Schizophrenia Research xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Increased resting-state global functional connectivity density of default mode network in schizophrenia subjects treated with electroconvulsive therapy

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ARTICLE INFO

Article history:
Received 17 March 2017
Received in revised form 26 October 2017
Accepted 29 October 2017
Available online xxxx

Keywords:
Schizophrenia
Modified electroconvulsive therapy (MECT)
Functional connectivity density (FCD)
Default mode network (DMN)

ABSTRACT

Modified electroconvulsive therapy (MECT) has been widely applied to help treat schizophrenia patients who are treatment-resistant to pharmaceutical therapy. Although the technique is increasingly prevalent, the underlying neural mechanisms have not been well clarified. We conducted a longitudinal study to investigate the alteration of global functional connectivity density (gFCD) in schizophrenia patients undergoing MECT using resting state fMRI (functional magnetic resonance imaging). Two groups of schizophrenia inpatients were recruited. One group received a four-week MECT together with antipsychotic drugs (ECT + Drug, n = 21); the other group only received antipsychotic drugs (Drug, n = 21). Both groups were compared to a sample of healthy controls (HC, n = 23). fMRI scans were obtained from the schizophrenia patients twice at baseline (t_1) and after 4-week treatment (t_2), and from healthy controls at baseline. gFCD was computed using resting state fMRI. Repeated ANCOVA showed a significant interaction effect of group × time in the schizophrenia patients in left precuneus (Pcu), ventral medial prefrontal cortex (vMPFC), and dorsal medial prefrontal cortex (dMPFC) (GRF-corrected $P < 0.05$), which are mainly located within the default mode network (DMN). Post-hoc analysis revealed that compared with baseline (t_1), an increased gFCD was found in the ECT + Drug group in the dMPFC ($t = 3.87$, $p = 0.00095$), vMPFC ($t = 3.95$, $p = 0.00079$) and left Pcu ($t = 3.33$, $p = 0.0034$), but no significant effect was identified in the Drug group. The results suggested that increased global functional connectivity density within the DMN might be one important neural mechanism of MECT in schizophrenia.

1. Introduction

Schizophrenia is a devastating mental disorder mainly characterized by positive symptoms such as hallucinations and delusions, as well as negative symptoms, and cognitive impairments (Freedman, 2003; van Os and Kapur, 2009). Schizophrenia is primarily treated through the use of antipsychotic pharmacotherapies and although major strides have been made towards understanding the illness and its treatment, a significant proportion of patients remain medication resistant and as a result there is often a need for supplementary approaches to treatment such as modified electroconvulsive therapy (MECT) (Xiang et al., 2015). Evidence from a systematic review suggests that ECT, combined antipsychotic drugs, may be considered an option for people schizophrenia who show limited response to medication alone (Tharyan and Adams, 2005). Despite a demonstrated utility of technique, the underlying therapeutic mechanisms have not been fully clarified. Therefore investigation into the mechanisms of ECT is necessary not only for the further refinement of ECT technology but also to guide the development of new pharmaceutical approaches (McCall et al., 2014).

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https://doi.org/10.1016/j.schres.2017.10.044
0920-9964/

Functional magnetic resonance imaging (fMRI) makes it possible to explore human brain in vivo and has been widely used in the research of psychiatric disorders. Multiple studies suggest that abnormal interactions between different brain regions are associated with the pathophysiology of schizophrenia, supporting a dysconnectivity hypothesis that certain alterations in anatomical and functional connectivity during the neural developmental process are fundamental to the schizophrenia neuropathology (Chen et al., 2017a; Dong et al., 2017; Duan et al., 2015; Fornito et al., 2012; Pettersson-Yeo et al., 2011; Stephan et al., 2009; Zhou et al., 2015). Previous evidence has shown that resting-state fMRI results are sensitive to psychosis and antipsychotic treatment (Abbott et al., 2013). Abbott et al. found that aberrant activation patterns or connectivity in patients with schizophrenia were no longer apparent or were "normalized" after treatment (Abbott et al., 2013). Many studies have attempted to clarify the mechanism of antipsychotic treatment, but results remain inconsistent due to wide range of pharmaceutical treatments and the heterogenous nature of schizophrenia (Fusar-Poli et al., 2007; Goghari et al., 2013; Lui et al., 2010; Sambataro et al., 2010; Sarpal et al., 2015). As for the neural impacts of ECT, several studies have demonstrated relationships between ECT and brain structural and functional changes, but these studies have principally focused on major depressive disorder (MDD) (Biedermann et al., 2012; Kong et al., 2017; Mulders et al., 2016; Perrin et al., 2012; van Waarde et al., 2015). Only one study reported the effects of right unilateral ECT on brain structure and function among schizophrenia patients as well as among major depressive disorder patients (Thomann et al., 2017). The authors observed diagnosis-unspecific changes of ECT in schizophrenia and major depression disorder, such as an increase in gray matter volume (GMV) in limbic regions and an increase in the right amygdala and hypothalamic Functional connectivity (FC). However, the sample size was too small, suggesting these findings cannot yet be taken as conclusive.

Functional connectivity (FC) measures, defined as instantaneous, zero-time lagged temporal correlations between spatially distinct neurophysiologic events (Friston, 1994), have been investigated in studies of schizophrenia primarily by using either model-driven seed-based methods or data-driven independent component analysis (ICA) (Fitzsimmons et al., 2013; Giraldo-Chica and Woodward, 2017; Hu et al., 2017; Littow et al., 2015; Mwansisya et al., 2017; Skatun et al., 2017; Zhou et al., 2015). For example, recent seed-based connectivity studies have identified functional dysconnectivity within and across many networks and/or pathways, such as the thalamocortical circuits (Giraldo-Chica and Woodward, 2017) and the default mode network (DMN) (Hu et al., 2017). In addition, a multicenter resting state fMRI study using ICA recently reported robust and consistent reductions in FC in schizophrenia spectrum disorders, indicating disrupted information flow in sensory, subcortical, and frontal brain regions (Skatun et al., 2017). However, seed-based methods rely on the a priori selection of appropriate seed regions based on previous studies and/or anatomical knowledge, which can substantially vary both the results and their interpretation depending on the experimenter's selection. Data-driven ICA attempts to address the bias of prior knowledge by separating the signals of the whole brain into components with statistically independent (and uncorrelated) time courses. Nonetheless, ICA requires the subjective distinction of noise and physiological signals and thus a restriction on components for further analysis. Due to the properties of statistical independence and uncertainty when determining the "true" numbers of independent components (IC), data might be incorrectly modeled and leave a relatively high residual variance (Hobson and Hillebrand, 2006; Lee et al., 2012). Recently, global functional connectivity density (gFCD) has been established to examine the density distribution of whole-brain resting-state FC (Tomasi and Volkow, 2010, 2011a, 2011b). Unlike seed-based or ICA methods, gFCD is a voxel-wise, data-driven method without any prior hypothesis, and it measures the number of resting-state functional connections of a given voxel with all other voxels in the entire brain. Brain regions with high gFCD are considered as functional hubs of the human brain that play important roles in brain function. Tomasi et al. suggested that gFCD might provide an impartial approach for exploratory analyses of the whole-brain functional connectivity and could be used to detect biomarkers of neuropsychiatric disorders (Tomasi et al., 2016). In a recent study, we utilized FCD to identify functional cortical hubs and deficits in functional connectivity in schizophrenia patients (Chen et al., 2015). FCD has also been demonstrated as an effective and reliable technique in the analysis of resting state data in multiple neuropsychiatric diseases including MDD (Chen et al., 2017b; Zhang et al., 2016a; Zou et al., 2016) (Chen et al., 2017b; Zhang et al., 2016a; Zou et al., 2016) and Parkinson's disease (Zhang et al., 2015).

To our knowledge, no study has yet reported the impacts of MECT on whole-brain FCD in schizophrenia. Here, we conducted a longitudinal resting-state fMRI study in which the effects of MECT in combination with antipsychotics were compared to the effects of antipsychotics alone within schizophrenia populations. gFCD was selected as the main biomarker to compare FC changes between different treatment groups. The relationships between gFCD and clinical variables among the schizophrenia populations were also investigated.

2. Method

2.1. Participants

Two groups of inpatients with acute schizophrenia were recruited consecutively in parallel at the Shanghai Mental Health Center (SMHC). All patient subjects met the following inclusion criteria: they were diagnosed as schizophrenia by senior clinical psychiatrists using the SCID-I/P (Structural Clinical Interview for DSM-IV-TR, Patient's version); they were 18–45 years old and right-handed; they had the total Positive and Negative Syndrome Scale (PANSS) scores ≥ 60 (Peralta and Cuesta, 1994) and did not present severe agitation or aggression.

We used convenient sampling when recruiting the participants. In current study, patients are considered to be medication-resistant, if they fail to respond to two or more adequate antipsychotic trials in past five years (Kane et al., 1988; Wimberley et al., 2016). Patients were administered a four-week MECT program in combination with antipsychotics (ECT + Drug group, $n = 21$) if they were identified as medication-resistant according to their previous treatment history. Informed consent for participation in MECT treatment was obtained from each patient and his/her family. Patients who were not identified as medication-resistant or who declined to receive MECT were managed with only antipsychotics (Drug group, $n = 21$). Both groups were matched by gender, age, education levels and baseline PANSS. The daily dosage of antipsychotic medication was converted to chlorpromazine equivalents (mg/d) shown in Table 1 (Leucht et al., 2015; Leucht et al., 2014). Potential patient subjects were excluded if they had any neurologic abnormalities, organic mental illness, other serious physical illnesses, dementia, brain injuries, substance abuse or addiction, inability to give informed consent or contraindications to MRI.

A group of healthy controls (HC group, $n = 23$) were recruited from the local community using advertisements and were matched to both patient groups according to age, gender, and educational level. Healthy controls reported no lifetime psychiatric disorders or a family history of psychosis in their first-degree relatives. Other exclusion criteria were the same as patient groups. The study protocol was approved by the Ethics Committee of SMHC and the written, informed consent of all subjects was obtained before participating in the study.

The Ethics Committee of SMHC approved the study protocol. The written, informed consent of all subjects was obtained before participating in the study.

2.2. Modified electroconvulsive therapy

Patients in the ECT + Drug group underwent standard clinical evaluations before MECT. Bilateral electrical stimulation was administered 3

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Table 1
Demographic and clinical data for all participants.

	HC (n = 23)	ECT + Drug (*n* = 21)	Drug (n = 21)	P value
Gender (M/F)	11/12	10/11	9/12	$x^2 = 0.136$, $p = 0.934^{a;n.s.}$
Age (year)	31.2 ± 5.9	29.2 ± 7.1	30.7 ± 6.9	$F = 0.494$, $p = 0.613^{b;n.s.}$
Education (year)	13.5 ± 2.5	12.3 ± 3.4	12.6 ± 2.9	$F = 0.976$, $p = 0.382^{b;n.s.}$
Duration of illness (months)	–	79.8 ± 54.4	78.7 ± 80.9	$t = 0.049$, $p = 0.961^{c;n.s.}$
Number of failed antipsychotic trials	–	3.1 ± 1.1	2.5 ± 1.1	$t = 1.81$, $P = 0.077$
Duration of prior medications (months)	–	3.9 ± 1.3	2.8 ± 1.4	$t = 2.61$, $P = 0.266$
Reason for changing medications	–	poor response	poor response or intolerance	–
Interval of scans (days)	–	36.1 ± 10.2	35.3 ± 14.6	$t = 0.221$, $p = 0.827^{c;n.s.}$
Chlopromazine equivalents (mg/d)	–	604.6 ± 565.6	532.6 ± 461.2	$t = 0.452$, $p = 0.653^{c;n.s.}$
Baseline PANSS score				
Total	–	71.6 ± 8.4	70.8 ± 9.7	$t = 0.425$, $p = 0.673^{c;n.s.}$
Positive	–	20.7 ± 2.6	19.1 ± 3.5	$t = 1.651$, $p = 0.107^{c;n.s.}$
Negative	–	19.3 ± 7.4	17.4 ± 5.1	$t = 0.967$, $p = 0.339^{c;n.s.}$
General	–	32.0 ± 3.8	34.2 ± 5.7	$t = -1.509$, $p = 0.139^{c;n.s.}$
Baseline FD(mm)	0.166 ± 0.091	0.179 ± 0.108	0.174 ± 0.118	$F = 0.083$, $p = 0.920^{b;n.s.}$
4 weeks PANSS score				
Total	–	49.7 ± 9.6	50.5 ± 12.6	$t = -0.234$, $p = 0.816^{c;n.s.}$
Positive	–	10.9 ± 3.0	12.0 ± 4.7	$t = -0.897$, $p = 0.375^{c;n.s.}$
Negative	–	14.6 ± 6.1	14.0 ± 5.3	$t = 0.297$, $p = 0.768^{c;n.s.}$
General	–	24.3 ± 3.33	24.5 ± 5.4	$t = -0.138$, $p = 0.891^{c;n.s.}$
4 weeks FD(mm)	–	0.219 ± 0.132	0.173 ± 0.113	$t = 1.208$, $p = 0.234^{c;n.s.}$

a. chi-square test; b. ANOVA; c. two sample t-test; n.s., not significant.
HC, health controls; FD, framewise displacement; PANSS, Positive and Negative Symptom Scale.

mornings a week with a Thymatron System IV (Somatics, Lake Bluff, IL, USA). Two stimulus electrodes were placed on the left and right temporal scalp. ECT conditions were similar for all patients (maximum charge delivered = 504 mC; output current = 0.9 A; frequency = 10–70 Hz; pulse width = 1.0 ms; and maximum stimulus duration = 8 s). Motor convulsions and induced tachycardia were monitored and electroencephalogram and electromyogram (when necessary) were recorded during ECT. Anesthesia was performed with intravenous etomidate (0.21–0.3 mg/kg) and propofol (1.82–2.44 mg/kg). Muscles were relaxed with intravenous succinylcholine (1 mg/kg). Intravenous atropine (0.5 mg) was employed to reduce airway secretion. Patients assigned to the ECT + Drug group did not alter their dosage of antipsychotics during the study period.

The total number of ECT was determined individually by the patient's senior psychiatrist according to both the efficacy and adverse events. In the present study, one session of ECT regularly includes 8–12 ECTs and at least 8 ECTs were administered in all patients irrespective of earlier response. Of 21 patients in ECT + Drug group,1 received 8 ECTs, 3 received 10 ECTs, 1 received 11 ECTs, and 16 received 12 ECTs. The mean number of ECT was 11.5 ± 1.1.

2.3. Data acquisition

Whole-brain imaging was performed on a 3.0 T Siemens Magnetom verio syngo MR B17 scanner. The patients underwent scanning once at baseline and once after the 4-week treatment period whereas healthy controls were scanned at baseline. Patient's initial MRI scans were acquired within 24 h prior to the first MECT session while the final MRI scan was obtained 24–48 h after the last MECT session. Subjects were instructed to keep their eyes closed, relax, not to focus their thoughts on anything in particular, and to keep awake.

Functional MRI data were collected using a gradient echo planar imaging (EPI) sequence (repetition time [TR] = 2000 ms; echo time [TE] = 30 ms; flip angle = 90°; field of view [FOV] = 220 mm × 220 mm; matrix = 64 × 64; 30 slices; slice thickness = 4 mm; voxel size = 3.4 × 3.4 × 3.4 mm) with a total scan time of 6 min 06 s (including 6 s dummy), resulting in 180 volumes to be obtained. In addition, high-resolution T1-weighted structural images were obtained using a magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence (TR = 2530 ms, TE = 2.56 ms, flip angle = 7°, inversion time = 1100 ms, FOV = 256 mm × 256 mm, matrix = 256 × 256, 224 slices, slice thickness = 1 mm; voxel size = 1.0 × 1.0 × 1.0 mm).

2.4. Data preprocessing

Image data preprocessing was carried out using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8) and DPABI (http://rfmri.org/dpabi) software packages. Conventional preprocessing steps were performed, which included (1) removing first 10 time points; (2) slice-timing correction; (3) realignment; (4) normalization of images with an EPI template in the Montreal Neurological Institute (MNI) atlas space and resampling to 3 × 3 × 3 mm^3; (5) linear detrending; (6) nuisance covariates regression including 24 motion parameters (Satterthwaite et al., 2013), individual white matter (WM) and cerebrospinal fluid (CSF) signals; (7) temporally scrubbing the "bad" time points (frame-wise displacement [FD] > 0.5); and (8) temporal filtering (band - pass 0.01–0.1 Hz)(Power et al., 2012). Group-level head-motion was further assessed using traditional statistical analysis. Two sample *t*-tests were performed to compare the differences of head-motion (mean FD, max translation and max rotation) between the two patient groups at t_1 (baseline) and t_2 (after treatment). Two paired t-tests were performed to compare the differences of head-motion between t_1 and t_2 for each patient group.

2.5. Voxel-wise global functional connectivity density

Global functional connectivity density (gFCD), a graph-based measure of whole-brain FC, is defined as the number of statistically significant FCs between a given voxel and the rest of voxels across the whole brain in a binary network. gFCD has been proposed to be a measure capable of quantifying the importance/centrality of a given voxel within the whole brain network (Tomasi and Volkow, 2010). Areas with the highest gFCD measures are thought to operate as functional hubs of whole brain with prominent roles in cognition, sensory function, and their dysfunction may be relevant to neuropsychiatric disorders.

According to the approach introduced by Tomasi and Volkaw (Tomasi and Volkow, 2010), we used the custom-written software from the Neuroscience Information Toolbox (NIT, http://www.neuro.uestc.edu.cn/NIT.html) to compute the voxel-wise global FCD maps. The preprocessed image time series of two voxels were considered connected if their Pearson linear correlation coefficient $r > T_c$; we

selected $T_c = 0.6$ considering that a low thresholds (e.g. $T_c < 0.4$) could lead to potential spurious weak correlations while an excessive thresholding (e.g. $T_c > 0.7$) may result in lower sensitivities (Tomasi and Volkow, 2010). In order to obtain reliable and robust results, gFCD measures were estimated using multiple T_c values (0.4, 0.5, 0.6, 0.7) to verify the stability of results according to the methodology introduced in our previous study (Luo et al., 2014). The gFCD at a given voxels x_0 was calculated as the number of significant functional connections between x_0 and all other voxels in the brain. gFCD maps were normalized by dividing by the mean value of each individual map and were spatially smoothed (6-mm full-width at half-maximum, FWHM) to minimize the effects of outliers across voxels.

2.6. Statistical analysis

Group-level analysis was performed using a two-way repeated ANCOVA with treatment as the between-subject factor group (ECT + Drug vs. Drug) and time as the within-subject factor (t_1 vs. t_2) while controlling for age, gender, education level and FD. To examine whether ECT + Drug and Drug differently modulated measures of gFCD, we focused on the interaction effect between group and time. All analyses based on whole brain gFCD maps were performed for multiple comparisons correction using a height threshold ($p = 0.005$) and an extent threshold based on Gaussian Random Field theory ($P_{corrected} = 0.05$) (Chen et al., 2017b; Tomasi et al., 2016; Tomasi and Volkow, 2012; Zhang et al., 2016b).

Regions that demonstrated a significant interaction effect and the main effect of time were selected for post-hoc analysis. The peak voxel of each region was used to define a 6 mm radius sphere as a region of interest (ROI). For each ROI, two sample *t*-tests were used to evaluate the group differences at t_1 and t_2, and two paired t-tests were used to compare the difference between t_1 and t_2 for each group. Each patient group was additionally compared to healthy control baseline using two sample *t*-tests. Two sample t-tests and paired t-tests were performed while controlling for the covariates of age, gender, education level, and FD. In addition, ANOVA was conducted between HC and both patient groups at t_1 and t_2, respectively. All reported *p* values were from two-tailed tests, and $p < 0.005$ was considered significant.

2.7. Correlation between altered gFCD and clinical features

To investigate the relationships between relative changes in gFCD in ROIs with significant interaction effects ($[gFCD_{t1}\text{-}gFCD_{t2}]/gFCD_{t1}$) and clinical variables (such as total disease course, CPZ equivalent units and PANSS reductive ratios), mean Z values of gFCD were extracted in the ROIs with significant differences. Kolmogorov-Smirnov tests were used to determine the normality prior to correlation analysis. As most clinical and measured variables did not meet the assumptions of a normality distribution, nonparametric Spearman rank correlations were instead used to assess clinical correlations within each patient group.

3. Results

3.1. Demographic and clinical data

Detailed demographic and clinical data for all participants are presented in Table 1. Schizophrenia patients did not differ from the controls in terms of age, gender and years of education. No difference in the courses of illness, or daily antipsychotic medication dosage during the study was found between the two patient groups. The ECT + Drug group and the Drug group also had no significant differences in mean framewise displacement (FD) values of the MRI scans or the PANSS scores at either baseline or four weeks.

3.2. Global FCD

The spatial distribution of the mean gFCD maps showed that the highest gFCD values were principally located in the PCC/Pcu, occipital, and prefrontal cortices (Fig. 1), similar to regions reported in previous studies (Chen et al., 2015; Luo et al., 2014; Tomasi and Volkow, 2010).

Repeated ANCOVA showed significant interactions between the patient groups (ECT + Drug vs Drug) with time (t1 vs t2) within the dorsal medial prefrontal cortex (dMPFC), ventral medial prefrontal cortex (vMPFC) and left Pcu (Fig. 2 and Table 2). Calculated gFCD values for these regions for each group at baseline are shown in Table 3. Post-hoc paired t-test analyses revealed that compared with the baseline t_1, regions which showed increased gFCD at t_2 were only found for within the ECT + Drug group at the in dMPFC ($t = 3.87$, $p = 0.00095$), vMPFC ($t = 3.95$, $p = 0.00079$) and left Pcu ($t = 3.33$, $p = 0.0034$) respectively. No regions in the Drug only group reached significance. Additionally, two sample *t*-tests showed that at t_2, the ECT + Drug group had a higher gFCD in vMPFC than the Drug group ($t = 3.70$, $p = 0.0014$). However, both patient groups failed to show any significant differences when compared to the healthy control group at ROIs located in the dMPFC, vMPFC and left Pcu at t_1 or t_2 (ANOVA; $p > 0.005$).

Apart from the selection of T_c as 0.6, a value which is typically chosen as the threshold to determine the gFCD, multiple additional T_c values were also considered to explore the reliability and robustness of gFCD measures. Variations of the threshold produced consistent results across different T_c values (Fig. S2).

3.3. Correlation between altered gFCD and clinical features

No significant correlations of gFCD with clinical variables were observed for for any ROI in the dMPFC, vMPFC and left Pcu, in either the ECT + Drug group or for the Drug group ($p > 0.01$).

4. Discussion

This is the first longitudinal study to investigate the effects of MECT on measures resting state measures of gFCD in schizophrenia patients alongside the use of antipsychotic therapy and comparing these measures to the use of antipsychotics alone. In comparison to routine pharmacotherapy, 4-week MECT plus antipsychotics appeared to increase the gFCD within in the Pcu, vMPFC, and dMPFC regions. All these regions have been reported previously identified as key areas of DMN. As the two patient groups were matched in terms of clinical scores and other demographic profiles at baseline, the present study provides new evidence that ECT enhances functional connectivity of the DMN as measured by gFCD within schizophrenic populations.

Since gFCD is a data-driven method that provides an impartial approach to investigate whole-brain connectivity, it might be able to detect the most significant changes in the functional networks that have been hypothesized to be associated with the schizophrenia neuropathology. The dysconnectivity hypothesis posits that schizophrenia is related to abnormal interactions between large-scale functionally integrated networks and cortical-subcortical pathways, such as the frequently-reported DMN, the central executive network (CEN), the salience network (SN), and the thalamocortical pathway (Arbabshirani et al., 2013; Chen et al., 2017a; Dong et al., 2017; Duan et al., 2015; Elton and Gao, 2014; Fornito et al., 2012; Friston, 2002; Jiang et al., 2017; Klingner et al., 2014; Lynall et al., 2010; Pettersson-Yeo et al., 2011; Skatun et al., 2017; Stephan et al., 2009; Tu et al., 2013; Woodward et al., 2012; Wotruba et al., 2014; Zhou et al., 2015). A growing number of studies have reported that disruptions in DMN may paly a critical role in the psychiatric symptoms and cognitive deficits present in schizophrenia (Bastos-Leite et al., 2015; Bluhm et al., 2007; Buckner, 2013; Garrity et al., 2007; Littow et al., 2015; Whitfield-Gabrieli and Ford, 2012; Zhu et al., 2012). Raichle et al. first proposed the structure of the DMN in 2001, based on their findings that some brain regions

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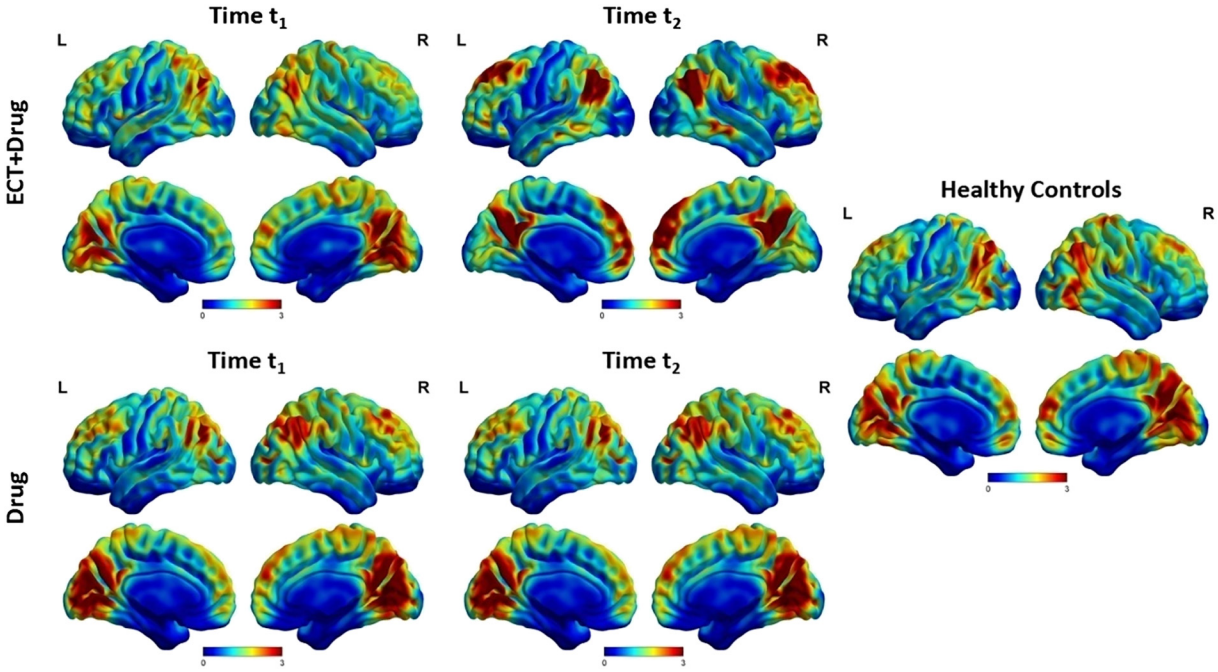

Fig. 1. The spatial distribution of the average global FCD maps for ECT + Drug group, Drug group, and healthy controls group.

were more active during rest than during a wide range of attention-demanding tasks (Raichle et al., 2001). The DMN mainly includes midline brain regions, such as the MPFC, PCC/Pcu, and bilateral inferior parietal lobe (IPL), as well as hippocampus and parahippocampus. Although the exact roles of the DMN have not been clearly identified, it is believed that the DMN plays an important part in attending to external and internal stimuli as well as during self-referential and reflective activity (such as episodic memory retrieval, inner speech, mental images, emotions,

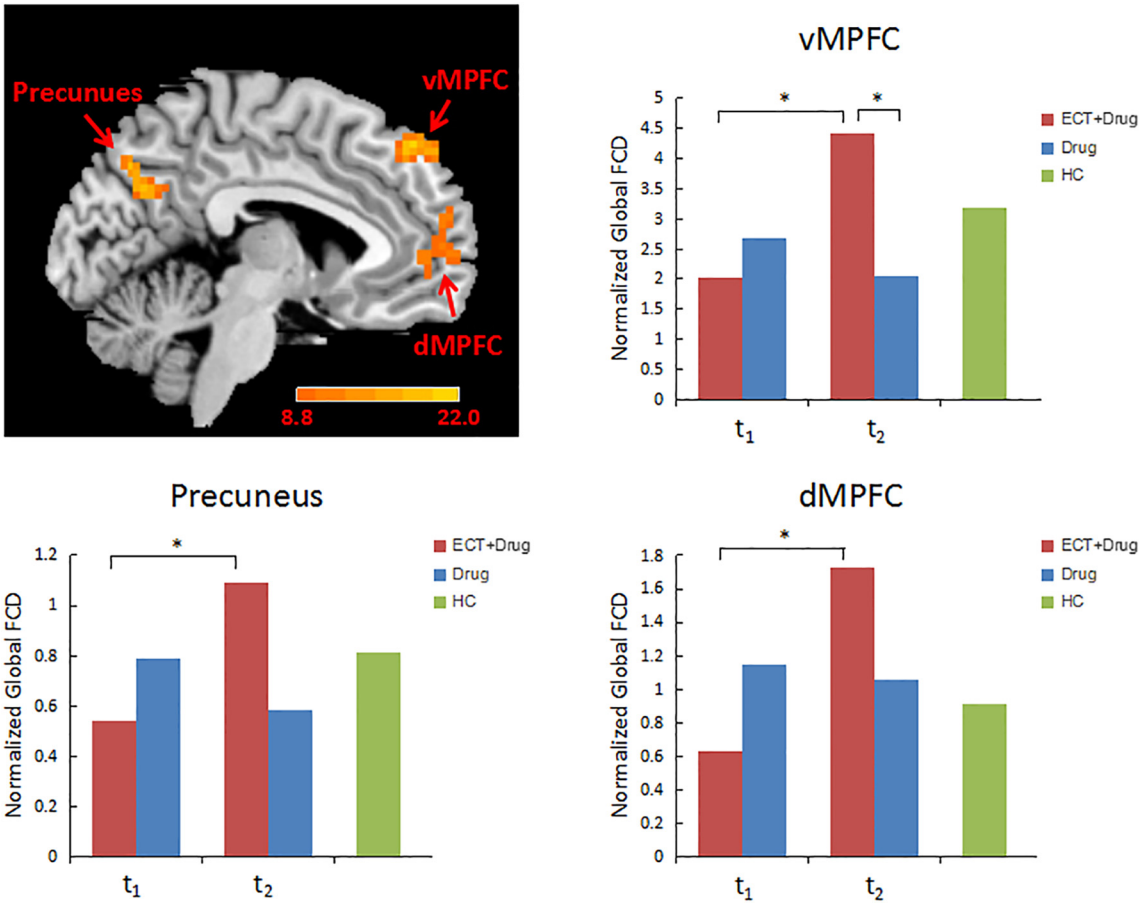

Fig. 2. Regions with significant interaction effect in the gFCD analysis.

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Table 2
Regions with significant interaction effect in repeated measure ANCOVA.

Region	Abb	AAL	MNI coordinate			Peak F	Cluster Size(voxels)
			x	y	z		
Ventral medial frontal cortex	vMPFC	Frontal_Sup_Medial_L	0	60	18	16.1	125
Dorsal medial frontal cortex	dMPFC	Frontal_Sup_Medial_R	9	57	42	14.0	92
Precuneus	Precuneus	Precuneus_L	−21	−60	27	13.8	72

and planning of future events) (Buckner et al., 2008; Raichle and Snyder, 2007). Garrity et al. reported an aberrant "default mode" FC in schizophrenia, showing an altered temporal frequency and spatial location of the DMN (Garrity et al., 2007). Moreover, alterations of the local activity within the DMN, functional connectivity between nodes of the DMN, and between the DMN and other networks have all been linked to the symptoms of schizophrenia (Hu et al., 2017).

Despite the DMN's status as the most widely studied resting state network (RSN), findings about DMN in schizophrenia are frequently inconsistent. The mixed findings are likely confounded by both clinical and methodological heterogeneity. Although, the majority of evidence points to schizophrenia-related DMN hypoconnectivity, both hypo and hyperconnectivity have been reported (Fornito et al., 2012; Narr and Leaver, 2015). In a recent review, Fornito et al. suggested that increased FC is more prominent in early stages of schizophrenia, whereas reduced FC characterizes later illness stages. The initial increase is proposed to be an early compensatory recruitment of hub regions, whereas the decline is associated with later deterioration of function (Fornito et al., 2017). Since the patients in our studies were medication-resistant and at later illness stages, the main treatment effect of MECT observed here could attribute to the "normalization" of the hypoconnectivity of DMN hub regions. We hypothesized that an explanation for the MECT treatment response might be related to an accelerated and extensive enhancement of FC within DMN hubs versus antipsychotic pharmacotherapy alone. A previous study explored the coherence of the DMN during ECT therapy of treatment-resistant major depressive disorder. It was reported that the decreased DMN coherence present in MDD was no longer present after ECT in clinical responders whereas it persisted in non-responders, implying that successful response to ECT may restore the integration of the precuneus within the DMN (Mulders et al., 2016). This work in combination with our presently reported study help extend our understanding of functional network changes that result from ECT-treatment and which may be used in the future to improve our ability to predict clinical outcomes.

In a review of the mechanisms of action for ECT, the authors implied that the benefit of ECT in schizophrenia tended not to be a specific "anti-schizophrenia" effect per se, but rather a more general antipsychotic effect, as ECT has shown effectiveness in treating psychosis associated with various conditions, despite their presumed divergent pathophysiologic mechanisms (Rosenquist et al., 2014). Therefore, ECT mechanisms may overlap with medication mechanisms, but ECT's strength lies in its ability to act as an extension of pharmacotherapies which may potentiate or complement their clinical benefits. Our results provide evidence that the enhanced FC of DMN hubs might be a possible mechanism of ECT for subjects with schizophrenia.

Previous findings have reported aberrant gFCD in multiple brain regions within schizophrenia, including decreased gFCD in areas primarily located in the posterior cortical and sensorimotor regions and increased gFCD in the regions located in the subcortical and limbic system regions (Zhuo et al., 2014; Zhuo et al., 2017). However, we failed to replicate these differences of gFCD in our patient groups either at baseline or at follow-up as compared to the healthy controls, possibly due to the relatively small sample size in each group. Therefore, it is still necessary to validate these findings in the future studies.

Several limitations should be considered when interpreting the findings of this study. First, an obvious limitation is the relatively modest sample size, as larger sample sizes would be more useful for the certainty of the impacts. Secondly, all patients of the ECT + Drug group were on antipsychotic drugs and were medication resistant, preventing an independent understanding of the effects of MECT monotherapy, as well as a potential bias within the results due to non-random grouping. Although we used a group of patients undergoing exclusive pharmacotherapy as a treatment control, comparisons regarding the effects of MECT must be viewed within the context of the hybrid treatment. However, our research demonstrates that MECT therapy in conjunction with antipsychotic therapy may help ameliorate failures of dysconnectivity of several key nodes within the DMN hub, addressing one of the fundamental elements in the functional etiology of schizophrenia. Finally, the patients had not been allocated randomly into each group, which could bring some potentially unknown bias into the analyses.

5. Conclusion

The present study has demonstrated that the enhancement of FC within key regions of the DMN might compose an important neural mechanism for the treatment effect of MECT within schizophrenia populations when used as an adjunct therapy to typical pharmaceutical approaches.

Role of the funding source

This work was supported by grants from Ministry of Science and Technology of China (2016YFC1306803), National Natural Science Foundation of China (81471638, 81671329, 81671332, 81361120403), Program of Shanghai Academic/Technology Research Leader (16XD1402400), Shanghai Science and Technology Committee (15411967200, 14411961400, 134119b0300, 15ZR1435500, 14411963400), National Key Clinical Disciplines at Shanghai Mental Health Center (OMA-MH, 2011-873), Shanghai Key Laboratory of Psychotic Disorders (13dz2260500), Shanghai Jiao Tong University Foundation (14JCRY04, YG2014MS40), SHSMU-ION Research Center for Brain Disorders (2015NKX001, 15ZH2015, W35XT), and Medicine Engineering Intersection Program of Shanghai Jiaotong University (YG2015ZD12), Research Grant from Shanghai Hospital Development Center (SHDC12014111), Doctoral Innovation Fund from Shanghai Jiaotong University School of Medicine (BXJ201639).

Contributors

JJW designed the experiment and wrote the protocol; HH, YYT and YCJ undertook the statistical analysis; MQX, LHX, ZTH, HRC and YL collected the image data and clinical information; AC, YPJ, JHS, DZY, CBL, CL and JJW reviewed this article critically and gave final approval of the version of the article to be published. All authors contributed to the manuscript and have approved the final manuscript.

Table 3
The gFCD values of regions with significant interaction effect across the three groups at baseline.

Region	Abb	Mean (SD)		
		ECT + Drug	Drug	HC
Ventral medial frontal cortex	vMPFC	0.624 (0.371)	1.144 (1.370)	0.902 (0.782)
Dorsal medial frontal cortex	dMPFC	2.007 (1.137)	2.663 (2.096)	3.172 (2.596)
Precuneus	Precuneus	0.539 (0.515)	0.785 (1.091)	0.807 (0.809)

Please cite this article as: Huang, H., et al., Increased resting-state global functional connectivity density of default mode network in schizophrenia subjects treated with elec..., Schizophr. Res. (2017), https://doi.org/10.1016/j.schres.2017.10.044

Conflict of interest

The authors declare no conflict of interest.

Acknowledgement

The first author acknowledges support from National Natural Science Foundation of China, Science and Technology Commission of Shanghai Municipality, and Special-Funded Program on National Key Scientific Instruments and Equipment Development of China.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2017.10.044.

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Please cite this article as: Huang, H., et al., Increased resting-state global functional connectivity density of default mode network in schizophrenia subjects treated with elec..., Schizophr. Res. (2017), https://doi.org/10.1016/j.schres.2017.10.044

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