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Nonlinear Regression in Parametric Activation Studies

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Parametric study designs can reveal information about the relationship between a study parameter (e.g., word presentation rate) and regional cerebral blood flow (rCBF) in functional imaging. The brain's responses in relation to study parameters might be nonlinear, therefore the (linear) correlation coefficient as often used in the analysis of parametric studies might not be a proper characterization. We present a noninteractive method, which fits nonlinear functions of stimulus or task parameters to rCBF responses, using second-order polynomial expansions. This technique is implemented in the context of the general linear model and statistical parametric mapping. We also consider the usefulness of statistical inferences, based on *F* fields, about similarities and differences of these nonlinear responses in different groups. This approach is illustrated with a 12-run $H_2^{15}O$ PET activation study using an auditory paradigm of increasing word presentation rates. A patient who had recovered from severe aphasia and a normal control were studied. We demonstrate the ability of this new technique to identify brain regions where rCBF is closely related to increasing word presentation rate in both subjects without constraining the nature of this relationship and where these nonlinear responses differ.

INTRODUCTION

Based on the premise that regional cerebral blood flow (rCBF) varies with the amount of cortical processing engaged by an experimental task, parametric or correlational designs can reveal information about the relationship between a study parameter (e.g., word presentation rate), a behavioral response (e.g., reaction time), and rCBF. The variable being correlated can either be continuous (e.g., reaction time) or discrete (e.g., word presentation rate). Examples are studies by Grafton *et al.* (1992) who demonstrated correlations between rCBF and the performance of a motor tracking task in the supplementary motor area and thalamus. 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. rCBF in Wernicke's area, however, was not associated with increased word rate but with the presence or absence of semantic content. This example illustrates the ability of a parametrical approach to characterize and differentiate brain regions by their rCBF response slope in relation to the task parameters.

As the type of the relationship between parameters and rCBF varies in different brain regions and is unknown in advance, the a priori definition of a fit function (e.g., a linear function used with the correlation coefficient) might lead to an insufficient or partial result.

We present an extension of the current analysis of parametric studies to overcome this restriction. A noninteractive method, which regresses nonlinear functions of stimulus or task parameters on rCBF responses (using a multilinear regression with second-order polynomial expansions) is introduced. The proposed regression model is nonlinear in the explanatory variables but not in the unknown parameters. This is different from "nonlinear regression" in the statistics literature where unknown parameters are nonlinear. In the first part of this paper we will show how this approach is implemented in the context of the general linear model and statistical parametric mapping (SPM).

The second aspect of this work is to introduce the SPM$\{F\}$ as a useful tool in this context. We assess the goodness of fit using spatially extended *F* statistics [i.e., SPM$\{F\}$ instead of SPM$\{Z\}$ (Friston *et al.*, 1995)]. As parametric studies might reveal differences and similarities of rCBF response patterns in different groups, we also consider statistical inferences about similarities and differences of those nonlinear rCBF response patterns in group studies. This new approach is demonstrated and compared to a linear correlation with a parametric $H_2^{15}O$ positron emission tomography (PET) activation study.

METHODS

Digital signal processing utilizes different techniques to characterize discrete signals by a combina-

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tion of a number of basis functions. Well-known examples are the Fourier expansion and the polynomial expansion. We adapt this technique to characterize rCBF responses in terms of a set of basis functions of a given parameter (e.g., study parameter or response) and show how rCBF responses can be approximated by a small number of these basis functions.

In general the goodness of fit of the regression depends on the type and number of the basis functions chosen and on the number of data points to be approximated. We expect rCBF responses in cognitive activation studies to be smooth and monotonic. In the context of this paper we restrict ourselves to a PET activation study with 12 runs per subject, resulting in 12 data points for regression. Given the smoothness and small number of data points, a small set of basis functions is appropriate to characterize the relationship.

The first two basis functions of the discrete cosine transformation and a second-order polynomial expansion were studied. Comparison of the goodness of fit for both approaches showed no marked difference. Cosine basis functions revealed slightly better results in modeling ceiling or floor effects (see Figs. 1 and 2). However, the second-order polynomial expansions were chosen because the coefficients are easier to interpret. Concerning the number of basis functions, additional tests showed that increasing the order of the polynomials beyond 2 did not increase the goodness of fit dramatically, but lowered the degrees of freedom for available statistical inference. In general the issue of an optimal number and type of basis functions is the domain of model selection and this will be the topic of a subsequent paper.

SPMs (Friston *et al.,* 1995) can be considered spatially extended statistical processes. In general SPM uses the general linear model to build *t* statistics. In the special case of parametric studies it is used to make statistical inferences about the correlation of rCBF and a study parameter.

The basic equation of the general linear model is

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

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,

$$p(x) = p_1x^n + p_2x^{n-1} + \cdots p_nx + p_{n+1}, \qquad (2)$$

to (1), it is evident that this is another representation of the general linear model.

Equation (1) can be written in matrix format:

$$\mathbf{X} = \mathbf{G}\beta + \mathbf{e}. \qquad (3)$$

$\mathbf{G}$ is the design matrix, which has one row for every scan and one column for every modeled (i.e., "designed") effect, β is the parameter matrix which has one row for each column of $\mathbf{G}$ and one column for every voxel in the volume, and $\mathbf{e}$ is the matrix of error terms. For different explanatory variables the matrix $\mathbf{G}$ can be partitioned into several matrices or column vectors of interest $\mathbf{G_1}$ $\mathbf{G_2}$ and noninterest $\mathbf{H}$ $\mathbf{G} = [\mathbf{G_1G_2H}]$ each with a unique parameter in β ($\beta = [\beta_1\beta_2\gamma]$).

In our case the polynomial basis functions are the explanatory variables used to model rCBF responses at different voxels. As we restricted our analysis to a second-order polynomial expansion, the column vector $\mathbf{G_1}$ contains the explanatory variable itself and $\mathbf{G_2}$ contains the squared values of this variable. The least-squares solutions $\mathbf{b_1}$ and $\mathbf{b_2}$ of β_1 and β_2 ($\beta = [\beta_1\beta_2\gamma]$) are the coefficients $p = [p_1p_2]$ of a second-order polynomial [see Eq. (2)] that best models the relation between rCBF and the variable in question. As mentioned above, the design matrix also contains a partition of confounding effects $\mathbf{H}$ where effects of no interest, such as global blood flow and block effects, are modeled.

To test the overall significance of the effects of interest we test the null hypothesis that their introduction does not significantly reduce the error variance, which is equivalent to testing the hypothesis that both β_1 and β_2 are 0. Thus the error sum of squares, after discounting the effects of interest ($\mathbf{G}$) are given by

$$\mathbf{R}(\Omega_0) = (\mathbf{X} - \mathbf{H}\,\mathbf{g})^T(\mathbf{X} - \mathbf{H}\,\mathbf{g}), \qquad (4)$$

where $\mathbf{g}$ is the parameter estimate of γ. The alternative hypothesis includes the effects of interest. The error sum of squares and products under the alternative hypothesis is therefore given by

$$\mathbf{R}(\Omega) = (\mathbf{X} - \mathbf{G}\,\mathbf{b})^T(\mathbf{X} - \mathbf{G}\,\mathbf{b}), \qquad (5)$$

and the F statistic for voxel i is given by

$$F_i = \frac{r}{r_0 - r} \cdot \frac{R_i(\Omega_0) - R_i(\Omega)}{R_i(\Omega)}, \qquad (6)$$

where F has the F distribution with $r_0 - r$ and r degrees of freedom. In general $r_0 = N - \text{rank}(\mathbf{H})$ and $r = N - \text{rank}(\mathbf{G})$ where N is the total number of scans.

In our special case the F statistic reflects the goodness of the regression. An image of the F statistic at every voxel constitutes a SPM$\{F\}$. The SPM$\{F\}$ can be interpreted as an image of the significance of the variance explained by the parameters of interest (i.e., the polynomials in $\mathbf{G}$) relative to error.

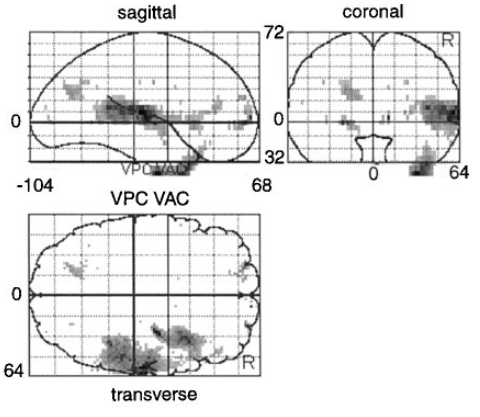
Due to the extremely large number of nonindependent univariate analyses, the probability that a region

reaches an uncorrected threshold by chance is very high. On the basis of the theory of Gaussian fields we characterize a local excursion of the SPM by its maximal F value. This simple characterization has a certain probability of chance occurrence. The probability of getting one or more voxel with a certain F value in a given SPM$\{F\}$ is the same as the probability that the largest F value of the SPM$\{F\}$ is greater than this F value. At high thresholds this probability equals the expected number of maxima. Therefore the problem of calculating a corrected P value can be reduced to finding the expected number of maxima at or above this threshold.

In a theoretical paper Worsley (1994) derived an equation for the probability that the largest F value of the SPM$\{F\}$ is greater than a threshold f on the basis of the smoothness of the underlying Gaussian component processes. The result in three dimensions is

$$P(F_{\max} \geq f) \approx \frac{\lambda(C)\det(\Lambda)^{\frac{1}{2}}\Gamma\left(\frac{1}{2}(m+n-3)\right)}{(2\pi)^{\frac{3}{2}}2^{\frac{1}{2}}\Gamma\left(\frac{m}{2}\right)\Gamma\left(\frac{n}{2}\right)} \cdot \left(\frac{nf}{m}\right)^{1/2(n-3)}\left(1+\frac{nf}{m}\right)^{-1/2(m+n-2)} \times \left\{(m-1)(m-2)\cdot\left(\frac{nf}{m}\right)^{2} - (2mn-m-n-1)\frac{nf}{m} + (n-1)(n-2)\right\}, \quad (7)$$

where f is the threshold, n and m are the degrees of freedom of the F statistic, $\lambda(C)$ is the Lebesgue measure of region C (here the number of voxels in the volume), and Λ is the variance–covariance matrix of the first derivate of the underlying Gaussian component pro-



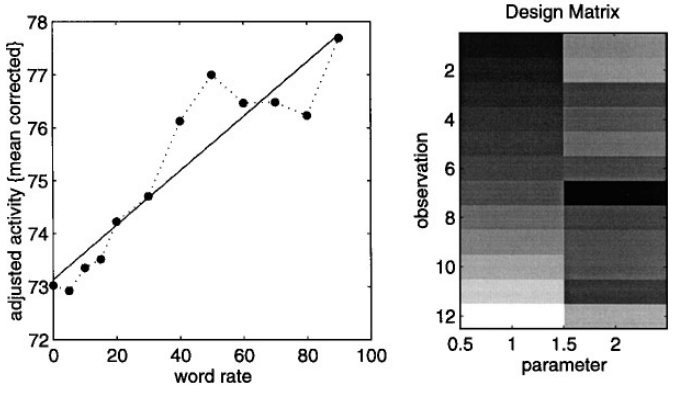
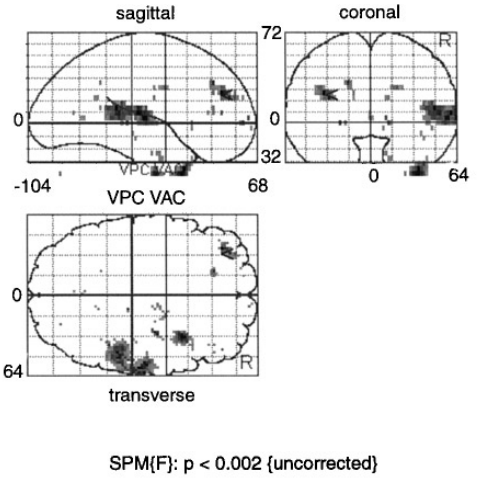


FIG. 1. SPM$\{F\}$ for linear regression in the patient who had recovered from an ischemic infarction in the territory of the left middle cerebral artery. Voxels over a threshold of $F = 15$ are shown. The plot shows adjusted activity in relation to word rate. The voxel investigated has the coordinates $x = 54$, $y = -18$, and $z = 4$ mm in respect to the standard space defined by Talairach and Tournoux (1988). $F = 75$; df 1, 9; $P < 0.0001$ (uncorrected).



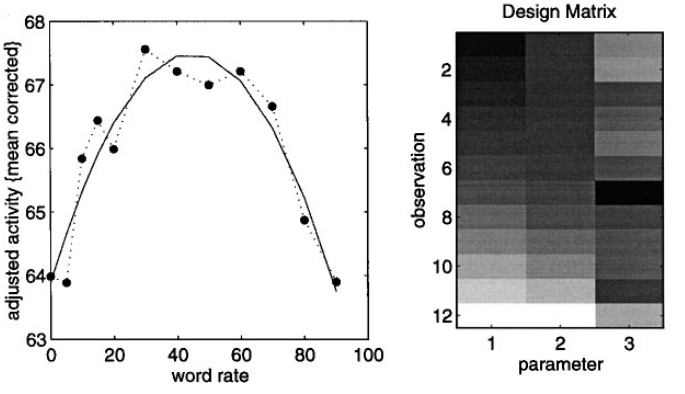
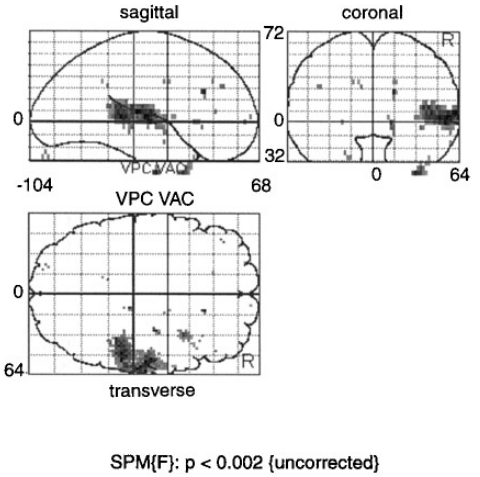


FIG. 2. SPM$\{F\}$ for nonlinear regression using polynomials. Voxels over a threshold of $F = 15$ are shown. The regression for a voxel in a left frontal region ($x = -34$, $y = 40$, and $z = 24$ mm) that was not apparent in the linear regression is shown. $F = 20$; df 2, 8; $P < 0.001$ (uncorrected).

cesses. $P(F_{\max} \geq f)$ therefore corresponds to a corrected P value for a voxel with $f = F$.

This general approach to parametric studies can also be extended to compare the nonlinear responses of different groups. This can be subdivided into statistical inferences on similarities and differences between groups. To test for differences, the polynomials appear twice in the design matrix. In the first partition the functions are replicated in both groups, whereas in the second partition the polynomials are inverted for the second group. This mirror-like appearance of the polynomial basis functions models differential responses in that case. The second, mirror part of the design matrix is the one of interest, whereas the first, symmetrical is a confounding covariate. Therefore the SPM$\{F\}$ is an image of the significance of the differences of rCBF responses in both groups. Defining the similarities as a confounding covariate in this case is necessary to make specific inferences about different rCBF responses in the two subjects.

To test for similarities, the symmetric polynomials (replicated for both groups) are covariates of interest and the SPM$\{F\}$ highlights where rCBF responses are similar in both groups.



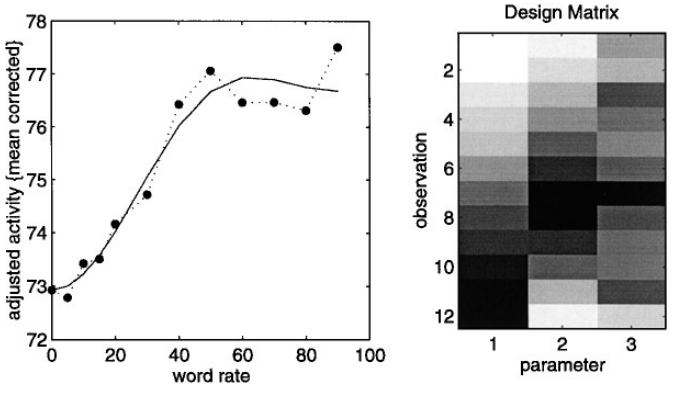
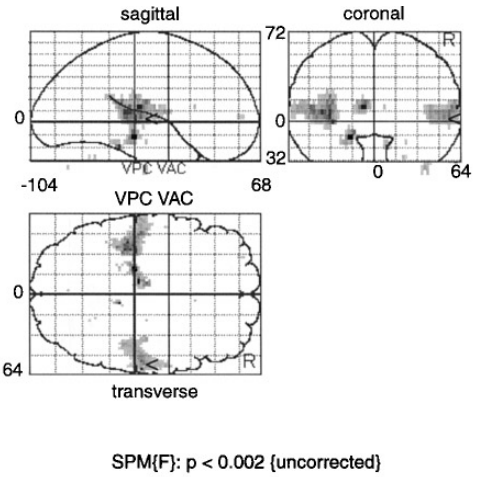


FIG. 3. As for Fig. 1 but using cosine basis functions instead of the linear regression. The regression for the same voxel as in Fig. 1 is plotted. $F = 63$; df 2, 8; $P < 0.0001$ (uncorrected). Note the ability of the cosine basis functions to better model floor and ceiling effects. The first two columns of the design matrix show the cosine basis functions.



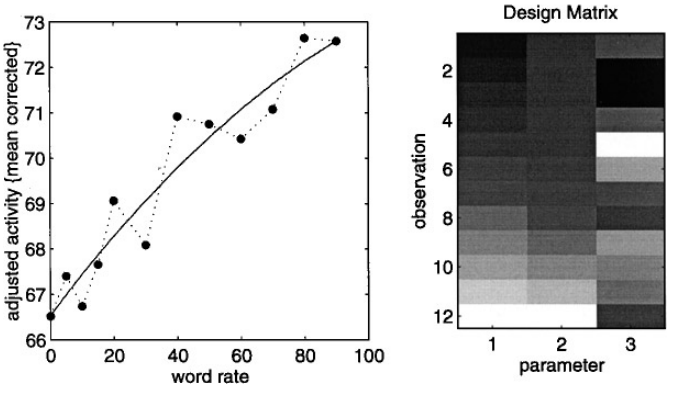


FIG. 4. SPM$\{F\}$ for nonlinear regression using polynomials in the control subject. Note the cluster of voxels in the left temporal region, absent in the patient. The plot for the same voxel as in Figs. 1 and 3 in the right superior temporal region is shown. $F = 37$; df 2, 8; $P < 0.0001$ (uncorrected).

AN EXAMPLE

The single case and comparison are illustrated with a 12-run $H_2^{15}O$ PET activation study using an auditory paradigm of increasing word presentation rates from 0 to 90 words per minute. The data were obtained with a CTI PET camera (Model 935B; CTI, Knoxville, TN). A patient, who had recovered from severe aphasia after an infarction largely confined to the left temporal lobe and involving the whole of the superior temporal gyrus, was studied. To illustrate the comparison of regression between different subjects, a normal volunteer was

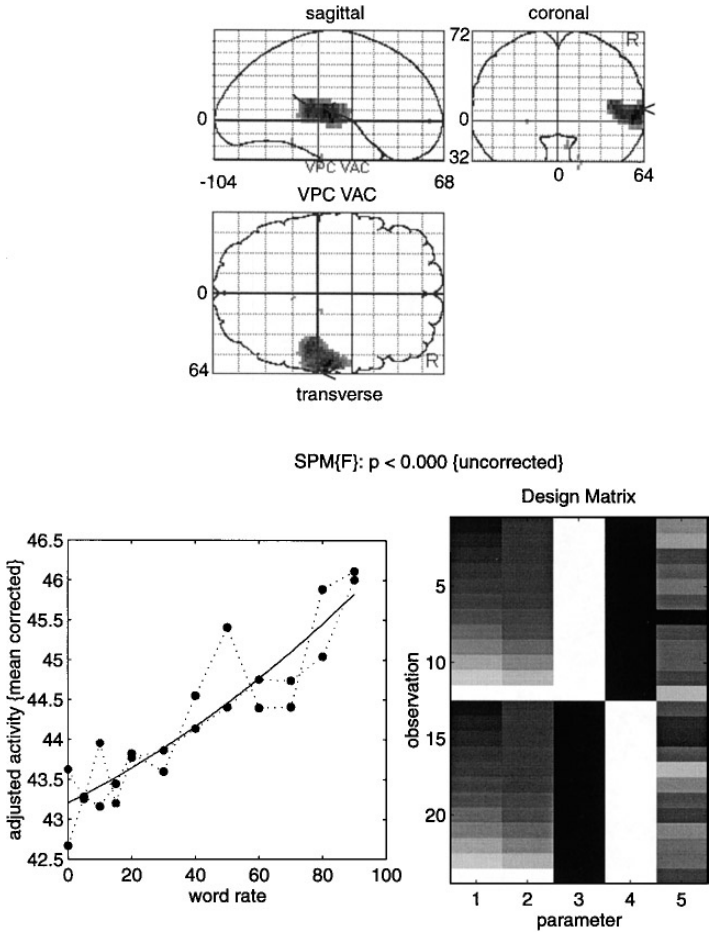


FIG. 5. SPM{*F*}, regression plot, and design matrix for the comparison of patient and control subject. Voxels over a threshold of $F = 15$ are shown. The regression for similar rCBF responses at a voxel *x*:62, *y*:−22, and *z*:12 mm are shown. $F = 49$; *df* 2, 19; $P < 0.0001$ (uncorrected).

investigated using the same paradigm. This paper emphasizes the implementation of this technique. Full results and neurobiological implications will be presented separately.

Figure 1 illustrates the standard linear approach and shows the SPM{*F*} in a maximum intensity projection, the corresponding design matrix in image format, and the regression plot for the patient. The SPM{*F*} shows voxels over a threshold of $F = 15$. Significant regions include the right perisylvian area and parts of the anterior temporal lobe. The linear regression of a voxel ($x = 54$, $y = -18$, and $z = 4$ mm; $F = 75$; *df* 1, 9; $P < 0.0001$ [uncorrected]) in the periauditory cortex is shown. Comparing the nonlinear approach shown in Fig. 2 to this SPM{*F*}, an additional area in the left frontal region reaches significance at the same threshold. As expected, the regression of this voxel (*x*:−34, *y*:40, *z*:24 mm) shows a highly nonlinear ("U-shaped") rCBF response in relation to word-rate (Fig. 2, bottom). As described above, the *F* values represent the significance of the variance introduced by the parameters of interest. In our case the *F* values directly reflect the goodness of fit. The solid line is the graphical representation of the regression and demonstrates the ability of the technique to approximate nonlinear rCBF responses.

Figure 3 shows the SPM{*F*} and regression plot of the same voxel as in Fig. 1 using cosine basis functions. The design matrix contains the two cosine basis functions and the values of global blood flow, defined as a covariate of no interest. Cosine basis functions are able to model floor and ceiling effects slightly better than the polynomials: $F = 63$ for the cosine and $F = 43$ for the polynomials (regression not shown), both *df* 2, 8. The higher *F* value ($F = 75$) for the linear regression at this voxel compared to the nonlinear techniques (polynomials $F = 43$, cosine basis functions $F = 63$) is related to fewer degrees of freedom by introducing a second covariate of interest in the nonlinear case. When the regressions of Figs. 1 and 3 are compared visually, the better fit through the cosine basis functions is evident.

Figure 4 shows a corresponding plot at the same voxel as in Figs. 1 and 3 for the normal subject. Note the

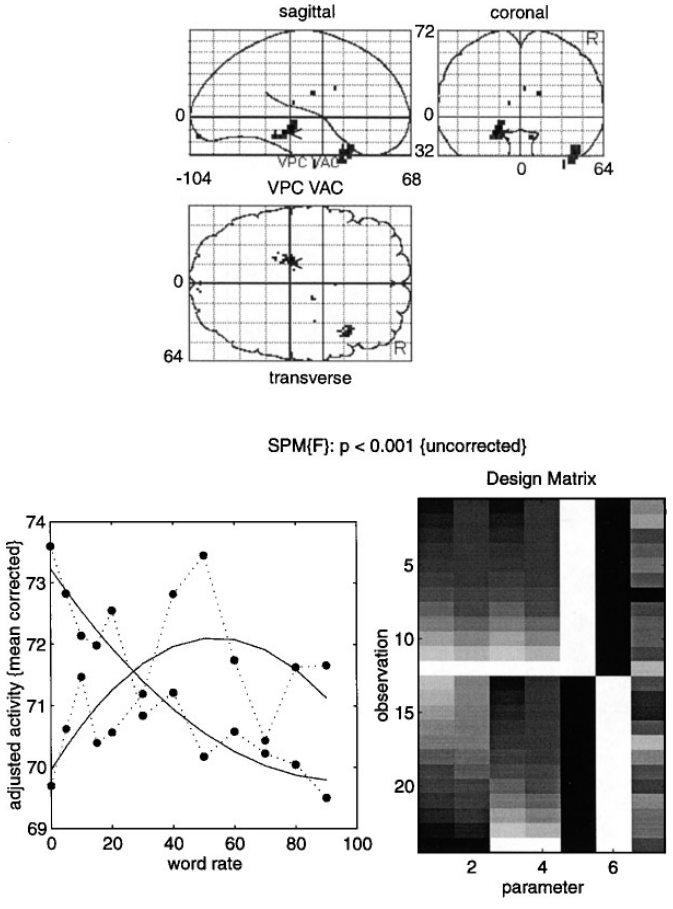


FIG. 6. SPM$\{F\}$, regression plot, and design matrix for the differences of rCBF responses in the patient and the control subject. Voxels over a threshold of $F = 10$ are shown. Regression for differential rCBF responses at a voxel x:−18, y:−26, and z:−12 mm are shown. $F = 17$; df 2, 17; $P < 0.0005$ (uncorrected).

similar rCBF response in the right temporal region. The control subject also shows a significant area in the left temporal region (an area that was involved by infarction in the patient).

SPM$\{F\}$ for similarities and plots of word rate against rCBF at a voxel in the right temporal region [x:62, y:−22, z:12 mm with respect to the standard space defined by Talairach and Tournoux (1988)] for both subjects and the design matrix in image format are shown in Fig. 5. The analysis shown reveals areas where rCBF responses to the study parameter are similar in the patient and in the control subject. The first two columns of the design matrix are the covariates of interest (i.e., commonalities). Confounding covariates are global blood flow (column 5) and block effects (columns 3 and 4). Since the patient did not show any significant regression in the left temporal region (see Fig. 1), the significant similarities are restricted to the right superior temporal region as shown in Fig. 5.

Figure 6 demonstrates the statistical inference about differences of rCBF responses to parameter for different groups. The first two columns of the design matrix are the covariates of interest (i.e., differences). Confounding covariates are the commonalities (columns 3 and 4), global blood flow (column 7), and block effects (column 5 and 6). There are two maxima apparent in the maximum intensity projection of the SPM$\{F\}$. To demonstrate the nonlinear regression we have chosen a voxel in the left hippocampus (x:−18, y:−26, z:−12 mm). Note the decrease of rCBF in relation to increasing word rates in the control subject, whereas the patient shows an increase in rCBF.

DISCUSSION

The application of a general nonlinear fitting technique allows detection of rCBF responses in brain regions which might not have been so evident using simple (i.e., linear) correlation coefficients. The general approach using polynomial expansions avoids predefined fit–functions and is able to model a variety of nonlinear rCBF responses without specifying the form of the expected regression.

Using this technique different brain areas can show differential responses to a study parameter, which can then be used to characterize each area involved in this task. On the other hand this technique may also improve the discrimination of different, but spatially nearby, areas, which are active in the same task but with different rCBF responses. A clinical application in this respect could be the investigation of cortical reorganization after cerebral injury (e.g., trauma or stroke) as well as physiologic correlates of learning. A possible study design could look for different responses in anatomically defined language areas (e.g., Broca's and Wernicke's area) in normal controls and compare those findings with data from patients suffering from different types of aphasia after a stroke, as shown in our example.

Although we have restricted our model to a second-order polynomial regression, other basis functions could be used. The use of cosine basis functions has some advantages in modeling ceiling or floor effects; however, the interpretation of polynomial coefficients is more intuitive than interpreting coefficients of cosine basis functions (i.e., a decomposition into linear and nonlinear effects). This may be important in experimental analysis where the introduction of nonlinearity (second-order polynomial) considerably improves the fit. In general the question of number and type of basis functions is an issue of model selection.

Statistical inferences on basis of the SPM$\{F\}$ reported here are uncorrected for multiple comparison. In those circumstances where a precise a priori anatomical

hypothesis exists, the correction of *P* values for multiple comparisons is not necessary. However, in cases where it is impossible to predict the spatial localization of the activation or in the case of activation outside the hypothesized area, reporting uncorrected *P* values is not statistically appropriate. Based on the equation given by Worsley (1994), it should be possible to estimate corrected *P* values on the basis of the theory of Gaussian fields. This depends on estimating the smoothness of the components of the *F* field and will be the subject of a subsequent article.

We have demonstrated nonlinear regression in the context of a PET activation study. Another major application is functional magnetic resonance imaging or magnetencephalography. Those imaging techniques allow repeated measurements on the same subject over a short period of time, which make them especially eligible for correlational or parametric designs. In general the technique presented here can be applied to those large data sets but the number and type of basic functions might have to be adjusted according to the nature of the rCBF response.

In conclusion, we hope that this novel approach will provide a richer characterization of nonlinear brain responses to stimulus or task parameters.

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REFERENCES

Friston, K. J., Holmes, A. P., Worsley, K. J., Poline, J. B., Frith, C. D., and Frackowiak, R. S. J. 1995. Statistical parametric maps in functional imaging: A general linear approach. *Hum. Brain Map.* **2:**189–210.

Grafton, S., Mazziota, J., Presty, S., Friston, K. J., Frackowiak, R. S. J., and Phelps, M. 1992. Functional anatomy of human procedural learning determined with regional cerebral blood flow and PET. *J. Neurosci.* **12:**2542–2548.

Price, C., Wise, R. J. S., Ramsay, S., Friston, K. J., Howard, D., Patterson, K., and Frackowiak, R. S. J. 1992. Regional response differences within the human auditory cortex when listening to words. *Neurosci. Lett.* **146:**179–182.

Talairach, P., and Tournoux, P. 1988. *Co-planar Stereotactic Atlas of the Human Brain: 3-Dimensional Proportional System: An Approach to Cerebral Imaging.* Thieme Verlag, Stuttgart/New York.

Worsley, K. J. 1994. Local maxima and the expected euler characteristic of excursion sets of χ^2, F and t fields. *Adv. Appl. Probl.* **26:**13–42.