Identifying first-episode drug naïve patients with schizophrenia with or without auditory verbal hallucinations using whole-brain functional connectivity: A pattern analysis study

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ARTICLE INFO

Keywords:
First episode schizophrenia
Auditory verbal hallucinations
Functional connectivity
Support vector machine

ABSTRACT

Many studies have focused on patients with schizophrenia with or without auditory verbal hallucinations (AVHs), but due to the complexity of schizophrenia, biologically based diagnosis of patients with schizophrenia remains unsolved. The objectives of this study are to classify between first-episode drug-naïve patients with schizophrenia and healthy controls, and to classify between patients with and without AVHs. Resting state fMRI data from 41 patients with schizophrenia (22 with and 19 without AVHs) and 23 normal controls (NC) were included to compute functional connectivity between brain regions. Classifiers based on support vector machine (SVM) were developed to classify patients with schizophrenia from NC, as well as between the two subgroups of patients. The classification accuracy was evaluated with a leave-one-out cross-validation (LOOCV) strategy. The accuracy in discriminating both subgroups of patients from NC was 81.3%, with 92.0% (sensitivity) and 65.2% (specificity) for the patients and NC, respectively. The classification accuracy in discriminating patients with and without AVHs was 75.6%, with 77.3% (sensitivity) and 73.9% (specificity) for patients with and without AVHs, respectively. The results suggest that functional connectivity provided good discriminative power not only for identifying patients with schizophrenia among NC, but also in discriminating patients with schizophrenia with and without AVHs.

1. Introduction

Burgeoning studies have focused on schizophrenia, a chronic, severe and disabling brain disorder (Insel et al., 2010). Nearly 60–80% of patients with schizophrenia are liable to experience auditory verbal hallucinations (AVHs) (Saha et al., 2005). To date, the diagnosis of schizophrenia has been largely based on behaviors and self-reported psychiatric symptoms (www.psychiatry.org/dsm5). Many have suggested that a more objective diagnosis method is to use neuroscience measures (Insel et al., 2010; Su et al., 2013). Although the underlying etiology and mechanisms of psychosis are still unclear, a number of functional connectivity studies using functional magnetic resonance imaging (fMRI) have demonstrated that psychosis is associated with dysfunctional integration or alteration of brain networks (Andreasen et al., 1998; Friston and Frith, 1995).

With the development of algorithms, a growing number of researchers have applied multivariate pattern analysis (MPA) methods on functional connectivity to classify patients with mental disorders, including autistic spectrum disorder (Ecker et al., 2010), depression (Craddock et al., 2009), and schizophrenia (Su et al., 2013). Previous research based on whole brain functional connectivity analysis (Craddock et al., 2009) has found that resting-state functional connectivity is disrupted in patients with schizophrenia (Honey et al., 2005; Welsh et al., 2010).

Multiple lines of evidence have revealed the disconnectivity pattern of schizophrenia patients, and of particular interest are schizophrenia...
patients with AVHs, through different blood oxygenation level-dependent (BOLD)-fMRI and diffusion tensor imaging-based approaches, including functional connectivity (Chang et al., 2017; Cui et al., 2016; Escartí et al., 2010; Shergill et al., 2000; Vercammen et al., 2010), effective connectivity (Cui et al., 2015; Li et al., 2017), voxel-mirrored homotopic connectivity (Chang et al., 2015), structural connectivity (Hubl et al., 2004), and resting-state networks analyses (Cui et al., 2017; Jafri et al., 2008; Lawrie et al., 2002). In general, these literatures present a full view of large-scale connectivity characteristics in schizophrenia, as well as the central symptom in this debilitating disorder.

AVHs: Schizophrenia with Auditory verbal hallucinations; Non-AVHs: schizophrenia without Auditory verbal hallucinations; NC: Normal controls.

| Demographic variables                  | Patients (AVHs vs. Non-AVHs)          | NC       | P value       |
|----------------------------------------|---------------------------------------|----------|---------------|
| Cases                                  | 41 (22 vs. 19)                        | 23       |               |
| Age, years (mean ± SD)                 | 23.59 ± 5.35 vs. 23.42 ± 4.93         | 25.61 ± 2.98 | 0.236 (F(2,61) = 1.48) |
| Gender (Male/Female)                   | 12/10 vs. 10/9                        | 13/10    | 0.332 (χ² = 0.94) |
| Left/Right Handed                      | 0/41                                  | 0/23     |               |
| Education Level, years (mean ± SD)     | 12.36 ± 2.40 vs. 12.42 ± 2.17         | 15.00 ± 2.61 | 0.001 (F(2,61) = 8.61)*** |
| Clinical variables                     |                                       |          |               |
| Duration of illness, months (mean ± SD)| 8.73 ± 7.04 vs. 14.16 ± 18.04        | –        | 0.200 (t = −1.30) |
| PANSS-positive symptoms                | 30.68 ± 6.11 vs. 20.11 ± 8.73         | –        | 0.000 (t = 4.54)*** |
| PANSS-negative symptoms                | 26.82 ± 3.80 vs. 22.37 ± 10.08        | –        | 0.083 (r = 1.81) |
| PANSS-general psychopathology          | 50.27 ± 7.80 vs. 48.26 ± 9.46         | –        | 0.461 (r = 0.74) |
| PANSS-total score                      | 107.77 ± 11.55 vs. 90.74 ± 23.56      | –        | 0.008 (r = 2.87)*** |
| HAIRS                                  | 26.36 ± 5.84                          | –        |               |

AVHs: Schizophrenia with Auditory verbal hallucinations; Non-AVHs: schizophrenia without Auditory verbal hallucinations; NC: Normal controls.

*** P < 0.001 (significant difference between schizophrenic patients and normal controls).

** P < 0.01.

*** P < 0.001 (significant difference between AVHs and Non-AVHs).
Exploring the determinants of differences underlying neurobiology functioning as identifying signatures seems to be a promising step to improve understanding the nature of schizophrenia and the diagnosis in psychiatric domain. Most recently, neuroanatomical subtypes of schizophrenia patients was linked with symptoms, aiding disease discrimination for biomarker-based diagnosis (Dwyer et al., 2018). Hence, whether functional abnormalities in relation to psychopathology in schizophrenia hold the capacity to classify disease or symptom needs to be addressed. To this end, classification study is a reliable option by means of MPA. Several studies have related to the classification of SZ vs. controls using resting-state fMRI functional connectivity (Anderson et al., 2010; Ariana and Cohen, 2013; Jafri et al., 2008; Shen et al., 2010). However, application of categorical methods using connectivity features in symptoms-based subtyping of schizophrenia, i.e., AVHs and Non-AVHs, has obviously lagged behind.

Here, we study this issue from data-driven perspective and use a MPA method to train an effective classifier to classify patients with schizophrenia. There are two goals: the first is to evaluate the discriminative power in identifying patients from controls using whole-brain resting-state functional MRI; the second is to evaluate the discriminating power in classifying patients with and without AVHs or to subdivide the patients with schizophrenia into subgroups with different symptomatology using the support vector machine method. This study is considered as an analytical proof of concept study, which may offer a complementary or confirmatory option.

2. Materials and methods

2.1. Participants

45 first-episode drug naïve patients with schizophrenia, including untreated inpatients undergoing their first hospitalization or outpatients seeking help for the first time after the first onset of the disease (Cui et al., 2017; Cui et al., 2018), were assigned to two groups according to the presence of AVHs symptom. 25 of them who reported AVHs at least once a day for the past four weeks were assigned to AVHs group. 20 patients who have never experienced AVHs or have not experienced them within two years before recruitment were allocated to Non-AVHs group, with consensus diagnoses from two senior clinical psychiatrists according to the Structural Clinical Interview for Diagnostic Statistical and Manual of Mental disorders, Fourth Edition, Text Revision (DSM-IV-TR). Demographically matched 24 normal controls (NC group) were included in this study. They were all right-handed and native Chinese speakers. Five subjects were excluded from analysis because of excessive head motion during the MRI scan (> 2.5 mm translation and > 2.5° rotation). The remaining 41 patients (22 with AVHs, 19 without AVHs, mean duration since a diagnosis of first-episode was 9.2 months) and 23 NC were included in the analysis. All participants gave their written informed consent prior to the study, which was in accordance with the Declaration of Helsinki and all experiments protocol were approved by ethics committee in Fourth Military Medical University (FMMU).

2.2. Clinical assessment

Patients meeting diagnostic criteria for schizophrenia according to DSM-IV-TR were assessed by two senior clinical psychiatrists using the Positive and Negative Symptom Scale (Kay et al., 1987) (PANSS total score ≥ 60). Further assessment of AVHs patients was based on the Hoffman Auditory Hallucination Rating Scale (AHRS) (Hoffman et al., 2003).
2.3. Magnetic resonance imaging

Magnetic resonance imaging (MRI) was performed on a 3 Tesla Magnetom Trio Tim scanner system (Siemens, Germany) at Xijing Hospital, FMMU. During the resting state scan, subjects were instructed to close their eyes, but remain awake. A standard birdcage head coil was used. Foam pads and headsets were used to reduce head motion and scanner noise. The fMRI images were collected using an echo-planar imaging (EPI) sequence. The parameters were: repetition time/echo time = 2000/30 ms, thickness/gap = 4/0.6 mm, field of view = 220 × 220 mm, flip angle = 90°, matrix = 64 × 64, number of slices = 33. Each resting state scan lasted about 10 min and generated 240 brain volumes. T1-weighted anatomical data were acquired using the 3D MPRAGE sequence: repetition time/echo time = 2530/3.5 ms, thickness/gap = 1/0 mm, field of view = 256 mm × 256 mm, flip angle = 7°, matrix = 256 × 256, number of slices = 192, resolution = 1 mm × 1 mm × 1 mm.

2.4. Data preprocessing

Using the DPARSF 2.3 (Yan and Zang, 2010), preprocessing included several steps: (1) For each subject, the first 10 volumes of scanned data were discarded for magnetic saturation. (2) The 230 volumes were corrected by registering for head motion. (3) The volumes were normalized by using T1 image segmentation. (4) Temporal band-pass filtering (0.01 Hz < f < 0.08 Hz) and spatial smoothing (8 mm full-width half-maximum kernel) were applied to the resulting images. (5) Nuisance regressors, including 6 motion parameters obtained by rigid-body head motion correction, global signal level, ventricular signal level, and white matter signals were regressed out. (6) The automated anatomical labeling (AAL) (Tzourio-Mazoyer et al., 2002) atlas template with 116 regions of interest (ROI) was used to extract time series of the BOLD time series. (7) The correlation (Pearson’s r coefficient) between each pair of ROI time series was computed to generate a correlation matrix (116 × 116) for each subject. The 6670 upper triangle elements of the matrix, excluding the diagonal of the matrix, were used as features in all subsequent MPA. With regard to head motion, no significance difference was found among groups on Jenkinson’s mean frame-wise displacement values ($P = 0.17$) (Yan et al., 2013; Zhu et al., 2015).

2.5. Feature selection and SVM

SVM was proposed by Vapnik (Vapnik, 2000) and has been applied in life sciences as a powerful tool for classification and prediction. Many studies have demonstrated that SVM is suitable for analyzing
Due to the large number of features in our study, feature selection with high discriminative power is essential to achieve high classification accuracy. In this study, SVM was used to discriminate between subjects belonging to different classes (for example, NC and patients). The Kendall tau rank correlation coefficient was used as the discriminative power indicator for each feature based on its relevance to classification (Guyon and Elisseeff, 2003; Su et al., 2013; Zeng et al., 2012).

Programs written in Matlab R2010a were used to calculate the tau. For example, for the \( i \)-th feature, tau is computed by:

\[
\tau_i = \frac{n_c - n_d}{m \times n},
\]

where \( m \) and \( n \) are the number of samples in the two groups, and \( n_c \) and \( n_d \) are the number of concordant and discordant pairs between the two groups, respectively.

For feature \( i \), let \( x_j \) and \( x_k \) denote the functional connectivity of the \( j \)-th sample from the control group and \( k \)-th sample from the patient group. Let \( y_j \) and \( y_k \) denote the class labels of the groups (e.g., +1 for controls and −1 for patients). The pair is concordant if the connectivity difference and class label difference has the same sign:

\[
\text{sign}(x_j - x_k) = \text{sign}(y_j - y_k).
\]

They are discordant if the signs are opposite:

\[
\text{sign}(x_j - x_k) = -\text{sign}(y_j - y_k).
\]

The discriminative power was defined as the absolute value of the tau. Features were ranked according to their discriminative powers and those above a certain threshold were included in the final features set in SVM classification. The threshold was chosen to give the best classification accuracy for the classifier.

When the high discriminative power feature set was selected, LIBSVM 3.18 (Chang and Lin, 2011) (default setting \( C = 1 \), as suggested in (Hsu et al., 2003), linear kernel) was used for classification. Due to the quantity of samples, LOOCV (Cawley and Talbot, 2004) was conducted by iterating the procedure with each of the samples left out. Classification accuracy was computed from the average of all the iterations. The training features (functional connections) differed slightly from iteration to iteration of the LOOCV procedure. The common features, considered as consensus functional connectivity (CFC) (Zeng et al., 2012), were selected as the final feature set through all the iterations. The occurrence number of each ROI in the CFC was calculated as the region weight as an indicator of the relative contribution to identification. The steps of the calculation are illustrated in Fig. 1.

To evaluate the performance of the classifier, we did a permutation test (Golland and Fischl, 2003; Zeng et al., 2012). The test was repeated 5000 times. For each permutation, the class labels of the training data were randomly permuted, and then an accuracy was obtained. The results were used as a baseline to gauge the statistical significance of the SVM procedure (Golland and Fischl, 2003).
3. Results

3.1. Subjects’ demographic and clinical characteristics

The demographic and clinical characteristics of the patients with schizophrenia and NC are listed in Table 1. There are obvious differences in education level ($F_{(2,61)} = 8.61$, $P = 0.001$) between patients and NC, but the three groups do not differ significantly in terms of age and gender. There were significant differences in PANSS positive scores ($t = 4.54$, $P < 0.001$) and PANSS total scores ($t = 2.87$, $P < 0.01$) between patients with and without AVHs (Table 1).

3.2. Permutation tests and classification results

For all the first-episode patients with schizophrenia and NC, the final classification accuracy of the training data set was 100% using 308 most discriminating functional connections. Using LOOCV, the linear SVM classifier achieved an accuracy of 81.3% for all subjects (90.2% for patients (sensitivity) and 65.2% for NC (specificity), $P < 0.0001$). The results of the permutation tests and the real classification accuracy (RCA), which was obtained from the real class labels, were shown in Fig. 2A.

Similarly, for the two subgroups of the patients, the overall accuracy of the classifier in LOOCV was 75.6% (77.3% and 73.7% for patients with and without AVHs, $P < 0.01$). The results of the permutation tests and RCA were shown in Fig. 2B.

3.3. Distribution and changes of functional connectivity

We ran the classifier with different threshold settings that ranged from 0.001 to 1 with a step size of 0.001. When the threshold was 0.365, the best accuracy (81.3%) was achieved in classifying patients from NC (Fig. 3A). When more features were included with lower thresholds, the accuracy decreased. This is consistent with other SVM studies (Dosenbach et al., 2010; Su et al., 2013).

171 CFC were used to achieve the best accuracy. They were projected to a human brain surface with BrainNet Viewer (Xia et al., 2013) (Fig. 4).

To help visualizing the results, the ROIs in the CFC were categorized into six groups (Su et al., 2013): (a) the default mode network (DMN, including thalamus, hippocampus, inferior temporal gyrus, the medial prefrontal cortex), which is a key factor in schizophrenia (Whitfield-Gabrieli et al., 2009); (b) the cingulo-opercular network (CON, including anterior prefrontal cortex, inferior parietal cortex, dorsal anterior cingulate, insula), which is considered to be the most important cognitive network (Dosenbach et al., 2007); (c) the cerebellum network, which plays an important role in both cognitive and motor functions (Andreasen et al., 1996), especially for patients with schizophrenia with auditory verbal hallucinations (Allen et al., 2008; Andreasen et al., 1996); (d) the visual cortical network (the lingual gyrus, fusiform gyrus, inferior occipital gyrus), which are involved in visual processing; (e) the frontal-parietal network (containing superior parietal, superior frontal cortex), which is involved in attention processing (Beckmann and Smith, 2005); and (f) other regions. (See Fig. 5.)
supplementary material for details).

To understand which connections were increased or decreased, the difference between the mean functional connectivity of the patients and NC were shown (Fig. 5). Among the 171 CFC, 83 of them (red curves) show increased strength in patients compared with controls, and 88 (blue curves) show decreased strength.

Similarly, a series of corresponding classification accuracies for classifying the two subgroups of patients were obtained (Fig. 3B). When the threshold was 0.544, the highest accuracy (75.6%) was achieved, corresponding to 13 CFC (Fig. 6).

3.4. Important regions identified by classification

In Fig. 4, several brain regions, i.e., the Frontal_Sup_Orb_R, Temporal_Pole_Sup_L, were weighted more than others in classifying patients from NC. The results suggest that these areas play more important roles in identifying the patients from NC. Similarly, Frontal_Mid_Orb_R, Temporal_Pole_Sup_R, exhibited greater weights than others in classifying patients with and without AVHs (Fig. 6).

4. Discussions

To our knowledge, this is the first SVM study on subgroups of schizophrenia (AVHs vs. non-AVHs) in spite of few individual investigations in classifying SZ patients and controls using resting-state networks (Skåtun et al., 2017) and combination of cerebral functional and anatomical features (Yang et al., 2016), holding a great promise for closing the gap between phenomenology and symptom biology of this complicated mental disease. In order to reduce the drug and treatment factors, we chose first-episode drug-naïve patients with schizophrenia. Brain regions important for discriminating patients with and without AVHs were located in the right orbital middle frontal area, right superior temporal pole area, and right inferior parietal area, which are associated with schizophrenia (Hazlett et al., 2000; Heckers et al., 1998; van den Heuvel et al., 2010). Overall, we achieved good discrimination between patients and NC and between the two subgroups of patients based on their functional connectivity. The majority of the functional connections that contributed to the discrimination were located within or cross the default mode, frontal-parietal and cerebellum networks.

4.1. CFC and threshold selection

In one SVM study on schizophrenia classification (Su et al., 2013), the authors aimed to achieve the highest classification accuracy and found that when more features were involved, the accuracy decreased. With about 200 features, the classification accuracy tended to be stable. Therefore they selected the first 200 features for classification. We constructed a directed method, the threshold range method, to select the most important brain regions for classification. The method was effective and generated results that were comparable to that of the method in Su et al. (2013).

4.2. Linear or nonlinear kernel

The SVM and LOOCV method are widely used techniques for

Fig. 6. The region weights and strengths of the connections used for classifying the two subgroups of patients, displayed on a surface rendering of the human brain. Regions are color-coded according to different functional networks. The region weights represent the number of occurrence of the certain ROI used for classification here in AAL atlas. The line colors represent the relative consensus functional connections that are scaled by their mean discriminative power during LOOCV.
In classification studies, either a linear or a non-linear kernel can be used, depending on the properties of the features in the data. Because the number of features (6670) is much greater than the number of subjects (64) in our study, a nonlinear kernel, for example, the radial basis function (RBF), would not improve the performance of the classifier. A linear classification was conducted in this study (Hsu et al., 2010).

4.3. Connection strengths and region weights

In the linear-SVM classifier between patients and NC, our findings indicate that 83 connection strengths between ROIs increased in the patient group compared to the NC, and 87 connection strengths decreased. Most of the increased connections were located in the DNN and temporal lobe; the decreased connections were located in the CON, cerebellum and frontal-parietal networks (Repovs et al., 2011).

We found that it is more difficult to discriminate patients with and without AVHs. To achieve the best classification accuracy, only 13 CFC were included in the classifier. The result strongly suggests that the two different subgroups of patients with schizophrenia have many common connections, making it difficult to obtain much CFC.

Recently, a clustering and classifying study has proven that resting-state functional connectivity is useful for neurophysiological subtype definition of depression and guidance of personalized therapy (Drysdale et al., 2017) providing an unprecedented opportunity to improve the individualized diagnosis and treatment by means of biologically based measurement using fMRI. Resting-state functional connectivity was used for classification in the current study. The diagnosis of patients with schizophrenia with or without AVHs was confirmed by the pattern analysis. Previous studies, as stated above, have shown the features of disconnection in schizophrenia patients with AVHs as compared to those without AVHs by means of functional connectivity (Chang et al., 2017; Cui et al., 2016; Shergill et al., 2000; Vercammen et al., 2010). Altered connections reflecting the neuropathology might contribute to symptomatology classification via SVM, resulting in accurate discrimination of subtypes in schizophrenia. At clinical level, clinical physicians may supply more accurate treatments or interventions to them.

4.4. Limitations and future directions

The sample size in this study is small, but the classification results are encouraging. More subjects should be enrolled to further test and validate the classification results. Meanwhile, we found connections that contributed to the discrimination were related to the default mode, in which head motion has been found to influence the connectivity (Zeng et al., 2014). We only attempted to classify two subtypes schizophrenia, patients with and without auditory verbal hallucinations. Future studies should expand the number of, subtypes of patients and train a more universal classifier for many subtypes of schizophrenia. Many studies have found that schizophrenia patients with and without AVH exhibited common disruptions of functional networks (Zhu et al., 2016), but we found the differences between two subtypes schizophrenia patients with and without AVH. In fact, the classification of patients with and without AVH is important at a clinical level. This result could inform treatments for different subtypes of schizophrenia.

In other studies, the ALFF (amplitude of low-frequency fluctuation), ReHo (regional homogeneity) and RFCs (regional functional connectivity strength) were used for classification (Long et al., 2012; Sui et al., 2013). In further study, we plan to integrate those indexes in an SVM analysis.

5. Conclusions

We showed that MPA of functional connectivity could be used not only to classify first-episode patients with schizophrenia from controls, but also to discriminate patients with schizophrenia with and without AVHs.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2018.04.026.

Acknowledgement

We are very grateful to all the participants. The research was funded by the Military Major Project in the Medical Science and Technology Program during the Twelfth Five-Year Plan (No. AWS13J003), the National Basic Research Program of China (973 Program, No. 2011CB707805) and the National Natural Science Foundation of China (No. 81301199).

Conflict of interest statement

We declare no conflict of interest.

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