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Depth-compensated diffuse optical tomography enhanced by general linear model analysis and an anatomical atlas of human head

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ABSTRACT

One of the main challenges in functional diffuse optical tomography (DOT) is to accurately recover the depth of brain activation, which is even more essential when differentiating true brain signals from task-evoked artifacts in the scalp. Recently, we developed a depth-compensated algorithm (DCA) to minimize the depth localization error in DOT. However, the semi-infinite model that was used in DCA deviated significantly from the realistic human head anatomy. In the present work, we incorporated depth-compensated DOT (DC-DOT) with a standard anatomical atlas of human head. Computer simulations and human measurements of sensorimotor activation were conducted to examine and prove the depth specificity and quantification accuracy of brain atlas-based DC-DOT. In addition, node-wise statistical analysis based on the general linear model (GLM) was also implemented and performed in this study, showing the robustness of DC-DOT that can accurately identify brain activation at the correct depth for functional brain imaging, even when co-existing with superficial artifacts.

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Introduction

Diffuse optical tomography (DOT) is an emerging neuroimaging technology that uses low-power near infrared light (650 to 950 nm) to measure the changes of cerebral blood flow and oxygenation associated with neuronal activity (Boas et al., 2004a; Villringer and Chance, 1997). Compared with other neuroimaging modalities, such as functional magnetic resonance imaging (fMRI), DOT has the advantage of being portable and cost effective, with excellent temporal resolution. The near infrared spectroscopy (NIRS) methods used to measure the hemodynamic response to brain activation were first described by several groups in 1993 (Chance et al., 1993; Hoshi and Tamura, 1993; Villringer et al., 1993). Early studies used a sparse array of light sources and detectors; the spatial resolution was comparable to the source-detector separation, namely, in a few centimeters. In the past decade, the technology has been advanced to high-density DOT (Boas et al., 2004b; Zeff et al., 2007), which records data with a high-density array of light sources and detectors and reconstructs volumetric images of brain hemodynamics by solving the forward and inverse problems of light propagation in tissue. High-density DOT significantly improves the spatial resolution and positional accuracy of optical brain imaging (Eggebrecht et al., 2012; White and Culver, 2010; Zhan et al., 2012).

One of the major problems needing attention in DOT development is its severe sensitivity decay along depth. It is known that optical sensitivity in DOT has an approximately exponential decay with increased depth (Dehghani et al., 2009a; Lee et al., 2005), which makes DOT measurements hypersensitive to hemodynamic fluctuations in the scalp rather than to the more pertinent signals from the brain. The ill-posed sensitivity matrix causes positional errors in image reconstruction since the severe sensitivity decay biases the reconstructed brain activation towards the superficial layer. A variety of approaches have been developed to minimize depth error in reconstructed images. A widely-used approach is to apply a spatially variant regularization (SVR) parameter to regular DOT reconstruction (i.e., SVR-DOT) (Culver et al., 2003; Dehghani et al., 2009a; Pogue et al., 1999). Another approach is a depth-compensated DOT (DC-DOT) (Niu et al., 2010), which modifies the depth-variant sensitivity matrix directly rather than modifying the regularization parameter. While these two approaches are

Abbreviations: 3D, three-dimensional; BOLD, blood oxygen level dependent; Con-DOT, conventional DOT without any spatially variant regularization or depth compensation; DC, depth compensation; DC-DOT, depth-compensated DOT; DCA, depth-compensated algorithm; DOT, diffuse optical tomography; fMRI, functional magnetic resonance imaging; FEM, finite element mesh; GLM, general linear model; Hb, deoxy-hemoglobin concentration; HbO_2, oxy-hemoglobin concentration; HRF, hemodynamic response function; MNI, Montreal Neurological Institute coordinates; MRI, magnetic resonance imaging; n, refractive index; NIRFAST, a FEM-based MATLAB package for modeling propagation of near infrared light in biological tissues; NIRS, near infrared spectroscopy; NIRS-SPM, a SPM-based software package for functional NIRS data analysis; OD, optical density; SCF, sensitivity correction factor; SNR, signal-to-noise ratio; SPM, statistical parametric mapping; SVR, spatially variant regularization; SVR-DOT, apply spatially variant regularization to regular DOT reconstruction; μ_a, absorption coefficient; μ_s', reduced scattering coefficient.

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mathematically similar, DC-DOT apparently has a wider effective range in depth and can adapt for both sparse and dense geometries (Kavuri et al., 2012). One concern about DC-DOT is that the true quantity of hemodynamic changes is lost due to necessary modification on the sensitivity matrix. To solve this problem, a scaling factor can be applied on either the modified sensitivity matrix or the reconstructed image. Tian et al. (2010) demonstrated that by applying a scaling factor on the reconstructed image, DC-DOT actually improves quantification accuracy.

Depth-compensated DOT to discriminate brain activities from superficial artifacts

DC-DOT also improves depth specificity of brain activation in the existence of non-activation physiological interferences. It is well known that optical signals from the brain contain several physiological fluctuations that originate from cardiac pulsation, respiration, change of blood pressure, and so on. These physiological fluctuations are systemic and contribute greater signal changes than local brain activities. Tian et al. (2011) have reported that DC-DOT is able to recover brain activation at correct depth even when systemic fluctuations coexist. The image quality can be further enhanced by adaptive removal (Tian et al., 2011; Zhang et al., 2007a, 2007b, 2009) or linear regression (Saager and Berger, 2005; Saager et al., 2011) of the systemic fluctuations that are sampled at a short source-detector separation (typically within 1.3 cm). Besides the systemic physiological fluctuations, currently there is increasing attention on the task-evoked superficial artifacts which can lead to false positive findings in functional brain activities (Kirilina et al., 2012; Takahashi et al., 2011). These superficial artifacts arise from local vascular oscillations in the scalp although the physiological origin is still controversial and might be varied. One goal of the present study was to investigate whether DC-DOT has the capability to discriminate brain activation from the superficial artifacts according to their depths.

Integration of DC-DOT with a standard anatomical atlas of human head

Previous studies in DC-DOT (Kavuri et al., 2012; Niu et al., 2010; Tian et al., 2010, 2011) have used a homogeneous, semi-infinite model of diffusion theory to recover volumetric images of brain activation. While this model is computationally efficient because of the capability to create analytic solutions, it significantly deviates from realistic human head anatomy. In order to localize and quantify brain activation accurately, it is necessary to use a computational model derived from real head anatomy. This requires acquisition of MRI images of each subject's head with optode positions marked, followed by generation of a subject-specific head model, which enables investigators to solve the forward and inverse diffusion equation more accurately (Dehghani et al., 2009a; Eggebrecht et al., 2012; Gibson et al., 2003; Zhan et al., 2012). However, this approach reduces the convenience and feasibility of optical brain imaging as a stand-alone technology. An alternative approach is to fit a standard MRI head template (atlas) for all subjects via affine registration (Cooper et al., 2012; Custo et al., 2010); this approach has proved to be consistent with and comparable to the subject-specific approach. Another goal of the present study, therefore, was to incorporate DC-DOT with a finite element model derived from an anatomical MRI atlas of human head. Based on this model, the depth specificity and quantification accuracy of DC-DOT can be assessed through computer simulations and human measurements under a selected functional stimulation.

Analysis of volumetric DC-DOT image series with general linear model

In addition, the present study also implemented model-based analysis according to the general linear model (GLM). GLM is a statistical linear expression that models measured signals as a linear combination of predicted responses to independent stimulation variables plus an error term. GLM can be used to analyze a variety of experimental data acquired by many measurement modalities. As an example, fMRI has popularly used GLM to model blood oxygen level-dependent (BOLD) signal changes. For time-dependent data series, such as those seen in fMRI or functional NIRS, GLM-based analysis matches both the temporal pattern and the magnitude of signals, thereby providing us with a robust tool to quantitatively characterize functional brain responses.

While GLM has been used as a standard data analysis method in fMRI (Beckmann et al., 2003; Bullmore et al., 1996; Friston et al., 1995), it can be helpful for functional NIRS data analysis especially in cases of severe light attenuation. Schroeter et al. (2004) first proposed the application of GLM as a standard data analysis strategy in functional NIRS. Later, Plichta et al. (2007) showed that model-based GLM provided a powerful test of visual cortex activation in a rapid event-related paradigm. It would be beneficial to compare and interpret both types of neuroimaging data if both functional NIRS and fMRI images can be studied using the same GLM framework. Towards this direction, Ye et al. (2009) have developed a software package (known as NIRS-SPM) for functional NIRS, based on a statistical parametric mapping (SPM) toolbox that is widely used in the field of fMRI. However, all of these studies have implemented GLM-based analysis that can only be applied to channel-wise NIRS data. Post-GLM topographic images are generated by interpolating data between adjacent channels and thus result in limited spatial resolution. To date, very few studies have applied GLM to volumetric image series achieved through DOT. Thus, the final goal of this study was to design, implement, and demonstrate a node-wise GLM approach to analyze the volumetric image series generated from brain atlas-based DC-DOT.

In order to demonstrate the overall improvement in DOT image quality by the three imaging and data analysis methods developed in this study, we utilized human sensorimotor activations evoked by a finger-tapping task to generate volumetric DC-DOT images. The primary sensorimotor regions of the human brain are optically accessible and have been intensively studied by researchers in this field as reviewed by Leff et al. (2011). Thus, the corresponding brain activations in response to a finger tapping task are well understood. While the emphasis of the present study was on advances and integration of three DOT-based imaging and data analysis methods, we measured sensorimotor activities during a well-known finger-tapping task among human subjects for a demonstrative purpose, without utilizing fMRI for validation.

Materials and methods

Anatomical atlas of human head

We used a standard MRI atlas of human head, known as ICBM 152 nonlinear asymmetric template, with a spatial resolution of $1 \times 1 \times 1$ mm^3 (http://www.bic.mni.mcgill.ca/ServicesAtlases/ICBM152NLin2009) (Fonov et al., 2009, 2011). This template was generated as an unbiased non-linear average among normal population in a broad range of ages (18.5 to 43.5 years); the anatomical structures were originally segmented using the ANIMAL + INSECT algorithm (Collins et al., 1999). In this study, a total of five head/brain tissues were defined: the scalp, skull, cerebrospinal fluid (CSF), gray matter and white matter. Optical properties of the segmented tissues at two wavelengths, 750 nm and 850 nm, were set according to current literature (Eggebrecht et al., 2012; Zhan et al., 2012), which are summarized in Table 1.

Probe geometry, spatial registration, and head atlas-based meshing

A rectangle probe was used to image the sensorimotor cortex on the left hemisphere in both simulation and human head measurements. The probe was composed of 21 sources and 21 detectors that were