Electroconvulsive Therapy Induces Cortical Morphological Alterations in Major Depressive Disorder Revealed with Surface-Based Morphometry Analysis

Jinping Xu

*Institute of Biomedical and Health Engineering
Shenzhen Institutes of Advanced Technology
Chinese Academy of Sciences, Shenzhen 518055, P. R. China
University of Chinese Academy of Sciences
Beijing 100049, P. R. China
jp.xu@siat.ac.cn*

Jiaojian Wang

*The Clinical Hospital of Chengdu Brain Science Institute
MOE Key Lab for Neuroinformation
University of Electronic Science
and Technology of China, Chengdu 625014, P. R. China
jiaojianwang@uestc.edu.cn*

Tongjian Bai

*Department of Neurology, The First Hospital
of Anhui Medical University, Hefei 230022, P. R. China*

Xiaodong Zhang and Tian Li

*Institute of Biomedical and Health Engineering
Shenzhen Institutes of Advanced Technology
Chinese Academy of Sciences, Shenzhen 518055, P. R. China*

Qingmao Hu

*Institute of Biomedical and Health Engineering
Shenzhen Institutes of Advanced Technology
Chinese Academy of Sciences, Shenzhen 518055, P. R. China
CAS Key Laboratory of Human-Machine Intelligence-Synergy Systems
Shenzhen Institutes of Advanced Technology
Chinese Academy of Sciences, Shenzhen 518055, P. R. China
qm.hu@siat.ac.cn*

Hongming Li

*Center for Biomedical Image Computing and Analytics
Department of Radiology, Perelman School of Medicine
University of Pennsylvania, Philadelphia, PA 19104, USA*

Li Zhang

Anhui Mental Health Center, Hefei 230022, P. R. China

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Qiang Wei

*Department of Neurology
The First Hospital of Anhui Medical University
Hefei 230022, P. R. China
weiqiang19890914@126.com*

Yanghua Tian

*Department of Neurology
The First Hospital of Anhui Medical University
Hefei 230022, P. R. China
Department of Neurology
Shannan People's Hospital, Shannan, 856000, P. R. China*

Kai Wang

*Department of Neurology
The First Hospital of Anhui Medical University
Hefei 230022, P. R. China
Department of Medical Psychology
Anhui Medical University, Hefei 230022, P. R. China
Anhui Province Key Laboratory of Cognition and Neuropsychiatric Disorders
Hefei 230022, P. R. China
Collaborative Innovation Center for Neuropsychiatric Disorders and Mental Health
Hefei 230022, P. R. China*

Accepted 21 January 2019

Published Online 12 March 2019

Although electroconvulsive therapy (ECT) is one of the most effective treatments for major depressive disorder (MDD), the mechanism underlying the therapeutic efficacy and side effects of ECT remains poorly understood. Here, we investigated alterations in the cortical morphological measurements including cortical thickness (CT), surface area (SA), and local gyrification index (LGI) in 23 MDD patients before and after ECT. Furthermore, multivariate pattern analysis using linear support vector machine (SVM) was applied to investigate whether the changed morphological measurements can be effective indicators for therapeutic efficacy of ECT. Surface-based morphometry (SBM) analysis found significantly increased vertex-wise and regional cortical thickness (CT) and surface area (SA) in widespread regions, mainly located in the left insula (INS) and left fusiform gyrus, as well as hypergyrification in the left middle temporal gyrus (MTG) in MDD patients after ECT. Partial correlational analyses identified associations between the morphological properties and depressive symptom scores and impaired memory scores. Moreover, SVM result showed that the changed morphological measurements were effective to classify the MDD patients before and after ECT. Our findings suggested that ECT may enhance cortical neuroplasticity to facilitate neurogenesis to remit depressive symptoms and to impair delayed memory. These findings indicated that the cortical morphometry is a good index for therapeutic efficacy of ECT.

Keywords: Major depressive disorder; electroconvulsive therapy; cortical thickness; surface area; local gyrification index.

1. Introduction

Electroconvulsive therapy (ECT) has been reported to be one of the most effective treatments with rapid action for major depressive disorder (MDD).¹ However, the widespread use of ECT is limited by its cognitive side effects, i.e. memory impairment.² Although ECT has been used in clinical practice for decades, the mechanism underlying the therapeutic

efficacy and side effects of ECT in MDD patients remains poorly understood. Most evidence from animal models supported the neurotrophic hypothesis that the effect of ECT is partially mediated by seizure-induced neurotrophic effects, resulting in increased rates of neurogenesis, synaptogenesis and glial proliferation.^{3–6} In addition, the neurotrophic effects may contribute to the antidepressant effect⁹

and cognitive side effects.^{7,8} These neurotrophic effects of ECT were detectable not only at the molecular and microstructural levels but also at the macroscopic level associated with brain structural changes.

To investigate the brain structural changes induced by ECT in MDD patients, a number of studies were performed using voxel-based morphometry (VBM), reporting changes in gray matter volume in various brain regions, such as the hippocampus,^{10–12} amygdala,^{13–15} and temporal lobe.^{16,17} However, a recent study using VBM did not identify changes in gray matter volumes in MDD patients after ECT even though the clinical symptoms were significantly improved.⁹ Given that the measurement of gray matter volumes using VBM includes information of cortical thickness (CT), surface area (SA) and cortical folding,¹⁸ delineating the exact changes in CT, SA and cortical folding in MDD patients after ECT will provide important insight to understand the mechanism of ECT.

Surface-based morphometry (SBM) analyses provide a way to directly measure CT, SA and cortical folding of the brain *in vivo*. These three measurements provide specific parameters that can reflect distinct developmental trajectories of cortical structures and are known to be determined by distinct biological factors.^{19,20} Specially, CT might be associated with neuronal density.^{21,22} Local SA mainly reflects the number and spacing of cortical columns in a cortical region²³ and is suggested to be driven by cellular events such as synaptogenesis, gliogenesis and intracortical myelination.²⁴ Cortical folding defined by the local gyrfication index (LGI) allows a larger cortical SA (there are a greater number of neurons) to fit in the skull. Cortical folding may be related to the developmental integrity of cortical circuits,²⁵ providing forces driving the extensive wiring of cortico-cortical connections along the brain surface.²⁶ Cortical LGI growth was thought to be related to the increase in dendritic arborization, the growth of the terminal axonal arborization, synaptogenesis, and glial proliferation.^{27,28} Thus, SBM analyses provide an important way to investigate the cortical alterations induced by ECT in MDD patients. Until now, only three studies have been performed and only identified changes in CT in MDD patients after ECT.^{10,29,30} However, the cortical alterations induced by ECT still needs to be fully

elucidated. Given the specificity of CT, SA and LGI, investigations of cortical alterations using multidimensional structural patterns might provide novel views to understand the mechanism underlying the therapeutic efficacy and side effects of ECT in MDD patients.

In this study, we investigated the cortical alterations induced by ECT in 23 MDD patients by examining the vertex-wise and regional CT, SA and LGI using the SBM approach. Paired two-sample *t*-tests were performed to explore the variations in CT, SA and LGI across the whole brain cortex as well as across 68 anatomically defined cortical regions in MDD patients before and after ECT. Partial correlational analyses were performed to explore the relationship between the changes in CT/SA/LGI in ECT-related regions during the whole brain analyses as well as regional analyses and the changes of the clinical scores in the MDD patients with age, gender and education as covariates. Moreover, multivariate pattern analysis using linear support vector machine (SVM) was applied to investigate whether the changed morphological measurements can be an effective index to classify MDD patients before and after ECT.

2. Materials and Methods

2.1. Participants

Patients were recruited from the Anhui Mental Health Center between 2012 and 2015, were diagnosed with MDD according to the Diagnostic and Statistical Manual of Mental Disorders-IV criteria³¹ and were referred for ECT if they showed resistance to drug therapy or severe suicidal tendencies. In this study, we excluded patients who were left-handed, substance dependent, pregnant, had life-threatening somatic disease, neurological disorders, other comorbid mental disorders or MRI-related contraindications before ECT, resulting in 23 patients. All these patients continued to take anti-depressant drugs during the ECT administration. All patients provided written informed consent. The study was performed in accordance with the latest revision of the Declaration of Helsinki and was fully approved by the Anhui Medical University Ethics Committee. The demographics and clinical data of the MDD patients are listed in Table 1.

Table 1. Demographic characteristics of the participants.

Participants		MDD	
Number of subjects		23	
Age		38.74 ± 11.02 (years)	
Gender (male:female)		11:12	
Education		8.83 ± 3.89 (years)	
Durations of illness		70.35 ± 83.27 (months)	
Number of Treatment		7.26 ± 2	
On-mediation		23 patients	
SSRIs		7 patients	
SNRIs		4 patients	
SSRIs+ SNRIs		1 patients	
SSRIs+ NaSSAs		1 patients	
SSRIs+ SARIs		1 patients	
SSRIs+ Antipsychotics		9 patients	
	Before ECT	After ECT	<i>p</i> value
AVLT-IR	19.65 ± 8.57	17.13 ± 6.47	$p = 0.178$
AVLT-DR	6.82 ± 3.16	3.91 ± 3.78	$p < 0.001$
HRSD scores	22.22 ± 4.74	3.83 ± 2.15	$p < 0.001$

Note: MDD, major depressive disorder; ECT, electroconvulsive therapy; SSRIs: selective serotonin reuptake inhibitors; SNRIs: serotonin–norepinephrine reuptake inhibitors; NaSSAs: norepinephrine and specificity serotonergic antidepressants; SARIs: serotonin antagonist/reuptake inhibitors; AVLT-IR, immediate recall of Auditory Verbal Learning Test; AVLT-DR, delayed recall of Auditory Verbal Learning Test; HRSD, Hamilton Rating Scale for Depression. Paired two-sample *t*-tests were performed to test the difference of AVLT-IR, AVLT-DR and HRSD scores in MDD patients before and after ECT.

2.2. Clinical measurements

The severity of depression was assessed with the 17-item Hamilton Rating Scale for Depression (HRSD)³² 12–24 h before the first ECT session and 24–72 h after the last ECT session. Moreover, the Auditory Verbal Learning Test (AVLT) was also used to assess verbal episodic memory, which includes immediate recall AVLT (AVLT-IR) and delayed recall AVLT (AVLT-DR). Considering the difficulty of the classic AVLT, a simplified version was used in this study. At first, a list of 15 words was read to the subjects with the speed of one word per second. After presentation, the subjects were immediately asked to recall as many words as possible. The AVLT-IR was repeated three times and recalled words were recorded for three trials. After 10 min, under the condition of no presentation before, the subjects were instructed to recall the 15 words presented during AVLT-IR and AVLT-DR. The total scores for AVLT-IR (trial 1–3) and AVLT-DR were separately analyzed.

2.3. ECT procedures

All patients underwent modified bi-frontal ECT using a Thymatron System IV Integrated ECT Instrument (Somatics, Lake Bluff, IL, USA). In our study, the first three ECT sessions were administered on consecutive days, and the subsequent ECT sessions were conducted every other day with a break over the weekends until patients reached symptom remission. The criterion for remission was defined as the HRSD score of patient was not more than 7. The mean of the total duration of ECT sessions was 14.6 ± 5.8 days. And the mean number of treatment was 7.26 ± 2 . The initial stimulation strength was set according to the age of each participant, and evenly increased until seizures were visually observed. All patients were given propofol anesthesia during the ECT. To help the patients relax their musculature and suppress the secretion of glands, succinylcholine and atropine were additionally administered. Moreover, we also used electroencephalography to monitor the seizure activity.^{15,33–35}

2.4. MRI data acquisition

All patients underwent two scans (12–24 h before the first ECT session and 24–72 h after the last ECT session) at the First Affiliated Hospital of Anhui Medical University using a clinical 3.0 T MRI scanner (Signa HDxt 3.0 T, GE Healthcare, Buckinghamshire, UK). The subjects were instructed to keep their eyes closed, stay relaxed and awake, and not to think of anything in particular during the scan. The parameters of the T1-weighted anatomic images were as follows: repetition time = 8.676 ms, echo time = 3.184 ms, inversion time = 800 ms, flip angle = 8°, field of view = $256 \times 256 \text{ mm}^2$, matrix size = 256×256 , slice thickness = 1 mm, voxel size = $1 \times 1 \times 1 \text{ mm}^3$ and sections = 188.

2.5. Cortical reconstruction and longitudinal analysis

To reduce within subject variability, longitudinal analysis were performed using the longitudinal processing pipeline³⁶ in FreeSurfer 5.0. (<http://surfer.nmr.mgh.harvard.edu/>). The longitudinal design can significantly reduce the confounding effect of inter-individual morphological variability by using each subject as his or her own control, and be unbiased with respect to any time point. It mainly consisted of three steps: (1) CROSS: all time points of all subjects were processed independently using the fully automated FreeSurfer “recon-all” standard procedure to obtain the information for constructing the subject template in the next step; (2) BASE: for each subject, a template was created from all time points to estimate average subject anatomy. An unbiased median image is used as the template and a full segmentation and surface reconstruction was performed; and (3) LONG: every time point is processed “longitudinally”. The longitudinal processing of each time point was initialized with information from the subject template and the results of step BASE to reduce variability.

This process consisted of the following procedures: (1) spatial normalization and nonuniform intensity: all inputs are resampled to the unbiased template voxel space to further reduce variability. A nonparametric nonuniform intensity normalization was used to correct the acquisition bias fields in this procedure; (2) Talairach registration: transferring the map to Talairach coordinate system using

a single global affine transformation; (3) brainmask creation: the brain mask is constructed as the union of the registered brain masks across time and is kept constant for all time points to reduce variability; (4) normalization and atlas registration; (5) subcortical segmentation: a fused segmentation is created for each time point by an intensity based probabilistic voting scheme; (6) surfaces reconstruction: similar to regular cortical surface construction in FreeSurfer, but the white and pial surfaces in each time point are initialized with the surfaces from the template to demonstrate an implicit vertex correspondence; and (7) cortical atlas registration and parcellations: establishing a coordinate system for the cortex by warping individual surface models into register with a spherical atlas in a way that aligns the cortical folding patterns. For more detail information, please refer to papers by Reuter *et al.*^{36–38} and website (<https://surfer.nmr.mgh.harvard.edu/fswiki/LongitudinalProcessing>).

The CT was calculated as the closest distance from the gray/white boundary to the gray/cerebrospinal fluid boundary at each vertex on the tessellated surface using T-average algorithm.³⁹ The SA for each vertex was calculated by assigning one-third of the area of each triangle to each of its vertices on the pial surface, representing the area of the tessellated triangles linked to the vertex. These two parameters were the output of FreeSurfer with its standard processing pipeline. The LGI, a measurement of cortical gyrification, was obtained with three main steps: (1) generating an artificial outer surface from the outer hull; (2) calculating the LGI of each vertex on the outer surface by measuring the ratio of local SA to the outer hull layer that tightly wraps the pial surface;⁴⁰ and (3) deriving the LGI map by redistributing the outer surface LGI values to each vertex on the pial surface. It is an indication of the sulcal cortex buried in its locality and thus denotes the extent of cortical folding.⁴¹

2.6. Vertex-wise SBM analyses

The CT, SA and LGI of the left and right hemisphere were smoothed with a circularly symmetric Gaussian kernel of 5 mm full width half maximum to improve signal to noise ratio and to further provide a normal distribution of the results. Between-group differences in CT, SA and LGI were investigated within the Qdec (query, design, estimate, contrast) application

of FreeSurfer (<https://surfer.nmr.mgh.harvard.edu/fswiki/Qdec>) with paired two-sample t test model in MDD patients before and after ECT. Finally, the results were corrected for multiple comparisons using Monte Carlo simulation (a pre-cached cluster-wise level of $p < 0.05$, a voxel-wise level of $p < 0.001$, and sign: absolute).

2.7. Regional CT, SA and LGI analyses

To increase the signal-to-noise by searching functionally homologous regions, CT, SA and LGI were averaged within each of the 68 anatomically defined regions from the Desikan–Killiany Atlas (Table 2) during the FreeSurfer segmentation procedures. Paired two-sample t -tests were performed to explore the regional differences in CT, SA and LGI in MDD patients before and after ECT using SPSS. A strict Bonferroni correction with $p < 0.05/68$ was used as the threshold value of significance for the multiple comparisons.

2.8. Correlational analyses

Partial correlational analyses were performed to explore the relationship between the changes in CT, SA and LGI in ECT-related regions during the whole brain analysis as well as in the anatomically defined cortical regions and the changes in AVLT-IR, AVLT-DR and HRSD scores in the MDD patients with age, gender and education as covariates. All correlational analyses were performed using SPSS 19. The significant level was set at $p < 0.05$, Bonferroni correction. To show the trend between changed morphological measurements and changed behavioral performances, all the correlations with $p < 0.05$ were also shown.

2.9. Multivariate pattern analysis using SVM

To explore whether the identified neural indices can effectively classify MDD patients before and after ECT, a linear SVM approach within a library for SVMs (LIBSVMs) toolkit running on MATLAB (<https://www.csie.ntu.edu.tw/~cjlin/libsvm/>) was performed. The mean vertex-wise CT, SA and LGI, as well as the mean regional CT and SA in all ECT-related regions were used as the features

Table 2. Cortical regions and abbreviations included in the Desikan–Killiany atlas performed with FreeSurfer v5.1.0.

Region	Abbreviations
Banks of the superior temporal sulcus	bSTS
Caudal anterior cingulate	CAR
Caudal middle frontal gyrus	cMFG
Cuneus	CUN
Entorhinal cortex	EC
Fusiform gyrus	FG
Inferior parietal gyrus	IPG
Inferior temporal gyrus	ITG
Isthmus cingulate	IC
Lateral occipital gyrus	LOG
Lateral orbitofrontal gyrus	LFGor
Lingual gyrus	LG
Medial orbitofrontal gyrus	MFGor
Middle temporal gyrus	MTG
Parahippocampal gyrus	ParaHIPP
Paracentral gyrus	ParaCG
Pars opercularis	pOPER
Pars orbitalis	pORB
Pars triangularis	pTRI
Pericalcarine cortex	PeriCAL
Postcentral gyrus	PostCG
Posterior cingulate	PCC
Precentral gyrus	PreCG
Precuneus	PreCUN
Rostral anterior cingulate	RAC
Rostral middle frontal gyrus	rMFG
Superior frontal gyrus	SFG
Superior parietal gyrus	SPG
Superior temporal gyrus	STG
Supramarginal gyrus	SMG
Frontal pole	FP
Temporal pole	TP
Transverse temporal gyrus	TTG
Insula	INS

for discrimination (38 features). ReliefF⁴² was used to obtain the optimal combination of these features. A leave-one-out cross-validation strategy was used because of our limited number of samples to estimate the generalization ability of our classifier. The receiver operating characteristic (ROC) curve and area under curve (AUC) were used to delineate the classification ability.

3. Results

3.1. Clinical measurements

The paired t -tests identified significantly decreased HRSD scores in MDD patients after ECT ($p <$

0.001), indicating excellent therapeutic effects of ECT. There was no significant difference between the AVLT-IR in MDD patients after ECT compared to that before ECT ($p = 0.178$). There were significantly decreased AVLT DR scores in MDD patients after ECT ($p < 0.001$).

3.2. Effects of ECT on CT

Increased vertex-wise CT was observed in the left temporal pole (TP), left fusiform gyrus (FG), left inferior parietal gyrus (IPG), left insula (INS) and visual part of the left FG, as well as in the right lateral occipital gyrus (LOG), right supramarginal gyrus (SMG), right superior temporal gyrus (STG), right INS and right precentral gyrus (PreCG) in MDD patients after ECT (Fig. 1(a)). Meanwhile, increased regional CT was observed in the bilateral FG, bilateral parahippocampus (ParaHIPP) and bilateral inferior temporal gyrus (ITG), as well as in the left STG, left IPG, left INS, left banks of the superior temporal sulcus (bSTS), right superior

frontal gyrus (SFG) and right rostral anterior cingulate (RAC) in the MDD patients after ECT (Fig. 1(b) and Table 3). Moreover, the increased vertex-wise and regional CT was also found in the left (TP), (FG) and bilateral INS in MDD patients after ECT (Fig. 1(c)).

3.3. Effects of ECT on SA

Increased vertex-wise SA was found in the left FG, left SMG, left INS and left lingual gyrus (LG), as well as in the right IPG, right STG, right ITG and right postcentral gyrus (PostCG) (Fig. 2(a)). Additionally, significantly increased regional SA of the bilateral FG, left rostral middle frontal gyrus (rMFG), left INS and right caudal middle frontal gyrus (cMFG) was also found in MDD patients after ECT (Fig. 2(b)). Moreover, the increased vertex-wise and regional SA was mainly found in the left FG and INS in MDD patients after ECT (Fig. 2(c)). The mean regional SA of these regions in MDD patients before and after ECT is listed in Table 4.

Fig. 1. Vertex-wise and regional analyses identified altered CT in MDD after ECT. All data were processed using the longitudinal pipelines in FreeSurfer. Paired t -tests were performed to identify the difference in vertex-wise CT in MDD before and after ECT. The significance level was set at a voxel-level of $p < 0.001$ and a cluster-level of $p < 0.05$, corrected by Monte Carlo simulations. Paired t -tests were performed to identify the differences in the regional CT in the MDD patients before and after ECT, and a strict Bonferroni correction with $p < 0.05/68$ was used as the threshold of significance for the multiple comparisons. All abbreviations of the brain regions are listed in Table 2.

Table 3. Cortical regions that showed significantly increased regional CT in the MDD patients after ECT. Paired two-sample *t*-tests were performed to explore the regional differences in MDD patients before and after ECT using SPSS. A strict Bonferroni correction with $p < 0.05/64$ was used as the threshold of significance for the multiple comparisons.

Regions	Before ECT	After ECT	<i>p</i> value	Cohen's <i>d</i> value	<i>t</i> value
bSTS.L	2.290 ± 0.178	2.359 ± 0.187	4.9×10^{-5}	0.377	-5.028
FG.L	2.736 ± 0.155	2.805 ± 0.151	1.3×10^{-4}	0.450	-4.628
IPG.L	2.350 ± 0.132	2.408 ± 0.114	3.3×10^{-5}	0.470	-5.191
ParaHIPPL	2.629 ± 0.315	2.696 ± 0.310	1.6×10^{-4}	0.214	-4.296
STG.L	2.512 ± 0.140	2.572 ± 0.155	2.6×10^{-4}	0.406	-4.366
TP.L	3.686 ± 0.260	3.842 ± 0.280	7.0×10^{-5}	0.577	-4.882
INS.L	2.925 ± 0.128	3.021 ± 0.149	9.6×10^{-9}	0.691	-8.899
FG.R	2.756 ± 0.149	2.827 ± 0.167	3.1×10^{-5}	0.448	-5.212
ITG.R	2.727 ± 0.142	2.802 ± 0.154	4.5×10^{-5}	0.506	-5.026
ParaHIPPR	2.652 ± 0.271	2.705 ± 0.248	2.9×10^{-4}	0.204	-4.296
RAC.R	2.596 ± 0.222	2.685 ± 0.238	1.5×10^{-4}	0.269	-4.548
SFG.R	2.613 ± 0.145	2.691 ± 0.141	1.9×10^{-4}	0.545	-4.460
TP.R	3.875 ± 0.273	4.000 ± 0.289	1.1×10^{-4}	0.444	-4.674
INS.R	2.900 ± 0.119	2.986 ± 0.095	7.4×10^{-7}	0.798	-6.822

Fig. 2. Vertex-wise and regional analyses identified altered SA in MDD patients after ECT. All data were processed using the longitudinal pipelines in FreeSurfer. Paired *t*-tests were performed to identify the difference in vertex-wise SA in MDD patients before and after ECT. The significance level was set at a voxel-level of $p < 0.001$ and a cluster-level of $p < 0.05$, corrected by Monte Carlo simulations. Paired *t*-tests were performed to identify the difference in the regional SA in MDD patients before and after ECT, and a strict Bonferroni correction with $p < 0.05/68$ was used as the threshold of significance for the multiple comparisons. All abbreviations of the brain regions are listed in Table 2.

Table 4. Cortical regions that showed significantly increased regional SA in the MDD patients after ECT. Paired two-sample *t*-tests were performed to explore the regional differences in MDD patients before and after ECT using SPSS. A strict Bonferroni correction with $p < 0.05/64$ was used as the threshold of significance for the multiple comparisons.

Regions	Before ECT	After ECT	<i>p</i> value	Cohen's <i>d</i> value	<i>t</i> value
FG.L	3433.91 ± 365.60	3484.00 ± 382.57	7.2×10^{-5}	0.133	-4.87
rMFG.L	5698.26 ± 870.20	5762.34 ± 906.25	9.2×10^{-5}	0.072	-4.76
INS.L	2290.69 ± 299.93	2340.34 ± 311.63	3.6×10^{-6}	0.162	-6.13
cMFG.R	1982.26 ± 321.90	2004.21 ± 325.24	9.7×10^{-5}	0.067	-4.74
FG.R	3246.86 ± 405.22	3295.56 ± 402.21	6.4×10^{-5}	0.120	-4.91

3.4. Effects of ECT on LGI

We only found that the vertex-wise LGI of the left middle temporal gyrus (MTG) significantly increased in the MDD patients after ECT (Fig. 3).

3.5. Correlational analyses

After multiple comparisons, only the changes in the regional CT in the left IPG were significantly correlated with the changes in the ALVT_DR score in MDD patients after ECT (Fig. 4).

In addition, we also found marginal correlations which showed the trend of the changed cortical measurements and behavioral performance (Fig. 5), such

Fig. 3. Vertex-wise LGI of the MTG was significantly increased in the MDD patients after ECT. All data were processed using the longitudinal pipelines in FreeSurfer. Paired *t*-tests were performed to identify the difference in vertex-wise LGI in MDD patients before and after ECT. The significance level was set at a voxel-level of $p < 0.001$ and a cluster-level of $p < 0.05$, corrected by Monte Carlo simulations. All other abbreviations of the brain regions are listed in Table 2.

Fig. 4. Partial correlations were performed with age, gender and education as covariates. After multiple comparisons, changes in the regional CT in the left IPG were significantly correlated with the changes in the ALVT_DR score in MDD patients after ECT.

as the changes in vertex-wise CT in the right LOG were marginally correlated with the changes in the HRSD scores, the changes in vertex-wise CT in the right PreCG were marginally correlated with the changes in the ALVT_DR scores, the changes in vertex-wise SA in the left INS were marginally correlated with the changes in the ALVT_IR scores, the changes in regional SA in the left INS were marginally correlated with the changes in the HRSD scores, and the changes in vertex-wise SA in the right ITG were marginally correlated with the changes in the ALVT_DR scores in MDD after ECT.

3.6. SVM results

With a combination of eight ECT-related features, including the vertex wise CT in left IPG, left TP,

Fig. 5. Correlations showed the trend of the changed morphological matrices and behavioral performances in MDD patients. Partial correlations were performed with age, gender and education as covariates.

right INS and right LOC and regional CT in the left FG, left TP, right FG and right ITG, SVM achieved a good performance with $AUC = 0.77$ to classify the MDD patients after ECT from MDD patients (Fig. 6).

4. Discussion

In the current study, we described that ECT induced cortical changes in widespread cortical regions, especially in the left INS and left FG in the MDD patients. Furthermore, correlations were also identified between the changes in the CT/SA in ECT-related regions and the changes in the clinical measurements in the MDD patients.

The longitudinal cortical alterations induced by ECT were widely observed in temporal and frontal regions, providing further evidence for the neuroplastic effects of ECT identified in animal and human experiments.¹⁵ Previous investigations based on animal models showed that repetitive electroconvulsive shock elicited widespread cell proliferation,⁴³ particularly in the hippocampus,^{4,44,45} amygdala³ and prefrontal cortex.^{46,47} In addition, many structural studies reported increase in the gray matter volume in the hippocampus and amygdala,^{15,48–51} which were accompanied by associations with symptom improvement in MDD patients after ECT. However, the number of investigations of ECT-related cortical alterations in other cortical areas is relatively small.

Fig. 6. The ROC curve of SVM classifier. A linear SVM approach was performed. The mean vertex-wise CT, SA and LGI, as well as the mean regional CT and SA in all ECT-related regions were used as the features for discrimination (38 features). After using ReliefF, a combination of eight features was served as the best solution for the SVM classifier.

To our knowledge, only three studies have been performed to reveal the alterations in CT related to ECT in MDD patients.^{10,29,30} The first study by Sartorius *et al.*¹⁰ showed increasing CT in the TP and INS in MDD patients after a mean of 11.3 ± 4.8 ECT treatments using voxel-based cortical thickness, and further corroborating with VBM results. However, no significant correlations with changes in psychopathology were found in his study. Then, two studies were performed using SBM at the same year, one revealed²⁹ significant increases in CT, including the bilateral TP, ITG, MTG and INS in MDD patients after a mean of 18 ± 7 ECT treatments; the other³⁰ showed increased CT after a mean of 11.2 ECT treatments in the bilateral ACC, ITG, STG, ParaHIPP, FG and prefrontal areas in MDD patients. In our study, patients received a mean of 7.26 ± 2 ECT treatments and showed cortical alterations in widespread cortical regions. Our findings were supported by those of the previous studies, and we further extended their findings by showing a widespread increase in CT, SA and LGI, as well as significant correlations with changes of clinical measurement in the MDD patients, which mainly reflect distinct alterations in the developmental trajectories of cortical structures related to ECT.

We found that both the vertex-wise and regional CT and SA significantly increased in the left INS and showed correlations with the clinical measurements. Our current findings were supported by those of previous studies in MDD patients. Using VBM analysis, increased grey matter volume in the INS was found in the patients with late-life depression after ECT.¹⁴ Dukart and colleagues reported that right unilateral ECT was correlated with regional increases in local grey matter volume of the INS.¹⁷ Using longitudinal analysis, van Eijndhoven *et al.*²⁹ also revealed significantly increased CT in the bilateral INS, as well as an association between changes in the mean CT of the right INS and the changes in the HRSD scores, a result that was consistent with our current findings. Moreover, the INS has also been reported to be related to treatment responses in MDD patients.⁵² An increasing amount of evidence, such as decreased interoceptive activity, altered connectivity,^{53,54} and grey matter reductions,⁵⁵ has suggested that the INS is an important structure in the pathophysiology of MDD.^{55,56} In addition, our findings suggested that ECT-induced cortical plasticity (CT and SA) of the left INS, and altered cortical properties were associated with treatment response, which suggested that the CT and SA of the left INS may serve as a potential neuroimaging biomarker for the therapeutic efficacy of ECT in MDD patients. Additionally, we found that the changes in CT/SA in the left INS were negatively correlated with the changes in the AVLT-IR scores, showing the possibility that the increased CT/SA of the left INS may be associated with the memory deficits in MDD patients after ECT, indicating that normal functioning of the brain is a dynamic balance of processes.

We also found that both the vertex-wise and regional CT and SA were significantly increased in the left FG in the MDD patients after ECT. The FG is a key region in the ventral processing stream of visual information and complex feature detection, which seems to be specifically correlated with facial expression.^{57–59} Functional and structural abnormalities in the FG have been widely reported, with studies particularly reporting reduced FG activation during face processing in MDD patients.^{60–62} Importantly, the fMRI signal in the left FG during affective face processing was found to be significantly associated with greater individual-level estimates of perceptual processing efficiency.⁶² A recent

study revealed altered functional and effective connectivities between the FG and amygdala in MDD patients after ECT.¹⁵ With all this evidence, the increased CT and SA in the left FG in our current study indicated that ECT could improve facial emotion processing in MDD patients.

In the whole brain analysis of the LGI, significant hypergyrification in the left anterior MTG which is part of the default mode network⁶³ was identified in the MDD patients after ECT. According to the tension-based theory of cortical morphogenesis,⁶⁴ the LGI results from forces driving the extensive wiring of cortico-cortical connections along the brain surface, reflecting the early neurodevelopment of cortical connectivity. Under this theory, the hypergyrification in the left MTG might result from the increased connectivity due to the white matter alterations induced by the ECT in MDD patients. However, another mechanical model of brain convolitional development, which suggested that differential growth rates of cortical layers directly affect the degree of cortical folding, has also been used to explain the cortical folding.⁶⁵ In fact, increased rates of neurogenesis, synaptogenesis and glial proliferation were found in animal models after ECT.^{3–6} Therefore, the increased LGI in the left MTG might be associated with the reconfiguring of the cortical architectures in this region. Moreover, the MTG has been reported to have a reduced gray matter volume, lower amplitude of low-frequency fluctuations and altered functional connectivity in MDD patients.^{66–68} Similar to our results, the regional homogeneity in the left MTG was reported to be increased after eight course of ECT in MDD patients.¹³ These results collectively suggested that the structure and function of the left MTG might be associated with the mechanism of ECT in MDD. Although previous studies suggested that the LGI plays an important role in MDD patients,^{69–72} this was the first study using LGI to directly demonstrate the cortical alterations induced by ECT in MDD patients. Our results suggested that the LGI is a useful index for estimating the cortical alterations, which providing new insight regarding the understanding of the mechanism underlying ECT in MDD patients.

Furthermore, the correlational analyses performed in the present study suggested close associations between the changes in the CT in right

LOG and the changes in the HRSD scores in MDD patients. The right LOG is part of the visual recognition circuit, which primarily participates in object identification⁷³ and affect identification.^{74,75} Moreover, disrupted connectivity between the visual recognition circuit and the subgenual anterior cingulate cortex and significant associations with the HRSD scores were identified in MDD patients.⁵⁴ Our findings of a significant correlation between the changes in the CT in the right LOG and the changes in the HRSD scores in MDD patients indicated that ECT may alleviate symptoms by modulating the structure of the visual cognition network to reduce the negative bias in emotion recognition.

In addition, we also found correlations between the changes in the AVLTL-DR scores and the changes in the SA in the right ITG, as well as with the changes in the CT in the left IPL in the MDD patients. Although the left IPL is widely considered to play a pivotal role in language processing,^{76–79} a recent parcellation study revealed that the posterior subregions of the IPL were engaged in episodic memory and working memory using functional connectivity and behavioral domain analyses.⁸⁰ The ITG has also been demonstrated to play an important role in working memory in several previous studies.^{81,82} Moreover, depressed patients have been shown abnormal activations in the ITG when they intended to forget negative words, which was used as a useful feature to discriminate depressed participants from the control participants.⁸³ Therefore, the correlations found in our study suggested that the cortical variations in the right ITG and left IPL in the memory network were closely associated with the memory impairment in MDD patients after ECT.

Although this paper provided new insight into the understanding of the mechanism underlying the therapeutic efficacy and side effects of ECT in MDD patients, some limitations still need to be addressed. First, our sample size was relatively small, making the statistical power weak especially the results of correlation analysis. Thus, any structural changes found in our study should be interpreted with caution, even though we performed strict multiple corrections. Moreover, these structural changes might also due to brain oedema since ECT can produce damage to the blood–brain barrier resulting in the brain oedema.^{84,85} Even though we didn't

find any obvious brain oedema in T1 images of MDD patients after ECT, it is difficult to exclude its effects as there might be some oedema invisibly by MRI T1. Second, all the MDD patients were taking anti-depressant medications during ECT administrations even they showed resistance to them. Future studies of medications-naïve patients are warranted to exclude the effects of anti-depressant medications. Third, we did not include normal controls because of the constraint of the longitudinal analysis method. However, we found that the altered surface measurements were closely correlated with altered clinical characteristics, suggesting that longitudinal analysis alone was enough to elucidate the mechanism of ECT. Finally, we only described structural alterations induced by ECT in the MDD patients, since structural alterations always associated with functional changes, fMRI and EEG^{86–90} are suited for investigating functional changing patterns induced by ECT in the MDD patients.

5. Conclusions

In conclusion, we described that the ECT induced significant increase in the CT, SA and LGI in a widespread of cortical regions, particularly in left INS and left FG in MDD patients reflecting distinct alterations in the developmental trajectories of cortical structures related to ECT. Further correlations were also identified between the changes in the CT/SA in ECT-related regions and the changes in the clinical measurements in MDD patients. In addition, these changed morphological measurements were an effective index to classify the MDD patients after ECT from MDD patients. Taken together, our findings suggested that ECT may enhance cortical neuroplasticity to facilitate neurogenesis to remit depressive symptoms, and the cortical morphology is a good indicator for therapeutic efficacy of ECT.

Acknowledgments

This work was supported by Natural Science Foundation of Guangdong Province (No. 2017A030313744 and No. 2016A030313180), the Science and Technology innovation program of Shenzhen (No. JCYJ20160531184531506), the National Natural Science Foundation of China (Nos. 31500867, 61671440 and 61672510) and the Shenzhen Key Basic Research Grant (No. JCYJ20160331191401141).

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