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Altered functional connectivity of the thalamus induced by modified electroconvulsive therapy for schizophrenia

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ABSTRACT

Background: Electroconvulsive therapy (ECT) has been shown to be effective in schizophrenia (SZ), particularly in drug-refractory cases or when rapid symptom relief is needed. However, its precise mechanisms of action remain largely unclear. To clarify the mechanisms underlying modified electroconvulsive therapy (mECT) for SZ, we conducted a longitudinal cohort study evaluating functional connectivity of the thalamus before and after mECT treatment using sub-regions of thalamus as regions of interest (ROIs).
Methods: Twenty-one SZ individuals taking only antipsychotics (DSZ group) for 4 weeks and 21 SZ patients receiving a regular course of mECT combining with antipsychotics (MSZ group) were observed in parallel. All patients underwent magnetic resonance imaging scans at baseline (t1) and follow-up (t2, ~4 weeks) time points. Data were compared to a matched healthy control group (HC group) consisting of 23 persons who were only scanned at baseline. Group differences in changes of thalamic functional connectivity between two SZ groups over time, as well as in functional connectivity among two SZ groups and HC group were assessed.
Results: Significant interaction of group by time was found in functional connectivity of the right thalamus to right putamen during the course of about 4-week treatment. Post-hoc analysis showed a significantly enhanced functional connectivity of the right thalamus to right putamen in the MSZ group contrasting to the DSZ group. In addition, a decreased and an increased functional connectivity of the thalamus to sensory cortex were observed within the MSZ and DSZ group after 4-week treatment trial, respectively.
Conclusion: Our findings suggest that changes in functional connectivity of the thalamus may be associated with the brain mechanisms of mECT for schizophrenia.

1. Introduction

Schizophrenia (SZ) is a common devastating psychotic disorder with onset usually in late adolescence or early adulthood, which has dramatic disability rate, morbidity and financial consequences (Lewis and Sweet, 2009; Owen et al., 2016). Some researchers considered it to be a state of 'fractured mind', with many researchers refining this definition in terms of pathological alterations in brain connectivity (Chen et al., 2017; Dong et al., 2017; Garrity et al., 2007; Jiang et al., 2017; Skudlarski et al., 2010).

The mainstay of treatment for SZ has been antipsychotic medication, but for one third of individuals this treatment is insufficient and they must be labeled as 'treatment refractory'. Physical stimulation treatments provide an alternative and compensatory approach to antipsychotic therapy. Electroconvulsive therapy (ECT) was initially developed as a treatment for SZ (Takebayashi, 2013), and has exhibited significant efficacy and safety for patients with severe mental illness including SZ and major depression disorder (MDD). In eastern nations such as India, China, parts of Africa, and other developing countries, ECT is often viewed as a first-line treatment of severe psychosis when

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symptoms require hospitalization, even following the introduction of first- and second-generation antipsychotics (Rosenquist et al., 2014), due to its rapidly reducing clinical symptoms. Despite the utility of ECT, there remain a number of individuals who do not show a clinical response to the treatment. Therefore, it is necessary to clarify the underlying mechanisms of the action of ECT to help identify patients who may respond best to ECT and better guide clinical practice.

The thalamus plays an important role in the processing and integration of information (Edward, 2007). The thalamus has recently received renewed interest in systems-neuroscience and SZ research because of emerging evidence highlighting its key role in coordinating functional interactions in cortical-subcortical circuits (Duan et al., 2015; Pratt et al., 2017). Converging neuroimaging investigations have revealed considerable thalamic abnormalities in SZ, decreased grey matter volume (Glahn et al., 2008a; McCarley et al., 1999; Okada et al., 2016; Shenton et al., 2001), disordered activity during cognition (Minzenberg et al., 2009), and diminished expression of biochemical markers of neuronal integrity such as N-acetyl aspartate (NAA) (Kraguljac et al., 2012) are included. In addition, several research groups have sequentially reported abnormal thalamic functional connectivity in SZ (Atluri et al., 2015; Klingner et al., 2014; Lerman-Sinkoff and Barch, 2016; Tu et al., 2015; Wang et al., 2015). Diminished prefrontal cortex (PFC)-thalamic connectivity and increased somatomotor-thalamic connectivity have been relatively consistent findings (Giraldo-Chica and Woodward, 2017). Disturbed thalamic functional connectivity in SZ could supply a core pathophysiological mechanism for cognitive deficits and certain symptoms (Anticevic et al., 2014; Ferrarelli et al., 2012; Lisman, 2012; Pinault, 2011; Pratt et al., 2017). Some studies have demonstrated correlations of thalamic functional activity to clinical psychopathology. Anticevic et al. found that mean over-connectivity of sensory-motor regions to the thalamus correlated positively with PANSS total score (Anticevic et al., 2014), while Cheng et al. observed frontal-thalamic hypoconnectivity related to negative symptoms in SZ (Cheng et al., 2015).

Neuroimaging has long been utilized to provide a measure of the effects of ECT on brain structure and function as well as to better understand its mechanisms of action (Nobler et al., 2000). Recent emerging rodent and non-human primate studies have linked brain plasticity to the action of electroconvulsive stimulation (ECS), an analogue of ECT in animal models. Human studies with ECT have found similar results although the human data are based on relatively few patient groups. Brain structural and functional connectivity relating to the frontal cortex (Madsen et al., 2005) and the medial temporal lobe (Hellsten et al., 2004; Newton et al., 2003; Perera et al., 2007) has been the most reported brain regions involved in the brain plasticity in populations with SZ treated with ECT. In a recent publication, based on the same presented dataset, we observed an increased global functional connectivity density in the default mode network (DMN) including the dosal medial prefrontal cortex (dMPFC), ventral medial prefrontal cortex (vMPFC) and left precuneus for SZ patients after 4-week ECT in conjunction with antipsychotics, a pattern which was not identified in the patients taking antipsychotics alone.

Several studies have reported functional connectivity change of some brain network involving mediodorsal thalamus after ECT in MDD (Leaver et al., 2016). Despite the rise of studies implicating the thalamus in both SZ and efficacious treatment, few studies have detailed the change of functional connectivity within the thalamus induced by ECT in SZ populations. It was worth noting that recent research has proposed that modified ECT (mECT) may significantly raise NAA concentration, an indicator of neural structural and/or functional integrity, in the left PFC and left thalamus among individuals with ECT-treated SZ in contrast to those treated solely with antipsychotics (Gan et al., 2017). Accordingly, we hypothesized that ECT could enhance the functional connectivity of thalamus with subcortical structure or reduce the functional connectivity of thalamus with cortical structure that might be relative to the effect on clinical symptomology. In this study, we designed a parallel contrast cohort including two SZ groups with one group only taking antipsychotic and another receiving mECT in combination with antipsychotics to determine the underlying mechanism of mECT.

2. Materials and methods

2.1. Subjects

In this nonrandom observational study, 42 inpatients with SZ were divided into two groups according to their treatment strategy. In this current study, patients are considered to be medication-refractory if they do not respond to two or more adequate antipsychotic trials in the past five years (Kane et al., 1988; Wimberley et al., 2016). Those patients were prescribed mECT therapy if they were diagnosed as drug-refractory and elected for the course of treatment. Thus, one patient group received a four-week mECT series together with antipsychotic drugs (MSZ group, n = 21); the other group only received antipsychotic drugs (DSZ group, n = 21) comprising patients who refused to undergo mECT or who were not identified as medication-refractory. Finally, for the MSZ group, 20 of 21 enrolled patients were drug-resistant. A healthy control sample (HC group, n = 23) was additionally recruited and matched to both patient groups by age, gender, and educational level (Table 1). All the inpatients were recruited from the Shanghai Mental Health Center (SMHC). The patients were diagnosed with SZ by trained clinical psychiatrists using the SCID-I/P (Structural Clinical Interview for DSM-IV-TR, Patient's version) and met the indication for mECT. Additionally, patients were screened for no history of mECT treatment within the past six months. The Positive and Negative Syndrome Scale (PANSS) was used to assess the psychiatric symptom severity and the

Table 1
Demographic and clinical data of participants.

Characteristic	MSZ (n = 21) Mean (SD)	DSZ (n = 21) Mean (SD)	P value[a]	HC (n = 23) Mean (SD)
Gender (M/F)[b]	10/11	9/12	0.757	11/12
Age (years)	29.2(7.1)	30.7(7.8)	0.524	31.2 ± 5.9
Education (years)	12.3(3.4)	12.6(2.9)	0.773	13.5 ± 2.5
Handedness (left/right)[b]	0/21	0/21	1.000	0/23
Smoking/nonsmoking[b]	3/18	3/18	1.000	7/16
Drinking/nondrinking[b]	0/21	0/21	1.000	3/20
Illness duration (months)[c]	79.8 (54.4)	78.7(80.9)	0.435	–
Number of failed antipsychotic trials	3.1(1.1)	2.5(1.1)	0.077	–
Duration of prior medications (months)	3.9(1.3)	2.8(1.4)	0.266	–
Reason for changing medications	Poor response	Poor response or intolerance	–	–
Interval of scans (days)	36.1 (10.2)	35.3(14.6)	0.827	–
Total number of MECT	11.5(1.1)	–	–	–
Chlopromazine equivalents (mg/d)[c]	604.6 (565.6)	532.6(461.2)	0.504	–
Baseline PANSS score				
Total	71.6(8.4)	70.8(9.7)	0.673	–
Positive	20.7(2.6)	19.1(3.5)	0.107	–
Negative	19.3(7.4)	17.4(5.1)	0.339	–
General	32.0(3.8)	34.2(5.7)	0.139	–
4-weeks PANSS score				
Total	49.7(9.6)	50.5(12.6)	0.816	–
Positive	10.9(3.0)	12.0(4.7)	0.375	–
Negative	14.6(6.1)	14.0(5.3)	0.768	–
General	24.3 (3.33)	24.5(5.4)	0.891	–

[a] p values were obtained using two sample *t*-tests except where noted.
[b] p values were obtained using the chi-square test.
[c] p values were obtained using the Mann-Whitney tests as a result of the substantial variability in each group.

total PANSS scores of all patients were over 60, but no patient presented severe aggression or agitation. All patients received antipsychotic medicine and daily antipsychotic medication dosage was converted to chlorpromazine equivalents (mg/d) (Woods, 2003)shown in Table 1. The healthy control subjects were recruited from the community through advertisement. They had neither lifetime psychiatric disorder nor family history of psychosis in their first-degree relatives. All these participants aged 18–45 years old. Participants were excluded if they had any neurologic abnormalities, organic mental disorders, other serious physical illnesses, dementia, brain injuries, substance abuse or dependence, or contraindications to MRI. The Ethics Committee of SMHC approved the study protocol. The written, informed consent of all subjects were obtained prior to participating in the study.

The details of medication usage are as follows: most of these patients were prescribed atypical antipsychotics. Of 21 patients in DSZ group, 10 were taking one antipsychotics, 10 were taking two antipsychotics and 1 was taking three antipsychotics. In the MSZ group, 3 were taking one antipsychotics, 12 were taking two antipsychotics, and 6 were taking three antipsychotics. Clozapine was prescribed for 2 patients in DSZ group and 5 patients in MSZ group. The antipsychotics taken by each patient remained unchanged during study period.

2.2. Modified electroconvulsive therapy

mECT was conducted 3 times weekly for one regular course using a therapeutic apparatus Thymatron System IV (Somatics, Lake Bluff, IL, USA). Before mECT, succinylcholine chloride (1.0 mg/kg) was applied as muscle relaxant, atropine (0.5 mg) was used to reduce airway secretion, etomidate (0.21–0.3 mg/kg) and propofol (1.82–2.44 mg/kg) were administered to maintain anesthesia. The intensity was based on 2/3 of patients' age (Petrides and Fink, 1996) and the electrodes were placed at bilateral temporal lobes. mECT parameters 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). Electroencephalogram (EEG) seizure was monitored to ensure adequate duration and quality. The antipsychotic therapy remained stable during mECT except for the discontinuation of pharmacotherapy in the morning on the day of mECT. The total number of ECT was determined individually based on both the therapeutic efficacy and adverse events by the clinic psychiatrist. In the current study, one regular course of ECT includes 8–12 ECTs. Of 21 patients in MSZ group, 16 received 12 ECTs, 1 received 11 ECTs, 3 received 10 ECTs, and the rest one received 8 ECTs. The mean number of ECT was 11.5 ± 1.1.

2.3. Data acquisition

Imaging data were acquired using a 3-T Siemens Magnetom veriosyngo MR B17 scanner. Functional MRI data were obtained using a gradient echo planar imaging (EPI) sequence (TR = 2000 ms; TE = 30 ms; flip angle = 90°; FOV = 220 mm × 220 mm; matrix = 64 × 64; slice thickness = 4 mm; 30 slices; voxel size = 3.4 × 3.4 × 3.4 mm; 180 volumes). In addition, high-resolution T1-weighted structural images were collected 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). The patients underwent scanning twice, once at baseline and again after the 4-week treatment while the controls were scanned only at baseline. Patients' initial MRI scans were obtained within 24 h prior to the first mECT session and the final MRI scan was collected 24–48 h after the last mECT session. During fMRI collection participants were instructed to keep their eyes closed and awake, relax, and not to focus their thoughts on anything in particular.

2.4. Data preprocessing

The data preprocessing pipeline was similar with previous study (Huang et al., 2017) and is only briefly described here. First, the first 10 time points were removed for signal equilibrium and to allow subject adaptation to the scanning noise; second, we conducted slice-timing correction, realignment correction, normalization and resampling to $3 \times 3 \times 3$ mm^3; third, the nuisance covariates including 24 motion parameters (Satterthwaite et al., 2013; Yan et al., 2013), white matter (WM) and cerebrospinal fluid (CSF) signals and linear trending were regressed out; then, we performed temporal scrubbing (Power et al., 2015) and temporal filtering (0.01–0.1 Hz); finally, the data was smoothed (FWHM = 6 mm). Differences due to head-motion (frame-wise displacement, FD) were assessed using repeated measure ANOVA and post-hoc analyses. Data preprocessing was performed in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8) and DPABI (http://rfmri.org/dpabi) software.

2.5. Functional connectivity analysis

As previous studies demonstrated individual thalamic sub-regions have associations with multiple cortical networks (Yuan et al., 2016), we applied the thalamic sub-regions rather than the whole thalamus as regions of interest (ROIs) for functional connectivity analysis. Sixteen thalamic ROIs were defined according to a prior brain atlas based on connectional architecture (Fan et al., 2016). The seed-based functional connectivity was analyzed with above 16 ROIs as seeds separately. Firstly, the average time sequence of each seed was obtained. Subsequently, the Pearson's correlation coefficients between time sequence of the seed and that of whole brain other voxels were calculated and further transformed to obtain z-score using Fisher r-to-z transformation. Functional connectivity analysis was performed using the REST Toolkit (http://restfmri.net/forum/REST).

2.6. Statistical analysis

Two sample *t*-tests were performed to compare the differences between the two patient groups at baseline (t_1). Two-way repeated measure ANCOVAs with the between-subject factor group (MSZ vs. DSZ) and the within-subject factor time (t_1 vs. t_2) were conducted. The interaction effect between group and time was estimated to investigate whether two treatment methods bring different alterations on thalamic functional connectivity. Multiple comparisons correction was performed for above analyses based on whole brain functional connectivity maps using a height threshold (min $z > 3.1$) for individual voxel and an cluster size based on Gaussian Random Field theory, which corresponds to cluster-level $P_{corrected} = 0.05/16$ due to 16 seeds (Friston et al., 1994). Based on the above analyses, regions of functional connectivity with significant interaction effects were extracted for post-hoc analysis. Two paired t-tests were used to compare the longitudinal alterations between t_1 and t_2 for each group. Two sample *t*-tests were performed to compare the differences between the two patient groups at baseline (t1). If the baseline functional connectivity showed significant differences between the two patient groups, the functional connectivity at pre-treatment was controlled as a covariate in following repeated measured ANOVA. Differences between patient groups and the HC group were also investigated using independent sample t-tests.

2.7. Correlation between altered functional connectivity and clinical features

The averages of functional connectivity alterations that exhibited significant interaction effects were extracted as the subtraction of coefficients between t1 and t2. As the functional connectivity alterations did not conform to the normal distribution, Spearman correlation analysis was conducted to estimate the relationship between each functional

Table 2
Interaction effect of time by group in term of functional connectivity with thalamic sub-regions as seeds.

Seed	Region	Coordinates (x, y, z)	Interaction effect		
			F value	p value	Cluster-size (mm^3)
STha.R	Putamen	30, 3, −3	18.8	9.5×10^{-5}	1350
RTtha.L	OS	−17, −89, 28	18.1	1.2×10^{-4}	999
cTtha.L	MFG	−39, 45, 27	18.1	1.2×10^{-4}	702
cTtha.R	OS	−18, −90, 27	18.4	1.1×10^{-4}	891

Abbreviation: STha.R, right sensory thalamus; RTtha.L, Left rostral temporal thalamus; cTtha.L, left caudal temporal thalamus; cTtha.R, right caudal temporal thalamus; OS, superior occipital cortex; MFG, middle frontal cortex.

connectivity alteration and clinical variables of symptom remission (PANSS positive, negative, general psychopathology and total reductive scores and ratios) for the MSZ and DSZ group.

3. Results

3.1. Demographic and clinical data

The detailed demographic and clinical data of all subjects are shown in Table 1. The two patient groups show no significant difference in terms of age, gender, years of the education, duration of illness, or daily antipsychotic medication dosage during this study. Additionally, the MSZ and DSZ groups did not show any significant group differences in mean framewise displacement (FD) values or PANSS scores at baseline and after 4-week treatment.

3.2. Functional connectivity analysis: differences between two patient groups at baseline

At baseline, there was no significant difference between two patient groups after the multiple comparisons correction. Even when the threshold was set at an exploratory level ($p < 0.001$, uncorrected), no significant difference between the two patient groups was observed.

3.3. Functional connectivity analysis: interaction effect and post-hoc

The repeated measure ANOVA showed that four functional connections with a significant interaction effect remained after multiple comparisons correction (Table 2 and Table 5). Post-hoc analyses revealed that for the functional connection of right sensory thalamus-right putamen (stha.R-Put.R) in the MSZ group showed significant increase ($T = 3.5$, $p = 0.002$) while the DSZ group showed decrease ($T = -2.3$, $p = 0.03$) after treatment (Table 3 and Fig. 1). In addition, for the functional connections of left rostral temporal thalamus-left superior occipital cortex (rTtha.L-OS.L); left caudal temporal thalamus-left middle frontal cortex (cTtha.L-MFG.L); and right caudal temporal thalamus-left superior occipital cortex (cTtha.ROS.L), the MSZ group showed significant decreases while the DSZ group showed significant increase after treatment (Table 3 and Fig. 1). Controlling the illness course, total medication period, CPZ and number of medication type as covariates also did not change the significance of p value of interaction.

3.4. Functional connectivity analysis: compared with healthy controls

For the seed of right pre-motor thalamus (mPMtha.R), patients showed significantly increased functional connectivity with the left supplementary motor area (SMA.L) compared with HCs (Table 4). In addition, for the seed of cTtha.R, patients exhibited significantly increased functional connectivity with the postcentral gyrus compared with HCs (Table 4). For the other seeds, there were no significant differences between the patients and HCs.

We extracted four FC showing significant interaction of ANCOVA and compared with HC using two-sample *t*-test. Interestingly, the results displayed FC of RTha.L-OS.L ($T = 2.06$, $p = 0.045$) and cTtha.R-OS.L ($T = 3.05$, $p = 0.004$)at baseline (t1) was higher for MSZ group than HC group respectively. And the two over-connectivity were both normalized to be normal after ECT therapy [RTtha.L-OS.L($T = -0.732$, $p = 0.468$); cTtha.R-OS.L($T = 0.889$, $p = 0.379$)] (Fig. 2).

3.5. Relationship between functional connectivity and symptom remission

No significant associations were observed between functional connectivity alterations (four functional connectivity: stha.R-Put.R, rTtha.L-OS.L, cTtha.L-MFG.L and cTtha.R-OS.L) and clinical variables of symptom remission (PANSS positive, negative, general psychopathology and total reductive scores and ratios) in MSZ and DSZ group (all p values >0.05).

3.6. The difference of functional connectivity between refractory and non-refractory individuals within MSZ or DSZ group

We divided patients into two subgroups according to the outcome after the period of treatment whether for MSZ group or for DSZ group, such that refractory subgroup or non-refractory subgroup with 50% reduction rate of total PANSS score as cutoff value (MSR vs MNR: refractory group for MSZ group vs non-refractory for MSZ group; DR vs DNR: refractory group for DSZ group vs non-refractory for DSZ group). Finally, there were 10 responders out of 21 patients in MSZ group and 12 responders out of 21 patients in DSZ group. The ratio of responders to non-responders between MSZ group and DSZ group did not display significant difference. There was no significant difference on demographic and clinical variables between MSR and MNR group or between DR and DNR group (Table 6).

Repeated measured two-way ANOVA was conducted with the between-subject factor (outcome: MSR vs. MNR for MSZ group; DR vs. DNR for DSZ group) and the within-subject factor (time: t1 vs. t2) within MSZ group or DSZ group separately; the interaction effect of outcome and time was used to investigate the specific changes observed among the responders in the MSZ or DSZ group. Two post-hoc paired *t*-tests were separately performed in the MSR and MNR groups or in the DR and DNR groups to detect the longitudinal changes after treatment. For the MSZ group, the results demonstrated that increased FC of right posterior parietal thalamus-right inferior temporal cortex (PPtha.R-Temporal_Inf_R) and PPtha.R-Cerebelum_6_R in MSR group while decreased FC of PPtha.R-Temporal_Inf_R and PPtha.R-Precuceus_R, PPtha.R-Cerebelum_6_R and PPtha.R-Cerebelum_6_L in

Table 3
Functional connectivity changes between t_1 and t_2 in the MSZ and DSZ groups.

Functional connectivity	Change (t_2-t_1): Mean (SE)		Paired t-test: t(p) value	
	MSZ	DSZ	MSZ	DSZ
STha.R-Putamen.R	0.223(0.063)	−0.100(0.043)	3.52(0.002)	−2.30(0.032)
RTtha.L-OS.L	−0.191(0.067)	0.152(0.048)	−2.84(0.010)	3.14(0.005)
cTtha.L-MFG.L	−0.206(0.063)	0.139(0.055)	−3.29(0.004)	2.53(0.020)
cTtha.R-OS.L	−0.118(0.056)	0.197(0.048)	−2.10(0.049)	4.11(0.0005)

Abbreviation: STha.R, right sensory thalamus; RTtha.L, Left rostral temporal thalamus; cTtha.L, left caudal temporal thalamus; cTtha.R, right caudal temporal thalamus; OS, superior occipital cortex; MFG, middle frontal cortex.

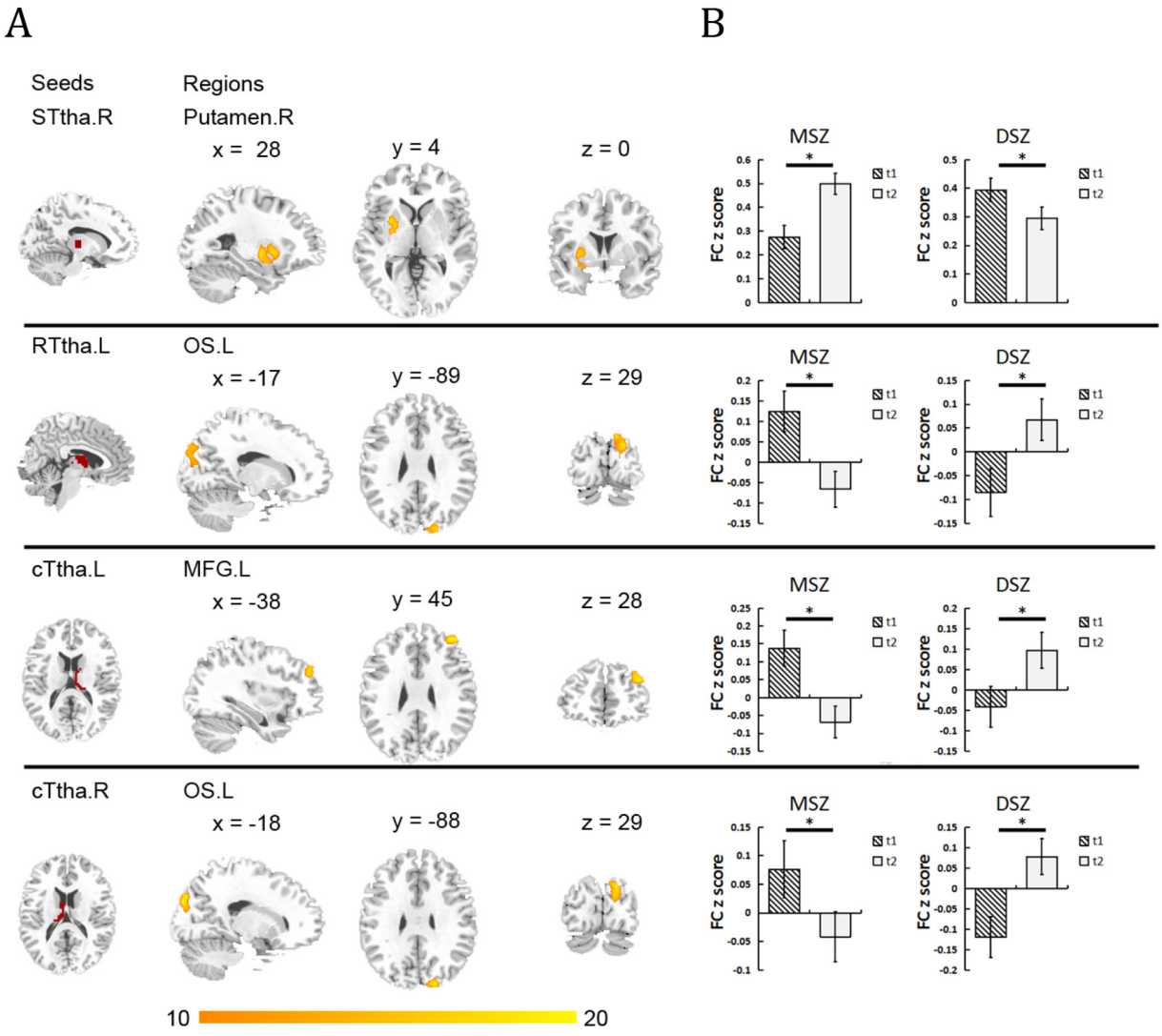

Fig. 1. Interaction effect of time by group in term of functional connectivity with thalamic sub-regions as seeds (A) and functional connectivity changes between t_1 and t_2 in the MSZ and DSZ groups (B). Abbreviation: STha.R, right sensory thalamus; RTtha.L, Left rostral temporal thalamus; cTtha.L, left caudal temporal thalamus; cTtha.R, right caudal temporal thalamus; OS, superior occipital cortex; MFG, middle frontal cortex.

MNR (Fig. 3). For the DSZ group, results demonstrated that increased FC of stha.R-Middle Temporal Gyrus_R in DR group while decreased FC of stha.R-Middle Temporal Gyrus_R in DNR group (Fig. 4).

4. Discussion

The advantage of this study is that including a patient control group taking only antipsychotics contrasting to a patient group receiving mECT combined with antipsychotics , which is important to further clarify the mechanism underlying the ECT for SZ. This is also the first study using ROI approach targeting the thalamus, specifically sub-regions of thalamus to investigate the change of functional connectivity induced by ECT in SZ populations. Contrasting to decreased functional connectivity of stha.R-Put.R (STha.R, right sensory thalamus; Put.R right putamen) in the DSZ group, MSZ group showed significantly increased functional connections after treatment. On the other hand, the MSZ group revealed significant decrease for functional connections of rTtha.L-OS.L (rTtha.L, left rostral temporal thalamus; OS.L, left superior occipital cortex), cTtha.L-MFG.L (cTtha.L, left caudal temporal thalamus; MFG.L, left middle frontal cortex) and cTtha.R-OS.L while the DSZ group showed increased connectivity after treatment. In addition, for the seed of cTtha.R, both patients groups as a whole (DSZ plus MSZ) exhibited significantly increased functional connectivity to the postcentral gyrus compared with healthy control subjects at enrollment.

The key result in this present study, as we hypothesized, was that MSZ group demonstrated significantly enhanced functional connections

Table 4
Differences between all SZ patients and HCs at baseline in term of functional connectivity with thalamic sub-regions as seeds.

Seed	Region	Coordinates (x, y, z)	Two sample t-tests		
			T value	p value	Cluster-size (mm^3)
mPMtha.R	SMA	−9, 15, 66	4.78	1.1×10^{-5}	1215
cTtha.R	Postcentral Gyrus	−48, −18, 36	4.31	5.8×10^{-5}	810

Abbreviation: mPMtha.R, right pre-motor thalamus; cTtha.R, right caudal temporal thalamus; SMA, supplementary motor area.

Table 5
Power analysis of FC changes between t_1 and t_2 in the MSZ and DSZ groups.

Group	FC change	Mean	SD	Effect size	α	Sample size	Achieved power
MSZ	Stha.R-Putamen.R	0.223	0.290	0.769	0.05	21	0.918
	RTtha.L-OS.L	−0.191	0.307	−0.621	0.05	21	0.772
	cTtha.L-MFG.L	−0.206	0.287	−0.717	0.05	21	0.878
	cTtha.R-OS.L	−0.118	0.258	−0.457	0.05	21	0.514
DSZ	Stha.R-Putamen.R	−0.010	0.199	−0.501	0.05	21	0.590
	RTtha.L-OS.L	0.152	0.221	0.686	0.05	21	0.849
	cTtha.L-MFG.L	0.139	0.251	0.552	0.05	21	0.672
	cTtha.R-OS.L	0.197	0.220	0.899	0.05	21	0.975

Abbreviation: STha.R, right sensory thalamus; RTtha.L, Left rostral temporal thalamus; cTtha.L, left caudal temporal thalamus; cTtha.R, right caudal temporal thalamus; OS, superior occipital cortex; MFG, middle frontal cortex.

Table 6
Characteristics of demographic and clinical data in the responders and non-responders for MSZ or DSZ groups.

Characteristic	MSZ: Mean (SD)			DSZ: Mean (SD)			HC (n = 23)
	MSR (n = 10)	MNR (n = 11)	p value [a]	DR (n = 12)	DNR (n = 9)	p value [a]	Mean (SD)
Gender (M/F)	5/5	5/6	0.835[b]	3/9	6/3	0.056[b]	11/12
Age (years)	30.4(7.7)	28.1(6.7)	0.472	31.0(6.6)	30.2(9.5)	0.827	31.2(5.9)
Education (years)	13.8(3.5)	10.9(2.9)	0.052	12.9(3.3)	12.1(2.5)	0.546	13.5(2.5)
Handness (left/right)	0/10	0/11	–	0/12	0/9	–	0/23
Smoking/nonsmoking	2/8	1/10	–	2/10	1/8	–	7/16
Drinking/nondrinking	0/10	0/11	–	0/12	0/9	–	3/20
Family history of schizophrenia (yes/no)	3/7	5/6	–	4/8	2/7	–	0/23
Illness duration (months)	70.3(53.8)	88.4(56.1)	0.462	51.3(76.7)	115.3(75.0)	0.071	–
Chlopromazine equivalents (mg/d)	333.8(218.5)	850.8(675.9)	0.032	406.2(420.5)	701.1(482.4)	0.151	–
Baseline PANSS score							
Total	70.4(6.4)	73.4(10.1)	0.435	68.8(7.7)	73.3(11.8)	0.303	–
Positive	21.8(1.9)	19.6(2.7)	0.051	18.4(3.6)	20.0(3.4)	0.322	–
Negative	17.1(6.3)	21.4(8.0)	0.196	17.3(3.8)	17.6(6.8)	0.925	–
General	31.5(3.7)	32.4(4.0)	0.612	33.0(4.4)	35.8(7.0)	0.277	–
4-weeks PANSS score							
Total	41.6(5.9)	57.1(5.2)	<0.001	42.0(5.3)	61.9(10.3)	<0.001	–
Positive	9.3(1.9)	12.3(3.1)	0.017	8.5(1.4)	16.6(3.4)	<0.001	–
Negative	10.8(3.4)	18.0(6.1)	0.004	12.6(4.0)	16.0(6.4)	0.152	–
General	21.5(2.0)	26.8(1.9)	<0.001	20.9(1.7)	29.2(4.9)	<0.001	–

Abbreviations: MSZ, schizophrenia patients treated by ECT; DSZ, schizophrenia patients treated by antipsychotic drugs; MSR, schizophrenia patients with symptom remission after ECT; MNR, schizophrenia patients without symptom remission after ECT; DR, schizophrenia patients with symptom remission after antipsychotic medications; DNR, schizophrenia patients without symptom remission after antipsychotic medications; HC, healthy controls; PANSS, Positive and Negative Syndrome Scale.
[a] p values were obtained from the two sample t-test except where noted.
[b] p values were obtained using the chi-square test.

of stha.R-Put.R after about 4-week treatment in contrast with DSZ group. This change could be in part due to the mechanisms of ECT since the two groups did not vary in terms of antipsychotic usage, but may also illustrate changes due to the interaction of ECT and antipsychotics. In our results, we confirmed ECT-related brain plasticity and extended the involved brain regions to the thalamus. There has been plenty of evidence that the thalamus or thalamic connectivity is aberrant in SZ (Cronenwett and Csernansky, 2010; Giraldo-Chica and Woodward, 2017; Glahn et al., 2008b; Pergola et al., 2015; Sim et al., 2006). Some reports reported that patients with SZ had smaller-than-normal grey matter volumes in the thalamus (Glahn et al., 2008a; McCarley et al., 1999; Okada et al., 2016; Shenton et al., 2001). Decreased expression of NAA, the neurochemical markers of neuronal integrity, in the thalamus for SZ had also been found by some studies (Kraguljac et al., 2012). In addition, in previous studies, diminished resting-state thalamic-PFC functional connectivity and increased thalamic-somatomotor connectivity have been among the most replicable findings in patients with SZ (Giraldo-Chica and Woodward, 2017).

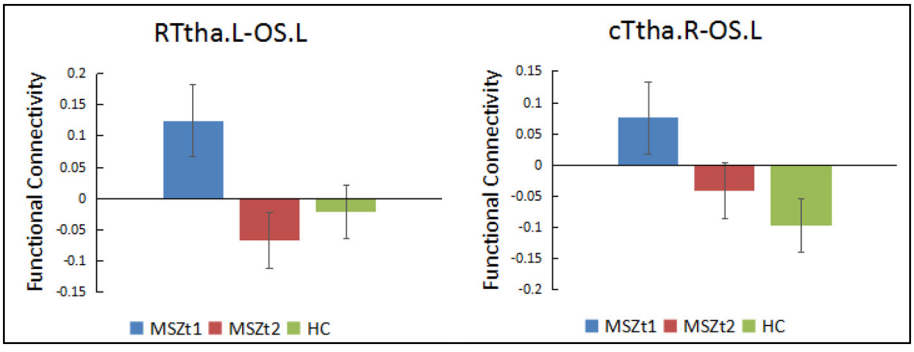

Fig. 2. Comparison of thalamic functional connectivity showing significant interaction of group by time between each patient group and HC group. Abbreviation: RTtha.L, Left rostral temporal thalamus; cTtha.R, right caudal temporal thalamus.

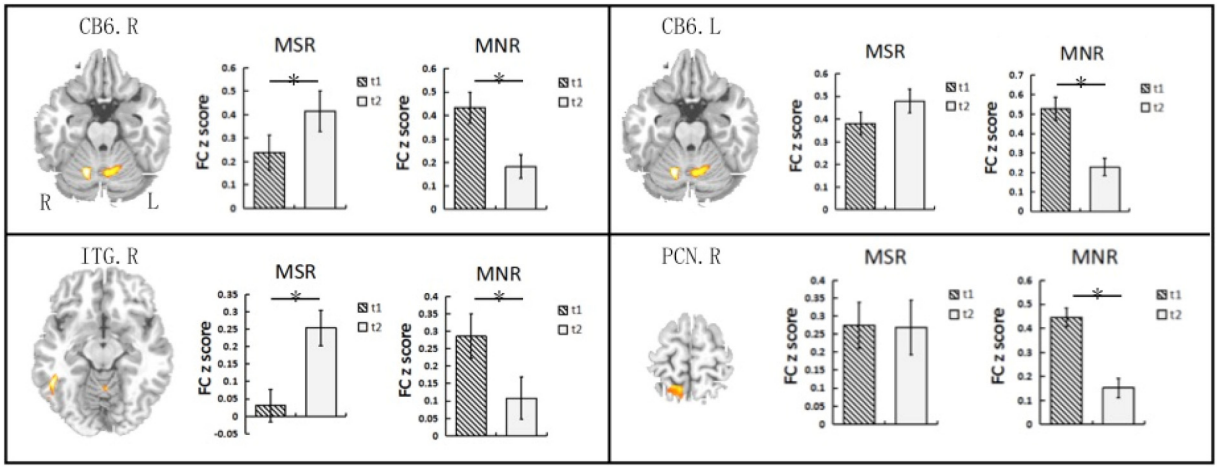

Fig. 3. Longitudinal changes of the thalamic functional connectivity after the pharmacological treatment (A) in the MSR group and (B) in the MNR group. Abbreviation: MSR, schizophrenia individuals with symptom remission after ECT; MNR, schizophrenia individuals without symptom remission after ECT. PPtha.R, Right posterior parietal thalamus; CB6.R, Right cerebellum_6; CB6.L, Left cerebellum_6; ITG.R, Right inferior temporal; PCN.R, Right precuneus.

Therefore, it seems reasonable that efficacious therapeutic mechanisms for SZ may involve structural, functional, or biochemical change in the thalamus. However, the brain regions with altered functional connectivity to thalamus in this study were not located in those most reported compromised ones such as PFC or somatomotor, but instead the putamen. Whereas, Welsh et al. found dysfunctional connectivity patterns of cortical-thalamo-striato-cortical circuitry in terms of decreased thalamo-cortical and thalamo-striatal functional connectivity in resting-state functional MRI (fMRI) for SZ using the mediodorsal nucleus (MD) as a seed region (Woodward et al., 2012). Therefore, the observation of mECT-induced increased thalamo-putamen functional connectivity is not un-expected.

Results that the MSZ group revealed a significant reduction with respect to functional connectivity of rTtha.L-OS.L, cTtha.L-MFG.L and cTtha.R-OS.L while the DSZ group showed increased connectivity after treatment was another important finding in this study. Notably, this is the first report of reduced thalamocortical functional connectivity (rTtha.L-OS.L, cTtha.R-OS.L, cTtha.L-MFG) in patients with SZ after ECT to our limited knowledge. As mentioned in the introduction of this article, hyper-functional connectivity between thalamus and somatomotor cortex has been observed in SZ (Giraldo-Chica and Woodward, 2017). The most striking evidence was that Anticevic et al. documented that thalamic hyper-connectivity extended to sensory cortical areas, including the superior temporal gyrus and occipital lobe in SZ (Anticevic et al., 2014). Therefore, decreased functional connectivity of thalamus-occipital areas (rTtha.L-OS.L, cTtha.R-OS.L) in SZ patients could be a potential mechanism of mECT in combination with antipsychotics.

There might be a shared mechanism treating SZ targeting the cortico-striato-thalamo-cortex (CSTC) loop whether for the ECT or for the antipsychotics considering converging evidence suggesting the importance of CSTC loop for psychiatric disease including SZ. Sarah Peters et al. reviewed and concluded the cortico-striato-thalamo-cortical loop increasingly appears to be central to mechanisms of cognitive control, as well as to a broad spectrum of psychiatric illnesses and their available treatments. Functional imbalances within the loop appear to impair cognitive control, and thereby leading to symptoms of psychiatric illness. Furthermore, treating such psychiatric illnesses using invasive or non-invasive brain stimulation techniques appears to modulate cortical-subcortical loop integrity, and these effects may be central to the therapeutic mechanisms of brain stimulation treatments in many psychiatric illnesses (Peters et al., 2016). Our findings seemly supported the viewpoint of Sarah Peters. In the present study, these two aforementioned key results are just opposite in MSZ and DSZ groups, that is, increased inner functional connectivity within subcortical nucleus (thalamus-putamen) along with decreased cortical-subcortical connectivity (rTtha.L-OS.L, cTtha.R-OS.L and cTtha.L-MFG) in MSZ, whereas decreased former and increased latter in the DSZ group. These opposing changes may differentiate the effects of mECT from antipsychotics alone. These two results when taken together may suggest a balance to maintain the normal activity in the circuit of CSTC. MECT and

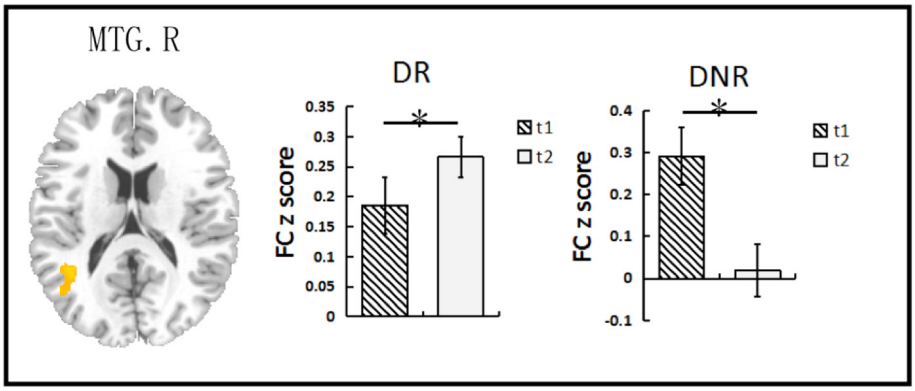

Fig. 4. Longitudinal changes of the thalamic functional connectivity after the pharmacological treatment (A) in the DR group and (B) in the DNR group. Abbreviation: DR, schizophrenia individuals with symptom remission after antipsychotics treatment; DNR, schizophrenia individuals without symptom remission after antipsychotics treatment. MTG.R, Right middle temporal gyrus.

antipsychotics could work to renormalize this balance through separate pathways. Increased functional connectivity of the thalamus-putamen area and decreased functional connectivity of the thalamus-cortical region in MSZ, may function similarly to the decreased connectivity of the thalamus-putamen and increased connectivity of thalamus-cortical region in DSZ, as both restored the connection of balance between thalamus to basal ganglion and the thalamus to cortical cortex. These alterations in connectivity may renormalize the overall connectivity strength of the basal ganglion to the cortex in the CSTC loop. In this present study, most of the patients were prescribed atypical antipsychotics and a few were taking typical antipsychotics. Previous studies have demonstrated different effects between these two kinds of antipsychotics. Usage of second-generation atypical antipsychotics has been reported to increase the volume of the thalamus and cortical grey matter, although it might not affect volume of basal ganglion, and may also help ameliorate volume increase of the basal ganglion caused by typical antipsychotics (Scherk and Falkai, 2006). Prior research has shown that antipsychotic drugs decrease the functional connectivity of the medial frontal cortex to hippocampus or nucleus accumbens after about 6 weeks medication (Bolding et al., 2012). Here, we extended findings of functional connectivity changes to the thalamus. Similar to previous reports of increased volume of the thalamus and cortical regions by atypical antipsychotics (Scherk and Falkai, 2006), an increased functional connectivity of thalamus to occipital and frontal cortex (rTtha.L-OS.L, cTtha.R-OS.L, cTtha.L-MFG) was shown in the DSZ group. Given that various antipsychotics have different pharmacokinetics, the alteration of functional connectivity observed in this study is a product of the heterogenous usage of antipsychotics in the DSZ. Precise features of action for each antipsychotic could not be explained in this current study, but may be addressed through a more specifically designed psycho-pharmacological investigation.

Overall, our findings showed an interesting point, that is, increased correlation of intra-subcortical nucleus (thalamus-putamen), paralleling with alteration from correlation into anticorrelation of cortical-subcortical nucleus (rTtha.L-OS.L/cTtha.R-OS.L/cTtha.L-MFG-thalamus) in MSZ, however, decreased correlation of intra-subcortical nucleus, paralleling with alteration from anticorrelation into correlation of cortical-subcortical nucleus in DSZ. This suggests distinct neural mechanism targeting cortical or subcortical network underlying the action on of ECT or interaction of ECT with antipsychotics from antipsychotics. All roads lead to Rome, the patients of two groups both showed clinical improvement which might by acquired via a potential basis restoring a balance between thalamus-subcortical and thalamus-cortical connectivity.

Despite results illustrating the differences between altered functional connectivity after mECT and pharmacological treatment, we did not identify any significant correlation of changes to improvement of clinical features in either the MSZ or DSZ group in this study. There was lack of consistent findings on correlations of hippocampal structural plasticity with treatment response in MDD in the previous literature, some found correlations (Abbott et al., 2014; Joshi et al., 2016) but some did not observe it (Bouckaert et al., 2016; Ota et al., 2015; Sartorius et al., 2016; Tendolkar et al., 2013; Thomann et al., 2017; Wolf et al., 2016). In addition, Liu et al. linked antidepressant effect of ECT to connectivity of subgenual anterior cingulate (Liu et al., 2015). In SZ, Thomann et al. did not link ECT-related hippocampal structural or functional plasticity to clinical measure (Thomann et al., 2017), although Robert et al. reported volume increase of lateral prefrontal/cingulate cortical network was accompanied by clinical improvement (Wolf et al., 2016). In our published article, we did not find a relationship between functional connectivity and clinical change (Huang et al., 2017), while we did relate hippocampal volume change to clinical improvement after ECT using the same sample as this article (Wang et al., 2019). This implied difference in mechanism of functional and anatomical plasticity induced by ECT or difference in mechanism of ECT for SZ and MDD or specificity in mechanism of ECT-related brain region. Other explanations for the absent relationship between treatment effect and thalamic functional connectivity may be plausible as well. For instance, as discussed by Robert et al. it is possible that these clinical measures assessed by PANSS may not fully capture improvement of specific symptom dimensions, such as e.g. cognition or affective processing or disorganized thoughts (Wolf et al., 2016). Taken together, the most marked differences in terms of functional connectivity between MSZ group and DSZ group might only be the underlying mechanism of action of ECT or antipsychotics, but which might not directly correlate to improvement of psychosis. ECT is not sufficient to explain clinical benefits, so that other neural mechanisms of action must exist which underpin more directly the effect of treatment on clinical response. This issue could shed light on a future study with larger sample size.

Relative to the HCs, patients from both MSZ and DSZ exhibited significantly increased functional connectivity of right caudal temporal thalamus with the postcentral gyrus, the motor areas. These results replicated previous findings (Anticevic et al., 2014; Cheng et al., 2015), and added evidence to that thalamocortical functional dysconnectivity is a core neurobiological abnormality in SZ as suggested previously by Giraldo-Chica and Woodward (Giraldo-Chica and Woodward, 2017).

To better understand the possible neural mechanisms in ECT and pharmacological treatment, we explored to compare between refractory and non-refractory individuals and observed increased FC of thalamus to temporoparietal region and cerebellum among responders and decreased FC of thalamus to cerebellum among non-responders for MSZ group. For the DSZ group, we found increased FC of thalamus to temporal region among responders and decreased FC of thalamus to temporal region among non-responders. These results showed that although FC observed increased in both two responders groups after two treatments, specific areas of FC increase are different in ECT and pharmacological treatment groups, this may be due to different neural circuits affected by ECT and antipsychotics. This deserves further investigation. In addition, only one of 21 patients in the MSZ group was drug no-refractory, which made us unable to further analyze the difference of mechanism between those drug-resistant and non-drug resistant. However, the difference of mechanism between those drug-resistant and non-drug resistant deserves further exploration using subgroup in the following studies after enlarging the sample pool.

5. Limitation

There are several limitations in our study. Firstly, the usage of antipsychotics medicine might be a confounding factor due to substantial heterogeneity in pharmacological treatments employed in both patients groups. Variations in antipsychotic usage may also introduce variability in terms of the interaction between mECT and specific drugs, further confounding an already diverse disease. Changes here ascribed to mECT, may therefore in part embody these interactions instead. Secondly, the relatively modest sample size in this study might produce relative weaker statistical power, restricting the regions identified in this study. Thirdly, the healthy control subjects were only scanned once, which makes us unable to perform longitudinal comparison of functional connectivity between healthy control subjects and patients with SZ. Fourthly, we did not find correlations between FC and clinical variable, which might be due to small sample, individual difference, impact of antipsychotics and heterogeneous symptoms, etc. It is possible that the differences found between, the MSZ and DSZ groups are simply ECT epiphenomena - for example it could be related to side effects. Unfortunately, we did not design to assess the side effect of ECT in this study at the start of the project and unable to analyze the correlation between FC and side effect. However, to our limited knowledge, this still makes it a possible evidence for mechanism not confirmatory in the absence of correlation with clinical scores. Fortunately, we are still conducting the following studies, and we would improve the experimental design including assessment of side effect. In the near future, we might find and present more convincing powerful results including

addressing this question. Fifthly, 4 weeks trail is still not adequate trial with antipsychotic to see all possible changes in functional connectivity. It may be far-fetched for investigating the effect of ECT in a patient with only 8–12 ECT. However, from clinical experience, most of the patients did show alleviation of symptoms after 6–8 ECT generally, in our study, most of the patients underwent more than 10 ECT and showed amelioration of symptom, which made us believe that there must have occurred some alteration in the brain through some unique mechanisms underlying ECT worth being explored. Clinically, guardians of patients or attending physician chose to stop ECT therapy but to continue antipsychotics alone therapy after a rapid amelioration of symptom generally after about no more than 12 ECT, which made us unable to observe for a longer period in this present observational study. Some previous studies investigating the action of ECT also found some significant results, in which number of conducted ECT for the patients also was 8–12 generally. We will longitudinally investigate the effect of longer ECT therapy in the following studies. Lastly, treatment selection in this study was non-random, but as the study was observational in nature, treatment was recommended by the physician consulting from the patient or family. The effectiveness of ECT, however, is not in specific doubt, and the purpose of this study was to identify mechanisms related to ECT therapy, therefore patients elected for participation based on physician determination that the treatment course was appropriate for them as is their ethical obligation. Despite this, because the study was not conducted in such a manner, effects related to the expectation of successful treatment and other patient attitudes may not be properly accounted for. A randomized study may be necessitated to more properly control for other non-therapeutic factors that may influence the results.

6. Conclusions

Significantly enhanced thalamic-putamen functional connectivity and reduced thalamic-sensory cortex connectivity were observed in SZ patients treated with mECT in combination with antipsychotics compared to those undergoing antipsychotic therapy alone. These findings indicate that changes to the functional connectivity of the thalamus might be relevant to mechanisms underlying the effect of mECT.

Authors' contributions

Junjie Wang who was the first author contributed to the data acquisition and writing of the first draft manuscript.

Yuchao Jiang who was the co-first author contributed to the data analysis and manuscript writing.

Yingying Tang who was the co-corresponding author contributed to the experimental design, data acquisition and interpretation of the results.

MengQing Xia, Jin Li, Jianhua Sheng, Tianhong Zhang , Li Hui , Hongliang Zhu all contributed to the recruitments of and clinical assessments.

Chunbo Li, Bharat B. Biswal and Jijun Wang all contributed to the interpretation of the results.

Adrian Curtin contributed to edition of the manuscript and interpretation of the results.

Qiufang Jia who was the corresponding author contributed to the experimental design and data interpretation.

Cheng Luo who was the co-corresponding author contributed to edition of the manuscript and data interpretation.

All authors have contributed to and approved the final manuscript.

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Declaration of competing interest

The authors report no conflicts of interests.

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