# Regional Homogeneity and Anatomical Parcellation for fMRI Image Classification: Application to Schizophrenia and Normal Controls

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**Abstract.** This paper presents a discriminative model of multivariate pattern classification, based on functional magnetic resonance imaging (fMRI) and anatomical template. As a measure of brain function, Regional homogeneity (ReHo) is calculated voxel by voxel, and then a widely used anatomical template is applied on ReHo map to parcelate it into 116 brain regions. The mean and standard deviation of ReHo values in each region are extracted as features. Pseudo-Fisher Linear Discriminant Analysis (PFLDA) is performed for training samples to generate discriminative model. Classification experiments have been carried out in 48 schizophrenia patients and 35 normal controls. Under a full leave-one-out (LOO) cross-validation, correct prediction rate of 80% is achieved. Anatomical parcellation process is proved useful to improve classification rate by a control experiment. The discriminative model shows its ability to reveal abnormal brain functional activities and identify people with schizophrenia.

## 1 Introduction

Schizophrenia is a chronic, severe, and disabling mental disorder that affects about 1 percent of general population. This disorder usually appears in the late teens or early twenties and then persists for a lifetime. Schizophrenia is characterized as diverse clinical presentations, such as hallucinations, delusions, anhedonia, avolition and impaired cognitive functions [1]. Current available schizophrenia diagnosis is mainly based on clinical symptoms and medical history. More objective approaches are needed to help diagnose schizophrenia and further to be extended to identify its subtypes or other psychotic disorders, which sometimes have similar symptoms with schizophrenia.

Functional neuroimaging studies have suggested the neural correlates of these clinical presentations. Due to the fact that brain functional activities not only exists when people perform specific tasks but also maintains in resting state, it is reasonable to hypothesize that abnormal brain activities also appears in schizophrenia when they are in resting state. Most current classification studies trying to distinguish psychiatry diseases from controls focused on structural images [2][3][4], but some recent studies also attempted to extract features from functional images [5][6].

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As a mapping of brain spontaneous activity, regional homogeneity (ReHo) was proposed to measure the temporal similarity of fMRI signals in resting state[7]. In previous studies, ReHo was successfully employed to verify the default mode network and located the region of interests (ROIs) without prior knowledge in a brain functional connectivity research [8][9]. Decreased ReHo pattern were also reported in the patients with schizophrenia [10]. In this paper, ReHo was used as a measure of brain activity, and the result map was subdivided into 116 regions according to an anatomical template [12]. The spontaneous activity differences between schizophrenia and normal controls will lead to different ReHo values in some specific brain regions, that is this classification algorithm based on. Features were extracted in each region and a classifier was then generated based on Pseudo-Fisher Linear Discriminant Analysis (PFLDA). The performance of the classifier was evaluated by using a leave-one-out (LOO) cross-validation approach.

The remaining paper is organized as follows. Materials are presented in Section 2, a general description of our classification approach is in Section 3, experiments on schizophrenia and discussion on results are given in Section 4. We summarize this paper in Section 5.

## 2 Materials

### 2.1 Subjects

55 patients with schizophrenia and 36 controls participated in this study, and then 7 patients and 1 control were excluded according to the following analysis. The remaining 48 (26 males and 22 females, age 23.5±6.6 years) patients were recruited from the inpatient unit at Institute of Mental Health, Second Xiangya Hospital of Central South University. Confirmation of diagnosis was made for all patients by clinical psychiatrists, using the Structured Clinical Interview for DSM-IV, Patient version [11]. The duration of illness was 27.5±38.6 months. The majority of subjects (33 of 48 subjects) were receiving atypical antipsychotic medications and the chlorpromazine equivalent dose was 467.4±215.5mg. Patients were free of any concurrent psychiatric disorders and had no history of major neurological or physical disorders leading to altered mental state. 35 (20 males and 15 females, age 27.1±6.2 years) healthy subjects were recruited by advertisements as control group. All subjects were right-handed and were given written, informed consent prior to take part in the study, which was approved by the Medical Research Ethics Committee of the Second Xiangya Hospital, Central South University.

### 2.2 Image Acquisition and Preprocessing

Imaging was performed on a 1.5-T GE scanner. Foam pads were used to limit head motion and reduce scanner noise. The fMRI scanning was carried out in darkness, and the participants were explicitly instructed to keep their eyes closed, relax, and to move as little as possible. Functional images were collected using a gradient-echo echo-planar sequence sensitive to BOLD contrast (TR/TE = 2000/40 ms, FA = 90°, FOV = 24 cm). Whole-brain volumes were acquired with 20 contiguous 5 mm thick transverse slices,

with a 1 mm gap and 3.75×3.75 mm in-plane resolution. For each participant, the fMRI scanning lasted for 6 minutes.

Subjects were excluded with larger than 1.5 mm maximum displacement in either of x,y,z directions or 1.5 degree of angular rotation. Image preprocessing was then performed using a statistical parametric mapping software package (SPM2, Wellcome Department of Imaging Neuroscience, London, UK). The first 10 volumes of each functional time series were discarded and the remaining 170 volumes were corrected for the acquisition delay between slices and for head motion. To further reduce the effects of other possible source of artifacts, such as six motion parameters, linear drift and the mean time series of all voxels in the whole brain, a linear regression was performed after the fMRI images were normalized to the standard echo planar imaging template, and resampled to $3 \times 3 \times 3$ mm$^3$. The fMRI data was temporally band-pass filtered (0.01-0.08 Hz) [13][14][15]

## 3 Methods

### 3.1 Regional Homogeneity

As a measurement of regional coherence of brain spontaneous activity, Regional homogeneity (ReHo) was defined as the temporal similarity of the low-frequency fluctuations (LLF) in fMRI data [7]. The method was described in brief as follows.

ReHo was calculated with Kendall's coefficient of concordance (KCC) [16], which was assigned to each voxel by calculating the KCC of time series of this voxel with its neighbors:

$$W = \frac{\sum_{i=1}^{N}(R_i)^2 - N(\overline{R})^2}{\frac{1}{12}K^2(N^3 - N)} \tag{1}$$

$$R_i = \sum_{j=1}^{K} r_{ij} \tag{2}$$

$$\overline{R} = (N + 1)K/2 \tag{3}$$

Where $W$ is the KCC, which ranges from 0 to 1; $R_i$ is the sum rank of the $i^{th}$ time point and $r_{ij}$ is the rank of the $i^{th}$ time point in the $j^{th}$ voxel; $\overline{R}$ is the mean of the $R_i$; $N$ is the number of time points of fMRI time series, here $N = 170$; $K$ is the number of one given voxel plus its neighbors, here $K = 27$. An individual $W$ map (ie. ReHo map) is then obtained on a voxel by voxel basis for each subject.

### 3.2 Anatomical Parcellation

After registered to standard stereotaxic space in the preprocessing step, the fMRI volumes were segmented into 116 regions by masking the Automated Anatomical Labeling map (AAL) [12]. This template was validated and widely used in many previous studies [5][17][18][19][20]. This parcellation divided the cerebra into 90 regions (45 in each hemisphere) and the cerebella into 26 regions (9 in each cerebellar hemisphere and 8 in the vermis) as Table 1.

**Table 1.** Cortical and subcortical regions defined in AAL template in standard stereotaxic space

| | | |
|---|---|---|
| Superior frontal gyrus, dorsolateral | Calcarine fissure | Postcentral gyrus |
| Superior frontal gyrus, orbital | Cuneus | Superior parietal lobule |
| Superior frontal gyrus, medial | Lingual gyrus | Inferior parietal lobule |
| Superior frontal gyrus, medial orbital | Superior occipital gyrus | Supramarginal gyrus |
| Middle frontal gyrus | Middle occipital gyrus | Angular gyrus |
| Middle frontal gyrus, orbital | Inferior occipital gyrus | Precuneus |
| Inferior frontal gyrus, opercular | Superior temporal gyrus | Paracentral lobule |
| Inferior frontal gyrus, triangular | Temporal pole: superior | Posterior cingulate gyrus |
| Inferior frontal gyrus, orbital | Middle temporal gyrus | Caudate nucleus |
| Olfactory cortex | Temporal pole: middle | Putamen |
| Gyrus rectus | Inferior temporal gyrus | Pallidum |
| Anterior cingulated | Heschl gyrus | Thalamus |
| Precentral gyrus | Fusiform gyrus | Insula |
| Supplementary motor area | Hippocampus | Cerebellum hemisphere |
| Median cingulated | Parahippocampal gyrus | Vermis |
| Rolandic operculum | Amygdala | |

### 3.3 Feature Extraction

To distinguish the abnormal brain activity in schizophrenia from normal controls, a feature extraction method was proposed. The fMRI volumes were first performed to calculate Kendall's coefficient of concordance voxel by voxel. The resulting ReHo values were then normalized to zero mean and unit variance of each subject to reduce total variance across subjects. The scaled ReHo map was then parcellated according to AAL template. The mean and standard deviation of ReHo value were calculated in each of 116 regions, so resulting into 232 measurements of each brain. Because the feature dimension was much higher than the training sample size, these measurements were processed with principle component analysis (PCA) and then projected into a lower-dimension space, and PC coefficients were obtained and taken as features.

### 3.4 Pseudo-fisher Linear Discriminant Analysis

Fisher Linear Discriminative Analysis (FLDA), a widely used technique for pattern classification, is designed to project data from $D$ dimensions onto an appropriate line on which projected samples are well separated [21][22].

Suppose that we have a set of $n$ $D$-dimensional samples $x$,

$$z = \omega^t x, \quad x = (x_1, x_2, \cdots, x_n)^t \tag{4}$$

Where $z$ is the scalar dot product on the line, $\omega$ is the projective direction.

Theoretically, this line can be found by maximizing the ratio of between-class separability to within-class variability. To this purpose, FLDA considers maximizing the following objective function:

$$J(\omega) = \frac{\omega^t S_b \omega}{\omega^t S_w \omega} \tag{5}$$

Where $S_B$ is the between classes scatter matrix and $S_\omega$ is the within classes scatter Matrix. The definitions of the scatter matrices are:

$$S_b = (m_1 - m_2)(m_1 - m_2)^t \tag{6}$$

$$S_w = \sum_{i=1}^{N_1}(x_1^i - m_1)(x_1^i - m_1)^t + \sum_{i=1}^{N_2}(x_2^i - m_2)(x_2^i - m_2)^t \tag{7}$$

Where $m_1$ and $m_2$ are mean feature vectors of each group, $N_1$ and $N_2$ are sample size of each group. Finally, the optimal $\omega^*$ can be determined by:

$$\omega^* = S_\omega^{-1}(m_1 - m_2) \tag{8}$$

However, the number of features are always much higher than the number of total training samples in neuroimaging research ($N_1 + N_2 \ll D$, $D$ is dimension of feature space). Computing inverse matrix of $S_\omega$ will lead to an ill-posed problem because FDA will yield unreliable results in this condition. Dimension reduction is needed to preprocess the features. In Pseudo-Fisher Linear Discriminative Analysis, principal component analysis (PCA) is firstly applied on sample features $x \in \Re^n$, samples are then projected to a lower dimensional space and new features $x' \in \Re^{n'}(n' \leqslant N_1 + N_2 - 1)$ are generated. In this study, we have performed PCA step to solve this ill-posed problem in section 3.3. After this, the classical FLDA procedure can be performed and the projective direction $\omega^*$ will be obtained.

After projecting data from $D$ dimensions onto that line, the last thing is to define threshold on it, which is determined by:

$$z_0 = (N_1 m_1^z + N_2 m_2^z)/(N_1 + N_2) \tag{9}$$

Where $m_1^z$ and $m_2^z$ are the mean of projective scores of the two classes, respectively.

## 4 Experiments Results

Our approach was implemented in 48 schizophrenia and 35 normal controls.

To evaluate the performance of proposed discriminative model, a full leave-one-out (LOO) cross-validation was performed. One subject was first selected as test, and the remaining were trained for classification model. Pseudo-Fisher Linear Discriminant Analysis (PFLDA) was employed as classifier. By repeating leave each subject out for test, the average classification rate was obtained. Finally, whole experiments were repeated by choosing the first m ($m \leqslant N_1 + N_2 - 1$) PC coefficients as features to test the stability of results. Besides the test subject, we had total 82 subjects thus m would be chosen from 1 to 81.

Classification results were shown in Fig 1, from which the best correct prediction performed on patients and controls were 83% and 74% when using 81 features, and the total correct prediction rate reached 80%.

The top 10 regions were obtained by tracing the features with largest weight in fisher classifier and listed as Table 2. Among of them, Inferior frontal gyrus, Superior and

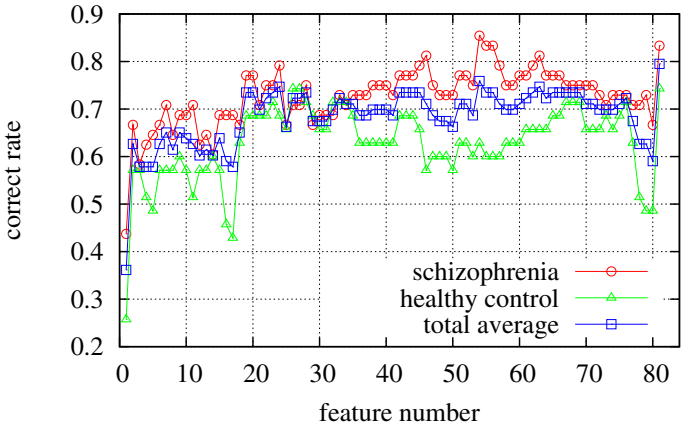


**Fig. 1.** Classification results. Circle line: correct prediction rate of schizophrenia. Triangle line: correct prediction rate of normal controls. Square line: average correct prediction rate of total subjects.

**Table 2.** Top 10 discriminative regions

| Index | Region | Feature | Index | Region | Feature |
|---|---|---|---|---|---|
| 1 | Superior parietal lobule, right | Mean | 6 | Cerebellum hemisphere, right | Mean |
| 2 | Pallidum, right | Mean | 7 | Inferior parietal lobule, right | Mean |
| 3 | Hippocampus, left | SD | 8 | Fusiform gyrus, right | SD |
| 4 | Amygdala, right | Mean | 9 | Calcarine fissure, left | SD |
| 5 | Olfactory cortex, right | Mean | 10 | Inferior frontal gyrus, orbital, left | Mean |

**Table 3.** Classification results under leave-one-out

| Discriminative model | Schizophrenia | Normal controls | Total |
|---|---|---|---|
| Proposed method | 83% | 74% | 80% |
| Control method | 81% | 66% | 74% |

Inferior parietal lobule, Pallidum, and some regions in limbic system including Hippocampus, Amygdala and Olfactory cortex had been widely reported related with schizophrenia [23][24]. The Cerebellum hemisphere, not reported widely, has also considered to be involved in schizophrenia [18].

To evaluate the effect of anatomical parcellation in classification process, a control experiment was designed. After obtaining ReHo map, PCA was directly performed for each subject and PC coefficients were taken as features. Different with the previous method, the parcellation step was removed in the control method, which was also the traditional way to extract features. Classification results were shown as Table 3, from which the best correct prediction performed on patients and controls were 81% and 66%, and the total correct prediction rate only reached 74%, which was obviously lower

than the previous method. Therefore, the parcellation information was proved to be important to improve the classification accuracy.

## 5 Conclusion

In this paper, a supervised multivariate classification method was proposed for distinguishing schizophrenia from normal controls by using the features containing both functional and anatomical information. Regional homogeneity of fMRI signals provided brain function information, and anatomical prior knowledge was given by AAL template. The experiment results indicated that the proposed method achieved satisfactory classification rate in this schizophrenia study. Compared with control experiment, anatomical parcellation process which took brain anatomical distribution into consideration was proved contribute to improve the discriminative power.

The best prediction rate is 80%, however, this may not enough to meet the requirement of clinical applications. Nonlinear approaches and feature selection method could be investigated in further research for improving the classification performance. Combining with other types of features could also be considered to further improve the efficiency of proposed discriminative model.

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