

Controlling the false positive rate in fuzzy clustering using randomization: application to fMRI activation detection

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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 article, 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. In both cases, the HRF-based feature space provides a greater sensitivity compared to the cross-correlation feature space and conventional cross-correlation analysis. Application of the proposed method to finger-tapping fMRI data, using HRF-based feature space, detected activation in sub-cortical regions, whereas both of the FCM with cross-correlation feature space and the conventional cross-correlation method failed to detect them. © 2004 Elsevier Inc. All rights reserved.

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1. Introduction

Functional magnetic resonance imaging (fMRI) measures changes in the blood oxygenation level produced by neural activity of the brain when a subject performs cognitive, sensory, or motor tasks. Most fMRI experiments use statistical techniques such as *t* tests or cross-correlation analysis to detect active voxels of the brain. In statistical methods, the resulting activation map is usually characterized with a significance level based on the false positive rate (type I error). For comparison studies, one should compare the results obtained by different methods at the same false-positive rate. The main drawback of these methods is their

assumptions about the noise structure, the statistical behavior of fMRI data, and the activation pattern. These assumptions may bias the results obtained by such methods, especially in complex experimental conditions and when applied to data from different subjects [1]. In addition, in these methods, detection is done based on only one statistical variable.

In addition to the above-mentioned model-based statistical methods, model-free methods such as principal component analysis (PCA) [2], independent component analysis (ICA) [3], and cluster analysis have been successfully applied for fMRI analysis [4]; among these, clustering methods have been most commonly used. The aim of clustering is to identify regions with similar temporal patterns of activation. For this purpose, a set of features are derived for each time-series and the clustering techniques partition the resulting feature space into some predefined number of

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clusters, and one or more clusters are chosen as “active clusters.” Different clustering methods, such as k -means [5], Kohonen clustering neural network [1], and hierarchical clustering [6] have been used in this field, but fuzzy C-means (FCM) has been the most popular method [5,7]. FCM computes the membership maps of the brain voxels to different clusters. After FCM convergence, the cluster with the most similar centroid to the stimulation pattern is selected as the active cluster and the membership degree of each voxel in this cluster (u) is compared with a threshold (u_a) in order to detect activated voxels.

An important limitation of FCM and other clustering techniques is their inability to assign statistical significance to the results. Choosing a different number of clusters or thresholding the membership degree at different levels leads to considerably different activation maps. Also, choosing a large threshold or a large number of clusters decreases the probability of false detection. Each result corresponds to a specific but unknown level of confidence. Consequently, one cannot compare the results obtained by statistical and clustering methods.

Aufferman et al. [8] proposed a method to assess the statistical significance for partitioning one cluster into two clusters or merging two clusters into one cluster using bootstrap and Fisher’s linear discriminant function. Using the projection of multi-dimensional data from two clusters onto a vector, they also introduced a measure that may be readily used as a heuristic for estimating cluster homogeneity. In another work, Jarmasz et al. [9] examined the homogeneity of a cluster. Members of each cluster are double checked in order to limit the number of false positives. They modeled each time-series as the cluster center multiplied by a scaling coefficient plus a residual sequence. Based on this assumption, they considered the cross-correlation coefficient between each time-series and the cluster center as a measure of similarity, and purified the cluster by removing data points with small similarity. Baumgartner et al. [10] performed the same significance test through resampling the centers of clusters in the time domain. This method avoids specific assumptions about the noise (residuals) in cluster validation. It may be also used to control the false-positive rate, but its performance needs to be studied. One drawback of the method is the use of the cross-correlation for cluster validation independent of the feature-space used. This may bias or mislead the results because of the limitations of correlation coefficients in distinguishing nuisance components. Furthermore, resampling in the time domain may violate the data exchangeability concept due to temporal correlation in fMRI time-series.

In this article we propose a method based on randomization in wavelet domain to evaluate the statistical significance of activation and to control the false-positive rate in fuzzy cluster analysis of fMRI. Making no specific assumption about the noise structure, the randomization procedure estimates the probability density function (pdf) of “the membership degree to the active cluster (u)” under the null

hypothesis (resting state condition). Using this pdf, we determine the threshold to control the false-positive rate. Our proposed method for controlling the false-positive rate is directly applied to the feature space used for clustering.

Clustering of the raw time-series is potentially capable of separating cognitive or hemodynamic effects without precisely modeling them. However, due to high noise level and existence of nuisance components in fMRI time-series, the results of clustering on the raw time-series are often unsatisfactory, unstable, and do not necessarily group data according to the similarity of their activation contents. Using an appropriate feature space extracted from fMRI time-series alleviates these problems. Scarth et al. [11] used the wavelet transform coefficients as features and then applied FCM. They reported lower sensitivity to noise and artifacts. Goutte et al. [5,12] considered a feature space generated by the cross-correlation between time pattern of stimulus and time-series of brain voxels. They showed that clustering this feature space yields an improved performance and robustness. They assumed a fixed reference as the expected pattern of activation in order to construct the feature space. However, the actual functional response, which may differ in various brain areas, different subjects, and under different conditions even in a simple visual or motor task, is far more complicated than the usually assumed boxcar waveform [1]. Here, we propose a feature subspace, which takes into account this variability, and compare it to the cross-correlation feature space.

We use the proposed approach for controlling the false-positive rate to construct a novel model-independent fMRI activation detection method. The method is applicable to any 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.

2. Materials

2.1. Resting state data

Four healthy volunteers participated in an fMRI study in which resting-state fMRI data were collected using a 1.5-Tesla Siemens Vision MRI scanner. Subjects wore earplugs and lay comfortably in the scanner with their eyes closed during the experiment. A total of 256 image volumes were scanned using a T_2^* -weighted gradient echo single-shot echo-planar imaging (EPI) sequence with repetition time (TR) = 3 s, echo time (TE) = 45 ms, Flip Angle = 90° , and field-of-view (FOV) = 250×250 mm². Each volume consisted of 15 transverse slices of size 64×64 with a pixel size of approximately 3.91×3.91 mm² and a slice thickness of 6 mm with no gaps.

2.2. 3T finger tapping data

An fMRI experiment was conducted on a 3-Tesla GE MRI scanner using a single-shot spiral scan sequence (TR = 2 s, TE = 30 ms, FOV = 220 × 220 × 96 mm³, matrix size = 64 × 64 × 24). Six healthy volunteers participated in this experiment. The subjects performed a finger to thumb opposition task with both hands in a block design fMRI paradigm. The task consisted of 12 periods of 36 s each, where each period contained 18 s of finger tapping followed by 18 s of rest.

2.3. 1.5 T Finger tapping data

Functional images were acquired from 6 additional normal volunteers using a T₂*-weighted gradient echo single-shot EPI sequence (TR = 3 s, TE = 50 ms, FOV = 250 × 250 × 100 mm³, matrix size = 64 × 64 × 20) on a 1.5-Tesla Siemens Vision MRI scanner. The subjects performed a finger to thumb opposition task. The task consisted of 4 periods of 84 s, where each period contained 30 s of left hand finger opposition, 12 s of rest, followed by 30 s of right hand finger opposition, and another 12 s of rest. A 3D high-resolution anatomical image volume was also acquired from each subject using a magnetization-prepared rapid acquisition gradient echo (MP-RAGE) sequence.

In all collected data sets (the 1.5/3-T motor data or the resting state data), the first four volumes of all functional images were discarded and the remaining volumes were motion corrected using the AFNI software package (Medical College of Wisconsin, Milwaukee, WI) [13]. Linear drifts and mean components were then removed from each voxel time-series.

2.4. Simulated data

For a realistic simulation of fMRI data, computer generated “activation” time-series were added to the measured time-series of a single slice from a resting state experimental fMRI data. One set of resting-state fMRI data, described in Section 2.1, was selected and the first four volumes of this set were discarded. The time-series data from a single slice were selected and simulated activation time-series were added to the baseline time-series of voxels in pre-defined regions of interest (spatial pattern) shown in Fig. 1. The “activated” areas have different sizes (3, 6, 8, and 12 pixels) and different contrasts (1%, 1.5%, 2%, and 2.5%). The simulated activation time-series consisted of 252 points obtained by convolving a *stimulation pattern* with the HRF and then adjusting its amplitude to the desired contrast. The stimulation pattern was a boxcar function with five 150-s periods. Each period consisted of 60 s ON condition followed by 90 s OFF or baseline condition. The HRF was modeled by the following gamma function.

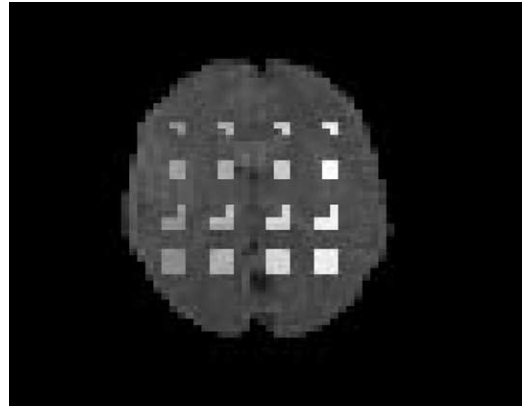


Fig. 1. Spatial pattern of activation in the simulated data. Activations were added to the dataset in the regions shown in this figure. The activation contrasts for the columns from left to right are 1%, 1.5%, 2%, and 2.5%, respectively.

$$h(t; \tau, \sigma) = \begin{cases} e^{-t/\sqrt{\sigma\tau}} \left(\frac{e \cdot t}{\tau} \right)^{\sqrt{\tau/\sigma}} & t > 0 \\ 0 & t < 0 \end{cases} \quad (1)$$

The parameter τ represents the location of the peak of the function and the parameter σ influences its width. In order to model the variability of the HRF, the parameters of the gamma function were varied between different activated voxels by randomly selecting the parameters τ and σ between 3 and 7 s and 0.05 to 0.21, respectively.

3. 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 3.1 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 [14]. 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 3.2. Finally, the membership degree of each voxel to the active cluster is compared to the threshold to determine the active voxels. Figure 2 shows a block diagram of the proposed method.

3.1. Feature extraction

Clustering raw fMRI time-series may lead to instability problems and the risk of clustering on the noise rather than on the activation signal because of poor fMRI signal-to-noise ratio (SNR) and the effect of nuisance components in the time-series. Therefore, the feature space defined by the

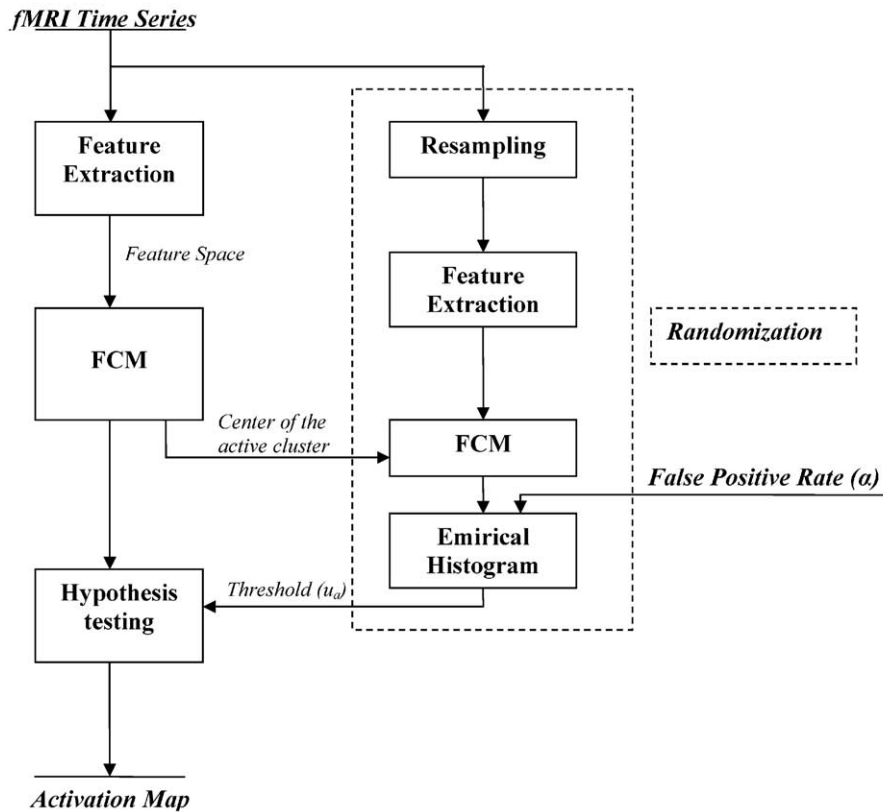


Fig. 2. Block diagram of the proposed method.

cross-correlation of a fixed reference time pattern and the fMRI time-series has been conventionally used for cluster analysis of the fMRI data [12]. However, the hemodynamic response function (HRF) of the brain has been shown to vary between different brain areas and subjects [15] decreasing sensitivity of this method.

The gamma HRF commonly used in statistical analysis of fMRI includes two unknown shape parameters that are usually selected a priori by the analyst. Hossein-Zadeh et al. [16] proposed a new method that approximates the gamma HRF over a wide range of parameters by a linear combination of three elementary signals. These elementary signals were derived from singular value decomposition of a large number of signals generated by systematically varying the parameters of gamma function. The elementary signals together accounted for 99% of the total variation in the data. Figure 3 shows these signals. Convolution of these elementary functions with the stimulation pattern provides three basis functions ($z_1[t]$, $z_2[t]$, $z_3[t]$) for the signal subspace. Therefore, each fMRI time-series may be written as in Eq. (2) where $e(t)$ is the error term considered as noise.

$$y(t) = \alpha_1 z_1(t) + \alpha_2 z_2(t) + \alpha_3 z_3(t) + e(t) \quad (2)$$

The unknown coefficients α_1 , α_2 , and α_3 may be obtained for each voxel through least squares (LS) estimation. We propose to use these coefficients along with a conventional cross-correlation coefficient cc (the cross-correlation

between $y[t]$ and the stimulation pattern) as a feature space for FCM clustering. We call this feature space HRF-based feature space. Considering the ability of the elementary functions to model the hemodynamic response variability, the coefficients α_1 , α_2 , and α_3 are supposed to provide appropriate features for clustering.

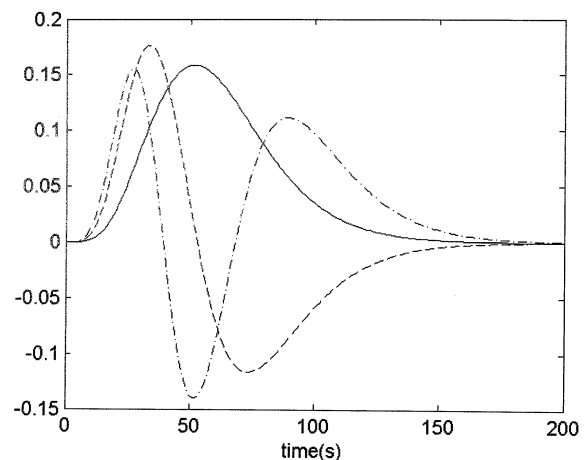


Fig. 3. Basis signals for describing the hemodynamic response.

3.2. False positive rate control

After FCM convergence, the cluster with the most similar centroid to the 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. This threshold strongly affects the statistical significance of the results, and has been chosen heuristically in previous work. By comparing u at each voxel with u_a , one tests the null hypothesis H_0 : “no activation” and rejects it if $u > u_a$. 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 propose a method based on randomization to estimate this pdf. We use the resampling procedure introduced by Bullmore et al. [17], which permutes the wavelet coefficients of fMRI time-series in order to make surrogate data under the null hypothesis. The 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, using the center of active cluster found before randomization and finding membership degrees of all voxels in the active cluster. These values construct an empirical histogram that 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.

The number of clusters is computed using the method proposed in [14]. To eliminate effects of the initial values, the cluster validity measure is computed several times using different random initial values, and the number of clusters obtained most often is used in FCM. As in [14], $m = 2$ is used as the fuzziness index of FCM.

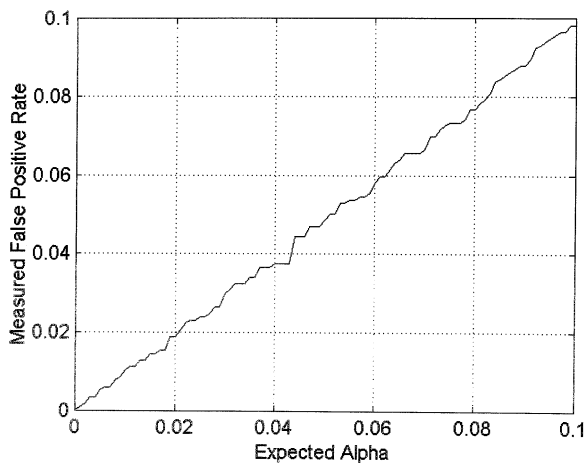


Fig. 4. The measured false positive rates of the proposed method versus their expected values for a resting state fMRI dataset.

Table 1

Numerical values of observed false positive rates versus expected alpha values in 4 resting state fMRI datasets

Alpha (expected)	Subject 1 (measured)	Subject 2 (measured)	Subject 3 (measured)	Subject 4 (measured)
0.01	0.0102	0.0111	0.0102	0.0111
0.02	0.0188	0.0205	0.0188	0.0205
0.03	0.0299	0.0307	0.0299	0.0307
0.04	0.0375	0.0435	0.0375	0.0418
0.05	0.0486	0.0520	0.0495	0.0512
0.06	0.0580	0.0623	0.0597	0.0614
0.07	0.0666	0.0708	0.0683	0.0708
0.08	0.0768	0.0811	0.0776	0.0811
0.09	0.0879	0.0904	0.0879	0.0904
0.10	0.0981	0.1024	0.0990	0.1024

4. 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 each of the resting state datasets described in Section 2.3 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 4 shows the observed (measured) false-positive rate versus the expected false-positive rate for a sample case. Note its closeness to the diagonal line. Table 1 shows the numerical values of the expected and actual false-positive rates for the 4 resting state datasets. A sample histogram (estimated normalized pdf) is shown in Fig. 5.

To evaluate the proposed method, it was compared to the conventional cross-correlation analysis [18]. 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 both the simulated and experimental motor datasets.

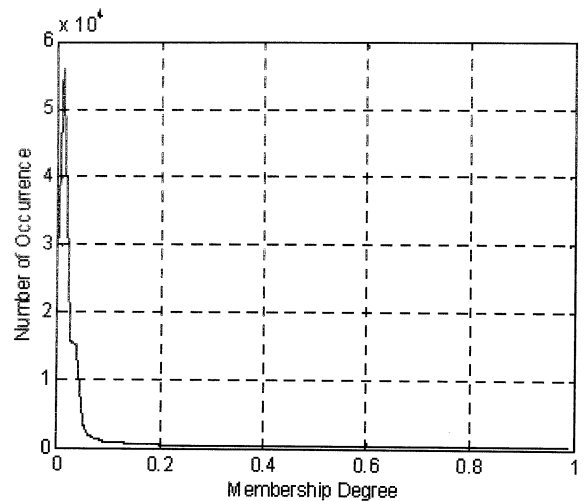


Fig. 5. Histogram of “membership degrees to active cluster” under the null hypothesis, obtained by randomization in an experimental fMRI dataset.

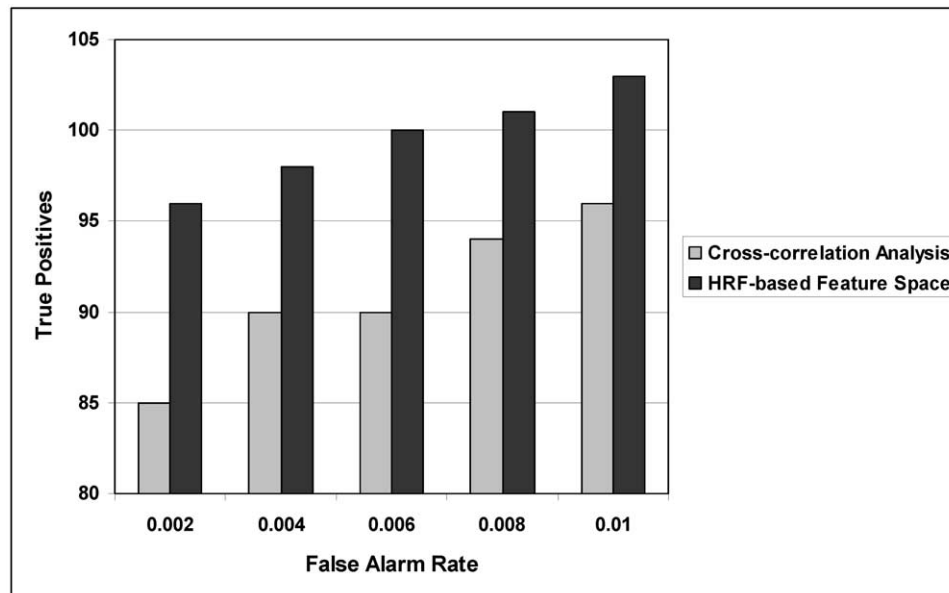


Fig. 6. Comparison of the number of correctly detected active voxels (true positives) in the simulated data for the proposed method with HRF-based feature space and the conventional cross-correlation analysis at different false positive rates. Note the higher sensitivity of the proposed method.

Figure 6 shows the number of true detected pixels in the simulated data at various false-positive rates, which can be considered as samples of the Receiver Operating Characteristics (ROC) curve in the interval $\alpha = [0.001, 0.01]$. 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. Figure 7 shows an example of the activation regions, detected by the proposed method considering the reference signal corresponding to the left hand movements, superimposed on the anatomical images. Figure 8 compares the results of applying the FCM method to the cross-correlation feature space and the HRF-based feature space, using different false-positive rates.

5. 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 complex computation. A complete analysis of a brain volume, with a 1333 MHz IBM compatible PC and the algorithm implemented in MATLAB 6.0 (Mathworks, Inc., Natick, MA) and MS Visual C++ 6.0 executed under Windows XP operating system, takes about 15 min.

The false-positive rate control step reduces the effect of the number of clusters. In the conventional thresholding of the membership degrees (choosing a heuristic threshold), using a different number of clusters produces considerably different results. However, choosing a different number of clusters in our method (which uses dynamic thresholding for false-positive rate control) reduces this difference. This is very important, noting that intensive search for a standard index to determine the number of clusters has not yet succeeded [19].

Although our proposed method for false-positive control can be applied with the FCM to any feature space, we have shown that the proposed method with HRF-based feature space provides improved detection sensitivity over the conventional cross-correlation method. In simulated data, where an ROC curve can be derived, the HRF-based feature space demonstrates an improved sensitivity (Fig. 6). Finger-tapping paradigm regularly produces activation in the sensorimotor cortex (SMC) supplementary motor area (SMA) and cerebellum. Activity in the SMC produces transient neural activity in subcortical regions [14]. Moritz et al. [15] 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. As shown in Table 2, the proposed method succeeded in detecting activation in thalamus, globus pallidus, and transverse temporal gyrus, where the

Table 2
Number of subjects who showed activation in specific regions for different methods

Detected Activation Region	HRF-based Feature Space	Conventional Cross-correlation Analysis	Correlation Coefficient Feature Space
SMA (Supplementary motor area)	12	12	12
SMC (Sensorimotor cortex)	12	12	12
Cerebellum	12	12	12
Globus pallidus	5	0	0
Thalamus	7	0	0
Transverse temporal gyrus	4	0	0

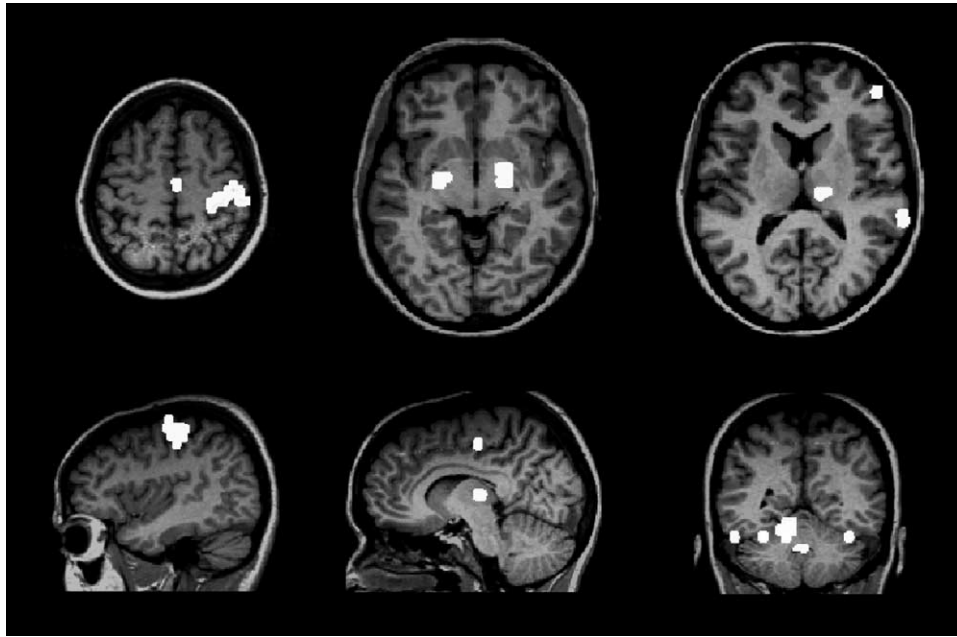


Fig. 7. Activation regions, detected by the proposed method considering the reference signal corresponding to the left hand movements, overlaid on the corresponding anatomical slices in a representative 1.5 T motor task dataset. At $\alpha = 0.005$, activation is detected in SMC (Sensorimotor Cortex), SMA (Supplementary Motor Area), thalamus, cerebellum, globus pallidus, and transverse temporal gyrus.

cross-correlation method failed to detect them. These subcortical areas are expected to activate during complex tasks. The finger to thumb opposition is considered complex when the subject does it carefully and finger by finger as in the experiments done for the fMRI data presented in this article. In addition, other investigators, e.g., [20], have reported activation of these subcortical areas in finger-tapping experiments. Therefore, they may not be considered false alarms. In the

absence of these evidences, some regions may be considered false alarms as a result of voxel-wise detection and not correcting for multiple comparisons.

Also, Fig. 8 illustrates that the HRF-based feature space surpasses the cross-correlation feature space in detection sensitivity. 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

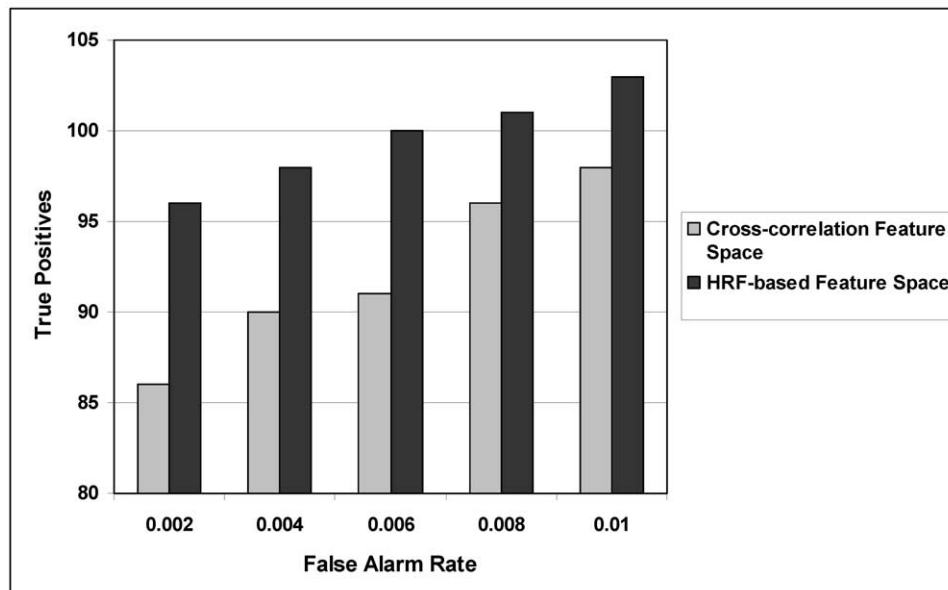


Fig. 8. Comparison of the number of correctly detected active voxels (true positives) in the simulated data for HRF-based feature space compared to cross-correlation coefficient feature space at different false positive rates using the proposed method. Note the superiority of the HRF-based feature space.

achieved in conventional methods such as cross-correlation. In addition, low dimension of the proposed feature space makes the convergence of the FCM considerably faster and eliminates the “curse of dimensionality” effect, which occurs in the high-dimensional feature spaces (such as raw time-series) [21].

Using the proposed method, one can easily find and compare brain activations obtained by different feature spaces. In this article, a comparison was made between two feature spaces: cross-correlation and HRF-based feature spaces. The results show the efficiency of the proposed feature space for fMRI activation detection, suggesting that it describes the activation process better than the cross-correlation.

6. Conclusion

A method for controlling the false-positive rate in FCM was proposed and its efficiency was 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 when compared to the conventional cross-correlation method showed a higher sensitivity. 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 results. The proposed method controls the rate of false-positive occurrence without any assumption about the noise at the expense of computational complexity of randomization. Using this method, we compared two feature spaces: the cross-correlation feature space, and the HRF-based feature space. 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 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.

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