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NeuroImage

www.elsevier.com/locate/ynimg
NeuroImage 31 (2006) 1169 – 1176

Are fMRI event-related response constant in time? A model selection answer

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Received 24 May 2005; revised 24 August 2005; accepted 30 August 2005
Available online 2 May 2006

An accurate estimation of the hemodynamic response function (HRF) in functional magnetic resonance imaging (fMRI) is crucial for a precise spatial and temporal estimate of the underlying neuronal processes. Recent works have proposed non-parametric estimation of the HRF under the hypotheses of linearity and stationarity in time. Biological literature suggests, however, that response magnitude may vary with attention or ongoing activity. We therefore test a more flexible model that allows for the variation of the magnitude of the HRF with time in a maximum likelihood framework. Under this model, the magnitude of the HRF evoked by a single event may vary across occurrences of the same type of event. This model is tested against a simpler model with a fixed magnitude using information theory. We develop a standard EM algorithm to identify the event magnitudes and the HRF. We test this hypothesis on a series of 32 regions (4 ROIS on eight subjects) of interest and find that the more flexible model is better than the usual model in most cases. The important implications for the analysis of fMRI time series for event-related neuroimaging experiments are discussed.

Introduction

The mechanisms coupling neuronal activity and the BOLD response (blood oxygen level dependent) (Ogawa et al., 1990) observed with fMRI are still poorly understood. The variations of the BOLD contrast, measured with fMRI, are often characterized by the response to a unitary and very short stimulus, i.e., the hemodynamic response function (HRF). Precise estimation of the HRF is important to help better quantify neuronal activity in BOLD data. While the analysis of those data is still an active field of research, most standard techniques rely on a pre-specified model of the hemodynamic impulse response function.

Recently, some progresses have been made in the non parametric estimation of the hemodynamic response function (HRF). These advances are implemented through the use of Bayesian models that allow the inclusion of temporal information taken from the physiological knowledge of the brain response, such as the regularity of the response (Goutte et al., 2000; Ciuciu et al., 2003; Marrelec et al., 2001). In particular, in Ciuciu et al. (2003), a general solution is presented that takes into account the specificities of actual fMRI data sets. In this work, a different function (HRF) is estimated depending on the event type (i.e., the kind of stimulus presented or the sort of task to be performed by the subject). Recent works have also proposed more accurate noise models (Woolrich et al., 2004, 2005), and others have included physiological information in more biologically plausible models (Buxton and Frank, 1997; Friston et al., 2000; Riera et al., 2004; Aubert and Costalat, 2002). Lately, Makni and colleagues introduced the idea that the HRF could be estimated with a constant shape but with varying magnitude across voxels in a given region of interest (Makni et al., 2004).

However, the estimations proposed so far have assumed a crucial hypothesis.

To the exception of two recent studies, previous works have assumed that each event of a given type (in other words each occurrence of a given experimental condition) evoked a BOLD response constant in shape and in magnitude. Some models have introduced an important flexibility across events, but stationarity in time is most generally assumed. Recently, it was suggested that this might not always be the case (Duann et al., 2002). In this latter work, the authors show convincingly that the evoked hemodynamic response may vary with time using independent components analysis over the entire dataset but do not explicitly test this model for a given region of interest. Previous works using electrophysiology or optical imaging also suggest that responses to trials may depend on ongoing activity (Arieli et al., 1996) or top down effects such as attention. One notable exception is the work of Lu et al. (2005), which propose a general framework to account for variation between events of the HRF shape and magnitude, and use an F test to show that the more complex model is generally

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1053-8119/$ - see front matter © 2005 Published by Elsevier Inc.
doi:10.1016/j.neuroimage.2005.08.068

more appropriate. However, the authors use a complex optimization procedure submitted to hard constraints in which the validity of the model selection through an F test has yet to be validated. Their approach is also limited to events synchronized with the TR and single-condition experiments. Lastly, the hemodynamic response is also constrained to be close to a standard model, while there is evidence in former works that the shape of the response may be variable across subjects, brain regions, or even experiments (Aguirre et al., 1998). It is worth noting that when the variability of the response can be linked to some known parameter, standard methods can be applied (see Buchel et al., 1998).

In this paper, we propose a more direct model to test for this hypothesis with an approach that can be used in any event-related fMRI experiment and present the results on several brain areas. For a given type of stimulus, we propose that the different event occurrences can induce responses of varying magnitude. A method able to select the most likely model (between fixed and variable event magnitude) is described. While a first version of this model was presented in Donnet et al. (2004) and validated on simulated data only, we propose here a more robust version of this model and study whether it is likely to be useful in actual fMRI analysis by testing its relevance on 32 regions of interest drawn on 8 subjects.

While the model presented here is clearly a simplification of the underlying biology since it does not include physiological modelling (for instance using the balloon model), it may still provide useful information on the temporal behavior of the brain response for a fixed stimulus or task. This model is more flexible than what has been generally proposed so far since it does not assume a specific shape for the hemodynamic response nor its magnitude stationarity with time.

The rest of the paper is organized as follows. First, the model of the data is presented with an emphasis on the underlying hypotheses. Second, we describe the methodology for parameter estimation, likelihood computation, and model selection. Third, we present the fMRI dataset used to test the model and then illustrate the results. Lastly, we discuss some consequences of our findings for fMRI data analyses.

Method

The model

Modelling the observed series with one event type

We denote the observed fMRI time series extracted from a given region of interest by $\boldsymbol{y} = (y_1, \ldots, y_n)'$ where $y_i = y(t_i)$ is the measurement at time t_i, with $t_i = i\mathrm{TR}$, TR being the time of repetition. n is the number of scans within the session. The hemodynamic response function is denoted by $h(t)$. Assuming a convolution model, we have:

$$y_i = \sum_{m=1}^{M} x(s_m)h(t_i - s_m) + \sum_{q=1}^{Q} l_q P_q(t_i) + \varepsilon_i, \quad i = 1 \ldots n \tag{1}$$

where

- $(x(s_m))_{m\,=\,1\ldots M}$ is the input time series, with $s_m = m\Delta_e$. Δ_e defines a finer grid than the one defined by TR because an event can occur at any time, not necessarily at the time of data sampling. Typically, TR is around 2–4 s, while the occurrence of an event may be defined every 100 ms or less (a typical value is TR/16).
- The second sum represents a low-frequency drift. In fMRI experiments, the BOLD data are contaminated by low-frequency phenomena due to physiological artefacts, scanner drifts, or subject movements. In general, the data are high-pass filtered before estimating the HRF. In this work, we choose to estimate simultaneously the HRF and the trend. For this, we model the low frequencies by a family of orthonormal functions $(P_1, \ldots, P_Q)$, such as one-dimensional discrete cosine transform. The number Q of basis functions depends on the lowest frequency $f_{\min}$ attributable to the drift term. It can be defined as $Q = [2n\mathrm{TR}f_{\min}] + 1$. The quantities $(l_q)_{(q\,=\,1\ldots Q)}$ represent the unknown weighting coefficients of the basis functions and have to be estimated.
- The sequence $\varepsilon = (\varepsilon_1 \ldots \varepsilon_n)$ is taken as a Gaussian white noise of variance σ^2. Although this is a simplifying assumption for fMRI data, it has been shown in Marrelec et al. (2001) that, in a Bayesian framework, the distribution of the error term does not influence the estimation of the HRF significantly. Since the same assumption is made for all models, it is unlikely that this distribution will greatly change the model selection results. The information of interest lies within the comparison of the likelihood of those models. Moreover, a more flexible model leads to a different noise estimation, which typically shows a lesser degree of time correlation (results not shown).

As in previous works, for the response function h, we assume that $h(u) = 0$ for $u \leq 0$. Furthermore, we truncate h, setting $h(u) = 0$ for $u > L\Delta_e$, where $L\Delta_e$ is typically 20 or 25 s.

If events are occurring at instants $\tau_1, \tau_2, \ldots \tau_J$, we have,

$$x(s) = 0 \quad \text{if} \quad \tau \notin \{\tau_1, \tau_2, \ldots \tau_J\},$$

$$x(\tau_j) = \alpha_j \quad 1 \leq j \leq J.$$

Thus, the model becomes:

$$y_i = \sum_{j=1}^{J} \alpha_j h(t_i - \tau_j) + \sum_{q=1}^{Q} l_q P_q(t_i) + \varepsilon_i \ , \quad i = 1 \ldots n \tag{2}$$

We define the matrices

$$H = (H_{ij})_{1 \leq i \leq n, 1 \leq j \leq J}, \quad A = (A_{im})_{1 \leq i \leq n, 1 \leq m \leq M} \quad \text{and} \quad P = (P_{iq})_{1 \leq i \leq n, 1 \leq q \leq Q}$$

by

$$H_{ij} = h(t_i - \tau_j), \; A_{im} = x(t_i - s_m) \quad \text{and} \quad P_{iq} = P_q(t_i)$$

and the vectors

$$\boldsymbol{a} = (\alpha_1, \ldots, \alpha_J)', \quad \boldsymbol{h} = (h_1, \ldots, h_L)' \quad \text{and} \quad \boldsymbol{l} = (l_1, \ldots, l_Q)'$$

where $\mathbf{v}'$ is the transposed of the vector $\mathbf{v}$.

P, H, and A have as many lines as there are temporal observations (n), H has as many columns as there are events (J), A has as many columns as there are time locations on the fine temporal grid, P has as many columns as there are functions in the chosen basis (Q). Then, we obtain the following matrix form:

$$\boldsymbol{y} = H\boldsymbol{a} + P\boldsymbol{l} + \varepsilon \tag{3}$$

$$= A\boldsymbol{h} + P\boldsymbol{l} + \varepsilon \tag{4}$$

This last formula is important because it states that the data can be considered as either the sum of the fixed HRF response