

Supportive Family Environments Can Improve Treatment Compliance, Social Cognition, Brain Activity in Patients With Schizophrenia - A Pilot Study

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Abstract

Background: Supportive family environments can improve the prognosis of patients with schizophrenia by enhancing treatment compliance, social cognition, and functional brain alterations. This study aimed to investigate the impact of supportive family environments on treatment compliance, social cognition, and the associated brain activity features in patients with schizophrenia.

Methods: Patients with schizophrenia (n=40) and healthy controls (n=25) were recruited, and divided into two groups, including (1) supportive family environment group and (2) non-supportive (poor) family environment group. The Adherence Rating Scale (MARS) was adopted to assess treatment compliance. The Basic Empathy Scale (BES) and Social Attribution Task-Multiple Choice were used to assess social cognition. The Positive and Negative Symptoms Scale (PANSS) was used to assess the severity of schizophrenic symptoms. gFCD was used to assess functional brain alterations.

Results: Compared to patients with non-supportive family environments, patients with supportive family environments showed better treatment compliance [8.5 (1.2) vs. 4.5 (1.5), P<0.05] and improved social cognition, as indicated through BES [72.8 (9.0) vs. 64.53 (7.5), P<0.05] and SAT-MC scores [11.50 (4.6) vs. 8.7 (5.0), P<0.05]. Higher brain activity (i.e., increased gFCD) was detected in the medial temporal gyrus, temporoparietal junction, anterior insula cortex, and lingual gyrus.

Conclusions: Findings from this pilot study indicate that supportive family environments not only improve the treatment compliance and social cognition of patients with schizophrenia, but also improve functional brain activity in regions associated with the social cognition processing circuit. Hence, a supportive family environment may substantially impact the prognosis of schizophrenia.

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INTRODUCTION

Schizophrenia is a psychiatric disorder that benefits from family-based care [1]. However, some families are unable to support their relatives with schizophrenia, due to factors like aging and stigma, which increases the functional disability of patients with schizophrenia [2]. Due to the lack of objective evidence, family members often question whether their care actually affects the social cognitive abilities and prognosis of family members with schizophrenia [3]. Hence, there is an urgent need to improve the social functioning of patients with schizophrenia. Based on these grounds, researchers need to demonstrate the positive effects that family members can have on their loved ones suffering from schizophrenia.

Treatment compliance plays a critical role in improving the social functioning and prognosis of patients with schizophrenia [4]. Beyond treatment compliance, overcoming stigma, training in self-life management, participation in social activities, and social skills training also impact the prognosis of patients. Some previous studies have addressed the importance of supportive family environments for improving treatment compliance in patients with schizophrenia and other psychiatric disorders [5]. In addition, supportive family environments lead to improved treatment compliance, which results in the enhancement of social skills and social cognition [6]. In recent years, social cognitive impairments has been

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thoroughly investigated in patients with schizophrenia [7-10]. Most of these studies have converged to indicate that schizophrenia is associated with substantial social cognitive impairments, which deteriorates the prognosis of the disease; however, overcoming the social cognitive impairments can lead to improved patient outcomes [11-15]. Recently, social cognitive impairments were associated with functional brain alterations, and these social cognitive-related brain alterations reciprocally interact with brain alterations associated with other symptoms of schizophrenia [16-18]. Hence, family support may interact reciprocally with treatment compliance and social cognition, leading to improved prognoses in schizophrenia [17, 19]. Considering the importance of family support, treatment compliance, and social cognition on the prognosis of schizophrenia, along with the reciprocal interaction between them, researchers need to assess how supportive and non-supportive family environments may impact treatment compliance and social cognition. In addition, the objective evidence of social cognition-related brain activity features can provide insight into the development of new strategies to improve the long-term prognosis of schizophrenia.

In this initial pilot study, we have investigated the influence of family support on treatment compliance, social cognition, and its associated functional brain activity features in patients with schizophrenia. Global functional connectivity density (gFCD) is an index commonly used to assess brain connectivity and metabolism [20]. In this study, we adopted gFCD to characterize the social cognition-related brain activity features. We hypothesized that supportive family environments would be associated with improved treatment compliance, better social cognition, and enhanced social cognition-related functional brain alterations.

METHODS

Patient Selection

From July 2016 to July 2019, patients were initially recruited to participate in this study. The Ethics Committee of Wenzhou Seventh People's Hospital approved this study (IRB No. Y20161239, Date: February 1, 2016), and written consent was provided from all patients or legal guardians prior to inclusion in the study. The patients were required to meet all of the inclusion criteria for this study, including: (1) schizophrenia diagnosis based on the Structured Clinical Interview (SCI) from the DSM-IV; (2) between 18 and 35 years of age; (3) actively taking an atypical antipsychotic agent; (4) disease symptoms were stable for more than two weeks; (5) residing in a stable family environment for three years or longer; and (6) the father and mother had a good relationship. The relationship between the mother and father was considered to be good when verified by five or more neighbors. The exclusion criteria for this study included: (1) history of substance abuse; (2) history of significant head trauma, seizure disorder, neurological

disorder, or mental retardation; and (3) history of violence in the past year. A total of 40 patients with schizophrenia remained after applying the inclusion and exclusion criteria.

In addition, 25 healthy controls were recruited for this study. The enrolled criteria of the healthy controls were as follows: (1) no history of mental disorder based on the Structured Clinical Interview (SCI) from the DSM-IV; (2) between 18 and 35 years of age; and (3) no positive family history of mental disorders. The same exclusion criteria used for the patient group were also applied to the healthy controls.

Assessment of Family Support and Patient Grouping

Based on five criteria, the quality of family support was assessed. The patients were categorized into two groups based on the degree of family support, with one group having a supportive family environment and the second having a non-supportive (poor) family environment. The following criteria were used to group patients: (1) father and mother lived together with their patients for more than three years; (2) father and mother take the patient to participate in social activities three or more times per week; (3) father and mother take the patients to participate in social work at least one time per week; (4) father, mother, and other relatives usually support the patients doing things he/she enjoys that poses no risk to the patient or community; (5) father and mother support the patient expanding his/her knowledge and encouraging the patient to become familiar with social information. To be included in the supportive family group, the patient had to meet all five items, while all other patients were placed in the non-supportive family environment group. While attempts were made to match the patients between the two groups, this was a limitation of the current study.

Patient Assessments

The Adherence Rating Scale (MARS) [21] was adopted to assess the treatment compliance of patients. The Basic Empathy Scale (BES) [22-25] and Social Attribution Task-Multiple Choice (SAT-MC) [23-25] were employed to assess social cognition. The BES was a 20-item assessment evaluated on the 5-point Likert scale, with higher scores indicating better empathic abilities. Next, the SAT-MC was comprised of a 64-s cartoon describing a social drama between two triangles (large and small) and one circle. After showing the animation two times, the patient received a 19 multiple-choice assessment. Lastly, the total severity of schizophrenia was assessed with the Positive and Negative Symptoms Scale (PANSS) [26].

MRI Data Acquisition

The Discovery MR750 3T from General Electric (Milwaukee, WI, USA), which contains an 8-channel phased-array head-coil, was used for imaging the participants. First, all participants were required to be in the supine position and asked to remain awake but rest for the scan. For the

imaging session, blood oxygen level-dependent (BOLD) resting-state fMRI was conducted using the gradient-echo-echo-planar sequence with these parameters: repetition time (TR) of 2,000 ms; echo time (TE) of 45 ms; 32 slices; 4-mm slice thickness; 0.5-mm gap; 220 × 220 field of view (FOV); 64 × 64 matrix size; and 90° flip angle (FA). The sensitivity-encoding (SENSE) technique was used with SENSE=2. The structural images were acquired using the high-resolution 3D Turbo-Fast Echo T1WI sequence with these parameters: 170 slices; TR/TE of 8.2/3.2; 1-mm slice thickness; no gap; 12° FA; 256 × 256 matrix size; and 256 × 256 FOV.

Data Pre-Processing

The MRI data were processed in SPM8 (<http://www.fil.ion.ucl.ac.uk/spm>). The first ten scan volumes were removed from the analysis to account for stabilization and environmental acclimation. Next, slice-timing and motion artifacts were accounted for in the remaining volumes. Head translation movement was less than 2 mm, and rotational movements were less than 2° for the patients. As covariates, we regressed head motion, white matter, and cerebrospinal fluid from each voxel, using the Friston model for head motion. Then, frame-wise displacement (FD) was determined and regression was performed if the FD of a specific volume was more than 0.5. Band-pass frequency filtration (0.01 to 0.08 Hz) was performed and the structural images were co-registered to the average functional image. Next, co-registration was performed using the Montreal Neurological Institute (MNI) space with a linear registration. Spatial normalization was accomplished using parameters from the linear co-registration. Lastly, 3-mm cubic voxels were created of the data for future analysis [27].

Calculation of gFCD

An in-house established Linux script was used to determine the gFCD of every voxel [28]. Pearson's correlation ($R > 0.6$) was used to assess intra-voxel functional connectivity [28, 29]. Only voxels within the cerebral grey matter were used to determine gFCD, and the gFCD at any voxel was defined as the total number of functional connections between the first voxel and all of the other voxels using a growth algorithm. This calculation was repeated for every voxel. Next, the gFCD was divided by the average voxel value to normalize the distribution of the data. Lastly, the FCD maps were spatially smoothed with a $6 \times 6 \times 6\text{-mm}^3$ Gaussian kernel to minimize intra-subject functional brain differences [30].

Statistical Analysis

The family-wise error (FWE) technique was employed to correct pre- and post-treatment differences in gFCD [31].

The student *t*-test was used to compare differences in social cognition between the two groups. Any *p*-values < 0.05 were considered to be statistically significant (one-tailed).

RESULTS

Clinical and Sociodemographic Information

In this study, limited by our strict inclusion criteria, we enrolled 40 patients and 25 healthy controls (Figure 1).

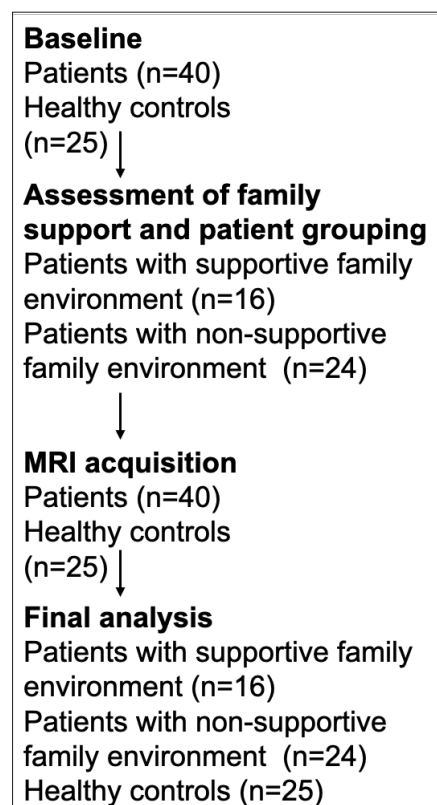


Figure 1. Flowchart of the patient selection process with two patient groups (n=40) and control group (n=25).

The healthy controls were used to assess alterations in brain activity. Using our criteria for defining supportive family environments, 16 patients were found to have good and supportive family environments, while the other 24 patients were found to poor family support. The clinical and sociodemographic information of the patients are shown in Table 1. Social cognition indicators, including BES and SAT-MC scores, were significantly different between the supportive and non-supportive family groups. However, there were no differences in age, sex, illness duration, the severity of psychotic symptoms, antipsychotic treatment dosage, and education level, among the groups (Table 1).

Table 1. Clinicodemographic data of the two patient groups and healthy controls.

Variable	Supportive family environment (n=16)	Non-supportive family environment (n=24)	Healthy controls (n=25)	t/F	P
Age (years)	35.4 (3.5)	35.0 (3.0)	35.5 (2.8)	0.430	0.640
Gender (female /male)	7/9	9/15	10/15	1.287	0.221
Education level (years)	16.1 (2.5)	16.5 (2.0)		0.145	0.894
Illness duration (years)	4.5 (3.0)	4.0 (1.5)	N/A	0.021	0.901
PANSS	79.5 (5.9)	78.6 (9.9)	N/A	0.587	0.499
Chlorpromazine (eq. dosage)	456.0 (100.5)	450.5 (108.3)	N/A	0.263	0.080
Compliance scores	N/A	N/A	N/A	N/A	N/A
MARS	8.5 (1.2)	4.5 (1.5)		2.589	0.014
Social cognition					
BES scores	72.8 (9.0)	64.53 (7.5)	84.08 (2.0)	8.450	<0.001
SAT-MC	11.50 (4.6)	8.7 (5.0)	13.70 (3.0)	10.230	<0.001

Data are shown as mean (standard deviation). PANSS, Positive and Negative Symptoms Scale; MARS, Adherence Rating Scale; BES, Basic Empathy Scale; SAT-MC, Social Attribution Task-Multiple Choice.

Treatment Compliance and Differences in Social Cognition

As demonstrated in Table 1, patients with supportive family environments displayed treatment compliance scores higher than those of patients with non-supportive family environments. In addition, the patients with supportive family environments had social cognition scores that were significantly higher than those of patients with non-supportive family environments. However, the social cognition scores of patients with supportive family environments were significantly lower than those of the healthy controls.

Differences in Functional Brain Activity

Compared to the healthy controls, non-supportive family environments, displayed reduced gFCD values in the medial temporal gyrus, temporoparietal junction, anterior insula cortex, and lingual gyrus (Figure 2).

Compared to the healthy controls, the patients with schizophrenia who had supportive family environments showed decreased gFCD in the medial temporal gyrus, temporoparietal junction, anterior insula cortex, and lingual gyrus (Figure 3).

However, the extent and scope of the functional brain alterations were smaller in the patients with non-supportive family environments when compared to the healthy controls (Figure 2, Figure 4).

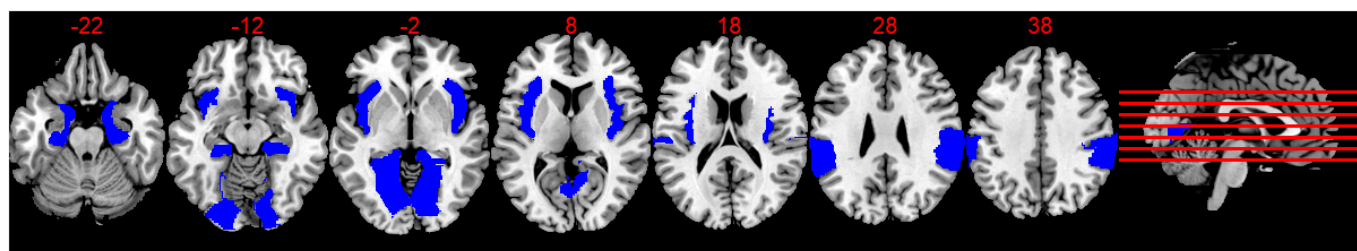


Figure 2. Patients with non-supportive family environments showed impairments of functional brain activity, as compared to the healthy controls.

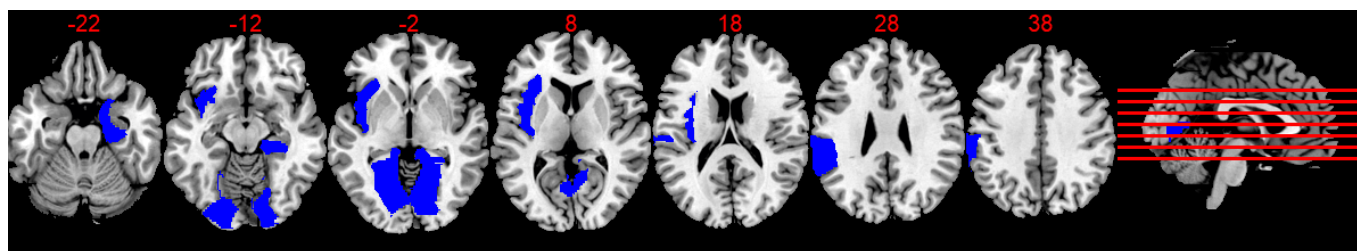


Figure 3. Patients with supportive family environments showed impairments of functional brain activity, as compared to the healthy controls.

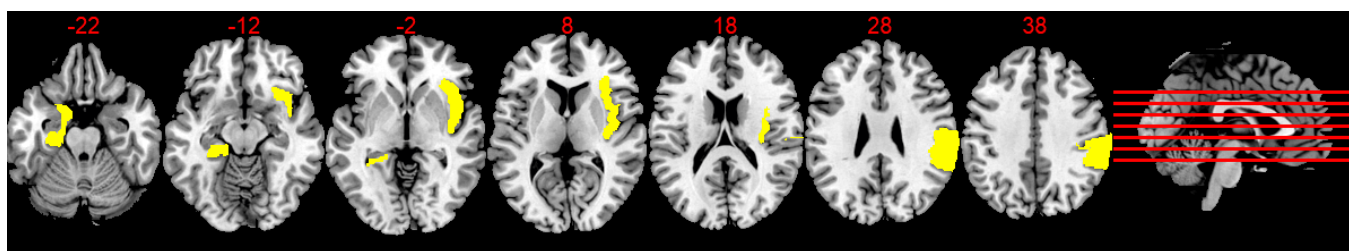


Figure 4. Compared to the patients with non-supportive family environments, the patients with supportive family environments showed increased functional brain activity.

Lastly, the patients with supportive family environments showed decreased gFCD in the medial temporal gyrus, anterior insula cortex, and lingual gyrus, as compared to the patients with non-supportive family environments (Figure 4).

DISCUSSION

This initial pilot study, to the best of our knowledge, is the first to investigate how supportive and non-supportive family environments can affect treatment compliance, social cognition, and social cognition-related functional brain activity in patients with schizophrenia. In this study, fMRI was used as an objective tool to characterize the alterations in social cognition associated with the quality of family support, along with the associated brain activity patterns. These findings can provide objective evidence for family members of patients with schizophrenia, demonstrating the vital role that positive and supportive family environments play in improving the long-term prognosis and management of patients with schizophrenia. This especially holds true for families in East Asia, where the stigma associated with psychiatric disorders can lead to abandonment and abuse in some cases.

A critical finding from the study concerns the stigma associated with schizophrenia. In the current study, more than 70% of family members believed in the negative stigma associated with schizophrenia, despite attempts by the government and international medical community to de-stigmatize the disease. The negative stigma can cause detrimental effects in some patients, as they may have fewer opportunities for social functions and activities. After this study, the stigma associated with schizophrenia remained high in the family members of our enrolled patients. Hence, patient and family education may be insufficient for improving patient outcomes, and other long-term rehabilitation strategies may be needed.

The second important finding from the current pilot study was that patients with supportive family environments experienced higher rates of treatment compliance than those patients with non-supportive family environments. The same was true in terms of social cognition as patients with supportive family environments showed better scores in social cognition. In this analysis, poor compliance was associated with minimal social activity, lack of

knowledge, and minimal encouragement from the parents. More importantly, poor treatment compliance was also associated with overprotectiveness and excessive worry by the parents, resulting in a lack of social activities and social learning, which leads to social cognitive impairments. Hence, nurses and doctors should educate the families about which behaviors may hinder the social growth and prognosis of patients with schizophrenia [14].

The third finding from the current pilot study relates to global functional brain activity. Compared to the healthy controls, all the patients in this study, despite having supportive or non-supportive family environments, displayed significant reductions in gFCD in the medial temporal gyrus, temporoparietal junction, anterior insula cortex, and lingual gyrus. As we expected, these brain regions consist of networks and circuits that are commonly associated with social cognitive processing [32-36]. Next, the patients with non-supportive family environments displayed more severe and widespread reductions in functional brain activity. However, as compared to patients with non-supportive family environments, the patients with supportive family environments displayed higher functional activity in the temporal gyrus, anterior insula cortex, and lingual gyrus. These brain alterations are better than those of the patients with non-supportive family environments. This finding indicated that family support could improve functional activity in the regions of the brain associated with social cognition.

Limitations

There are some limitations to the present study. First, some bias may have been added to the study when the patients were artificially matched in the groups. Secondly, we assessed the quality of family support using criteria designed by our laboratory. The criteria are strict and not generally accepted by the research community. For future studies, we aim to develop an improved method for assessing family support. In addition, we aim to use this improved method in a large sample cohort study in the future. Lastly, we only focused on social cognition-related brain regions in the current study, yet a comprehensive evaluation of brain activity should be considered in the future.

CONCLUSION

In the current pilot study, we demonstrated that supportive family environments were associated with better treatment compliance, improved social cognition, and increased functional activity in brain regions associated with social cognition. Our pilot study provides objective evidence to support our hypothesis that the quality of family support plays a vital role in the prognosis of patients with schizophrenia.

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Data availability statement: The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

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