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Effect of Sex on Treatment Compliance and Brain Activity Alterations in Patients with Schizophrenia: A Pilot Study

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Abstract

Background: As antipsychotic agents are the primary treatment for schizophrenia, treatment compliance plays an important role in the prognosis of patients. Previous studies have reported that sex can influence the adverse effects and compliance of antipsychotics. However, sex-related effects on treatment compliance and brain activity patterns remain to be investigated in schizophrenia. We conducted a pilot study to (1) investigate how sex may influence treatment compliance in patients with schizophrenia and to (2) characterize brain activity features associated with sex-specific differences in treatment compliance.

Methods: We enrolled 53 male and 45 female patients with schizophrenia in this pilot study. The Adherence Rating Scale (MARS) was adopted to evaluate the treatment compliance of patients, while global functional connectivity density (gFCD) was used to assess brain activity features. The positive and negative assessment scale (PANSS) was adopted to assess the psychotic symptoms.

Results: Using the 3T-MRI functional technology, male patients demonstrated increased gFCD in the prefrontal lobe, posterior parietal cortex, cingulate cortex, central anterior sulcus, and superior frontal gyrus, especially in the left hemisphere. However, both male and female patients showed decreased gFCD as compared to healthy controls ($P<0.001$, FEW-corrected).

Conclusions: Despite the limitations of this pilot study, our findings suggest that males with schizophrenia show better treatment compliance and higher brain activity, primarily in the central executive network and dorsal attention network, as compared to females. These findings provide clues for further exploration of treatment compliance-related mechanisms in schizophrenia.

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INTRODUCTION

Treatment compliance plays a critical role in the successful long-term management of schizophrenia [1-5]. However, poor treatment compliance is common among patients with schizophrenia [6]. In China, it has been estimated that only 48% of patients with schizophrenia are treatment compliant. Interestingly, when the government established an intervention, the percentage of compliant patents increased to 61%, yet this indicates that only four in ten patients with schizophrenia are properly medicated [7]. Hence, there is an urgent drive in China to improve treatment compliance in patients with schizophrenia, as treatment compliance is directly associated with improved long-term prognoses, reduced disease burden, and improved quality of life. Also, patients who are compliant with their medications need less caregiving, which minimizes family burden. Hence, researchers must investigate the subjective and objective factors that may contribute to treatment compliance, as this will aid in the development of new strategies to improve treatment compliance.

Previous studies have reported that sex can influence treatment compliance in patients with schizophrenia, yet these findings were inconsistent [8-10]. Many of the studies postulated that the inconsistencies could be

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attributed to differences in the samples, disease stage, education level, severity of psychotic symptoms, and the adverse effects often associated with antipsychotic agents [11-15]. To the best of our knowledge, minimal studies have reported on the influence of sex on treatment compliance in patients with schizophrenia. Besides, there is little information about treatment compliance-induced brain activity alterations. Previous mounting studies have converged to demonstrate that schizophrenia is a disease of brain disconnection and dysfunction [16-20]. However, brain activity patterns are significantly different between males and females in certain parts of the brain [21-24] and could even influence the IQs of healthy individuals [25]. While the influence of sex is important, there is limited knowledge about the relationship between sex, treatment compliance, and brain activity alterations in patients with schizophrenia. From the studies mentioned above, we hypothesize that a reciprocal relationship may exist between sex, treatment compliance, and patient outcome. From epidemiological studies, we can observe strong reciprocal interactions between sex, treatment compliance, insight, and treatment outcomes.

Brain connectivity and regional brain metabolism are commonly assessed with global functional connectivity density (gFCD). In previous studies, gFCD could reflect differences in many psychotic symptoms and was an excellent index to characterize the brain features of some psychotic symptoms [26-30]. To uncover the mutual relationship between sex, treatment compliance, and brain features, we conducted a pilot study that used gFCD to characterize the brain features associated with treatment compliance in patients with schizophrenia. In addition, we investigated whether different sexes could affect treatment compliance and its associated brain activity features. We hypothesized that (1) treatment compliance might be impacted by sex, (2) treatment compliance is likely associated with brain activity features, and that (3) sex difference may be associated with different treatment-related brain activity patterns.

METHODS

Inclusion and Exclusion Criteria

Participants were required to meet the following inclusion criteria to be included in this study. The inclusion and exclusion criteria are outlined in Table 1. From July 2016 to July 2019, 110 patients were enrolled to participate in the study. The Ethics Committee of Wenzhou Seventh People's Hospital approved this study, and all patients or legal guardians were required to provide written informed consent (IRB date: 2016-01-07, IRB no.: 20160539).

Comprehensive insight was defined as the patient knowing that he/she had AD, understanding the symptoms of AD, and knowing that he/she needs treatment, including long-term psychology treatment [31]. A history of violence in the past year was defined as a history of rage and verbal or physical attacks on another person [32].

Study Population

The 110 patients were divided into two groups based on their sex. The male group consisted of 60 patients, while the female group consisted of 50 patients. The inclusion and exclusion criteria are described in Table 1.

Table 1. Inclusion and exclusion criteria of the patients with schizophrenia and healthy controls.

Inclusion criteria	Exclusion criteria
Schizophrenia diagnosis based on DSM-IV	History of substance abuse
Between 18 to 35 years of age	History of head trauma, seizures, neurological disorders, or mental retardation
Being treated with an atypical antipsychotic	Being seen by a psychiatrist for any reason
Symptoms stabilized for > 3 months	History of violence in the past year
Comprehensive insight	

Assessment of Patients

For the assessment of treatment compliance, the Adherence Rating Scale (MARS) was adopted [31]. To assess the total severity of psychotic symptoms, the Positive and Negative Symptoms Scale (PANSS) was employed [32]. Lastly, the Treatment Emergent Symptom Scale (TESS) was adopted to assess the adverse effects associated with the antipsychotics [33].

MRI Data Acquisition

MRI was performed on a 3-T General Electric Discovery MR750 system (Milwaukee, WI, USA). The MRI had an eight-channel phased-array head coil. The patients were required to lay down on their backs in the supine position and to stay awake and minimize any potential bodily movements for the duration of the scan. Whole-brain resting-state fMRI (rs-fMRI) data with blood oxygen level-dependent (BOLD) signals were obtained using the gradient-echo echo-planar imaging sequence. The parameters were as follows: repetition time (TR) = 2,000 ms; echo time (TE) = 45 ms; number of slices = 32; slice thickness= 4 mm; gap=0.5 mm; field of view (FOV) = 220 × 220; matrix size = 64 × 64; and flip angle (FA) = 90°. Parallel imaging was used to obtain the scans with sensitivity encoding (SENSE) techniques (SENSE factor = 2). The structural images were recorded with the high-resolution 3D Turbo-Fast Echo T1WI sequence. The following parameters were used: number of slices = 170, TR/TE = 8.2/3.2, slice thickness = 1 mm, no gap, FA = 12°, matrix size = 256 × 256, and FOV = 256 × 256.

Data Processing

The resting-state fMRI data were analyzed with SPM8 (http://www.fil.ion.ucl.ac.uk/spm). The initial ten volumes were removed to account for stabilization and subject familiarity. Correction algorithms were used to perform slice time correction and artifacts reduction in the volumes that remained after removing the initial ten. Both

translation and rotational movements of the head were found to be less than 2 mm and 2°, respectively. Regression was used to account for the time series of each voxel for the covariates, like a signal from the white brain matter and cerebrospinal fluid. Finally, the anomalies from head motions were normalized using the Friston 24-parameter model. For frame-wise displacement (FD), any volume with an FD of higher than 0.5 was also regressed out of this study. Next, band-pass frequencies (0.01 to 0.08 Hz) were used to assess the data. The average functional MR image was co-registered with each structural image for effective comparison. Then, the images were transformed into a common coordinate space using the Montreal Neurological Institute (MNI) space. Next, spatial normalization was performed using parameters that were determined during the linear co-registration process. Lastly, the processed images were sampled into 3-mm cubic voxels [26].

Calculation of gFCD

The gFCD of each voxel was calculated using the Linux script created by our lab and previously reported [27, 34-36]. Inter-voxel functional connectivity was assessed using Pearson's linear correlation and a correlation coefficient threshold of R> 0.6 [27, 34-36]. The gFCD calculations were restricted to the grey matter mask. For a given voxel at t(0), the gFCD was determined to be the sum of functional connections, denoted as m(t0), between t0 and the other voxels using an algorithm of growth. This process was repeated for each t0 voxel. Next, the normality of the distribution was improved by dividing gFCD by the mean qualified voxel. Lastly, the Gaussian kernel was used to spatially smooth the FCD maps with 6×6×6-mm^3, which effectively minimized the differences in functional brain activity between the subjects. In order to determine the treatment compliance-related brain activity features, all other variables (e.g., symptoms severity, antipsychotic dosage, age, education level) were set as covariates [27, 34-36].

Statistical Analysis

The gFCD differences between pre – and post-treatment were corrected using the family-wise error (FWE) method [37]. Two-tailed *p*-values <0.05 were considered to be statistically significant [37].

RESULTS

Clinical and Sociodemographic Information

In this study, we acquired the MRI data of 53 male and 45 female patients after applying the inclusion criteria (**Figure 1**). Fifty healthy controls were also enrolled in the study. The clinical and sociodemographic information of the patients and healthy controls are listed in **Table 2**. Besides illness duration (*P*=0.977), several factors were found to be significantly different between the groups, including age, the severity of psychotic symptoms, antipsychotics dosage, compliance score, TESS, and education level (all *P*<0.05; Table 2).

Table 2. Clinical and sociodemographic information of the patients with schizophrenia and healthy controls.

Variable	Males (n=53)	Females (n=45)	Healthy controls (n=50)	*t/F*	*P*
Age (years)	39.4 (4.5)	33.0 (4.0)	38.5 (4.8)	3.230	0.011
Education level (years)	16.5 (3.5)	14.5 (3.7)	16.0 (4.0)	4.130	0.004
Illness duration (years)	6.5 (3.8)	6.7 (2.5)	N/A	0.011	0.977
PANSS score	64.5 (5.9)	68.6 (9. 9)	N/A	1.037	0.035
TESS score	15.2 (3.5)	11.0 (2.7)	N/A	2.250	0.001
Chlorpromazine (eq. dosage)	500.0 (100.5)	428.5 (75.3.3)	N/A	3.632	<0.001
Compliance scores					
MARS	9.0 (0.2)	4.5 (1.3)		5.589	<0.001

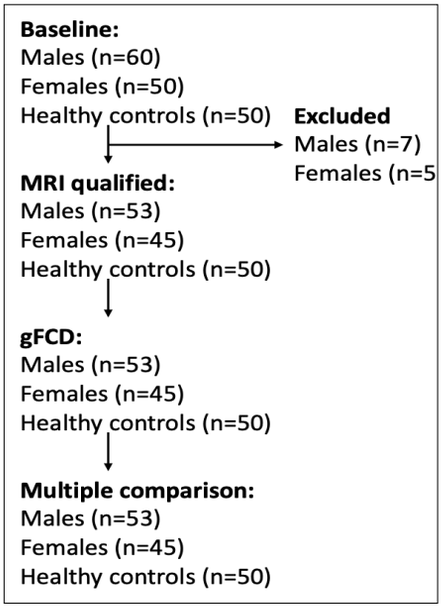

Figure 1. Flowchart of the patients with schizophrenia and healthy controls enrolled in the study.

Differences in Treatment Compliance

As demonstrated in Table 2, the males had significantly higher MARS scores than females. Simultaneously, males were more educated with higher antipsychotic agent dosages, TESS scores, and lower PANSS scores. While the male patients experienced more severe adverse effects associated with higher dosages of antipsychotics, both treatment compliance and outcomes were higher in males than females with schizophrenia.

Brain Functional Activity Features

Compared to the healthy controls, the male and female patients all demonstrated gFCD reductions, primarily in the frontal lobe, temporal lobe, parietal lobe, insular lobe, hippocampus, and thalamus. In contrast, gFCD increases were found in the striatum and caudate (Figure 2).

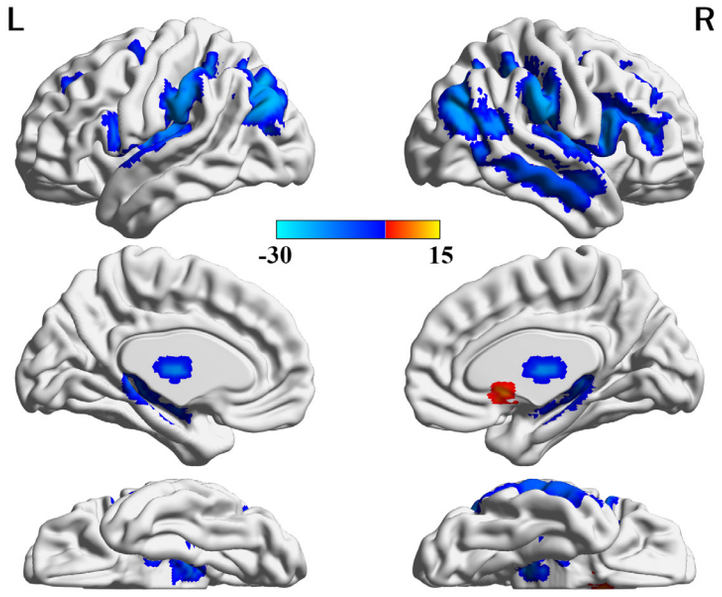

Figure 2. Both male and female patients with schizophrenia demonstrated gFCD reductions, which were primarily localized in the frontal lobe, temporal lobe, parietal lobe, insular lobe, hippocampus, thalamus, while gFCD was increased in the striatum and caudate, as compared to the healthy controls.

Compared to the healthy controls, the female patients displayed more severe and widespread reductions in functional brain activity, as determined by gFCD values (Figure 3).

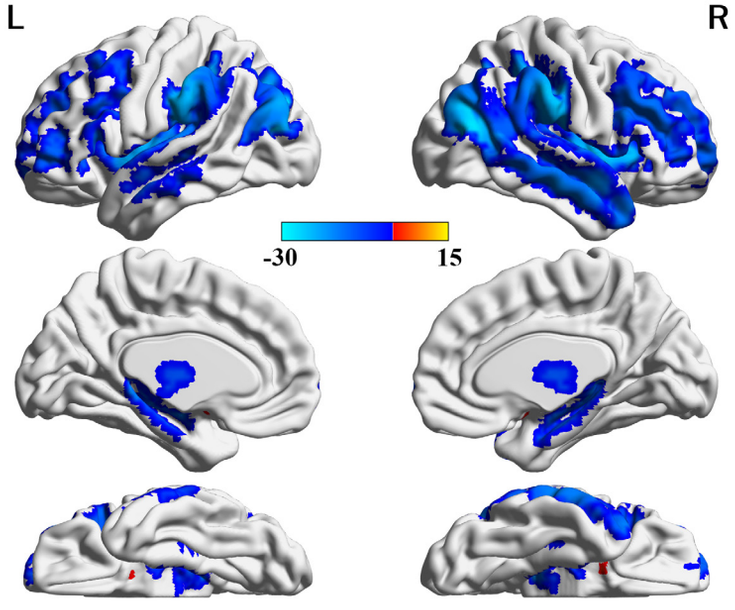

Figure 3. Female patients with schizophrenia demonstrated more severe and widespread reductions in brain activity (gFCD), as compared to the healthy controls.

Compared to the healthy controls, the male patients demonstrated decreased gFCD in the medial prefrontal cortex, cingulate cortex, posterior parietal cortex, central anterior sulcus, and superior frontal sulcus (Figure 4).

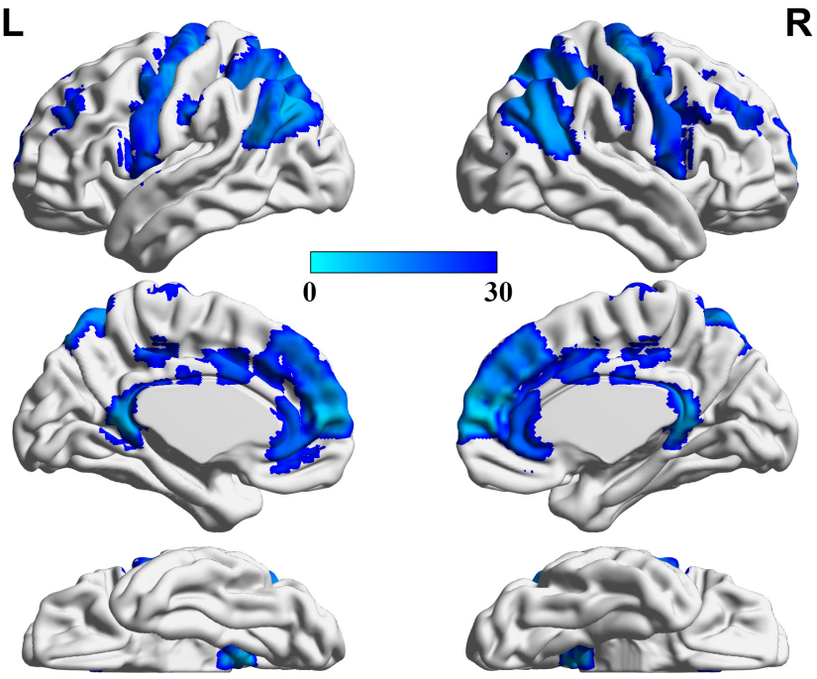

Figure 4. Male patients with schizophrenia demonstrated reduced gFCD in the medial prefrontal cortex, cingulate cortex, posterior parietal cortex, central anterior sulcus, and superior frontal sulcus, as compared to the healthy controls.

Compared to the female patients, the male patients demonstrated increased gFCD in the prefrontal lobe, posterior parietal cortex, cingulate cortex, central anterior sulcus, and superior frontal gyrus, especially in the left hemisphere of the brain (Figure 5).

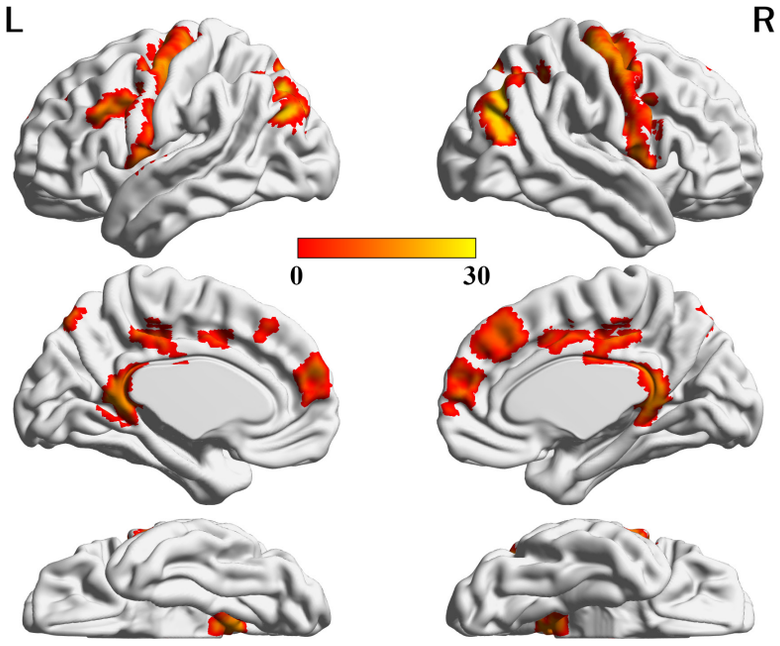

Figure 5. Male patients with schizophrenia demonstrated increased gFCD in the prefrontal lobe, posterior parietal cortex, cingulate cortex, central anterior sulcus, and superior frontal gyrus, especially in the left hemisphere of the brain, as compared to the female patients with schizophrenia.

DISCUSSION

To the best of our knowledge, this is the first pilot study that investigates show sex affects treatment compliance in patients with schizophrenia, along with associated functional brain activity features. In this study, we adopted fMRI techniques to characterize and compare the treatment-related brain activity patterns between males and females with schizophrenia. The findings from this pilot study provide objective evidence that sex can affect treatment compliance, and the effects should be considered by caretakers and families of patients with schizophrenia.

The first finding from this pilot study that we must address is that, in our enrolled patients, male patients had more severe side effects and required higher dosages of antipsychotic agents. However, they showed better treatment outcomes than female patients. These findings are inconsistent with some studies that have reported females as having better compliance than male patients [38-40]. We believe this difference may be due to the patient population, as our patients were recruited from an outpatient center, while most other studies use patients from inpatient departments. We believe this pilot study provides "real world" data, although a larger study is needed to verify our findings. However, our findings indicate that female patient with schizophrenia may need additional support in terms of treatment compliance. We hypothesize that the lower treatment compliance may be due to the negative stigma and weight-related adverse effects associated with the use of antipsychotics.

Secondly, our pilot study found reductions in gFCD in the frontal lobes, temporal lobe, parietal lobes, insular lobes, hippocampus, and thalamus of patients with schizophrenia. These brain regions are pivotal components of cognition, affection, and executive functioning [41-43]. The reduced gFCD found in these regions suggests that, despite the alleviation of schizophrenic symptoms in the patients, functional brain activity was also disturbed. We should consider optimal strategies in the future to overcome brain impairments in the treatment of schizophrenia patients.

Third, as compared to female patients with schizophrenia, the male patients demonstrated good treatment compliance that was accompanied by an increased gFCD in the medial PFC, cingulate cortex, posterior parietal cortex, central anterior sulcus, and superior frontal sulcus (P<0.001, FEW-corrected). This finding indicates the presence of good treatment-related functional brain activity alterations in the central executive network and dorsal attention network. This objective evidence demonstrates that treatment compliance leads to improved long-term prognoses.

Limitations

There are several limitations in the present pilot study. First, they may be some bias in how we enrolled patients and artificially divided them by sex. Secondly, we regress out many variables for investigating the brain activity features specific to treatment compliance, yet this method is not generally accepted. Thus, this factor may also influence our findings. In future studies, we will conduct a larger sample cohort study to support our pilot study. Third, we only focused on the favorable treatment of compliance-related functional brain activity alterations in this pilot study. In the future, we will analyze more brain activity alterations related to both favorable and unfavorable treatment compliance, which will help us better understand the connection.

CONCLUSION

Our findings from the current pilot study suggest that male patients with schizophrenia have better treatment compliance, which is associated with higher functional brain activity in components of the central executive network and dorsal attention network. These findings provide objective evidence and clues about how to improve treatment compliance in both male and female patients with schizophrenia in the future.

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Conflicts of interest: The authors declare that they have no conflict of interest.

Data availability statement: The datasets generated and analyzed during the present study are available from the corresponding author on reasonable request.

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