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Unstructured Group Support Enhances Compliance to Pharmacological Treatment by Improving Social Cognition in Patients with Bipolar Disorder: A Pilot fMRI Study

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ABSTRACT

Objective: Unstructured group support (UGS) has been shown to improve the prognosis of patients with bipolar disorder (BP). However, objective evidence is needed to support implementation of UGS intervention. This study aimed to investigate the effectiveness of UGS intervention and the associated alterations in the objective indexes, mainly global function connectivity density (gFCD), in BP patients.

Methods: Remitted BP patients were enrolled and randomly assigned into a UGS group (received UGS intervention for 26 weekly UGS sessions, and a sham group (received sham intervention). The effects of UGS on adherence to the prescribed medications, social cognition, and quality of life were examined and compared between these 2 groups. Magnetic resonance imaging (MRI) was performed to determine the functional index and gFCD values, as an objective measurement of functional alterations in the brain.

Results: The compliance rate was significantly greater in the UGS group than in the sham group at the 2-year follow-up, after 26 weekly intervention sessions. The proportion of patients with increased levels of compliance to pharmacological treatment, improved social cognition, and improved quality of life were significantly higher in the UGS group than in the sham group. Furthermore, consistent with these subjective measurements, the fMRI study revealed that gFCD values significantly increased in the regions of the brain that are related to social cognition, in patients with UGS intervention.

Conclusion: UGS improves the compliance to pharmacological treatment, quality of life, and social cognition of remitted BP patients. Notably, these findings offer the first objective evidence that UGS enhances gFCD in BP patients. Thus, UGS implementation can help improve the psychiatric care for BP patients.

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INTRODUCTION

A variety of medications have been shown to be effective in the treatment of bipolar disorder (BP). However, adherence to prescribed medications remains difficult for BP patients, which can lead to relapse and other serious consequences in psychiatric care. Unstructured group support (UGS) enables participants to devise ways to remain well, mainly through discussing collective experience and sharing mutual information.[1] Despite the unstructured nature of these support groups, the participants are peer-led and collectively decide an agenda for discussion. Therefore, these groups not only offer a meeting place where patients with BP can meet with each other, but also provides a common purpose to actively seek effective ways to learn from each other and get better in the future.[2,3]

Previous studies have reported that UGS has good acceptivity, and can help improve the outcome in patients with BP in the short term.[3] Administering UGS intervention in the early stage of illness of BP would benefit the patients to a greater extent. Hidalgo-Mazzei et al.[4] reported that UGS plus treatment with medication can benefit bipolar II subjects by improving social function and reducing relapse. Morriss et al.[5] reported that UGS intervention enhanced the compliance to medication and reduced

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the cost burden of treatment in patients with BP.[5] Scott et al.[1] demonstrated that UGS reduced relapse by improving the cognitive ability and compliance to pharmacological treatment.[1] Collectively, these studies converged to suggest that the short-term effectiveness and cost benefit of UGS were equivalent to those of group psychoeducation, although the long-term effectiveness of the UGS intervention could not be better than that of group psychoeducation. In particular, a number of previous studies have demonstrated that in the early stage of the illness, UGS intervention improves the compliance to medication and the cognitive ability.[1-5]

Social cognition mainly refers to the social knowledge and recognition of emotion, which have been shown to mediate the correlation between neurocognition and social functioning. Ospina et al.[7] reported that social cognition exerts an impact on the neurocognition-functioning association in patients with BP, and that neurocognition and social cognition contribute to the functional outcomes of BP patients in an interactive manner, in which neurocognition directly affects community functioning.[6] A number of previous studies have found that social cognition is impaired in patients with BP, and that this plays a pivotal role in the impairment of their cognitive ability .[7,8] Therefore, it has been suggested that improving social cognition can help to improve neurocognition, and in turn improve the compliance to treatment medication and the quality of life of patients with BP.[9-14]

Previous studies have reported that social cognition impairment is correlated to some dysfunctions in brain functional activity. In fact, a number of key regions in the brain, such as the temporo-parietal junction, medial prefrontal cortex (mPFC), precuneus, and temporal poles, have been identified to be associated with social cognition, and the amygdala and orbitofrontal cortex have been found to play a key role in the person's social networking skills.[15-18] These important findings converge to suggest that social cognitive impairment has neural bases. More importantly, a majority of these brain regions related to social cognition are also involved in alterations in brain functional activity with the symptoms of BP.[15-18] Hence, from these neural bases, the social cognition and symptoms of BP exist with reciprocal action. However, to the best of our knowledge, the features of brain activity and social cognition in BP patients, and the relationship between UGS intervention and social cognition, remain largely unexplored.

Global function connectivity density (gFCD) has been widely adopted to assess brain functional connectivity and regional brain metabolism in previous studies. As an objective index, gFCD can reflect the processing capability of the entire brain.[19-22] Hence, in the present pilot study, gFCD was applied as the objective tool to evaluate the effectiveness of UGS in the improvement of social cognition in patients with remitted BP at the early stage of the illness. The following were hypothesized: (1) 26-week UGS intervention sessions can improve the social cognition impairment in patients with BP; (2) along with improved social cognition, the gFCD in brain regions associated with social cognition could be enhanced; (3) the compliance to medication treatment and the quality of life of patients with BP could be improved as a result of improved social cognition.

METHODS

Participants and Study Design

In the present pilot study spanning 2 years, female BP patients were recruited as participants, considering that male BP patients are frequently affected by substance abuse, especially alcohol abuse, which may affect the analysis.[14] Screened female BP patients, who fully met the following criteria, were eventually studied: (1) criteria for bipolar disorder in DSM-IV; (2) the maintenance of the clinical remission state during the term of this study, as assessed by 2 experienced psychiatrists, with HAMD-17 item scores of <7 and young manic rating scale (YMRS) scores <5; (3) no metal implants in the body (e.g., metal implants in the neck or head, or cardiac pacemaker, fixation elements, or artificial joints); (4) no tattoos; (5) no medical history of psychiatric disorders, neurologic diseases, or other major health problems; (6) right-handedness on the basis of the Edinburgh Handedness Inventory; (7) corrected-to-normal or normal vision, as well as normal color vision, as examined in the vision tests; (8) no major self-reported life events during the study period; (9) no alcohol or other substance abuse throughout the study. The exclusion criteria for patients and healthy controls were as follows: (1) moderate-to-severe physical disease (e.g., respiratory, cardiovascular, endocrine, neurological, liver, or kidney disease); (2) presently receiving electroconvulsive therapy; (3) a history of loss of consciousness for more than 5 minutes, regardless of the cause; (4) left-handedness, as determined by the Annett Hand Preference Questionnaire; (5) magnetic resonance imaging (MRI) contraindications, including claustrophobia; (6) IQ <80 (ascertainment by Wechsler adult intelligence scale-revised China (WAIS-RC); and (7) subjects who are pregnant or suckling a baby during the lactating period. A total of 40 female BP patients were enrolled from the Inpatient Department of Wenzhou Seventh People's Hospital (Wenzhou, Zhejiang, China). To determine alterations in gFCD in BP, 20 female healthy controls were enrolled in this study, and their characteristics are listed in Table 2. The 40 female BP patients were randomly assigned into 2 groups (with 20 patients in each group): the UGS group, in which BP patients received UGS intervention from the first week of their acquired first

clinical remission and hospitalized treatment, and were discharged from the hospital; the control group, in which BP patients did not receive UGS intervention, and talked about interesting topics such as shopping experiences and comedy.

The study protocol was reviewed and approved by the Ethics Committee of Wenzhou Seventh People's Hospital. A written informed consent was provided by each participant.

Unstructured Group Support Intervention

The UGS intervention included a total of 26 sessions, with 2 one-hour sessions per week. In the UGS group, each session provided the participating patients with control, not only for the processes of delivering group intervention, but also in the overall aim of the intervention for each participant. A manual on the UGS intervention was prepared by the therapists, and was given to the participants as a handout during the first session.[23] In order to optimize the UGS, one expert peer patient and 2 health professionals met with groups of up to 20 participants, and were present to facilitate the group discussion, encourage participation, prevent unhelpful group behaviors (e.g. bullying and scapegoating), prevent factual misinformation, and clear up factual uncertainty, when directly requested.

Follow-Up

The study groups were followed-up for 8 months from May 2017 (upon completion of the 26-week UGS intervention) to December 2017, during which the participating patients were invited to the study room in the hospital for measurement of outcomes, including the compliance to the pharmacological treatment, social cognition, and quality of life. The psychiatrists and staff who performed the assessments were fixed during the study, Figure 2.

MRI Scanning

MRI data were acquired using a 3.0 T MR system (Discovery MR750, General Electric, Milwaukee, WI, USA). Tight but comfortable foam padding was used to minimize head motion, and earplugs were used to reduce scanner noise. Sagittal 3D T1-weighted images were acquired using a brain volume sequence with the following parameters: repetition time (TR) = 8.2 ms; echo time (TE) = 3.2 ms; inversion time (TI) = 450 ms; flip angle (FA) = 12°; field of view (FOV) = 256 mm × 256 mm; matrix = 256 × 256; slice thickness = 1 mm, no gap; and 188 sagittal slices. Resting-state functional MRI (fMRI) data were acquired using a gradient echo single-shot echo planar imaging sequence with the following parameters: TR/TE = 2000/45 ms; FOV = 220 mm × 220 mm; matrix = 64 × 64; FA = 90°; slice thickness = 4 mm; gap = 0.5 mm; 32 interleaved transverse slices; and 180 volumes. All the study subjects were instructed to keep their eyes closed, relax, move as little as possible, think of nothing in particular, and not fall asleep during the fMRI scans.[19-22]

The fMRI Data Pre-processing

Resting-state fMRI data were preprocessed using SPM8 software (http://www.fil.ion.ucl.ac.uk/spm). For each subject, the first 10 volumes were discarded to allow the signal to attain equilibrium, while the participants adapted to the scanning noise. The remaining volumes were corrected for the acquisition time delay between slices. Realignment was then performed to correct the motion between time points. The fMRI data for all of the subjects were within the defined motion thresholds (i.e., translational and rotational motion of less than 2 mm and 2°, respectively). We also calculated the frame-wise displacement (FD), which indexes the volume-to-volume changes in head position. There was no significant difference in the mean FD ($t = -1.47$; $P = .305$) between the patients (0.092 ± 0.010) and controls (0.080 ± 0.025). The average blood oxygen level-dependent signals of the white matter and ventricles were removed by regression, following procedures as described previously,[23] in which several nuisance covariates (the 6 motion parameters, their first-order derivatives, and the average BOLD signals from the ventricles and white matter) were regressed out of the data. Global signal regression has been considered a controversial strategy for processing resting-state fMR,[24,25] because global signals have also been found to reflect neurobiologically important information.[25,26] Thus, we did not remove the global signal in the fMRI data pre-processing.

Considering that the signal spike caused by head motion may significantly contaminate the final resting-state fMRI results, even after regressing out the linear motion parameters, we further regressed out the spike volumes when the FD of the specific volume exceeded 0.5. The datasets were then band-pass filtered over a frequency range of 0.01 to 0.08 Hz. In the normalization step, individual structural images were linearly (12 affine parameters) co-registered with the mean functional image. The structural images were then segmented and normalized to the Montreal Neurological Institute (MNI) space using a high-level nonlinear warping algorithm, according to the diffeomorphic anatomical registration through the exponentiated Lie algebra technique, as described previously.[27] Finally, each filtered functional volume was nonlinearly transformed in the MNI space using the deformation parameters of the 2 co-registration steps, and was resampled into a 3-mm cubic voxel.

The gFCD Calculation

The gFCD of each voxel was calculated using an in-house script written on a Linux platform, following the method as described previously.[19,20] We first computed Pearson's

linear correlations between the time series of each pair of all of the GM voxels and obtained a whole-brain FC matrix for each subject. The computation was constrained within a cerebral GM mask, which was generated by thresholding (a threshold of 0.2) a prior GM probability map in SPM8. Pairs of voxels with a correlation coefficient of $r > 0.6$ were considered significantly connected. For a given voxel x0, gFCD was computed as the number of functional connections between x0 and the remaining GM voxels that satisfied the correlation coefficient threshold (i.e., $r > 0.6$). To confirm whether the correlation threshold would influence intergroup comparisons, we further calculated the gFCD using the same process, except for a correlation coefficient threshold of $r > 0.4$. To minimize variability across subjects, grand mean scaling of gFCD was performed by dividing the gFCD value of each voxel by the mean gFCD value of all of the cerebral GM voxels. Finally, the gFCD maps were spatially smoothed using a 6 mm × 6 mm × 6 mm FWHM Gaussian kernel. This minimized the impact of anatomical differences between study subjects, gender, age, illness duration and education level, which all regressed out as co-variants (FEW correction).[19-22] Multiple comparison was performed with the Bonferroni correction method using 0.05/3 as threshold.[19-22] Voxel-wise intergroup comparisons gFCD (with $r > 0.6$) were performed using a GLM, adjusted for age and sex. We repeated the voxel-wise intergroup comparisons of gFCD using a permutation-based inference tool for nonparametric statistics ("randomize", part of FSL). The number of permutations was set to 5000, and the significance threshold was set at $P < .001$ after correcting for family-wise error using the threshold-free cluster enhancement option in FSL.

Measurement of Outcomes

The compliance to the pharmacological treatment was defined as previously reported,[24] and evaluated by the treating psychiatrist. Briefly, the patient's compliance level was assigned to one of the following 4 categories: (1) high, for patients who adhered to the medication, appointments and interventions, 80-100% of the time; (2) moderate, for patients who complied with all aspects of treatments and intervention, 60-79% of the time; (3) low, for patients who complied, 20-59% of the time; and (4) noncompliant, for patients who adhered to the treatments <20% of the time.[28] The social cognition assessment was performed using the Social Impairment Rating Scale to assess the alteration in social cognition.[29-31] The World Health Organization Quality of Life self-questionnaire (WHO-QoL-26) was used to assess the quality of life.[30] In the examination for BP, the total severity of hypomanic/manic or depressive symptoms was assessed using the HAMD, HAMA, or HMRS.[8] To monitor the symptoms of relapse, structural interviews were conducted by senior professional psychiatrists at one week, according to the diagnostic criteria of BP in DSM-IV, in order to determine whether the patient had relapsed.

Determination of Substance Abuse

A urine test was conducted to determine substance abuse per month. The status of alcohol or nicotine abuse was reported by the relatives of the participants.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) version 20.0 (IBM SPSS Corp.; Armonk, NY, USA) was used for the statistical analysis. A one-tailed test, also referred to as a directional hypothesis, was used to test for the possibility of relationship. Nominal data were expressed in percentage and frequency, while parametric data were presented as mean ± standard deviation (SD). The YMRS/HAM-D scores at baseline and at the different time points during the follow-up period were compared using the paired *t*-test. Variance analysis was conducted to compare the compliance rate between these 2 groups. A value of $P < .05$ was considered statistically significant between groups. Multiple comparison correction was made using the Bonferroni correction, also known as the Bonferroni test in statistical analysis.

RESULTS

Sociodemographic and Clinical Characteristics of the Study Patients

A total of 40 female BP patients who fulfilled the inclusion criteria and matched 20 healthy controls were enrolled in the present study. These patients were randomly assigned into 2 groups: the UGS group ($n = 20$), which received 26 weekly sessions of UGS; the sham group ($n = 20$), which received sham intervention. The demographic and clinical characteristics of the female BP patients in these 2 groups are summarized in Table 1. The mean age of these study patients was 35.4 years, with age ranging from 34-40 years. There were no significant differences in sociodemographic and clinical characteristics, and these were comparable between the 2 study groups (Table 1). During the study period spanning 2 years, all participants underwent 2 independent MRI scans. None of the participants withdrew from this study.

Comparison of Compliance to the Pharmacological Treatment, Social Cognition, and Quality of Life Between the Two Groups

The compliance to pharmacological treatment, social cognition, and quality of life were compared between the UGS group and sham group, and the findings are presented in Tables 1, 3, and 4. After the 26 weekly sessions of UGS intervention, the medicine compliance and quality of life differed significantly between the UGS group and the sham group. The compliance rate was higher in the UGS group than in the sham group, especially during the follow-up period. The quality of life scores were higher in the UGS group, when compared with the sham group. The social cognition scores were also higher in the UGS group than in the sham

Table 1. Baseline Sociodemographic and Clinical Characteristics of the Study Patients in the UGS and Sham Groups

Characteristics	UGS group	Sham group	*t*	*P*
Age [years, mean (SD)]	35.4 (2.6)	34.8 (3.9)	0.355	.589
Educational level [years, mean (SD)]	14.5 (4.3)	14.0 (5.0)	0.771	.223
Illness duration [years, mean (SD)]	2.2 (1.0)	2.4 (1.0)	0.503	.411
HAMD [Mean (SD)]	5.5 (2.1)	5.7 (1.9)	0.558	.392
HAMA [Mean (SD)]	6.5 (2.5)	6.5 (3.0)	0.932	.069
HMRS [Mean (SD)]	4.5 (1.3)	4.0 (1.5)	0.936	.056
Compliance rate, high rank rate (high number of patients/total patients)	100%	100%	N/A	N/A
Social cognition scores [Mean (SD)]	10.5 (2.5)	10.0 (3.5)	1.490	.351
Quality of life scores	52.0 (8.5)	51.0 (11.8)	0.702	.188

UGS, unstructured group support; HAMD, hypomanic/manic or depressive symptoms; HMRS, hypomanic/manic or depressive symptoms.

group. The self-comparison at the different time points demonstrated that the compliance, quality of life, and social cognition improved at 6 months after completion of the UGS intervention, and this maintained a stable trend in the next 18 months, although some varied in these 2 groups. This trend demonstrates that UGS significantly improved the medicine compliance, quality of life, and social cognition of patients, when compared to the sham group. Notably, none of the patients in the UGS group relapsed during the study term, while 6 patients (30%) relapsed in the sham group, suggesting a hypomanic pattern.

The gFCD Alterations

The gFCD alterations at the indicated time points are presented in Figure 1. At baseline, BP patients in the UGS group and sham group presented with a significantly decreased gFCD in the orbitofrontal cortex, prefrontal cortex, temporal cortex, and parietal cortex, while this increased in the thalamus and cingulate cortex (Figure 1A, UGS *vs*. HCs; Figure 1B, Sham *vs*. HCs), when compared to healthy controls. There was no significant difference in the peak value of gFCD between the UGS group and sham group (Figure 1C, UGS *vs*. Sham). At the 24-month follow-up time point, an increase in gFCD located in the orbitofrontal cortex, prefrontal lobe, and anterior parietal lobe presented in patients in the UGS group, when compared to the sham group (Figure 1D, UGS *vs*. Sham). However, patients in both the UGS and sham groups presented with a reduced gFCD in the orbitofrontal cortex, prefrontal cortex, temporal cortex, and parietal cortex, and an increased gFCD in the thalamus, cingulate cortex, and striatum, when compared with healthy controls (Figure 1E, UGS vs. HCs; Figure 1F, Sham vs. HCs).

DISCUSSION

The present pilot study on the effectiveness of UGS intervention, and its associated alterations in the objective index of gFCD in BP patients has yielded the following major novel findings: (1) After completion of the 26 weekly sessions of UGS intervention, the pharmacological treatment compliance, social cognition, and quality of life significantly improved in the UGS group vs. the sham group; (2) In agreement with these subjective measures, the values of gFCD in brain regions associated with social cognition, including the orbitofrontal cortex, prefrontal lobe, and anterio parietal lobe, significantly increased in the UGS group vs. the sham group; (3) UGS intervention was associated with fewer relapses than sham intervention. Collectively, the findings provide the first objective evidence that UGS intervention can improve the medicine compliance, social cognition, and quality of life. Considering recent findings that gFCD can also reflect brain metabolism alterations,[31-34] the present pilot study suggests that UGS intervention can enhance the connection between the orbitofrontal cortex, prefrontal lobe, anterior parietal lobe, and the entire brain, as well as the metabolism in these brain regions.

Table 2. Sociodemographic characteristics of the healthy controls and the comparison with UGS and sham groups

	Age [years, mean (SD)]		Educational level [years, mean (SD)]		Social cognition scores [Mean (SD)]		Quality of life score	
Sociodemographic characteristics of the healthy controls ($N = 20$)								
	36.0 (3.5)		14.5 (2.5)		18.5 (2.5)		95.0 (2.5)	
	t	*P*	*t*	*P*	*T*	*P*	*T*	*P*
Comparison between UGS and sham groups								
UGS groups	0.755	.231	1.203	.094	7.580	<.001	18.253	<.001
Sham groups	0.586	.5421	1.009	.073	6.356	<.001	14.520	<.001

UGS, unstructured group support.

Table 3. Comparison of Compliance to Pharmacological Treatment, Social Cognition, and Quality of Life Between the Two Groups During the First Year of Follow-Up

Variable	UGS group	Sham group	*T*	*P*
6 month-follow-up				
Illness duration, years, mean (SD)	2.7 (1.0)	2.9 (1.0)	1.203	.059
HAMD, Mean (SD)	5.0 (2.0)	5.5 (2.4)	1.332	.054
HAMA, Mean (SD)	6.0 (2.5)	6.5 (2.5)	1.300	.051
HMRS, Mean (SD)	5.0 (1.0)	4.9 (2.0)	0.998	.100
Compliance scores, Mean (SD)	100%	100%	N/A	N/A
Social cognition scores, Mean (SD)	14.5 (2.0)	12.0 (3.0)	1.098	.015
Quality of life scores	72.0 (12.5)	55.0 (10.5)	5.452	.000
Group	UGS group		Sham group	
	T	*P*	*t*	*P*
Self-comparison between 6 months and baseline				
Compliance scores, Mean (SD)	N/A	N/A	N/A	N/A
Social cognition scores, Mean (SD)	5.852	.000	1.023	.150
Quality of life score	9.580	.000	0.982	.162
12 months follow-up time point				
Illness duration, years, Mean (SD)	3.2 (1.0)	3.4 (1.0)	0.988	0.070
HAMD, Mean (SD)	5.5 (2.5)	5.5 (2.0)	1.025	.060
HAMA, Mean (SD)	5.0 (2.0)	5.5 (2.0)	0.956	.102
HMRS, Mean (SD)	5.0 (1.5)	8.0 (2.0)	−1.525	.015
Compliance scores, Mean (SD)	100%	80%	4.903	.000
Social cognition scores, Mean (SD)	16.5 (2.5)	12.0 (2.5)	3.356	.000
Quality of life scores	75.0 (10.5)	50.0 (14.5)	10.230	.000
Group	UGS group		Sham group	
	t	*P*	*t*	*P*
Self-comparison between 12 months and baseline				
Compliance scores, Mean (SD)	8.402	.000	−2.009	.000
Social cognition scores, Mean (SD)	11.570	.000	−1.586	.012
Quality of life scores	15.235	.000	−2.498	.025

UGS, unstructured group support.

Previous studies reported that the orbitofrontal cortex plays a pivotal role in the interplay of self-monitoring and emotional processing which underlie the generation of emotions that guide social behavior and social emotion.[35,36] Simultaneously, the prefrontal lobe has been shown to exert a key role in the social cognitive processes, which could account for the prominence of temporal and social terms in the associated pattern of thought.[37,38] It has been further noted that the anterior parietal lobe, with an important role in the default mode network, may also participate in social cognition processing.[39,40] Collectively, these previous studies have demonstrated that the orbitofrontal cortex, prefrontal lobe, and anterior parietal lobe are the pivotal components of the circuits involved in social cognition processing. In this pilot study, we observed that gFCD was altered in the orbitofrontal cortex, and this finding converged with previous studies in support of the orbitofrontal lobe as an important component in modulating social cognition.

In this study, the UGS group showed an increase in gFCD in these regions, suggesting that UGS intervention can improve the social cognition in patients with BP. The social cognition assessment also demonstrated that social cognition was improved after 6 months of follow-up and after 26 weekly sessions of UGS intervention, and this can be maintained for up to 24 months of follow-up time. The results of social cognition assessment were consistent with the improvement in brain functional activity, and were in support of the theory that UGS can improve the social cognition of patients with BP. Many previous studies also reported that among the patients with BP, schizophrenia, even major depression disorder, the social cognitive and neurocognitive impairments all related to the circuit which is mainly comprised of the orbitofrontal cortex, prefrontal lobe, and anterior parietal lobe.[41-44] Our findings converged with previous reports to support the hypothesis that normalization of the brain circuit functional activity can improve the patient's social cognitive impairments, and

Table 4. Comparison of Compliance to Pharmacological Treatment, Social Cognition, and Quality of Life Between the Two Groups During the Second Year of Follow-Up

Variable	UGS group	Sham group	*t*	*P*
18 month-follow-up time point				
Age, years, Mean (SD)	36.9 (2.6)	36.3 (3.9)	0.578	.426
Educational level, years, Mean (SD)	14.5 (4.3)	14.0 (5.0)	0.705	.250
Illness duration, years, Mean (SD)	3.7 (1.0)	3.9 (1.0)	0.996	.079
HAMD, Mean (SD)	5.0 (2.0)	5.5 (2.5)	0.908	.069
HAMA, Mean (SD)	4.0 (2.0)	4.5 (2.5)	1.203	.049
HMRS, Mean (SD)	5.0 (1.0)	10.0 (1.5)	−2.188	.007
Compliance scores, Mean (SD)	100%	60%	6.588	.000
Social cognition scores, Mean (SD)	16.5 (2.0)	10.0 (3.0)	5.377	.000
Quality of life Scores	70.0 (8.5)	50.0 (10.5)	6.520	.000
Group	UGS group		Sham group	
	T	*P*	*T*	*P*
Self-comparison between 18 months and baseline				
Compliance scores, Mean (SD)	14.225	.000	−6.253	.000
Social cognition scores, Mean (SD)	15.677	.000	−1.505	.047
Quality of life scores	14.200	.000	−3.250	.028
Variable	UGS group	Sham group	t	*P*
24-month follow-up time point				
Age, years, Mean (SD)	37.4 (2.6)	36.8 (3.9)	0.999	.050
Educational level, years, Mean (SD)	14.5 (4.3)	14.0 (5.0)	0.566	.475
Illness duration, years, Mean (SD)	4.2 (1.0)	4.4 (1.0)	0.755	.211
HAMD, Mean (SD)	5.5 (2.0)	5.0 (2.5)	0.650	.317
HAMA, Mean (SD)	6.0 (2.0)	6.5 (2.0)	0.652	.359
HMRS, Mean (SD)	6.0 (2.0)	14.0 (2.5)	−9.342	.000
Compliance scores, Mean (SD)	100%	40%	10.22	.000
Social cognition scores, Mean (SD)	16.0 (2.0)	12.0 (3.0)	1.235	.019
Quality of life scores	72.0 (8.0)	48.0 (12.0)	14.111	.000
Group	UGS group		Sham group	
	t	*P*	*T*	*P*
Self-comparison between 24 months and baseline				
Compliance scores, Mean (SD)	8.574	.000	−1.258	.045
Social cognition scores, Mean (SD)	9.000	.000	−1.157	.048
Quality of life scores	8.569	.000	−2.505	.032

provide clues for further study to investigate the method to protect the social cognitive ability of BP patients. However, the gFCD alterations were not correlated to the social cognition scores in this study, which was mainly why the results suggested the group difference between the unstructured group (USG) and sham group.

Notably, we found that medicine compliance and quality of life were also improved, which was associated with the improvement in social cognition. These findings are consistent with many previous studies, suggesting that medicine compliance, quality of life, and social cognition are reciprocal actions in patients with BP, and that improving the medicine compliance or improving the social cognition can be positively reciprocal, jointly improving the quality of life of these patients.[41-44]

The present study may have limitations. First, only patients with BP in the clinical remission state were enrolled. According to previous studies, the rate of patients with BP who have acquired clinical remission is very low (approximately 30%). Hence, sample bias cannot be avoided. Second, for the 26 weekly sessions for patients with BP, only female patients were selected in this study, after considering that the compliance of female patients was better than that of male patients, as reported previously. Hence, these present findings may have been weakened by this sample bias. However, the objective index and brain

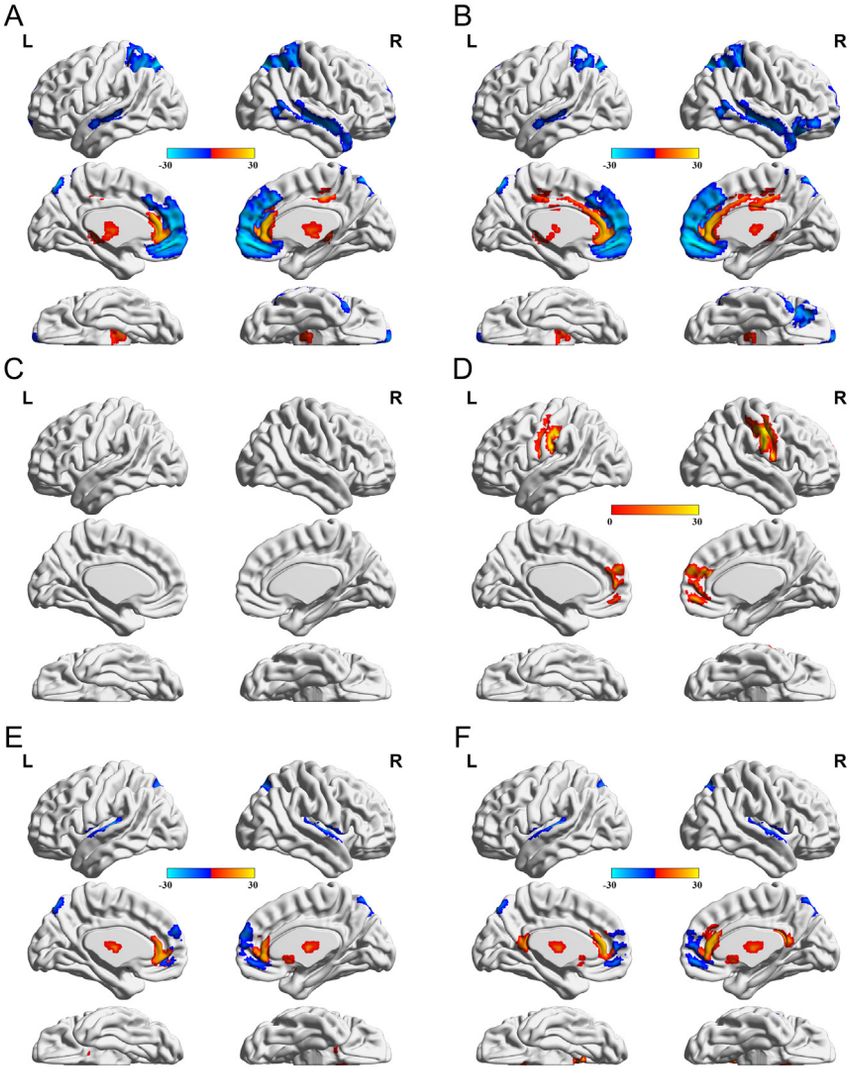

Figure 1a-f. Alterations in the global function connectivity density of the study subjects. Comparison of global function connectivity density (gFCD) between (a) UGS vs. HCs, and (b) Sham vs. HCs at baseline. When compared to healthy controls, patients in the UGS group and sham group showed a significant decrease in gFCD in the orbitofrontal cortex, prefrontal cortex, temporal cortex, and parietal cortex, but a significant decrease in gFCD in the thalamus and cingulate cortex; (c) Comparison of gFCD between the sham group vs. UGS group; (d) Comparison of gFCD between the sham group and UGS group at the 24-month follow-up. Patients in the UGS group presented with significantly increased gFCD in the orbitofrontal cortex, prefrontal lobe, and anterior parietal lobe; (e) Comparison of gFCD between HCs vs. the UGS group. The gFCD was significantly decreased in the orbitofrontal cortex, prefrontal cortex, temporal cortex, and parietal cortex, but increased in the thalamus, cingulate cortex, and striatum in patients with UGS intervention; (f) Comparison of gFCD between healthy controls and patients in sham group. The gFCD was significantly decreased in the orbitofrontal cortex, prefrontal cortex, temporal cortex, and parietal cortex, but was increased in the thalamus, cingulate cortex, and striatum in the sham group.

function index can strengthen the explanation for these findings. Third, according to ethics, patients in the sham group should have been given UGS intervention after the completion of the study. However, as it is known, treatment time can influence the compliance of patients with BP.

In conclusion, these present findings demonstrate that UGS intervention can improve the compliance to pharmacological treatment, quality of life, and social cognition of remitted BP patients. Notably, these findings have offered the first objective evidence that UGS intervention enhances the gFCD of patients with BP. Thus, UGS implementation can help improve the psychiatric care for BP patients.

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

Ethics Committee Approval: Ethics commitee approval was received from the Wenzhou Seventh Peoples Hospital Ethics Committee (IRB:2016-14).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

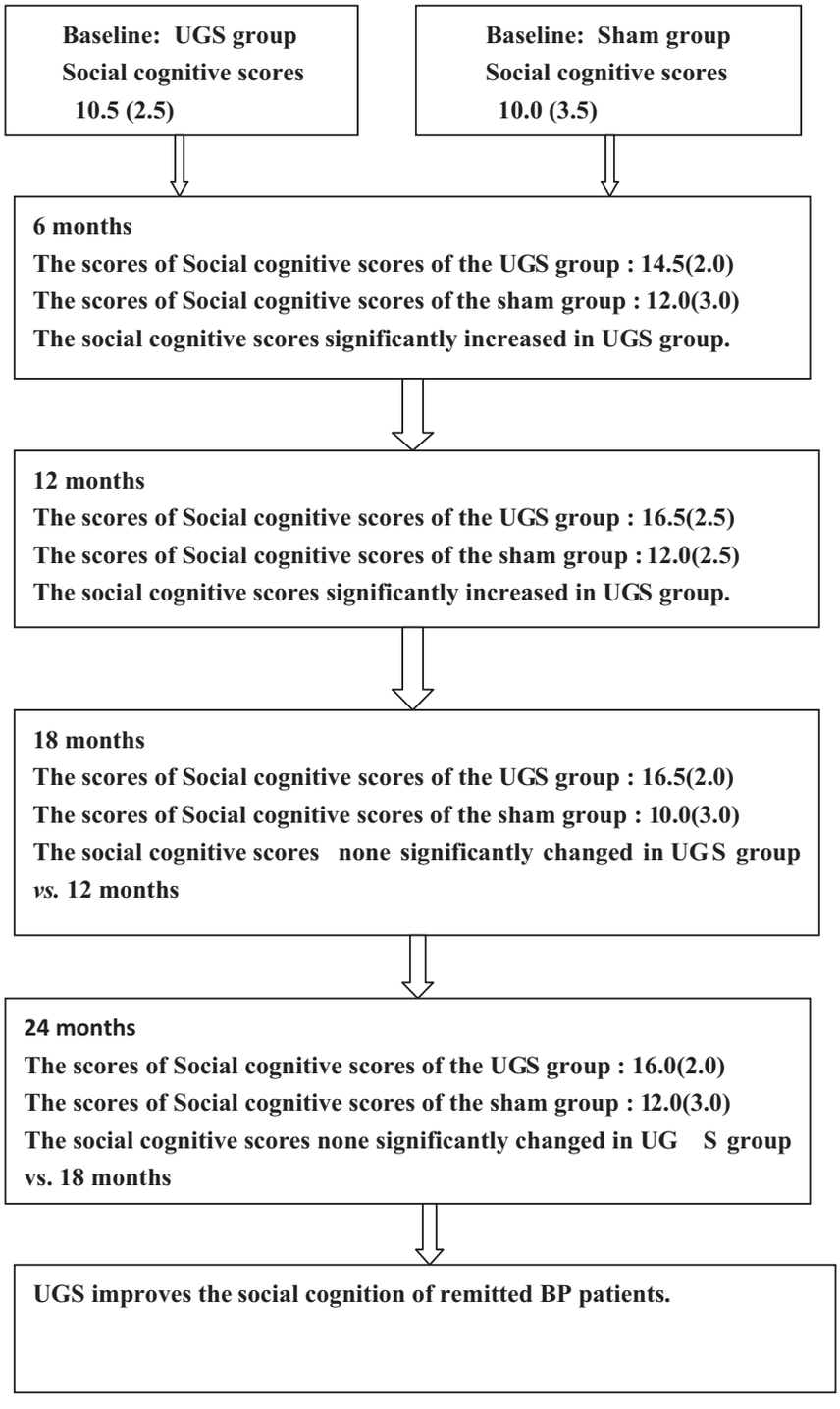

Figure 2. The flowchart of social cognitive alterations according to timeline.

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REFERENCES

1. Scott J, Colom F, Popova E, et al. Long-term mental health resource utilization and cost of care following group psychoeducation or unstructured group support for bipolar disorders: a cost-benefit analysis. *J Clin Psychiatry*. 2009;70(3):378-386. [CrossRef]
2. Colom F, Vieta E, Sánchez-Moreno J, et al. Psychoeducation for bipolar II disorder: an exploratory, 5-year outcome subanalysis. *J Affect Disord*. 2009;112(1-3):30-35. [CrossRef]
3. Morriss RK, Lobban F, Jones S, et al. Pragmatic randomised controlled trial of group psychoeducation versus group support in the maintenance of bipolar disorder. *BMC Psychiatry*. 2011;11:11114. [CrossRef]
4. Hidalgo-Mazzei D, Mateu A, Reinares M, et al. Self-monitoring and psychoeducation in bipolar patients with a smart-phone application (SIMPLe) project: design, development and studies protocols. *BMC Psychiatry*. 2015;15:1552. [CrossRef]
5. Morriss R, Lobban F, Riste L, et al. Clinical effectiveness and acceptability of structured group psychoeducation versus optimised unstructured peer support for patients with remitted bipolar disorder (PARADES): a pragmatic, multicentre, observer-blind, randomised controlled superiority trial. *Lancet Psychiatry*. 2016;3(11):1029-1038. [CrossRef]
6. Schmidt SJ, Mueller DR, Roder V. Social cognition as a mediator variable between neurocognition and functional outcome in schizophrenia: empirical review and new results by structural equation modeling. *Schizophr Bull*. 2011;37(Suppl 2):S41-S54. [CrossRef]
7. Ospina LH, Nitzburg GC, Shanahan M, et al. Social cognition moderates the relationship between neurocognition and community functioning in bipolar disorder. *J Affect Disord*. 2018;235:7-14. [CrossRef]
8. Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disord*. 2018;20(2):97-170. [CrossRef]
9. Kim Y, Kwon A, Min D, et al. Neurophysiological and psychological predictors of social functioning in patients with schizophrenia and bipolar disorder. *Psychiatry Investig*. 2019;16(10):718-727. [CrossRef]
10. Fernández-Sotos P, Torio I, Fernández-Caballero A, et al. Social cognition remediation interventions: a systematic mapping review. *PLoS ONE*. 2019;14(6):e0218720. [CrossRef]
11. Lewandowski KE, Whitton AE, Pizzagalli DA, et al. Reward learning, neurocognition, social cognition, and symptomatology in psychosis. *Front Psychiatry*. 2016;7:7100. [CrossRef]
12. Lee J, Altshuler L, Glahn DC, et al. Social and nonsocial cognition in bipolar disorder and schizophrenia: relative levels of impairment. *Am J Psychiatry*. 2013;170(3):334-341. [CrossRef]
13. Kessing LV, Miskowiak K. Does cognitive dysfunction in bipolar disorder qualify as a diagnostic intermediate phenotype? A perspective paper. *Front Psychiatry*. 2018;9:9490. [CrossRef]
14. Van Overwalle F, Baetens K. Understanding others' actions and goals by mirror and mentalizing systems: a meta-analysis. *Neuroimage*. 2009;48(3):564-584. [CrossRef]
15. Powell J, Lewis PA, Roberts N, García-Fiñana M, Dunbar RI. Orbital prefrontal cortex volume predicts social network size: an imaging study of individual differences in humans. *Proc Biol Sci*. 2012;279(1736):2157-2162. [CrossRef]
16. Bickart KC, Dickerson BC, Barrett LF. The amygdala as a hub in brain networks that support social life. *Neuropsychologia*. 2014;63:235-248. [CrossRef]
17. Frangou S. Neuroimaging markers of risk, disease expression, and resilience to bipolar disorder. *Curr Psychiatry Rep*. 2019;21(7):52. [CrossRef]
18. MacDonald K, Krishnan A, Cervenka E, et al. Biomarkers for major depressive and bipolar disorders using metabolomics: a systematic review. *Am J Med Genet B Neuropsychiatr Genet*. 2019;180(2):122-137. [CrossRef]
19. Zhuo C, Zhu J, Qin W, et al. Functional connectivity density alterations in schizophrenia. *Front Behav Neurosci*. 2014;8:8404. [CrossRef]
20. Zhuo C, Zhu J, Wang C, et al. Brain structural and functional dissociated patterns in schizophrenia. *BMC Psychiatry*. 2017;17(1):45. [CrossRef]
21. Zhuo C, Zhu J, Wang C, et al. Different spatial patterns of brain atrophy and global functional connectivity impairments in major depressive disorder. *Brain Imaging Behav*. 2017;11(6):1678-1689. [CrossRef]
22. Zhuo C, Xu Y, Zhang L, Jing R, Zhou C. The effect of dopamine antagonist treatment on auditory verbal hallucinations in healthy individuals is clearly influenced by COMT genotype and accompanied by corresponding brain structural and functional alterations: an artificially controlled pilot study. *Front Genet*. 2019;10:1092. [CrossRef]
23. Camacho EM, Ntais D, Jones S, et al. Cost-effectiveness of structured group psychoeducation versus unstructured group support for bipolar disorder: results from a multi-centre pragmatic randomised controlled trial. *J Affect Disord*. 2017;211:27-36. [CrossRef]
24. Fox MD, Zhang D, Snyder AZ, Raichle ME. The global signal and observed anticorrelated resting state brain networks. *J Neurophysiol*. 2009;101(6):3270-3283. [CrossRef]
25. Murphy K, Birn RM, Handwerker DA, Jones TB, Bandettini PA. The impact of global signal regression on resting state correlations: are anti-correlated networks introduced? *NeuroImage*. 2009;44(3):893-905. [CrossRef]
26. Schölvinck ML, Maier A, Ye FQ, Duyn JH, Leopold DA. Neural basis of global resting-state fMRI activity. *Proc Natl Acad Sci USA*. 2010;107(22):10238-10243. [CrossRef]
27. Ashburner J, Friston KJ. Voxel-based morphometry—the methods. *NeuroImage*. 2000;11(6 Pt 1):805-821. [CrossRef]
28. Kutzelnigg A, Kopeinig M, Chen CK, et al. Compliance as a stable function in the treatment course of bipolar disorder in patients stabilized on olanzapine: results from a 24-month observational study. *Int J Bipolar Disord*. 2014;2(1):13. [CrossRef]
29. Konstantakopoulos G, Ioannidi N, Typaldou M, Sakkas D, Oulis P. Clinical and cognitive factors affecting psychosocial functioning in remitted patients with bipolar disorder. *Psychiatriki*. 2016;27(3):182-191. [CrossRef]

30. Bulteau S, Grall-Bronnec M, Bars PY, et al. Bipolar disorder and adherence: implications of manic subjective experience on treatment disruption. *Patient Prefer Adherence*. 2018;12:1355-1361. [CrossRef]
31. Bickart KC, Brickhouse M, Negreira A, et al. Atrophy in distinct corticolimbic networks in frontotemporal dementia relates to social impairments measured using the Social Impairment Rating Scale. *J Neurol Neurosurg Psychiatry*. 2014;85(4):438-448. [CrossRef]
32. Han L, Pengfei Z, Zhaohui L, et al. Resting-state functional connectivity density mapping of etiology confirmed unilateral pulsatile tinnitus patients: altered functional hubs in the early stage of disease. *Neuroscience*. 2015;310:27-37. [CrossRef]
33. Thompson GJ, Riedl V, Grimmer T, et al. The whole-brain "global" signal from resting state fMRI as a potential biomarker of quantitative state changes in glucose metabolism. *Brain Connect*. 2016;6(6):435-447. [CrossRef]
34. Mortensen KN, Gjedde A, Thompson GJ, et al. Impact of global mean normalization on regional glucose metabolism in the human brain. *Neural Plast*. 2018;2018:6120925. [CrossRef]
35. Beer JS, John OP, Scabini D, Knight RT. Orbitofrontal cortex and social behavior: integrating self-monitoring and emotion-cognition interactions. *J Cogn Neurosci*. 2006;18(6):871-879. [CrossRef]
36. Abdi Z, Sharma T. Social cognition and its neural correlates in schizophrenia and autism. *CNS Spectr*. 2004;9(5):335-343. [CrossRef]
37. Weilbächer RA, Gluth S. The interplay of hippocampus and ventromedial prefrontal cortex in memory-based decision making. *Brain Sci*. 2016;7(1):4. [CrossRef]
38. Adenzato M, Brambilla M, Manenti R, et al. Gender differences in cognitive theory of mind revealed by transcranial direct current stimulation on medial prefrontal cortex. *Sci Rep*. 2017;7:41219.
39. Fox JM, Abram SV, Reilly JL, et al. Default mode functional connectivity is associated with social functioning in schizophrenia. *J Abnorm Psychol*. 2017;126(4):392-405. [CrossRef]
40. Tamir DI, Thornton MA, Contreras JM, Mitchell JP. Neural evidence that three dimensions organize mental state representation: rationality, social impact, and valence. *Proc Natl Acad Sci USA*. 2016;113(1):194-199.
41. Silva R, Cardoso D, Abrunheiro S, Almeida M, Apóstolo J. Effectiveness of caregiver-provided cognitive interventions on cognition, social functioning and quality of life among older adults with major neurocognitive disorder: a systematic review protocol. *JBI Database System Rev Implement Rep*. 2016;14(11):31-42. [CrossRef]
42. Hiser J, Koenigs M. The multifaceted role of the ventromedial prefrontal cortex in emotion, decision making, social cognition, and psychopathology. *Biol Psychiatry*. 2018;83(8):638-647. [CrossRef]
43. Husain SF, Tang TB, Yu R, et al. Cortical haemodynamic response measured by functional near infrared spectroscopy during a verbal fluency task in patients with major depression and borderline personality disorder. *EBiomedicine*. 2020;51:102586. [CrossRef]
44. Knowland D, Lim BK. Circuit-based frameworks of depressive behaviors: the role of reward circuitry and beyond. *Pharmacol Biochem Behav*. 2018;174:42-52. [CrossRef]