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Thalamic volume, resting-state activity, and their association with the efficacy of electroconvulsive therapy

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ABSTRACT

Electroconvulsive therapy (ECT) is the most effective antidepressant treatment. Biological predictors of clinical outcome to ECT are valuable. We aimed to examine multimodal magnetic resonance imaging (MRI) data that correlates to the efficacy of ECT. Structural and resting-state functional MRI data were acquired from 46 individuals (25 depressed individuals who received ECT, and 21 healthy controls). Whole-brain grey matter volume (GMV) and fractional amplitude of low frequency fluctuations (fALFF) were investigated to identify brain regions associated with post-ECT Hamilton Depression Rating Scale (HAM-D) total scores. GMV and fALFF values were compared with those in healthy controls using analysis of covariance (ANCOVA). Remission was defined by HAM-D ≤ 7. A multiple regression analysis revealed that pretreatment smaller GMV in the left thalamus was associated with worse response to ECT (i.e. higher post-ECT HAM-D). Pretreatment higher fALFF in the right anterior insula, and lower fALFF in the left thalamus and the cerebellum were associated with worse outcomes. The left thalamus was identified in both GMV and fALFF analyses. Nonremitters showed significantly smaller thalamic GMV compared to remitters and controls. We found that pretreatment thalamic volume and resting-state activity were associated with the efficacy of ECT. Our results highlight the importance of the thalamus as a possible biological predictor and its role in the underlying mechanisms of ECT action.

1. Introduction

Depression is a common, disabling, and debilitating psychiatric condition. Major depressive disorder (MDD) affects approximately 6% of the adult population worldwide each year (Bromet et al., 2011). First-line treatments, including antidepressant medications and psychotherapy, are effective only for two-thirds of patients (Rush et al., 2006), and the remaining one-third of patients are categorized as treatment-resistant depression (TRD). Electroconvulsive therapy (ECT) is the most effective antidepressant treatment for TRD (Kellner et al., 2012b). ECT has a rapid antidepressant effect (Spaans et al., 2015; Veltman et al., 2018) and it is also an effective treatment for suicidal ideation (Kellner et al., 2005). Although both patients and their relatives have showed overall positive attitudes toward ECT (Takamiya et al., 2019a), ECT is a demanding procedure with frequent general anesthesia, and it has transient cognitive side effects (Semkovska and McLoughlin, 2010; Vasavada et al., 2017; Nuninga et al., 2018). Identifying patients who will respond or not respond to ECT before treatment initiation may help clinicians, patients, and their relatives consider the potential benefits and costs of ECT. Moreover, brain regions that relate to clinical improvement may help us better understand the underlying mechanisms of ECT action.

Neuroimaging techniques seem to be useful to address these issues. Studies using structural magnetic resonance imaging (MRI) have consistently shown an ECT-induced volume increase in the hippocampus (Takamiya et al., 2018; Sartorius, 2019), although increased hippocampal volume returned to baseline after several months (Nordanskog et al., 2014; Bouckaert et al., 2016; Takamiya et al., 2019b). Recent research has found that an ECT-related hippocampal volume increase was mostly derived from the dentate gyrus (Takamiya et al., 2019b; Nuninga et al., 2019), which supports the neuroplastic hypothesis of ECT action (Bouckaert et al., 2014). In contrast, the predictive values of pretreatment hippocampal volume were inconsistent (Levy et al., 2019): some research found pretreatment volume in the hippocampus

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(Joshi et al., 2016; Jiang et al., 2018) or dentate gyrus (Nuninga et al., 2019) was associated with the efficacy of ECT, whereas others did not (Ten Doesschate et al., 2014; Takamiya et al., 2019b). Therefore, investigations of other brain regions using whole-brain voxel-based morphometry (VBM) may be helpful to expand our understanding of predictors of ECT response. Resting-state functional magnetic resonance imaging (rs-fMRI) is another way to investigate the human brain and may complement volume analyses. Fractional amplitude of low frequency fluctuations (fALFF) quantifies local dynamic fluctuation in the blood-oxygen-level dependent (BOLD) signal using the power spectrum method, and it is considered to reflect spontaneous neural activity (Zang et al., 2007; Zou et al., 2008). Moreover, fALFF values correlated with regional brain activity measured by positron emission tomography (PET) (Aiello et al., 2015). A previous study of 16 patients with MDD reported that an elevated baseline fALFF in the subcallosal cingulate cortex (SCC) was associated with ECT response (Argyelan et al., 2016). Compared to the consistent findings of the longitudinal effect of ECT on limbic regions (Takamiya et al., 2018), pretreatment biomarkers that predict ECT response are still unclear and need more investigation. Moreover, identifying brain regions in both GMV and fALFF data in the same cohort may be helpful to elucidate the neural correlates of biological predictors, although it still remains unclear whether GMV and fALFF are correlated (Hu et al., 2014; Guo et al., 2014; Qing and Gong, 2016). While a response or reduction rate in depression severity may reflect an immediate relief of symptoms, remission has become the goal of depression treatment, because residual symptoms are associated with poor prognosis (e.g. a higher rate of relapse) (Thase, 2003; McIntyre and O'Donovan, 2004). Hence, identifying neural correlates of remission or residual symptoms might be a critical step toward the practical use of neuroimaging in clinical psychiatry (Chi et al., 2015).

The aim of this study was to identify pretreatment structural and functional brain biomarkers that are predictive of remission after ECT (remission-predictive regions). In the current study, we used a comprehensive approach by combining whole-brain grey matter volume (GMV) and fALFF analyses to investigate brain regions identified in both GMV and fALFF analyses.

2. Subjects and methods

2.1. Participants and clinical assessments

This study was approved by the ethics committee of the Komagino hospital and performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants and/or their surrogate family members. The study design was prospective and observational. The study was registered at UMIN-CTR (UMIN000019475). Patients who met the following inclusion criteria were recruited at Komagino Hospital: (i) Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) diagnosis of major depressive disorder (MDD), or bipolar (BP) I or II disorder experiencing a major depressive episode (MDE) with melancholic features confirmed by Mini-International Neuropsychiatric Interview (M.I.N.I.); (ii) clinical indications for ECT, including pharmacotherapy resistance or requiring a rapid improvement of severe symptoms; (iii) age $\geq$50 years. Exclusion criteria included: (i) Any concurrent Axis I diagnosis other than MDD or BP; (ii) concurrent drug or alcohol dependence; (iii) a diagnosis of neurological or degenerative disorders (e.g. epilepsy and dementia); (iv) unstable or severe medical illness (e.g. myocardial infarction within one month); (v) pregnancy; (vi) ECT treatment within the last three months; (vii) patients with mandatory admission by the local government. Healthy controls were recruited from the same area. Healthy controls were screened by using the M.I.N.I. and were excluded if they had a history of psychiatric disorders. Subjects in this study partly overlap with a previous investigation of hippocampal subfields (Takamiya et al., 2019b).

Clinical and MRI assessments were conducted within one week before the first ECT. Depressive symptoms were evaluated using the 17-item Hamilton Depression Rating Scale (HAM-D), and remission was defined as HAM-D total score $\leq$7. Post-ECT assessments were conducted one week after the last ECT.

2.2. ECT procedure

ECT treatment was provided in clinical settings by each participant's attending psychiatrist. Participation in our research study did not influence any clinical decisions for ECT. Informed consent for ECT treatment was obtained independently and prior to recruitment for the study. ECT was performed using a brief-pulse (0.5 ms) square-wave device (Thymatron system IV device; Somatics, Inc., Lake Bluff, IL, USA). Participants received bitemporal ECT, which is usually selected in clinical settings in Japan. The initial stimulus intensity was determined by the half age method. Treatments were performed two to three times a week, in accordance with clinical judgment, and treatments were continued until a plateau was reached and no more improvement was seen in the last two sessions based on clinical assessments. Electroencephalogram (EEG) was recorded to ensure at least 20-sec of epileptiform EEG activity after ECT. Patients could be stimulated again at 1.5x intensity after a 1-min interval until they showed at least 20-sec of epileptiform activity. Patients could only be stimulated up to two times in one ECT session. Propofol (1 mg/kg) was used for general anesthesia, and succinylcholine (0.5–1.0 mg/kg) was used to induce muscle relaxation. Participants continued their psychotropic medications throughout the course of ECT. Incidental use of benzodiazepines or antipsychotics for sleep or anxiety was permitted.

2.3. Image acquisition

Imaging (MRI) data were acquired using a 3-T GE Signa HDxt scanner at Komagino Hospital. Whole-brain rs-fMRI scans comprising a total of 188 echo-planar imaging volumes (the first eight volumes were dummy scans) were acquired with the following parameters: TR = 2000 ms, TE = 28 ms, matrix = 64 × 64, slice thickness = 3.5 mm, 36 continuous axial slices, and voxel size = 3.75 × 3.75 × 3.5 mm. During the acquisition, all subjects were instructed to close their eyes and remain awake. High-resolution 3D T1-weighted images were acquired using a fast spoiled gradient recalled echo sequence (fSPGR: TR = 6.9 ms, TE = 2.9 ms, sagittal orientation, matrix = 256 × 256 mm, slice thickness = 1.0 mm, voxel size = 0.9 × 0.9 × 1.0 mm^3, 174 slices).

2.4. Structural image preprocessing

Each image was inspected for scan artifacts and gross anatomical alterations. Preprocessing of structural images, including segmentation, normalization, modulation, and smoothing, was conducted using the Statistical Parametric Mapping software package (SPM12, http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) in a Matlab (ver. R2016a; the MathWorks Inc., Natick, MA, USA) environment. The individual T1-weighted images were segmented into grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) using the segment tool in SPM12. Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) approach was applied for normalization to the Montreal Neurologic Institute (MNI) space (Ashburner, 2007). The segmented, normalized and modulated GM images were smoothed with an 8-mm full-width at half-maximum (FWHM) Gaussian kernel.

2.5. Functional image preprocessing

All preprocessing was performed using the Data Processing Assistant for Resting-State fMRI (DPARSF (Chao-Gan and Yu-Feng, 2010), http://www.restfmri.net), which is based on SPM and the toolbox for the Data

Processing & Analysis for (Resting-State) Brain Imaging (DPABI) (Yan et al., 2016). The preprocessing included removal of the first eight dummy scans, slice timing correction with the midpoint slice as the reference slice, realignment, nuisance covariates regression, and normalization to the Montreal Neurological Institute (MNI) space using the DARTEL tool (Ashburner, 2007). The scrubbing method was not applied because the calculation of fALFF is based on Fast Fourier transformation (FFT) and these metrics depend on temporal continuity. We utilized the Friston 24-parameter model (six head motion parameters, six head motion parameters one time point before, and the 12 corresponding squared items) (Friston et al., 1996) to regress out head motion effects from the realigned data. Moreover, mean frame wise displacement (FD) with Jenkinson's relative root mean square (RMS) algorithm (Jenkinson et al., 2002) was used to address the residual effects of micromovements in group analyses. Jenkinson's definition of FD was used due to its consideration of voxel-wise differences in motion in its derivation (Yan et al., 2013). Individual data with a mean FD greater than 2*SD above the group mean (threshold: 0.18 mm) were excluded (Di Martino et al., 2014), and the mean FD was used in group analyses as a nuisance covariate. The signals for WM and CSF were regressed out to reduce respiratory and cardiac effects.

The fALFF was calculated using the DPARSF. A ratio of the low-frequency amplitude within 0.01–0.1 Hz from FFT to the power spectrum of the entire frequency range (0–0.25 Hz) was computed at each voxel to obtain the fALFF. This fALFF approach has proven to reduce non-physiological noise in the BOLD signal (Zou et al., 2008). Subject-level Z-score maps were acquired by subtracting the mean value for the entire brain, and then dividing by the whole brain standard deviation (Yan et al., 2013). The maps were smoothed by 8-mm FWHM Gaussian kernel.

2.6. Statistical analysis

Descriptive statistics were used to describe the study participants. Distributions of all variables were inspected using histograms, q-q plots, and Shapiro-Wilk tests.

To identify remission-predictive regions, a whole brain multiple regression analysis was conducted using the SPM12. In a multiple regression model, the post-ECT HAM-D score was included as a dependent variable, and each individual GMV or fALFF map was included as an independent variable. Age, sex, and baseline HAM-D score were included as nuisance covariates. Individual total intracranial volumes (TIVs) were included as additional nuisance covariates in GMV analyses, and individual FD values were included as additional nuisance covariates in fALFF analyses. Because the distribution of the post-ECT HAM-D scores were positively skewed, they were natural log transformed to obtain a normal distribution.

The statistical threshold for voxel-wise whole-brain analyses was set at cluster-level family-wise error (FWE) corrected $p < 0.05$ (two-tailed) with an individual voxel threshold $p = 0.001$. A cluster threshold was determined by Monte-Carlo simulations (1000 iterations) as reported in a previous publication (Redlich et al., 2016).

As exploratory analyses, an analysis of covariance (ANCOVA), including age and sex as covariates, was used to detect group (remitters, nonremitters, and controls) differences in GMV and fALFF in remission-predictive regions that were identified in whole brain multiple regression analyses. TIV or FD was included as an additional covariate in the analyses for GMV or fALFF respectively. We also investigated whether any clinical characteristics correlated with GMV or fALFF in remission-predictive regions. SPSS ver 24.0 (IBM Inc., Armonk, NY, USA) was used for exploratory analyses. R ver 3.4.3 was used to make figures. Statistical significance was defined by a p-value of < 0.05 (two-tailed). Raw p-values were reported. Results after correction for multiple comparisons were also reported.

To examine overlapped regions between the findings of GMV and fALFF analyses, results of statistical maps were overlaid on the same template in Mango (http://ric.uthscsa.edu/mango/mango.html) and overlapped regions were identified using MarsBar (http://marsbar.sourceforge.net/).

Table 1
Clinical characteristics of participants.

	Healthy Controls	ECT patients	P-values
Number	21	25	
Age (years)	63.1 (7.2)	67.1 (8.3)	0.07
Female, n (%)	13 (61.9%)	18 (72.0%)	0.68
Bipolar disorder, n (%)		5 (20.0%)	
Psychotic features, n (%)		17 (68.0%)	
Family history, n (%)		10 (40%)	
Illness duration (year)		5.0 (1.13–19.5)	
Number of ECT		10.8 (1.5)	
Baseline HAMD-17	1.0 (1.2)	33.0 (7.1)	< 0.001
Baseline MMSE	29.0 (1.3)	25.8 (3.2)	0.002
Antidepressants, n (%)		21 (84.0%)	
Antipsychotics, n (%)		19 (76.0%)	
Benzodiazepines, n (%)		4 (16.0%)	
Mood stabilizers, n (%)		1 (4.0%)	

Each variable is described as mean (SD) for continuous variables.
Illness duration is described as median (IQR) because of non-normal distribution.

3. Results

3.1. Clinical demographics

Twenty-five patients (67.1 ± 8.3 years old; 18 female) and 21 healthy controls (63.1 ± 7.2 years old; 13 female) participated in the study (Table 1). ECT significantly improved depressive symptoms (HAM-D = 33.0 ± 7.1 before ECT; HAM-D = 6.0 ± 5.2 after ECT) (Paired *t*-test: $t = 14.9$, $df = 24$, $p < 0.001$), and 18 patients (72%) met the remission criteria after ECT. One patient and one healthy control did not complete rs-fMRI assessments. Two patients' rs-fMRI data and one healthy control's rs-fMRI data were excluded due to excessive micromovements (> 0.18 mm).

3.2. Baseline remission-predictive regions

Whole-brain multiple regression analyses revealed that pretreatment left thalamic volume was negatively associated with post-ECT HAM-D ($T = 5.26$, $Z = 4.08$, cluster size = 723 voxels); pretreatment fALFF in the left thalamus ($T = 8.15$, $Z = 5.05$, cluster size = 124 voxels) and the cerebellum ($T = 5.16$, $Z = 3.90$, cluster size = 85 voxels) were negatively associated with post-ECT HAM-D; and pretreatment fALFF in the right anterior insula ($T = 5.33$, $Z = 3.98$, cluster size = 68 voxels) was positively associated with post-ECT HAM-D (Figs. 1 and 2; Table 2). Only one cluster in the left thalamus was identified in both GMV and fALFF analyses. A further investigation revealed that the identified cluster was mainly located in the pulvinar and medial dorsal nucleus within the thalamus (Supplementary Fig. 1). There was no significant correlation between GMV and fALFF values in the overlapped region ($r = 0.20$, $df = 20$, $p = 0.36$) (Supplementary Fig. 2).

3.3. Pretreatment group comparisons of remission-predictive regions

ANCOVA revealed significant GMV differences among remitters, nonremitters, and healthy controls in the left thalamus ($F_{2, 40} = 6.70$, $p = 0.003$), and fALFF differences in the left thalamus ($F_{2, 34} = 3.57$, $p = 0.039$), in the cerebellum ($F_{2, 34} = 3.90$, $p = 0.03$), and in the right insula ($F_{2, 34} = 7.99$, $p = 0.001$). Even after correction for multiple comparisons, the results of the left thalamic GMV and the right insular fALFF were significant ($p < 0.05/4 = 0.0125$). Group comparisons

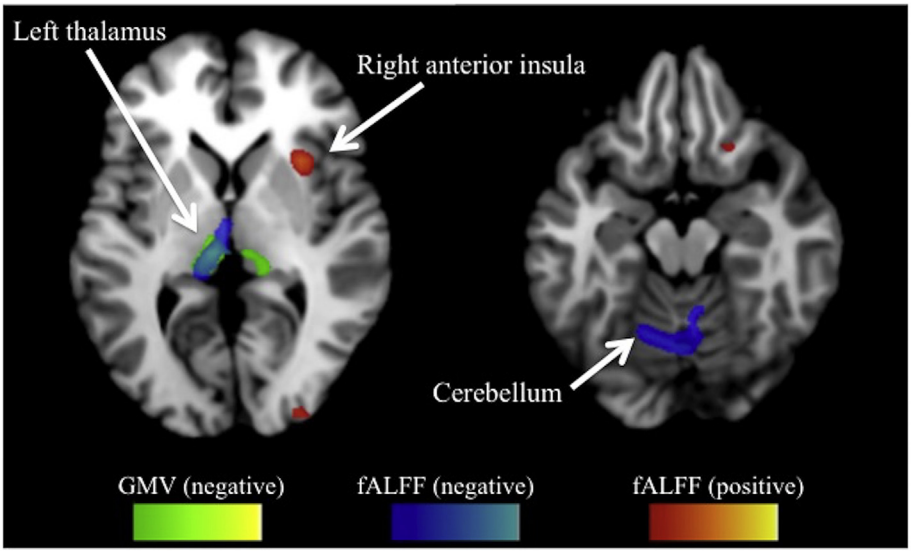

Fig. 1. Results of whole-brain multiple regression analyses. (A) Pretreatment left thalamic volume was negatively associated with post-ECT HAM-D scores (green in the figure). Pretreatment fALFF in the left thalamus and in the cerebellum were negatively associated with post-ECT HAM-D scores (blue in the figure), and the fALFF in the right insula was positively associated with post-ECT HAM-D scores (red in the figure). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

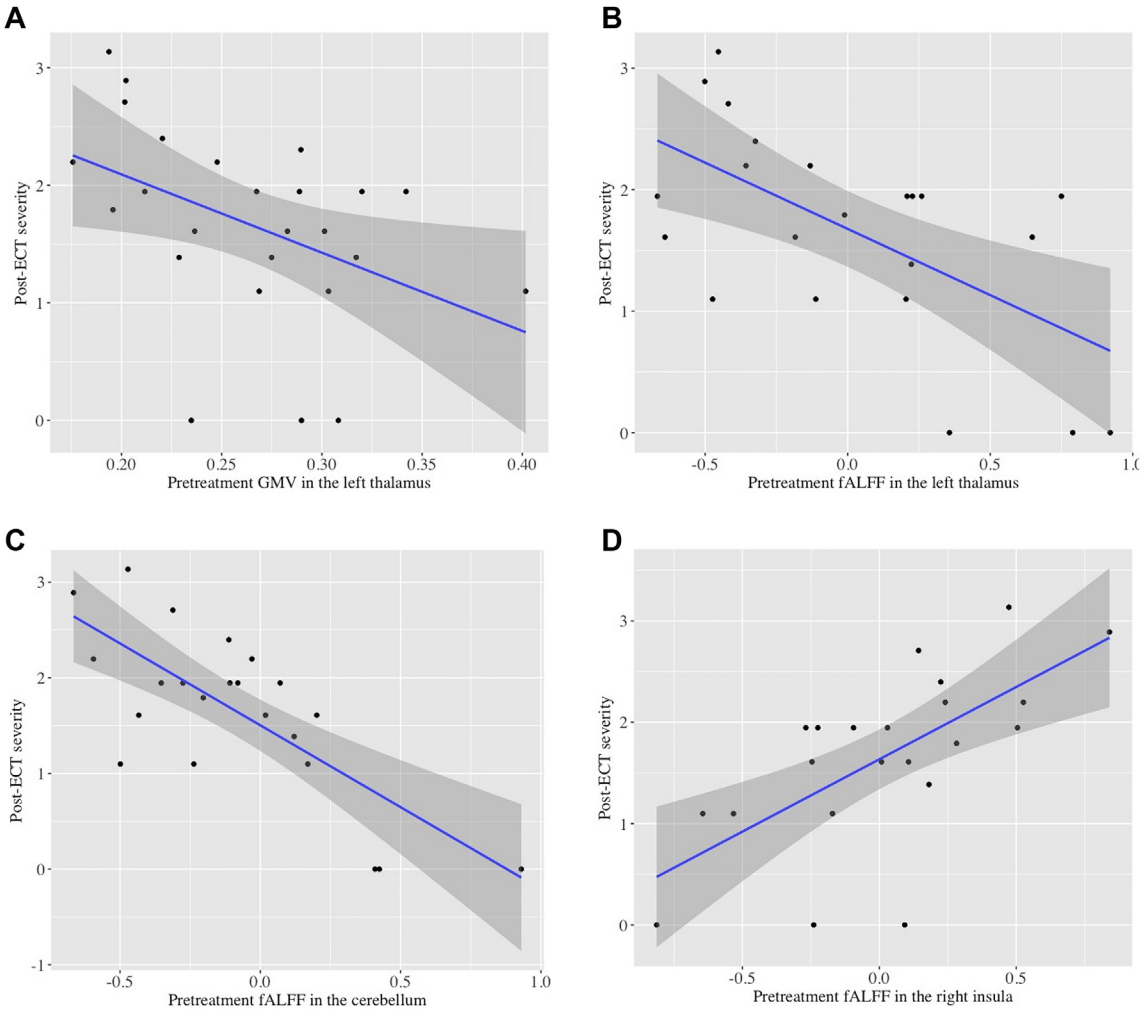

Fig. 2. Relationship between GMV/fALFF and residual depression severity after ECT. Pretreatment GMV in the left thalamus (A), fALFF in the left thalamus (B), and fALFF in the cerebellum (C) showed negative correlation with post-ECT residual severity. Pretreatment fALFF in the right insula (D) showed positive correlation with post-ECT residual severity. Post-ECT severity (y-axes) represents natural log transformed post-ECT total HAM-D scores.

Table 2
Pretreatment GMV and fALFF associated with post-ECT depression severity.

Brain Regions	Peak MNI coordinates			T values	Z scores	Cluster Size (voxels[a])
	x	y	z			
Grey matter volume						
Negative correlation						
Left thalamus	−10	−32	−3	5.26	4.08	723
Positive correlation						
None						
Fractional amplitude of low-frequency fluctuations						
Negative correlation						
Left thalamus	−3	−15	9	8.15	5.05	124
Cerebellum	0	−63	−15	5.16	3.90	85
Positive correlation						
Right insula	30	15	6	5.33	3.98	68

Abbreviation GMV: grey matter volume, fALFF: fractional amplitude of low frequency fluctuation, ECT: electroconvulsive therapy.
[a] In GMV analyses, one voxel size is 1.5 × 1.5 × 1.5 mm^3, whereas in fALFF analyses, one voxel size means 3.0 × 3.0 × 3.0 mm^3.

revealed that nonremitters showed smaller thalamic GMV and elevated fALFF in the right insula compared to remitters and controls (Supplementary Fig. 3).

3.4. Clinical demographics and remission-predictive regions

GMV in the left thalamus showed a negative correlation with age ($r = -0.67$, $df = 23$, $p < 0.001$), and GMV in the left thalamus showed significant differences between those with a family history of mood disorders and those without ($t = 3.7$, $df = 23$, $p = 0.001$). These results were still significant after correction for multiple comparisons. Results of other clinical demographics are reported in the supplementary material.

4. Discussion

The main finding of the current study was that pretreatment smaller thalamic GMV and fALFF were associated with higher post-ECT residual severity (i.e. worse response to ECT). Our results highlight the possible importance of the thalamus in the context of biological predictors for ECT remission and its role in the underlying mechanisms of ECT action.

4.1. Thalamus and depression

The thalamus is a central hub of a cortico-striatal-thalamic-cortical (CSTC) loop, which mediates emotional, cognitive, and motor function (Krack et al., 2010). The thalamus has direct anatomic connections with the hippocampus, anterior cingulate cortex (ACC), and medial prefrontal cortex (MPFC), all of which are implicated in depression. Although thalamic volume reduction has been reported in previous meta-analyses (Kempton et al., 2011; Arnone et al., 2016), it seems to be relatively less robust compared to results of other brain regions (e.g. volume reduction in the hippocampus) (Schmaal et al., 2016). Differences in patients' characteristics across studies may explain these inconsistent results regarding the thalamus. According to previous studies, late-life depression (Bora et al., 2012) and melancholic depression (Soriano-Mas et al., 2011), both of which are the majority of our cohort, have shown reduced thalamic volume.

Abnormalities in resting-state thalamic activity, especially pulvinar activity, were reported in depression (Hamilton et al., 2012). The pulvinar has connections with the amygdala, insula, and dorsal ACC, and plays a key role in emotional attention and awareness (Pessoa and Adolphs, 2010). Resting-state thalamic activity has been reported as one possible predictor for antidepressant treatments. Pretreatment reduced fALFF in the right thalamus were associated with a better response to antidepressant medications in depressed patients in the early course of treatment (Yamamura et al., 2016). One of our results (specifically, that pretreatment reduced fALFF in the thalamus was associated with a worse response) was the exact opposite of the prior fALFF study. This discrepancy may be due to patients' characteristics: the previous study included middle-aged (mean 45 years old) non-TRD patients without psychotic symptoms, whereas our study included geriatric (mean 67 years old) TRD patients who needed ECT, and our study included many patients with psychotic features. One previous PET study reported that pretreatment reduced metabolism in the left thalamus in patients with TRD was associated with a worse response to anterior cingulotomy (Dougherty et al., 2003), which was similar to our result. Given all this evidence, the thalamic activity may be related to treatment-resistancy or disease progression, and it may be used to stratify heterogeneous depressed patients.

We found that pretreatment thalamic volume was significantly smaller in nonremitters compared to that of remitters and healthy controls, and pretreatment thalamic volume of remitters did not show significant differences compared to healthy controls. Although speculative, thalamic abnormalities may be one of the possible neurobiological bases of patients who did not remit after ECT (i.e., ultra-resistant depression). In addition, we found that a family history of mood disorder was associated with smaller thalamic volume. Our results may suggest that family history or genetic loading has influence on brain structure (e.g. thalamic volume), which mediates the variability of one's clinical response to ECT. Family history was considered a predictor of ECT response among ECT experts (Kellner et al., 2012a), but it has not been well studied so far (Haq et al., 2015). Thalamic volume was influenced by genetic variants in the serotonin transporter-linked promoter region (5-HTTLPR) (Ancelin et al., 2019). Future studies should focus on associations among clinical demographics (i.e. family history) or genetic variants, brain structure, and ECT response to test this hypothesis.

As an additional investigation, we examined whether the identified overlapped region included the habenula in addition to the thalamus (supplementary material), and we found the identified cluster included the habenula. The habenula is a diencephalic structure that is located next to the third ventricle. The lateral habenula sends its efferent projections to several neurotransmitter systems, including serotonin, noradrenaline and dopamine (Herkenham and Nauta, 1979), all of which are implicated in the pathophysiology of depression. Moreover, a previous study showed that DBS of the lateral habenula was effective in a patient with treatment-resistant psychotic depression (Sartorius et al., 2010). A postmortem study revealed that patients with mood disorders showed smaller habenula volume compared to controls, but patients with schizophrenia did not (Ranft et al., 2010). Smaller habenula volume was reported in patients with TRD who received ECT (Sartorius et al., 2016), although the predictive value of the habenula was not reported in the previous study. Given the importance of the habenula in depression, future studies using a high-field MRI, which can detect the structure of the habenula, may be needed to confirm the predictive value of the habenula for antidepressant treatments.

4.2. Thalamus, cerebellum, and ECT

In the current study, pretreatment resting-state thalamic and cerebellar function were negatively associated with post-ECT residual severity: pretreatment smaller thalamic and cerebellar activity predicted less robust response to ECT. The thalamus and the cerebellum have been considered to be critical regions in the context of ECT-induced generalized seizures. Bitemporal ECT-induced generalized seizures increased cerebral blood flow (CBF) near the stimulation site (i.e. the insula and the temporal regions) and the thalamus, in the early phase of seizures (Enev et al., 2007). In the post-ictal period, elevated cerebellar CBF was observed (Blumenfeld et al., 2009). The thalamus and the upper brain stem are considered to be important structures for seizure

propagation (Enev et al., 2007; Blumenfeld et al., 2009), and the cerebellum may contribute to seizure termination and/or to post-ictal suppression, because the cerebellum sends inhibitory outputs to influence thalamocortical circuits (Blumenfeld et al., 2009; Salgado-Benitez et al., 1982). One critical component of the therapeutic efficacy of ECT was seizure activity (Cronholm and Ottosson, 1996), and seizure quality was associated with ECT efficacy in depressed patients (Minelli et al., 2016). ECT increased thalamic CBF only when ECT successfully induced generalized seizure (Takano et al., 2011), and a recent study showed that only ECT responders showed increased CBF in the thalamus (Leaver et al., 2018). Considering all this evidence, the interactions between the cerebellum and the thalamocortical pathways may relate to the quality of ECT-induced generalized seizures, and the following clinical improvement.

4.3. Right anterior insula and antidepressant treatment response

The anterior insula is a functional node for the integration of sensory and motor information via the thalamus, and plays a critical role in interoceptive awareness (Critchley et al., 2004), and in various emotional and cognitive functions (Augustine, 1996). The anterior insula is anatomically connected to the distributed brain regions related to depression, including the anterior cingulate cortex, amygdala, and hypothalamus (Augustine, 1996). Reduced insular volume in depression was reported in previous meta-analyses (Arnone et al., 2016; Wise et al., 2017), and disrupted effective connectivity among insula and other networks was also reported in melancholic depression (Hyett et al., 2015).

The current study shows that pretreatment elevated activity in the right anterior insula was associated with nonremission after ECT. Our result adds evidence to previous studies reporting the associations between increased metabolism in the right anterior insula and a less robust response to antidepressant treatments, including medications, psychotherapy (Dunlop et al., 2015), and vagus nerve stimulation (VNS) (Conway et al., 2012). Given all the evidence, including the current study, pretreatment elevated activity in the right anterior insula may be a biomarker for a worse prognosis regardless of treatment modality.

4.4. Limitations

Some limitations of the study should be acknowledged. First, we included only late-life melancholic depressed patients who received bitemporal ECT. These limited inclusion criteria were chosen in order to minimize heterogeneity in our sample and it may be one strength of our study, but in contrast, it is difficult to generalize our results to non-geriatric, non-melancholic patients who receive right unilateral ECT. Second, our participants continued taking medications, which may affect the pretreatment MRI measurements, although additional analyses including medication dosage as covariates did not change our main results (supplementary material). Because our participants were severely depressed patients, discontinuation of medications before the first ECT was not feasible. Third, the small number of nonremitters limits the power to detect potential differences among remitters, non-remitters, and controls. Although it seems to be difficult to include a similar number of nonremitters to remitters in our study population because old age is one of the most replicated predictors for ECT remission (Van Diermen et al., 2018), future studies with a larger cohort or multi-site collaborative work (Oltedal et al., 2017) are needed to explore the underlying neurobiology of patients who did not respond to ECT (i.e. ultra-resistant depression).

5. Conclusion

Pretreatment thalamic volume and resting-state activity predicted the efficacy of ECT. Our results highlight the importance of the thalamus as a critical region not only for predictors of ECT remission, but also for the underlying mechanisms of ECT action.

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Conflicts of interest

The authors declare no conflicts of interest.

Author contribution

AT and TK designed the study. AT, RT and KS recruited the participants. SN acquired all MRI data. AT analysed the data with YT's help. AT conducted a literature search and wrote the first draft. KC, RT, YT, SN, KS, SK, JH, BY, MM, and TK wrote the final manuscript. All authors contributed to and have approved the final manuscript.

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Appendix A. Supplementary data

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