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Statistical analysis of high density diffuse optical tomography

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ABSTRACT

High density diffuse optical tomography (HD-DOT) is a noninvasive neuroimaging modality with moderate spatial resolution and localization accuracy. Due to portability and wear-ability advantages, HD-DOT has the potential to be used in populations that are not amenable to functional magnetic resonance imaging (fMRI), such as hospitalized patients and young children. However, whereas the use of event-related stimuli designs, general linear model (GLM) analysis, and imaging statistics are standardized and routine with fMRI, such tools are not yet common practice in HD-DOT. In this paper we adapt and optimize fundamental elements of fMRI analysis for application to HD-DOT. We show the use of event-related protocols and GLM de-convolution analysis in un-mixing multi-stimuli event-related HD-DOT data. Statistical parametric mapping (SPM) in the framework of a general linear model is developed considering the temporal and spatial characteristics of HD-DOT data. The statistical analysis utilizes a random field noise model that incorporates estimates of the local temporal and spatial correlations of the GLM residuals. The multiple-comparison problem is addressed using a cluster analysis based on non-stationary Gaussian random field theory. These analysis tools provide access to a wide range of experimental designs necessary for the study of the complex brain functions. In addition, they provide a foundation for understanding and interpreting HD-DOT results with quantitative estimates for the statistical significance of detected activation foci.

Introduction

With recent improvements in spatial resolution and brain specificity, along with the advantages of non-ionizing portable and wearable technology, high density diffuse optical tomography (HD-DOT) has become a promising neuroimaging modality for translation to clinical settings and cognitive studies in child brain development (Bluestone et al., 2001; Boas et al., 2004a, 2004b; Eggebrecht et al., 2012; Gibson et al., 2005, 2006; Habermehl et al., 2012; Joseph et al., 2006; White and Culver, 2010a, 2010b; Zeff et al., 2007). However, thus far HD-DOT reports have lacked event-related designs and accurate statistical tools that are common to fMRI and crucial for imaging complex cognitive processes. In this work we focus on developing these analytical tools for HD-DOT. To validate the methods we acquired and analyzed event-related data in several healthy adult volunteers.

In order to extract the brain response to a given task using simple block averaging, task blocks need to be well separated in time (Bandettini et al., 1993; Blamire et al., 1992; Fransson et al., 1999). Blocked experimental designs suffer from predictable task timing and often lead to bored subjects and difficulties in maintenance of attention to task. Rapid "event-related" designs provide faster and more complex naturalistic paradigms (Friston et al., 1995). Developed within the statistical framework of a general linear model (GLM), event-related designs incorporate linear models of the response function into the analysis of time-series data, and enable un-mixing of the response to fast and event-related stimuli (Clark et al., 1997; Dale and Buckner, 1997; Friston et al., 1998; Josephs et al., 1997; Zarahn et al., 1997).

While some papers have implemented selected portions of statistical parametric mapping (SPM) techniques in the framework of GLM, none have done so in a comprehensive manner. For instance, some near infrared spectroscopy (NIRS) studies have implemented GLM to de-convolve overlapping responses (Abdelnour and Huppert, 2009; Ciftci et al., 2008; Cohen-Adad et al., 2007; Hu et al., 2010; Koh et al., 2007; Plichta et al., 2006, 2007; Schroeter et al., 2004; Ye et al., 2009; Zhang et al., 2005). Some have evaluated Bonferroni corrections to the multiple comparison problem when setting thresholds for statistical significance (Hu et al., 2010; Plichta et al., 2006, 2007), and some have implemented sophisticated SPM approaches with special considerations for spatially interpolated NIRS data (Ye et al., 2009). However these NIRS studies have not addressed HD-DOT data and imaging.

HD-DOT uses a dense array of optodes (compared to NIRS) which results in higher spatial resolution and its overlapping measurements

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results in spatially smoother data. With a forward model that describes the light propagation in the underlying tissue, HD-DOT reconstructs three-dimensional images of hemodynamic activity (Boas and Dale, 2005; Boas et al., 2004b; Custo et al., 2010; Eggebrecht et al., 2012; Heiskala et al., 2009; Koch et al., 2010; Zeff et al., 2007). Recently with a quantitative voxel-wise comparison against fMRI, it is shown that this technique can provide lateral resolution at the gyral-level and localization errors on the order of ~5 mm (Eggebrecht et al., 2012). With these advances, HD-DOT comes closer to representing dense and continuous imaging fields and closer to resembling fMRI data (Eggebrecht et al., 2012; Habermehl et al., 2012). The improved image quality in turn motivates the use of fMRI based statistical approaches. Here we adapt statistical methods from standard fMRI analyses and evaluate the underlying assumptions in the context of HD-DOT imaging. In particular we evaluate local temporal and spatial autocorrelation structures of random fields from the residuals of a GLM. We implement a cluster analysis based on random field theory (RFT) to control the false positive rate in the statistical maps. To account for the potential spatial variance in the HD-DOT point spread function we use a non-stationary RFT approach.

The body of this paper is arranged as follows: We begin by describing the data acquisition including the imaging array, subjects, and experimental designs. We then outline the preprocessing, and SPM procedure including; linear modeling of data, dealing with the temporal autocorrelations, and addressing the multiple comparison problem. We then present empirical *in vivo* results of functional event-related HD-DOT data acquired during visual activation in human adults. Finally we evaluate the performance of the GLM-SPM tools.

Methods

Subjects and experimental protocol

Six healthy right-handed subjects (age range: 17–30 years) were scanned. The research was approved by the Human Research Protection Office at Washington University School of Medicine. Subjects were seated in an adjustable chair in a sound-isolated room facing a 19-inch LCD screen at a viewing distance of 75 cm. All measurements were done with a continuous wave high-density DOT system. The imaging cap with 24 sources (flashing 750 nm and 850 nm LEDs) and 28 detectors was placed on the back of subject's head. For more details on the HD-DOT instrumentation see references Eggebrecht et al. (2012) and Zeff et al. (2007). The visual stimulus consisted of left and right flickering checkerboard wedges (flickering at 10 Hz), presented in a counterbalanced random order. The block design consisted of 10 blocks (5 left, 5 right) with an inter stimulus interval of 30 s. In the event design 15 left and 15 right stimuli were presented with inter stimulus intervals that were randomly distributed between 2 and 15 s. In both designs stimuli duration was 5 s. There was a 30 second long fixation at the beginning of stimulus presentation. All subjects had been previously scanned with MRI (Siemens Trio (Erlangen, Germany) 3 T scanner) for another study. Their anatomical T1-weighted MPRAGE (echo time (TE) = 3.13 ms, repetition time (TR) = 2400 ms, flip angle = 8°, 1 × 1 × 1 mm isotropic voxels) and T2-weighted (TE = 84 ms, flip angle = 120°, 1 × 1 × 4 mm voxels) images were used to generate subject-specific head models.

HD-DOT preprocessing

Raw detector data were decoded to source-detector pair data, and converted to log-ratio to mean values. The data then were band-pass filtered (0.02 Hz–0.25 Hz) to remove long-term trends and pulse artifacts. All signals from the first-nearest neighbor channels were averaged to create a measure of the superficial hemodynamics. This nuisance signal was removed by linear regression from all channels. Additionally, data were down-sampled to 1 Hz. We used the subjects' T1- and T2-weighted images to segment their heads into five putative different tissue types, including scalp/skin, skull, CSF, white, and gray matter and created the subjects' head meshes (Eggebrecht et al., 2012). Light propagation inside the mesh was modeled using the diffusion approximation and a sensitivity matrix was generated using the finite-element modeling software (NIRFAST). The sensitivity matrix was inverted and smoothed with a Gaussian kernel, and used to reconstruct absorption coefficient changes for each wavelength (750 nm and 850 nm). The field of view (FOV) for a typical subject was a cube containing 26 × 41 × 69 voxels, covering occipital cortex, with isometric voxel size of 2 × 2 × 2 mm^3. Relative changes in the concentrations of oxygenated (HbO), deoxygenated (HbR), and total hemoglobin (HbT) were obtained from the absorption coefficient changes by the spectral decomposition of the extinction coefficients of HbO and HbR at these two wavelengths (Fig. 1).

For visualization of results, we up-sampled the images to 1 mm^3. Volumetric activations are overlaid on subject-specific T1-weighted images (with masking skin/scalp and skull). For the cortical surface representation of results all volumetric activation data are mapped onto the subject-specific cortical surface in the Caret 5.65 software package (Van Essen et al., 2001) (http://brainvis.wustl.edu/wiki/index.php/Caret:About).

General linear model

The general linear model expresses hemodynamic changes at each voxel of the brain as a linear combination of independent variables (i.e. response to different stimuli) and an error term (Friston et al., 1995). Mathematically the GLM is presented by Eq. (1):

$$Y = X\beta + e \tag{1}$$

The data $Y \in R^{T \times N}$ are arranged in a matrix that has the dimensions of time (with T elements) and position (a three dimensional space indexed by a single index variable n with N elements). The design matrix $X \in R^{T \times S}$ has S columns that each represents the modeled response to one of the S different stimuli or conditions. The spatial patterns of responses are embedded in $\beta \in R^{S \times N}$. The error term $e \in R^{T \times N}$ has the same dimension as the data, and is assumed to be zero-mean Gaussian noise (the assumption of independent errors) with variance matrix $\Sigma_e = \sigma^2 I$ (σ^2 is variance in the error and I is identity matrix). With these assumptions the method of least squares produces the minimum variance unbiased estimate of the β parameters (Gauss–Markov theorem):

$$\hat{\beta} = \left(X^t X\right)^{-} X^t Y \tag{2}$$

The parameter estimate variance is given by:

$$\mathrm{Var}\left\{c^t \hat{\beta}\right\} = \hat{\sigma}^2 c^t \left(X^t X\right)^{-} c \tag{3}$$

In Eq. (3), c is the contrast vector which extracts the parameter of interest from $\hat{\beta}$, and has the same length as the number of rows of $\hat{\beta}$ (e.g. to extract the response to the first condition/stimulus type, c = [1 0], and to extract the response to second condition/stimulus c = [0 1] is used, respectively).

With the above assumptions, under the null hypothesis (no activation, $H_0 : c^t \hat{\beta} = 0$), the following statistic,

$$t = \frac{c^t \hat{\beta}}{\sqrt{\hat{\sigma}^2 c^t \left(X^t X\right)^{-} c}} \tag{4}$$

has a t-distribution with degrees of freedom equal to T–S (Moore and McCabe, 2002).