Using Larger Dimensional Signal Subspaces to Increase Sensitivity in fMRI Time Series Analyses

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Abstract: It has been explained previously how using large dimensional signal-subspaces can reduce/eliminate bias in the estimated fMRI response (Burock and Dale [2000]: Hum Brain Mapp 11:249–260). It has also been explained how one can project this less biased estimate onto a one-dimensional subspace of interest (Burock and Dale [2000]: Hum Brain Mapp 11:249–260). In cases where there are multiple, correlated characterized response components per event type, separately projecting the full hemodynamic response onto one-dimensional subspaces of interest can lead to bias. We present an approach for both estimating the full hemodynamic response and obtaining from it unbiased estimates of effects of theoretical interest (in the context of ordinary least-squares estimation). The latter estimates are identical to those obtained by projecting the original data into the space defined by the (possibly multi-dimensional) effects of theoretical interest, but the ensuing statistical inference can be more sensitive. *Hum. Brain Mapping 17:13–16, 2002.* © 2002 Wiley-Liss, Inc.

Key words: fMRI; regression; restriction; basis

INTRODUCTION

Blood oxygenation level dependent functional magnetic resonance imaging (BOLD fMRI) yields time series reflecting the oxygenation state of hemoglobin in venous blood [Kwong et al., 1992; Ogawa et al., 1993]. Changes in neural activity lead to changes in fMRI signal under normal physiological conditions [Ogawa et al., 1998; Logothetis et al., 2001]. Testing for such temporal changes in fMRI signal using the general linear model (GLM) [Friston et al., 1995; Worsley and Friston, 1995] can be conceptualized as comprising two sequential steps. In the first, the entire data vector is projected into the column space of a design matrix (i.e., a set of predictor variables is simultaneously fit to the data). Of particular relevance here is that the residuals of this initial fitting stage are used to generate an estimate of the error variance, which plays a crucial role in subsequent statistical tests (*t*- or *F*-tests). To avoid bias in the estimated error variance, the design matrix should ideally be able to represent any possible response [Johnston, 1972]. In the second step, fit components of theoretical interest are tested for statistical significance. These fit components are specified by contrast vectors, which constrain (or restrict) the aspect of the fit being tested. This note concerns the use of restriction matrices [Johnston, 1972; Burock and Dale, 2000] to test for particular fMRI response components at the contrast stage when using a design matrix that initially allows for more lenient response fitting.

It will be useful to introduce the concept of characterized and uncharacterized response components. Charac-

Contract grant sponsor: NIMH; Contract grant number: 1 R03 MH63627-01.

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Received for publication 28 August 2001; accepted 4 February 2002
DOI 10.1002/hbm.10036

terized components of the response are defined as those that have scientific meaning or are plausible based on the current state of knowledge about the system under study. Most likely, such meaning will have been acquired by a response component through its consistent previous observation. By this definition, characterized waveforms (but not their weightings) are known before the performance of the experiment. Note that characterized components can contain both effects of interest and effects of no-interest [Friston et al., 1995] relative to the hypothesis being tested. Uncharacterized components are defined as being not explicitly known a priori, and so are simply taken to be the orthogonal complement of the characterized components with respect to some larger space (see Theory). Admitting the possibility of uncharacterized components allows (albeit, in a limited sense) for unexpected yet systematic behavior of the fMRI response.

THEORY

Restriction matrices

Although the concept of restriction matrices is basic to the GLM [Johnston, 1972], Burock and Dale [2000] explicitly introduced the concept of restriction matrices to the fMRI literature. Their specific approach will be subsequently referred to as "B&D" in the current note.

A k' by k restriction matrix $\mathbf{R}$ allows one to test for the presence of signal in a given k' ($1 \leq k' \leq k$) dimensional subspace of the columns of a rank k design matrix ($\mathbf{G}$). Each row of $\mathbf{R}$ is simply a contrast vector. $\mathbf{R}$ may thus be considered a k'-dimensional contrast. The null hypothesis, H_o, is expressed as

$$H_o: R\beta = q \quad (1)$$

where $\mathbf{q}$ is a k' by 1 vector whose ith row represents the amplitude under H_o of the ith contrast ($\mathbf{q} = \mathbf{0}$ in most fMRI applications), and β is the parameter vector of the design matrix [Johnston, 1972; Worsley and Friston, 1995]. H_o can be assessed with an F-test for general k', though only the special case of $k' = 1$ will be explicitly considered here. Note that β is estimated at the initial fitting step using $\mathbf{G}$, whereas $\mathbf{R}$ comes into play only at the contrast specification step.

As mentioned in the Introduction, systematic components in the data that are not in the span of the design matrix will positively bias the estimate $\hat{\sigma}^2$ of the error variance. The utility of the restriction matrix approach is that it allows one to estimate characterized effects while initially modeling the signal in a larger subspace. By doing so, one attempts to model more systematic components in the data, and hence reduce the bias on $\hat{\sigma}^2$ (Johnston, 1972). The goal of this note concerns the specification of $\mathbf{R}$ such that $\mathbf{R}\hat{\beta}$ is an unbiased estimator of a desired linear combination (represented by the contrast vector $\mathbf{c}$) of characterized waveform amplitudes regardless of whether the characterized components are explicitly represented in the large design matrix. B&D dealt with this problem for a special case; this special case and its limitations are discussed below.

In B&D, the temporal response to each type of event is modeled in the design matrix with a standard basis (i.e., the response amplitude at each peri-stimulus time point is separately represented). As a consequence, β in B&D directly represents the temporal response to the modeled events; $\mathbf{R}$ is simply taken to comprise the appropriately weighted, hypothesized waveforms themselves. B&D implicitly assumes that there is only one characterized response associated with each event type. This assumption was valid for their simulations. A problem arises, however, if there are multiple, correlated characterized waveforms per event type, as can arise in certain designs [Zarahn, 2000]. In such cases, estimation of the desired linear combination of characterized waveform amplitudes with B&D is biased. A second issue is that it is not immediately obvious what form $\mathbf{R}$ should have when event-related responses are modeled in the design matrix other than with a standard basis. Below, the choice of $\mathbf{R}$ is generalized to deal with these issues.

General restriction matrix approach

The specification of $\mathbf{R}$ is a change-of-bases problem. Details of the derivation are not presented. The expectation of the fMRI response[2] $\mathbf{y}$ is assumed to be representable in two k dimensional temporal bases, which are the column spaces of $\mathbf{G}_A$ and $\mathbf{G}_B$

[1]In that paper, feasible generalized least-squares was used instead of ordinary least-squares estimation. Though this does not fundamentally change the approach to be described, the assumptions of orthogonality are slightly different under the two types of estimation. Therefore, the current method only properly pertains to ordinary least-squares estimation.

[2]To clarify, $\mathbf{y}$ is the fMRI response for an entire experiment, and is not necessarily a single "event-related" response. Thus, $\mathbf{y}$ can contain overlapping responses from multiple occurrences of multiple event types.

$$E[\mathbf{y}] = G_A\beta_A = G_B\beta_B. \quad (2)$$

Moreover, $\mathbf{G}_A$ and $\mathbf{G}_B$ are assumed to share the same column space. The heuristic distinction made between the two bases is that $\mathbf{G}_A$ is constructed based on some minimal constraint (e.g., finite duration response), whereas $\mathbf{G}_B$ is constructed in part based on stronger prior knowledge. In particular, $\mathbf{G}_B$ is partitioned to reflect the possibility that the fMRI response can possess both characterized[3,2] and uncharacterized components

$$G_B = [G_c\ G_u] \quad (3)$$

where the columns of $\mathbf{G}_c$ define a characterized basis and the columns of $\mathbf{G}_u$ define an uncharacterized basis. Let β_A be the parameter vector in the GLM corresponding to $\mathbf{G}_A$, and let β_c be the partition of the parameter vector of $\mathbf{G}_B$ corresponding to $\mathbf{G}_c$. In practice, β_A will be estimated, even though the hypotheses of interest are most transparently expressed as linear combinations of β_c. The restriction matrix problem is to find an $\mathbf{R}$ such that $E[\mathbf{R}\hat{\beta}_A] = c^T\beta_c$.

By definition, an explicit form for $\mathbf{G}_u$ will not be known. It was explained previously how $\mathbf{G}_u$ is taken to be the orthogonal complement of $\mathbf{G}_c$ with respect to $\mathbf{G}_A$ (such that $\mathbf{G}^T_c\mathbf{G}_u = \mathbf{0}$). If this assumption is adopted, $\mathbf{G}_u$ does not even need to be given an explicit form, and subsequent computations are made very simple.

Given these hypotheses, a unique solution to the problem of finding an $\mathbf{R}$ such that $E[R\hat{\beta}_A] = c^T\beta_c$ is to let

$$\mathbf{R} = \mathbf{c}^T(\mathbf{G}_c^T\mathbf{G}_c)^{-1}\mathbf{G}_c^T\mathbf{G}_A. \quad (4)$$

Although $\mathbf{R}\hat{\beta}_A$ possesses the same variance as $\mathbf{c}^T\hat{\beta}_c$ ($\hat{\beta}_c$ being the estimate of β_c computed directly from the data using $\mathbf{G}_c$ as the design matrix), their estimated variances can be systematically different. This is because if $\mathbf{G}_c$ were used as the design matrix, signal components in the span of the column space of $\mathbf{G}_u$ would contribute systematically to $\hat{\sigma}^2$.

RESULTS

Bias in $\hat{\sigma}^2$ due to possibly incomplete modeling of fMRI responses with solely characterized components was examined in an event-related design involving the subject being presented letters to be remembered across a delay.[4] Define $\%\Delta\hat{\sigma}^2$ as

$$\%\Delta\hat{\sigma}^2 = 100 \cdot \frac{\hat{\sigma}_c^2 - \hat{\sigma}_A^2}{\hat{\sigma}_A^2}$$

where $\hat{\sigma}_c^2$ and $\hat{\sigma}_A^2$ are the estimated error variances obtained from using $\mathbf{G}_c$ and $\mathbf{G}_A$ as the design matrices, respectively. $\%\Delta\hat{\sigma}^2$ averaged across all voxels in the brain was 12.8%. When restricted to the suprathreshold[5] local maxima for the *t*-test (using $\hat{\sigma}_c^2$ as $\hat{\sigma}^2$) assessing the amplitude of neural responses to the letter presentation, $\%\Delta\hat{\sigma}^2$ was 25.7%. This suggests that in this dataset, the stronger the expression of characterized response components, the stronger the expression of uncharacterized response components.

DISCUSSION

It is well known that bias in error variance estimation might be mitigated by using a design matrix that can represent all plausible response components, as opposed to simply those of clear theoretical interest [Johnston, 1972]. A method has been presented for specification of restriction matrices to allow for the estimation of desired linear combinations of characterized fMRI waveform amplitudes when using such 'larger' design matrices. The approach as described is valid for ordinary least-squares estimation of GLM parameters (e.g., as employed in the SPM99 package; Wellcome Department of Neurology), though it could be easily extended to generalized least-squares estimation [Burock and Dale, 2000]. Unlike B&D, this approach is not limited to standard bases and yields unbiased estimates even when there are multiple, correlated characterized components per event type [Zarahn, 2000].

[3]For clarity, $\mathbf{G}_c$ itself could be partitioned into effects of interest and those of no-interest [Friston et al., 1995]. This has no effect on estimation.

[4]Sternberg Item Recognition Paradigm [Sternberg, 1966]; GE EPI-BOLD 5.7, TR/TE = 3,000/50 msec, flip angle = 90°, FOV = 24 cm, matrix = 64 × 64, slice thickness = 7 mm, 15 axial slices; data processing and analysis performed with SPM99 (Wellcome Department of Neurology); the columns of $\mathbf{G}_A$ comprised a Fourier series (order = 4, fundamental period = 36 sec); data were spatially smoothed with an isotropic Gaussian kernel (FWHM = 8 mm); the columns of $\mathbf{G}_c$ comprised convolutions of a hemodynamic response function (using the default parameters in SPM99) with rect functions corresponding to event components [Zarahn, 2000]; patient was a 19-year-old female diagnosed with schizophrenia.

[5]$\alpha = 0.05$, corrected for multiple comparisons using Gaussian random field theory as implemented in SPM99 [Worsley et al., 1996].

Assumed orthogonality of characterized and uncharacterized components

Andrade et al. [1999] discussed how orthogonalizing predictor variables with respect to others changes inference on the coefficients of the latter. For example, say non-orthogonal predictors **e** and **f** comprise a design matrix [**e f**]. Imagine that **e** is orthogonalized with respect to **f** (yielding **e***), and that a new design matrix [**e*** **f**] is created. The coefficient of **f** obtained using this design matrix will reflect the expression of both **e** and **f** in the data. That is, the coefficient of **f** in the context of **e*** will be biased with respect to the coefficient of **f** that would have been obtained from the original design matrix, [**e f**].

As characterized and uncharacterized components are assumed to be orthogonal in the current method, one might contemplate the question "What if the characterized and uncharacterized components are not actually orthogonal? Would not inference on the characterized components then be biased by the orthogonalization?" The answer is subtle: recall that we do not start off with a set of known uncharacterized components that are then orthogonalized with respect to the characterized components. Rather, we simply define the uncharacterized components as the orthogonal complement of the characterized components with respect to some larger space. This does not obviate the point of Andrade et al. [1999], but simply reflects the fact that the definition of the characterized components (and so the uncharacterized components) depends on the current state of knowledge about the fMRI response. Furthermore, as explained below, it is not the case that the current method involves orthogonalization of known effects of no-interest relative to effects of interest.

Contrasting characterized/uncharacterized and interest/no-interest

The dichotomy of characterized and uncharacterized effects used here is not identical to that of effects of interest and effects of no-interest [Friston et al., 1995]. The relationship between the two dichotomies is that although every effect of interest is a characterized effect (and every uncharacterized effect is an effect of no-interest), there can be characterized effects that are effects of no-interest. In fact, every effect that one can represent explicitly before the performance of the experiment is a characterized effect, and characterized effects need not be mutually orthogonal. Therefore, one need not be concerned that the orthogonality assumption will induce confounding of effects of interest by characterized effects of no-interest [Andrade et al., 1999].

The characterized/uncharacterized dichotomy is not practically relevant in most (non-fMRI) GLM applications. This is because in almost all regression circumstances one deals solely with characterized response components, whether they are of interest or not. For example, consider a psychological study in which the effect of age on reaction time is under examination, with gender and IQ included as effects of no-interest in the GLM. In this example, not only the effect of interest (age) but also the effects of no-interest (gender and IQ) would fall into the class of characterized effects.

NOTE

The MATLAB 5.3 (Mathworks, South Natick, MA) code used in conjunction with the SPM99 program (Wellcome Department of Neurology) implementing the theory outlined in this work is available from the author.

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