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Event-Related fMRI

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Abstract: We present a method for detecting event-related responses in functional magnetic resonance imaging (fMRI). The occurrence of time-locked activations is formulated in terms of the general linear model, i.e., multiple linear regression. This permits the use of established statistical techniques that correct for multiple comparisons in the context of spatially smooth and serially correlated data. Responses are modelled using event-related temporal basis functions. Inferences are then made about all components of the model, using the F-ratio at all voxels in the image, to produce a statistical parametric map (SPM[F]). This method allows for the experimental design to relate the timing of events to the acquisition of data to give a temporal resolution (with respect to the event-related response) far better than the scanning repeat time. *Hum. Brain Mapping 5:243–248, 1997.* © 1997 Wiley-Liss, Inc.

Key words: event-related; basis functions; general linear model; functional imaging

INTRODUCTION

This paper concerns event-related functional magnetic resonance imaging (fMRI). The importance of fMRI to functional neuroimaging is that it offers high temporal and spatial resolution with whole-brain coverage. The aim of this work was to develop experimental designs and analysis techniques that fully exploit these advantages.

These techniques facilitate new *genres* of fMRI experiment. An experiment need not be constrained by successive trials being of the same type, as in current "block" designs. This is vital in psychological paradigms because responses to stimuli can be characterized without being confounded by the subject's attentional set. An example of this is the use of oddball paradigms where the effect of novelty can be assessed. In addition, the increased latitude of design allows for the analysis of uncontrollable events, e.g., hallucinations.

The statistical inference provided by these techniques is tailored specifically to time-locked activation. The hemodynamic response to each event is modelled explicitly. The model accounts for both the stimulus-dependent and regionally specific aspects of the response. These inferences may concern simply the significance of activation, or demonstrate significant differences between responses to different event types (analogous to N300/P400 mismatch measurements in electrophysiology).

This paper focuses on continuous multiplane echo-planar imaging (EPI) fMRI experiments. Although multislice EPI may entail a repeat time (TR) that is comparable to that of hemodynamic responses, we achieve an improved temporal resolution using a method that has proved very useful in cardiac imaging. We characterize the finer temporal structure by making repeated measurements while varying the phase of the stimulus relative to the acquisi-

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tion. This sampling latency can be varied over the experiment in many different ways. In this paper, we use a fixed increment of the acquisition phase for each successive stimulus. We then build a model for the hemodynamic response, comprising Fourier series temporal basis functions. The general linear model (GLM) provides the basis for statistical analysis and gives unbiased and least squares parameter estimates (in this instance, the Fourier coefficients of the response). Furthermore, by employing the GLM, we are able to obtain SPMs corrected for multiple comparisons in the context of Gaussian random field theory. This is a further application of the statistical parametric map (SPM{F}) to make inferences about the significance of all the components of a model.

The paper is divided into the following parts: theory underlying the current work; application of the technique to an fMRI experiment; and discussion of the technique and implications for future work.

THEORY

Continuous-time model

Consider a single position, $\underline{r}$, within the brain. We assume that the stimulus can be characterized by a *stimulus function,* s(t), that is convolved by a regionally specific *hemodynamic response function*, $h_{\underline{r}}(t)$, to obtain the response $x_{\underline{r}}(t)$, i.e.,

$$x_{\underline{r}}(t) = s \otimes h_{\underline{r}} + e_{\underline{r}}(t) = \int_0^t s(t-\tau)h_{\underline{r}}(\tau)d\tau + e_{\underline{r}}(t). \quad (1)$$

$e_{\underline{r}}(t)$ is the residual timecourse and includes physiological noise, both spontaneous activity and (equivalently) any variable component of the evoked activity.

We now assume that $h_{\underline{r}}(t)$ may be expressed in terms of a basis function expansion

$$h_{\underline{r}}(t) = \sum_{b=1}^{n_{BAS}} g_b(t)\beta_{\underline{r},b} \quad (2)$$

where n_{BAS} is the total number of basis functions; $g_b(t)$ are the functions, themselves; and $\beta_{\underline{r},b}$ are the corresponding weights.

Substituting (2) into (1) and reversing the order of integration and summation, we obtain a general linear model for the fMRI response.

$$x_{\underline{r}}(t) = \sum_{b=1}^{n_{BAS}} \left[\int_0^t s(t-\tau)g_b(\tau)d\tau \right] \beta_{\underline{r},b} + e_{\underline{r}}(t) \quad (3)$$

It is interesting to note that the integral term represents $s \otimes g_b$. Previous linear models have also been of this form but have assumed either a fixed form for the hemodynamic response to a unit stimulus [Friston et al., 1994] or have included only two smoothbasis functions [Friston et al., 1995a]. By including more terms we are able to model higher-frequency components and regional variations in the response.

The stimulus function, s(t), can in general be any function of time, but in this paper we will consider periodic, discrete, impulse-like stimuli. An appropriate stimulus function s(t) is defined as:

$$s(t) = \sum_{m=1}^{n_{STIM}} \delta(t - m\tau_{ISI}) \quad (4)$$

where n_{STIM} is the total number of stimuli and τ_{ISI} equals the interstimulus interval.

Substituting (4) into (3) and using the shift theorem we obtain:

$$x_{\underline{r}}(t) = \sum_{m=1}^{n_{STIM}} \sum_{b=1}^{n_{BAS}} g_b(t - m\tau_{ISI})\beta_{\underline{r},b} + e_{\underline{r}}(t). \quad (5)$$

Clearly, because the response is caused by the stimulus, $h_{\underline{r}}(t) = 0$ for $t < 0$. For the purposes of this paper we will assume that the response to one stimulus has also returned to zero by the time of the next stimulus, i.e., $h_{\underline{r}}(t) = 0$ for $t > \tau_{ISI}$.[1] We can model $h_{\underline{r}}(t)$ in terms of similarly time-limited $g_b(t)$ and note that, in this case, (5) reduces to

$$x_{\underline{r}}(t) = \sum_{b=1}^{n_{BAS}} g_b(t \bmod \tau_{ISI})\beta_{\underline{r},b} + e_{\underline{r}}(t). \quad (6)$$

Discrete-time model

We will now use the continuous-time model above to derive a discrete-time form for the analysis of multislice EPI data.

[1]Although longer term components may exist we may not, in any case, be able to distinguish them reliably from low-frequency scanning noise.

A single voxel can be sampled by EPI (along with the other voxels in that slice) in less than 100 msec. Since this is short compared with hemodynamic responses, we may assume that the measured signal for scan n, from the point $\underline{r}$, is simply $x_{\underline{r}}(nTR + \tau_{\underline{r}})$. TR equals the scanner (volume) repeat time and $\tau_{\underline{r}}$ equals the time from the beginning of each volume scan to when the slice containing the position $\underline{r}$ is scanned. We can expand $x_{\underline{r}}(nTR + \tau_{\underline{r}})$, using (6):

$$x_{\underline{r}}(nTR + \tau_{\underline{r}}) = \sum_{b=1}^{n_{BAS}} g_b((nTR + \tau_{\underline{r}}) \bmod \tau_{ISI})\beta_{\underline{r},b} + e_{\underline{r}}(nTR + \tau_{\underline{r}}). \quad (7)$$

$e_{\underline{r}}$ may now include additional sources of noise from the scanning process.

The nature of the modulo function allows us to choose TR and τ_{ISI} such that during the course of the experiment the hemodynamic response is sampled uniformly. Figure 1 illustrates a uniform *effective sampling period* of TR/2, as used below in the illustrative experiment. From a signal-processing perspective, the choice of effective sampling period is one of sensitivity of the discrete-time measurement to activation. The shorter the effective sampling period, the greater the potential bandwidth of the model. The effective sampling period would typically be chosen to be sufficiently short to allow the model to include all the significant frequency components of any (reasonable) $h_{\underline{r}}$.

In this paper the basis functions, g_b, constitute a Fourier sequence based on a fundamental period τ_{ISI}. We note that this sequence spans the space of all possible response phases such that one model, that is independent of $\tau_{\underline{r}}$, suffices for the entire volume. This phase-insensitivity allows us to simplify the linear model ($\beta'_{\underline{r},b}$ are the parameters corresponding to the simplified model):

$$x_{\underline{r}}(nTR + \tau_{\underline{r}}) = \sum_{b=1}^{n_{BAS}} g_b(nTR \bmod \tau_{ISI})\beta'_{\underline{r},b} + e_{\underline{r}}(nTR + \tau_{\underline{r}}) \quad (8)$$

Statistical analysis and inference

Equation (8) can be expressed in the usual matrix form for the general linear model.

$$\mathbf{X} = \mathbf{G}\boldsymbol{\beta} + \mathbf{e} \quad (9)$$

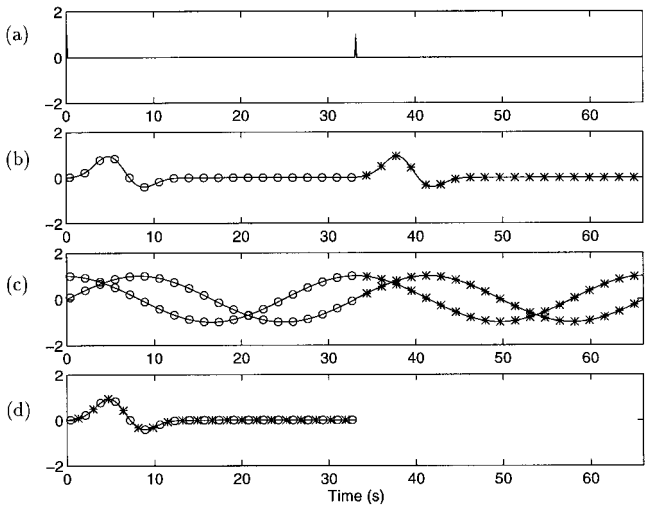

Figure 1.
Two epochs of an event-related fMRI experiment. **a:** Stimulus function, s(t). **b:** Typical response function, x(t) (solid line), and scanner sample points (odd epochs, circles; even epochs, asterisks). **c:** Two fundamental basis functions, $g_b(t)$. **d:** Hemodynamic model, h(t), showing samples reordered according to latency after stimulus.

This states that **X**, the *data matrix*, which has one column per voxel and one row per scan, can be expressed as the product of **G**, the *design matrix*, and **β**, the *parameter matrix* plus the *error matrix*, **e**. **G** has one column for every modelled effect (in this case, the basis functions, g_b) and one row for each scan. **β** has one row per effect (in this case, $\beta'_{\underline{r},b}$) and one column per voxel. **e** represents error terms for each element of **X**. Least-squares parameter estimates, **b**, for **β** in (9) are

$$\mathbf{b} = (\mathbf{G}^T\mathbf{G})^{-1}\mathbf{G}^T\mathbf{X}. \quad (10)$$

Following Friston et al. [1994], effects of no interest (e.g., low-frequency components and other confounds like the global mean) can be appended to **G**.

The null hypothesis is that the variance explained by all of the effects of interest is zero (this is equivalent to $\beta'_{\underline{r},b} = \underline{0}$). The measure of significance in this context is based on the F-ratio which is determined, as described in Friston et al. [1994], using the extra sum of squares principle. The F-ratio for each voxel in the image produces an SPM{F} . Using Gaussian field theory we make corrected inferences on the basis of the SPM{F} about voxels that show significant event-related activation [Worsley, 1994].

In the context of fMRI time series, the calculation of the F-ratio is rendered a little more complicated by

virtue of temporal autocorrelations in the original data [Friston et al., 1995b]. These autocorrelations can arise from physiological effects or postprocessing (i.e., temporal smoothing). In general, and in the analysis presented below, we computed the SPM{F} after taking into account temporal autocorrelations following temporal smoothing along the lines of Worsley and Friston [1995].

APPLICATION

In this section we apply the above theory to an fMRI time series in which a subject listened to single words.

Data acquisition and preprocessing

The MRI data were 16-slice, 64 × 64 voxel volumes with 3-mm^3 isotropic voxels, acquired at 2 T on a MAGNETOM Vision (Siemens, Erlangen, Germany). The slice ordering was consecutive, decending: 1,280 volumes were acquired at TR = 1.7 sec, TE = 40 msec in 10 blocks of 128 volumes. The first eight volumes of each block were discarded because of spin saturation (T_2) effects.

The subject listened binaurally to single words presented at 1 word / 19.5 TR, (i.e., ISI = 33.15 sec). The stimuli were synchronized with the scanner so that alternate words were presented precisely halfway through or between volumes.

The data were spatially realigned, normalized into the space of Talairach and Tournoux [Friston et al., 1995c], subsampled to 2 × 2 × 2 mm, and smoothed with a Gaussian kernel of 5 mm.

Statistical analysis and results

The event-related model was centered on the stimulus presentation and comprised 16 complex Fourier sequence harmonics up to 0.5 Hz. The covariates of no interest included a discrete-cosine high-pass filter set [Holmes et al., 1997] and the global volume mean. The ensuing SPM{F} and the model fit for a periauditory voxel are shown in Figure 2. The SPM{F} shows significant activation in the auditory and periauditory cortex. The form of the signal time-course is as expected for brief sensory stimulation. The SPM shown has been thresholded at $P < 0.001$ (uncorrected). The highlighted voxel shown in Figure 2 has an F value of 13.2 (32, 730 degrees of freedom) with a significance of $P < 0.001$ corrected according to Worsley [1994].

DISCUSSION

In this paper we have presented a method for detecting event-related responses in fMRI. The tenets of this method are:

1. The detection of time-locked activation is formulated in terms of a linear model. The importance of this is that it allows the use of established statistical techniques to make inferences corrected for multiple comparisons in the context of spatially smooth, serially correlated data.
2. The response is modelled using event-related temporal basis functions. The form of the basis functions and the order of the model may be selected based on considerations of their face validity and statistical power.
3. Inferences are made about all components of the model at once, using the F-ratio at all voxels in the image, to produce an SPM{F}. This is distinct from conventional SPM{t} maps in which a t-statistic is used to test the influence of one linear compound of the model (i.e., contrast).
4. The method allows for the experimental design to relate the timing of events to the acquisition of data in order to achieve a temporal resolution (with respect to the event-related response) in excess of the scanning repeat time. This means that one can obtain a very high temporal resolution without using a very short TR (and the ensuing loss in coverage).

We will now discuss issues of estimation and inference.

Basis functions

Clearly the form and order of the basis functions are important. In this paper we have chosen Fourier terms. This choice is motivated primarily by their insensitivity to the precise phase of acquisition. This is particularly important for sliced EPI, where the acquisition of different slices may vary by as much as 6 sec. In addition, they remain invariant under convolution (sinusoidal functions remain sinusoidal after any convolution), which makes them particularly simple to apply to protracted events (e.g., the delay period between ''prepare'' and ''go'' cues). This choice may be contrasted with alternatives (e.g., Gamma functions) which will give a different fit depending on the slice. However, we can generalize the sine and cosine formulation to other functions by including the temporal

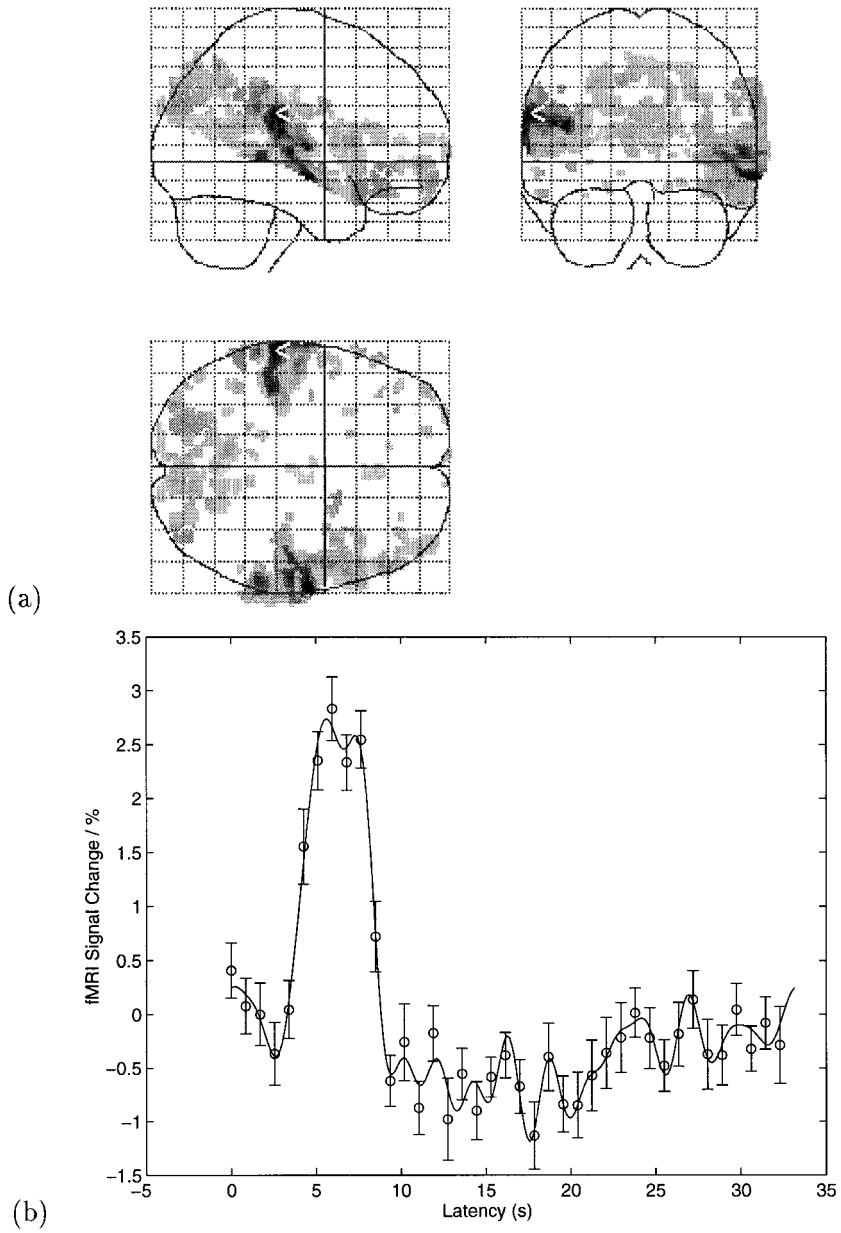

Figure 2.

a: SPM{F} of an auditory event-related experiment presented as a maximum intensity projection on a template brain renormalized in Talairach space. Height threshold, $P < 0.001$ (uncorrected). Extent threshold, 3 voxels. **b:** Time course from highlighted voxel. Model (solid line) and adjusted data (mean ± standard errors).

derivatives of such other functions as extra basis functions. This renders non-Fourier models less sensitive to artifactual phase differences.

In this paper we have deliberately modelled very-high-frequency response components in order to demonstrate that the technique can provide for a higher temporal resolution than would normally be imposed by the interscan interval (i.e., sampling frequency). The advantages of more comprehensive models is that they can provide a complete, detailed characterization. If there is evidence for fine temporal structure, then the data are more properly modelled with a larger number

of basis functions. It should be noted, however, that the real hemodynamic signal, attributable to underlying neuronal activity, will generally be smooth by virtue of being convolved by the hemodynamic response function. In this case, modelling high frequency components is redundant. The advantage of a smaller, more parsimonious model is that fewer degrees of freedom are used in the general linear model, and so more are available for statistical inference (and hence the model may be more powerful). However, in some circumstances, e.g., high field strengths, the hemodynamic response function may include high-frequency components, e.g., an initial dip. Obviously, the choice of frequency components included in a model will be dictated by the nature of the data and the questions being asked of them.

SPM{F} and extensions

The SPM{F}, the inferential device underpinning this method, has already been employed for nonlinear regression [Büchel et al., 1996]. Although not demonstrated here, we may use the extra sum of squares (ESS) principle with the SPM{F} to compare different models and orders (i.e., including different numbers of basis functions) to make a statistically informed choice of models. The ESS also allows us to test explicitly for differential event-related activation while discounting common effects and vice versa. A natural extension will be to multifactorial designs (i.e., s(t) will be multidimensional) in which both main effects and interactions are of interest.

Assumptions

The events must occur repeatedly and should evoke stereotyped and reproducible responses.

We have assumed linear, time-invariant hemodynamic response functions. However, by using long ISIs, as in this paper, it is reasonable to assume there will be a negligible interaction (either linear or nonlinear) between successive responses.

CONCLUSIONS

In conclusion, we have presented a flexible yet robust technique for characterizing and making inferences about the location and form of evoked hemodynamic responses to transient events in fMRI. The approach employs standard techniques and is easily implemented in the context of functional neuroimaging.

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