GROUP INFERENCE IN FMRI USING CANONICAL CORRELATION ANALYSIS

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ABSTRACT

In this paper, a method based on the canonical correlation analysis (CCA) is developed for analysis of multi-subject fMRI data The CCA produces a linear combination of fMRI data (across subjects), and a linear combination of bases of signal subspace, so as they have maximum correlation with each other.
Since, the method proposed in here, is a multivariate analysis**,** we can simultaneously, use time series of analogous voxels of all subjects and optimal bases of signal subspace. This in turn, increases the flexibility through detecting different shapes of hemodynamic response in different regions and subjects. Using proposed method for analyzing the simulated data illustrates that, this method is more sensitive for detecting active voxels. Applying this method on experimental fMRI data, demonstrates that this method, has the ability of detecting more activated regions than that of general linear model (GLM).

1. INTRODUCTION

Two main reasons motivate investigators for group studies. The first reason is investigating the differences between individuals which may be important in many disciplines of psychology. And the second is to investigate the between group differences e.g., difference between the active regions of a healthy group and those of a non-healthy group in cognitive strategies during tasks [1]. We purposed a new method for these investigations.
Some previous methods, based on correlation, have been extensively applied to single subject analysis and are still considered as robust approaches for functional MRI (fMRI) analysis. The conventional cross-correlation and t-test methods can not be applied to fMRI data sets for multi-subject analysis, directly.
The methods based on General Linear Model (GLM) framework have been widely used for group analysis of fMRI data. For applying these methods, one must do the following stages. In the first stage, a statistical map is derived for each subject and the "effect" of interest, and its standard error are derived for each voxel of each subject. In the second step, (the second level) the "effects" and "standard errors" of different subjects are combined with each other. Finally, the decision is made with the use of group t-test [2]. In order to overcome some deficiencies in previous GLM methods, a new GLM method called "variance ratio smoothing" has been presented, by Worsley et al. [3].
In this paper by using the multivariate analysis (canonical correlation analysis) we develop a new method for testing the correlation between a set of fMRI data and the bases of a signal subspace.
Applying multivariate analysis methods, such as canonical correlation analysis proposed in here, provide us with the ability of multi subject analysis in a single-level and consequently, the sensitivity of group analysis to time series of different voxels, increases.
In the conventional multi-subject analyses, the brain hemodynamic system is assumed to have an impulse response correspondent to a Gamma function or difference of two Gamma functions [3]. Because of the variation of the hemodynamic response function among different subjects/regions, this assumption may reduce the sensitivity of group analysis for detecting active regions with different hemodynamic response functions. In this paper by using the bases of a signal subspace according to Hossein-Zadeh et. al [4], the sensitivity of the method for detecting different regions are increased.
CCA method has been used previously in single-subject analysis [5]. In former reference, Friman et al. applied the canonical correlation analysis on the time series of a neighborhood and the bases of a signal subspace (the Fourier series bases of the stimulation pattern), in order to detect the activated areas.

2. THEORY

Canonical correlation analysis (CCA) is a multivariate method developed by Hotelling in 1936 [6]. This method may be considered as an extension of the conventional cross-correlation analysis. This method has been previously applied to the single subject analysis of fMRI data [5]. We proposed to use this method for multi-subject analysis of the fMRI data. This has two

advantages: First, this method can use the time series of similar voxels of all subjects simultaneously and adaptively. Secondly, by using the bases of a signal subspace, it increases the detection sensitivity through detecting different shapes of hemodynamic response.
Suppose that the fMRI time series are put in the rows of matrix X. A linear combination of these time series (with weights w_x) can be formed by $\mathbf{x} = w_x^T \cdot X$. If the bases of the signal subspace are put in the rows of matrix Y, then a linear combination of the bases can be similarly formed via $\mathbf{y} = w_y^T \cdot Y$. Therefore the cross correlation coefficient between two resulted time series is

$$\rho = \frac{w_x^T S_{xy} w_y}{\sqrt{w_x^T S_{xx} w_x w_y^T S_{yy} w_y}} \quad (1)$$

Where S_{xy} and S_{yx} are inter-set correlation matrices and S_{xx} and S_{yy} are intra-set correlation matrices. The main objective is to maximize the correlation above. According to the canonical correlation theory [5], the unknown vectors w_x and w_y and ρ must fulfill the below relation.

$$\begin{cases} S_{XX}^{-1} S_{XY} S_{YY}^{-1} S_{YX} \hat{W}_X = \rho^2 \hat{W}_X \\ S_{YY}^{-1} S_{YX} S_{XX}^{-1} S_{XY} \hat{W}_Y = \rho^2 \hat{W}_Y \end{cases} \quad (2)$$

The w_x and w_y, obtained from the above expressions, are eigenvectors of the matrices $S_{xx}^{-1} S_{xy} S_{yy}^{-1} S_{yx}$ and $S_{yy}^{-1} S_{yx} S_{xx}^{-1} S_{xy}$, corresponding to their largest eigenvalue. And the largest eigen-values of these matrices are equal and become the square of the maximum correlation.

3. MATERIAL AND METHOD

3.1. Experimental data

A set of sensory-motor fMRI data is analyzed in this research. This set is provided by fMRI data center [7]. The task was event-related fMRI experiment in a 1.5 T scanner. During the experiments, 128 T2*-weighted volume images were acquired using asymmetric spin echo pulse sequence. Each volume image, consisted of 16 slices and each slice was composed of 64×64 pixels. A set of anatomical images was also obtained from each subject, which consists of 128 sagital slices with 256×256 resolution. Eleven young non-demented subjects were selected from these data. Their Anatomical images were transferred to the standard space of Talairach and Tournoux, and used for spatial normalization of functional images and transferring them into the standard atlas. Also the anatomical images were used to localize the active regions, in the AFNI software (Medical College of Wisconsin, Milwaukee, WI) [8]. The sub sampling process was conducted as 3×3×3 mm to provide 54×64×50 voxels.

Also the images were motion corrected using the AFNI software package [8]. Then a linear drift and the mean component were removed from time series of each voxel.

3.2. Simulated data

Two types of simulated data were used in this study. The first were 11 set of simulated rest data which was used for obtaining the histograms of methods under null hypothesis (no activation in the group). And the second were 11 set of simulated data with some active voxels.
Each of the first sets contains 172800 time series with 124 points. For generating the rest time series the Gaussian noise, was used with the mean value being similar to real data sets, and variance being equal to 2-hundredth of the mean value. Also, each of the second sets contains 172800 time series with 124 points. They had active voxels in one slice, according to spatial pattern depicted in Fig. 1(a). The contrasts of the activation regions vary as %1, %1.25, %1.5, and %1.75 horizontally, and the noise variances selected randomly in the interval [4 10]. Simulated activation time-series consisted of 124 points, which have been obtained, convolving stimulation pattern with the HRF and then adjusting amplitude to desired contrast. The stimulation pattern was the same as stimulation pattern of experimental data. HRF has been applied according to the following Gamma function:

$$h(t;\tau,\sigma) = \begin{cases} \exp\left(-t/\sqrt{\sigma\tau}\right)\left(\frac{e.t}{\tau}\right)^{\sqrt{\tau/\sigma}} \\ 0 \end{cases} \quad (3)$$

In the above equation, τ shows the location of the peak and σ is related to the width of the peak [4]. In order to model HRF variations, parameters τ and σ were selected randomly within intervals [3 7] and [0.05 0.21] respectively. This process was applied for each voxel.

(a) (b) (c)

Figure 1. (a)The spatial pattern of activation in simulated data, (b and c) Activated areas detected by CCA (b), and GLM (c) methods at false alarm rate of 0.0001.

3.3. Method

The proposed method in here consists of three steps for activation detection in multi-subject fMRI studies. In the first step, a matrix is defined as data for each voxel of brain. This step includes putting time-series of a voxels of all subjects in the rows of a matrix. Fig. 2 shows the simple flowchart for analyzing the data. In the second step, by convolving stimulated pattern with the elementary functions, three time-series will be generated.

Putting these three time-series in a matrix, a signal subspace is made. In the third step, the desired statistical value (ρ) is obtained for each voxel, according to Eq. (2). In the end, values of ρ were thresholded with a threshold obtained from the simulated rest data according the below paragraph. In order to implement the methods based on GLM framework, the FMRISTAT Toolbox has been used [9].

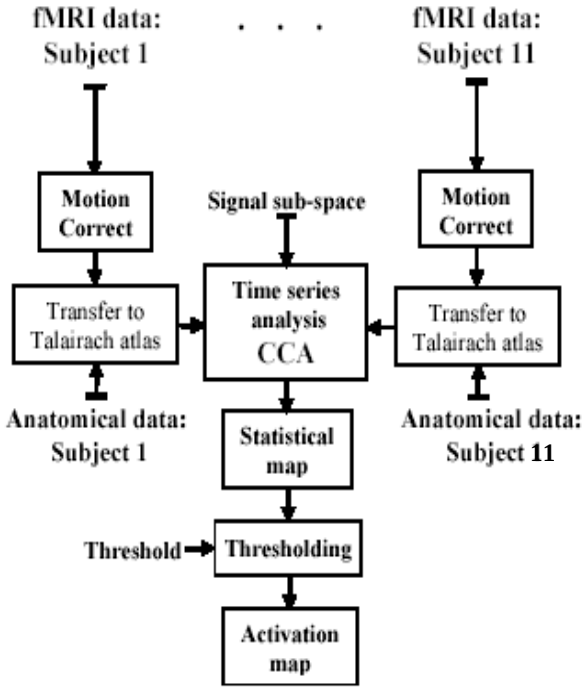


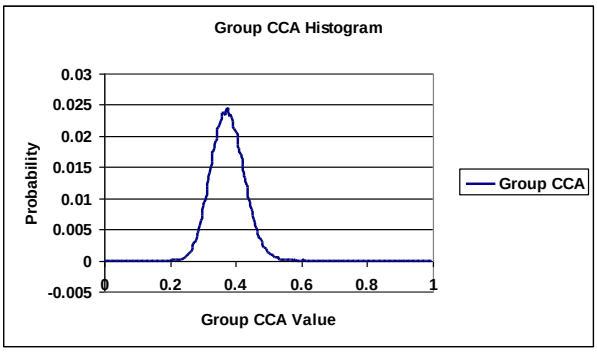
Figure 2. Block diagram of the proposed methods for multi-subject analysis.

4. RESULTS AND DISCUSSION

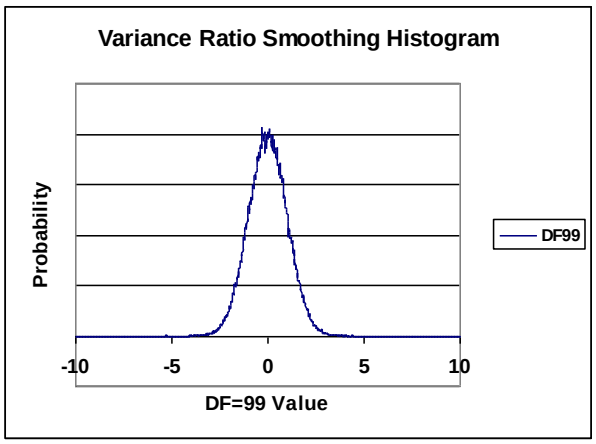
To evaluate the proposed method, it was compared to the GLM method (with variance ratio smoothing).

Since the proposed method is a single level analysis and GLM is a two level method, and computing the threshold for controlling the type I error is difficult to drive analytically for CCA method, thresholds were found for each method using the simulated rest data. In each method we compare a parameter with a threshold to decide about the activation contents of a voxel. Analysis of rest data produces realizations of this parameter under null hypothesis, which can be used to construct the empirical histogram of it under null hypothesis. These histograms were used for obtaining the thresholds of each parameter for different false alarm rates. Fig. 3 shows the histograms, obtained by applying methods to simulated data. Also, Table 1 shows the numerical values of thresholds for different false alarm rates for both CCA and GLM.

The methods were also applied to both simulated and experimental fMRI data sets. Fig 2(b,c) shows activated regions detected by these methods at false alarm rate of α=0.0001. And Fig. 4 shows the number of true detected active voxels in the simulated data set at different false alarm rates in the interval $\alpha\epsilon$[0.001 0.00007]. These results show that the proposed method provides improved detection sensitivity over the GLM method.



(a)



(b)

Figure 3. Empirical histograms of the statistical parameters of CCA (a) and GLM (b) under the null (H_0) hypothesis obtained from simulated rest study.

Table 2 lists the activation regions detected by CCA and GLM and Fig. 5 shows these regions. Comparison of results has been made in false alarm rate of 0.0002, and all single voxels were removed from the activation maps. As shown in Table 2 and Fig. 5 two method succeeded to detect activation in occipital cortex (BA 17, 18), precentral gyrus, superior frontal gyrus, marginal cingulate gyrus, thalamus, and precuneus as they were reported in previous fMRI investigations of visual task by [10-13].

Table 1. Thresholds of different methods in various false alarm rates (obtained from simulated rest data).

Specificity	CCA	GLM(DF= 99)
α = .001	0.53809	3.3335
α = .0007	0.5437	3.4291
α = .0005	0.54841	3.5314
α = .0002	0.56275	3.7835
α = .0001	0.57151	3.8874
α = .00007	0.57657	3.9847
α = .00005	0.58208	4.0175
α = .00002	0.60451	4.0868
α = .00001	0.61014	4.3654

The proposed method detected activations in cerebellum, inferior frontal gyrus, cingulate gyrus (BA 24), and cuenus, where GLM method didn't detect any activation (Fig. 5) Considering the previous reports [12] which detected activation in these areas, they may not be considered as false alarms.

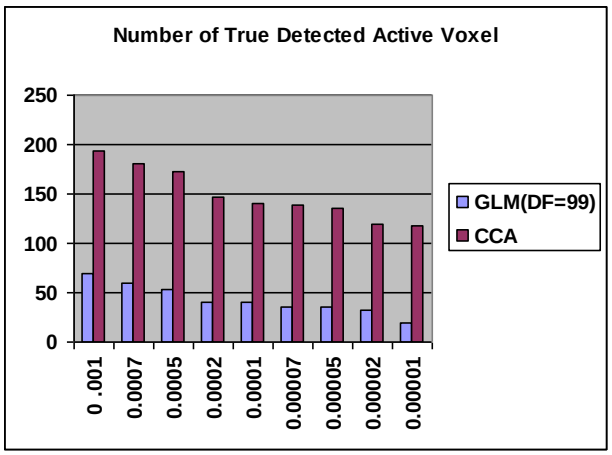


Figure 4. True detected active voxels (true positives) in the simulated data for CCA and GLM methods

5. CONCLUSION

We presented a novel method for activation detection in multi-subject studies of fMRI data using CCA framework. This method is applied on simulated and experimental fMRI data. The comparison between the results of CCA and that of GLM on simulated data shows that the proposed method detected more positive active voxels in all false alarm rates. Also, the proposed method is capable to detect more significantly activated regions in experimental data, compared to GLM method.

Table 2. Activated areas detected by two analysis methods in the experimental data.

	GLM	CCA
Occipital cortex	*	*
Precentral gyrus	*	*
superior frontal gyrus	*	*
marginal cingulate gyrus	*	*
thalamus	*	*
precuneus	*	*
cerebellum	--	*
inferior frontal gyrus	--	*
cingulate gyrus	--	*
cuenus	--	*

The method proposed in here have more ability to cover wide range of HRF variations which is basically due to using bases of a signal subspace. The proposed method in the group analysis level avail themselves of all of the time series while the methods based on GLM take the use of merely two parameters obtained from each of the time series. Based on the two mentioned factors, the proposed method has more sensitivity in comparison with the previous methods.

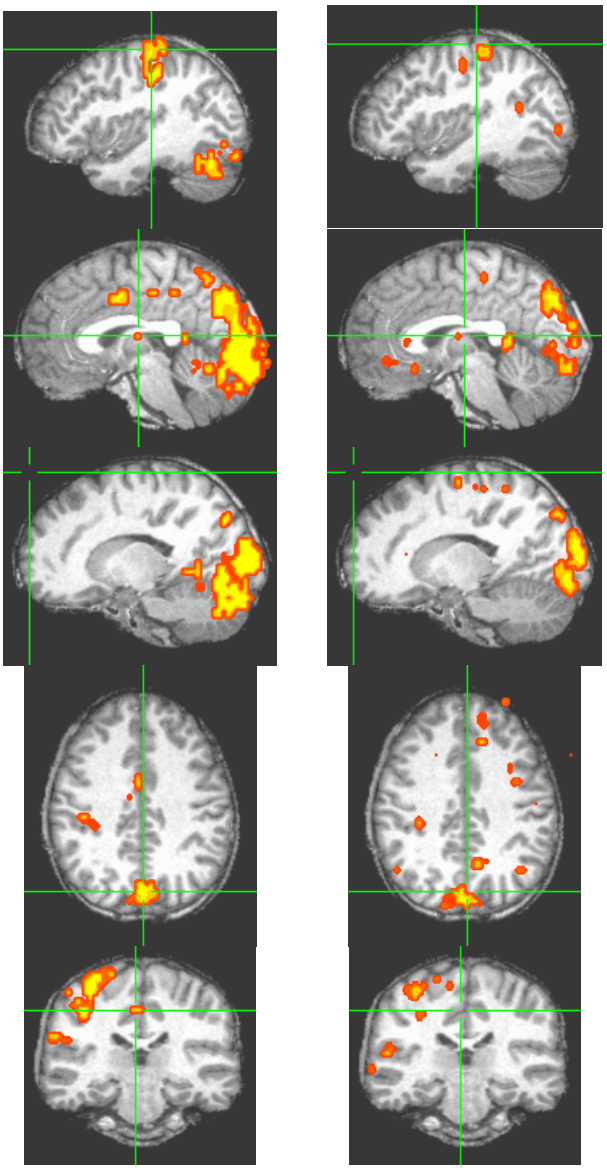


Figure 5. Five different views of brain activated areas detected by CCA (left column) and GLM (right column). Activation is detected in: 1st row) cerebellum and precentral gyrus; 2nd row) Thalamus and cingulated gyrus; 3rd row) cerebellum, occipital cortex and superior frontal gyrus; 4th row) precuneus; 5th row) inferior frontal gyrus and mariginal cingulate gyrus.

6. REFERENCES

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