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Spatial and temporal hemodynamic study of human primary visual cortex using simultaneous functional MRI and diffuse optical tomography

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Abstract

The blood oxygenation level dependent (BOLD) functional MRI and near infrared optical tomography have been widely used to investigate the hemodynamic response to functional stimulation in the human brain. In this paper, we present a complete methodology of integrating the two imaging modalities to study the underlying physiological mechanism of hemodynamic response in the human primary visual cortex. The integration was made feasible thanks to the development of an MRI-compatible optical probe. The optical imaging was conducted using a frequency-domain near infrared spectrometer. The 3-dimensional optical image reconstruction was based on diffuse optical tomography (DOT) using the perturbative approach. The sensitivity function of the forward problem was obtained using Monte Carlo method. From our preliminary observation, the spatial activation pattern of deoxyhemoglobin is consistent with the BOLD signal map. The patterns of oxy- and deoxyhemoglobin are very similar. The temporal hemodynamic response shows an increased total hemoglobin concentration, which indicates an increment of cerebral blood volume (CBV) during physiological activation.

I. Introduction

The quest to human brain function demands imaging techniques for studying cerebral hemodynamic and neuronal responses to functional stimulations. Blood oxygenation level dependent (BOLD) functional magnetic resonance imaging (fMRI) study has become one of the most important methods of investigating the hemodynamics in the human brain because it provides high-resolution images associated with multiple physiological parameters closely related to cerebral activity [1], [2]. However, its effectiveness has been restricted as its underlying physiological mechanism has yet been fully understood. BOLD fMRI study also suffers from relatively low temporal resolution dictated by the hemodynamic response and this makes it difficult to study the fast response of neuronal activity. In contrast, near-infrared spectroscopy (NIRS) not only provides direct measurement of oxy- and deoxyhemoglobin concentrations (the so-called “slow” signal), it also provides information regarding neuronal response (the “fast” signal) by measuring the scattering of the light. In addition, its response time is on the order of milliseconds. Previous studies have demonstrated that the integration of the two methods can uncouple the contributions due to blood flow and deoxyhemoglobin concentrations to the BOLD signal [3]–[6] in addition to the fast optical neuronal responses [7]. However, NIRS is not a true imaging technique in the sense that its achievable spatial resolution is essentially the source-detector distance, typically 1–3 cm laterally and worse longitudinally [8], which makes the co-registration of optical and the high-resolution fMRI results difficult.

In this paper, we are presenting a complete methodology of simultaneous BOLD fMRI and diffuse optical tomography (DOT) with high spatial resolution and chemical specificity for studying the human primary visual cortex. It can be readily applied to any other fMRI methods as well as other cortical areas close to the surface of the head. Compared with existing technology, following advances have been achieved: (a) the development of a fully MRI-compatible optical probe; (b) the recovery of optode positions *in situ* from MR images for accurate image co-registration; (c) the construction of the sensitivity function of the forward problem of optical image reconstruction using Monte Carlo simulations based on subject-specific realistic head model obtained from structural MR images; (d) the adoption of true 3-dimensional image reconstruction algorithms that provides more accurate localization.

II. Theory

The inverse problem of optical image reconstruction [9] was formulated in terms of a perturbative approach using the Born approximation. The general solution to the first-order perturbative approximation of the heterogeneous diffusion equation in the frequency-domain can be obtained [10]. For the purpose of hemodynamic response study as presented in this paper, only the absorption term was retained. In its discretized form of this approximation, the change in optical signal is expressed as a linear combination of voxels-wise changes in optical properties and coefficients dependent on the baseline optical properties of the voxels. For multiple channels (optical source-detector combinations) of measurement, the equations can be written in a matrix form $AX = B$, where the measurement vector B is the change in optical signal from its baseline, the coefficient matrix A is given by the Monte Carlo simulations using baseline optical properties, and the solution X is the change in optical properties during activation. A variety of image reconstruction algorithms can be applied to solve the inverse problem.

III. Experiment

The optical probe (Figure 1) is attached to the back the head and aligned with the primary visual cortex of the subject (Figure 2). A pair of non-magnetic goggles (Resonance Technology) with LCD screens was positioned in front of the subject's eyes inside the birdcage head coil. The visual stimulation paradigm consisted of five blocks each with 28.8 s fixation followed by 19.2 s of a black-and-white checkerboard pattern flashing on for 50 ms and off for 1.95 s (2 Hz).

The BOLD fMRI study is performed on a 3-tesla head scanner (Allegra, Siemens) using a standard echo-planar imaging (EPI) pulse sequence (FOV 240×240 mm², resolution 64×64 , voxel size $3.75 \times 3.75 \times 4.00$ mm³, gap 0.4 mm, $\theta = 60^\circ$, TE 25 ms, TR 2000 ms). A 3-D MR image of the same imaging volume is taken for co-registration of the fMRI data with the structural images. A high-resolution 3-D MR image, termed the "probe localizer," is acquired to assist automatic recovery of the positions of optodes. Finally, a T1-weighted high-resolution 3-D full-head structural image (MPRAGE) is acquired for optical image reconstruction and serves as the basis for co-registration of different imaging modalities.

The optical signal is recorded by the near infrared spectrometer (Imagent, ISS), which is synchronized with the fMRI study and the visual stimulation by a "trigger" signal from the MR scanner. The optical sources are laser diodes (690 and 830 nm) which are amplitude modulated at 150 MHz and time-multiplexed. Optical signal reaching the prisms are detected and amplified by the photomultiplier tubes (PMT) before being converted into AC, DC, and phase signals for each of the 64 source-detector combinations, or channels, at each wavelength.

The topology of optodes is designed so that the optical channels are overlapped and the distribution of source-detector distances evenly covers the optimal range – between approximately 20 and 30 mm [4]. The optical probe has 16 pairs of 400- μm -diameter core plastic clad multimode silica source fibers (FT-400-EMT, Thorlabs) and 4 detector fiber bundles (Fiberoptics Technology). An MRI visible marker is attached adjacent to each of the 16 optical source and detector fibers so that accurate source- and detector-positions can be recovered from MRI images for data processing.

IV. Data Processing

The flowchart of data processing procedures is shown in Figure 3.

A. Recovery of optode positions from MR images

The most commonly used method to digitize the optical source- and detector-positions with respect to the subject's head is by measuring a polarized 3-D electromagnetic field with a specially designed sensor. This method is convenient but suffers from artifacts from multiple sources, even though various correction methods have been developed [11]. In this paper, since the optical and fMRI data are acquired simultaneously inside the MRI scanner, it is convenient to determine the positions of the optodes using MRI, and register both optical and fMRI results onto the anatomical MR image of the brain. By doing this, the accuracy of co-registration is expected to be comparable to the resolution of the MR images and the chance of introducing human error as a result of extra measurement is virtually eliminated.

The location of the entire optical probe in the coordinate system defined by the 3-D structural MR image (MPRAGE) was determined by identifying several markers from the images. As described previously, a high-resolution 3-D MR image of the optical probe, termed a “probe localizer”, is acquired *in situ* to determine the deformation of the optical probe based on the marker-positions. By extracting the positions, orientations, and rotations of the marks from MR images, the coordinates of the optodes can be recovered (Figure 4). If necessary, these coordinates can be converted into the Talairach coordinate system for brain mapping across multiple subjects. The spatial relationship between the positions of the markers and their corresponding optodes was determined offline by taking a reference MR image for the optical probe. The reference is a high-resolution 3-D MR image of the optical probe on a layer of oil-containing material – so that the actual positions of optodes appear as dark spots on a bright background.

B. Monte Carlo Simulations

The coefficient matrix A is determined using the Monte Carlo method. We evaluated and adapted a relatively mature and well documented software package [12], which was modified to produce the photon “pathway” in addition to the “history” files. The pathway file contains the exact path of each detected photon in the simulations. The history file records how long every detected photon has been traveling in each type of tissues. By following the paths of all simulated photons that migrate from a given source to a given detector, and averaging their complex weight (i.e. fluence) for a given voxel, the sensitivity function of the forward problem is obtained for the given measurement channel. Both the optical signal and the sensitivity function were normalized afterwards. Such simulated sensitivity function was verified against the analytical solution for a semi-infinite homogeneous media, which gives satisfactory agreement.

C. Optical Image Reconstruction

For the usual spatial resolution, $4 \times 4 \times 4 \text{ mm}^3$, of optical image reconstruction used in this work, the number of measurements ($M = 64$) is much less than the number of voxels ($N =$

$10^3 \sim 10^4$) within the field of interest. Applying physiological and spatial *a priori* constraints is a method that effectively helps solving such underdetermined and ill-conditioned inverse problems [13]. From the structural MR image, the brain tissue can be used as a spatial constraint to the solution. Another spatial constraint to the solution is via the estimation of the optical sensitivity region, which consists of voxels with significant contributions to the optical signal. The method is to find voxels that produce signal with magnitude greater than the noise level of the optical signal of all channels/measurements. In other words, the forward problem is solved one voxel at a time (with maximum possible activation, e.g. 5% from the baseline value was used in this paper); and the result (estimated optical signal due to activation from that particular voxel) is compared with the normalized noise level (obtained from experiment) to determine if the particular voxel is sensitive to the given measurement channel. The size of the solution space after abovementioned treatment was reduced to $\sim 10^2$.

The effects of access order on the speed of convergence and the accuracy of image reconstruction have been numerically investigated among so-called systematic (“detector-first”), sequential (“source-first”), and random access orders [14]. In this paper, we adapted the sequential access order which was considered optimal in terms of the quality of image reconstruction.

To validate our data processing procedures and evaluate image reconstruction algorithms, we simulated hemodynamic activation by embedding an “activated” sphere with a diameter of 20 mm into a realistic head model. The optical properties of the sphere were the same as the gray matter except for a 10% increase in absorption coefficient. The sphere is positioned directly beneath the surface of the visual cortex of the left hemisphere, approximately half the radius left of the center of the optical probe. Optical properties used for Monte Carlo simulations are listed in Table 1.

We have evaluated several frequently used image reconstruction algorithms: matrix inversion, singular value decomposition (SVD), algebraic reconstruction techniques (ART), and simultaneous iterative reconstruction technique (SIRT). Among the algorithms we have evaluated, SIRT gave the best result and was adapted for image reconstruction for human subjects.

V. Results

The result presented in this paper was obtained from a single subject and averaged over 4 measurements for a visual stimulation rate of 2 Hz. The hemodynamic response (changes in oxy- and deoxyhemoglobin concentrations, i.e., $\Delta[\text{HbO}_2]$ and $\Delta[\text{Hb}]$) of activated voxels is shown in Figure 5 along with the BOLD signal from the fMRI study. The time-series hemodynamic response averaged over activated voxels is also shown.

The spatial activation pattern of deoxyhemoglobin concentration is consistent with the BOLD signal map. The patterns of oxy- and deoxyhemoglobin concentrations are very similar. The temporal hemodynamic response shows an increased total hemoglobin concentration, which indicates an increment of cerebral blood volume (CBV) during physiological activation.

VI. Conclusions

We have developed and tested *in vivo* a complete functional imaging technique combining MRI and DOT. Although DOT images are inferior to those acquired using MRI in terms of spatial resolution, the strength of DOT is in providing biochemically specific time-resolved and spatially localized information on cerebral processes. In addition to humans, this

technique can be applied readily to small animal imaging, where the small size of the brain requires a MC approach.

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Figure 1.
The MRI-compatible optical probe with 16 pairs of sources and 4 detectors.

Figure 2.
The placement of optical probe onto the head within the birdcage head coil.

Figure 3.
Data processing procedures

Figure 4.
Recovery of optode positions from MR images.

Figure 5.

(a) BOLD signal map compared with (b) and (c) the spatial hemodynamic response obtained from optical imaging. (d) The temporal hemodynamic response averaged over voxels that have activation larger than 20% of the maximum value.

Table 1

Baseline optical properties used in Monte Carlo simulations of light transport in the human head.

Tissue type	μ_a (mm ⁻¹)	μ'_s (mm ⁻¹)	g	n
Scalp and skull	0.014	0.860	0	1.4
Cerebrospinal fluid	0.004	0.100	0	1.4
Gray matter	0.010	1.110	0	1.4
White matter	0.010	1.110	0	1.4