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Characterizing Stimulus–Response Functions Using Nonlinear Regressors in Parametric fMRI Experiments

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Parametric study designs proved very useful in characterizing the relationship between experimental parameters (e.g., word presentation rate) and regional cerebral blood flow in positron emission tomography studies. In a previous paper we presented a method that fits nonlinear functions of stimulus or task parameters to hemodynamic responses, using second-order polynomial expansions. Here we expand this approach to model nonlinear relationships between BOLD responses and experimental parameters, using fMRI. We present a framework that allows this technique to be implemented in the context of the general linear model employed by statistical parametric mapping (SPM). Statistical inferences, in this instance, are based on *F* statistics and in this respect we emphasize the use of corrected *P* values for *F* fields (i.e., SPM{F}). The approach is illustrated with a fMRI study that looked at the effect of increasing auditory word-presentation rate. Our parametric design allowed us to characterize different forms of rate-dependent responses in three critical regions: (i) bilateral frontal regions showed a categorical response to the presence of words irrespective of rate, suggesting a role for this region in establishing cognitive (e.g., attentional) set; (ii) in bilateral occipitotemporal regions activations increased linearly with increasing word rate; and (iii) posterior auditory association cortex exhibited a nonlinear (inverted U) relationship to word rate. © 1998 Academic Press

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INTRODUCTION

Based on the premise that hemodynamic responses vary with the amount of cortical processing engaged by an experimental task, parametric or correlational designs can provide information about the relationship between a stimulus parameter (e.g., word presentation rate) or behavioral response (e.g., reaction time) and the neurophysiological response elicited. The variable being correlated can either be continuous (e.g., reaction time) or discrete (e.g., word presentation rate). Examples include studies that have demonstrated correlations between regional cerebral blood flow (rCBF) and the performance of motor tracking tasks in the supplementary motor area and thalamus (Grafton *et al.*, 1992). Price *et al.* (1992) investigated the correlation between rCBF and frequency of aural word presentation in normal subjects. They found a linear relationship between rCBF and word rate in the periauditory regions. Responses in Wernicke's area, however, were not associated with increased word rate but with the presence or absence of semantic content. That example illustrates the ability of a parametric approach to characterize and differentiate brain regions using their response profile in relation to the task parameters. Recently this method was used to differentiate cortical areas involved in pain affect (Rainville *et al.*, 1997). The authors used hypnotic suggestion to alter the unpleasantness of noxious stimuli without changing the perceived intensity. A parametric analysis revealed significant changes in pain-evoked activity within the anterior cingulate cortex, whereas primary somatosensory cortex activation was unaltered.

In this respect functional magnetic resonance imaging (fMRI) offers certain advantages over positron emission tomography (PET). fMRI allows repeated measurements on the same subject in one session (Kwong *et al.*, 1992), which makes it especially eligible for parametric study designs. This is in contrast to PET studies, in which the number of experimental conditions is limited by radiation exposure. In the context of parametric designs, fMRI allows one to study more, and a finer gradation of, task or stimulus parameters.

As the form of the relationship between experimental parameters and hemodynamic responses may vary among different brain regions and is unknown in advance, the *a priori* definition of a fit function for a regression analysis (e.g., linear) might result in a partial and misleading characterization of the data.

To overcome this restriction we presented a framework (Büchel *et al.*, 1996) that allows one to characterize brain responses as a linear combination of (basis) functions of the experimental parameter (e.g., $f(x) =$

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$a + bx + cx^2$) , where x is word presentation rate) in question. This approach has two advantages: (i) it can model parsimoniously a range of responses, constrained only by the type and order of the basis functions used and (ii) the form of the relationship (determined by the coefficients of the basis functions, e.g., a, b, and c) can be different for each voxel. This approach models different responses in different brain regions with a single model (i.e., single set of basis functions for all voxels). Using nonlinear functions of the task parameter (e.g., the quadratic term cx^2) allows nonlinear responses to be modeled in the context of a general linear model.

Here we extend this framework to accommodate parametric fMRI experiments. After introducing the special problems arising in fMRI, we will exemplify the technique with an experiment investigating the effect of rate of auditory word presentation.

THEORY

The key issue here is that one has model responses or activations (as opposed to activity) as a nonlinear function of the experimental parameter(s). This reduces to modeling an interaction between the parameter and the task or stimulus (as opposed to a simple main effect of parameter). Digital signal processing utilizes different techniques to characterize discrete signals by a linear combination of basis functions. Well-known examples are the Fourier expansion and the polynomial expansion. We adapt this to characterize BOLD signal responses in fMRI in terms of a set of basis functions of a given parameter (e.g., stimulus parameter or response index) to show how BOLD signals can be approximated by a small number of these basis functions. The use of polynomials in the context of the general linear model is the well-known case of polynomial regression.

fMRI signals can be contaminated by low-frequency components that might be caused by instrumentation drifts or aliased higher frequency signals. These high-frequency components like heart rate (1 Hz) and respiration (0.1 Hz) are undersampled with typical TRs of 3 to 7 s and can, according to Nyquist's theorem, be expressed as low-frequency signal components. The problem of low-frequency noise is typically solved in fMRI by alternating task and control conditions at a fairly high frequency (i.e., every 20–40 s). This allows one to high-pass filter the fMRI time series, filtering out low-frequency instrumentation and physiological noise, while preserving the higher frequency (i.e., task-related) components of the signal (Holmes *et al.*, 1997). A high-pass filter can be implemented easily within the framework of the general linear model, using cosine functions of time, modeling all frequencies lower than the experimental frequency (see Holmes *et al.*, 1997, for details).

In contrast to PET, in which the expansion of the stimulus or task parameter itself is used as a regressor, in fMRI one has to expand the underlying stimulus or activation function (e.g., boxcar or sine wave) that is modulated by the parameter. Figure 1 (top) shows an example of a second-order polynomial expansion of a standard boxcar function using time as a parameter. Intuitively this approach can be seen as expanding the differences between activation and control conditions or more formally as an interaction between condition and parameter. The different amplitude of the boxcar functions reflects the level of the task parameter for that condition.

Instead of using simple linear and second-order expansions as shown in Fig. 1 (top), we generally use orthogonal basis functions (Fig. 1, bottom, and see below). Orthogonal basis functions span the parameter space in an efficient way and have the advantage that the parameter estimates are independent of each other under the null hypothesis. This is useful because linear combinations (contrasts) of those parameter estimates could be used to test for specific effects (e.g., presence of a second-order component) using statistical parametric maps (SPMs) of the t statistic.

In general the goodness of fit of the regression depends on the type and number of basis functions employed and on the number of data points approximated. One generally expects BOLD signal changes, in cognitive activation studies, to be smooth and conform to a monotonic function of task parameters or stimuli. Using a hierarchical set of basis functions (e.g., polynomials) voxel-specific model selection is straightforward using the extra-sum-of-squares principle in the context of the general linear model (Draper and Smith, 1981). The strategy for a polynomial expansion is as follows: Start with a basic model, comprising only the standard boxcar (and confounds like global signal and cosines for high-pass filter). At each step, consider adding a higher order term to the model. Compute the (extra-sum-of-squares) F statistic for the null hypothesis that the new term is redundant, i.e., that the additional variance explained is insignificant. In SPM this is achieved by specifying the new term as a covariate of interest, with all previous terms and confounds as covariates of no interest. If there is evidence against the null hypothesis, the term is included and the next higher order term considered. If there is insufficient evidence against the null hypothesis, model selection stops. This approach to model selection is known as forward model selection in the statistical literature. Although possible, the smoothness of the expected stimulus–response function makes it unlikely that a higher order term (e.g., fourth order) can explain a significant amount of variance in the absence of any significant lower order

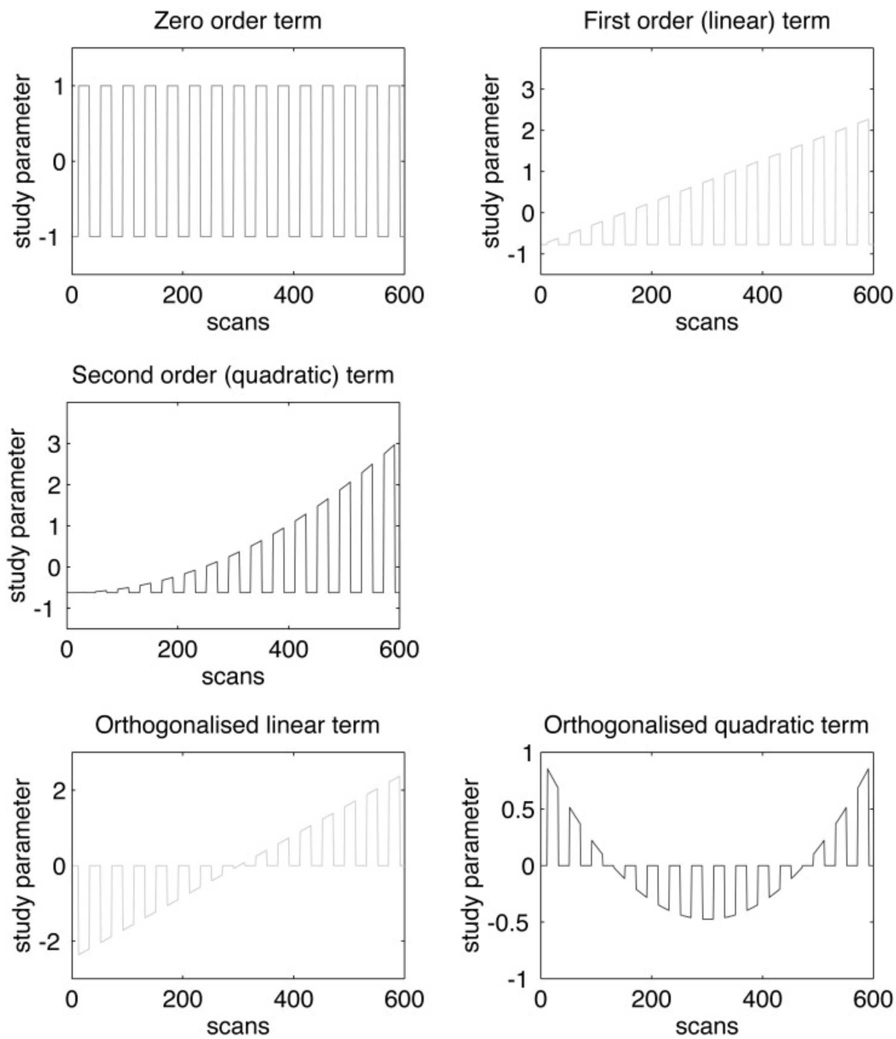

FIG. 1. A simple example to introduce the concept of a polynomial expansion in terms of the boxcar function typically used in fMRI. The first graph shows the standard boxcar function. The second and third show the first- and second-order terms, respectively. These are simply the element-wise product of a linear (or quadratic) term and the boxcar function. The lower graphs show the first- and second-order terms after orthogonalization.

terms (e.g., third order). An alternative approach to model selection is to start with the most complex model and work backward, toward more parsimonious models. We have chosen forward selection here for simplicity.

In the case of polynomials, the first- and second-order effects have an intuitive interpretation in terms of linear and nonlinear (i.e., quadratic) effects. This is the reason for using a polynomial expansion in our example. However, it should be noted that any basis set (e.g., wavelets, Fourier sets) can be used within the same framework described here.

Statistical parametric maps (Friston *et al.*, 1995b) can be considered spatially extended statistical processes. In general SPM uses the general linear model to build F- or t-statistic fields (i.e., SPM$\{F\}$ or SPM$\{t\}$). In the special case of parametric studies SPM$\{F\}$s are used to make inferences about the regression of BOLD signal on a study parameter (or the expansion of a study parameter).

The basic equation of the general linear model is

$$x_{ij} = g_{i1}\beta_{1j} + \cdots + g_{ik}\beta_{kj} + e_{ij}. \tag{1}$$

Here β_{kj} are k unknown parameters for each voxel j. The coefficients g are explanatory or modeled variables under which the observation (i.e., scan) was made. Comparing a standard polynomial expansion,

$$p(x) = p_1 x^n + p_2 x^{n-1} + \cdots + p_n x + p_{n+1}, \tag{2}$$

to Eq. (1), it is evident that this is simply a general linear model.

Standard procedures have been developed for applying the general linear model to serially correlated imaging time series, which provide voxel-specific parameter estimates (e.g., basis function coefficients) and statistics (F or t) assessing the significance of the explanatory effects designated interesting. Uninteresting effects are designated confounds. Images of the voxel-specific F statistics (SPM$\{F\}$) are used to make inferences that can be corrected for the volume analyzed using the theory of Gaussian random fields (Friston *et al.*, 1995b; Worsley, 1994).

AN EMPIRICAL EXAMPLE

It is known from PET studies that the rCBF in temporal regions shows a positive correlation with presentation rate of spoken words (Price *et al.*, 1992). As an example, we present data from a similar study using fMRI. We used five different presentation rates: 10, 15, 30, 60, and 90 words per minute. The order of blocked presentations was randomized. Between each word condition there was a period of silence for 34 s, equivalent to 20 scans.

Imaging was performed using a Siemens Magnetom Vision scanner (Siemens, Erlangen) operating at 2 T and equipped for echoplanar imaging. A gradient-echo echoplanar sequence was used to acquire 16 slices of thickness 3 mm and in-plane resolution of 3 × 3 mm (TR/TE 1700 ms/40 ms). The scanning session comprised 608 image volumes, starting with 8 dummy scans to allow for equilibration of T_1 saturation effects followed by 600 images for which baseline (no stimuli presented) alternated with activation (auditory stimuli presented) every 20 vol (34 s). Figure 2 shows the scanning procedure graphically. The first and last baseline conditions used 10 instead of 20 scans.

We demonstrate the analysis of this experiment using an orthogonal polynomial expansion, up to second order. The terms modeled represent an interaction between presentation rate r and a boxcar stimulus function box. The linear term is simply $lin = r \cdot box$ and the second-order term is $sec = r^2 \cdot box$. In general the nth-order term is given by $r^n \cdot box$. The orthogonalization of the first-order term with respect to the zeroth-order term was effected according to (Büchel and Friston, 1997)

$$lin^0 = lin - box(box^{\mathrm{T}}box)^{-1}box^{\mathrm{T}}lin, \qquad (3)$$

where lin^0 is the orthogonalized linear term lin. The orthogonalization of the second-order term with respect to the zeroth- and first-order terms is performed in a similar fashion,

$$sec^0 = sec - [lin^0 box]([lin^0 box]^{\mathrm{T}}[lin^0 box])^{-1}[lin^0 box]^{\mathrm{T}}sec, \qquad (4)$$

where sec^0 is the orthogonalized second-order term sec, with respect to the first- (i.e., lin^0) and zeroth-order effect (i.e., box). This serial orthogonalization can be applied up to any order, using any basis functions.

Since the order of different presentation rates was counterbalanced, the convolved boxcar (Fig. 3) looks different from the example in Fig. 1 (top). Figure 3 shows all three covariates (i.e., explanatory variables g_i): the standard boxcar function (i.e., zeroth order), the linear (i.e., first order) term, and the quadratic (i.e., second order) term. Note that prior to model fitting, these covariates are convolved with a hemodynamic response function (Friston *et al.*, 1995a). The first analysis used the simple boxcar, modeling the difference between word presentation and the silent baseline condition, irrespective of word rate. The design matrix is shown in Fig. 4 (right). This figure also shows the SPM$\{F\}$ thresholded at $P < 0.05$ (corrected). Significant areas include the periauditory regions, bilateral frontal regions, and regions at the occipitotemporal junction.

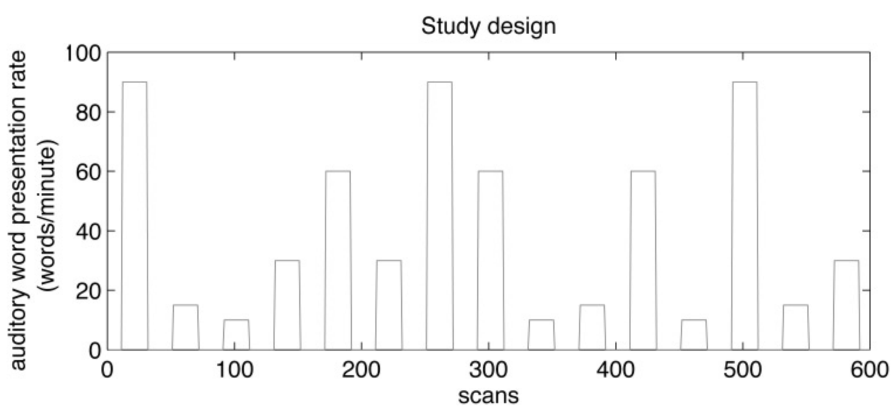

FIG. 2. The experimental design of the study. The different word rates were presented in random order and intercalated with a silent baseline condition.

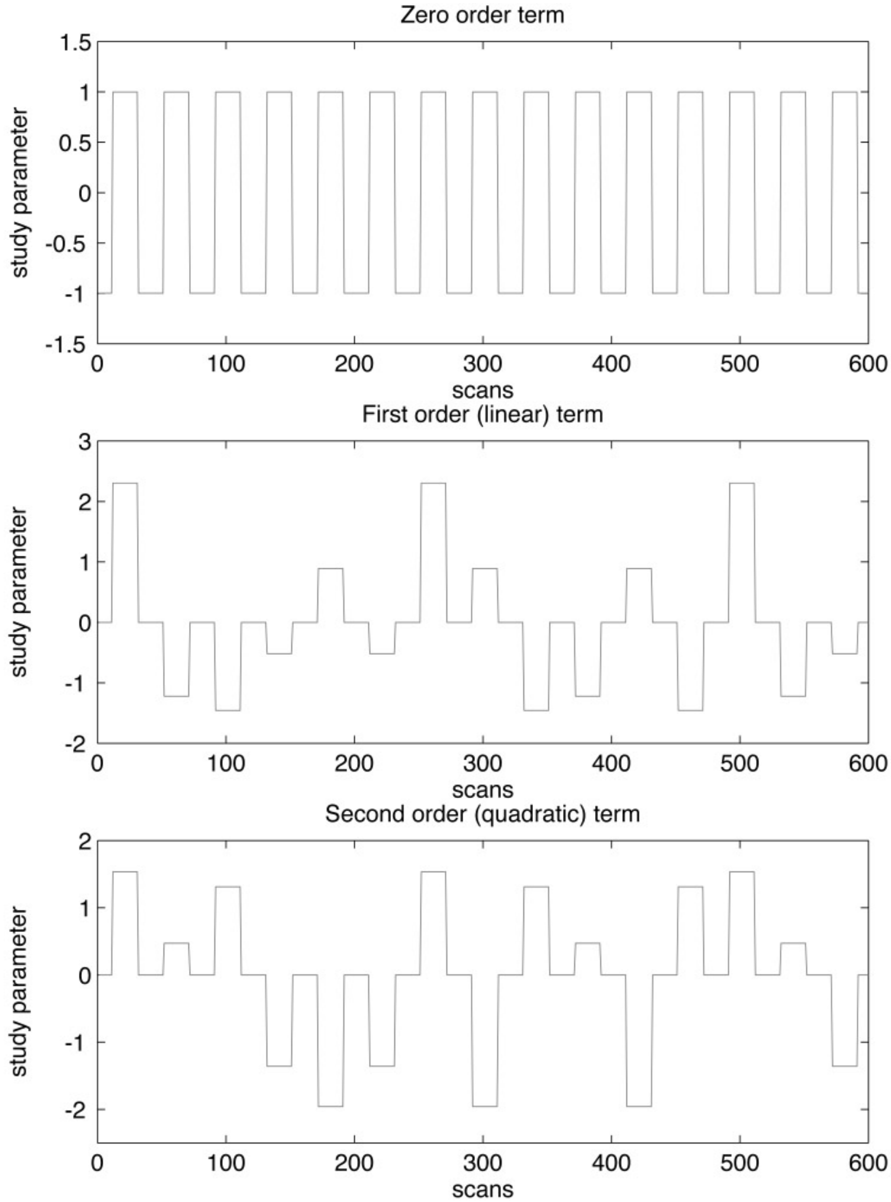

FIG. 3. The different regressors (zero-, first-, and second-order expansion of presentation rate) used in the model described in the text. Note the difference between the first-order term (middle) and that in Fig. 2. This is due to the fact that this first-order expansion is orthogonal to the boxcar function (top). The bottom shows the second-order (quadratic) term, again orthogonalized with respect to the other covariates.

In a second step we extended the analysis to allow for a linear relationship between word rate and BOLD signal changes. The design matrix is shown in Fig. 5. The only covariate of interest is the linear term (second graph in Fig. 3), the remaining columns (confounds or covariates of no interest) represent the zeroth-order term (standard boxcar—first graph in Fig. 3) and the cosine terms of the high-pass filter. The SPM$\{F\}$ for this model is shown in Fig. 5. The definition of the zeroth-order term as a confound is necessary as we are now interested only in those voxels for which the introduction of the first-order term can explain a significant amount of variance. Significant regions were again found in primary and secondary auditory cortices bilaterally and at the occipitotemporal junction. Note that bilateral frontal regions are not significant anymore. This is due to the fact that responses were sufficiently accounted for by the boxcar model. The introduction of a more comprehensive model (i.e., the first-order term) did not lead to a significant improvement in fit.

In the third step we tested whether the addition of a second-order term gave a better characterization of the relationship between BOLD signal and word rate. The design matrix for this second order model is shown in

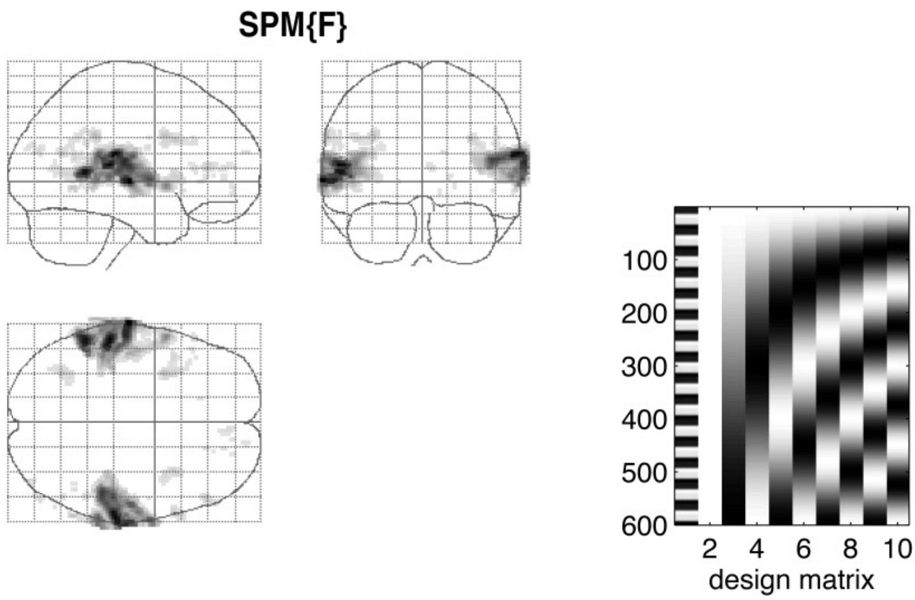

FIG. 4. SPM$\{F\}$ of the simple zeroth order model. The design matrix (right) shows the covariates used in this model. The first column models the difference between word presentation and baseline irrespective of word rate. Columns 2 to 10 represent the confound partition and include a constant (2) and cosine terms, modeling the high-pass filter. The SPM$\{F\}$ is shown as a maximum-intensity projection. The brain (left) is shown from right, top, and back. The map is thresholded at $P < 0.05$ (corrected). Significant regions include auditory and periauditory cortices, bilateral frontal areas, and areas at the occipitotemporal junction, bilaterally.

Fig. 6. Note that the only covariate of interest is the second-order or quadratic term. The linear term has now been moved to the confound partition of the design matrix. This allows us to assess the significance of the additional explanatory power of the nonlinear effect in the presence of the linear and zeroth-order terms. Figure 6 (left) shows the SPM$\{F\}$ thresholded at $P < 0.05$ (corrected). The significant voxels in this SPM$\{F\}$ are confined to bilateral posterior auditory association cortex at the temporoparietal junction.

Comparing Figs. 4, 5, and 6 it is evident that the significant clusters for each analysis overlap. With

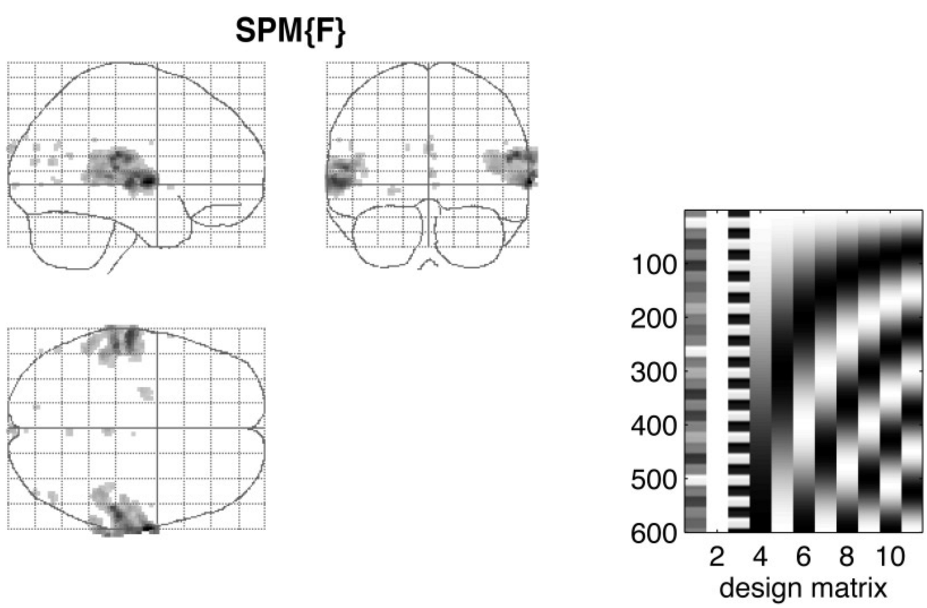

FIG. 5. SPM$\{F\}$ of the first-order (linear) model. The first column models the linear response to word rate. Columns 2 to 11 represent the confound partition and include a constant (2), the zeroth-order term (3), and cosine terms, modeling the high-pass filter. The SPM$\{F\}$ is thresholded at $P < 0.05$ (corrected). Significant regions include auditory and periauditory cortices and areas at the occipitotemporal junction bilaterally. Note that, in comparison to the zeroth-order model in Fig. 4, the frontal areas are no longer significant.

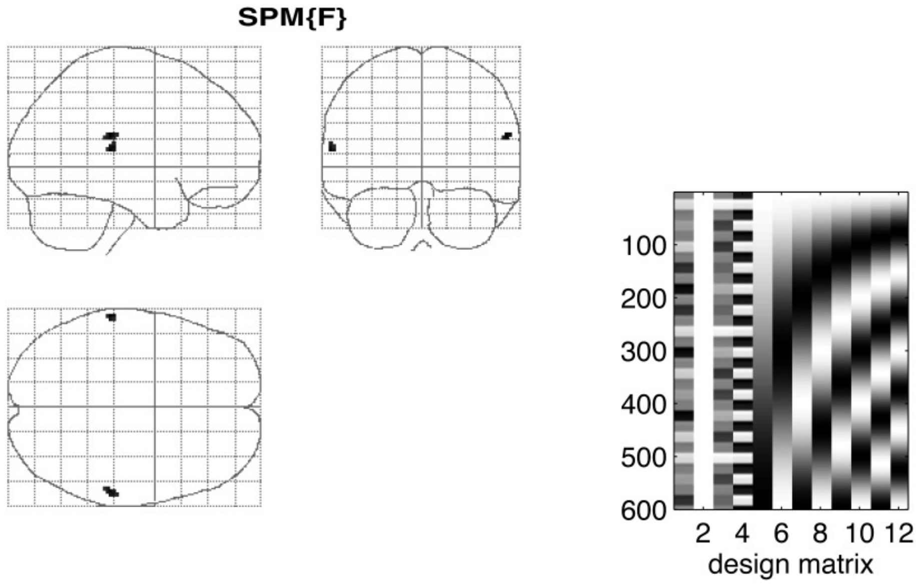

FIG. 6. SPM{F} of the second-order model. The first column of the design matrix reflects the second-order (quadratic) term modeling a nonlinear relationship between word-presentation rate and BOLD responses. Columns 2 to 12 represent the confound partition and include a constant (2), the zeroth-order (boxcar) term (4), the linear term (3), and the cosine terms, modeling the high-pass filter. The SPM{F} is thresholded at $P < 0.05$ (corrected). Significant regions are reduced to bilateral posterior periauditory regions. Note that in comparison to the linear model in Fig. 5 the regions at the occipitotemporal junction are no longer significant.

increasing the order of the model the regions of significant activation get smaller. Part of this effect is due to a reduction of sensitivity as the higher order terms "use up" degrees of freedom. It is also evident that some regions are significant in the zeroth-order model, but are not significant in the first- or second-order model. This indicates that the inclusion of a first or second term in the model does not account significantly for more of the variance in these voxels. Similarly other regions (e.g., the occipitotemporal regions) may show linear rate dependency but no nonlinear effects. Figure 7 shows the BOLD signal of three different regions plotted against word presentation rate to illustrate response profiles that show no rate dependency (prefrontal), linear dependency (occipitotemporal), and nonlinear dependency (posterior periauditory). Comparing the plots for the right frontal area with the region at the occipitotemporal region, or the peri-auditory region, suggests a reduced rate dependency. A further difference is evident between the curves from the periauditory region and the region at the occipitotemporal junction. Comparing Figs. 5 and 6 it is evident that the only region in which the introduction of a second-order term led to a significantly better fit is in bilateral posterior periauditory regions, but not in the occipitotemporal region.

In supplementary analyses differential response profiles among these regions could be tested for by looking for a region-by-condition interaction. However, this would be beyond the scope of voxel-specific inferences implicit in SPM.

DISCUSSION

The use of nonlinear basis functions in conjunction with the general linear model facilitates the detection of BOLD responses in brain regions that might not have been so evident using simple (i.e., linear) regression. The general approach using polynomial expansions can model a variety of nonlinear hemodynamic responses without prespecifying the exact form of the expected regression. Here we have extended this approach to fMRI, in which experimental and statistical model design, accounting for low-frequency components of the signal, required us to look for an interaction between the expansion and a boxcar function.

This technique may improve the discrimination of different regions that are active in the same task but with a different response. An example in our study is the dissociation of regions at the occipitotemporal junction, showing a linear relationship between BOLD signal and word presentation rate and periauditory regions that show an inverted U relationship between word rate and BOLD responses. This nonlinear effect in posterior periauditory cortex might be related to the fact that at a presentation rate of more than 60 wpm, implicit word processing becomes impossible and therefore the signal decreases again. A more physiological explanation relates to a hemodynamic or neural refractiveness as characterized in Friston *et al.* (1998). A nonlinear relationship between BOLD signal and the presentation rate of syllables has been previously reported (Binder *et al.*, 1994). The nonlinearity of the response was similar to the inverted U form presented

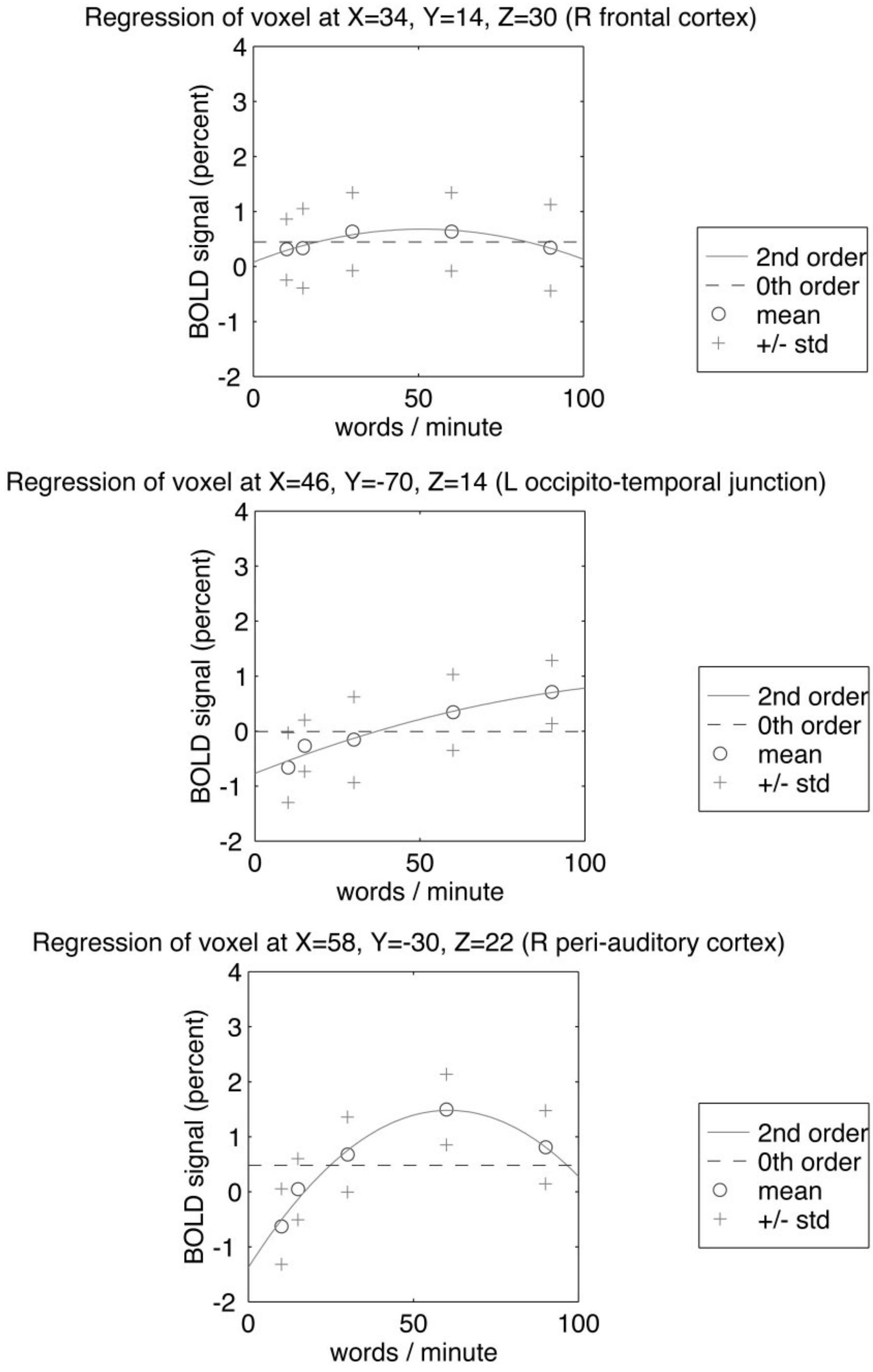

FIG. 7. Examples of different regressions for different brain regions. The top shows the relationship between word rate and hemodynamic responses in a right frontal area. A second-order polynomial fit (solid line) and the raw data (○) are shown. To demonstrate the nonsignificant difference with a zeroth-order fit (regression line parallel to the x axis), the zeroth-order fit is also plotted (dashed line). The middle shows the same plots for a region at the occipitotemporal junction, this time on the left. The difference between the dashed and the solid line clearly indicates the significant (Figs. 4 and 5) linear relationship between word rate and BOLD signal changes in this region. The bottom shows the regression of word rate on response for the periauditory region with a significant nonlinear response (Fig. 6). The inverted U shape shows a peak at about 60 wpm.

above. However, the form of their response showed an asymptotic effect at higher frequencies (120–150 syllables per minute), whereas in our study a decrease in activation between 60 to 90 words per minute is noted. This difference could be due to a shorter processing time for syllables relative to words, given their lack of meaning and the shorter duration.

Another example is the bilateral frontal activations that show only a weak dependency on word-presentation rate. These regions are activated during the word conditions relative to the silent baseline condition. The rate independence, in this prefrontal region, suggests some form of categorical (e.g., present–absent) response to the presentation of words, which might be linked to attentional processing or other discrete changes in cognitive set. Using a similar idea, Rees *et al.* (1997) dissociated different (phasic and tonic) attentional effects by manipulating stimulus presentation rate. It should be noted, however, that a region that is significant in the analysis using only a zeroth- and first-order term (Fig. 5) and a region that is significant with the full model (i.e., zeroth-, first-, and second-order terms —Fig. 6) may not be significantly different when compared directly (i.e., no significant region by effect interaction).

Although we have restricted our model to a second-order polynomial regression, other basis functions could be used. However, the interpretation of polynomial coefficients is more intuitive than coefficients of some other basis functions (e.g., cosines, exponentials). This may be important in an analysis in which the introduction of nonlinearity (i.e., second-order terms) improves the fit considerably, as has been demonstrated in this study. In general, questions about the number and type of basis functions are issues of model selection. We have demonstrated a simple approach to model selection in the case of hierarchical (orthogonal) polynomial models that involves sequential generation of SPM$\{F\}$s. Note that this approach allows the most appropriate model to be selected for each voxel.

In our example we used orthogonal basis functions. However, the technique presented here is perfectly valid if the basis functions are nonorthogonal. Although not dealt with explicitly, orthogonal basis functions allow a simpler analysis using t tests for the significance of each polynomial term. In this case the two-sided t test for the significance of a parameter estimate would be equivalent to the F test described above. We have chosen to illustrate the more general approach because it is not restricted to orthogonal basis functions and embodies a simple form of model selection.

CONCLUSION

We have presented a framework within which to analyze parametric activation studies using fMRI. We have dealt with fMRI-specific confounds by modeling effects of an experimental parameter on differences between baseline and activation instead of the signal per se. Using this analysis we are able to distinguish between three different types of responses to increasing word-presentation rate: (i) a categorical on–off response irrespective of word rate in bilateral prefrontal cortex, (ii) a linear relationship between activations and word rate at the occipitotemporal junction, and (iii) a nonlinear, inverted U relationship between word rate and hemodynamic responses in the posterior periauditory cortex. This demonstrates the strength of the approach, namely the facility to characterize different cortical regions by their response to task parameters. In conclusion we hope that this approach will provide a richer characterization of nonlinear brain responses to stimulus or task parameters using fMRI.

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