NeuroImage 49 (2010) 2113–2122

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Technical Note

Investigating hemodynamic response variability at the group level using basis functions

Jason Steffener [a,b,*], Matthias Tabert [c,d], Aaron Reuben [a,b], Yaakov Stern [a,b]

[a] Cognitive Neuroscience Division of the Taub Institute, Columbia University College of Physicians and Surgeons, New York, NY 10032, USA
[b] Department of Neurology, Columbia University College of Physicians and Surgeons, New York, NY 10032, USA
[c] Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York, NY 10032, USA
[d] Department of Geriatric Psychiatry, New York State Psychiatric Institute, New York, NY 10032, USA

ARTICLE INFO

Article history:
Received 11 September 2009
Revised 5 November 2009
Accepted 6 November 2009
Available online 12 November 2009

Keywords:
fMRI
Hemodynamic response
Delay
Brain imaging
Basis sets
Group analysis

ABSTRACT

Introduced is a general framework for performing group-level analyses of fMRI data using any basis set of two functions (i.e., the canonical hemodynamic response function and its first derivative) to model the hemodynamic response to neural activity. The approach allows for flexible implementation of physiologically based restrictions on the results. Information from both basis functions is used at the group level and the limitations avoid physiologically ambiguous or implausible results. This allows for investigation of specific BOLD activity such as hemodynamic responses peaking within a specified temporal range (i.e., 4–5 s). The general nature of the presented approach allows for applications using basis sets specifically designed to investigate various physiologic phenomena, i.e., age-related variability in poststimulus undershoot, hemodynamic responses measured with cerebral blood flow imaging, or subject-specific basis sets. An example using data from a group of healthy young participants demonstrates the methods and the specific steps to study poststimulus variability are discussed. The approach is completely implemented within the general linear model and requires minimal programmatic calculations.

Introduction

Previous work has demonstrated that the hemodynamic response (HDR) to neural activity measured with blood oxygen level dependent (BOLD) fMRI varies across the brain and across individuals (Aguirre et al., 1998; Handwerker et al., 2004). This poses a problem for accurate quantification of an individual's BOLD activation when a canonical hemodynamic response function (HRF), i.e., a generalized model of the HDR is used. A simple solution to this problem has been to estimate an individual's HDR using simple visual or motor tasks (D'Esposito et al., 1999; Zarahn et al., 1997), resulting in an estimate of an individual's specific HRF model for use in their statistical analyses. Although this approach is an advance over the canonical HRF model, it has its own drawbacks: it requires additional scans, which cannot be acquired retrospectively, and fails to capture any intraindividual variance that may exist between the region used to derive the HRF and regions of interest for the main experiment. Therefore, this method still leaves potentially unaccounted for variance in the estimate of the BOLD HDR across regions of the brain.

One approach to capturing intraindividual variance in the BOLD HDR is with basis sets. Instead of a single function to model the HDR, a basis set uses multiple (typically two or three) related functions. Through weighted combinations of the functions, many HDR shapes may be modeled, allowing for investigations of hemodynamic variability in a variety of patient populations with various sensory stimuli (Ford et al., 2005; Handwerker et al., 2004; Salek-Haddadi et al., 2006; Stevens et al., 2005; Wierenga et al., 2008). The most prominent basis set currently used is derived from a series expansion of the standard 'double-gamma' HRF model (Friston et al., 1998; Glover, 1999). Other similar basis sets have been developed using a principal components analysis (PCA) of large sets of physiologically plausible BOLD HRFs (Friman et al., 2003; Liao et al., 2002; Woolrich et al., 2004). Of particular note is the work by Liao et al. (2002) who designed a basis set to be sensitive to large delays in the BOLD response to stimulation. This approach demonstrates the feasibility that basis sets may be developed to address specific physiological or clinical questions.

Unfortunately, one drawback of using any basis set is that many model fits result in physiologically ambiguous or implausible results (Calhoun et al., 2004; Woolrich et al., 2004). Restrictions on the potential model fits are therefore required to limit a basis set to plausible shapes. One approach to do so is to only investigate estimated HDRs that have a time to peak within a specific time window (Calhoun et al., 2004; Henson et al., 2002). While this approach may improve analyses at the individual level, translating these results to higher-level statistical analyses presents it own difficulties (Calhoun et al., 2004; Friman et al., 2003; Kiehl and Liddle, 2001; Worsley and Taylor, 2006). The main such difficulty regards the

* Corresponding author. 630 West 168th St, P&S 16 New York, NY 10032, USA. Fax: +1 212 342 1838.
E-mail address: js2746@columbia.edu (J. Steffener).

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doi:10.1016/j.neuroimage.2009.11.014

manner of excluding or including the variance accounted for by the multiple basis functions. One approach to deal with this variance is to fit a basis set and then only perform higher level analyses on the primary basis function, thus excluding the variance attributed to the secondary basis function(s) (Kiehl and Liddle, 2001). An alternative approach is to include the variance accounted for by all functions in the set at higher level analyses by using the magnitude calculated across the basis function estimates for higher level analyses (Calhoun et al., 2004).

The specific implementation of Calhoun et al. (2004) addresses some of the concerns of using a basis set for group-level analyses. This approach, however, is not general enough for use with other basis sets and requires specific normalization of the regressors in the model. The result is that the specific ratio described in their work is only meaningful with the basis set they used and would have a different meaning if directly applied to other basis sets, i.e., FLOBS as implemented with the FSL package. In addition, the canonical HRF, and its first derivative basis set, is specifically sensitive to temporal shifts, making it unsuitable for study of other physiological variations such as poststimulus undershoot variations. For instance, systematic differences in the size of the poststimulus undershoot between young and elder healthy participants were found in one study (Wierenga et al., 2008), while another study found no significant differences in the BOLD HDR shape between age groups (D'Esposito et al., 2003). In addition, growing application of BOLD fMRI to study disease states (Matthews et al., 2006) may introduce important variations in BOLD HDR shapes which need to be addressed. Specifically, studies of the hemodynamic responses to epileptiform discharges have shown large variability in the BOLD response as a function of proximity to the discharge site (Lemieux et al., 2008; Salek-Haddadi et al., 2006).

Importantly, the current advance of cerebral blood flow imaging (CBF fMRI) also requires that many of the original questions regarding the shape and variability of hemodynamic responses be revisited with this hemodynamic marker. For instance, in a recent study using BOLD and CBF fMRI, age-related differences were found, within subject, in the poststimulus undershoot using CBF but not in BOLD (Ances et al., 2009). This suggests that the underlying hemodynamic response of CBF and BOLD fMRI differ and the same HRF model may not be optimal. Therefore, with CBF fMRI, new hemodynamic response models, and therefore basis sets, will need to be developed to be specifically sensitive to this new imaging modality (Woolrich et al., 2006; Yang et al., 2000). This is a clear instance in which there is a need for a general approach to group-level analyses with basis functions.

This technical note presents an approach using the general linear modeling framework (i.e., using the SPM or FSL packages) to address the two main limitations of using a basis set: the need for model fitting restrictions and the need for a means of translating individual-level improvements in model fitting to higher-level analyses. The approach is straightforward and applicable to any basis set, allowing for flexible designations of physiological limitations, thereby correcting many of the difficulties presented when using basis sets. The specific normalizations of the design matrix required for this approach are calculated so that they may be performed after model estimation; therefore, no modifications are required to the design matrix as created by SPM or FSL. Furthermore, with such a general framework, it is possible to investigate more subtle questions regarding hemodynamic responses to neural activity. One potential application of this method will be to investigate the physiological origins of variations in the poststimulus undershoot measured with BOLD and CBF fMRI. An approach to addressing such a question is used as a specific example and laid out in detail later in the paper. Other applications will include the study of the spatial dynamics of BOLD responses to epileptic seizures (Lemieux et al., 2008) or investigation of the spatial variability of the temporal delay of BOLD responses. Data from a group of young participants engaged in a simple visual experiment are used to demonstrate the methods and software to implement the key calculations (for SPM or FSL) are posted at: http://cumc.columbia.edu/dept/sergievsky/cnd/steffener.html.

Methods

Participants

Ten young healthy volunteers (50% females; mean age = 23.9 years ± 5.4; education = 15.4 ± 2.4 years) participated in the fMRI study. The study was approved by the New York State Psychiatric Institute IRB and all subjects provided informed consent.

fMRI parameters

Scanning used a Philips Medical Systems Intera 1.5 T machine with echo planar imaging (EPI) capabilities (TR/TE = 3000/50 ms, flip = 90°, slice thickness = 5 mm (no gap), 32 slices, orientation angle of 30° to the AC–PC line, FOV = 20 × 20 cm, and a 64 × 64 matrix). High-resolution T1-SPGR images were acquired to aid in coregistration and anatomical localization (TR/TE = 25/3 ms, flip = 45°, slice thickness = 2 mm (no gap), FOV = 23 × 23 cm, and a 256 × 256 matrix).

Task description

The visual task used a 2-Hz reversing checkerboard for 12 s alternated with 30 s of fixation on a central cross-hair for five cycles projected to the center of the subject's field of view via a rear projection screen. A laptop computer (Dell 5150) using a custom-developed program (LabView 7.1, National Instruments Corp.) presented the stimulus. An extra 6 s (2 scans) of data were acquired and discarded at the beginning of each functional run to account for MR saturation effects. The final result was 80 EPI scans comprising a single functional run.

Image preprocessing

All image preprocessing and statistical analyses were implemented using SPM5 (Wellcome Department of Cognitive Neurology). All EPI images were corrected for motion by realigning to the first volume of the series. The T1-weighted (structural) image was coregistered to the first EPI volume using mutual information. This coregistered high-resolution image was then used to determine the linear and nonlinear parameters for transformation into a standard space defined by the Montreal Neurologic Institute (MNI) template brain supplied with SPM5. This transformation was then applied to the EPI data which were resliced using bilinear interpolation to 2 × 2 × 2 mm final voxel dimensions and spatially smoothed with an 8 × 8 × 8 mm FWHM (full-width at half-maximum) Gaussian kernel.

Subject-level statistical modeling

The functional data were modeled using a box-car representation of the stimulus vector convolved with the basis set consisting of the canonical double-gamma model of the HRF and its first derivative using SPM5's default parameters (Fig. 1A). The regression model using the basis set was therefore

$$x_1 = s^{*}HRF \tag{1}$$

$$x_2 = s^{*}\left(\frac{\partial HRF}{\partial t}\right) \tag{2}$$

$$y_t = \beta_0 + \beta_1 \cdot x_1 + \beta_2 \cdot x_2 + \varepsilon_t \tag{3}$$