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The distinguishing intrinsic brain circuitry in treatment-naïve first-episode schizophrenia: Ensemble learning classification

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ABSTRACT

Schizophrenia is frequently characterized as a prototypical disorder of integration of brain function involving almost all intrinsic connectivity networks. However, a consistent conclusion regarding the most distinguishing brain circuitry in schizophrenia has not yet been reached. In this study, we used a novel network-based ensemble method to explore the most distinguishing brain circuitry in treatment-naive first-episode schizophrenia ($n = 41$) and healthy controls ($n = 38$) who underwent the task-free functional MRI scanning. Ensemble method showed commendable discrimination ability (84.7% for classification accuracy, 91.9% for sensitivity, 74.5% for specificity, all $p < 0.05$ for permuted test). The most distinguishing connections were located in the right paralimbic system and bilateral default mode network. Notably, distinguishing aberrations were significantly correlated with symptom severity (negative score: $R^2 = 0.58$, $P < 0.05$, Bonferroni corrected; positive score: $R^2 = 0.74$, $P < 0.05$, Bonferroni corrected) in schizophrenia patients. These most distinguishing aberrations present good potential for the underlying symptoms, and provide great insight into the mechanism of schizophrenia. Our results suggested that the ensemble method was a powerful tool to help with clinical diagnosis of schizophrenia and to explore the mechanism of schizophrenia.

1. Introduction

Schizophrenia is a complex syndrome lacking integration between thought, emotion, behavior cognitive and affective deficits [1]. The disease affects nearly 1% of the world's population [2]. Early diagnosis can significantly improve treatment response and reduce associated costs [3]. The absence of stable and reliable biomarkers makes current diagnosis of schizophrenia, which mainly relies on clinical manifestations by experienced clinician, a challenging task [4]. In recent years, studies have discovered that many intrinsic connectivity networks (ICNs) are altered differently in schizophrenia during the rest [5–7]. Many brain circuitries or ICN, such as the default network, working memory related circuitry, frontal-subcortical neuronal circuits, limbic system, circuitry about facial expressions of emotion, are thought to be the core features in schizophrenia [8–11]. The ICNs have also been to identify schizophrenia patients from healthy controls [12–16]. However, results from these studies are far from reaching a consistent conclusion, and the most distinguishing brain circuitry in schizophrenia is still unknown.

Previous studies focus on certain network or few altered networks separately, the power of discrimination is treated as a degree of aberration [5,17]. However, this approach may lead to a biased conclusion. When specific network that has limited discrimination information is used as feature subset, a robust conclusion can hardly be drawn. More seriously, the altered degree of networks changes when considered together with other networks [18]. In other words, the conclusion reached by limited discrimination information will be different in the presence of other networks. Machine learning is a good solution to these problems [14,16,19–21]. Especially, ensemble learning presents a unique advantage. Ensemble learning can achieve better generalization ability and alleviate the possible data over-fitting problem existing widely in neuroimaging data [18,22–24].

In our study, network based ensemble learner was built to explore the most distinguishing aberration in treatment-naive first-episode schizophrenia patients. Connections between and within sub-networks were considered as feature subsets [25] and were aggregated by stacking algorithm [26]. We expected to find the most distinguishing ICNs in schizophrenia patients. Notably, these

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Table 1
Characteristics of schizophrenia patients and healthy controls.

	Sch ($n=41$)	HC ($n=34$)	p
Age (years), Mean ± SD	24.98 ± 4.79	25.12 ± 4.58	0.90[a]
Gender, male : female	26:15	21:13	0.94[b]
Duration of illness (months), Mean ± SD	8.29 ± 2.58	–	–
Alcohol, yes/no	6 / 35	7 / 27	0.40[b]
Cigarette, yes/no	9 / 32	8 / 26	0.86[b]
Years of education, Mean ± SD	10.37±2.8	11.12±2.8	0.25[a]
Handness, right/left	41 / 0	34 / 0	–
PANSS positive score	25.78 ± 3.60	–	–
PANSS negative score	18.32 ± 5.18	–	–
PANSS general score	48.29 ± 6.47	–	–
PANSS total score	92.39 ± 10.92	–	–

[a] p Value was obtained by two-sample t-test.
[b] p Value was obtained by χ^2 two-tailed test.

aberrations might have close relationship with symptom severity in schizophrenia patients.

2. Materials and methods

2.1. Participants

A total of 42 antipsychotic-naive patients with first-episode schizophrenia were recruited from consecutive admissions at the Second Affiliated Hospital of Xinxiang Medical University. The following inclusion criteria were also fulfilled: (1) Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR fourth edition, text revision, American Psychiatric Association, 2000) criteria for schizophrenia and (2) absence of co-morbid Axis I diagnosis. Schizophrenia was independently diagnosed by two well-trained psychiatrists based on the Structured Clinical Interview for DSM-IV-TR, patient version (SCID-I/P) and were interviewed again after six months for a final diagnosis of schizophrenia. Positive and Negative Syndrome Scale (PANSS) was used to evaluate psychiatric symptomatology. Parts of subject were excluded, due to translational and rotational displacement exceeded 2.0 mm or 2.0°. A total of 41 patients (mean age, 24.98; age range, 18–37; male, 26; female, 15) and 34 healthy controls (mean age, 25.12; age range, 18–32; male, 21; female, 13) were included in this study (Table 1). Healthy controls did not present any history of psychiatric or medical conditions. Participants were excluded when they met any of the following criteria: (1) a history of neurological disorders or family history of hereditary neurological disorders, (2) head injury resulting in loss of consciousness, (3) alcohol or substance abuse, and (4) presence of any metallic object in their body.

All procedures were approved by the ethics committee of the Second Xiangya Hospital and the Second Affiliated Hospital of Xinxiang Medical University. All participants written informed consent and were permitted to discontinue participation from this research at any time.

2.2. Data acquisition

Our data were collected using a Siemens 3T Trio scanner (Siemens Medical Systems, Erlangen, Germany) at the Second Affiliated Hospital of Xinxiang Medical University. Scanning was conducted following clinical assessment on the same day. Functional images were acquired using an echo-planar imaging sequence (EPI) with the following parameters: TR/TE = 2000/30 ms, 33 slices, 64×64 matrix, 90° flip angle, field of view = 220×220 mm^2, inter-slice gap = 0.6 mm, and voxel size = $3.44 \times 3.44 \times 4$ mm^3. For each participant, 240 volumes were obtained. All subjects were instructed to relax, to hold still, and to keep their eyes closed during the scan.

2.3. Data preprocessing

Data preprocessing was carried out with the Data Processing Assistant for Resting-State fMRI package (DPARSF_A, http://www.restfmri.net). The first ten volumes of functional images were discarded because of the instability of the initial MRI signal and adaptation of participants to the circumstance. Slice-timing and realign were corrected for images. Subjects were discarded when translational and rotational displacement exceeded 2.0 mm or 2.0°. One patient and four controls were excluded based on these criteria. To further exclude effect of motion, frame-wise displacement (FD) of controls and patients was calculated and compared between groups. These was no significant difference in (FD) ($p=0.99$) [27–32]. Removal of detected outliers, the outlier removal approach used here is similar to the "scrubbing" method proposed by Power et al. [33]. Rather than remove affected time points from data, we replaced outliners with the best estimate using a third-order spline fit to clean the portions of time course. Images were normalized to the standard EPI template (re-sampled into $3 \times 3 \times 3$ mm^3) implemented SPM8, smoothed using an $8 \times 8 \times 8$ mm^3 FWHM Gaussian kernel and detrended to reduce low-frequency drift. Finally, Friston 24 motion parameters [34], global mean signal, white matter signal and cerebrospinal fluid signal were regressed out as nuisance covariates. Images were band-pass filtered (0.01–0.1 Hz) to remove high-frequency physiological noise.

2.4. Ensemble learner and evaluation on the performance

In this study, stacking method was selected. As one of the ensemble learning method, stacking method worked by deducing the biases of generalizers with respect to a provided learning set [26]. With two-level learners, stacking method involved first-level learners, which were generated from a feature subset and then combined with the second-level learner. The second-level learner could get a better classification accuracy though generalizing the outputs of the first-level learners. Meanwhile, the overall discrimination ability of each feature subset was judged by the second-level learner [26]. This ability was of vital importance in exploring the core altered brain circuitry in schizophrenia when considering all networks together.

The present study included the following steps (Fig. 1).

(1) The averaged signals of 90 brain regions of the Automated anatomical labeling (excluding cerebellum) template were calculated. We then computed the Pearson's correlation between each pair of signals. Thus, a weighted 90×90 functional connectivity matrix for each subject was obtained.
(2) The 90 nodes in the AAL template was divided into 12 (taking into account the different hemispheres) discrete interconnected sub-networks: default mode network (SNR1), attention network (SNR2), visual recognition network (SNR3), auditory network (SNR4), sensory-motor areas (SNR5), and subcortical network (SNR6) [35–38].
(3) All connections $(90 \times 90 - 90) \div 2 = 4005$ were divided into 12 within networks feature subsets (connections linking nodes within one sub-network) and 66 $(12 \times 12 - 12) \div 2 = 66$ between networks feature subsets (connections linking nodes in each paired sub-networks). Overall, 78 subsets were obtained.
(4) The 78 feature subsets were then sent into the first-level learners. Outputs of the first-level learners were biased estimations (so-called weak learner C1, C2, etc., as shown in Fig. 1), which were based on one feature subset with limited discrimination information.
(5) Outputs of the first-level learners were combined by the second-level learner. Thus, all limited discrimination infor-

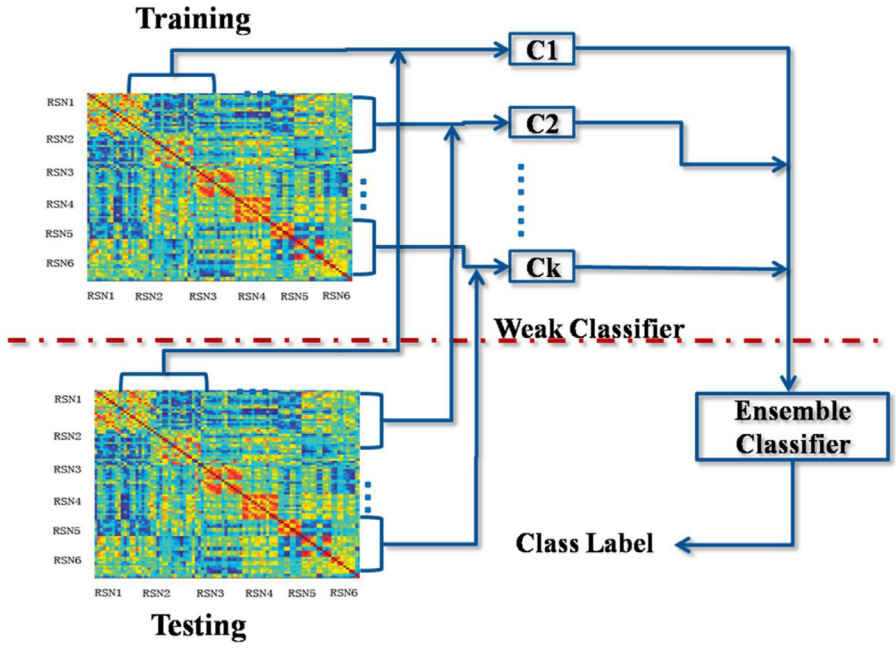

Fig. 1. Schematic of network based ensemble. Connections within and between pairs of networks (mentioned in method) were treated as sub-feature sets to train the first-level learners (weak learners, such as C1, C2, and so on). Then these first-level learners were combined by a second-level learner. The output of the second-level learner was the final classification result.

mation was collated to be a stronger learner (ensemble learner in Fig. 1). Linear kernel support vector machine (SVM) was used as learners at two levels.

(6) To evaluate the performance of this algorithm, a 10-fold cross-validation strategy was employed. The original data were randomly divided into ten disjoint subsets, and one of these subsets was used as the test set. The rest were considered as the training set. Ensemble classifiers were built for each training set and tested with its corresponding test subject. Accuracy, sensitivity, and specificity were used to quantify the performance, and their equations are presented as follows:

$$\text{Accuracy} = \frac{\text{TP} + \text{TN}}{\text{TP} + \text{FN} + \text{TN} + \text{FP}} \quad (1)$$

$$\text{Sensitivity} = \frac{\text{TP}}{\text{TP} + \text{FN}} \quad (2)$$

$$\text{Specificity} = \frac{\text{TN}}{\text{TN} + \text{FP}} \quad (3)$$

where TP was true positives meaning the number of controls (a binary label with 1 for controls and −1 for patients was used here) were correctly classified; TN was true negatives meaning the number of patients were correctly classified; FP was false positives meaning the number of patients classified as controls; FN was false negatives meaning the number of controls classified as patients.

(7) Permutation test was used to test the statistical significance of the accuracy obtained with the validation sample. The labels of the validation groups were randomly permuted and applied to the model. This process was repeated 10,000 times to determine a null-distribution of accuracies and the p-value of the accuracy was also calculated [4].

2.5. Association with symptom severity

To investigate the relation between these altered connections with symptom severity, these most distinguishing connections (Arbitrarily, the top 1% of the ranked connections having the highest weight values were selected as the most distinguishing connections) were used to predict the patients' positive score, negative score using Support Vector Regression (SVR) in LIBSVM [39]. The proportion of variance (R^2) was estimated to measure the performance of the regression algorithm in predicting symptom severity using a leave-one-out cross validation (LOOCV). The statistical significance was assessed using nonparametric analysis [40]

2.6. Validation

We also used Power's 264 brain atlas to validate this result. Power et al. defined 264 brain seed regions and provided the module well based on resting fMRI and meta-task fMRI [41–43].

3. Results

3.1. Demographic information

Sample characteristics were shown in Table 1. No significant difference was found between schizophrenia patients and controls in sociodemographic characteristics like age, gender, alcohol and so on.

3.2. Overall classifier performance

The accuracy of our model reached 85.7% (91.9% for sensitivity, 74.5% for specificity, $p < 0.05$ for the permuted test). The area under the ROC curve (AUC) of the proposed method was 0.902, indicating a commendable classification power. To compare with the performance of each weak learner and ensemble learning, the accuracy was calculated (Fig. 2). Meanwhile, the accuracy of the combined feature subsets was also calculated to demonstrate that our ensemble had a better classification performance. We considered the top n subsets (where $n = 2$–78) whose sequence was according to the accuracy drawn in Fig. 2 (histogram). The accuracy was calculated and drawn in Fig. 2 (blue line). Results showed that when more feature subsets were considered, the classification accuracy was higher until it finally reached steady-state. In addition, results

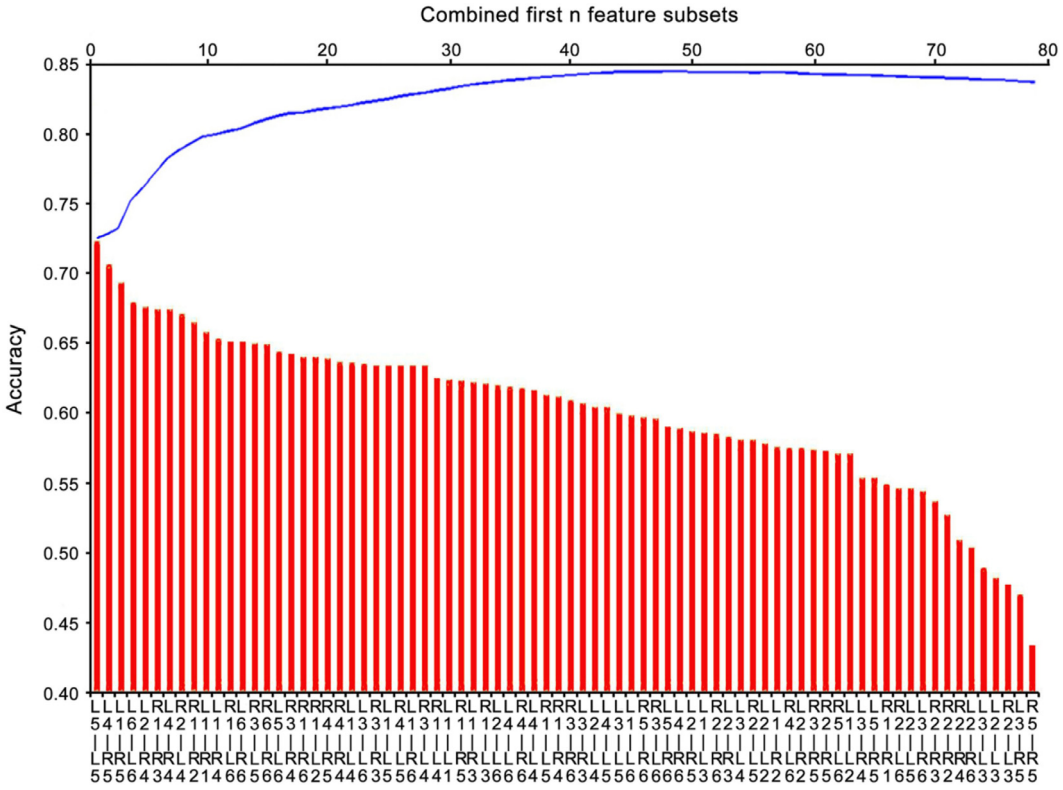

Fig. 2. Accuracy of all weak learners using feature subsets(histogram) and ensemble learner (blue line). *X*-coordinate (below) represented feature subsets, *Y*-coordinate indicated the accuracy obtained by feature subsets. For instance, L5-R5 (the first one) presented the connections between the left sensory-motor areas and right sensory-motor areas, and its accuracy is 71%. Blue line meant accuracy of combined feature subsets. *X*-coordinate (upper) presented the top n ($n = 1$–78) feature subsets that were combined using ensemble learning. The figure showed that each feature subset had limited discrimination information. When combined together, accuracy of overall performance were better than that of the subassembly of feature subsets.

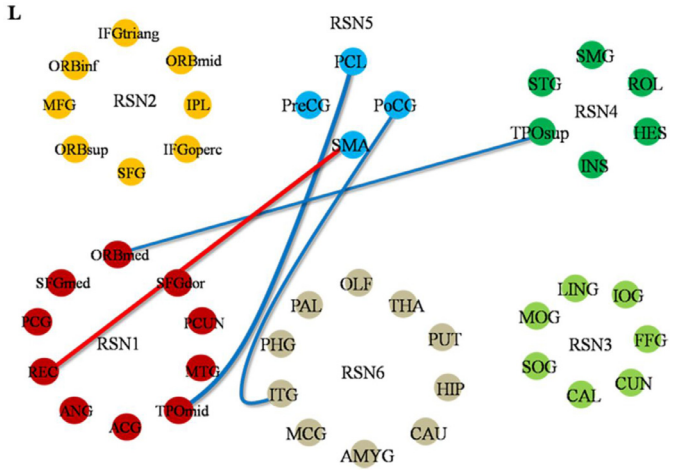

Fig. 3. The most altered connections in the left hemisphere. The blue line indicated that the strength of connections decreased than those in patients, whereas the red colors line that the strength of connections increased than those in patients. The thickness of the line corresponded to the weight value. These altered connections were mainly located between the DMN and sensory-motor areas.

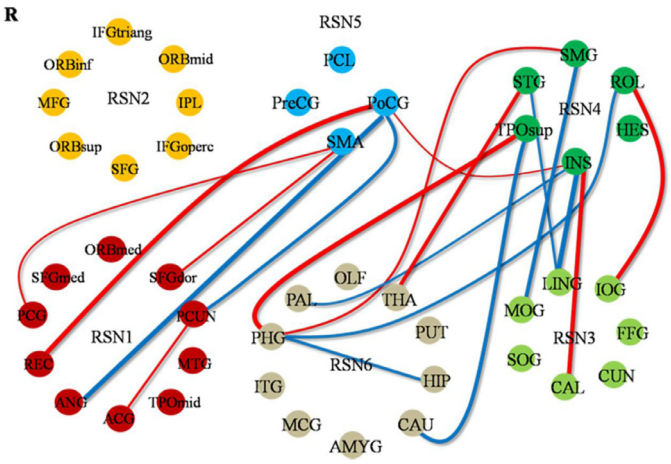

Fig. 4. The most altered connections in right hemisphere. The blue line meant that the strength of connections decreased compared with those in patients, whereas the red lines meant that the strength of connections increased than those of the patients. The thickness of the line corresponded to the weight value. These altered connections mainly embodied the dysfunctions of the DMN and paralimbic system.

indicated that each feature subset had limited discrimination information. When combined together, the overall performance became better than that of subassembly of feature subsets.

To show the advantages of ensemble method against a traditional method. We used all 4005 connectivity (simply stored in a single vector) as features to recognize schizophrenia patients from HCs. Two tailed two sample *t*-test ($p < 0.05$) was used to extract features and 10-fold cross-validation strategy was employed to evaluate the performance of this algorithm. As a result, the accuracy of traditional method was 72.6%, it was lower than that of ensemble method.

3.3. The most distinguishing brain circuitry identified in treatment-naive first-episode schizophrenia

To identify the most distinguishing aberrations in schizophrenia patients, the top 1% connections with the highest weight were determined and were drawn (Figs. 3–5 and Table 2). Names and abbreviations of ROI in Figs. 3–5 were in Table 3.

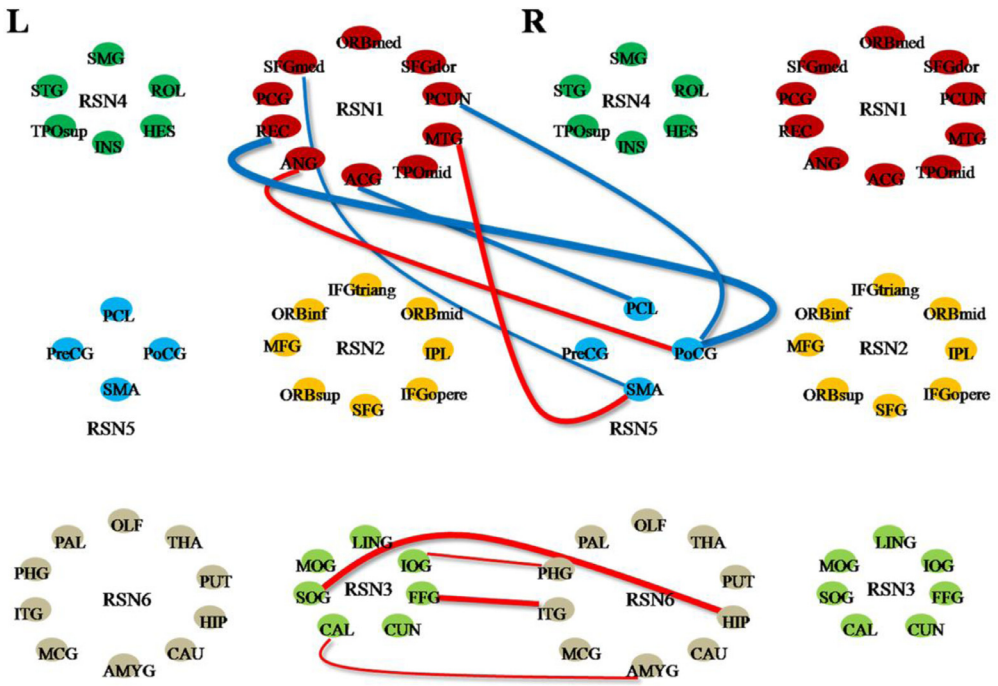

Fig. 5. The most altered connections between hemispheres. The blue line meant that the strength of connections decreased than those in patients, whereas the red line indicated that the strength of connections increased compared with those in patients. The thickness of line corresponded to the weight value. Connections between the left DMN and right sensory-motor areas were altered. In addition, connections between the right subcortical network and left visual recognition network increased in schizophrenia patients.

In the left hemisphere, altered connections were mainly located between the DMN and sensory-motor areas (Fig. 3). Connection linking the inferior temporal gyrus and postcentral gyrus was decreased in schizophrenia patients.

The condition became more complex in the right hemisphere, compared with the left hemisphere, more connections were altered. These altered connections were densely distributed between the DMN and sensory-motor areas. Connections within the paralimbic system and connections linking the paralimbic system and other networks (such as the auditory network and visual recognition network) were also pronounced in our result (Fig. 4). Moreover, the insula and superior temporal pole played important roles in these altered connections. In addition, aberrations of DMN and paralimbic system were linked by direct and indirect pathways: direct connection between the anterior cingulate cortex (ACC) and precuneus and indirect connection between the insula and precuneus through postcentral gyrus in schizophrenia.

Altered inter-hemispheric connections were also manifested in schizophrenia patients. Connections between the left DMN and right sensory-motor areas were altered. In addition, connections between the right subcortical network and left visual recognition network increased in the patients (Fig. 5).

In summary, the most distinguishing connections were located in the bilateral DMN and right paralimbic system (Figs. 3–5). The paralimbic system, including the orbitofrontal cortex (OFC), insular cortex (INS), temporal pole (TP), parahippocampal gyrus (PHG) and cingulate cortex (CC) were developed in concert in the embryonic period, and regions in this system shared cytoarchitecture and connectivity [44,45]. We discovered connections within the right paralimbic system were altered in schizophrenia patients. Another noticeable altered network was the DMN. Unlike in the paralimbic system, bilateral DMNs were altered in schizophrenia patients.

3.4. Altered connections in schizophrenia were associated with symptom severity

We observed that top 1% connections significantly predicted the positive scores (R^2=0.58, $P < 0.05$, Bonferroni corrected), and the PNASS negative scores (R^2=0.74, $P < 0.05$, Bonferroni corrected).

3.5. Validation results

We used different brain atlas to validate our main results. As a result, the accuracy of the network-based ensemble method (82.6%) was better than that of a single classifier using individual subset (Fig. S1 in Supplementary material).

4. Discussion

We used network-based ensemble method to explore the most distinguishing brain circuitry in treatment-naive first-episode schizophrenia patients. Resting-state functional connectivity networks presented a reliable classification ability with classification accuracy of 84.7% (91.9% for sensitivity, 74.5% for specificity, $p<0.05$ for permuted test, 0.902 for AUC) using a 10-fold cross-validation strategy. The bilateral DMN and the right paralimbic system were identified as the most distinguishing brain circuits in treatment-naive first-episode schizophrenia patients. Notably, the most altered connections were significantly associated with symptom severity of schizophrenia patients. Our results suggested that the ensemble method was a powerful tool to help with clinical diagnosis of schizophrenia and to explore the mechanism of schizophrenia.

Table 2
Altered connections in patients. The symbol '↓' indicates that the mean strength of connectivity in patients is smaller than that in controls, and '↑' indicates that the mean strength of connectivity in patients is larger than that in controls. Connections marked with '*' are not drawn (to show clearly) in Figs. 3–5.

Region	Region	Weight	Abnormal	
ANG.R	PoCG.R	0.0381	↓	
REC.R	PoCG.R	0.0378	↑	
REC.L	PoCG.R	0.0365	↓	
LING.R	INS.R	0.0320	↓	
TPOsup.R	PHG.R	0.0307	↑	
IOG.R	ROL.R	0.0288	↑	
CAL.R	INS.R	0.0286	↑	
REC.L	SMA.L	0.0270	↑	
MTG.L	SMA.R	0.0264	↓	
TPOmid.L	PCL.L	0.0260	↓	
SOG.L	HIP.R	0.0259	↑	
STG.R	THA.R	0.0257	↑	
PCUN.L	PoCG.R	0.0255	↓	
ANG.L	PoCG.R	0.0253	↑	
MOG.R	SMG.R	0.0252	↓	
TPOsup.R	CAU.R	0.0249	↓	
PCUN.R	PoCG.R	0.0248	↓	
PoCG.L	ITG.L	0.0247	↓	
ACG.L	PCL.R	0.0247	↓	
FFG.L	ITG.R	0.0245	↑	
ORBmed.L	TPOsup.L	0.0244	↓	
HIP.R	PHG.R	0.0242	↓	
PCL.R	PAL.L	0.0238	↑	*
SFGmed.R	STG.L	0.0237	↓	*
ROL.R	PHG.R	0.0236	↓	
SMG.R	PHG.R	0.0233	↑	
SFGdor.R	SMA.R	0.0229	↑	
PCUN.R	ACG.R	0.0227	↑	
LING.R	TPOsup.R	0.0227	↓	
INS.R	PAL.R	0.0226	↓	
SFGmed.R	INS.L	0.0226	↓	
CUN.L	CAL.R	0.0225	↓	*
IFGtriang.L	MFG.R	0.0223	↑	*
PCG.R	SMA.R	0.0223	↑	
SFGmed.L	SMA.R	0.0223	↑	
INS.R	PoCG.R	0.0223	↑	
PCUN.R	PreCG.L	0.0219	↓	*
PCL.L	ITG.R	0.0216	↑	*
CAL.L	AMYG.R	0.0214	↑	
IOG.L	PHG.R	0.0213	↑	

4.1. Discrimination performance of ensemble learner

Many other studies used resting-state functional connectivity to differentiate schizophrenia patients from healthy controls [12–16,46]. 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. The first strategy relied too much on mathematical method and ignored physiological signification, those feature that were discarded mathematically might have vital positions in emergence and development of disease [47]. In the current study, two sample *t*-test was used to select features, the accuracy was lower than that of ensemble method. Although the accuracy of traditional method might be more higher using other feature selection/extraction method, the physiological signification of selected/extracted features were not clear. Our results presented that it was easy to ignore features of discrimination ability to some extent. As for the second strategy, we proved that focusing on partial feature subsets would lead to a biased conclusion. Ensemble learner performed better than the weaker learners (Fig. 2). Network-based ensemble method showed stronger discrimination ability than a single classifier using individual or combined feature subsets. As we expected, the discrimination ability of individual sub-networks could not be simply treated as the altered degree, as indicated by previous studies [5,17]. The discrimination ability of sub-network changed when other networks were considered together. For example, connections within the left RSN5 had the most powerful discrimination ability. However, when other sub-networks were taken into account, the situation became difficult to anticipate. Using one or parts of the networks would have biased the estimation of the discrimination ability of the different networks in schizophrenia. Ensemble learning achieved a better performance, showing good generalization [18]. In this study, our method demonstrated more reliable performance. Ignoring differences of approach, salience network, subcortical and prefrontal brain regions were the most consistent distinguishing aberrations in patients with patients.

Table 3
Names and abbreviations of regions of interest (ROI).

Regions	Abbr.	Regions	Abbr.
Amygdala	AMYG	Orbitofrontal cortex (middle)	ORBmid
Angular gyrus	ANG	Orbitofrontal cortex (superior)	ORBsup
Anterior cingulate gyrus	ACG	Pallidum	PAL
Calcarine cortex	CAL	Paracentral lobule	PCL
Cuneus	CUN	Parahippocampal gyrus	PHG
Fusiform gyrus	FFG	Postcentral gyrus	PoCG
Heschl gyrus	HES	Posterior cingulate gyrus	PCG
Hippocampus	HIP	Precentral gyrus	PreCG
Inferior occipital gyrus	IOG	Precuneus	PCUN
Inferior frontal gyrus (opercula)	IFGoperc	Putamen	PUT
Inferior frontal gyrus(triangular)	IFGtriang	Rectus gyrus	REC
Inferior parietal lobule	IPL	Rolandic operculum	ROL
Inferior temporal gyrus	ITG	Superior occipital gyrus	SOG
Insular	INS	Superior frontal gyrus (dorsal)	SFGdor
Lingual gyrus	LING	Superior frontal gyrus (medial)	SFGmed
Middle cingulate gyrus	MCG	Superior parietal gyrus	SPG
Middle occipital gyrus	MOG	Superior temporal gyrus	STG
Middle frontal gyrus	MFG	Supplementary motor area	SMA
Middle temporal gyrus	MTG	Supramarginal gyrus	SMG
Olfactory	OLF	Temporal pole (middle)	TPOmid
Orbitofrontal cortex (inferior)	ORBinf	Temporal pole (superior)	TPOsup
Orbitofrontal cortex (medial)	ORBmed	Thalamus	THA

4.2. Aberration of right paralimbic system in treatment-naive first-episode patients

Connections in the right paralimbic system were seriously altered in case of schizophrenia. The paralimbic system, which plays an important role in the process of mediating the internal and external environments, is engaged in various functions, such as mood regulation, processing, motivation, and decision-making [48–52]. Thus, paralimbic system has been thought to hold an important place in the pathophysiology of psychopathy [53]. In schizophrenia, incentive salience hypothesis has received tremendous attention. Aberrant salience attribution, which is caused by the dysfunction of the dopaminergic mesolimbic pathway, results in an over-attribution of incentive to irrelevant environmental events or internally generated mental events (such as inner speech or self-generated actions) [54–57]. Anterior insula cortex (AIC) and dorsal anterior cingulate cortex (dACC) are thought to play key positions in salience processing [58]. Dysfunction of salience, especially in the right hemisphere, was pronounced in our result. Right AIC is thought to causally modulate the relationship between the CEN and a set of brain regions involved in self-referential activities constituting the DMN, which has a strong causal influence enabling the recruitment of contextually relevant brain regions [59]. Meanwhile, abnormal coordination between the right subcortical pathway (including caudate and pallidum) was found in our results, which possibly reflected the altered aberrant salience attribution resulting from abnormal DA metabolism. Connections within the right paralimbic system, which had higher weight indicating a more powerful discrimination ability, turned out to be most distinguishing brain circuitry in schizophrenia patients.

4.3. Aberration of bilateral DMN in treatment-naive first-episode patients

Another the most distinguishing brain circuits in schizophrenia were the bilateral DMN, which mediates the consideration of one's own thoughts and feelings, self-referential processing, and is involved with remembering one's past, planning one's future, and forming one's beliefs [60–63], has been consistently considered to be particularly relevant to the origin and experience of mood and psychotic symptoms of schizophrenia [64]. In schizophrenia, patients show failure to allocate attentional resources to tasks (such as oddball task and working memory tasks) [65,66]. In the resting-state, altered functional connections within the DMN are also frequently observed in schizophrenia or in people at high risk for schizophrenia [67–69]. These aberrations are associated with symptom and poor social cognition in cases of schizophrenia [70–72].

4.4. The most distinguishing circuitry were association with symptom severity

The most distinguishing connections were significantly correlated with the PNASS positive and negative scores of patients with schizophrenia. Studies assum that symptom in schizophrenia are resulted from aberrant assignment of salience that is the result of abnormal DA metabolism. The alternating balance of attention to internal thoughts and feelings is the result of the relationship of the DMN and TPN task-positive networks, and this relationship is altered in schizophrenia suggesting the decreased capacity to switch between internal and external modes of attention [69,70,73]. Finally, schizophrenia patients demonstrated the inability to distinguish the internal thoughts and external perceptions. The boundary between them end to blur, and the hallucinations and delusions may occur [74]. In schizophrenia, delusions, that is the effort to make sense of aberrant salience, are always imbued with psychodynamic themes, which are related to the function of DMN relevant to the individual [56]. The persistent aberrant salience might impel patients from reforming their beliefs or psychotic insight. In addition, psychotic insight serves as a guiding cognitive scheme for further thoughts and actions. Meanwhile, for example auditory hallucinations are thought to be related with internal speech, which is modulated by ACC and DMN, in the absence of external stimuli [75,76]. The aberration DMN and the aberration of salience also participated cooperatively act in the emergence of the psychopathological symptoms of schizophrenia.

4.5. Limitations

One main limitation of the present study was the employment of AAL template resulting in the vague definition of some regions including AIC and dACC. However, the advantage of the study embodied that whole brain regions could be considered altogether. We can then systematically explore aberrations in all brain networks and identify the core aberrations in case of schizophrenia. Another limitation was that our results did not have replication in another cohort of schizophrenia patients. Future studies might use another cohort of schizophrenia patients validate these results.

5. Conclusion

We found that the bilateral DMN and the right paralimbic system were identified as the most distinguishing brain circuits in schizophrenia patients. Notably, these the most distinguishing connections were significantly correlated with symptom severity in schizophrenia patients, suggesting that these connections play a pivotal role in the pathological mechanism of schizophrenia. Our results suggested that the ensemble method was a powerful tool to help with clinical diagnosis of schizophrenia and to explore the mechanism of schizophrenia.

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Declaration of Competing Interest

We do not have any conflict of interest to individuals or groups.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neucom.2019.07.061.

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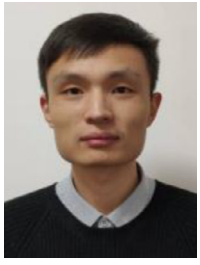

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