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Accurate Activation Map Detection using Bootstrap Resampling of Single fMRI Data

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Abstract— **Functional magnetic resonance imaging (fMRI) is an effective method for measuring the brain neuronal activities. Numerous statistical methods are used for fMRI analyzing. However, determining the true activated regions among the whole apparent activated voxels is a vital but challenging task. The activation pattern of fMRI data analysis is affected under the presence of source of variations such as noise, artifacts, and physiological fluctuations. Finding an accurate and reliable activation map from a single data analysis is essential for true interpretation of an individual data especially when it should be used in neurosurgical planning. We introduced a resampling process (called Bootstrapping) through the original EPI data, with the aim of evaluating the reproducibility of the activation changes throughout a task-related signal variation.**

***Index Term*– fMRI, Bootstrap Resampling, GLM, Activation Map, Reliability.**

I. Introduction

Functional magnetic resonance imaging (fMRI) is a non-invasive tool which uses local blood oxygenation level for measuring brain neuronal activities. Many methods have been introduced for fMRI analysis based on statistical techniques such as t-test, f-test, ANOVA and cross correlation to determine whether the activation in voxels of brain follows the task-related signal variation [1, 2]. Determining the true activated regions among the whole activated voxels is achieved by selecting a threshold. Due to presence of noise, artifacts and physiological fluctuations in fMRI data series, finding more accurate and reliable activation map from a single data analysis is difficult.

Test-retest analysis [3-6] has been used to assess the reliability of fMRI data. In this method, the utilized task is repeated several times and fMRI data is acquired using the same imaging parameters performed consecutively. The reliability of these datasets is assessed after their individual analysis. The main drawback of the test-retest method is that it takes more scan time which is hard for a patient to bear. Moreover, all the imaging parameters should be identical and the patient is expected to act similarly during each task repetition.

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In order to overcome the problem of the test-retest method the resampling techniques have been proposed. The technique of resampling the data into many new created datasets is called boosting or bagging. Resampling with replacement is usually called jackknife and bootstrap [7]. The major idea of this approach is to use all the independent samples to generate bootstrap datasets. One of the most important aims of the resampling technique is to assess the reliability and reproducibility of a dataset for an analyzing method. The jackknife method [8, 9] was used to compute the reliability and confidence intervals of fMRI parameters during bilateral finger tapping. They showed that the jackknife method acts as well as conventional methods and often even better. The bootstrap method severally has been used to generate many repeated samples from fMRI datasets for the assessment of the fMRI analyzing methods. Auffermann et al. [10] utilized the bootstrap method to assess the significance of the self-organizing maps clustering algorithm applied on event-related data. The consistency of components extracted using Independent Component Analysis (ICA) method was also evaluated by this resampling technique [11].

There are inter-subject and within-subject sources of variation that effect on the validity of the functional analysis of fMRI data. The inter-subject variations can be eliminated using the statistical grouping methods used in fMRI group analysis. The sensitivity of different fMRI grouping methods which provide useful map from individual brain activation patterns was assessed by bootstrapped samples [12]. The jackknife technique deletes each single subject in turn and recalculates the statistical grouping method in order to evaluate their sensitivity to individual fMRI datasets.

Moreover, the within-subject variations such as noise, artifact and head motion vary the activation pattern obtained by single fMRI analysis. The aim of this work was to find the reproducible activation map throughout a task-related signal variation in individual fMRI data analysis. This can be achieved by using a resampling process (called Bootstrapping) on the original EPI dataset, and then to perform a GLM based activation analysis on all copies of the data.

II. Methods

A. FMRI Paradigm Design

Six healthy subjects were asked to perform motor and language block-design tasks. These simple block-design tasks consisted of 8 blocks (4 activation and 4 rest blocks),

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each for 25s alternating with 25s of rest. 64 sequential image volumes were obtained during each task presentation. During the motor task, the subjects were requested to flex and extend left metacarpophalangial joint. Language task was performed asking the subjects to generate words when the letters were presented reversely.

B. Imaging Method

All fMRI data were obtained using a 1.5T GE® Signa scanner. T1-Weighted spin-echo sequence was used to generate high-resolution structural maps of the subject's brain with the same dimension and orientation of the functional images. The fMRI scan was done using a gradient echo planar imaging (EPI) pulse sequence (TR=3125ms, TE=40.3ms, FOV=22cms, slice thickness of 6mm, Matrix size=64*64, Flip angle=90, and bandwidth=62.5kHz). Image acquisition included fifteen axial slices, parallel to the "anterior commissure - posterior commissure" line according to the Talairach atlas (Talairach 1988). During each 25s of rest or activation, eight images containing 15 different slices were acquired every 3.125s.

C. Bootstrap Resampling

Bootstrap resampling was used to replace the time series images (i.e. volumes) of fMRI data randomly in order to create a large number of datasets with no need to repeat the experiment multiple times.

For this purpose, the volumes of each original fMRI data were divided into 4 sections consisting of rest, activation, onset and fall-off parts. These divided rest and activation blocks are shown in Fig. 1.

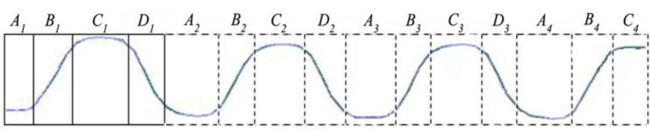

Fig. 1. The volumes of the original fMRI data divided into 4 sections containing rest, activation, onset and fall-off parts.

According to this figure, the *A*, *B*, *C* and *D* sets was defined as below:

$$A = \cup_{i=1}^{l} A_i = \{A_1, A_2, \dots, A_n\}$$
$$B = \cup_{i=1}^{l} B_i = \{B_1, B_2, \dots, B_m\}$$
$$C = \cup_{i=1}^{l} C_i = \{C_1, C_2, \dots, C_p\}$$
$$D = \cup_{i=1}^{l} D_i = \{D_1, D_2, \dots, D_q\} \quad (1)$$

where A_i, B_i, C_i and D_i are the subsets of A, B, C and D and l is the number of their repetition. The members of A_i', B_i', C_i' and D_i' were randomly selected from A, B, C and D sets, respectively (i.e., $A_i' \subset A, B_i' \subset B, C_i' \subset C, D_i' \subset D$). Thus, the bootstrapped data series, S', were set as follow:

$$S' = \{A_1', B_1', C_1', D_1', \dots, A_l', B_l', C_l', D_l'\} \quad (2)$$

After implementing the bootstrap resampling procedure, the new created fMRI datasets were prepared for analyzing.

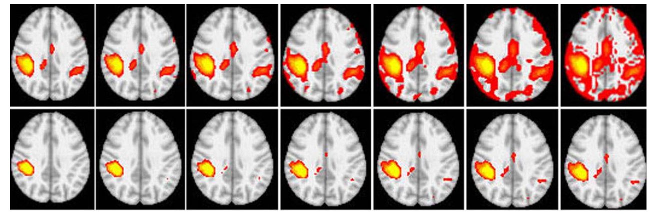

Fig. 2. First row from left to right: Activated regions obtained by analyzing the individual fMRI data stimulated with left hand movement task using the thresholds from 2.3 to 0.01. Second row from left to right: Activated regions obtained by analyzing the bootstrap sampled of the same fMRI dataset in 100th reproducibility percentage using the thresholds from 2.3 to 0.01.

D. Preprocessing and Image Analysis

The preprocessing methods were applied on the bootstrap sampled fMRI datasets. These include extraction the brain from non-brain areas, removing motion artifacts, improving signal to noise ratio (SNR), and removing drifts from raw data. For data analysis the General Linear Model (GLM) algorithm carried out using FEAT (fMRI Expert Analysis Tool) as part of FSL (FMRIB Software Library) software. All the analysis parameters were kept constant for analyzing all the bootstrap samples.

E. Finding the Reliable Activation Map

After analyzing the bootstrap sampled fMRI data, the reliability of activation areas needs to be checked for each individual data. For this purpose, the activation areas obtained by a significant p-value less than 0.05 were considered for all bootstrap samples. A range of z-threshold values (e. g. 2.3 to 0.01) were applied to them as a critical factor for discrimination between active and inactive voxels.

In order to find the most reliable and valid activation regions, the common areas of the GLM analysis outputs of the bootstrap sampled datasets were found using each z-threshold separately. Also, a threshold was considered for reproducibility percentage defined as the number of common activated voxels found in bootstrapped fMRI samples. Thus, any activated voxel repeated in more number of analyzed results were considered as more reliable.

III. Results

The common activated areas of the bootstrap fMRI datasets were extracted after analyzing all the sampled datasets. The activated voxels reproduced from all of the bootstrap samples were considered for the thresholds equal to 2.3, 2, 1.5, 1, 0.5, 0.1, and 0.01. Reducing the z-threshold caused more widening in the activated regions. One slice of the analyzed fMRI data stimulated with left hand movement is shown in Fig. 2 together with the same slice results using the other utilized threshold. Also the regions found by analyzing the bootstrap sampled fMRI datasets which repeated in all the analysis outputs are shown in this figure.

By decreasing the threshold value, more voxels would be found in the common areas.

In order to assess the number of voxels appeared by reducing the utilized threshold, we considered the bootstrap analyzed output using the threshold equal to 2.3 as the base result for our comparison method. It was supposed that in this threshold the bootstrap result has no extra voxels. By decreasing the threshold value, some other voxels appeared as activated voxels. The number of appeared voxels in comparison with the base result (i.e., the result obtained using the threshold equal to 2.3) were counted for the bootstrap fMRI datasets using the mentioned thresholds. This procedure was replicated for all the bootstrap sampled of the language and motor activated fMRI datasets. In addition, the percentages of the activated voxels overlapped with the Talairach atlas regions related to the implemented tasks were computed. The averages of obtained values are inserted in Table I for both presented tasks.

TABLE I
Number of the appeared voxels and the percentage of the activated voxels overlapped with Talairach atlas mask while the analysis output with threshold equal to 2.3 is considered as the base image.

Presented tasks	z-threshold	number of the appeared voxels		Percentage of the activated voxels overlapped with Talairach atlas mask	
		Individual data	Bootstrap samples	Individual data	Bootstrap samples
Language	2	392	67	29.95	73.49
	1.5	1084	128	29.16	68.835
	1	1837	189	27.82	63.31
	0.5	2613	315	26.68	58.61
	0.1	3299	484	25.69	54.21
	0.01	3439	548	25.01	52.19
Hand Movement	2	209	18	31.31	88.56
	1.5	677	36	27.45	87.1
	1	1246	64	22.44	81.94
	0.5	1901	101	18.77	78.19
	0.1	2477	138	16.44	72.40
	0.01	2620	151	15.38	65.88

The number of common activated voxels in fMRI analyzed results from the bootstrapped samples at different z-threshold values indicated that they were not very sensitive to selection of the threshold value. This was not proved in activated voxels found in individual fMRI data analysis and by decreasing the z-threshold the rate of the added voxels increased more than the bootstrap dataset analyses.

For the purpose of assessing the reproducibility percentile, the bootstrap sampled fMRI results using the maximum threshold (i.e., the threshold equal to 2.3) were considered. By selecting the value of the reproducibility percentile, the common activated areas were appeared which were repeated more than the selected percentile. The less reproducibility percentile, the wider activation map were achieved. Similar to the above process, the number of appeared voxels and their maximum value were computed. In this procedure, the bootstrap sampled results using the threshold equal to 2.3 and with 100% of the reproducibility was considered as the origin result for comparison. It was assumed that the activation map of this result has no extra voxels and the appeared voxels were counted in comparison with the based activation area. The computed values are entered in Table 2 for the percentile values equal to 95%, 90%, 85%, and 75%.

TABLE II
Number of the activated voxels and the percentage of the activated voxels overlapped with Talairach atlas mask obtained using different reproducibility percentile.

Presented tasks	Reproducibility percentile	number of activated voxels	Percentage of the activated voxels overlapped with Talairach atlas mask
Language	100	304	68.33
	95	653	56.41
	90	864	52.42
	85	1041	51.28
	75	1495	47.27
Hand Movement	100	84	85.94
	95	141	76.36
	90	173	72.11
	85	211	69.28
	75	330	56.8

As shown in Table II, decreasing the reproducibility percentile cause the increasing in the number of the activated voxels. The added voxels only enlarge the activation map whereas the percentage of the activated voxels overlapped with Talairach atlas mask increase by reducing the reproducibility percentile. This fact shows that the accurate regions are repeated in all the bootstrap analysis outputs.

In order to compare the activation pattern of the bootstrap sampling with the individual fMRI data analysis, their obtained activation areas are shown in Fig. 3 for the presentation of left hand movement task. The analysis results of the individual data using threshold equal to 2.3 is shown in Fig. 3(a), whereas Fig. 3(b) represents the bootstrap resampling results of 100th percentile using threshold value equal to 0.01. The bootstrap results illustrate that the activated regions are the accurate and reproducible areas repeated in all the bootstrap samples.

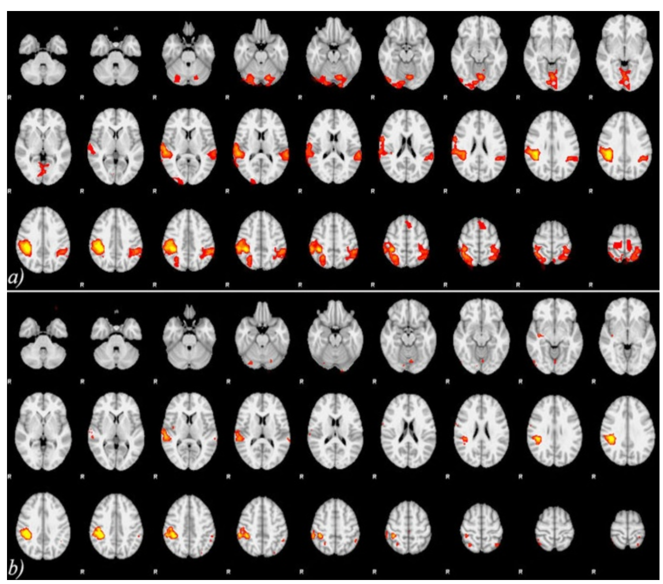

Fig. 3. (a) The results of the individual data analysis using z-threshold equal to 2.3, (b) bootstrap resampling results of 100th percentile using threshold value equal to 0.01. The fMRI data acquired using left hand movement task.

IV. Discussion

FMRI block designed paradigms are arranged in order to let the blood hemodynamic response to reach to the high level and remain in this situation until it drops by stopping the activation duration. In such paradigms the stimulus repeats many times in the activation block where keep the activation effect stable. Moreover, the rest block duration causes the hemodynamic response reaches to its baseline. The time series of fMRI data acquired during the presentation of a block designed tasks are expected to follow the rest/activation pattern. But, there are within-subject variations such as fluctuations and permutations in the time series model caused by system noise, artifacts, head motion or less concentration of the subject during task implementation which affects on the activation pattern. Since the images acquired in each block (activation or rest) should be the same as each other and their differences occur under the influence of within-subject variations, they can be replaced by other fluctuated images from other activation occasions. This is why we expected that the bootstrapping can decrease the false positive voxels which are not able to show their false activation in various reproduced samples. Thus bootstrapping on fMRI data increases reliability of the apparent activated voxels obtained in the single analysis activation map. It can also reproduce true consistent activated regions in all resampled EPI datasets in 100 percent of cases when an optimum z-threshold is selected. Therefore a better accuracy is expected in single fMRI analysis results using this simple validating process.

According to the authors' knowledge, until now, the bootstrapping technique has been used to compute the confidence intervals of fMRI parameters [8, 9] and also to assess the validity and consistency of fMRI analysis methods [10, 11]. Besides, the bootstrap resampling technique has been utilized to evaluate the sensitivity of different fMRI grouping algorithms [12].

We have performed this method on single fMRI datasets to find the reliable and reproducible activated regions containing few uncertain areas in order to be used in neurosurgical planning where there are not any grouping methods to remove the doubtful regions. In addition, since the percentages of the activated voxels overlapped with the Talairach atlas masks are increased in bootstrapping, higher specificity is obtained without any decrease in sensitivity. Insensitivity of the number of common activated voxels obtained in bootstrapped samples due to various thresholds also confirms that the activated voxels are representing true activation. In a constant z-threshold value, achieving higher reproducibility of activation in bootstrapped samples demonstrates more reliability of the activated voxels.

V. Conclusion

We found that bootstrapping on original EPI data increases activation reliability on apparent activated voxels obtained in the single analysis activation map. The bootstrap results illustrated that the activated regions can be reproducibly repeated in all copies of EPI data (100%) when an optimum z-threshold is selected on a true activation map. This confirms a better accuracy in activation map in single fMRI analysis results. In addition, the percentages of the activated voxels overlapped with the Talairach atlas masks for each activation task are increased in bootstrapping. Therefore, this technique can be used on EPI datasets from an individual subject for validating the initial activated voxels in order to be used in neurosurgical planning.

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