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Multidimensional Wavelet Analysis of Functional Magnetic Resonance Images

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Abstract: Analysis of functional magnetic resonance imaging (fMRI) data requires the application of techniques that are able to identify small signal changes against a noisy background. Many of the most commonly used methods cannot deal with responses which change amplitude in a fashion that cannot easily be predicted. One technique that does hold promise in such situations is wavelet analysis, which has been applied extensively to time-frequency analysis of nonstationary signals. Here a method is described for using multidimensional wavelet analysis to detect activations in an experiment involving periodic activation of the visual and auditory cortices. By manipulating the wavelet coefficients in the spatial dimensions, activation maps can be constructed at different levels of spatial smoothing to optimize detection of activations. The results from the current study show that when the responses are at relatively constant amplitude, results compare well with those obtained by established methods. However, the technique can easily be used in situations where many other methods may lose sensitivity. *Hum. Brain Mapping 6:378–382, 1998.* © 1998 Wiley-Liss, Inc.

Key words: wavelets; functional magnetic resonance imaging; image analysis; activation mapping

INTRODUCTION

A fundamental statistical problem in the analysis of functional magnetic resonance imaging data is the identification of those brain regions showing significant hemodynamic responses to an experimental stimulus. In a typical experiment involving blood oxygen level-dependent (BOLD) contrast [Ogawa et al., 1993] and using an magnetic resonance imaging (MRI) system with a 1.5 Tesla magnet, the local signal change during activation might be only 1–2%. The small relative size of the change in image intensity and the existence of possible artifacts, particularly movement, which can produce changes of similar magnitude, have led to intensive work in MRI physics and statistics to optimize identification of activated brain regions.

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A large number of statistical approaches have been investigated in the quest for optimal sensitivity and specificity in analysis of fMRI time-series [Lange, 1996; Rabe-Hesketh et al., 1997]. In common with many other centers, our group has made extensive use of periodic alternation of experimental conditions (often called "A/B designs") in paradigm design. Such experiments lend themselves to a variety of analytic approaches, including simple t-tests between the pooled data in the two states, correlational analysis, Kolomorov-Smirnov tests, and approaches based on Fourier-based analysis at the frequency of alternation of the experimental conditions. The last approach has the advantage of yielding voxelwise estimates of the hemodynamic delay between the stimulus and the peak vascular response [Bullmore et al., 1996]. These methods have achieved some success in identifying activated brain regions but all suffer from the obvious drawback that their success will be dependent on the fidelity with which the experimental response matches the statistical model employed for analysis. Many (but not all) methods of analysis assume either that the amplitude of the response is constant throughout the experiment [Rabe-Hesketh et al., 1997] or that it changes in a fairly simple and predictable fashion. If this assumption is violated, there could be a significant loss of power to detect activation. However, there are a number of potential analytic approaches that do not assume a constant response amplitude or a simple model for amplitude changes. One such method that is frequently used for the analysis of nonstationary signals is wavelet analysis. This article describes its use for the detection of activations in fMRI experiments. We compare the results obtained with those found with techniques more commonly encountered in fMRI, and report some preliminary findings on enhancing sensitivity by varying the spatial scale on which the analysis is performed.

EXPERIMENTAL PROCEDURES

Image Acquisition

Gradient echo echoplanar brain images were obtained on a 1.5 Tesla GE Signa system retrofitted with an Avdanced NMR operating console. A quadrature birdcage headcoil was used for radio-frequency (RF) transmission and reception. At each of 10 5-mm slices with an interslice gap of 0.5 mm, or 14 7.0-mm slices with an interslice gap of 0.7 mm, 100 T_2*-weighted images (TE 40 msec, TR 3 sec) with an in-plane resolution of 3 mm were obtained depicting BOLD contrast. Slice orientation was near-axial. An inversion recovery echo planar imaging (EPI) data set was also acquired at 43 near-axial 3-mm-thick planes parallel to the AC/PC plane: TE 80 msec, TI 180 msec, TR 16 sec, in-plane resolution 1.5 mm, 8 signal averages.

Experimental design

The experiments reported here were designed to produce auditory and visual responses in the superior temporal gyrus and occipital cortex, respectively. They used an AB design in which there were alternating presentations of control (A) or active (B) conditions. The total duration of each experiment was 5 min, during which a total of 100 images was acquired at 3-sec intervals . An auditory/visual costimulation paradigm was employed. The visual stimulus was 30 sec of pattern-flash photic stimulation (8 Hz) via lightproof goggles (condition B) and 30 sec of darkness (condition A). The auditory stimulus was exposure to a prerecorded voice reading a passage from a book (39 sec, condition B), alternating with listening to a blank tape (39 sec, condition A).

Image preprocessing

Prior to estimation of responses, motion-related effects in fMRI data sets were estimated and corrected by three-dimensional (3D) realignment, followed by regression of each realigned time series on the vector of estimated rotations and translations at each voxel [Brammer et al., 1997].

Wavelet analysis

Wavelet transformation operates by computing inner products between a signal (f(x)) and analysis functions derived by rescaling and translation from a wavelet function, often referred to as the "mother wavelet." The formulation below is that given by Unser [1996]:

$$\Psi_{a,b}(x) = a^{-1/2}\,\Psi\left(\frac{(x-b)}{a}\right)$$

where ψ is the "mother wavelet" and a and b are rescaling and translation parameters, respectively. The attractiveness of wavelet transformation in the context of time-series analysis stems from the fact that it preserves both temporal and frequency information. It can thus respond to changes in response amplitude at different time points within a number of frequency bands, which can be used to advantage in analyzing responses of varying amplitude in fMRI experiments.

There are a large number of different types of mother wavelet and various types of wavelet transformation. In this article, the biorthogonal wavelet bases described by Daubechies [1988] are applied to analysis of fMRI data, using an efficient implementation of the nonredundant wavelet transform involving dyadic ($a = 2^j$, $b = k.2^j$) rescaling of the mother wavelet [Mallat, 1989]. Wavelet analysis of a signal with 2^j data points will thus produce j detail levels of output, one for each rescaling of the mother wavelet. Analysis was performed on slices of fMRI data with two spatial and one time dimension (x, y, and t). The three-dimensional extension of the algorithm of Mallat [1989]was implemented as described by Press et al. [1992]. The orthogonality of the wavelet bases of Daubechies [1988] allows wavelet transformation to be used to implement spatial or temporal band-pass filtering of the input data. By setting the coefficients of the finer detail levels in the spatial dimensions to zero and performing the inverse wavelet transform, spatially smoothed versions of the data set can be reconstructed. These are then analyzed using a strategy aimed at identifying clusters of statistically significant wavelet coefficients in the t dimension at detail levels appropriate to the experimental design frequency. This was accomplished by the method outlined by Hilton et al. [1996], which involves initial computation of an estimate of the noise standard deviation by the method of Donoho and Johnstone [1994]. Such an estimate can be obtained from the median absolute value (MAV) of the wavelet coefficients at the finest length scale.

$$\hat{\sigma} = \mathrm{MAV}/0.6745$$

The existence of clusters of significant wavelet coefficients is then tested at the detail level(s) of interest by computing the cumulative sum process of the squared coefficients.

$$B^z\left(\frac{i}{n}\right) = \frac{1}{\sigma\sqrt{2n}}\sum_{k=1}^{i}(d_j(k)^2 - \overline{d_j^2})$$

In this formulation, $d_j(1)$ .... $d_j(n)$ are the wavelet coefficients at some detail level (j) of interest and $1 \leq i \leq n$.

Hilton et al. [1996] suggested using the supremum functional

$$K = \max_{1 \leq i \leq n} \left| B^z\left(\frac{i}{n}\right)\right|$$

which is a Kolomogorov-Smirnov (KS) test statistic, and thresholding at the appropriate *P* level for significance.

Pseudogeneralized least squares and correlational analysis

In addition to using wavelet analysis to identify activated brain regions, two other analytical techniques were employed for comparative purposes. These were pseudogeneralized least squares analysis (PGLS) using sinusoidal regression [Bullmore et al., 1996] and estimation of cross-correlation with the boxcar input function with a correction for hemodynamic delay [Bandettini et al., 1993]. These techniques have been used in our own and other laboratories and have been shown to perform well in identifying responses to periodic boxcar (A/B) input functions of the type employed in this study.

In PGLS sinusoidal regression, the time series is fitted to a model of the form

$$Y(t) = \gamma\sin(\omega t) + \delta\cos(\omega t) + \acute{\gamma}\sin(2\omega t) + \acute{\delta}\cos(2\omega t) + \ddot{\gamma}\sin(3\omega t) + \ddot{\delta}\cos(3\omega t) + \alpha + \beta t + \rho_t$$

The power of the response at any voxel at the frequency of alternation of the A/B conditions is given by $\gamma^2 + \delta^2$. The standard error of the power is

$$\sqrt{2(SE(\gamma))^4 + 2(SE(\delta))^4}$$

The fundamental power quotient (FPQ) is computed at each voxel by dividing the power by its standard error. In addition to the "observed" FPQ, 10 estimates of the FPQ are computed at each voxel after random permutation of the time series. Critical FPQ values for any desired level of significance can be obtained from the distribution of "randomized" FPQs computed over the whole image [Bullmore et al., 1996].

In correlational analysis, the correlation coefficient (r) is computed at each voxel and significance assessed using the known distributional characteristics of r with appropriate degrees of freedom [Bandettini et al., 1993].

RESULTS

Distribution of responses between detail levels and choice of wavelet basis

Dyadic wavelet transformation of a 100-point time series produces information at seven detail levels (see above). In a preliminary series of experiments, analysis of the data from a visual-auditory costimulation experiment was carried out by PGLS sinusoidal regression. Areas in the temporal and occipital cortices that were activated by auditory and visual stimulation, respectively, were identified and the mean time series in each region computed and subjected to wavelet analysis. The KS statistic was computed by the method of Hilton et al. [1996] for each the seven detail levels in the "auditory" and "visual" mean time series. In both cases, the peak KS statistic was found at detail level 4, as would be predicted from the experimental design frequency. We will therefore concentrate on the results of analysis at this detail level when describing the results of wavelet analysis of whole images. Daubechies [1988] defined a number of wavelets with different numbers of coefficients. These differ in compactness and smoothness and might be expected to have somewhat different properties in the context of fMRI analysis. After extensive investigations, we found that the sensitivity to detect activations increased with the number of coefficients in the wavelet up to but not beyond 12 coefficients. The 12-wavelet set of Daubechies [1988] was therefore used for subsequent analysis.

Comparison of PGLS, correlational, and wavelet analysis

One of the primary aims of this study was to establish whether wavelet analysis could detect activations following visual and auditory stimulation with a sensitivity at least comparable to that of established methods. Prior to analysis, the data in each axial slice were smoothed using a two-dimensional Gaussian filter (FWHM, 7 mm). Analysis was then carried out by PGLS sinusoidal regression, wavelet analysis at detail level 4 using the 12-coefficient set of Daubechies [1988], and correlational analysis, all with a voxelwise type I error rate of 0.0005. All three methods detected bilateral activations in the superior temporal activations following auditory stimulation, and occipital cortical activation following visual stimulation. There were no significant areas of activation outside of these regions, which are precisely those that would be predicted from previous imaging data in our own and other laboratories. In comparative terms, wavelet analysis appeared the most sensitive, detecting the largest number of activated voxels. However, in the current experiment, where the response amplitude was relatively constant, the results with the other methods were very similar. Thus, PGLS and correlational analysis detected 95% and 88%, respectively, of the voxels identified as activated by wavelet analysis. The relative results with PGLS and correlational analysis accord with the predictions of Bullmore et al. [1996] that the former should be more sensitive.

Spatial "scale-space" mapping using wavelets

We have utilized the spatial smoothing possibilities offered by 3D wavelet transformation of each axial slice of fMRI data to attempt a preliminary spatial scale-space mapping of visual and auditory activations. This was accomplished by carrying out a forward dyadic 3D wavelet transform of the data from each axial slice using the 12-coefficient set of Daubechies [1988] and then setting the wavelet coefficients of one or more of the detail levels in the two spatial dimensions to zero before carrying out the reverse transform, using the method of Hilton et al. [1996] to compute

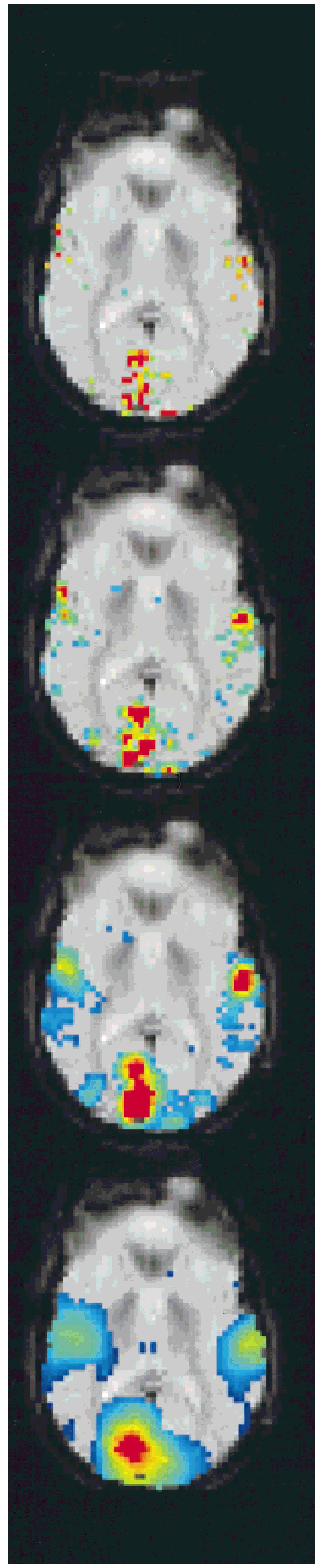

Figure 1.

Wavelet analysis of auditory and visual activations following increasing levels of spatial smoothing. Shown are four images of the slice with the strongest responses to auditory/visual stimulation. The activation maps were obtained after setting the wavelet coefficients of increasing numbers (0, 1, 2, and 3) of the finest spatial detail levels to zero, following 3D (x, y, and t) wavelet transformation using the 12-coefficient basis of Daubechies [1988]. This is broadly equivalent to smoothing the images over local neighborhoods of 1×1, 2×2, 4×4, and 8×8 voxels, respectively (top to bottom). The transform was then reversed, and clusters of significant wavelet coefficients at the detail level characteristic of the auditory and visual responses were identified by one-dimensional wavelet transformation in the t dimension and computation of KS statistics, as descibed in the text. The absolute magnitudes of the KS statistics computed at each voxel are shown by the color scale (blue, lowest; red, highest).

voxelwise KS statistics. Figure 1 shows a series of activation maps in the visual-auditory costimulation experiment computed by setting progressively larger numbers of spatial detail levels to zero (and thus removing more and more high-frequency spatial components) before carrying out analysis in the time dimension. It can be seen that in the larger areas of activation, e.g., in the occipital cortex, sensitivity to detect activations grows with progressive smoothing up to the maximum used in this study, where the finest three detail levels are set to zero. However, more focal activations, particularly those in the superior temporal gyrus, show peak responses, with intermediate levels of spatial smoothing.

DISCUSSION AND CONCLUSIONS

Wavelet analysis offers a number of clear attractions in the context of detecting fMRI activations. It is well-suited to the detection of transient events in time series and adapts well to periodic signals of decreasing or increasing amplitude. Analysis of such signals by more common models which assume constant amplitude responses throughout an experiment will entail loss of power and possible failure to detect activations. However, before using wavelet analysis to detect activations under such circumstances, we have sought to validate it using experimental paradigms which produce at least approximately constant amplitude responses in 5-min experiments. Thus, in the present series of experiments, we employed an alternating A/B periodic design to invoke auditory and visual responses and compared the ability of wavelet analysis to detect activations with that of sinusoidal regression analysis (which has been extensively validated on single subjects [Bullmore et al., 1996] and groups [Brammer et al., 1997] in our own laboratory and elsewhere), and with cross-correlation with the input (boxcar) function [Bandettini et al., 1993]. The areas of activation detected using all three methods at a voxelwise type I error rate of 0.0005 were very similar. However, sinusoidal regression and wavelet analysis appeared to be more sensitive than correlational analysis. This is encouraging, and provides a preliminary comparative validation of the statistical approach suggested by Hilton et al. [1996] for identifying significant clusters of wavelet coefficients.

It is also possible to make use of wavelet transformation in the two spatial dimensions of each slice of fMRI data to perform spatial smoothing. Starting at the finest spatial detail levels, setting the coefficients of each detail level to zero before reversing the transformation will effectively halve the spatial resolution in that dimension. We have shown that this technique can be used to find the optimal spatial detail levels for detection of activations. The technique described here is a very simple implementation of this idea. One could treat the two spatial dimensions separately, rather than smoothing each to the same extent, and obtain smoothing with differential x and y characteristics, thus applying additional geometric constraints in determining optimal local smoothness. Use of redundant wavelet transformations would also permit the optimal spatial frequency bands to be identified with more precision.

This report can only give a brief sketch of the potential of wavelet transformation, and we have restricted our initial analysis to situations which give the best direct comparisons with more established analytic techniques. We now have abundant evidence that, in conditions where responses change significantly in amplitude during experiments, wavelet analysis can detect activations that might well be missed by many more commonly used methods.

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