Activation Detection in Multi-Subject Studies of fMRI Using GLRT

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***Abstract*-- A new method based on generalized likelihood ratio test (GLRT) for activation detection in multi-subject studies of functional MRI (fMRI) is proposed. In this method, we test the correlation between the fMRI time series of different subjects and the bases of a signal subspace which increases the flexibility of method in detecting different shapes of hemodynamic response. The proposed multivariate method can be applied to group studies where the conventional cross-correlation method cannot be used due to its univariate property. This method is applied to both experimental and simulated fMRI data and the results are compared to those of general linear model (GLM). We show that the proposed method detects more significant activated regions in analyzing experimental data and more true voxels in simulated data.**

I. INTRODUCTION

INVESTIGATING the variation of brain activated regions among different individuals in a group, and also the inter-group differences, motivated researchers to establish strategies for group analysis of functional MRI (fMRI) data [1]. As a robust approach for fMRI analysis, cross-correlation method has been extensively applied to single subject analysis. However, it cannot be applied directly to fMRI data sets for multi-subject analysis.

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. Finally, the decision is made with the use of group t-test [2]. In order to overcome deficiencies in previous GLM-based methods, a new approach, called "variance ratio smoothing" has been presented by Worsley, et al [3]. Instead of using the whole variance (random effect analysis) or just variance in each voxel (fixed effect analysis), they used the variance of effect in the vicinity of each voxel. This caused an increase in the degrees of freedom in the t-test.

In this paper, using the generalized likelihood ratio test (GLRT), 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 the proposed method 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 past investigations on multi-subject analyses, the brain hemodynamic system was modeled as a linear and time-invariant system with an impulse response correspondent to a Gamma function or difference of two Gamma functions [3]. Because of the variation of the hemodynamic response among different subjects/regions, this assumption may reduce the sensitivity of the group analysis for detecting active regions. In this paper, for modeling the hemodynamic response function, the bases of a signal subspace according to Hossein-Zadeh, et al [4] are used.

In another research, GLRT framework was used for activation detection of single subject fMRI data [5]. In this research, a model was first fitted on the complex fMRI data. In order to test the presence of activation component in the fMRI time series, the authors used the GLRT procedure.

II. THEORY

Let us put the fMRI time series of a voxel (corresponding to different subjects) in the rows of an $n_1 \times t$ matrix X. The bases of the signal subspace (obtained form convolving the stimulated pattern with HRF function or HRF elementary functions [4]) are put in the rows of an $n_2 \times t$ matrix Y. Suppose that matrix Q is formed by: $Q = \begin{bmatrix} X \\ Y \end{bmatrix}$. As we know, the main objective of fMRI analysis is to make a decision about the presence of activation signal in the time series of matrix X. This is usually done by testing the correlation between rows of the above matrices. This hypothesis testing can be done through generalized likelihood ratio test (GLRT).

GLRT is a sub-optimal method to determine which of the considered hypotheses represents the best description of the existing data [5]. If the probability-density-function of data is a

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function of vector $\boldsymbol{\theta}$ (parameters), and the null and alternative hypotheses are defined as $H_0 : \boldsymbol{\theta} \in \Omega_0$ and $H_1 : \boldsymbol{\theta} \in \Omega_1$, then GLRT (for testing H_0 against H_1) is defined as follows [5,6].

$$\lambda(Q) = L_0 / L_1 \tag{1}$$

In this case, L_0 *and* L_1 are maxima of the probability density functions (pdf)s of the data in the vicinity of Ω_0 and Ω_1 respectively, which are usually obtained via maximum likelihood estimation (MLE).

According to GLRT theory, if $v_1,\ldots,v_t$ are considered as n-dimensional observations of an $N_n(\boldsymbol{\mu}, \boldsymbol{\Sigma})$ distribution, and S and $\hat{\Sigma}$ are supposed to be MLE of Σ_Q (random data correlation matrix) under H_1 and H_0 hypotheses respectively, then GLRT can be obtain as follows:

$$-2\log\lambda = np(a - \log g - 1) \tag{2}$$

where a and g are the geometrical and arithmetic mean values of $S^{-1}\hat{\Sigma}$ matrix [6]. Now, in our fMRI analysis case, the H_0 hypothesis is the lack of correlation between rows of matrices X and Y. The GLRT used for testing this hypothesis is related to the eigenvalues of the following matrix, which can be derived by Eq. (4) [6].

$$\hat{\boldsymbol{\Sigma}}^{-1}\mathbf{S} = \begin{bmatrix} \mathbf{I} & \mathbf{S}_{XX}^{-1}\mathbf{S}_{XY} \\ \mathbf{S}_{YY}^{-1}\mathbf{S}_{YX} & \mathbf{I} \end{bmatrix} \tag{3}$$

$$-2\log(\lambda) = -n\log\left|\mathbf{I} - \mathbf{S}_{YY}^{-1}\mathbf{S}_{YX}\mathbf{S}_{XX}^{-1}\mathbf{S}_{XY}\right| = -n\log\prod_{i=1}^{k}(1-\lambda_i) \tag{4}$$

where λ_i's are the non-trivial eigenvalues of $\mathbf{S}_{YY}^{-1}\mathbf{S}_{YX}\mathbf{S}_{XX}^{-1}\mathbf{S}_{XY}$ and $k = \min\{n_1, n_2\}$. In general, according to Bartlet approximation for large t (where t is the number of scans), one can use chi-squared distribution with $n_1.n_2$ degrees of freedom for the following expression under the null hypothesis [7].

$$-\left(n - \tfrac{1}{2}(n+n+3)\right)\log\left|\mathbf{I} - \mathbf{S}_{YY}^{-1}\mathbf{S}_{YX}\mathbf{S}_{XX}^{-1}\mathbf{S}_{XY}\right| \sim \chi^2_{\mathbf{n_1 n_2}} \tag{5}$$

III. Materials and Methods

A. Experimental Data

A set of sensory-motor fMRI data is analyzed in this research. This set is provided by fMRI data center (http://www.fmridc.org). They were acquired during an 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 acquired from each subject, which consists of 128 sagittal slices with 256×256 pixels. Eleven young non-demented subjects were selected from these data. Their functional images were motion corrected using the AFNI software package (Medical College of Wisconsin, Milwaukee, WI) [8]. Then their anatomical images were transferred to the standard space of Talairach and Tournoux and the resulted transform is used for spatial normalization of functional images in the AFNI software package. The anatomical images were used to localize the active regions in the AFNI software. For each volume of functional data, the sub sampling process produced a volume image with 54×64×50 voxels and voxel size of 3×3×3 mm.

A linear drift and the mean component were removed from time series of each voxel.

B. Simulated Data

Two groups of simulated data were used in this study. The first group consists of 11 sets of simulated rest data, which is used for obtaining the histograms of parameters under null hypothesis (no activation in the group). The second group consists of 11 sets of simulated data that have some predefined active voxels.

Each set of the simulated data contains 172,800 time series with 124 points. For simulating the rest data (group 1), Gaussian noise was used with the mean value similar to real data sets and variance of 2% of the mean value. In the second group, in addition to the Gaussian noise, activation was added to some voxels according to the spatial pattern depicted in Fig. 1(a). The contrasts of the activation regions varied as 1%, 1.25%, 1.5%, and 1.75% horizontally and the noise variances were selected randomly in the interval [4 10]. Simulated activation time-series consisted of 124 points, which have been obtained through convolving the stimulation pattern with the HRF and then adjusting the amplitude of the resultant signal to the desired contrast. The stimulation pattern was the same as that of the experimental data. The HRF was modeled according to the following Gamma function:

$$h(t;\tau,\sigma) = \begin{cases} \exp\left(-t/\sqrt{\sigma\tau}\right)\left(\dfrac{e.t}{\tau}\right)^{\sqrt{\tau/\sigma}} \\ 0 \end{cases} \tag{6}$$

where 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 to each voxel.

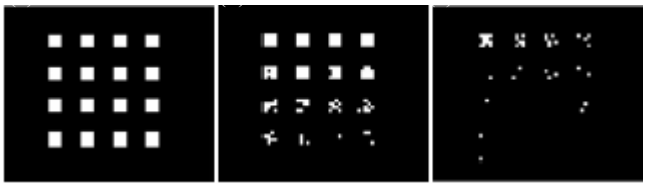


Fig. 1. The spatial pattern of activation in simulated data (a), Activated areas detected by GLRT (b), and GLM (c) methods at false alarm rate of 0.0001.

C. Methods

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

stimulated pattern with the elementary functions, three time-series will be generated. By putting these three time-series in a matrix, a signal subspace is made. In the third step, the desired statistical value ($\mathrm{Ln}(\lambda)$) is obtained for each voxel, according to (4). At the end, values of $\mathrm{Ln}(\lambda)$ are thresholded with a threshold obtained from theory noted in (5) or from the simulated rest data according to the following paragraph. In order to implement the methods based on GLM framework, the FMRISTAT Toolbox has been used. This toolbox is available at *http://www.math.mcgill.ca/keith/fMRIstat/*.

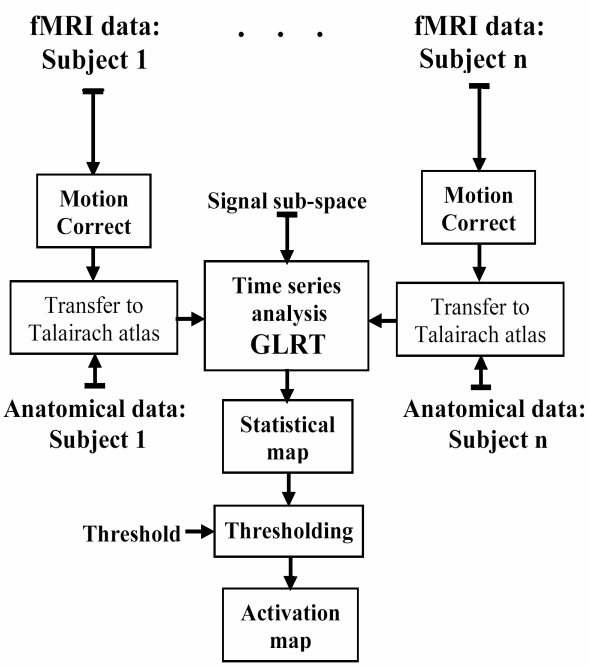
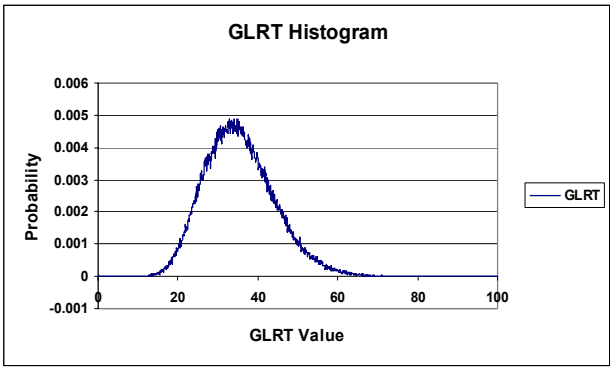


Fig. 2. Block diagram of the proposed methods for multi-subject analysis.

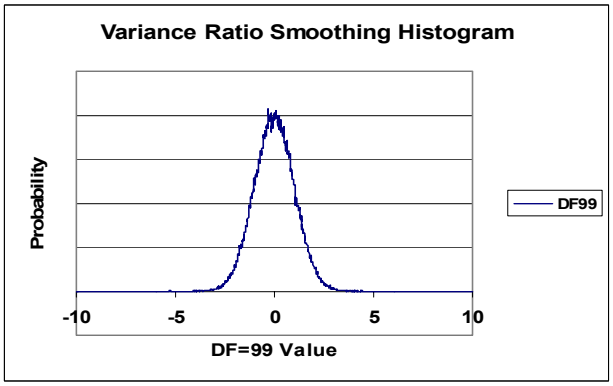
IV. Results and Discussion

To evaluate the proposed method, it was compared to the GLM method (GLM with variance ratio smoothing). For controlling the type I error, the threshold in GLM can be found via analytic expressions and statistical distribution of parameters. However, we used the simulated rest data to obtain the thresholds numerically for both GLM and GLRT. Since the proposed method is a single level analysis and GLM is a two level analysis method, we used the thresholds obtained from the simulated data to achieve similar conditions for both methods. In each method, analysis of rest data produces realizations of its parameter under the null hypothesis, which can be used to construct an empirical histogram. These histograms were used for obtaining the thresholds of each parameter for different false alarm rates. Fig. 3 shows the histograms, obtained by applying the above procedure. Also, Table I shows the numerical values of thresholds for different false alarm rates for both GLRT and GLM.

The methods were applied to both simulated and experimental fMRI data sets. Fig. 4 shows the number of true detected active voxels in the simulated data set at different false alarm rates in the interval $\alpha\epsilon[0.00001\ 0.001]$. Figs. 5-6 show activated regions in the experimental data set detected by the methods at false alarm rate of α=0.0001. These results show that the proposed method provides improved detection sensitivity over the GLM method.



(a)



(b)

Fig. 3. Empirical histograms of the statistical parameters of GLRT (a) and GLM (b) under the null hypothesis (H_0) obtained from simulated rest data.

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

false alarm rate	GLRT	GLM(DF= 99)
α = .001	67.965	3.3335
α = .0007	69.429	3.4291
α = .0005	71.032	3.5314
α = .0002	75.126	3.7835
α = .0001	76.977	3.8874
α = .00007	78.283	3.9847
α = .00005	78.904	4.0175
α = .00002	81.775	4.0868
α = .00001	82.19	4.3654

Table II lists the activation regions detected by GLRT and GLM and shown in Figs. 5-6. Comparison of results has been made at false alarm rate of 0.0002 and all single voxels were removed from the activation maps. As shown in Table II and Figs. 5-6, the two method succeeded to detect activation in occipital cortex (BA 17, 18), precentral gyrus, superior frontal gyrus, marginal cingulate gyrus, thalamus, and precuneus that

were also reported in previous fMRI investigations of visual task by [9-12].

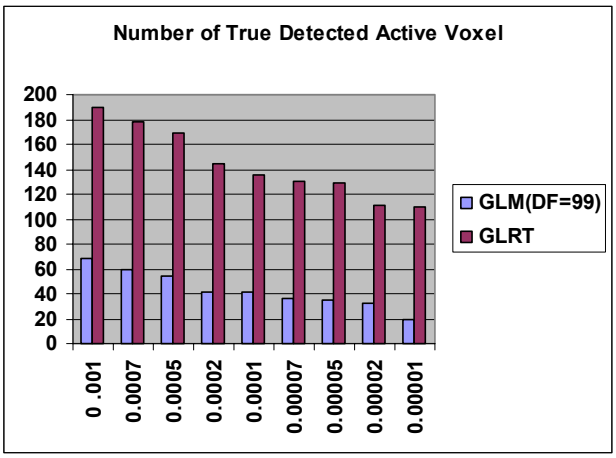


Fig. 4. True detected active voxels (true positives) in the simulated data for GLRT and GLM methods.

The proposed method detected activations in cerebellum, inferior frontal gyrus, cingulate gyrus (BA 24), and cuenus, where GLM method did not detect any activation (Fig. 5). Considering the previous reports [11] which detected activation in these areas, they may not be considered as false alarms.

Table II
Activated areas detected by two analysis methods.

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

V. Conclusion

In this paper, a new method is presented for activation detection in group fMRI data using GLRT framework. This method is applied to simulated and experimental fMRI data. The comparison between the results of GLRT and GLM on simulated data shows that the proposed method detects more active voxels at all false alarm rates. Also, the proposed method detects more significant activated regions in experimental data compared to GLM method.

Due to using bases of a signal subspace, the method proposed in here covers a wide range of HRF variations. The proposed method at the group analysis level uses all of the time series while the methods based on GLM use merely two parameters obtained from each of the time series. Thus, the proposed method has a higher sensitivity compared to the previous methods.

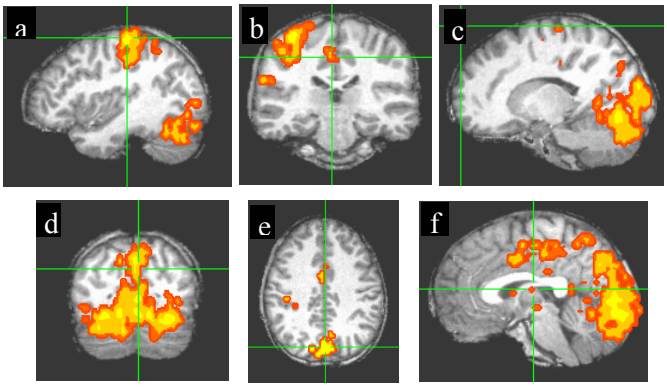


Fig. 5. Six different views of brain activated areas detected by applying GLRT on the group data. The activated areas are overlaid on the high resolution structural images. Activation is detected in: a) Cerebellum and precentral gyrus; b) inferior frontal gyrus and marginal cingulate gyrus; c) cerebellum, occipital cortex and superior frontal gyrus; d) cuneus; e) precuneus; f) Thalamus and cingulated gyrus from sagittal view.

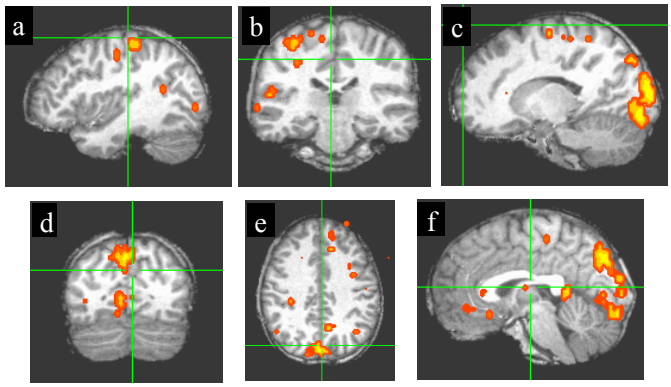


Fig. 6. Activation areas found by GLM, in six different views of brain (corresponding to views of Fig. 5). The activated areas are overlaid on the high resolution structural images. Images show areas in: a) Cerebellum (*not detected*) and precentral gyrus (detected); b) inferior frontal gyrus (*not detected*) and marginal cingulated gyrus (detected); c) Cerebellum (*not detected*), occipital cortex (detected) and superior frontal gyrus (detected); d) Cuneus (*not detected*); e) Precuneus (detected); f) Thalamus (detected) and cingulated gyrus (not detected) from sagittal view.

VI. References

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