STATISTICAL INFERENCE IN FUZZY CLUSTER ANALYSIS OF FUNCTIONAL MRI

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ABSTRACT
Fuzzy cluster analysis (FCA) of functional magnetic resonance images, suffers from some drawbacks such as a priori definition of number of clusters and unidentified statistical significance of results. Here, we introduce a method to control the rate of false positive detection in FCA which gives a meaningful statistical significance to the results. Using this method, we also derive the optimal number of clusters. In this study by measuring the rate of false alarm detection while analyzing 6 experimental datasets, we evaluate the introduced method for making statistical inference.

KEY WORDS:
fMRI, fuzzy clustering, statistical test, randomization, cluster validity.

1. Introduction

In neuroimaging, model-free analysis has been mostly carried out using clustering methods [1]. Defining the right number of clusters is one of the main issues in clustering brain voxels. For this purpose, some cluster validity measures have been proposed but this intensive search for a standard index has not yet succeeded [2]. Another drawback of FCM and other clustering techniques is their inability to assign statistical significance to the results. As a result, one cannot compare the results obtained by statistical methods and clustering methods.

Here, we introduce a method based on randomization to evaluate the statistical significance of activation in the fuzzy clustering analysis of fMRI. Making no specific assumption 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, we can determine u_a in order to control false positive rate [3].

We also suggest a method for determining the number of clusters using the procedure we introduced for false positive control.

2. Experimental Data

Functional images were acquired from 6 normal volunteers using a single-shot GRE spiral scan sequence (TR=2 sec, TE=30 ms, FOV=220×220×96 mm^3, matrix size=64×64×24) on a 3 Tesla GE MRI scanner (General Electric, Milwaukee, WI, USA). The subject performed a finger tapping task with both hands. The task consisted of 12 periods of 36 seconds, where each period contained 18 seconds of finger tapping, followed by 18 seconds of rest.

3. Methods

Our proposed method consists of three steps. First, a set of features are extracted for each fMRI time series. In this paper the HRF-based feature space used in [3] has been used. In second step, FCM will be applied on proposed feature space for different number of clusters in order to select the optimal number of clusters using the method described in Section 3.2. Finally, FCM will be applied with the optimal number of clusters. After FCM convergence, the statistical significance of the results will be assessed using the method described in Section 3.1.

3.1 Statistical Inference

After FCM convergence, the cluster with the most similar centroid to stimulation pattern is selected as the active cluster and the membership degrees of each voxel to this cluster (u) is compared with a threshold u_a in order to detect activated voxels. By comparing u at each voxel with u_a one tests the null hypothesis H_0: "no activation", and rejects it if $u>u_a$. To set the statistical significance (the type I error) of this test at level α, the threshold u_a must be found such that $prob(u>u_a \mid H_0) = \alpha$. This requires the probability density function (pdf) $f_u(u|H_0)$,

which cannot be derived theoretically. We use a method based on randomization for finding this pdf. In this research, we use the resampling procedure introduced by Bullmore, *et al* [4], which permutates the wavelet coefficients of fMRI time series in order to make surrogate data under the null hypothesis. The wavelet coefficients (obtained using Daubechies basis with 4 vanishing moments) of the fMRI time series are permutated 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 on each set of randomized data while we hold the center of active cluster found before randomization unchanged, and then the membership degrees of all voxels in the active cluster will be computed. These values construct an empirical histogram which estimates the required pdf $f_u(u|H_0)$. Using this histogram, one finds a proper threshold corresponding to the desired α. Thresholding the active cluster membership degree map of brain voxels with this threshold generates statisticaly meaningful results.

3.2 Cluster Validity

Logically choosing the optimal number of clusters in FCM leads to accurate detection of fMRI activation. The area under the Receiver Operating Characteristics (ROC) curve is commonly considered as a good criterion for characterizing the detection accuracy. We are facing two issues in using ROC curves in fMRI data analysis with fuzzy clustering: first we cannot control the false alarm rate in activation detection via fuzzy clustering; second, there is no way to measure true positive detections when applying the method on experimental fMRI data. The first issue has been addressed with the method described in the pervious section. To overcome the second issue, we used the fact that truly activated voxels tend to be spatially clustered, while falsely activated voxels will tend to be scattered so that one does not expect random spatial activations. These scattered voxels mainly appear as single voxels which are treated in many investigations as false detections and they are removed from the results. We used the number of detected single voxels (voxels with no activated neighbors) as a criterion for estimating the false positive detection in experimental data. In fact, based on spatial connectivity of active voxels, we are looking for the number of clusters that produces the most compact activation regions with less single voxels.

For a particular number of clusters, we do the following setps; first we apply the method proposed in the previous section for various values of α in order to find their corresponding thresholds; using these thresholds then we find the corresponding active regions by thresholding the active cluster membership map obtained from fuzzy c-means clustering (FCM); Next an estimate of true positive detections is made by excluding the single voxels and counting the remaining voxels. We use these estimates in order to derive an estimate of β for different values of α. This produces a ROC curve for the specified cluster number. The area under this ROC curve in the interval [0,0.1] (the common interval for alpha used in fMRI) is used as the cluster validity measure. By performing these steps one can measure the cluster validity for different number of clusters and then select the optimal number which has the maximum measure.

4. Results

An estimate of the false alarm rate of an fMRI detection method can be made by applying the method to the resting state data. In order to provide the resting state data, time series of activated voxels were discarded from each of the 6 fMRI experimental data. After computing the cross-correlation map for each data, the active voxels were detected for false alarm rate of 0.1, and their time series were discarded from the data. This ensures that the remaining voxels are in the resting state. The method, described in Section 3.1, was applied on each resting state data, and activated voxels were detected by assuming different false alarm rates. An estimate of the actual (occurred) false alarm rate is then made in each case by dividing the number of detected voxels to the number of voxels in the analyzed resting state data.

Fig. 1 graphs the expected false alarm rate versus the observed (measured) false alarm rate for all 6 subjects. This figure demonstrates the validity of the statistical values assigned to the results. This validity has been shown in [3] using the resting state data. Here, we have shown the capability of the method on a real dataset.

We have also examined our method for defining the number of clusters on experimental dataset, and compared it to the results of SCF cluster validity measure proposed by Fadili, *et al* [5]. In 4 out of 6 subjects, the two methods derived the same number of clusters, whereas in 2 subjects the results were different by 1.

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. Moritz, *et al* [6] reported activation detection in subcortical regions by changing the temporal duration of the reference function. In the experimental fMRI data, using HRF-based feature space revealed activation in sub-cortical regions where the cross-correlation feature failed to detect them. Fig. 2 shows an example. These results are consistent with those of [6].

5. Conclusion

A method for making statistical inference in fuzzy cluster analysis of fMRI is introduced and its validity is

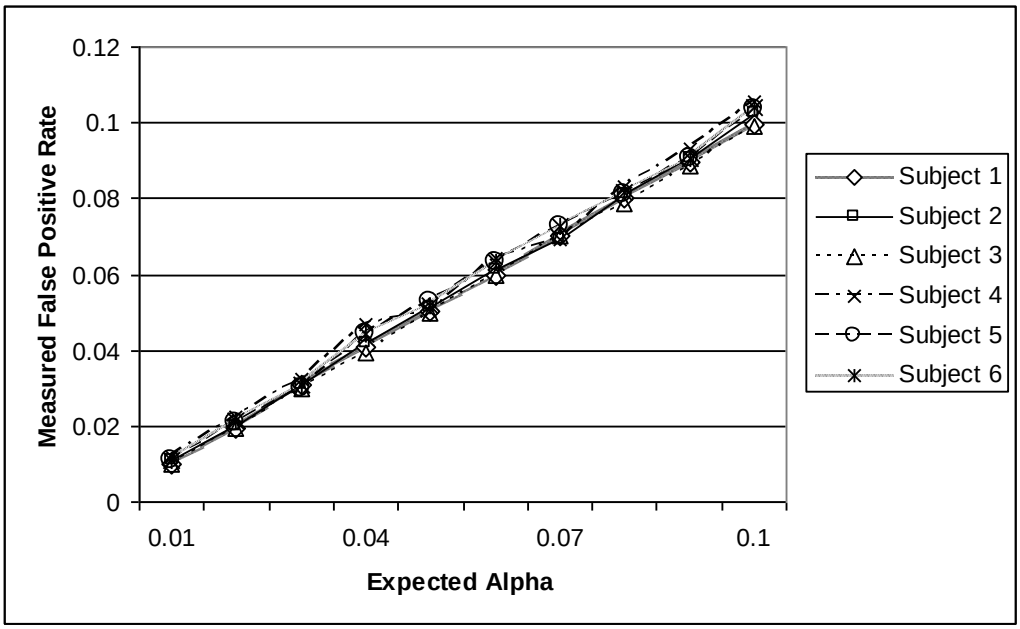

Fig. 1. The measured false positive rates versus their expected value for the 6 subjects.

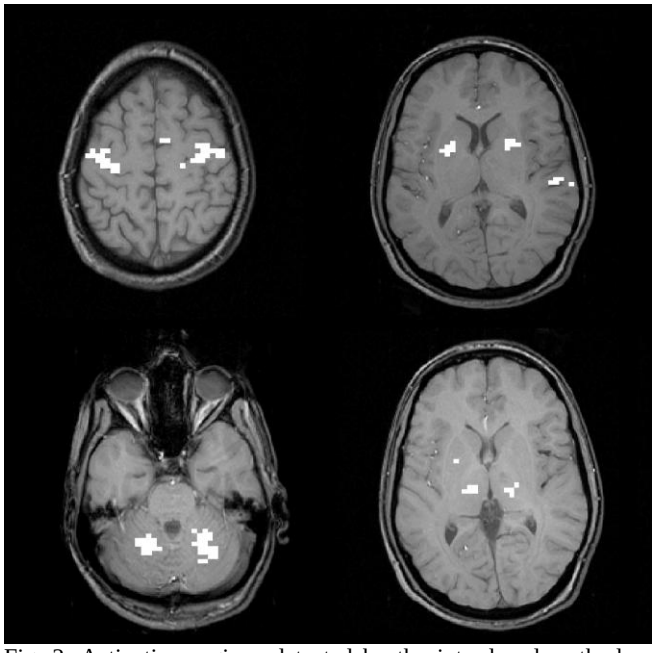

Fig. 2. Activation regions detected by the introduced method, overlaid on the corresponding anatomical slices. Activation is detected in SMC, SMA, thalamus, cellebrum, putamen, and temporal gyrus at $\alpha = 0.005$.

measured by the analysis of 6 experimental fMRI datasets. Using the introduced method, it is possible to compare the FCM with other fMRI activation detection methods. One can also evaluate the performance of different FCM-based methods, such as using different feature spaces. An exact comparison between the different methods cannot be made without considering the statistical significance of the results. Using the introduced method, we compared HRF-based feature space with the cross correlation feature space. In the analysis of 6 finger-tapping fMRI data, activation was detected in sub-cortical regions using HRF-based feature space, where the cross-correlation feature space failed to detect them. Our proposed cluster validity measure also showed less sensitivity to the initial values of FCM compared to SCF method.

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