FREQUENCY DOMAIN HYBRID INDEPENDENT COMPONENT ANALYSIS OF FUNCTIONAL MAGNETIC RESONANCE IMAGING DATA

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ABSTRACT

Independent component analysis (ICA) of functional magnetic resonance imaging (fMRI) data reveals spatially independent patterns of functional activation. The purely data-driven approach of ICA makes statistical inference difficult. The purpose of this study was to develop a hybrid ICA in the frequency domain that enables statistical inference while preserving advantages of a data-driven ICA. Three normal volunteers were scanned with fMRI while they performed a working memory task. Their data were analyzed with frequency domain hybrid ICA. In each of the subjects, the patterns of activation corresponded to areas expected to be active during the fMRI task. This investigation demonstrates that a hybrid ICA in the frequency domain can statistically map functional activation while preserving the ability of ICA to blindly separate noise sources from the data.

1. INTRODUCTION

Independent component analysis (ICA) [1] is a method for factoring probability densities of measured signals into a set of densities that are as statistically independent as possible under the assumptions of a linear model. ICA has been applied to functional magnetic resonance imaging (fMRI) data [2]. ICA of fMRI data reveals spatially independent patterns of functional activation. The chief advantage of ICA is that assumptions about the expected fMRI response are not needed. However, when compared to traditional fMRI analysis techniques, ICA has disadvantages. First, there is no framework for testing statistical hypotheses. The lack of framework makes it difficult to determine if an independent component (IC) is related to the fMRI task or stimulus. In an ICA of fMRI data the investigator determines, by inspection, if an IC is task-related. This method lacks a quantitative measure of the confidence in the IC and introduces user bias. Second, the number of channels is equal to the number of brain volumes imaged during a scan session. An experiment with n time points has n channels and, therefore, n ICs after processing. In an fMRI experiment, n is often several hundred. This means that the user must inspect as many as several hundred ICs to select the significant activation maps. Third, Lange *et al.* [3] determined with ROC (receiver operating characteristics) analysis that for common fMRI signals, ICA has a rate of accuracy for detecting activations in fMRI data sets that is approximately one-fourth the rate of regression analysis.

Despite the problems of ICA of fMRI data, a role for ICA may be de-noising. Since the probability distributions of fMRI noise are different from the signals of interest, ICA can easily separate them. One approach to utilize ICA to account for noise sources in fMRI data has been proposed. Hybrid ICA (HYBICA) combines the data-driven approach of ICA with the hypothesis-driven approach of linear regression in the time domain [4]. FMRI data, X, a matrix with t time points by v voxels, are linearly modeled with a set of hypothesized regressors, G. The inverse of the unmixing matrix, W, contains time courses that correspond to each of the ICs. In HYBICA, W^{-1}, is the set of regressors used to model the data:

$$X = W^{-1}\beta + \varepsilon \tag{1}$$

where $\varepsilon \sim N(0, \sigma^2)$ and β is a parameter matrix containing parameters for each voxel in a brain volume. The matrix is estimated with least squares methods.

The columns of W^{-1} are combined by projecting a reference function onto the subspace of $\mathbb{R}^t$ spanned by the first k columns of W^{-1}. After each combination, a new model for X is fit and the model is evaluated with a cross validation technique. The model that minimizes this error is selected.

HYBICA assumes *a priori* that the exact timing of both the subject's response and her/his hemodynamic response to the experimental condition is known. This knowledge is represented in the reference function for the experiment. In practice, these parameters vary from one subject to the next. In this situation, the frequency of the response may be a better criterion since it is independent of the phase. The purpose of this study was to propose and evaluate a form of HYBICA in the frequency domain (fHYBICA) for fMRI data.

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Note: All images are displayed in the right=left convention.

2. MATERIALS AND METHODS

2.1. Scan Parameters

Functional images were acquired with a 1.5T commercial MRI scanner equipped with 40mT/m gradients. The specific parameters were: 20 coronal slice locations with whole brain coverage; slice thickness 7mm; slice gap 1mm; 64 × 64 pixel image matrix with an in-plane resolution of 3.75mm × 3.75mm; field of view 240mm, TR/TE 2000/40ms; flip angle 90°. A set of high-resolution SPGR anatomic images was also acquired from each subject for functional image coregistration.

2.2. fMRI Paradigm

Three normal volunteers were scanned while they performed a working memory task. The protocol used in this study was approved by our institution's internal review board. The paradigm consisted of a 16 second rest period followed by ten sequential blocks. Each block consisted of the following text for the following times: "Memorize," 2s; a random sequence of eight letters, 4s; "Remember," 8s; "Recall," 2s; presentation of a single letter, 2s; "Relax," 12s. If the single letter was contained in the previous sequence of letters, the subject was instructed to squeeze a pneumatic bulb. Previously seen letters and foils were randomly assigned to the task blocks. The paradigm was prepared with a computer presentation software package designed for psychophysical applications. The words were LCD-projected onto a screen attached to the scanner table near the feet of the volunteer. The text was visible with a mirror attached to the scanner's RF head coil.

2.3. Image Processing

The first four functional scans for each slice location were discarded due to incomplete saturation of the signal. The AFNI package [5] was used to co-register the functional images. The co-registered functional images were processed with an ICA algorithm [6] after a principal component analysis (PCA) reduction (preserving 99.99% of the variance in the data) to determine spatially independent patterns of activation and their corresponding time courses. A square wave that captured the timings of the periods of each block was convolved with a rough approximation of the hemodynamic response. A periodogram, R, of the convolved square wave was used as the reference function. The time courses W^{-1} determined from ICA were linearly detrended and transformed to the frequency domain. The periodograms, P, of these time courses were computed and then ordered based on their correlation to the reference function R such that:

$$P = [p_1, p_2, \cdots, p_t] \tag{2}$$

where

$$|\mathbf{cor}(p_1, R)| > |\mathbf{cor}(p_2, R)| > \cdots > |\mathbf{cor}(p_t, R)|. \tag{3}$$

In fHYBICA, the columns of P provide the basis for a linear regression model of the data. Some columns of P correspond to noise and others correspond to a response from the fMRI experiment. Presumably the columns with greatest correlation to R have the greatest relationship to the fMRI task. To distinguish between the task-related regressors and the confounds (i.e., noise sources), P is partitioned:

$$P = [P_k | P_{t-k}] \tag{4}$$

The first k columns are task-related and the last $t-k$ columns are confounds. To increase the number of degrees of freedom in the model, the P_k columns are combined into a single task-related regressor, R_k. The task-related regressor is computed by projecting the reference function R onto the subspace of $\mathbb{R}^t$ spanned by the columns of P_k:

$$R_k = P_k (P_k^T P_k)^{-1} P_k^T R \tag{5}$$

The regressors of interest in fHYBICA are the columns of:

$$P_R = [R_k | P_{t-k}] \tag{6}$$

The choice of k is determined empirically by evaluating all possible choices of k, namely $k = 1, 2, \cdots t$. When $k = 1$, no columns of P are combined (i.e., the model is entirely data-derived). Conversely, when $k = t$, all columns are combined and, consequently, $R_{k=t} = R$. In this situation, no data-derived noise sources are modeled and the result is a standard regression model in the frequency domain. A criterion for k was adapted from [4]. For each choice of k, a parameter, β_k, for the model:

$$X = P_R \beta_k + \varepsilon \tag{7}$$

is estimated with a least squares technique. $\hat{\beta}_k$ is a matrix that contains parameter estimates for each voxel. The selection of the optimal k is based on:

$$\min_k S(2 - |\mathbf{cor}(R_k, R)|) \tag{8}$$

where S is a measure of the PRESS statistic (Predicted Residual Sum of Squares) [4], a leave-one-out cross-validation error measure. This criterion represents a trade-off between fitting well the expected response R and generalizing to novel data.

2.4. Statistical Inference

Statistical inference [7] is made on the first row of the parameter estimate $\hat{\beta}_{ij}^{\mathrm{opt}}$ corresponding to the optimal k. The null hypothesis is $H_o : \beta_{1j}^{\mathrm{opt}} = 0 \; \forall \; j$. This implies that the task-related regressor R^{opt} is unrelated to the data. The test statistic T is defined as:

$$T := \frac{\hat{\beta_{1j}^{\mathrm{opt}}}}{\sqrt{\hat{\sigma_j^2}\gamma_{11}}} \tag{9}$$

where the variance is estimated from the j-th diagonal of $\hat{\sigma^2} = \frac{1}{n-k+1}(X - P_R\hat{\beta_{1j}^{\mathrm{opt}}})^T(X - P_R\hat{\beta_{1j}^{\mathrm{opt}}})$ and $\gamma_{11} = [(P_R^T P_R)^{-1}]_{11}$. The test statistic $T \sim \mathbf{t}_{DF=n-k+1}$ is sampled from Student's $\mathbf{t}$ density, where $n = t$ is the number of rows in P_R. Statistical maps of $T > 5$ were generated and co-registered with anatomic images to display task-related areas of the brain.

3. RESULTS

The fHYBICA successfully mapped task-related areas in the frontal lobe, temporal lobe, and visual cortex in all subjects. PCA reduced the dimension of each data set by approximately 50% for each subject. The optimal numbers of combined components determined with the error measure in equation (8) for the three subjects were 110, 58, and 59. Fig. 1 shows a plot of the error measure and the optimal task regressor for a single subject. The error decreases rapidly through the first ten combinations and remains fairly constant with increasing combinations (Fig. 1a). The optimal task regressor contains a peak at the task frequency of 0.033 Hz (Fig. 1b). The harmonic frequencies did not contribute significantly to the optimal task regressors of any subjects. Figure 2 examines a single voxel with a task-related response selected from the primary visual cortex. The raw fMRI time course shows a response to the ten blocks of the working memory task (Fig. 2a). Both the raw periodogram (Fig. 2b) and the fitted periodogram (Fig. 2c) show peaks at the 0.033 Hz task frequency. To check the validity of the assumption of normally-distributed errors, a histogram of the residuals for this voxel was computed (Fig. 2d). The residual errors appear to approximate a normal density.

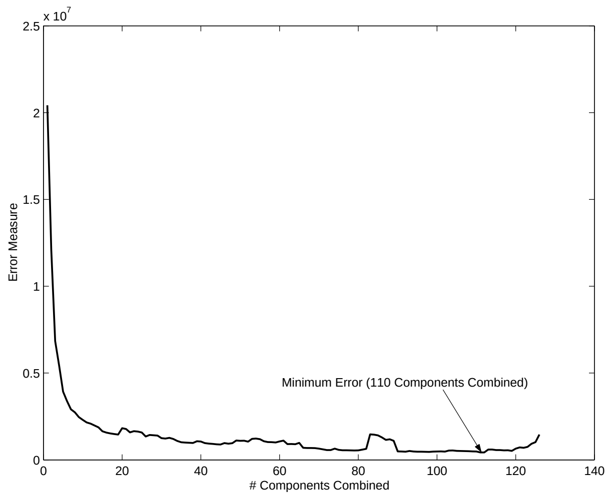
Functional activation was found in all subjects in the visual cortices, left posterior superior temporal gyrus near Wernicke's area, and right pre-motor areas (Fig. 3). The functional map was generated with data from the same subject as Fig. 1. The black regions display functionally active regions with a significance of $T > 5$. In two of the three subjects, there was significant activation in areas of the right dorsolateral prefrontal cortex (Fig. 3). The results of standard ICA were reviewed for each subject. Only activation in the visual cortices was found consistently in each subject. The visual activations identified were contained in two or more ICs. The boundaries of the activated regions were not as well-defined as fHYBICA.

4. DISCUSSION

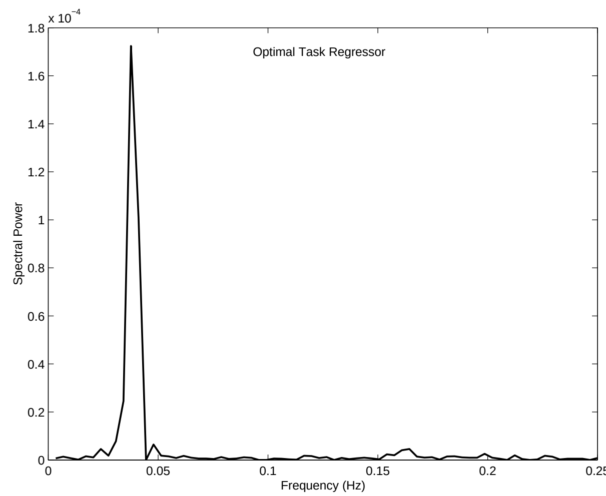
The results demonstrate that it is possible to detect task-related functional activation with fHYBICA. In the working memory task, areas of the brain needed to process the visual stimulus, interpret the text on the screen, encode or recall the stimulus to/from memory centers, and possibly to respond by squeezing the pneumatic bulb are demonstrated. The activation identified in the visual cortex likely corresponds to the visual processing of the stimulus. The more high-level processing of the text was likely to have occured in the posterior superior temporal gyrus near Wernicke's area. It is generally accepted that this region is responsible for language comprehension. Several studies [8] have suggested a role for the frontal lobe in memory. In the two subjects, the activation in the dorsolateral prefrontal cortex could have been related to memory functions, but further studies are necessary to support this hypothesis. The premotor area is responsible for initiation of motor functions [9]. At the end of each task block, the volunteer must decide whether or not to squeeze the bulb. The activation found in the premotor area is likely related to this decision. The lack of primary motor cortex activation was expected since the squeezing of the bulb was not at the frequency of the task. The times when the subject should have squeezed the bulb were randomly assigned to five of the ten task blocks.

This method addresses two of the major problems of ICA while preserving some of its advantages. First, it eliminates the bias introduced by the need for the user to select the ICs that contain response patterns that correspond to the fMRI experiment. Second, it provides a statistical framework for determining the significance of the regions identified as related to the fMRI task. The residual errors in the fHYBICA model tend to be approximately sampled from a normal distribution. This is important since the statistical inference made from the $\mathbf{t}$-test of the regression parameters depends on this assumption. FHYBICA preserves the ability of ICA to blindly separate noise from the data since the noise sources are included in the regression model. Unlike standard HYBICA, this method has the advantage that it does not depend on the phase of the response.

However, this preliminary investigation of fHYBICA has limitations. While this study does demonstrate that fHYBICA can identify regions of the brain that are related to an fMRI task, it does not quantitatively address its performance relative to more established methods of analysis. ROC analysis with simulated data is a method to perform such a comparison of the detection accuracy. The small number of subjects only allows for an illustration of fHYBICA of fMRI data. Conclusions about regions active during the working memory test used in this study require a greater number of subjects. Finally, the periodogram was used as an estimator for the spectral density of the fMRI responses. The peri-



(a) Plot of error for each possible k.



(b) Optimal task-related regressor.

Fig. 1. For each combination of components, the error is evaluated (a). The combination that minimizes the error is selected as the optimal model. The task-related regressor from the optimal model (b) contains a peak at the period of the fMRI task.

odogram is not a consistent estimator of the spectral density [10]. A smooth periodogram is a better estimator, but the choice of smoothing requires justification.

5. CONCLUSIONS

The preliminary results from the frequency domain HYBICA demonstrate the promise of this method for analysis of functional MRI data. Unlike standard ICA, fHYBICA provides a statistical framework for hypothesis testing. Frequency domain HYBICA appears to be a robust method for combining these components in a hypothesis-driven model while preserving advantages of a data-driven ICA. Additional studies are needed to quantitatively compare the detection accuracy of fHYBICA with established fMRI data analysis techniques.

6. REFERENCES

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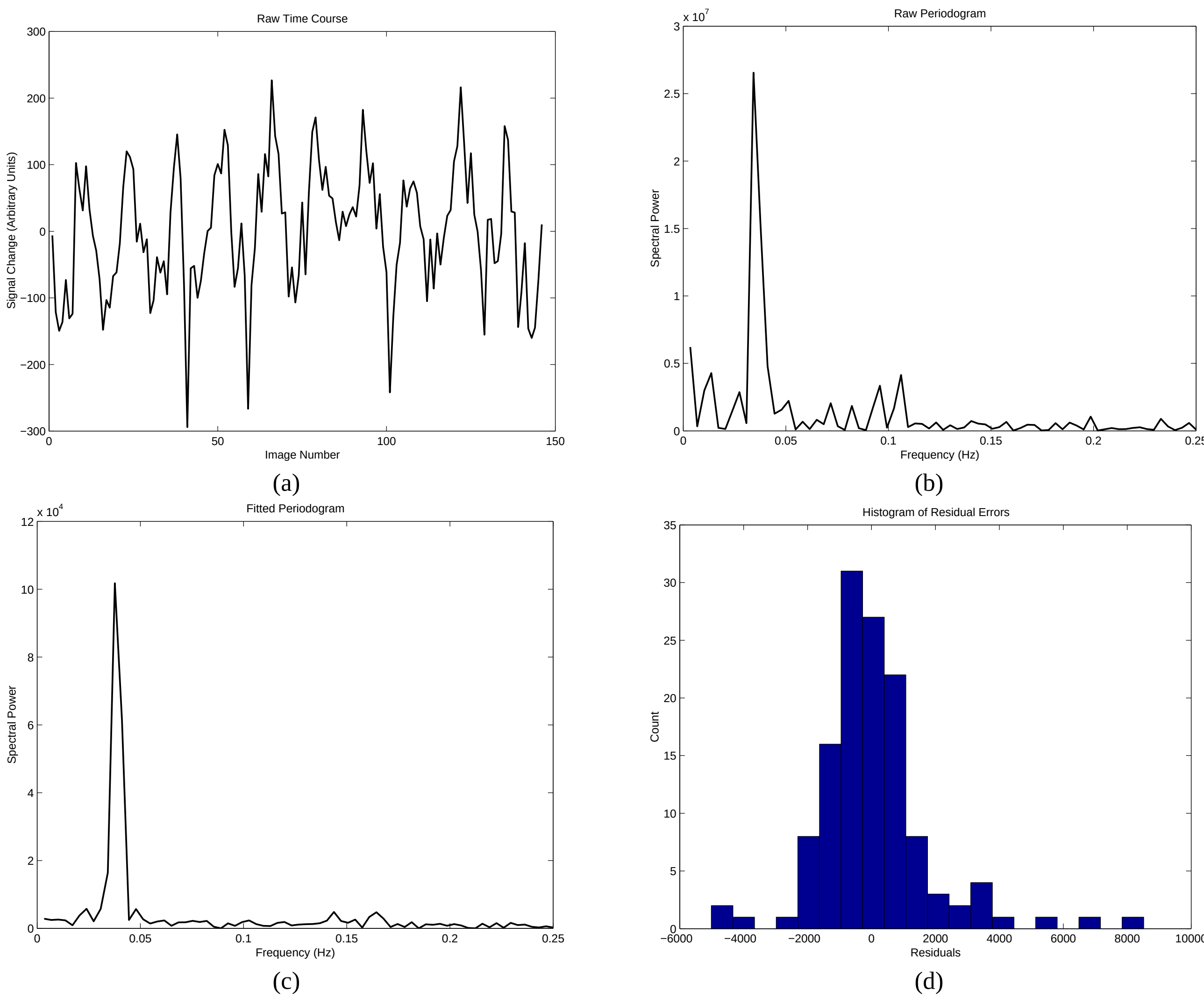

Fig. 2. The time course from a single voxel in the primary visual cortex (a) shows the fMRI response to the ten blocks in the memory task. A periodogram (b) of the time course in (a) demonstrates a high spectral content at the period of the fMRI task. The response of this voxel was fitted with fHYBICA (c). A histogram of the residual errors from the fit (d) indicates that they are approximately sampled from a normal distribution.

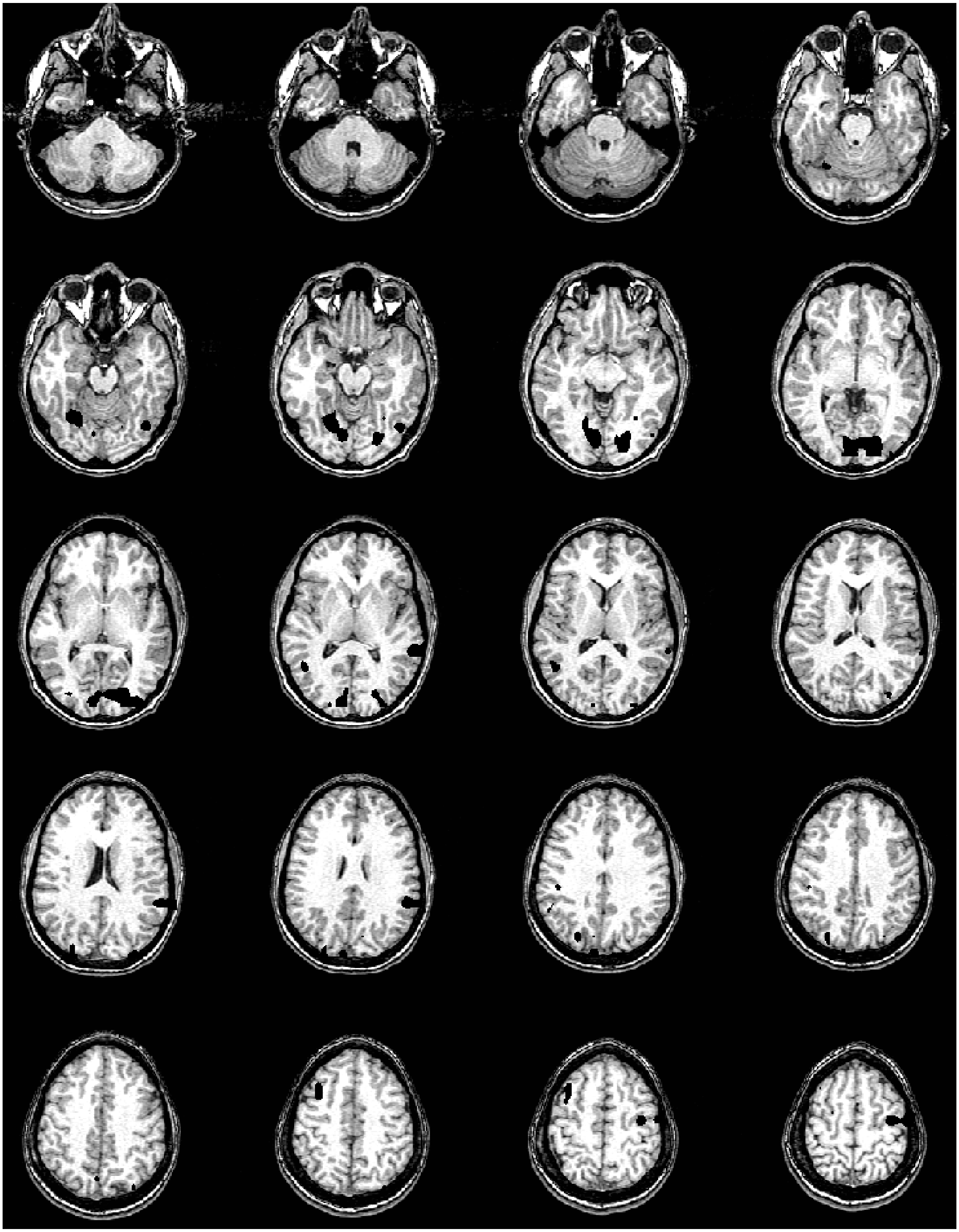

Fig. 3. Whole-brain activation maps ($T > 5$ shown in black) computed with fHYBICA. Activated regions include: left premotor cortex, right dorsolateral prefrontal cortex, left posterior superior temporal gyrus, and visual cortices.