Study of the FMRI blood oxygen level dependent effect by near-infrared spectroscopy

Vlad Toronov[1], Andrew Webb[1], Scott Walker[1], Rajarsi Gupta[2], Jee H. Choi[2], Enrico Gratton[2], and

Dennis Hueber[3]

[1]Beckman Institute for Advanced Science and Technology , University of Illinois at Urbana-Champaign,

405 N. .Mathews Avenue, Urbana, IL 61801-3080

[2]Laboratory for Fluorescence Dynamics, Department of Physics, University of Illinois at Urbana-Champaign,

1110 W. Green Street., Urbana, IL 61801-3080

[3]ISS Incorporated,1602 Newton Drive, Champaign, Il 61822

ABSTRACT

In order to study the behavior of cerebral physiological parameters and to further the understanding of the fMRI blood-oxygen-level-dependent (BOLD) effect, we have recorded simultaneously multi-source frequency-domain near-infrared and BOLD fMRI signals during motor functional activation in humans. From the near-infrared data we obtained information on the changes in cerebral blood volume and oxygenation. In order to relate our observations to changes in cerebral blood flow we employed the "balloon" model of cerebral perfusion. Our data showed that the deoxyhemoglobin concentration is the major factor determining the time course of the BOLD signal.

1. INTRODUCTION

The BOLD effect is a complex biophysical phenomenon [1, 2, 3]. Particularly, Buxton with coauthors recently proposed a model of the BOLD signal [3]:

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

where S is the fMRI signal intensity from the particular voxel, Q is the deoxyhemoglobin content, V is rCBV, the subscript 0 indicates the respective values at rest, $q = Q/Q_0$, and $v = V/V_0$. 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 intra-vascular 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 both by a decrease in deoxyhemoglobin content and by an increase in rCBV.

Although NIRS can not compete with fMRI in terms of spatial resolution, the unique biochemical specificity of NIRS makes it a perfect complementary method to resolve difficulties in physiological interpretation of the BOLD signal [4]. Particularly, using light sources at two different near-infrared wavelengths one can measure independently tissue oxy- and deoxyhemoglobin concentrations [5]. Therefore, using NIRS data acquired

Saratov Fall Meeting 2002: Optical Technologies in Biophysics and Medicine IV,
Valery V. Tuchin, Editor, Proceedings of SPIE Vol. 5068 (2003)

simultaneously with BOLD fMRI one can directly assess both underlying physiological parameters of the BOLD signal, the blood oxygenation and rCBV.

NIRS data can be also used to obtain changes in rCBF and $CMRO_2$ by employing the "balloon" model [3]. The model is given by the system of two ordinary differential equations:

$$\frac{dq}{dt} = \frac{1}{\tau_0}\left[f_{in}(t)\frac{E}{E_0} - f_{out}(t)\frac{q(t)}{v(t)} \right] \qquad (2a)$$

$$\frac{dv}{dt} = \frac{1}{\tau_0}\left[f_{in}(t) - f_{out}(t) \right] \qquad (2b)$$

where f_{in} and f_{out} are the input and output rCBF normalized to the baseline value of rCBF F_0, E is the oxygen extraction fraction (OEF), and the time constant τ_0 equals F_0 / V_0. As shown in [6], OEF can be expressed as a function of f_{in} using the equation

$$E(f_{in}) = 1 - (1 - E_0)^{1/f_{in}} \qquad (3)$$

The authors of [3] and [7] used the "balloon" model in order to connect the BOLD fMRI signal with rCBV simultaneously measured using an arterial spin labeling (ASL) technique. A weakness of this approach is that it provides a rough estimate of only one variable, rCBV, ing the "balloon" model (2)-(3). Both groups identified the measured rCBF with f_{in}, and modeled f_{out} as a polynomial function of v, assuming significant (up to 30%) changes in rCBV. Using NIRS one can directly test the correctness of this assumption. Furthermore, applying Equations (1)-(3) to NIRS data one can independently obtain both f_{in} and f_{out}. Since $CMRO_2$ is proportional to the product of rCBF and OEF, which can be obtained using Equation (3), NIRS also allows assessment of the time course of $CMRO_2$.

The particular aims of our study were to assess directly the contributions of changes in deoxyhemoglobin concentration and in rCBV to the BOLD signal during functional cerebral activation in humans, and to investigate the temporal behavior of rCBF, rCBV, rCBO, and $CMRO_2$. To achieve these aims we recorded simultaneously BOLD echo-planar images at 1.5 Tesla and frequency-domain near-infrared signals during motor activation.

2. METHODS

In this study we obtained the optical properties of tissue from the slopes of the AC and phase of the harmonically modulated optical signals measured at several source-detector distances [5]. This multichannel method allowed us (i) to measure not only changes in oxy- and deoxyhemoglobin concentrations, but also their baseline values, which are necessary for obtaining parameters q and v in Equations (1)-(3); (ii) to significantly reduce the effect of hemodynamic fluctuations in superficial tissues near sources and detectors on the measured signals, and (iii) to eliminate the crosstalk between light absorption and scattering.

To clarify how cerebral oxy- and deoxyhemoglobin concentrations obtained from NIRS data can be applied to Equations (1)-(3), let us note that variables q and v can be related to [HHb] and [HbO_2] as $q(t) = 1 - ([HHb]_0 - [HHb])/[HHb]_0$ and $v(t) = ([tHb] - [tHb]_0)/[tHb]_0$. We assumed here that the total deoxyhemoglobin content within the voxel Q is equal to [HHb] multiplied by the voxel volume, and that, at a constant hematocrit, the blood volume fraction is proportional to the total hemoglobin concentration [tHb], which is the sum of [HHb] and [HbO_2]. Then Eq. (1) can be rewritten in terms of hemodynamic concentration changes as

$$\frac{S(t)-S_0}{S_0} = A_P P(t) + A_R R(t) \quad (4)$$

where $P(t)$=1-$q(t)$, $R(t)$=$v(t)$-1, A_P=$V_0(k_1+k_2)$, and A_R=$V_0(k_2+k_3)$. The coefficients A_P and A_R can be obtained from a bivariate regression analysis of the BOLD signal using an experimental time series with $P(t)$ and $R(t)$ as the regressors. One can also obtain the flow parameters f_{in} and f_{out} in the "balloon" model by substituting $q(t)$=1-$P(t)$ and $v(t)$=1+$R(t)$ into the system of Equations (2) and then by solving this system regarding f_{in} and f_{out}.

The fMRI and NIRS instrumentation and setup, including optical sensor, were same as in the study of functional hemodynamics during numerical calculations, described in the previous section. One should note that the multichannel approach requires calibration of the optical sensor, which includes determination of the correction amplitude factors and phase terms from measurements of a calibration phantom with known optical properties [5]. These values are then used to calibrate the data obtained using the same sensor *in vivo*. We used a silicone calibration block (ISS) with optical properties at 758 and 830 nm close to the known optical properties of the adult head: $\mu_a(758) = 0.107\ cm^{-1}$; $\mu_a(830) = 0.104\ cm^{-1}$; $\mu_s'(758) = 7.4\ cm^{-1}$; $\mu_s'(830) = 6.9\ cm^{-1}$, where μ_a is the absorption coefficient and μ_s' reduced scattering coefficient.

Calibration could be subject to errors due to the differences in the optical coupling between the light sources/detectors and the medium. Particularly, hair alters the coupling of the light sources and detectors with the skin in an irregular way. The other problem associated with hair is that it causes significant attenuation of light, which results in an unacceptably low signal-to-noise ratio of the phase of the modulated light signals (although the AC and DC noise usually was low enough to detect functional hemodynamic changes). We found that even the roots of the shaved dark hair may attenuate the light to such an extent that the measurements using phase are strongly compromised. Therefore, for this study we selected naturally hairless subjects. The optical sensor was centered at the measured C3 position of the left hemisphere. In cases when the analysis of the fMRI data revealed poor collocation between the activation focus and the optical sensor, the experiments were repeated with the optical sensor attached over the activation focus found during the previous fMRI scan.

Each experiment included ten 10-s stimulation epochs, which were separated by ten 17-s control epochs. During stimulation epochs subjects performed light palm squeezing with the right hand. The total length of one data record was about 5 minutes. The measurements were performed on four healthy right-handed male hairless volunteers, 18 to 57 years old. Informed consents were obtained from all subjects. The optical sensor was centered at the measured C3 position of the left hemisphere. To increase the signal-to-noise ratio in the measured changes $[HHb]_0$- [HHb] and $[tHb]_0$-[tHb] (denoted as $\Delta[HbO_2]$ and Δ[HHb], respectively) we performed time-locked averaging of the traces related to ten stimulation-relaxation cycles. BOLD signal in the activated voxels of EPIs was also subjected to time-locked averaging.

3. RESULTS

Figure 1 shows averaged traces for regression variables P and R, and the BOLD signal. The BOLD signal is scaled to the range of the variable P. One can see that temporal variations in R were much less correlated with the BOLD signal than variations in P, whose time course was very close to the time course of the BOLD signal. The values of correlation coefficient between P and BOLD signal in all measurements were very close to unity, in accordance with the high covariance between P and BOLD signals seen in Fig. 6. The values of the correlation coefficient between R and the BOLD signal were significantly smaller. For one subject they were even negative. The ratio of regression coefficients A_P and A_R was always positive, indicating that an increase in the blood volume correlates with an increase in the BOLD contrast. However, the values of the r^2 statistic for the regression only increased slightly when the blood volume changes were included in the regression model. This shows that the contribution of blood volume changes to the BOLD signal was very small compared to the contribution of the

deoxyhemoglobin changes. This conclusion is also supported by the fact that the changes in R were significantly smaller than changes in P.

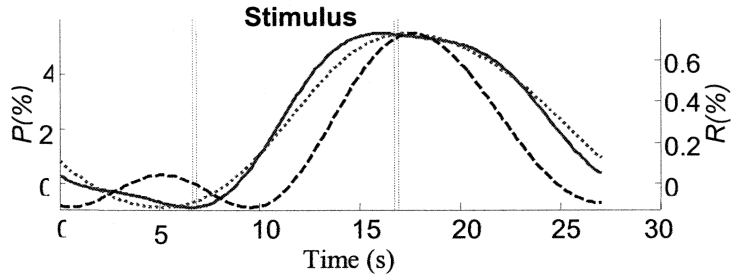

Fig.1 Typical pattern of changes in P (solid line), R (dashed line) and BOLD signal (dotted line). The BOLD signal is scaled to the range of P. Vertical marks indicate the beginning and the end of stimulation.

We used the NIRS data and the balloon model to investigate changes in the parameters of rCBV, f_{in} and f_{out}. The values of E_0 and τ_0 were chosen close to those suggested in [3]. In all subjects the time course of deoxyhemoglobin signals closely followed the changes in f_{in}. Unlike deoxyhemoglobin, the time course of the blood volume did not exhibit significant similarity with the changes in the flow. An increase in τ_0 resulted primarily in a longer delay between changes in P and f_{in}. The delay was approximately equal to τ_0 for all subjects. Analyzing the time course of f_{in} and f_{out} in the balloon model, we found that for all subjects the difference between f_{in} and f_{out} was much smaller than the range of changes in both of these variables.
Although our results do not contradict the basic assumptions of the "balloon" model [3], the small value of the rCBV increase during functional activation indicates that, as a matter of fact, there is no "balloon" effect. This leads to the simplification of the system of Equations (2). Indeed, since the changes in $v=1+R$ are small, in order to describe the BOLD signal one can use Equation (2a) alone, with $v\approx 1$. Also, instead of modeling f_{out} by a function of v as in [3] and [7], one can assume that $f_{out}\approx f_{in}=f$. Then, the system reduces to only one Equation:

$$\frac{dq}{dt}=\frac{1}{\tau_0}\left[\frac{E(f)}{E_0}-q(t)\right]f(t), \qquad (5)$$

where $f(t)$ is the blood flow through the activated region, and $E(f)$ is given in the Equation (3). Since the BOLD signal reflects changes in $q(t)$, both independent variables $q(t)$ and $f(t)$ in Equation (5) could be measured during combined BOLD and ASL protocol.

The use of the slopes of the AC and phase of the optical signals measured at several source-detector distances significantly improved the quality of the measurements of the time course of cerebral hemodynamic signals compared to our previous measurements employing just light intensity changes measured at a single source-detector distance. In spite of possible calibration errors, the very high correlation between the deoxyhemoglobin and the BOLD signals indicate that the time course of the hemodynamic signals was determined with high accuracy. This result shows that although the localization of the activated area could cause errors in the magnitudes of hemodynamic changes, a simple method based on the model of homogeneous turbid medium allows accurate measurement of the time course of functional cerebral hemodynamic signals.

4. CONCLUSIONS

We found that at 1.5 T the change in the deoxyhemoglobin concentration is the major factor determining the time course of the BOLD signal in the human motor cortex during motor stimulation. The influence of the rCBV is qualitatively in agreement with recently established theory, but is much smaller then the influence of the deoxyhemoglobin concentration. The increase in the cerebral blood oxygenation during functional activation is due to the increase in the rCBF velocity, and occurs without a significant swelling of the blood vessels. The BOLD signal follows changes in rCBF with a time delay approximately equal to the ratio of the baseline values of rCBV and rCBF. The relationship between the BOLD signal and rCBF can be quantified using Equation (5). We have also found that the time course of hemodynamic signals obtained using multichannel near-infrared method is in much better agreement with BOLD measurements that signals obtained from single source-detector channels.

REFERNCES

1. Ogawa S., Lee T.M., Kay A.R., Tank D.W., Brain magnetic resonance imaging with contrast dependent on blood oxygenation, Proc. Natl. Acad. Sci. USA **87**, 9868-9872 (1990)
2. Boxerman J.L., Bandettini P.A., Kwong K.K., Baker J.R., Davis T.L., Rosen B.R., Weisskoff R.M. The intravascular contribution to fMRI signal change: Monte Carlo modeling and diffusion-weighted studies in vivo. Magn. Reson. Med. **34,** 4-10 (1995)
3. Buxton R.B., Wong E.C., Frank L.R., Dynamics of blood flow and oxygenation changes during brain activation: the balloon model, Magn. Reson. Med. **39**(6), 855-864, (1998)
4. Villringer A., Chance B., Non-invasive optical spectroscopy and imaging of human brain function, Trends Neurosci. **20**(10), 435-42 (1997)
5. Fantini S., Franceschini M. A., Maier J. S., Walker S. A., Barbieri B., and Gratton E., "Frequency-domain multichannel optical detector for noninvasive tissue spectroscopy and oximetry", Optical Engineering **34**, 32-42 (1995)
6. Buxton, R.B., Frank, L.R. (1997). A model for the coupling between cerebral blood flow and oxygen metabolism during neural stimulation. J. Cereb. Blood. Flow. Metab., 17, 64-72.
7. Feng, C.M., Liu, H.L., Fox, P.T., Gao, J.H. (2001). Comparison of the experimental BOLD signal change in event-related fMRI with the balloon model. NMR Biomed. 14, 397-401.