flow less than 1% of the bottom layer (brain). We varied the dynamical properties of the brain layer and computed an estimate for the flow in the bottom layer with a semi-infinite medium model. This simulation underestimated flow by a factor of 5.0 ± 1.2 due to partial volume effects over the entire range of parameters. This underestimation was verified with *in vitro* measurements with a human skull filled with an Intralipid–ink solution that mimicked the optical and flow properties of the human brain.

Figure 1(c) shows the corrected hemoglobin concentration and flow changes from the study shown in Fig. 1(b). As expected there was a sustained rise in oxyhemoglobin, a decrease in deoxyhemoglobin, and an increase in CBF. If the probe was placed ~2 cm frontal to the motor cortex, the effect of the finger

tapping was clearly absent, demonstrating the local nature of the response [Fig. 1(d)].

Images obtained with fMRI with the same blocked finger-tapping paradigm allowed us to localize the activation more precisely. Statistical maps show perfusion [Fig. 1(e)] and BOLD [Fig. 1(f)] activation. The CBF increase was 48% compared with the optically measured mean increase of 42%. The BOLD change was 1.7% compared with the mean ΔHb decrease from optical data of 3 μM. Although BOLD signals do not directly correspond to either of the measured parameters, they can be used to estimate a range and shape for the hemoglobin concentration variation.

Figure 1(g) shows the corrected all-optical hemodynamic curves averaged across all subjects. The corrected mean flow change is $39 \pm 10\%$, which is well within the range of values determined by MRI,[20,21] [$H_2{}^{15}O$],[22] and [$^{11}CH_3$] (Ref. 23) positron emission tomography, [$^{133}X_e$] (Ref. 24) for similar measurement stimuli, i.e., 21%–60%. The corrected mean oxyhemoglobin and deoxyhemoglobin changes were 12.5 ± 2.8 and -3.8 ± 0.8 μM, respectively, whereas the change in the total hemoglobin concentration was 8.3 ± 2.3 μM. Again, these observations agree quantitatively with increases reported by use of the BOLD technique of 2–4%.[14,20]

The increase in $CMRO_2$ due to finger tapping was $10.1 \pm 4.4\%$ within the range of values (9%–29%) from hybrid MRI measurements [Fig. 1(g)].[20] The ratio of rCBF to $rCMRO_2$ is 3.8 ± 1.1, which agrees with data reported from hybrid MRI techniques[20,25] that range from 2 to 4. Although our calculations of $rCMRO_2$ rely on approximations of vascular compartmentalization, as well as the partial volume correction, they represent a good first estimate and pave the way for future all-optical studies of oxygen metabolism.

When the stimulus duration was 30 instead of 60 s, the measured amplitude did not change significantly, but the peak duration was halved. No response was visible on the side ipsilateral to the stimulated hand, and measurements when the probe was placed far away from the sensorimotor cortex did not exhibit any significant changes in signal. The results from all studies showed signal changes were repeatable to within 5% over a period of two weeks.

In conclusion, we have demonstrated a hybrid instrument that combines diffuse optical and correlation spectroscopies to measure concurrent variations of blood flow, blood oxygenation, and oxygen metabolism through the intact skull of an adult human brain during sensorimotor cortical activation. Our observations are consistent with other studies of the same stimuli employing different measurement techniques.

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