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Analysis of first-episode and chronic schizophrenia using multi-modal magnetic resonance imaging

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Abstract. – OBJECTIVE: The brain structure and function differences among first-episode schizophrenia (FESZ) patients, chronic schizophrenia (CSZ) patients, and normal control (NC) subjects were investigated using structural and functional magnetic resonance imaging (MRI). Also, a support vector machine (SVM) combined with recursive feature elimination (RFE) was used for classification.

PATIENTS AND METHODS: First, 44 FESZ patients, 44 CSZ patients, and 56 NC subjects were recruited, and structural MRI images were acquired. The regional gray matter volumes (GMVs) of 90 regions of interest (ROIs) were calculated, two-sample t-tests were conducted to analyze the GMV differences among the groups, and the partial correlations between the Positive and Negative Syndrome Scale (PANSS) scores and altered regional GMVs were calculated. Individual functional MRI images of the three groups were measured. The individual regional homogeneity (ReHo), amplitude of low-frequency fluctuations (ALFF), and degree of centrality (DC) values of the 90 ROIs were calculated and used to evaluate the differences among the groups. Then, the partial correlations between the PANSS scores and altered regional ReHo, ALFF, and DC were determined. An SVM combined with RFE was employed for classification using both structural and functional MRI input features. The sensitivity and specificity were measured to quantify the SVM performance.

RESULTS: The GMVs in the bilateral calcarine of FESZ and CSZ patients were significantly lower than that of NC subjects. Compared to the NC group, the GMV was significantly reduced in numerous additional brain regions of the CSZ group. In comparison to the NC group, the patient groups exhibited significant ReHo increases in several regions and ReHo reductions in the occipital lobe. ReHo in the insula and left postcentral gyrus of CSZ patients were significantly lower than that of the NC subjects. Compared with the NC group, both patient groups exhibited ALFF aberrances in numerous regions. A significant reduction of ReHo, ALFF, and DC in certain regions were also found in patient groups compared with that of NC group. Significant positive correlations were found between the PANSS scores and ReHo and ALFF of the temporal and frontal lobes, while these correlations were negative in the occipital lobe. The SVM with RFE achieved excellent classification performance. The best performance was obtained using the following inputs: the ReHo and ALFF for FESZ/NC classification; the DC, ReHo, and ALFF for FESZ/CSZ classification; and the ReHo and ALFF for CSZ/NC classification.

CONCLUSIONS: Our data indicate that compared with the FESZ patients, brain GMV aberrances was increased in the CSZ patients. The functional features including DC, ReHo, and ALFF, could facilitate FESZ diagnosis, which is more sensitive than structural features in classification. The SVM with RFE presents excellent classification performance and assists SZ diagnosis.

Key Words:
Magnetic Resonance Imaging, Schizophrenia, Multi-modal.

Introduction

Schizophrenia (SZ) is a commonly encountered form of major psychosis of which clinical manifestations include hallucinations, delusions, or behavioral disorders accompanied by losses in cognition and social function. The prognosis of SZ tends to be poor, and its sufferers are prone to reoccurrences, leading to high medical fees

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and rehabilitation costs[1]. For a long time, clinical SZ diagnosis has been based on medical history, clinical symptoms, and physical and mental examinations, with clinical scales being used as auxiliary diagnostic tools. However, these diagnostic methods are primarily according to subjective symptoms and lack objective diagnostic indicators, which may lead to misdiagnoses or failures to diagnose SZ. The resulting treatment delays frequently cause immense economic burdens and mental scars on SZ patients and their families, and could even endanger lives in severe cases. The establishment of an objective diagnostic method for SZ is thus an important and urgent issue in the field of medical science. Furthermore, the therapeutic mechanisms of SZ drugs are based on neurobiological transmission hypotheses to date, and the mechanisms on the impact of brain functions remain to be fully elucidated. Due to the poor prognosis of SZ and the immense burden it inflicts on society and the families of sufferers, SZ is a topic of great interest in scientific research.

Conventional SZ diagnoses are highly subjective and often provide results that are inconsistent with the actual state of disease. The use of magnetic resonance imaging (MRI) analysis and processing techniques with objective imaging biomarkers will fundamentally change SZ diagnosis and the assessment of treatment efficacy, thereby improving the objectivity and accuracy of clinical diagnosis[2]. The combination of multi-modal MRI techniques and magnetoencephalography is one of the current developmental trends in brain imaging, as these composite techniques can circumvent many of the weaknesses of previous MRI-based techniques. Conventional MRI techniques with single-modal analysis are characterized with significant variability as well as a lack of reproducibility. Therefore, the aims of this study were to perform multi-modal, multi-level analyses of the results of functional and structural brain imaging[3], and to combine these techniques with support vector machine (SVM) classification, i.e., to use the M3 method (multi-modal imaging and multi-level characteristics with multi-classification). Hence, multi-dimensional analyses were integrated for diagnosing SZ and evaluating therapeutic efficacy[4].

A multitude of studies has revealed significant correlations between frontal gray matter volume (GMV) and disease progression in SZ patients. Nonetheless, contradictory findings have also been reported, possibly due to the numbers of samples and analytical methods being used in each study. In this work, we used multi-modal indicators to search for differences and similarities between chronic and first-episode SZ patients. The findings are expected to provide a systematic understanding of the characteristics and patterns of change in the brain functions of SZ patients and we attempted to establish reliable neuroimaging markers for SZ diagnosis and treatment efficacy assessments.

Patients and Methods

Research Participants

The participant data were collected from first-episode SZ patients, chronic SZ patients, and healthy individuals. The patients were recruited from The Affiliated Brain Hospital of Guangzhou Medical University (Guangzhou Hulai Hospital), while the healthy control participants were openly recruited from society through posters and forums. The tested groups were screened and matched according to age, gender, duration of education, IQ, race, and handedness.

Inclusion criteria of patient groups:

1) Matching the DSM-IV-TR diagnostic criteria for SZ, based on structured clinical interviews for DSM-IV-TR disorders (SCID).
2) Hospitalization, with biological parents who were both Han Chinese.
3) Aged 18-45.
4) Positive and negative syndrome scale (PANSS) scores of 60 or higher (each item is scored on a scale 1 to 7). Of the seven positive symptoms, at least three items were required have scores of 4 or higher, with P3 (hallucinatory behavior) being scored 4 or higher. The Hoffman auditory hallucinations rating scale was also used for patients who suffer from auditory hallucinations.
5) Providing written informed consent or have a guardian who provided written informed consent if the patient was incapable of providing consent during the onset of the disease.

Exclusion criteria of patient groups:

1) Meeting the DSM-IV diagnostic criteria for schizoaffective disorder, mood disorders, mental retardation, pervasive developmental disorders, delirium, dementia, impaired memory, or other types of cognitive impairments.
2) Suffering from severe and unstable somatic symptom disorders and/or diagnosed diabetes, thyroid diseases, high blood pressure, and heart disease.

3) Having narrow-angle glaucoma.
4) Having a history of epileptic seizures, apart from febrile convulsions.
5) Meeting the DSM-IV-TR diagnostic criteria for alcohol and drug dependence (except for nicotine dependence).
6) Having used long-acting antipsychotic preparations prior to being selected, within one treatment interval (five treatment intervals were required for participants who had been injected with Risperidone microspheres).
7) Having regularly used clozapine for 1 month prior to selection.
8) Having been treated using electric shock treatment (ECT) for 6 months prior to selection.
9) Having suffered or currently suffering from neuroleptic malignant syndrome or severe tardive dyskinesia.
10) Being severely suicidal or severely disinhibited.
11) Having laboratory examination results that were clearly abnormal (AST or ALT levels ≥2 times higher than the normal upper limit; BUN levels ≥1.5 times the normal upper limit; Cr levels ≥1.2 times higher than the normal upper limit).
12) Having poor therapeutic compliance or no guardian.
13) Having prolonged QTc interphases (male ≥ 450 ms, female ≥ 470 ms in electrocardiograms).
14) Being pregnant or lactating or planning to have children.
15) Having been adequately proven to exhibit therapeutic failure using two different antipsychotic drugs with two different action mechanisms (the criterion for therapeutic failure was the persistence of severe mental symptoms in the patient despite adequate dosage, adequate treatment, and full compliance).
16) Having contraindications for the antipsychotic drugs recommended in this study.
17) Having suffered head trauma accompanied by more than 5 min of unconsciousness.
18) Having contraindications for MRI (the MR safety review form was required to be completed when the participant signed the informed written consent form).

Elimination and removal criteria of patient groups:
1) Violating the research scheme, for example, not meeting the entry criteria, using prohibited drugs, and not complying with the study requirements.
2) Having adverse drug reactions and being unable to tolerate the smallest dosages.
3) Exhibiting poor medicine adherence.
4) Withdrawing informed consent.
5) Becoming pregnant.
6) Being lost to follow-up.
7) Being judged unsuitable for further participation in this study by the researchers.

Inclusion criteria of healthy control group:
1) Having normal intelligence according to rough intelligence tests; being able to perform neurological tests; and having no color blindness (partial or full), deafness, stammering, or other disorders that could affect neurocognition.
2) Having biological parents who were both Han Chinese.
3) Being aged between 18 and 45 (each participant was independently selected for inclusion, with age, gender, and education level being considered simultaneously, to produce the closest possible match with the patient groups. This group was the control for the patient groups, and the data collection was completed within 2 months).
4) Signing a written informed consent form.

Exclusion criteria of healthy control group:
1) Meeting the diagnostic criteria for Axis I disorders in DSM-IV, based on SCID.
2) Having relatives within three generations on the maternal or paternal side who met the diagnostic criteria for Axis I disorders in DSM-IV.
3) Suffering from severe and unstable somatic symptom disorders and/or diagnosed diabetes, thyroid diseases, high blood pressure, and heart disease.
4) Having a history of epileptic seizures, apart from febrile convulsions.
5) Being pregnant or lactating.
6) Having suffered from head trauma accompanied by more than 5 min of unconsciousness.
7) Having contraindications for MRI (the MR safety review form was required to be completed when each participant signed the informed written consent form).

Chronic SZ patients with 2 years or longer course of disease show no significant improvement and/or patients have two or more onsets of the disease. First-episode SZ patients have only had their first onset of SZ, for whom the course of

the disease is less than 2 years, and they have yet to be treated using psychiatric drugs.

A total of 44 chronic SZ patients and 44 first-episode SZ patients were recruited from the Outpatient and Inpatient Departments of The Affiliated Brain Hospital of Guangzhou Medical University (Guangzhou Hulai Hospital), as well as 56 healthy controls; the ages of the participants ranged from 18 to 45. All of the test participants were screened using SCID, and the participants in the patient groups all met the DSM-IV-TR clinical diagnostic criteria for SZ. The PANSS and Hoffman auditory hallucination rating scales were also used to evaluate the psychiatric symptoms of these 88 patients. The Weschler Adult Intelligence Scale and the Chinese edition of the MATRICS Consensus Cognitive Battery were used to assess the cognitive abilities of the 88 patients and 56 normal individuals. The questionnaires used in this study were Chinese translations of the original questionnaires, to ensure the credibility of the tests. After classification tests had been performed on the 88 SZ patients, the 44 chronic SZ patients were grouped into the chronic schizophrenia (CSZ) group, while the 44 first-episode SZ patients were assigned into the first-episode schizophrenia (FESZ) group. In addition, the 56 healthy participants who met the inclusion criteria and were recruited from society were grouped into the normal control (NC) group.

All of the participants were adequately informed about the details of this experiment and signed informed consent forms prior to the tests and MRI examinations. This study strictly adhered to the requirements of the Declaration of Helsinki and was conducted with the permission of the Ethics Committee of Guangzhou Hulai Hospital.

Collection of Structural MRI Data

The data required for this work were obtained through the collaboration of Guangzhou Hulai Hospital and the researchers participating in this experiment. Before the experiment was conducted, each of the doctors and participants signed a written cooperation agreement. The items that the participants had to pay attention to during the experiment were explained prior to the experiment. In addition, each participant was required to ensure that no metal objects were present inside or outside his or her body, to ensure the effectiveness of the data acquisition process. Each operational cycle in the data acquisition process was performed by a professional imaging technician. The MRI scanner used to scan the participants was a Phillips 3.0T MR system (Amsterdam, The Netherlands). The scanning was performed inside a standard head coil. The 3D structural imaging scans were conducted using the 3D T1-weighted magnetization-prepared rapid gradient echo along the anterior commissure-posterior commissure line (AC-PC line). The scanning parameters were as follows: FOV: 256×256 mm; TR = 7.6 ms; TE = 3.7 ms; flip angle = 8°; number of slices = 180; slice thickness = 1 mm; matrix dimensions = 256×256; voxel size = 1×1×1 mm^3. Functional imaging was performed along the AC-PC line, and the echo-planar imaging sequence was used to perform the imaging scans. The scanning parameters were as follows: FOV: 256×256 mm; TR = 2000 ms; TE = 40 ms; flip angle = 90°; number of slices = 36; slice thickness = 4 mm; matrix dimensions = 64×64. All of the images were transferred in DICOM format to a specialized Taiway image processing station (Taipei, Taiwan).

Image Processing and Analysis

The acquired data were processed and analyzed. We used SPM8 (London, UK) to perform the segmenting and non-linear transformation of the images, as well as post-processing operations such as standardization and smoothing.

Voxel-based morphometry and resting-state functional MRI analytical methods were used to perform correlation analyses of the processed imaging data and other forms of objective data that were acquired from the participants, including clinical and demographic statistics, cerebral GMV, ReHo, ALFF, and DC.

Machine-learning-based support vector classification theory was used to perform machine learning classification modeling, feature extraction and classification on the processed imaging data. We determined the optimal method for classifying SZ by comparing the results of different classification methods, thus providing a useful reference for SZ diagnosis and the search for its early-stage biomarkers.

Statistical Analysis

(1) Single-factor analysis of variance (ANOVA) was used to calculate the clinical and demographic statistical differences among the tested groups.

(2) Post-hoc analysis of Tukey's test was performed on the results obtained using ANOVA to determine whether significant differences were present among the group averages.

(3) The x^2-test was used to analyze the gender data in the demographic statistics, and the significance level was defined as $p < 0.05$.

Image-Based GMV Analysis

(1) The generalized linear model in SPM8 was used to perform pixel-based statistical analysis of the smoothened gray matter images. The covariates in the generalized linear model included whole-brain GMV, age, gender, and education level.

(2) Pixel-based statistical analysis of the GMV differences among the three tested groups was performed using the ANOVA model.

(3) When there were significant differences among the GMVs of the tested groups, post-hoc analysis of the GMV differences between an arbitrary pair of groups was performed.

The statistical result map was calibrated through multivariate regression, and the significance level was $p < 0.05$ (the statistical level for each voxel was $p < 0.001$, with the size of each voxel cluster being 173 voxels). This multivariate regression calibration was performed using the Monte Carlo simulation in the AlphaSim tool of the AFNI software suite. Also, region-of-interest (ROI) analysis was performed on the GMV of each brain area, with the ROI being defined as the voxel clusters showing significant inter-group differences in the pixel-based GMV difference analysis. The correlations between the GMVs of the brain area ROIs and the clinical data were analyzed via partial correlation analysis, with the control variables including age, gender, education level, and whole-brain GMV.

ReHo Analysis of the Brain

Pixel-based statistical analysis of the ReHo differences among the three groups was performed using the ANOVA model. The covariate effects being controlled included age, gender, and education level. When there were significant differences among the ReHo values of the three tested groups, Tukey's post-hoc analysis of the ReHo differences between arbitrary pairs of groups was performed. The ReHo values in this analysis were also used in machine learning, as described in Result 6.

ALFF Analysis of the Brain

As in the ReHo analysis, pixel-based statistical analysis of the ALFF differences among the three tested groups was performed using the ANOVA model, and the covariate effects being controlled included age, gender, and education level. When there were significant differences among the ALFFs of the three groups, post-hoc analysis of the ALFF differences between an arbitrary pair of groups was performed. The ALFF values in this analysis were also used in machine learning for classification.

DC Analysis of the Functional Connectivity in the Brain

As in the statistical analyses of the ReHo and ALFF, pixel-based statistical analysis of the DC differences among the three tested groups was performed using the ANOVA model, and the covariate effects being controlled included age, gender, and education level. When there were significant differences among the DCs of the three tested groups, the Tukey's post-hoc analysis of the DC differences between an arbitrary pair of groups was performed. The DC values in this analysis were also used in machine learning for classification.

Results

Analysis of Clinical Characteristics and Demographics

The detailed demographic statistics of the participants have presented in Table I. It indicated that the age distribution of the CSZ group was significantly larger than that of the FESZ and NC groups ($p < 0.05$). There were no significant differences among the gender and brain volume distri-

Table I. Analysis of clinical characteristics and demographics.

	FESZ patients (n=43)	NC (n=56)	SZ patients (n=39)	F value (x^2)	*p*-value
Age (years):	26.42±8.02	25.07±5.85	29.97±6.97	5.94	<0.000[1b]
Gender (female:male):	15:28	23:33	15:24	0.39*	0.82*
Years in education (years):	10.37±3.29	12.14±2.42	11.44±2.76	4.84	0.003a
Brain volume (mm^3):	1193.27±111.65	1203.59±108.70	1154.97±120.88	2.224	0.14
PANSS-P Score:	25.21±3.93	7.05±0.30	23.39±3.31	632.15	<0.0001[a,b]
PANSS-N Score:	21.42±7.84	8.79±2.70	22.39±6.40	85.18	<0.0001[a,b]
PANSS-G Score:	40.49±9.21	17.18±2.34	39.13±6.82	205.38	<0.0001[a,b]
PANSS-TS core:	87.12±18.09	33.02±4.74	84.897±12.31	305.07	<0.0001[a,b]

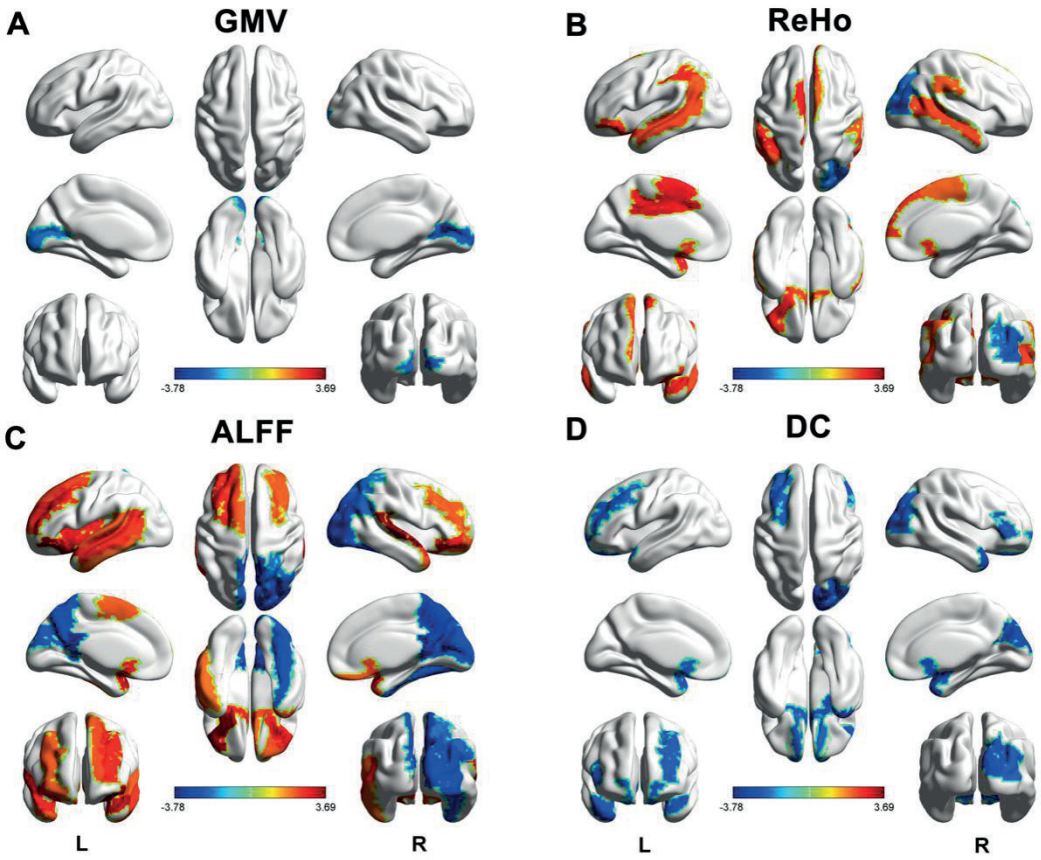

Figure 1. Comparison between the GMV (A), ReHo (B), ALFF (C), and DC (D) values of the FESZ and NC groups.

butions of the three groups ($p > 0.05$). However, significantly longer education duration was found in the NC group than that in the FESZ group ($p < 0.05$). We found significant differences among the clinical questionnaires of all of the groups by performing two-sample *t*-tests. The PANSS score in NC group was significantly lower than that in the CSZ and FESZ groups ($p < 0.05$), as normal people do not exhibit clinical SZ symptoms, compared with chronic and first-episode SZ patients. Between the CSZ and FESZ groups, the PANSS positive item score in CSZ group displayed lower than that the FESZ group ($p < 0.05$), which may be related to the alleviation of positive symptoms in chronic SZ patients following treatment. However, there are no significant differences in the negative item, general psychopathology, and total scores between CSZ and FESZ groups.

Brain GMV Abnormalities

Compared with the NC group, the GMV in the bilateral calcarine of FESZ and CSZ groups was significantly reduced ($p < 0.05$), as shown in Figure 1A. However, compared to the NC group, in the CSZ group, GMVs in the bilateral precentral gyrus, left superior frontal gyrus, orbital surface of the bilateral superior frontal gyrus, bilateral middle frontal gyrus, orbital surface of the bilateral middle frontal gyrus, bilateral insula, bilateral anterior cingulate gyrus, bilateral middle cingulate gyrus, bilateral posterior cingulate gyrus, bilateral hippocampus, bilateral amygdala, bilateral calcarine, bilateral lingual gyrus, right middle occipital lobe, left inferior occipital lobe, left inferior parietal lobe, bilateral supramarginal gyrus, bilateral angular gyrus, right precuneus, bilateral anterior transverse temporal gyrus, right superior temporal gyrus, left temporal pole, and bilateral middle temporal gyrus were significantly decreased ($p < 0.05$) (Figure 2A). Of note, compared with the CSZ group, in the FESZ group, significantly increasing level of GMV was found in the orbital surface of the bilateral precentral gyrus, orbital surface of the right middle frontal gyrus, bilateral supplementary motor area, middle and superior frontal gyri of the bilateral frontal lobe,

orbital and middle parts of the bilateral frontal lobe, bilateral rectus gyrus, bilateral insula, bilateral cingulate gyrus (anterior, middle, posterior), right middle occipital lobe, left inferior parietal lobe, left angular gyrus, and right middle temporal gyrus ($p < 0.05$)(Figure 3A).

Partial correlation analysis of the correlations between the GMVs of the individual ROIs and the clinical data was performed, with the manipulated variables including age, gender, education level, and whole-brain GMV. No significant correlations were found among the clinical data (total, negative item, positive item, and general psychopathology PANSS scores).

Abnormalities in Brain ReHo, ALFF, and DC

Compared with the NC group, in the FESZ group, we found significant increases of ReHo in the orbital part of the left inferior frontal gyrus, bilateral supplementary motor area, bilateral olfactory bulb, middle and superior frontal gyri of the right frontal lobe, left middle cingulate gyrus, left inferior parietal lobe, right supramarginal gyrus, left angular gyrus, left putamen, right globus pallidus, left superior temporal pole, and bilateral middle temporal gyrus ($p < 0.05$), while significant decreases of ReHo were noted in the right superior and right middle occipital lobes ($p < 0.05$) (Figure 1B). Compared with the NC group, in the CSZ group, there was significant elevation of ReHo in the bilateral middle cingulate gyrus, right superior parietal lobe, left caudate, left globus pallidus, and left superior temporal pole ($p < 0.05$) and significant reduction was observed in the right insular cortex, left middle occipital lobe, left inferior occipital lobe, and left postcentral gyrus ($p < 0.05$) (Figure 2B). Compared with the CSZ group, in the FESZ group, ReHo in the left precentral gyrus, orbital part of the bilateral inferior frontal gyrus, middle and superior frontal gyri of the right frontal lobe, left postcentral gyrus, left inferior parietal lobe, left supramarginal gyrus, left anterior transverse temporal gyrus, bilateral superior temporal gyrus, and bilateral middle temporal gyrus were significantly elevated ($p < 0.05$), whereas ReHo in the right superior

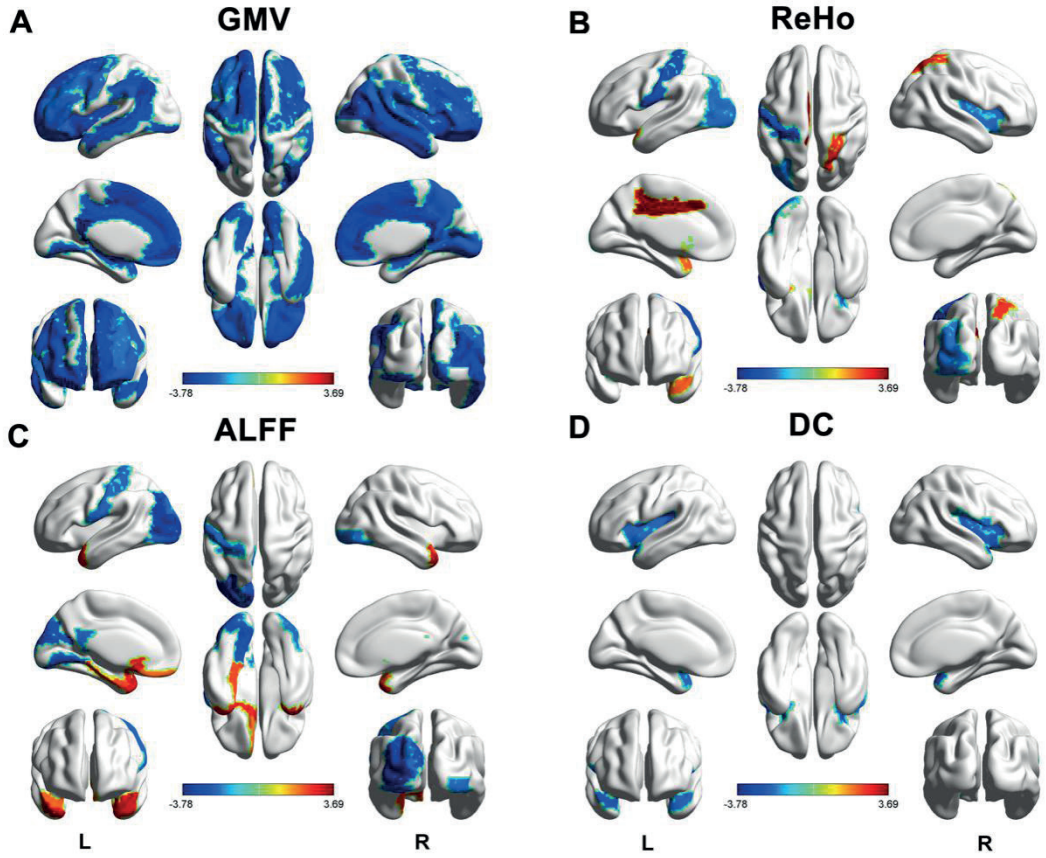

Figure 2. Comparison between the GMV (A), ReHo (B), ALFF (C), and DC (D) values of the CSZ and NC groups.

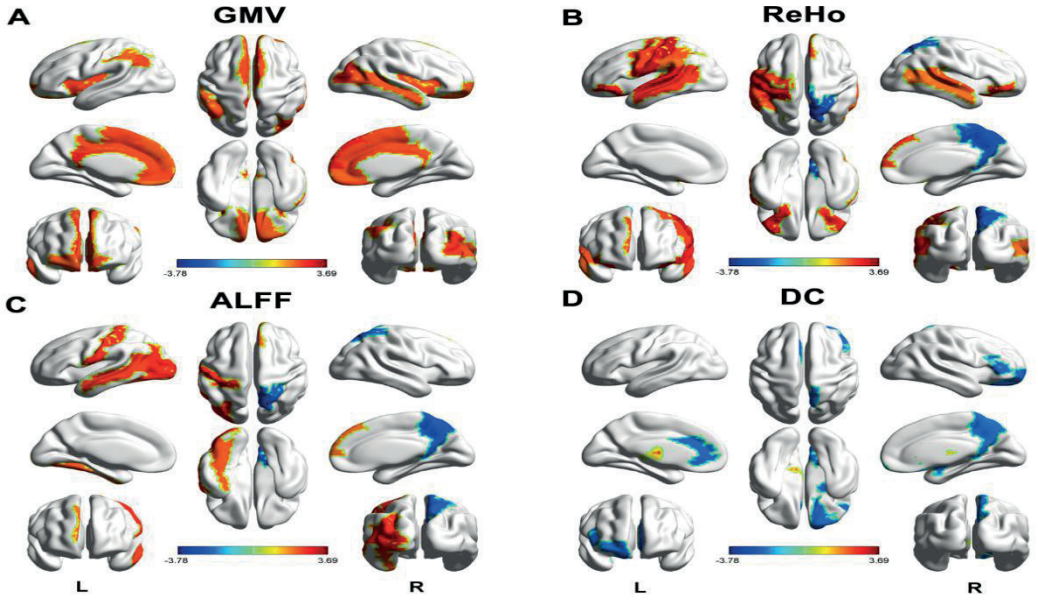

Figure 3. Comparison between the GMV (A), ReHo (B), ALFF (C), and DC (D) values of the FESZ and CSZ groups.

parietal lobe, right precuneus, and right paracentral gyrus were significantly down regulated ($p < 0.05$) (Figure 3B).

Compared with the NC group, in the FESZ group, significant growing expression of ALFF in the left superior frontal gyrus, bilateral middle frontal gyrus, orbital surface of the right middle frontal gyrus, orbital surface of the bilateral inferior frontal gyrus, left supplementary motor area, bilateral olfactory bulb, right rectus gyrus, left insular cortex, left putamen, bilateral superior temporal gyrus, bilateral superior temporal pole, left middle temporal gyrus, right middle temporal pole, and left inferior temporal gyrus were shown ($p < 0.05$). Significant decreases in ALFF were noted in the bilateral posterior cingulate gyrus, right calcarine, bilateral cuneus, right superior occipital lobe, right middle occipital lobe, right inferior occipital lobe, right fusiform gyrus, right superior parietal lobe, right angular gyrus, and bilateral precuneus ($p < 0.05$) (Figure 1C). Compared with the NC group, ALFFs in the CSZ group were significantly increased in the left olfactory bulb, left rectus gyrus, left parahippocampal gyrus, left putamen, bilateral superior temporal pole, and bilateral middle temporal pole ($p < 0.05$) and significant decreases in the left posterior cingulate gyrus, left cuneus, left lingual gyrus, left superior occipital lobe, left middle occipital lobe, bilateral middle occipital lobe, and left postcentral gyrus ($p < 0.05$) (Figure 2C). Compared with the CSZ group, in the FESZ group, significant increases of ALFF in the middle and superior frontal gyri of the right frontal lobe, left middle occipital lobe, left inferior occipital lobe, left fusiform gyrus, left postcentral gyrus, and left middle temporal gyrus ($p < 0.05$), whereas the right superior parietal lobe and right precuneus displayed significant decreases in ALFF ($p < 0.05$) (Figure 3C). Compared with the NC group, the FESZ group was found with significant decreases of DC in the orbital surface of the bilateral superior frontal gyrus, left middle frontal gyrus, triangular part of the left inferior frontal gyrus, bilateral olfactory bulb, right amygdala, right cuneus, right superior occipital lobe, right middle occipital lobe, bilateral superior temporal pole, and right middle temporal pole ($p < 0.05$), and no brain regions were shown with significant increases of DC (Figure 1D). Compared with the NC group, it was shown that in CSZ group, DC was significantly decreased in the bilateral Rolandic operculum, bilateral insula, left anterior transverse temporal gyrus, and bilateral superior temporal pole ($p < 0.05$), while no significant increase of DC was observed in brain regions (Figure 2D). Compared with the CSZ group, in the FESZ group, significant increases in DC was presented in the left thalamus ($p < 0.05$) and significant

decreases in DC in the orbital surface of the right superior frontal gyrus, orbital surface of the right middle frontal gyrus, triangular part of the right inferior frontal gyrus, left anterior cingulate gyrus, right amygdala, and right precuneus ($p < 0.05$) (Figure 3D).

Correlation Analysis Between Clinical Data and ReHo, ALFF, and DC

No significant correlations were found between the ReHo, ALFF, and DC values of the ROIs and the clinical data (total, positive item, negative item, and general psychopathy PANSS scores) in the partial correlation analyses between the CSZ and NC groups. The features that were significantly different between the CSZ and FESZ groups were extracted for correlation analysis with the PANSS scores of the CSZ group. It was found that only the ALFF of the left fusiform gyrus displayed a positive correlation with the PANSS negative symptoms, with a correlation coefficient of 0.072 and $p = 9.2 \times 10^{-3}$. As the left fusiform cortex is responsible for functions such as the visual processing of linguistic text, this result is consistent with some of the negative symptoms of SZ. Hence, abnormalities in the ALFF of the left fusiform gyrus may be a pathological marker of negative SZ symptoms, although this point will require verification via follow-up studies. The features were significantly different between the FESZ and CZZ groups. These data were shown in Table II and demonstrated that the ReHo and ALFF of the right superior parietal lobe displayed correlations with the negative symptom and total PANSS scores of the FESZ group.

Table III revealed that the ALFFs of the frontal and temporal lobes were positively correlated with each of the PANSS item scores, while the ALFF of the occipital lobe was negatively correlated with each of the PANSS item scores. A similar relationship was also found between the ReHo and PANSS scores.

Results of the Automated Classification Study

Based on pairwise classification of each participant group, we discovered that the use of SVMs and recursive feature elimination (RFE) yielded excellent classification results for the provided dataset, compared with standard SVM classification and F-score feature-selection-based classification. We calculated the sensitivities and specificities of the classifier models in the classification of tested samples. We also drew receiver operating characteristic (ROC) curves, which were also known as sensitivity curves, based on the data. The ROC curves were plotted for each classification method using the true positive rate (sensitivity) as the vertical axis and the false positive rate (1-specificity) as the horizontal axis. These ROC curves were useful for improving medical analyses and the diagnosis of illnesses. When the GMV, ReHo, ALFF, and DC features were independently used as classification features for training, as shown in Figure 4, the use of DC as an independent classification feature resulted in the largest area under the classification curve. Meanwhile, the use of GMV as an independent classification resulted in the worst classification efficacy.

When the four aforementioned features were used in pairs for training, which yielded the results shown in Figure 5, the application of ReHo and ALFF as classification features resulted in the largest area under the classification curve, and therefore the best classification efficacy. All of the pairings that included GMV as a classification feature had poor classification efficacies.

When three features were selected from the four available features for training, as shown in

Table II. Correlations between the PANSS scores of the FESZ group and the features that are significantly different between the FESZ and CSZ groups.

Feature	PANSS score	Brain region	*p*	Correlation coefficient
ALFF	Total	Right superior parietal lobe	6.50×10^{-3}	-7.31×10^{-3}
	Negative symptoms	Right superior parietal lobe	6.50×10^{-3}	-0.017
ReHo	Total	Orbital part of the inferior frontal gyrus	6.73×10^{-3}	5.85×10^{-3}
	Negative symptoms	Right superior parietal lobe	4.99×10^{-3}	6.74×10^{-3}
	Positive symptoms	Orbital part of the inferior frontal gyrus	3.97×10^{-3}	0.028

Table III. Correlations between the PANSS scores of the FESZ group and the features that are significantly different between the FESZ and NC groups.

Feature	PANSS score	Brain region	p	Correlation coefficient
ALFF	Total	Right orbital surface of the middle frontal gyrus	0.72×10^{-3}	10.11×10^{-3}
		Orbital part of the left inferior frontal gyrus	7.31×10^{-3}	4.54×10^{-3}
		Orbital part of the right inferior frontal gyrus	3.41×10^{-3}	4.54×10^{-3}
		Right cuneus	4.85×10^{-3}	-14.20×10^{-3}
		Right superior occipital lobe	0.76×10^{-3}	-14.69×10^{-3}
		Right middle occipital lobe	1.98×10^{-3}	-10.53×10^{-3}
		Right inferior occipital lobe	1.30×10^{-3}	-12.2×10^{-3}
		Right superior parietal lobe	6.50×10^{-3}	-7.30×10^{-3}
		Left inferior temporal gyrus	6.60×10^{-3}	-4.59×10^{-3}
	Positive symptoms	Left superior frontal gyrus	3.83×10^{-3}	0.018
		Left middle frontal gyrus	5.23×10^{-3}	0.022
		Orbital surface of the right middle frontal gyrus	0.69×10^{-3}	0.047
		Right superior occipital lobe	5.37×10^{-3}	-0.057
		Right middle occipital lobe	7.97×10^{-3}	-0.042
	Negative symptoms	Orbital surface of the right middle frontal gyrus	8.65×10^{-3}	0.019
		Orbital part of the right inferior frontal gyrus	3.19×10^{-3}	0.011
		Right inferior occipital lobe	9.72×10^{-3}	-0.023
		Right superior parietal lobe	6.50×10^{-3}	-0.017
	General psychopathology	Orbital surface of the right middle frontal gyrus	4.43×10^{-3}	-0.89
		Left cuneus	5.20×10^{-3}	1.69
		Right cuneus	3.23×10^{-3}	2.00
		Right superior occipital lobe	1.62×10^{-3}	1.49
		Right middle occipital lobe	4.38×10^{-3}	1.02
		Right inferior occipital lobe	2.05×10^{-3}	1.17
ReHo	Total	Orbital part of the left inferior frontal gyrus	6.73×10^{-3}	5.85×10^{-3}
		Left olfactory bulb	4.15×10^{-3}	8.49×10^{-3}
		Right olfactory bulb	0.25×10^{-3}	-0.11
		Right superior occipital lobe	1.09×10^{-3}	-0.11
		Right middle occipital lobe	5.62×10^{-3}	-74×10^{-3}
	Positive symptoms	Orbital part of the left inferior frontal gyrus	3.97×10^{-3}	0.028
		Right olfactory bulb	9.82×10^{-3}	0.038
		Right globus pallidus	9.16×10^{-3}	0.024
	Negative symptoms	Right olfactory bulb	4.38×10^{-3}	0.021
		Right superior occipital lobe	6.71×10^{-3}	-0.022
	General psychopathology	Right olfactory bulb	0.41×10^{-3}	0.021
		Right superior occipital lobe	3.43×10^{-3}	-0.020

Figure 6, all four combinations led to excellent classification efficacies, since each combination achieved an accuracy of 90% or higher.

When the GMV, ReHo, ALFF, and DC features

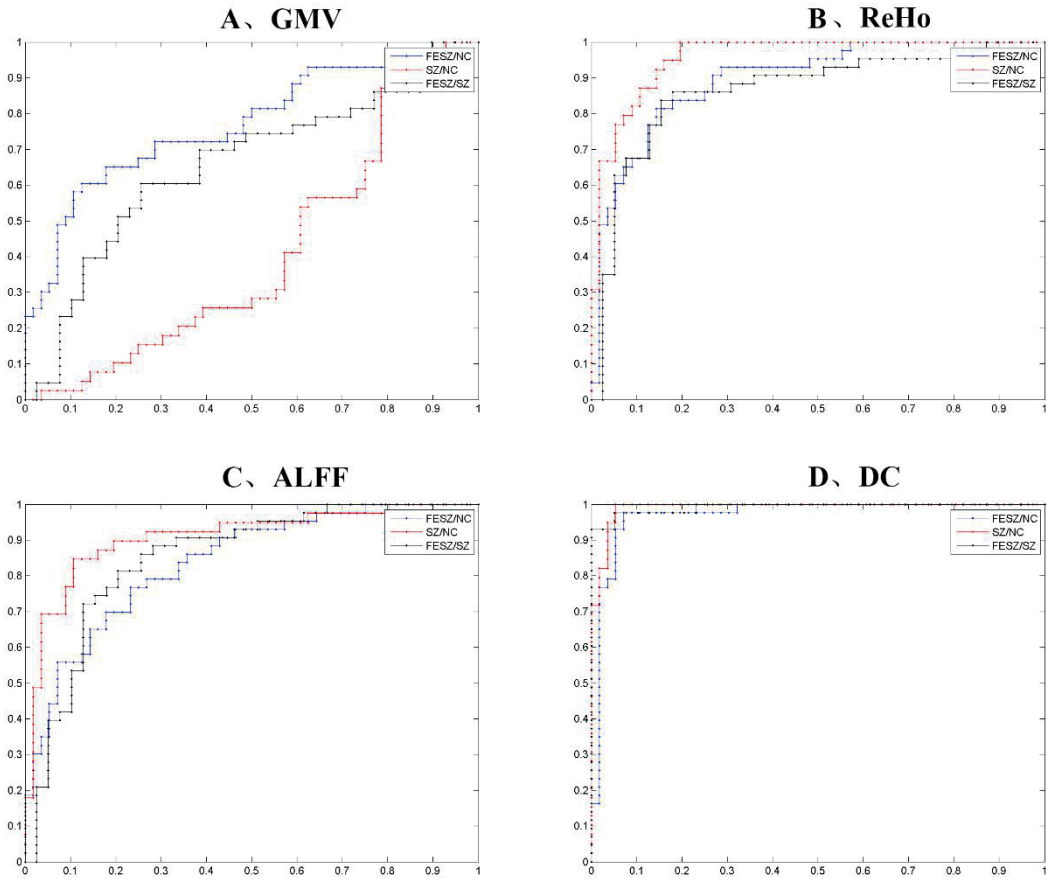

Figure 4. The four features including GMV (A), ReHo (B), C (ALFF), and DC (D) were independently used for training.

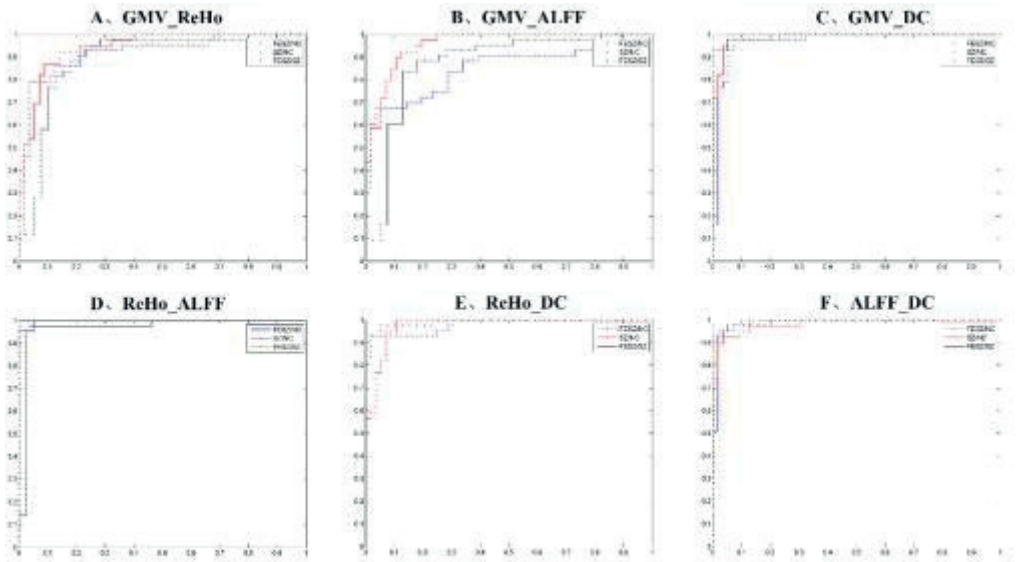

Figure 5. The features were used in pairs for training. A, GMV and ReHo. B, GMV and ALFF. C, GMV and DC. D, ReHo and ALFF. E, ReHo, and DC. F, ALFF and DC.

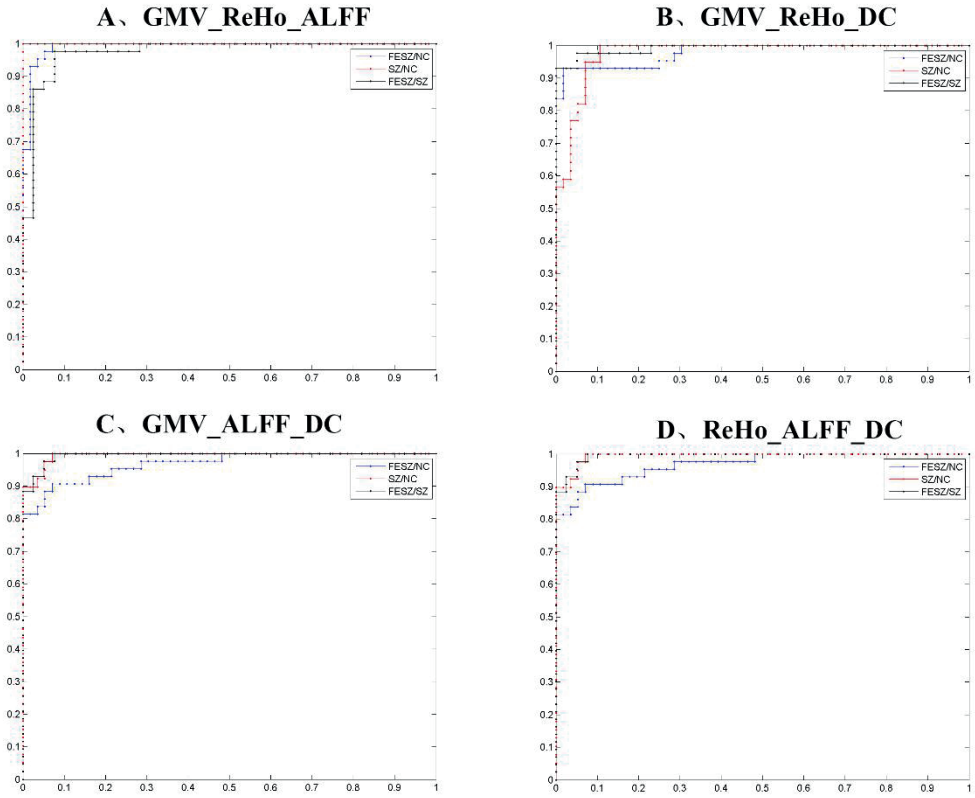

Figure 6. Three features were selected from the four available features for training. A, GMV, ReHo, and ALFF. B, GMV, ReHo, and DC. C, GMV, ALFF, and DC. D, ReHo, ALFF and DC.

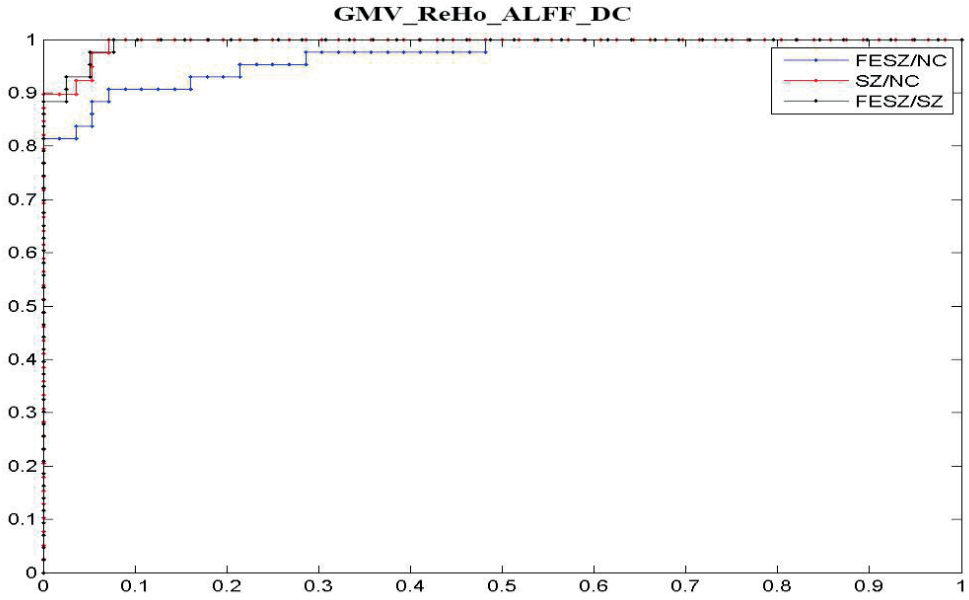

Figure 7. The four features of GMV, ReHo, ALFF, and DC were all grouped together as a classification feature.

were all grouped together as classification features, the classification accuracies of 85% or higher were achieved, as shown in Figure 7.

Discussion

Compared with the NC group, both the FESZ and CSZ groups were found with decreases of GMV in the bilateral calcarine; decreases in GMV were also found in the bilateral hippocampus, bilateral cingulate gyrus, bilateral insula, bilateral amygdala, orbital part of the frontal lobe, and temporal poles of the CSZ group. The brain areas described above are parts of the limbic system, which is closely related to the regulation of visceral activities, mood regulation, social behavior, attention and memory processes, learning processes, and decision-making[7-11]. The limbic system is also strongly interconnected with other parts of the brain and nervous system. It is noteworthy that the patient groups (FESZ and CSZ) only displayed brain regions with decreases in GMV compared with the NC group, without exhibiting any brain regions that had significant increases in GMV. This finding is strongly consistent with those of previous studies. Hence, the atrophy of certain brain regions is an important material basis for the loss of brain function and abnormalities associated with SZ. The comparison between the FESZ and NC groups only revealed a significant decrease in GMV in the bilateral calcarine, whereas the comparison between the CSZ and NC groups revealed broad and significant GMV reductions in the bilateral frontal lobes, limbic system, bilateral occipital lobe, and bilateral temporal lobe. Impairment of the functions of these structures is related to the hallucinations, delusions, and mood disorders associated with CSZ. These CSZ symptoms will therefore persist and display little improvement over time, due to this irreversible atrophy of wide areas of the brain. Molina et al[12], Premkumar et al[13], and Molina et al[14] found that the GMVs in the prefrontal cortices of CSZ patients were lower than those of first-episode patients and healthy participants and that the course of the disease was significantly correlated with volume reductions in the left dorsolateral prefrontal cortex, right supplementary motor area, prefrontal lobe, occipital lobe, thalamus, and putamen. We obtained similar results in this study, providing some evidence for the neurodegenerative hypothesis for SZ. Previous investigations[15,16] have shown that abnormalities in ReHo are always found in the occipital lobe, precuneus, parietal lobe, frontal lobe, temporal lobe, and cerebellum of early-onset SZ patients, CSZ patients, and the relatives of the patients. The results of our work are highly consistent with those of these previous studies. It is noteworthy that previous researches have demonstrated that brain structure aberrances and brain areas with functional abnormalities in various neuropsychiatric disorders overlap with each other to a certain extent[17,18]. In this investigation, overlaps between brain regions with GMV abnormalities and ReHo abnormalities are present, including in parts of the bilateral cingulate gyrus and temporal lobe. The cingulate gyrus and temporal lobe are both parts of the limbic system and are intimately related to functions such as mood regulation. Thus, this discovery provides further evidence for conjectures that a high correlation exists between limbic system aberrances and SZ. Nonetheless, GMV abnormalities that correspond to ReHo abnormalities (e.g., in the occipital lobe, cingulate gyrus, temporal lobe, parietal lobe, and *globus pallidus*) in the FESZ patients were not found in the structural images. This result proves that the early stages of SZ manifest in the form of functional disorders rather than structural alterations, which is why functional indicators such as ReHo are more sensitive to the early stages of SZ. Some of the most striking symptoms of SZ are positive symptoms such as auditory hallucinations, delusions, and thinking disorders. Activation of the left superior temporal gyrus, inferior parietal cortex, middle frontal gyrus, and other subcortical brain regions was detected in the functional images of the SZ patients, which is generally consistent with the brain areas that displayed increases in ReHo in the FESZ and CSZ groups.

Conclusions

We demonstrated that the functional features including DC, ReHo, and ALFF, were more sensitive than structural features in classification, which provides a significantly broader platform for the diagnosis of various mental illnesses in the future.

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Conflict of Interest

The Authors declare that they have no conflict of interest.

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