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RESEARCH ARTICLE

Mean deviation based identification of activated voxels from time-series fMRI data of schizophrenia patients [version 1; peer review: 1 approved, 1 approved with reservations]

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Abstract

Background: Schizophrenia is a serious mental illness affecting different regions of the brain, which causes symptoms such as hallucinations and delusions. Functional magnetic resonance imaging (fMRI) is the most popular technique to study the functional activation patterns of the brain. The fMRI data is four-dimensional, composed of 3D brain images over time. Each voxel of the 3D brain volume is associated with a time series of signal intensity values. This study aimed to identify the distinct voxels from time-series fMRI data that show high functional activation during a task.

Methods: In this study, a novel mean-deviation based approach was applied to time-series fMRI data of 34 schizophrenia patients and 34 healthy subjects. The statistical measures such as mean and median were used to find the functional changes in each voxel over time. The voxels that show significant changes for each subject were selected and thus used as the feature set during the classification of schizophrenia patients and healthy controls.

Results: The proposed approach identifies a set of relevant voxels that are used to distinguish between healthy and schizophrenia subjects with high classification accuracy. The study shows functional changes in brain regions such as superior frontal gyrus, cuneus, medial frontal gyrus, middle occipital gyrus, and superior temporal gyrus.

Conclusions: This work describes a simple yet novel feature selection algorithm for time-series fMRI data to identify the activated brain voxels that are generally affected in schizophrenia. The brain regions identified in this study may further help clinicians to understand the illness for better medical intervention. It may be possible to explore the approach to fMRI data of other psychological disorders.

Keywords

fMRI, Schizophrenia, Time-series, Classification

Open Peer Review

Approval Status

	1	2
version 2 (revision) 20 Dec 2018		view

version 1 08 Oct 2018	view	view

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2. **Sagarika Bhattacharjee**, Nanyang Technological University, Singapore, Singapore

Any reports and responses or comments on the article can be found at the end of the article.

This article is included in the **Brainhack Global** collection.

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Author roles: Chatterjee I: Conceptualization, Formal Analysis, Investigation, Methodology, Project Administration, Resources, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing

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Introduction

Schizophrenia is a severe mental disorder that affects different regions of the brain, often involving hallucinations and delusions. Functional magnetic resonance imaging (fMRI) data comprising 3D brain scans acquired over time (thus resulting in a 4D set) is often used to study brain regions affected by schizophrenia. Each voxel of the 3D brain volume is associated with a time series of signal intensity values. General linear model (GLM)¹ and independent component analysis (ICA)² are often employed to study the voxel activity by transforming the 4D time-series data to a 3D spatial map.

The present work involves a novel application of mean deviation on time-series fMRI data to identify the distinct voxels that show high functional activation during a task. The work aims to identify the relevant brain regions that are affected in schizophrenia. Further, the identified voxels (features) are used to distinguish between schizophrenia patients and healthy subjects.

Methods

fMRI data

The time-series fMRI data having 1.5T strength was taken from the FBIRN phase – II data repository³ available at site 0009 and site 0010. From the dataset, four different runs of auditory oddball task data of 34 schizophrenic patients (group G1) and 34 healthy controls (group G2) were extracted. Every run of each subject's data contains 140 brain volumes acquired in 280 seconds time (TR = 2 seconds). Table 1 shows the dataset details.

Pre-processing of the fMRI data was done using SPM8 toolbox in Matlab2014b. The temporal variation was corrected using slice timing correction, followed by the motion correction using realignment. Each of the fMRI scans was spatially normalized into standard Montreal Neurological Institute (MNI) space using an EPI template yielding voxel dimension of 3×3×3 mm³. Finally smoothing was done using a 9×9×9 mm³ full width at half maximum (FWHM) Gaussian kernel, resulting in a 3D brain volume containing 53×63×46, i.e., 1,53,594 voxels.

Data analysis

The activation pattern of the voxels was analysed in two phases.

Phase I. In the first phase, identification of voxels exhibiting high activation pattern (anytime during its time-course) is carried out for each subject. As the study focused on the variation in the signal intensity of the voxels (V) over time, absolute mean deviation ($\bar{V}_d$) for each of the 140 time points was computed

for each voxel, and the median (M) of the 140 values of $\bar{V}$ was found. Mean deviation ($\bar{V}$) values were compared with α times M (α was chosen to be 3, based on experimentation) to identify whether a voxel exhibited high level of activation at any time during the 140 units of time. This voxel-wise analysis was performed for all the voxels of a given subject. Thus, a set of relevant voxels showing high degree of activation was obtained for each subject.

Phase II. In the second phase, a common subset of voxels exhibiting high degree of activation across all the subjects within a group was obtained. Finally, both the subsets belonging to groups G1 (schizophrenia patients) and G2 (healthy controls) were merged to get the set S . The voxels in set S were back-tracked to MNI brain space and finally mapped into Talairach's space⁴ to identify the brain regions. This procedure has been described in Algorithm 1.

Classification. The set S was used to distinguish between schizophrenia patients and healthy subjects using two classifiers, viz., support vector machine (SVM) with sigmoid kernel⁵ and extreme learning machine (ELM) classifier⁶.

Experimental settings. All the implementations were done in MATLAB2014b. Parameter α was varied in the range^{1,7} in steps of 1 to identify the number of voxels that exhibited a high level of activations during the task. When the value of α was taken as 1 and 2, a large number of voxels showed activation level higher than α times M , resulting in set S having voxels that represents almost the entire brain. However, for $\alpha = 3$, it was found that set S contained only 1580 distinct voxels that mapped to the brain regions which are generally affected in schizophrenia. When α was taken as more than 3, the number of voxels in the set S were close to zero rendering it too small for any meaningful analysis. Thus, $\alpha = 3$ was found to be the most suitable value.

Further, the set S of voxels obtained $\alpha = 3$ was used to fine-tune the classifiers. The SVM classifier gave the best results for the regularization parameter $C = 1.09$, and sigmoid kernel based ELM classifier gave best the results with 503 hidden neurons.

To evaluate the distinguishing capability of the voxels/features in set S , a comparison was done between the classification accuracy obtained using S and the accuracy obtained using the voxels set given by the GLM based approach. In this case, GLM was applied using SPM8 toolbox to convert the 4D time-series fMRI data to 3D contrast map for each subject. The

Table 1. Dataset details.

Subject	Sample size	Age (Mean & Std Dev)	Male/Female
Healthy	34	37.76 (± 12.25) years	24/10
Schizophrenia	34	39.76 (± 10.8) years	27/7

GLM yielded an activation map comprising around 60000 voxels out of 153594 which were activated during the task.

Algorithm 1. The proposed approach

Notations:

m (=34): the number of subjects in each group

n (=140): the number of observations in a run

$\mathbf{V}_i$: time-series of i^{th} voxel

i.e. $\mathbf{V}_i = [v_{i,1} \ v_{i,2} \ v_{i,3} \ \dots \ v_{i,n}]$:

μ_i : mean of $\mathbf{V}_i$ i.e. $\mu_i = \frac{\sum_{j=1}^n v_{i,j}}{n}$

Steps:

1. Calculate absolute mean deviation for each voxel using $\bar{V}_{d_i} = |\mathbf{V}_i - \mu_i|$.
2. Find median M_j of $\bar{V}_{d_i}$.
3. For each subject $k \in \{1, 2, \dots, m\}$, select the set $\mathbf{V}_{s_k}$ of voxels that show deviation higher than αM_j .
4. Find the group wise intersection of the voxels selected in step 3 for groups G1 and G2

$$\text{i.e. } \mathbf{V}_{s_{G1}} = \bigcap_{k=1}^m \mathbf{V}_{s_k} (G1)$$

$$\mathbf{V}_{s_{G2}} = \bigcap_{k=1}^m \mathbf{V}_{s_k} (G2)$$

5. Merge the two sets, obtained in step 4 to obtain set $\mathbf{S}$

$$\text{i.e. } \mathbf{S} = \mathbf{V}_{s_{G1}} \cup \mathbf{V}_{s_{G2}}$$

6. Map $\mathbf{S}$ into the brain space to identify affected regions.

Results

A comparison of the results of the classification accuracies obtained using feature sets given by the GLM and the proposed approach is shown in Table 2. The features selected by the proposed approach when backtracked to Talairach's space revealed the brain regions that are generally affected in schizophrenia⁸⁻¹⁰, which validates the efficacy of the approach. The distribution of the selected voxels that distinguish the schizophrenia patients from the healthy subjects is shown in Figure 1 (a-d). Figure 2 (a-c) show the activated voxels when plotted on a sample fMRI image for an axial, coronal and sagittal view of the brain.

Discussion

Unlike other conventional methods such as GLM to select the voxels showing a statistically significant response to the

experimental conditions⁷, the proposed approach identifies the neural activity in a particular voxel over time, irrespective of any experimental condition. The proposed approach does not require any details for the task and conditions. It works on the temporal values of each voxel for each subject's data one by one. Like other multi-voxel pattern analysis (MVPA) methods^{7,11,12}, this approach also tries to find the participation of multiple voxels when selecting the final set of relevant voxels across a particular group of the subjects.

The classification accuracies, as shown in Table 2, demonstrate the efficacy of the proposed methodology. The reduced set of 1580 voxels achieved a much higher accuracy when compared to the GLM approach. Figures 1a-d show the distribution of the selected voxels for each level of brain regions. These regions show distinct changes in functional activation in schizophrenia patients when compared to healthy controls, and thereby distinguish between schizophrenia and healthy subjects with high classification accuracy. Most of the regions identified in the study comply with the existing literature¹³⁻¹⁶. The regions such as superior frontal gyrus, cuneus, lingual gyrus, medial frontal, middle occipital gyrus, superior temporal gyrus, anterior cingulate, and declive show the changes in functional activation. Studies showed functional changes in superior frontal gyrus¹³, superior temporal gyrus¹⁵, lingual gyrus¹⁵, and cuneus¹⁵. Even functional abnormality in anterior cingulate was found in several studies^{16,17}. The literature also suggests functional changes in middle occipital gyrus¹⁸. When observed at the cell level of brain regions in Talairach's space, this study shows distinguishable functional changes in Brodmann's area (BA) 18, 10, 9, 17, 19, 32, 21, 37, 11, and BA 6. Previous studies^{14,19} also showed changes in functional activation in these areas of the brain.

Conclusions

This work describes a simple and fast feature selection algorithm based on mean deviation for time-series fMRI data to identify the activated brain voxels that are generally affected in schizophrenia. The proposed approach was found to be efficient in selecting a minimal set of relevant voxels directly from time-series 4D fMRI data. The obtained voxel set was capable of distinguishing between healthy and schizophrenic subjects. One may explore the possibility of applying this approach to fMRI data of other psychological disorders.

Table 2. Comparison showing classification accuracy with feature set obtained after GLM and the proposed approach using SVM and ELM classifiers.

	GLM	Proposed approach
Number of voxels	~ 60,000	~ 1580
SVM with Sigmoid kernel	32.45%	76.47%
ELM with Sigmoid kernel	57.35%	61.46%

GLM, general linear model; SVM, support vector machine; ELM, extreme learning machine.

Figure 1. Identified brain regions at different levels of hierarchy, namely, hemisphere level (a), lobes level (b), gyrus level (c), and Brodmann's area level (d).

Figure 2. Voxels identified by the proposed approach plotted over a functional brain image in different views of the brain, i.e., axial (a), coronal (b) and sagittal (c) plane.

Data availability

The Matlab source codes, a text file containing dataset details including subject ID and their age, and the instructions for the study can be found at: https://github.com/IndraChatterjee/AnomalyDetection_TimeSeries_fMRI_Schizophrenia.

The complete source codes are archived in a publicly accessible record at: <https://doi.org/10.5281/zenodo.1438539>²⁰

License: CC0

The four runs of auditory oddball task fMRI data from the FBIRN phase II repository can be downloaded from

<http://schizconnect.org/> querying 1.5T fMRI data for healthy and schizophrenia subjects available at site 0009 and 0010. The list of subjects chosen for this study is mentioned in the 'DataDetails_FBIRN15T.txt' file available at the GitHub repository. Users are required to sign-up to SchizConnect to download data and conditions of use are as written in the [data use agreement](#) of the FBIRN project.

Author endorsement

Cameron Craddock confirms that the author has an appropriate level of expertise to conduct this research, and confirms that the submission is of an acceptable scientific standard. Cameron Craddock declares the following competing interests: I am

the Chair of Brainhack, and this organisation awarded this paper this year's Brainhack poster prize. Affiliation: Associate Professor of Diagnostic Medicine, Dell Medical School, The University of Texas at Austin, Austin, TX, USA.

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<http://www.doi.org/10.5281/zenodo.1438539>

Open Peer Review

Current Peer Review Status:

Version 1

Reviewer Report 22 November 2018

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Sagarika Bhattacharjee

Department of Psychology, Nanyang Technological University, Singapore, Singapore

The present study describes an methodology that classifies schizophrenia patients from healthy controls.

The study claims to demonstrate high classification accuracy.

The study has significant relevance to the neuroscience community however I have following concerns:

1. The functional significance of the brain regions involved needs to be elaborated so that their activation could be validated. The description of the role of obtained brain regions in schizophrenia patients and healthy individuals will indicate that the obtained regions are actually involved in schizophrenic patients and not a result of Type II error.
2. It will be good to provide some details about the demographics, level of education, duration of disease, medication history of the participants in order to evaluate the role of these confounding factors in the obtained results. These factors might cause some variation in the fMRI signals and just wondering if any of these parameters were taken as covariate in the analysis.
3. The fMRI signals obtained are task state and not resting state. These signals were obtained while doing oddball paradigm. So, I was wondering whether such classification would apply to schizophrenia patients only when they are doing this particular task, or it would apply to all schizophrenic patients irrespective of their state.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

I cannot comment. A qualified statistician is required.

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: I know the author personally from a conference

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 09 Dec 2018

Indranath Chatterjee, University of Delhi, Delhi, India

I am thankful to the respected referee for her insightful comments and valuable suggestions.

I have updated the manuscript in accordance with the suggestions and queries. The suggested changes are made in the discussion section of the revised manuscript. I have also included some demographic details of the subjects in the dataset table. As I have not incorporated any covariates in this study, the limitation and the scope of future works are added in the discussion section.

Competing Interests: No competing interests were disclosed.

Reviewer Report 01 November 2018

<https://doi.org/10.5256/f1000research.17921.r39310>

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Sahil Bajaj

Social, Cognitive and Affective Neuroscience Laboratory (SCAN Lab), Department of Psychiatry, College of Medicine, University of Arizona, Tucson, AZ, USA

Here author describes an interesting algorithm to identify the activated brain voxels affected in schizophrenia from time-series fMRI data.

I think this is an interesting paper and a nice example which can be implemented in more severe cases of mental distress.

However, I have few minor concerns:

- How did the author remove the effect of gender, I noticed that there are way more males in the data than females.
- I can see some voxels outside the brain and which are at the skull. I am not sure why did the author get those voxels and if the author made any effort to exclude those voxels?

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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