Spatially-Thresholded Independent Component Analysis (sthICA): Generating Voxelwise Statistical Inferences from ICA Analysis of FMRI Data

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Introduction

Data-driven analysis techniques for functional MRI (fMRI) data such as Independent Component Analysis (ICA) [1] are increasing in popularity. However, ICA suffers from the lack of a built-in procedure for testing hypotheses and generating statistical inferences. We propose a version of ICA, termed spatially thresholded ICA (sthICA), which uses a Generalized Gaussian Mixture Model (GGMM) as a method for post-hoc thresholding of IC maps and the generation of voxelwise statistical inferences. Unlike a previously proposed hybrid ICA (HYBICA) method [2], the method does not require the ad-hoc separation of IC timecourses into "signal" and "confound" subspaces. The method may also be used in complete or even overcomplete ICA models (e.g. with # of sources >= # acquired time frames). The method is validated via simulation and shown to provide a robust method of generating voxelwise statistical inferences with comparable sensitivity to a standard General Linear Model (GLM). The sthICA technique is based on a previously proposed probabilistic ICA model [3].

Theory

Assuming n voxels in the brain, and m acquired frames, the univariate GLM and the multivariate (noisy) ICA technique use the same basic model $X = A\,S + E$ where X is the n-X-m data matrix, A is an m-X-p ($p <= m$) design (GLM) or mixing (ICA) matrix, and S is an n-X-p matrix of activation intensities (GLM) or independent sources (ICA), which may be estimated using $S \approx W\,X$, where $W = A^+$. In the case of the univariate GLM model typically a T-score map is subsequently constructed by dividing the values in S by their standard errors (estimating E by $X - A\,S$, and using appropriate corrections for temporal autocorrelations) on a voxel-by-voxel basis; the null distribution for statistical inferences is a T-distribution with the appropriate number of degrees of freedom. For the GLM, all confounds must be accurately specified in the design matrix. The HYBICA approach infers all regressors from the data, but each regressor must be correctly classified as confound or non-confound. Failure to include all confounds in the model will result in biased parameter estimates, while inclusion of spurious confounds will result in sensitivity loss due to overlearning. The multivariate ICA model, however, offers the possibility of using the spatial (rather than temporal) distribution to estimate the noise (null) distribution. Since the standard error for the parameter estimates is proportional to the square root of the (temporal) noise variance, the IC maps could be converted to T-score maps (up to a global scaling factor) if the noise variances were known. A previously proposed approach [3] is to approximate the noise variance by the total variance (which is of course exact for noise voxels). While this results in a downwards bias in the estimation of the T-scores for active voxels (since the noise variance is overestimated), for fMRI datasets, with typically on the order of a hundred or more acquired frames, this results in minimal sensitivity loss. Moreover, the null distribution is accurately captured in the noise voxels. It has been previously proposed to fit the entire voxel distribution to a Gaussian Mixture Model (GMM) [3] in order to separate out the noise distribution from the active distribution. While a T-distribution with a large number of degrees of freedom will resemble a Gaussian, the presence of non-uniform temporal autocorrelation across voxels may result in a slightly super- or sub-Gaussian null distribution. Hence we propose to use a Generalized Gaussian Mixture Model (GGMM, Figure 1). Typically only two GGMM mixtures will be included (noise and active), and the noise (null) distribution readily separated out by *a priori* conditions (the noise distribution should have the mean closest to zero, as well as the largest fraction of voxels). As long as the null distribution is accurately modeled, it may be used to generate voxelwise statistical inferences. Since the proposed approach also explicitly models for the variance of the null distribution, the method automatically corrects for temporal autocorrelations.

$$P(s; F_i, \mu_i, \alpha_i, \beta_i) = \sum_i \frac{F_i \alpha_i}{2\beta_i \Gamma\left(\frac{1}{\alpha_i}\right)} \exp\left[-\left(\frac{|s-\mu_i|}{\beta_i}\right)^{\alpha_i}\right]$$

Figure 1. Description of the Generalized Gaussian Mixture Model: s = source distribution, F_i = fraction of voxels associated with the ith mixture, u_i = mean of the ith mixture, α_i = determines kurtosis of the ith mixture, β_i = proportional to variance of the ith mixture. (The model reduces to a standard Gaussian Mixture Model in the limit $\alpha \rightarrow 2$.)

Materials and Methods

The sthICA technique was tested via simulated data generated via routines written in IDL (Research Systems Inc., Boulder, CO). Noise was generated using a $1/f$-like + white noise structure [4], with specific parameters obtained empirically from the noise power spectrum of fMRI data obtained at 3T. Random phases were added to each frequency component, and variance in the autocorrelative structure across voxels was obtained by shifting the coefficients for negative frequency components such that $A(-\omega) = A(\omega+1)$. Each voxel time course was then normalized to have a standard deviation determined from a uniform distribution ranging from 0.5 to 1.0. Three sources were added with time courses consisting of sine waves of frequencies of 5, 6, and 7 and amplitudes of 1 (peak-to-peak), and magnitudes determined by assigning a uniform distribution between 0.5 and 1.5 to voxels randomly selected from one-sixth of the total number of voxels. After variance-normalizing all time courses, the dimensionality was reduced to 8 components via PCA and the infomax ICA algorithm [5] was performed. For each of the three original sources, the best-matching ICA component was chosen and the GGMM and GMM performed on the intensity distribution (two mixtures). The suitableness of the fitted GGMM and GMM models were also investigated by performing the chi-squared goodness-of-fit test with a bin size of 0.02. The c.d.f was computed from the noise GGMM and GMM mixtures, and the cutoff for an alpha of 0.05 determined. The simulation was repeated 200 times. For comparison, the simulated data was also processed using a standard GLM; temporal autocorrelations were handled by scaling the parameter distributions so that the variance of the parameter estimates for the known "ground truth" noise voxels was unity.

Results and Discussion

Results are displayed in Table I. The GGMM was found to correct for almost all of the bias found using the standard GMM. For the GGMM fits, the average chi-squared per degree of freedom (X^2/DOF) was under 1 (0.99), indicating an excellent fit to the data. The empirical false positive rate of 4.97% agreed very well with the nominal alpha of 0.05. The true positive rate of 81.1% also was comparable to the sensitivity shown with the GLM results. In fact, the ICA displayed slightly better sensitivity than the GLM, because the GLM parameter estimates are only optimal under the condition of white Gaussian noise. Since a significant amount of temporal autocorrelation (taken from real fMRI data) and voxel-to-voxel variation in temporal autocorrelation were modeled, the method is expected to be robust for most fMRI datasets. Further research will investigate the effectiveness of other possible strategies such as voxelwise normalization by the effective number of degrees of (temporal) freedom to make the sthICA technique robust for fMRI datasets with wider variability in temporal noise characteristics.

Conclusion

A method of generating voxelwise statistical inferences from ICA analysis of fMRI data is proposed. The method was found to exhibit minimal bias and comparable sensitivity to a standard GLM, while automatically correcting for temporal autocorrelations.

	sthICA (GGMM)	GMM	GLM
False Positive Rate	0.0497	0.046	0.05
True Positive Rate	0.811	0.799	0.729
X^2/DOF	0.99	1.03	-

Table I. Comparison of the sthICA method, using both a GGMM and a GMM model, with a standard GLM for analysis of simulated fMRI data with temporal autocorrelations (nominal $\alpha = 0.05$).

References

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