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ECT-induced brain plasticity correlates with positive symptom improvement in schizophrenia by voxel-based morphometry analysis of grey matter

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ABSTRACT

Background: Electroconvulsive therapy (ECT) is often considered as an augmentation of antipsychotic treatment for schizophrenia in drug-refractory cases. However, the mechanisms underlying the observed therapeutic effects are still not understood.
Objective: We aimed to investigate changes in whole brain grey matter volume (GMV) before and after modified ECT. GMV was determined using voxel-based morphometry (VBM) whole brain analysis. Correlations of brain structural changes with clinical improvement were also investigated.
Methods: Twenty-one schizophrenia patients treated with a full course of ECT combined with antipsychotics (ECT group) and 21 schizophrenia patients treated only with antipsychotics (Drug group) were observed in parallel. Magnetic resonance imaging scans were performed at baseline (T1) and follow-up (T2) for each patient. Data were compared to a healthy control group (HC group) of 23 persons who were only scanned at baseline. Demographic data were matched between the three groups.
Results: Significant interactions of group by time were found within four brain regions: the left parahippocampal gyrus/hippocampus, right parahippocampal gyrus/hippocampus, right temporal_pole_mid/superior temporal gyrus, and right insula. Post-hoc analysis revealed an increase of GMV across all four regions amongst ECT group, but a decrease of GMV within the Drug group. Furthermore, the ECT group showed a significant positive correlation of GMV change in the right parahippocampal gyrus/hippocampus with a reduction of positive subscore in the positive and negative syndrome scale. Both treatment groups did not differ significantly in terms of GMV from the HC group in these regions either at T1 or at T2.
Conclusion: Our findings indicate that ECT may induce brain plasticity as indexed by grey matter volume change during the treatment of schizophrenia via distinct mechanics from those by antipsychotic medications. ECT may ameliorate the positive psychotic symptoms of patients suffering from schizophrenia by preferentially targeting limbic brain areas such as the parahippocampal gyrus/hippocampus.

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Introduction

Schizophrenia (SZ) is a devastating psychiatric disorder that affects about 1% of the population and is one of the top ten causes of disability worldwide [37]. This disorder is typically characterized by psychotic features such as delusion, hallucination, and disorganized behavior due to reduced ability of reality testing, which is the ability to differentiate internal stimuli (thoughts and feelings) from external perception. In spite of the introduction of effective antipsychotic medications, 20–30% of patients with SZ fail to obtain remission from psychosis [26]. Physical therapies may provide an additional avenue of treatment for individuals whom antipsychotic treatment alone is ineffective. Electroconvulsive therapy (ECT) has been shown to be generally safe and effective in SZ, particularly in cases of resistance to drug treatment or when rapid symptom reduction is needed. In some developing countries, ECT is viewed as a first-line treatment of severe psychosis when symptoms require hospitalization [34]. Despite a history of usage in psychiatry, the precise mechanisms of action for ECT remain poorly understood.

ECT treatment typically mirrors the effectiveness of antipsychotic drugs at reducing the magnitude of psychotic symptoms, but ECT's effectiveness in patients who are antipsychotic-refractory suggests a unique or preferential mechanism of action for some patients [34]. ECT has been proposed to act by modulating local brain plasticity by stimulating neurogenesis in combination with other molecular mechanisms such as synaptogenesis, gliogenesis or angiogenesis [7]. In animal studies of rodents and non-human primates, neurotrophic effects of electroconvulsive stimulation (ECS), the animal analog of human ECT, have been observed to exist in the frontal cortex [23] and in the medial temporal lobe [15,25,30]. Other animal studies have shown ECS may also promote the maturation of dendritic spines and increase spine density [44].

In patient populations, it has been postulated that ECT may also exert neurorestorative effects due to its reported ability to increase the levels of hippocampal neurotrophic factors [35]. Several works have reported neurotrophic effects of ECT in MDD and SZ populations on peripheral brain-derived neurotrophic factor (BDNF) levels [5,22]. Recently, using a proton magnetic resonance spectrum (^{1}H MRS) technique, Gan et al. found that modified ECT could significantly raise N-acetylaspartate (NAA) concentration, an indicator of neural structural and/or functional integrity, in the left prefrontal cortex (PFC) and left thalamus of ECT-treated SZ group relative to patients undergoing exclusive antipsychotic treatment [14].

In line with the observation of structural changes due to ECS and neurotrophic factors in ECT, several studies have reported ECT-induced volume changes in the medial frontal regions and hippocampus in patients undergoing treatment for major depression disorder (MDD) [1,6,27,29,38]. While it is reasonable to suggest that structural changes induced by ECT might also exist in distributed brain regions in SZ, relatively fewer neuroimaging studies have been conducted in schizophrenic populations. To our knowledge, only one study has investigated ECT-related brain structural changes in an SZ patient population, in which associated changes in SZ patients were compared to changes in MDD patients undergoing the same treatment. Wolf and Thomann et al. analyzed these changes using two different neuroimaging analysis approaches to quantify structural volume, source-based morphometry (SBM) and voxel-based morphometry (VBM) based on region-of-interest (ROI), and demonstrated that ECT was associated with both diagnosis-specific and trans-diagnostic structural changes for MDD and SZ [39,42]. Using the SBM method, they documented that medial temporal lobe (MTL) network regions, including the hippocampal and parahippocampal cortex, showed a significant volume increase attributed to ECT in both diagnostic groups. In MDD, a network called ACC/MPFC comprising the anterior cingulate cortex (ACC) and medial prefrontal cortex (MPFC) showed a grey matter volume (GMV) increase following ECT. However, a left dorsal lateral prefrontal cortex (DLPFC) network showed a GMV increase in SZ after ECT and linked this increase to reduction of PANSS total scores [42] In second work, they reported ECT-induced volumetric increases in the amygdala of both MDD and SZ patients, as well as an increase in the right insula in SZ patients as quantified by VBM [39]. However, a limitation of their study was the relatively small sample size of 9 SZ patients, all of which were receiving simultaneous ECT and antipsychotic therapy, leaving open the question as to whether the observed GMV changes can be disentangled from the impact of concurrent antipsychotic treatment. Therefore, further investigation was necessary in order to distinguish changes attributed to exclusive antipsychotic therapy with the effect of ECT.

In the present study, we investigated two groups of patients with SZ, one patient group received a course of ECT in conjunction with antipsychotic therapy, and the other patient group only received antipsychotic treatment. This study was constructed to compare changes that might be attributed to antipsychotics with those that might be attributed to hybridized therapy. Clinical status and structural MRI measurements were obtained at two time points (baseline, T1 and follow-up, T2, after about 4 weeks of management of acute psychosis). The aims of our study were: (1) to examine changes in regional GMV across the entire brain associated with ECT therapy using VBM method; and (2) to explore the correlations of these brain structural changes with clinical improvement. We hypothesized that the regional volume of the limbic structures, in particular the hippocampal and adjacent regions, should increase after the ECT treatment. Additionally, we expected that these regional volume changes would be related to the improvement of clinical symptoms.

Methods

Subjects

Forty-two inpatients with SZ were recruited from the Shanghai Mental Health Center (SMHC). All patients met criteria for SZ or schizoaffective disorder based on the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) [11] as conducted by senior psychiatrists. The severity of psychotic symptoms was assessed by the Positive and Negative Syndrome Scale (PANSS) [20]. All patients had a total PANSS score of 60 or more and had not received ECT during the past six months.

The allocation of patients was non-randomized. Two groups of inpatients with acute schizophrenia were recruited in parallel. Patients who were identified as medication-resistant according to their prior treatment history and with whom informed consent on ECT was obtained from each patient and his/her family were considered to be eligible for to receive four weeks of ECT in combination with antipsychotics (ECT group, $n = 21$). Patients who were not medication-resistant or did not agree to receive ECT were treated with only antipsychotics (Drug group, $n = 21$). Both groups were matched according to gender, age, education levels and baseline PANSS scores. The exclusion criteria included 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. The majority of patients were prescribed multiple atypical antipsychotics. Among the ECT group, 3 were taking one antipsychotic, 12 were taking two antipsychotics, and 6 were taking three antipsychotics. Among Drug group, 10 were taking one antipsychotic, 10 were taking two antipsychotics and 1 was taking three antipsychotics. Clozapine was prescribed for 2 patients in the Drug group

and 5 patients in the ECT group. The daily dose of antipsychotics for each patient was converted into chlorpromazine equivalents [43]. Both the Drug and ECT groups continued their current antipsychotic therapy throughout the course of the study and apart from experimental inclusion in ECT treatment patients did not receive any additional intervention.

A healthy control sample (HC group, n = 23) was recruited from the community by advertisement and matched to both patient groups by age, gender, and educational level. Controls reported neither lifetime psychiatric disorder nor a family history of psychosis in their first-degree relatives. Otherwise the exclusion criteria remained the same as patient groups.

The study protocol was approved by the ethics committee of SMHC, and was performed in compliance with local regulations and the principles expressed in the Declaration of Helsinki. All the participants gave written informed consent after being provided with a detailed description of the study.

Electroconvulsive therapy

The ECT group was treated with bitemporal ECT between 08:00 a.m. to 11:00 a.m. using a Thymatron IV instrument (Somatics, Lake Bluff, IL, USA). Two stimulus electrodes were placed on the left and right temporal scalp. Anesthesia was performed with intravenous propofol (1.82–2.44 mg/kg) and etomidate (0.21–0.3 mg/kg), succinylcholine (1.0 mg/kg) was used for muscle relaxation, and atropine (0.5 mg) was administrated to reduce airway secretion. Patients were pre-oxygenated and then manually ventilated for the duration of anesthesia. Initial electrical dose was determined as 2/3 of patients' age [31] and subsequent dosing was determined according to seizure morphology adequacy. The main ECT parameters were as following: maximum charge delivered, 504 mC; output current, 0.9A; frequency, 10–70 Hz; pulse width, 1.0 ms; maximum stimulus duration, 8 s.

Electroencephalogram (EEG) seizure was monitored to ensure adequate duration and quality. ECT was delivered 3 times per week, lasting for 4 weeks. Prescribed antipsychotic medications were unchanged during the whole ECT treatment except for abstaining from pharmacotherapy in the morning on the day of ECT. The total number of ECT sessions was determined individually based on both the therapeutic efficacy and adverse events by the clinical psychiatrist. In the current study, one regular course of ECT includes 8–12 ECT sessions. Of 21 patients in ECT group, 16 received 12 ECTs, 1 received 11 ECTs, 3 received 10 ECTs, and 1 received 8 ECTs. The mean number of ECTs was 11.5 ± 1.1.

MRI data acquisition and processing

The patients in the ECT group were scanned twice: 24 h before the first ECT session (T1, pre-ECT), and 24–48 h after completion of last ECT session (T2, post-ECT, ~4 weeks). Patients in the Drug group also were scanned twice with an interval of 4 weeks apart. HC subjects were scanned once at baseline. During scanning, subjects were instructed to keep their eyes closed and awake, not to focus their thoughts on anything in particular. Additionally, all the patients underwent a clinical PANSS assessment at both baseline (T1) and follow-up (T2) time points.

Structural MRI acquisition

Structural MRI scans were acquired on a 3-Tesla scanner (Siemens VerioSyngo MR B17) with a 32-channel head coil. Head position was fixed with foam padding to minimize movement. All data were acquired using a 3D T1-weighted magnetization prepared rapid gradient echo (MPRAGE) sequence (TR = 2530 ms, TE = 2.56 ms, field of view = 256 × 256 mm^2, matrix size = 256 × 256, flip angle = 7°, slice thickness = 1.0 mm, 224 contiguous slices, voxel size = 1.0 × 1.0 × 1.0 mm^3).

Image preprocessing

All image-preprocessing steps were carried out using the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm.html) and SPM8 software package (Statistical Parametric Mapping software: www.fil.ion.ucl.ac.uk/spm) implemented in Matlab, 2011b (MathWorks, Natick, MA). First, the images were visually inspected by experienced member (Y. Tang) for the presence of any artifacts which would prevent further analyses. Then, the 3D-MPRAGE series of images were manually reoriented to the anterior-posterior commissure (AC-PC) line. The following preprocessing steps were divided into two pipelines for longitudinal and cross-sectional analysis using the method described by Takeshi Asami et al. [3].

(1) The longitudinal pipeline was used for the comparison of two patient groups, consisting of within-subject midway coregistration to account for baseline-to-follow-up variance, automated tissue classification, and spatial registration followed by scaling with the Jacobian determinants [3,40]. The DARTEL (Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra) approach was used to enable a more accurate spatial normalization [4], building a study-specific template created from images of all subjects at two time points. These images were affine transformed to MNI (Montreal Neurological Institute) space, and finally, maps of GMV were smoothed with a Gaussian kernel of 8-mm FWHM (full-width-at-half-maximum) [3].
(2) The cross-sectional pipeline was conducted for comparison between each patient group and healthy controls group, comprising the procedures undertaken in the longitudinal pipeline except for the use of an individualized baseline-to-follow-up DARTEL-based template [3].

Statistical analysis

Statistical Analysis of Imaging Data Statistical analysis of whole-brain imaging data was calculated in the SPM8 software package (www.fil.ion.ucl.ac.uk/spm) implemented in Matlab 2014A (MathWorks, Natick, MA). Analysis of regions of interest (ROI) was performed using the SPSS 20.0 software package (www.spss.com/statistics).

Whole-Brain Analysis (1) To investigate regional structural changes, we created a full factorial design matrix with the factors group and time, where group (ECT *vs.* Drug) was a between-subject factor and time was a within-subject factor. (2) A general linear model was separately employed for estimating cross-sectional differences in regional GMV between each patient group and the healthy control group at baseline and at follow-up time point using an independent-sample *t*-test. In designing matrices, total intracranial volume was included as covariate to control for the effects. Results were evaluated at cluster-wise $p < 0.05$ family-wise error (FWE) correction with a cluster extent threshold of 215 consecutive voxels.

ROI Analysis The MarsBar 0.43 toolbox [24]was used to extract GMV (based on the peak coordinates of the above analyses) of brain regions showing significantly statistical interactions of group by time or main effect of time observed from the whole-brain analysis. Anatomic locations of designated ROIs were located with xjview software (http://www.alivelearn.net/xjview). In order to compare the change rate of GMV in these brain regions between the two patient groups, the independent-sample *t*-test was used. If the difference was significant, this indicated ECT intervention produced differential structural changes in terms of GMV compared to

antipsychotics treatment alone. A paired-sample *t*-test was used to compare the GMV at pre- and post-treatment within each patient group and evaluate the change trends within each group.

Correlation Analysis The relationship between clinical psychopathology scores and GMV changes was assessed using Pearson's production correlation coefficients r or Spearman's correlation coefficients ρ accordingly after being evaluated for normality with the Kolmogorov-Smirnov test. Significant correlations were determined using a threshold of $p < 0.05$ (two-side) after Bonferroni correction for multiple comparisons.

Results

Demographic and clinical variables

There were no significant differences in the age, education degree, and gender among the three groups. Additionally, there were no significant differences between ECT and Drug groups in the illness duration, chlorpromazine equivalent and PANSS score at baseline (See Table 1). The details of antipsychotics usage in patients of two groups were shown in Table 2.

Improvements in PANSS total score and subscale scores of positive, negative, and general symptoms (calculated as ($PANSS_{Baseline}$ - $PANSS_{FollowUP}$)/$PANSS_{Baseline}$) were observed in both ECT and Drug groups over time (ECT group: $t = 11.78$, $t = 11.80$, $t = 4.82$, $t = 7.73$, all $p < 0.001$; Drug group: $t = 8.22$, $t = 7.71$, $t = 5.27$, $t = 8.71$, all $p < 0.001$). However, no differences between ECT and Drug groups were found in magnitude of reduction or in the numeric PANSS total scores or the positive, negative and general subscales at either T1 or T2 (all $p > 0.1$).

Interaction of group by time on the whole-brain GMV

Full factorial analysis did not show a significant main effect of group or time on regional GMV corrected with FWE. However, there was a significant interaction of group by time in four clusters including the left parahippocampal gyrus/hippocampus, the right temporal_pole_mid/superior temporal gyrus, the right parahippocampal gyrus/hippocampus and the right insula (See Fig. 1) after cluster-level FWE correction with $p < 0.05$. Therefore, these four clusters with significant interactions of group by time were chosen as ROIs for the following analyses (See Table 3).

Left parahippocampal gyrus/hippocampus ROI analysis did not show a main effect for either group ($F = 1.080$, $p = 0.305$) or time ($F = 3.691$, $p = 0.062$) on GMV, however, the interaction of group by time was significant ($F = 24.257$, $p < 0.001$). Similarly, for the three remaining ROI sites, the interaction of group by time was significant (right temporal_pole_mid/superior temporal gyrus, $F = 16.740$, $p < 0.001$; right parahippocampal gyrus/hippocampus, $F = 24.905$, $p < 0.001$; right insula, $F = 18.748$, $p < 0.001$). For these three ROIs, neither the effect of group nor the effect of time was significant.

Cross-sectional GMV differences between ECT and drug groups

At baseline, post-hoc independent-sample t-tests revealed that the GMV of both the left and right parahippocampal gyrus/hippocampus amongst ECT group were significantly smaller than those among Drug group (left parahippocampal gyrus/hippocampus, $p = 0.006$; right parahippocampal gyrus/hippocampus, $p = 0.003$). The GMV of the right temporal_pole_mid/superior temporal gyrus did not show any between-group difference ($p = 0.116$) and neither did the GMV of the right insula ($p = 0.338$).

At follow-up, these between-group differences in GMV were not significant for either the left and right parahippocampal gyrus/hippocampus ($p = 0.231$ and $p = 0.069$). However, the GMV of the temporal_pole_mid/superior temporal gyrus ($p = 0.011$) and right insula ($p = 0.010$) were larger amongst the ECT group than the Drug group.

Longitudinal GMV changes within ECT and drug groups

Within the ECT group, post-hoc paired-sample t-tests demonstrated that the GMV increased significantly at follow-up compared to baseline in each of the four ROIs: the left parahippocampal gyrus/hippocampus (T1, 0.6449 ± 0.0429, T2, 0.6877 ± 0.0445, $p < 0.001$), right temporal_pole_mid/superior temporal gyrus (T1,

Table 1
Demographic and clinical information [mean (SD)].

Characteristic	ECT	Drug	HC	p value amongst 3 groups	p value[a] between ECT&Drug groups
Group size	21	21	23		–
Age (years)	29.2(7.1)	30.7(6.9)	31.2 ± 5.9	0.61	0.52
Gender (M/F)[b]	10/11	9/12	11/12	0.93	0.76
Education (years)	12.3(3.4)	12.6(2.9)	13.5 ± 2.5	0.38	0.77
Handness (left/right)[b]	0/21	0/21	0/23	–	–
Smoking/nonsmoking[b]	3/18	3/18	7/16	0.30	1.00
Illness duration (months)[c]	79.8(54.4)	78.7(80.9)	–	–	0.43
Number of failed antipsychotic trials	3.1(1.1)	2.5(1.1)	–	–	0.08
Duration of prior medications (months)	3.9(1.3)	2.8(1.4)	–	–	0.27
Reason for changing medications	poor response	poor response or intolerance	–	–	–
Interval of scans (days)	36.1(10.2)	35.3(14.6)	–	–	0.83
Total number of ECT	11.5(1.1)	–	–	–	–
Chlorpromazine equivalents (mg/d)[c]	604.6(565.6)	532.6(461.2)	–	–	0.50
T1-PANSS score					
T1-PANSS Total	71.6(8.4)	70.8(9.7)	–	–	0.67
T1-PANSS Positive	20.7(2.6)	19.1(3.5)	–	–	0.11
T1-PANSS Negative	19.3(7.4)	17.4(5.1)	–	–	0.34
T1-PANSS General	32.0(3.8)	34.2(5.7)	–	–	0.14
4-week PANSS score				–	
T2-PANSS Total	49.7(9.6)	50.5(12.6)	–	–	0.82
T2-PANSS Positive	10.9(3.0)	12.0(4.7)	–	–	0.38
T2-PANSS Negative	14.6(6.1)	14.0(5.3)	–	–	0.77
T2-PANSS General	24.3(3.33)	24.5(5.4)	–	–	0.89

[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.

Table 2
The usage and dosage of antipsychotics of the schizophrenic patients in drug and ECT groups.

ID	Drug			ECT		
	Antipsychotics	Average dose (mg/d)	Chlorpromazine equivalents (mg/d)	Antipsychotics	Average dose (mg/d)	Chlorpromazine equivalents (mg/d)
01	Olanzapine	17.5	845.5	Risperidone	3	150
	Amisulpride	200				
	Paliperidone ER	4.5				
02	Risperidone	3	150	Quetiapine	5	250
				Paliperidone ER	6	
03	Olanzapine	5	250	Amisulpride	900	2256.8
	Risperidone	3		Aripiprazole	10	
				Clozapine	200	
04	Risperidone	4	200	Clozapine	75	316.7
				Aripiprazole	12.5	
05	Risperidone	5.5	275	Paliperidone ER	6	800
				Haloperidol	9	
				Quetiapine	150	
06	Risperidone	4	200	Risperidone	3	283.3
				Quetiapine	100	
07	Amisulpride	700	1340.5	Risperidone	5	650
				Olanzapine	20	
08	Ziprasidone	100	366.7	Risperidone	1	162.5
	Olanzapine	10		Paliperidone ER	4.5	
09	Clozapine	200	550	Paliperidone ER	3	891
	Risperidone	3		Clozapine	25	
				Amisulpride	400	
10	Clozapine	100	400	Olanzapine	20	650
	Risperidone	4		Haloperidol	5	
11	Olanzapine	5	325	Risperidone	3	300
	Paliperidone ER	9		Olanzapine	7.5	
12	Risperidone	4	200	Olanzapine	20	480
				Perphenazine	8	
13	Penfluridol	7.14	1266.7	Chlorpromaz	250	325
	Quetiapine	350		Paliperidone ER	3	
14	Paliperidone ER	3	108.3	Ziprasidone	80	283.4
	Aripiprazole	2.5		Olanzapine	7.5	
15	Risperidone	3	150	Risperidone	4	200
16	Olanzapine	20	400	Ziprasidone	80	1682.3
				Quetiapine	300	
				Amisulpride	600	
17	Aripiprazole	15	200	Risperidone	2.5	325
				Olanzapine	10	
18	Ziprasidone	120	200	Olanzapine	7.5	616.7
				Ziprasidone	40	
				Clozapine	200	
19	Amisulpride	500	1024.2	Olanzapine	15	1549
	Aripiprazole	5		Amisulpride	600	
				Risperidone	2	
20	Amisulpride	800	1532	Olanzapine	15	337.5
				Paliperidone ER	1.5	
21	Quetiapine	900	1200	Paliperidone ER	7.5	187.5

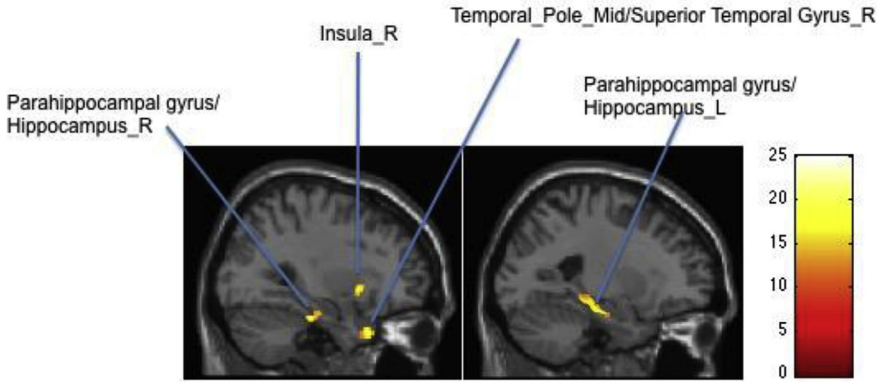

Fig. 1. Brain regions with voxel-based morphometry analyses showing significant interaction of group by time in grey matter volume (GMV). Results are displayed at significance threshold of $p < 0.05$ with FWE correction at cluster-level. Coordinates correspond to Montreal Neurological Institute standard space. Colorbar indicates t value. _L and _R indicates left and right respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 3
Brain regions showing significant interaction of group by time on grey matter volume (GMV) with whole-brain analysis.

Brain regions	MNI coordinate			Cluster size	$p^{\#}$ value	t^{*} value
	X	Y	Z			
ParaHippocampal gyrus/Hippocampus_L	−27	−31	−12	438	0.003**	4.92
TMP temporal pole_R/Superior Tempral Gyrus_R	28	18	−39	427	0.004**	4.77
Insula_R	36	0	4	417	0.004**	4.98
ParaHippocampal gyrsus/Hippocampus_R	28	−22	−24	577	0.001**	4.61

MNI = Montreal Neurological Institute. t^{*} peak level. $p^{\#}$ cluster level, FWE-corrected. _L means left, _R means right.

0.6387 ± 0.0640, T2, 0.6765 ± 0.0577, $p = 0.009$), right parahippocampal gyrus/hippocampus (T1, 0.6948 ± 0.0343, T2, 0.7319 ± 0.0434, $p < 0.001$) and right insula (T1, 0.7588 ± 0.0458, T2, 0.7823 ± 0.0476, $p = 0.029$).

Within the Drug group, post-hoc paired-sample t-tests showed the GMV decreased significantly in the four ROIs: the left parahippocampal gyrus/hippocampus (T1, 0.6894 ± 0.0560, T2, 0.6707 ± 0.0472, $p = 0.024$), right temporal_pole_mid/superior temporal gyrus (T1, 0.6672 ± 0.0517, T2, 0.6278 ± 0.0614, $p = 0.009$), right parahippocampal/hippocampus (T1, 0.7272 ± 0.0322, T2, 0.7091 ± 0.0365, $p = 0.014$), and right insula (T1, 0.7726 ± 0.0473, T2, 0.7401 ± 0.0547, $p = 0.001$).

Relative changes in GMV between ECT and drug groups

The relative change in GMV was calculated by ($GMV_{FollowUP}$ - $GMV_{Baseline}$)/$GMV_{Baseline}$. Between-group differences in the relative change in GMV were all significant in these four ROIs: the left parahippocampal gyrus/hippocampus, $t = 4.904$, $p < 0.001$; right temporal_pole_mid/superior temporal gyrus, $t = 4.181$, $p < 0.001$; right parahippocampal gyrus/hippocampus, $t = 5.001$, $p < 0.001$; and right insula, $t = 4.979$, $p < 0.001$) (See Fig. 2).

Cross-sectional GMV differences among two patients groups and HC

The Drug group did not show any significant differences in whole-brain level GMV compared to the HC group at either T1 or T2 (ACNOVA; both $p > 0.05$). However, the ECT group had a significantly smaller GMV in the right anterior cingulate (ACC) than the HC group at both T1 and T2 (ACNOVA; $p = 0.015$ for T1, $p = 0.003$ for T2, FWE-corrected).

Correlations of GMV measure and clinical symptoms

We specifically explored the relationships between change in the PANSS positive symptom subscale and relative changes of GMV in the four ROIs as prior research had indicated that ECT's primary clinical effect was an improvement in positive symptoms. For the ECT group, improvements in PANSS positive subscores were positively correlated with the magnitude of relative change GMV in the right parahippocampal gyrus/hippocampus ($\rho = 0.574$, $p = 0.028$ with Bonferroni correction). However, for the Drug group, changes in the PANSS positive subscores were not significantly correlated with GMV changes in any of these four brain regions. (See Fig. 3).

Discussion

This is the first study to investigate GMV changes attributing to the application of ECT in patients with schizophrenia (SZ) and attempt to distinguish the effects of hybridized ECT therapy from standard antipsychotic approaches by including another SZ group treated only with antipsychotics. Additionally this work is the first study to investigate structural changes associated with bitemporal-ECT in SZ to our limit knowledge. We observed significant FWE-corrected regional GMV increases in limbic structures such as the medial temporal lobe (including left parahippocampal gyrus/hippocampus and right parahippocampal gyrus/hippocampus), the right insula and the right temporal_pole_mid/superior temporal gyrus after therapy in the ECT group. At the same time, significant GMV decreases in these same brain regions were observed in the Drug group. In addition, the relative increases of GMV in the right parahippocampal gyrus/hippocampus region was significantly correlated with the relative reduction in the positive symptom subscore in patients receiving ECT with concurrent antipsychotic treatment.

In the present study, some local brain areas, specifically limbic brain regions such as bilateral hippocampus/parahippocampal, the right insula, and the right temporal_pole_mid/superior temporal gyrus showed increased GMV following theraputic bitemporal ECT for SZ. This was not unexpected as these particular regions have been previously identified to exhibit an abnormally reduced GMV in SZ [18]. Observed changes in most of these regions were also in agreement with the results of a previous study in which increased GMV was found in the right hippocampus and insula after treatment with right unilateral ECT in patients with SZ [39]. In this study, brain regions showing GMV alterations outside the right hemisphere and not observed in the aforementioned study, may be attributed in part to the bilateral stimulation delivery method used in this study. The dramatic increase of GMV in these regions in SZ after ECT, mostly overlapped with changed regions reported in individuals with MDD who were treated with ECT [6,10], supporting a shared mechanism of brain plasticity may underlie the actions of ECT irrespective of clinic diagnosis [39]. Neuroplasticity, including neurogenesis, synaptogenesis, angiogenesis, gliogenesis, or other changes in neurons and glial cells may contribute to ECT-related increments in hippocampal and adjacent structural volumes [7,8,16]; [28]. Neurogenesis, the process by which neurons are generated from neural progenitor cells, is observed to occur in the hippocampus throughout life even during adulthood [21]. In light of ECT's reported ability to increase levels of hippocampal neurotrophic factors [35], neurorestorative effects on dendrite or synaptic plasticity may be expected to contribute to increased brain volume in the hippocampal and adjacent areas. According to the neurotrophin hypothesis, aberrant neurogenesis is caused by a lower expression of BDNF. In a previous study comprising 119 SZ patients, brain volume reductions were related to a common genetic variant within the BDNF gene [17]. A meta-analysis has reported an increase of serum BDNF level after ECT in MDD [33]. Recently, a study with a relatively large sample-size has also documented increased serum BDNF levels after ECT treatment in SZ [22], indicating ECT might promote the release or generation of BDNF independent of psychiatric diagnosis. In addition, vascular endothelial growth factor (VEGF) might contribute to observed increases of regional brain volume via the promotion of blood vessel growth, given clinical reports of increased blood VEGF after ECT in the treatment of MDD [41], as well as preclinical research suggesting that VEGF plays a key role in the underlying mechanisms of ECS [12,36].

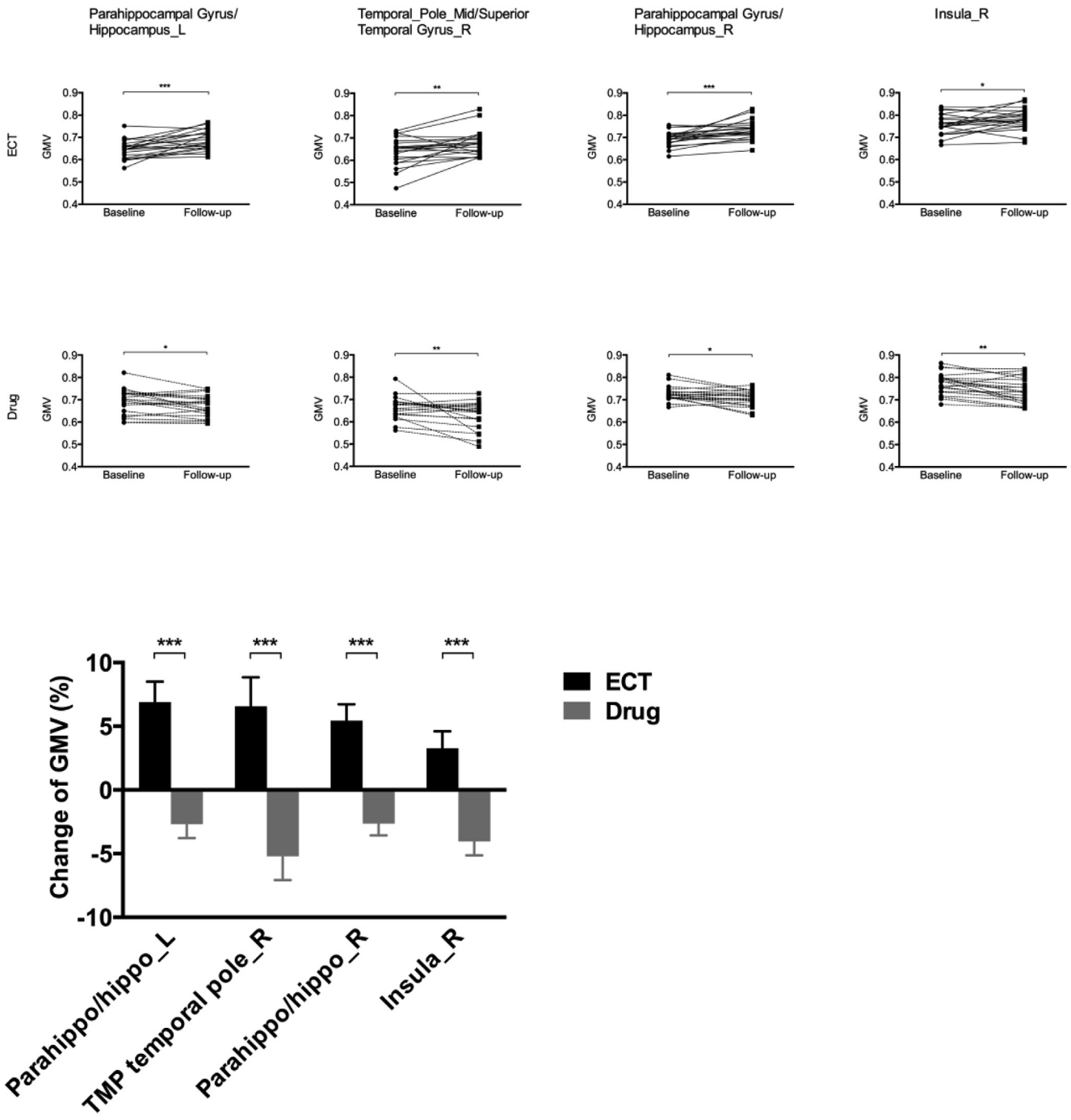

Fig. 2. Changes of grey matter volume (GMV) between baseline and follow-up time points in four brain regions for the two patient groups. Parahippo/hippo indicates Parahippocampal gyrus/hippocampus. _L and _R indicates left and right respectively.

In a prior systematic review, SZ patients treated with antipsychotics showed reduced GMV, particularly in the frontal, temporal lobes and limbic lobes [37]. Fusar-Poli P et al. also concluded in their meta-analysis that SZ is characterized by progressive GMV decreases which may be associated with antipsychotic treatment [13]. Additionally, Dazzan et al. found that patients treated with typical antipsychotics had grey matter deficits in the left middle temporal gyrus when compared to individuals treated with atypical antipsychotics [9]. In the present study, most patients were prescribed atypical antipsychotics and a few were taking typical antipsychotics (See details in Table 2). It is possible that this mixture of medication usage and the complicated pharmacokinetics of various antipsychotic agents might account for decreased GMV in the patient group only receiving antipsychotics. Only 5 patients in the current study were taking clozapine alongside ECT, which is not large enough for a separate analysis of the impact of clozapine plus ECT on brain plasticity yet. However, this represents a promising research direction as other authors such as Petrides et al. have noted and demonstrated a synergy between ECT and clozapine [32].

Overall, in the current study, treatment using exclusive antipsychotic therapy and antipsychotics augmented with ECT therapy

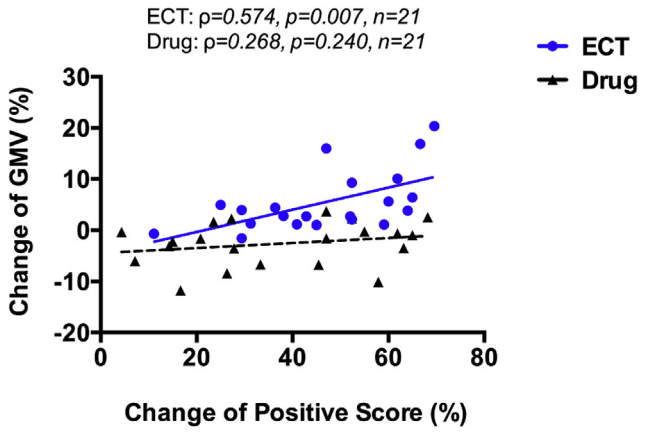

Fig. 3. Correlations between GMV change in the right parahippocampal gyrus/hippocampus and PANSS positive score change for the two patient groups. GMV indicates grey matter volume. PANSS indicates positive and negative syndrome scale.

resulted in opposing volume changes within limbic brain structures. These results appear to indicate that neuroplasticity is a common mechanism shared by both ECT and pharmaceutical antipsychotic medication as a whole. However, while neuroplasticity itself may be common, the manner in which these two treatments approaches might engage neurotrophic growth may operate via distinct mechanics.

In the present study, observed structural plasticity in the right parahippocampal gyrsus/hippocampus was related to positive symptom improvement in the ECT group. These results were in line with a previously identified relationship of clinical parameter changes associated with hippocampus volume increase in MDD following ECT treatment [19]. Our findings add to the existing literature by demonstrating that ECT-induced structural plasticity in the hippocampus relates to its therapeutic effect for SZ. Our results support speculation that “therapeutic” seizures involve and activate deeper brain structures like the diencephalon, basal ganglia or hippocampal formations in order to achieve clinical improvement [2,35]. While, Thomann et al. did not observe any significant association between ECT-related GMV changes of limbic structures (including amyglada/hippocampus and insula) with clinical measures in SZ, a lack of observed significance might be attributed to the modest sample of only 9 SZ patients and known heterogeneity of Schizophrenia disorders [42].

Relative to the HC group, a reduced GMV in the right ACC at both baseline and follow-up was found in the ECT group, consistent with previous studies [18]. However, it seemed ECT-induced changes in brain plasticity might be unrelated to this region because no changes in GMV were observed following ECT treatment.

Conclusions

Our findings indicate that ECT may induce brain plasticity as indexed by grey matter volume change during the treatment of schizophrenia via distinct mechanics from those by antipsychotic medications. ECT may help ameliorate the positive psychotic symptoms of patients suffering from schizophrenia by preferentially targeting limbic brain areas such as parahippocampal gyrus/hippocampus.

Limitations

The strongest limitation of this study is the inability to account for changes that might be due to specific antipsychotic usage or antipsychotic-ECT interactions. Although we have attempted to distinguish the effects of antipsychotic usage from ECT therapy by using a matched group of patients who underwent antipsychotic therapy alone, a study which attempts to narrow or control for specific antipsychotic therapy may be able to account for changes that may otherwise arise from variances in antipsychotic class (typical/atypical) as well as additional uncertainties arising from poly-pharmacy approaches. Patients here were assigned to therapy in a distinctly non-random manner after consultation with their physician, additionally treatment was non-blinded and no sham technique or comparison was used, making this study an observational one rather than a rigorous Randomized Controlled Trial (RCT). 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.

Additionally, the changes here ascribed to ECT are actually observed under hybrid ECT and antipsychotic therapy. In order to state with certainty that the changes observed are credited with ECT, it may be necessary to explore the usage of ECT in a context without antipsychotic usage. Although ECT-based therapies are generally effective and well-tolerated, the decision to select this technique as a primary, rather than adjunct treatment, is something that must be considered by the attending physician with the patient's best interests in mind. Due to the heterogeneous nature of schizophrenia, another difficult-to-avoid limitation arises from the mixture of specific negative and positive symptoms as well as variations in the duration of illness, which in addition to regular neurophysiological variation, can add uncertainty to neuroimaging work in the psychiatric field. A final limitation was the use of a relatively small sample and smaller subsample taking atypical antipsychotics medication which limited our ability to examine the influences of atypical-antipsychotics on the decrease of GMV on the Drug group. Future studies may wish to enlarge the subject pool in order to strengthen observed results and explore the effect of atypical-antipsychotics.

Competing interests

The authors report no conflicts of interests.

Author's contributions

Junjie Wang contributed to the data analysis, data acquisition and writing of the first draft manuscript.

Yingying Tang contributed to the study design, data acquisition and manuscript writing.

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

MengQing Xia and Tianhong Zhang contributed to the recruitments of subjects and clinical assessments.

Yuanqiao Zhao, Zhenying Qian and Yu Li contributed to the recruitments of patients.

Xiaochen Tang contributed to data analysis.

Chunbo Li contributed interpretation of the results.

Jijun Wang wrote the protocol and contributed to data interpretation.

All authors have contributed to and approved the final manuscript.

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References

[1] Abbott CC, Jones T, Lemke NT, Gallegos P, McClintock SM, Mayer AR, Bustillo J, Calhoun VD. Hippocampal structural and functional changes associated with electroconvulsive therapy response. Transl Psychiatry 2014;4:e483.
[2] Abrams R, Taylor MA. Diencephalic stimulation and the effects of ECT in endogenous depression. Br J Psychiatry 1976;129:482–5.
[3] Asami T, Bouix S, Whitford TJ, Shenton ME, Salisbury DF, McCarley RW. Longitudinal loss of gray matter volume in patients with first-episode schizophrenia: DARTEL automated analysis and ROI validation. Neuroimage 2012;59:986–96.
[4] Ashburner J. A fast diffeomorphic image registration algorithm. Neuroimage 2007;38:95–113.
[5] Bocchio-Chiavetto L, Zanardini R, Bortolomasi M, Abate M, Segala M, Giacopuzzi M, Riva MA, Marchina E, Pasqualetti P, Perez J, Gennarelli M. Electroconvulsive Therapy (ECT) increases serum Brain Derived Neurotrophic Factor (BDNF) in drug resistant depressed patients. Eur Neuropsychopharmacol 2006;16:620–4.
[6] Bouckaert F, De Winter FL, Emsell L, Dols A, Rhebergen D, Wampers M, Sunaert S, Stek M, Sienaert P, Vandenbulcke M. Grey matter volume increase following electroconvulsive therapy in patients with late life depression: a longitudinal MRI study. J Psychiatry Neurosci 2016;41:105–14.
[7] Bouckaert F, Sienaert P, Obbels J, Dols A, Vandenbulcke M, Stek M, Bolwig T. ECT: its brain enabling effects: a review of electroconvulsive therapy-induced structural brain plasticity. J ECT 2014;30:143–51.
[8] Chen F, Madsen TM, Wegener G, Nyengaard JR. Repeated electroconvulsive seizures increase the total number of synapses in adult male rat hippocampus. Eur Neuropsychopharmacol 2009;19:329–38.
[9] Dazzan P, Morgan KD, Orr K, Hutchinson G, Chitnis X, Suckling J, Fearon P, McGuire PK, Mallett RM, Jones PB, Leff J, Murray RM. Different effects of typical and atypical antipsychotics on grey matter in first episode psychosis: the AESOP study. Neuropsychopharmacology 2005;30:765–74.
[10] Dukart J, Regen F, Kherif F, Colla M, Bajbouj M, Heuser I, Frackowiak RS, Draganski B. Electroconvulsive therapy-induced brain plasticity determines therapeutic outcome in mood disorders. Proc Natl Acad Sci U S A 2014;111:1156–61.
[11] First MB. Structured clinical Interview for the DSM (SCID). The encyclopedia of clinical psychology. 1995.
[12] Fujiki M, Abe E, Nagai Y, Shiqi K, Kubo T, Ishii K, Abe T, Kobayashi H. Electroconvulsive seizure-induced VEGF is correlated with neuroprotective effects against cerebral infarction: involvement of the phosphatidylinositol-3 kinase/Akt pathway. Exp Neurol 2010;225:377–83.
[13] Fusar-Poli P, Smieskova R, Kempton MJ, Ho BC, Andreasen NC, Borgwardt S. Progressive brain changes in schizophrenia related to antipsychotic treatment? A meta-analysis of longitudinal MRI studies. Neurosci Biobehav Rev 2013;37:1680–91.
[14] Gan JL, Duan HF, Cheng ZX, Yang JM, Zhu XQ, Gao CY, Zhao LM, Liang XJ. Neuroprotective effect of modified electroconvulsive therapy for schizophrenia: a proton magnetic resonance spectroscopy study. J Nerv Ment Dis 2017 Jun;205(6):480–6.
[15] Hellsten J, Wennström M, Bengzon J, Mohapel P, Tingström A. Electroconvulsive seizures induce endothelial cell proliferation in adult rat hippocampus. Biol Psychiatry 2004;55:420–7.
[16] Hellsten J, West MJ, Arvidsson A, Ekstrand J, Jansson L, Wennström M, Tingström A. Electroconvulsive seizures induce angiogenesis in adult rat Hippocampus. Biol Psychiatry 2005;58:871–8.
[17] Ho BC, Andreasen NC, Dawson JD, Wassink TH. Association between brain-derived neurotrophic factor Val66Met gene polymorphism and progressive brain volume changes in schizophrenia. Am J Psychiatry 2007;164:1890–9.
[18] Honea R, Crow TJ, Passingham D, Mackay CE. Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies. Am J Psychiatry 2005;162:2233–45.
[19] Joshi SH, Espinoza RT, Pirnia T, Shi J, Wang Y, Ayers B, Leaver A, Woods RP, Narr KL. Structural plasticity of the Hippocampus and amygdala induced by electroconvulsive therapy in major depression. Biol Psychiatry 2016;79:282–92.
[20] Kay SR, Opler LA. The positive-negative dimension in schizophrenia: its validity and significance. Psychiatr Dev 1987;5:79–103.
[21] Kukekov VG, Laywell ED, Suslov O, Davies K, Scheffler B, Thomas LB, O'Brien TF, Kusakabe M, Steindler DA. Multipotent stem/progenitor cells with similar properties arise from two neurogenic regions of adult human brain. Exp Neurol 1999;156:333–44.
[22] Li J, Ye F, Xiao W, Tang X, Sha W, Zhang X, Wang J. Increased serum brain-derived neurotrophic factor levels following electroconvulsive therapy or antipsychotic treatment in patients with schizophrenia. Eur Psychiatr 2016;36:23–8.
[23] Madsen TM, Yeh DD, Valentine GW, Duman RS. Electroconvulsive seizure treatment increases cell proliferation in rat frontal cortex. Neuropsychopharmacology 2005;30:27–34.
[24] Matthew Brett, J.-L. A., Romain Valabregue, Jean-Baptiste poline region of interest analysis using the MarsBar toolbox for SPM 99.pdf. Neuroimage.
[25] Newton SS, Collier EF, Hunsberger J, Adams D, Terwilliger R, Selvanayagam E, Duman RS. Gene profile of electroconvulsive seizures: induction of neurotrophic and angiogenic factors. J Neurosci 2003;23:10841–51.
[26] Nieuwdorp W, Koops S, Somers M, Sommer IE. Transcranial magnetic stimulation, transcranial direct current stimulation and electroconvulsive therapy for medication-resistant psychosis of schizophrenia. Curr Opin Psychiatr 2015;28:222–8.
[27] Nordanskog P, Dahlstrand U, Larsson MR, Larsson EM, Knutsson L, Johanson A. Increase in hippocampal volume after electroconvulsive therapy in patients with depression: a volumetric magnetic resonance imaging study. J ECT 2010;26:62–7.
[28] Öngür D, Pohlman J, Dow AL, Eisch AJ, Edwin F, Heckers S, Cohen BM, Patel TB, Carlezon WA. Electroconvulsive seizures stimulate glial proliferation and reduce expression of Sprouty2 within the prefrontal cortex of rats. Biol Psychiatry 2007;62:505–12.
[29] Ota M, Noda T, Sato N, Okazaki M, Ishikawa M, Hattori K, Hori H, Sasayama D, Teraishi T, Sone D, Kunugi H. Effect of electroconvulsive therapy on gray matter volume in major depressive disorder. J Affect Disord 2015;186:186–91.
[30] Perera TD, Coplan JD, Lisanby SH, Lipira CM, Arif M, Carpio C, Spitzer G, Santarelli L, Scharf B, Hen R, Rosoklija G, Sackeim HA, Dwork AJ. Antidepressant-induced neurogenesis in the hippocampus of adult nonhuman primates. J Neurosci 2007;27:4894–901.
[31] Petrides G, Fink M. The "half-age" stimulation strategy for ECT dosing. Convuls Ther 1996;12:138–46.
[32] Petrides G, Malur C, Braga RJ, Bailine SH, Schooler NR, Malhotra AK, Kane JM, Sanghani S, Goldberg TE, John M, Mendelowitz A. Electroconvulsive therapy augmentation in clozapine-resistant schizophrenia: a prospective, randomized study. Am J Psychiatry 2015;172:52–8.
[33] Rocha RB, Dondossola ER, Grande AJ, Colonetti T, Ceretta LB, Passos IC, Quevedo J, da Rosa MI. Increased BDNF levels after electroconvulsive therapy in patients with major depressive disorder: a meta-analysis study. J Psychiatr Res 2016;83:47–53.
[34] Rosenquist PB, Miller B, Pillai A. The antipsychotic effects of ECT: a review of possible mechanisms. J ECT 2014;30:125–31.
[35] Sartorius A, Hellweg R, Litzke J, Vogt M, Dormann C, Vollmayr B, Danker-Hopfe H, Gass P. Correlations and discrepancies between serum and brain tissue levels of neurotrophins after electroconvulsive treatment in rats. Pharmacopsychiatry 2009;42:270–6.
[36] Segi-Nishida E, Warner-Schmidt JL, Duman RS. Electroconvulsive seizure and VEGF increase the proliferation of neural stem-like cells in rat hippocampus. Proc Natl Acad Sci U S A 2008;105:11352–7.
[37] Smieskova R, Fusar-Poli P, Allen P, Bendfeldt K, Stieglitz RD, Drewe J, Radue EW, McGuire PK, Riecher-Rossler A, Borgwardt SJ. The effects of antipsychotics on the brain: what have we learnt from structural imaging of schizophrenia?–a systematic review. Curr Pharmaceut Des 2009;15:2535–49.
[38] Tendolkar I, van Beek M, van Oostrom I, Mulder M, Janzing J, Voshaar RO, van Eijndhoven P. Electroconvulsive therapy increases hippocampal and amygdala volume in therapy refractory depression: a longitudinal pilot study. Psychiatr Res 2013;214:197–203.
[39] Thomann PA, Wolf RC, Nolte HM, Hirjak D, Hofer S, Seidl U, Depping MS, Stieltjes B, Maier-Hein K, Sambataro F, Wustenberg T. Neuromodulation in response to electroconvulsive therapy in schizophrenia and major depression. Brain Stimul 2017 May - Jun;10(3):637–44.
[40] Thomas AG, Marrett S, Saad ZS, Ruff DA, Martin A, Bandettini PA. Functional but not structural changes associated with learning: an exploration

of longitudinal voxel-based morphometry (VBM). Neuroimage 2009;48:117–25.
[41] Tseng PT, Cheng YS, Chen YW, Wu CK, Lin PY. Increased levels of vascular endothelial growth factor in patients with major depressive disorder: a meta-analysis. Eur Neuropsychopharmacol 2015;25:1622–30.
[42] Wolf RC, Nolte HM, Hirjak D, Hofer S, Seidl U, Depping MS, Stieltjes B, Maier-Hein K, Sambataro F, Thomann PA. Structural network changes in patients with major depression and schizophrenia treated with electroconvulsive therapy. Eur Neuropsychopharmacol 2016;26:1465–74.
[43] Woods SW. Chlorpromazine equivalent doses for the newer atypical antipsychotics. J Clin Psychiatr 2003;64:663–7.
[44] Zhao C, Warner-Schmidt J, Duman RS, Gage FH. Electroconvulsive seizure promotes spine maturation in newborn dentate granule cells in adult rat. Dev Neurobiol 2012;72:937–42.