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Recognition of early-onset schizophrenia using deep-learning method

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Abstract

Functional connectivity at resting state was found altered in early-onset schizophrenia patients. However, its potential as biomarker of clinical diagnosis is unknown. To test whether resting-state functional connectivity can be a potential biomarker of classifying patients from controls, 39 early-onset schizophrenia patients and 31 healthy controls were included in our study. Resting-state functional MRI networks were built with the whole brain atlas as classification features to distinguish patients from healthy controls. Three-stage deep-learning network was used to deduce dimension reduction, and feedforward back propagation neural networks were used as classifier. As the result, the classification accuracy reached 79.3% (87.4% for sensitivity, 82.2% for specificity, $p < 0.05$ for permuted test). Our works showed us that resting-state connectivity presented good potential classification capacity and can be used as biomarker of clinical diagnosis.

Keywords: Functional connectivity, Pattern recognition, Deep-learning

Introduction

Schizophrenia is a complex syndrome lacking integration between thought, emotion, and behavior cognitive and affective deficits (Fornito et al. 2012). The disease affects nearly 1% of the world's population (McGrath et al. 2008). Early diagnosis can significantly improve treatment response and reduce associated costs (McGlashan 1998). The absence of stable and reliable biomarkers makes current diagnosis of schizophrenia, which mainly relies on clinical manifestations by experienced clinician, a challenging task (Nieuwenhuis et al. 2012). In recent years, fMRI has turned out a powerful tool to study psychosis. Especially, resting-state functional connectivity, in the absence of explicit task, captures a spontaneous, stable, and intrinsic property of brain functional organization (Shehzad et al. 2009; Fox and Raichle 2007). Dysfunctional connectivity in resting state was found in schizophrenia patients (Woodward et al. 2011; Whitfield-Gabrieli et al. 2009; Rotarska-Jagiela et al. 2010). Whether resting-state functional connectivity has potential to be diagnostic indicators is unknown.

Small number of subjects and much too higher-dimensional data in fMRI make it a challenge to design an accurate, robust classifier to discriminate and research schizophrenia. To address this critical issue, different types of feature extraction, selection methods have been proposed to reduce the dimensionality of feature space. However,

traditional feature selection or extraction methods mainly rely too much on mathematical method and ignore physiological significance; those features that are discarded mathematically may have vital positions in emergence and development of disease. Making an accurate prediction with high-dimensional data seems a difficult job (Liu et al. 2012). In recent years, deep-learning turns out to be a good solution to this problem (Hinton and Salakhutdinov 2006). By applying autoencoder method, high-dimensional data were mapped in low dimension, this method presented good practicability (Hazlett et al. 2017). The model used in our research was first raised by Hinton and Salakhutdinov (2006); its core idea is that high-dimensional data can be converted to low-dimensional codes by training a multilayer neural networks with a small central layer to reconstruct high-dimensional input vectors. Comparing with most used PCA, this model shows a distinct advantage.

In current study, resting state was calculated and used as classification features and sent to Three-stage deep-learning network. Then feedforward back propagation neural networks were used as classifier to classify patients from controls. We expected to find that resting-state functional connectivity presented good potential classification capacity.

Materials and methods

Participants

A total of 39 EOS patients were recruited from the Second Affiliated Hospital of Xinxiang Medical University. All patients were independently diagnosed by research psychiatrists and satisfied the following criteria: (1) DSM-IV-TR criteria for schizophrenia (Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision, American Psychiatric Association, 2000); (2) no co-morbid Axis I diagnosis; (3) duration of illness is less than 2 years; (4) anti-psychotic-naive. Patients were interviewed again after 6 months for a final schizophrenia diagnosis. The symptoms were evaluated using the Positive and Negative Syndrome Scale (PANSS). A total of 31 age-, gender-, education-, and IQ-matched healthy adolescents were included in this study. All HCs did not have any past or current neurological disorders, family history of hereditary neurological disorders, and history of head injury resulting in loss of consciousness and substance abuse.

This study was approved by the Ethics Committee of the Second Affiliated Hospital of Xinxiang Medical University, and informed written consents were obtained from all subjects.

Data acquisition

All subjects were instructed to rest with their eyes closed, not to think of anything in particular, and not to fall asleep during the resting-state fMRI (rs-fMRI) scanning (Marx et al. 2004; Pang et al. 2015; Wei et al. 2014). fMRI data were collected using the 3T MRI scanner (Siemens-Trio, Erlangen, Germany) of the Second Affiliated Hospital of Xinxiang Medical University. Scanning and clinical assessments were performed in 1 day. Functional images were collected transversely using an echo-planar imaging (EPI) sequence with the following settings: TR/TE = 2000/30 ms, flip angle = 90°, FOV = 220 × 220 mm², slices = 33, matrix = 64 × 64, inter slice gap = 0.6 mm, and

voxel size = $3.44 \times 3.44 \times 4 \text{ mm}^3$. The scan lasted for 480 s for each subject, and 240 volumes were acquired.

Image preprocessing

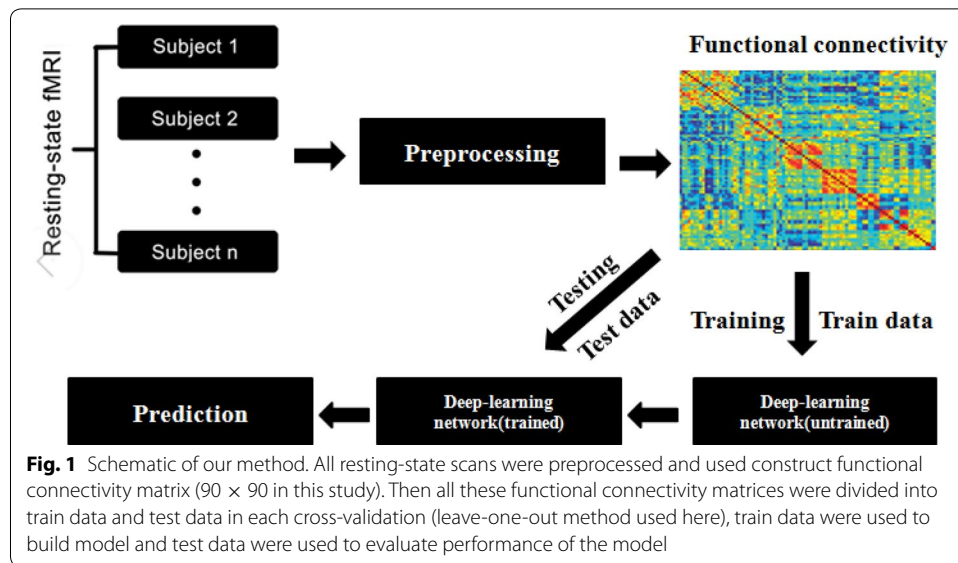
Data preprocessing was conducted using the Statistical Parametric Mapping Software (SPM8, <http://www.fil.ion.ucl.ac.uk/spm8>). The first 10 volumes of each participant were discarded because of the instability of the initial MRI signal and adaptation of the participants to the circumstance, leaving 230 volumes. The remaining rs-fMRI images were corrected for slice acquisition and head motion using a least squares approach with a 6-parameter spatial transformation. Four patients and one healthy control with head motion scans exceeding 2 mm or 1° rotation were excluded. Subsequently, the corrected images were normalized according to the standard SPM8 Montreal Neurological Institute (MNI) template (Power et al. 2012) and re-sampled to $3 \times 3 \times 3 \text{ mm}^3$ voxel size. The resulting images were linearly detrended and filtered using a typical temporal band-pass, including slow-5 band-pass (0.01–0.027 Hz) and slow-4 band-pass (0.027–0.073 Hz) separately (Yu et al. 2014; Gohel et al. 2014). Friston 24 motion parameters, cerebrospinal fluid, and white matter signals were included in the multiple regression model to reduce the effects of head motion and non-neuronal BOLD fluctuations (Friston et al. 1994; Tomasi and Volkow 2012). Given that resting-state FCD is sensitive to minor head movements, we calculated the mean frame-wise displacement (FD) to further determine the comparability of head movement across groups. The largest mean FD of each subject was less than 0.3 mm and two-sample *t* test showed that there was no significant difference in the mean FD between the two groups (HC: 0.09 ± 0.05 ; EOS 0.10 ± 0.03 ; mean \pm SD, $p = 0.33$). Then, the “bad” time points as well as their 1-back and 2-forward time points were removed from the time series by employing a “scrubbing” method with a FD (Power et al. 2012; Long et al. 2016) threshold of 0.5 mm. Participants retaining more than 80% of the original signals after scrubbing were included in the analysis. The number of time points that remained was non-significantly different between HC (227.8 ± 6.98) and EOS patients (225.1 ± 6.72) ($p = 0.09$).

Extraction of regional time series and construction of functional connectivity network

Images were smoothed using an $8 \times 8 \times 8 \text{ mm}^3$ FWHM Gaussian kernel. The averaged signals of 90 brain regions of the AAL (excluding brain areas in the cerebellum) template were calculated. We then computed the Pearson's correlation between each pair of signals. Thus, a 90×90 connectivity matrix for each subject was obtained.

Deep-learning analysis

Functional connectivity was treated as classification features and sent to autoencoder. As done in previous studies (Hinton and Salakhutdinov 2006; Hazlett et al. 2017), the model was evaluated via a standard tenfold cross-validation. The core of model was a weighted three-stage neural/deep-learning network, where the first stage reduces 4005 measurements to 400, the second stage reduces 400 to 20, and the third stage reduces 20 to only 2 measurements. At each stage, the measurements (in the progressively smaller sets) are the weighted combination of input measurements from the previous stage (Fig. 1).



Results

Demographic information

Sample characteristics are shown in Table 1. No significant difference was found between schizophrenias and controls in sociodemographic characteristics like age, gender, and so on.

Performance of deep-learning

The accuracy of deep-learning method reached 79.3%, the sensitivity reached 87.4%, and the specificity reached 82.2%. Then, to evaluate the significance of the accuracy, per-muted test was the used. By permuting 10,000 times, the *p* value was smaller than 0.05, this result showed us that the accuracy of deep-learning was significant (Table 2).

Table 1 Demographic and clinical characteristics in the study

| Demographics, mean (SD) | EOS <i>n</i> = 37 | Control <i>n</i> = 30 | <i>p</i> value |
|--------------------------------|----------------------|--------------------------|--------------------|
| Age (year) | 15.5 (1.8) | 15.3 (1.6) | 0.57 ^a |
| Gender (male/female) | 20/17 | 13/17 | 0.53 ^b |
| Education (years) | 8.5 (1.48) | 8.7 (1.42) | 0.605 ^a |
| Duration of psychosis (months) | 16.0 (14.4) | – | – |
| Handedness (right/left) | 37/0 | 30/0 | – |
| PANSS positive symptoms | 20.42 (5.72) | – | – |
| PANSS negative symptoms | 20.91 (8.41) | – | – |
| PANSS general symptoms | 33.28 (6.69) | – | – |
| PANSS total symptoms | 74.62 (10.61) | – | – |

^a *p* value was obtained by two-sample *t* test

^b *p* value was obtained by χ^2 two-tailed test

Table 2 Performance of deep-learning method

| Classification | Sensitivity | Specificity | <i>p</i> value (permuted) |
|----------------|-------------|-------------|---------------------------|
| 79.3% | 87.4% | 82.2% | < 0.05 |

Discussion

In current study, we used deep-learning method to verify the potential of functional connectivity in resting state used as biomarker of clinical diagnosis. Resting-state connectivity presented good potential classification capacity (79.3% for classification accuracy, 87.4% for sensitivity, 82.2% for specificity, $p < 0.05$ for permuted test).

Many other studies used resting-state functional connectivity to differentiate schizophrenia patients from controls (Mikolas et al. 2016; Cabral et al. 2016; Arbabshirani et al. 2013; Shen et al. 2010; Du et al. 2012; Skåtun et al. 2016). Two strategies were used in these studies to overcome over-fitting problem. First, feature selection/extraction method was used to reduce the dimensionality of feature space, then selected features were used to classify patients with schizophrenia from controls. Second, focusing on feature subsets and test their ability of classification. The first strategy rely too much on mathematical method and ignore physiological signification; those features that are discarded mathematically may have vital positions in emergence and development of disease (Liu et al. 2012). As for the second strategy, focusing on partial feature subsets would lead to a biased conclusion (Dietterich 1997). Deep-learning used in our study has been proved to be a good solution to these problems (Hinton and Salakhutdinov 2006). Here, we just proved that deep-learning method could be a feasible tool to recognize schizophrenia patients from controls.

Early diagnosis can significantly improve treatment response and reduce associated costs (McGlashan 1998). The absence of stable and reliable biomarkers makes current diagnosis of schizophrenia, which mainly relies on clinical manifestations by experienced clinician for now, a challenging task. Previous studies had found that resting-state functional connectivity was altered in schizophrenia patients (Woodward et al. 2011; Whitfield-Gabrieli et al. 2009; Rotarska-Jagiela et al. 2010). Our study found that resting-state functional connectivity presented good potential classification capacity and could be used as a biomarker of clinical diagnosis.

Authors' contributions

JZ conceived and designed the study. YZ collected the clinical data. SH and WH analyzed the data and also wrote the paper. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

None.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Second Affiliated Hospital of Xinxiang Medical University, and informed written consents were obtained from all subjects.

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