

CONTROLLING THE FALSE POSITIVE DETECTION RATE IN FUZZY CLUSTERING OF FMRI DATA

Hesamoddin Jahanian^{1,2}, Hamid Soltanian-Zadeh^{1,2,3}, Gholam A. Hossein-Zadeh²

¹Signal and Image Processing Group, School of Intelligent Systems, IPM, Tehran, Iran

²Control and Intelligent Processing Center of Excellence, Elec. Eng. Dept., University of Tehran, Tehran, Iran

³Image Analysis Lab. Radiology Dept., Henry Ford Health System, Detroit, MI, USA

ABSTRACT

Despite its potential advantages for fMRI analysis, fuzzy C-means (FCM) clustering suffers from limitations such as the need for a priori knowledge of the number of clusters, and unknown statistical significance and instability of the results. We propose a randomization-based method to control the false positive rate and estimate statistical significance of the FCM results. Using this novel approach, we develop an fMRI activation detection method. The ability of the method in controlling the false positive rate is shown by analysis of false positives in activation maps of resting-state fMRI data. Controlling the false positive rate in FCM allows comparison of different fuzzy clustering methods, using different feature spaces, to other fMRI detection methods. In this paper, using simulation and real fMRI data, we compare a novel feature space that takes the variability of the hemodynamic response function into account (HRF-based feature space) to the conventional cross-correlation analysis and FCM using the cross-correlation feature space.

1. INTRODUCTION

In neuroimaging, model-free analysis has been mostly carried out using clustering methods. The aim of clustering techniques is identifying regions with similar temporal patterns of activation. The most popular clustering method is the fuzzy C-means (FCM) algorithm [1]. An important limitation of FCM and other clustering techniques is their inability to assign statistical significance to the results. FCM gives the membership maps of brain voxels in different clusters. After FCM convergence, the cluster with the most similar centroid to stimulation pattern is selected as the active cluster and the membership degree of each voxels to this cluster (u) is compared with a threshold u_a in order to detect activated

voxels. By comparing u at each voxel with threshold u_a , one tests the null hypothesis H_0 : ‘no activation’ against the alternative hypothesis H_1 , and rejects H_0 if $u > u_a$. This threshold which determines the significance degree of the results has been hitherto chosen heuristically by investigators. We propose a method, based on randomization, to evaluate the statistical significance of activations and to control the false detection rate in fuzzy clustering analysis of fMRI. Making no specific assumptions about the noise structure, the randomization procedure can provide the distribution of “the membership degree to the active cluster (u)” under the null hypothesis (resting state condition). Using this probability density function, one can choose the required threshold u_a in order to control the false positive rate at level α . Using this approach, every active voxel will have a statistical significance (p value).

Clustering has been hitherto performed on the raw fMRI time series in most of the previous literature [1], [2]. Because of poor SNR of fMRI time series and confounding effects, the results of clustering on the raw time series are often unsatisfactory, and FCM does not necessarily group data according to the similarity of their pattern of response to stimulation. Moreover, increasing the size of clustering space leads to practical difficulties such as ‘the curse of dimensionality’.

Using an appropriate feature space extracted from fMRI time-series alleviates these problems. The feature space defined by the cross-correlation of a fixed reference time pattern and the fMRI time-series has been conventionally used for cluster analysis of the fMRI data [3]. However, the hemodynamic response function (HRF) of the brain has been shown to vary between different brain areas and subjects [1], [4] decreasing sensitivity of this method. Here, we use a feature subspace, which takes into account this variability. We use the proposed approach for controlling the false positive rate to construct a novel model-independent fMRI activation detection method. The proposed method for controlling the false positive rate is applicable to any fuzzy clustering

algorithm using any feature space and yields statistically meaningful results. It allows application and comparison of different clustering methods and feature spaces in fMRI data analysis. Using the proposed method, we compare the proposed feature space to the cross-correlation feature space.

2. METHODS

Our proposed method for fMRI activation detection consists of three steps. In the first step, a set of features is extracted from each fMRI time-series. This step will be explained in Section 2.1 for the proposed feature space. Other feature spaces can also be used here. In the second step, FCM will be applied to the feature space. For defining the number of clusters, we used the method described in [2]. As in [2], $m = 2$ is used as the fuzziness index of FCM. After FCM convergence, the cluster with the most similar centroid to the stimulation pattern is selected as the active cluster. Next, we find a statistically meaningful membership threshold for the membership map of the active cluster as described in Section 2.2. Finally, the membership degree of each voxel to the active cluster is compared to the threshold to determine the active voxels.

2.1. Feature Extraction

By systematic analysis of HRF variations Hossein-Zadeh *et al* [5] proposed a new method that approximates the gamma HRF over a wide range of parameters by a linear combination of three elementary signals. Convolution of these functions with the stimulation pattern provides three basis functions ($z_1(t)$, $z_2(t)$, $z_3(t)$) for signal subspace [6]. Therefore each fMRI time series may be considered as: $y(t) = \alpha_1 z_1(t) + \alpha_2 z_2(t) + \alpha_3 z_3(t) + e(t)$, where $e(t)$ is the error term considered as noise.

The unknown coefficients α_1 , α_2 , and α_3 were estimated for each voxel (through an LS estimation) and were used along with a conventional cross correlation coefficient cc (the cross correlation between $y(t)$ and the stimulation pattern) to provide a feature space for FCM clustering. We call this feature space HRF-based feature space.

2.2. False Positive Rate Control

After FCM convergence, the membership degree of each voxel to the active cluster (u) is compared with a threshold u_a in order to detect activated voxels. This threshold strongly affects the statistical significance of the results, and has been chosen heuristically in the past. For controlling the type I error of this test at level α , the threshold u_a must be found such that $prob(u > u_a | H_0) = \alpha$.

This requires the probability density function (pdf) $f_u(u|H_0)$, which is difficult to derive analytically. We use the resampling procedure introduced by Bullmore *et al.* [7] to estimate this pdf. In this method the wavelet coefficients (obtained using the Daubechies basis with 4 vanishing moments) of the fMRI time-series are permuted at different levels of resolution (in 4 levels), and then an inverse wavelet transform is applied on them to generate various realizations of data under null hypothesis. FCM clustering is then applied to the randomized data and the center of active cluster found before randomization is used to find membership degrees of all voxels in the active cluster. These values construct an empirical histogram which estimates the required pdf $f_u(u|H_0)$. Using this histogram, we find the threshold corresponding to the desired α . Thresholding the active cluster membership-degree map of brain voxels with this threshold yields statistically meaningful results.

3. EXPERIMENTAL RESULTS

Resting state fMRI data were used to evaluate the ability of the proposed method in controlling the false positive detection rate. The proposed method was applied to 4 resting state datasets and activated voxels detected for different false positive rates. The actual (occurred) false positive rate was then computed for each case by dividing the number of detected voxels to the number of brain voxels in the dataset. Figure 1 shows the observed (measured) false positive rate versus the expected false positive rate for one of the datasets. Note its closeness to the diagonal line. Table 1 shows the numerical values of the expected and actual false positive rates for the 3 other resting state datasets.

To evaluate the proposed method, it was compared to the conventional cross-correlation analysis. To study the efficiency of the proposed feature space, the FCM was also applied to the feature space defined by the cross-correlation values. The methods were applied to the simulated data and 12 finger tapping datasets. For a realistic simulation of fMRI data, computer generated ‘activation’ time series were added to the measured time series of a single slice of a resting state experimental fMRI data in 116 voxels and with different contrasts (1%, 1.5%, 2%, and 2.5%). The activation time series was obtained by convolving a stimulation pattern with a Gamma function that models the hemodynamic response function. In order to model the variability of the HRF, the parameters of the Gamma function were varied randomly between different activated voxels. Figure 2 shows the number of true positives in the simulated data at various false positive rates. In the experimental fMRI data, using HRF-based feature space revealed activation in sub-cortical regions where the cross-correlation feature space

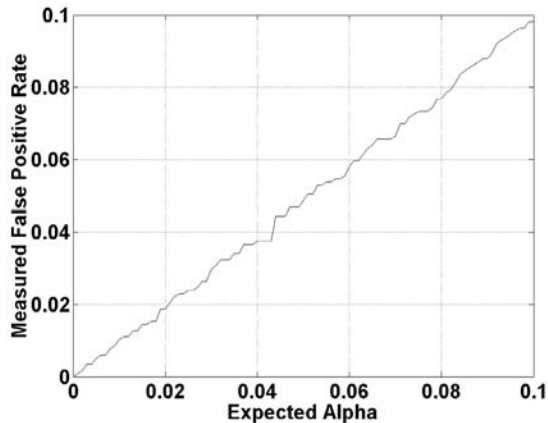


Fig. 1. The measured false positive rates of the proposed method versus their expected values for a resting state fMRI dataset.

and the conventional cross-correlation analysis failed to detect them. Figure 3 shows an example of the activation regions detected by the proposed method at $\alpha=0.005$, superimposed on the anatomical images. Activation is detected in SMC (Sensorimotor Cortex), SMA (Supplementary Motor Area), thalamus, cerebellum, GP (globus pallidus), and TTG (transverse temporal gyrus). Table 2 lists the detected activation regions in all 12 experimental datasets using the proposed method, the conventional cross-correlation method, and FCM clustering of the cross-correlation values.

4. DISCUSSION

In this work, we used the pdf of u under the null hypothesis to find the threshold corresponding to the desired false positive rate. The result of analyzing the resting state dataset confirmed the ability of the proposed method to control the false positive rate. This is obtained at the expense of the required computation.

The proposed method for false positive control can be applied with the FCM to any feature space. Here we showed that the proposed method with HRF-based feature space provides improved detection sensitivity over the cross-correlation feature space and the conventional cross-correlation analysis (see Figure 3). Finger-tapping paradigm regularly produces activation in the sensorimotor cortex (SMC) supplementary motor area (SMA) and cerebellum. Activity in the sensorimotor cortex produces transient neural activity in subcortical regions [4]. Moritz *et. al* [4] reported activation detection in subcortical regions by changing the temporal duration of the reference function. In experimental fMRI data, using HRF-based feature space, the proposed method revealed activation in sub-cortical regions. In addition, it detected activation in thalamus, GP (globus pallidus), and TTG (transverse temporal gyrus) where the

Table 1. Numerical values of observed false positive rates versus expected alpha values in 3 resting state fMRI datasets.

<i>Alpha</i> (<i>expected</i>)	<i>subject 1</i> (<i>measured</i>)	<i>subject 2</i> (<i>measured</i>)	<i>subject 3</i> (<i>measured</i>)
0.01	0.0102	0.0111	0.0102
0.02	0.0188	0.0205	0.0188
0.03	0.0299	0.0307	0.0299
0.04	0.0375	0.0435	0.0375
0.05	0.0486	0.0520	0.0495
0.06	0.0580	0.0623	0.0597
0.07	0.0666	0.0708	0.0683
0.08	0.0768	0.0811	0.0776
0.09	0.0879	0.0904	0.0879
0.1	0.0981	0.1024	0.0990

cross-correlation feature space and the conventional cross-correlation analysis failed to detect them (see Table 2). This superiority stems from the fact that we have taken into account the variability of the hemodynamic response in the HRF-based feature space, which cannot be achieved in conventional methods such as cross-correlation.

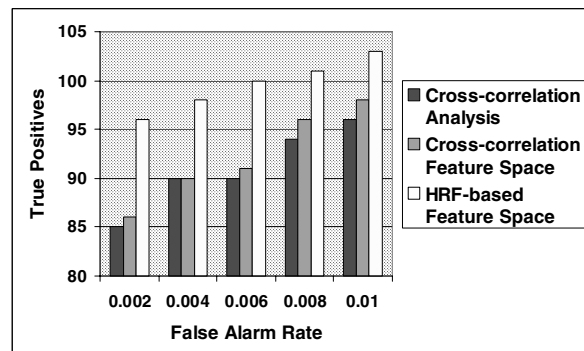


Fig. 2. Comparison of the number of true positives in the simulated data for the proposed method with HRF-based feature space and cross-correlation feature space to the conventional cross-correlation analysis at different false positive rates.

5. CONCLUSION

A method for controlling the false positive rate in FCM was proposed and its efficiency evaluated using resting state fMRI data. Fixing the false positive rate in activation detection using FCM makes it possible to compare the FCM with other fMRI activation detection methods. The proposed method showed a higher sensitivity than the conventional cross-correlation. Using the proposed method, one can also evaluate the performance of different FCM-based methods, such as using different feature spaces. A valid comparison between these methods cannot be done without considering the statistical significance of the results. The proposed

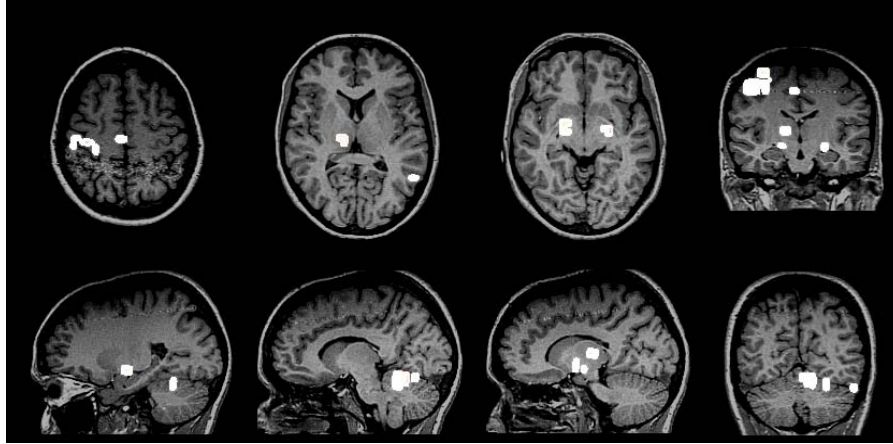


Fig. 3. Activation regions detected by the proposed method with HRF-based feature space at $\alpha = 0.005$, overlaid on the corresponding anatomical slices in one of the motor task datasets. Activation is detected in SMC (Sensorimotor Cortex), SMA (Supplementary Motor Area), thalamus, cerebellum, GP (globus pallidus), and TTG (transverse temporal gyrus).

method controls the rate of false positive occurrence without any assumption about the noise at the expense of complexity of randomization. Using this method, we compared two feature spaces: cross-correlation feature space, and HRF-based. Our comparison on simulated and experimental data showed improved sensitivity of HRF-based feature space over the cross-correlation feature space and the conventional cross-correlation analysis. In the analysis of finger-tapping fMRI data using HRF-based feature space, activation was detected in sub-cortical regions where the cross-correlation feature space and conventional cross-correlation analysis failed to detect them. This suggests that the widely used statistical activation detection methods, which use a single variable, may not capture brain activation variability. The proposed method provides a framework for investigating the mechanisms of brain activation from different points of view with concurrent use of different features. Here, we investigated the activation from the response variability point of view.

Table 2. Number of subjects who showed activation in the specific regions using different analysis methods.

<i>Detected Activation Region</i>	<i>HRF-based Feature Space</i>	<i>Conventional Cross- correlation Analysis</i>	<i>Cross- correlation Feature Space</i>
SMA	12	12	12
SMC	12	12	12
Cerebellum	12	12	12
GP	5	0	0
Thalamus	7	0	0
TTG	4	0	0

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