



Cortical Thickness and Surface Area Abnormalities in Bipolar I and II Disorders

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Objective Although bipolar II disorder (BD II) is not simply a mitigated form of bipolar I disorder (BD I), their neurobiological differences have not been elucidated. The present study aimed to explore cortical thickness (CT) and surface area (SA) in patients with BD I and BD II and healthy controls (HCs) to investigate the shared and unique neurobiological mechanisms of BD subtypes.

Methods We enrolled 30 and 44 patients with BD I and BD II, respectively, and 100 HCs. We evaluated CT and SA using FreeSurfer and estimated differences in CT and SA among the three groups (BD I vs. BD II vs. HC). We adjusted for age, sex, educational level, and intracranial volume as confounding factors.

Results We found widespread cortical thinning in the bilateral frontal, temporal, and occipital regions; cingulate gyrus; and insula in patients with BD. Alterations in SA, including increased SA of the pars triangularis and decreased SA of the insula, were noted in patients with BD. Overall, we found BD II patients demonstrated decreased SA in the right long insula compared to BD I patients.

Conclusion Our results suggest that decreased SA in the right long insula is crucial for differentiating BD subtypes.

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Keywords Cortical thickness; Surface area; Bipolar disorder; Bipolar subtype; Long insula.

INTRODUCTION

Bipolar disorder (BD) is a recurrent and debilitating mental illness characterized by the presence of manic, hypomanic, and depressive episodes.¹ More than 1% of the global population is affected by BD, regardless of region, race, and socioeconomic status.² Due to cognitive and functional impairments, BD is one of the primary causes of disability among young people (i.e., working population aged 20–50 years), leading to individual and social disease burdens.^{2,3} Two subtypes of BD, type I (BD I) and II (BD II), differ in that BD I involves a full-blown manic episode, while BD II is characterized by major depres-

sive disorder combined with hypomanic episodes.¹ Mood disturbances in manic episodes seen in BD I patients are severe and cause marked impairments in social functioning; however, studies have indicated that the clinical course of BD II is characterized by more recurrences, chronicity, short remission periods, higher suicide rates, and lower quality of life.⁴⁻⁷ This shows that BD II is not simply a mitigated form of BD I, suggesting that it is necessary to explore BD subtypes as different disease entities in neuroimaging studies.⁸ Unfortunately, the neurobiological differences between BD subtypes have not been thoroughly elucidated, as previous studies have focused on patients with BD I or have not distinguished between subtypes.^{7,8}

Previous studies focused primarily on BD I, and many have mainly investigated cortical volume using voxel-based morphometry⁸ or cortical thickness (CT) using surface-based morphometry. Gray matter volume is a function of two distinct morphometries: CT and surface area (SA).^{9,10} While CT reflects the number of neurons within each column, SA is reflective of the number of columns and the overall size of the cortex.^{10,11} As these two parameters are the products of distinct, well-differ-

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entiated ontogenic processes, CT and SA can be separately affected by genetic or extrinsic factors.^{12,13} In addition, SA may be determined earlier in the neurodevelopmental period, such as during embryonic and neonatal life, and is less affected by environmental factors.^{12,14} Therefore, in terms of brain endophenotype, investigating CT and SA together with gray matter volume enhances the sensitivity for detecting subtype differences using cortical morphometry and provides more information underpinning the pathophysiology of BD.^{8,9}

Previous studies have shown relatively consistent results regarding CT in patients with BD. A meta-analysis found widespread cortical thinning in the anterior cingulate cortex, orbitofrontal cortex (OFC), paracingulate, superior temporal gyrus, and prefrontal regions in patients with BD compared to that in healthy controls (HCs).¹⁰ Large studies, such as the ENIGMA consortium, have worked to elucidate cortical abnormalities in patients with BD and reported substantially decreased CT in the bilateral frontal, temporal, and parietal regions, including the ventrolateral prefrontal cortex (VLPFC), which has long been implicated in BD neurobiology.^{11,15} Conversely, there are some inconsistent results regarding SA in BD patients. Some studies,^{11,16-20} including the ENIGMA consortium, have failed to detect significantly altered SA, but others have found enlarged SA in the superior frontal region; temporal pole;¹³ postcentral, precuneus, supramarginal, and superior temporal gyrus; insula,²¹ and pars triangularis²² and decreased SA in the fronto-temporal cortices.⁸

As described, there are few studies comparing BD subtypes that have explored both CT and SA. Regarding differences in CT between BD subtypes, previous research has not detected significant differences between BD subtypes,^{11,23,24} however, some studies have found cortical thinning in the right medial orbitofrontal, left superior temporal,²⁵ and right temporal cortices⁸ in patients with BD I compared to that in patients with BD II. Moreover, differences in cortical SA between BD subtypes have been explored, but there have been no significant regions showing differences between BD I and II.^{8,11}

Therefore, we aimed to explore CT and SA in patients with BD I and BD II and HCs to investigate shared and unique neurobiological mechanisms. We hypothesized that patients with BD I and II would show common and distinct cortical abnormalities. We expected to identify a differential marker to compare BD subtypes. Finally, we aimed to better understand the associations between symptom severity and illness duration based on CT and SA.

METHODS

Participants

Between January 2015 and March 2019, 30 and 44 patients

diagnosed with BD I and BD II, respectively, were recruited from outpatient clinics in Korea University Anam Hospital in Seoul, South Korea. Board-certified trained psychiatrists (BJ Ham and KM Han) confirmed the diagnosis of BD I and BD II using the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I) based on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV). The inclusion criteria for patients with BD were as follows: 1) age 19–64 years and 2) current euthymic or depressive state. Exclusion criteria for the patient and HC groups were as follows: 1) major psychiatric disorders other than BD (based on the DSM-IV criteria), including substance use or personality disorders, as comorbidities; 2) serious medical diseases or primary neurologic illnesses such as renal failure, cerebrovascular disease, organic brain damage, and epilepsy; 3) comorbid personality disorder; 4) comorbid alcohol or substance addiction (based on the DSM-IV criteria); 5) pregnancy; and 6) any contraindication for magnetic resonance imaging²⁶ such as implanted pacemaker or claustrophobia. One hundred age- and sex-matched HCs were recruited via advertisements within the community. Board-certified psychiatrists performed an interview to confirm that the HCs had no current or previous Axis I or Axis II disorders. We evaluated the severity of mood symptoms in 74 BD patients using the 17-item Hamilton Depression Rating Scale (HDRS)²⁷ and Young Mania Rating Scale (YMRS).²⁸ Informed consent was obtained from all participants after providing a thorough explanation of the study. The present study was approved by the Institutional Review Board of Korea University Anam Hospital (IRB No: 2015AN0009) and followed the principles of the Declaration of Helsinki.

MRI data acquisition and image processing

All participants underwent T-1 weighted imaging, performed on a 3.0 Tesla Siemens Trio whole-body imaging system (Siemens Medical Systems, Erlangen, Germany). T1-weighted images were acquired parallel to the anterior commissure-posterior commissure line using T1-weighted magnetization-prepared rapid gradient-echo (MP-RAGE) imaging (repetition time=1,900 ms, echo time=2.6 ms, field of view=220 mm, 256×256 matrix size, 176 coronal slices without gap, 1×1×1 mm³ voxels, flip angle=16°, and number of excitations=1).

We used FreeSurfer (5.3 development version; Laboratory for Computational Neuroimaging, Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, MA, USA; <http://surfer.nmr.mgh.harvard.edu>) to create a 3D model of cortical surface reconstructions computed from T-1 images and to analyze CT and SA. Previous publications have described in detail the technical aspects of this pipeline.²⁹⁻³⁵ Briefly, this process includes the motion correction of volumetric T1-weighted images, removal of non-brain tissue using a hybrid watershed/

surface deformation procedure, automated Talairach transformation of each subject's native brain, segmentation of the gray matter-white matter volumetric structures,³² inflation of the cortical surface to an average spherical surface to locate both the pial surface and the gray matter-white matter boundary, intensity normalization, and automated topology correction.^{33,34,36} The transition of gray/white matter and the pial boundary were detected by finding a marked change in intensity through surface deformation. Automatic parcellation per hemisphere into 74 cortical gyri and sulci and the calculation of CT and SA were performed using the FreeSurfer package according to the Des-

trieux atlas.³⁷ In our current analysis, we extracted the values of gray matter thickness and SA of 76 cortical gyri from bilateral hemispheres.

Statistical analysis

In our primary analysis, we used one-way analysis of covariance to estimate differences in CT and SA. Group variables (BD I vs. BD II vs. HC) were included as independent variables, with the extracted gray matter thickness or SA values of the 76 bilateral cortical gyri as dependent variables. We included age, sex, educational level, and total intracranial volume

Table 1. Demographic and clinical characteristics of patients with BD and HCs

Characteristics	BD I (N=30)	BD II (N=44)	HC (N=100)	p-value (F, t, χ^2)
Age (yr)	38.03±11.46	32.41±9.80	35.09±11.58	0.103 (F=2.302)
Sex (male/female)	9/21	15/29	37/63	0.771 (χ^2 =0.521)
Education level				0.364 (χ^2 =4.324)
Elementary and middle school	1	1	5	
High school or college/university	26	42	83	
Above graduate school	3	1	12	
Total intracranial volume	1410±101	1416±129	1465±151	0.057 (F=2.909)
HDRS	4.77±4.07	8.36±5.48	1.78±1.92	6.88×10 ⁻¹⁹ (F=53.940)
YMRS	1.97±2.46	0.75±1.24	NA	0.017 (t=2.504)
K-MDQ	8.13±4.22	9.32±2.87	NA	0.186 (t=-1.342)
HAS	5.87±4.06	7.80±6.36	NA	0.146 (t=-1.468)
BIS	50.73±8.63	55.20±10.88	NA	0.064 (t=-1.883)
Family history of mood disorder (N)	10	18	NA	0.509 (χ^2 =0.435)
Euthymic (or remission) state/depressive state	23/7	23/21	NA	0.034 (χ^2 =4.513)
Duration of illness (months)	97.83±95.10	50.09±72.60	NA	0.024 (t=2.326)
Drug-treated patients (N)	30	43	NA	0.406 (χ^2 =0.691)
Medication (N)				
SSRI	3	10		
SNRI	1	3		
NDRI	2	8		
NaSSA	0	2		
Combination of AD	0	2		
Lithium	8	4		
AED	18	37		
Lithium+AED	4	0		
AED+AED	1	0		
AP	28	27		
Combination of AP	14	4		

The p value for comparison in age, TICV, and HDRS scores were obtained using the ANOVA test. The p value for sex and educational level distribution was obtained by chi-squared test. The p value for comparison in YMRS, K-MDQ, BIS, HAS scores were obtained using student's t-test. BD, bipolar disorder; HC, healthy control; BD I, bipolar I disorder; BD II, bipolar II disorder; HDRS, Hamilton Depression Rating Scale; YMRS, Young Mania Rating Scale; K-MDQ, Korean version of Mood Disorder Questionnaire; HAS, Hamilton Anxiety Rating Scale; BIS, Barratt Impulsiveness Scale; SSRI, selective serotonin reuptake inhibitor; NDRI, norepinephrine-dopamine reuptake inhibitor; NaSSA, noradrenergic and specific serotonergic antidepressant; Combination of Ads, combination of two or more antidepressants; AED, anti-epileptic drugs; AP, antipsychotics; AD, antidepressants

Table 2. Comparison of cortical thickness between patients with BD I and BD II and HCs

Cortical regions	BD I (N=30)	BD II (N=44)	HC (N=100)	All groups	
	Mean±SD	Mean±SD	Mean±SD	F	p
Left hemisphere					
L Frontomarginal gyrus	2.264±0.028	2.265±0.023	2.403±0.015	16.903	2.07×10 ⁻⁷
L Inferior occipital gyrus	2.325±0.036	2.407±0.030	2.529±0.020	14.553	1.49×10 ⁻⁶
L Subcentral gyrus	2.606±0.035	2.620±0.029	2.764±0.019	12.947	5.92×10 ⁻⁶
L Transverse frontopolar gyrus	2.543±0.038	2.612±0.032	2.705±0.021	7.824	5.65×10 ⁻⁴
L Anterior cingulate gyrus	2.687±0.024	2.657±0.020	2.851±0.013	39.210	1.09×10 ⁻¹⁴
L Anterior mid-cingulate gyrus	2.602±0.031	2.576±0.026	2.744±0.017	18.195	7.10×10 ⁻⁸
L Dorsal posterior cingulate gyrus	2.611±0.052	2.562±0.043	2.911±0.028	28.064	3.11×10 ⁻¹¹
L Ventral posterior cingulate gyrus	2.235±0.069	2.157±0.058	2.554±0.038	19.600	2.26×10 ⁻⁸
L Cuneus	1.947±0.059	1.984±0.049	1.763±0.033	8.344	3.52×10 ⁻⁴
L Pars opercularis	2.675±0.033	2.754±0.028	2.845±0.018	11.296	2.51×10 ⁻⁵
L Pars orbitalis	2.673±0.043	2.661±0.036	2.820±0.023	8.977	1.98×10 ⁻⁴
L Pars triangularis	2.563±0.030	2.624±0.025	2.714±0.017	11.151	2.85×10 ⁻⁵
L Short insular gyrus	3.189±0.073	3.277±0.060	3.533±0.040	11.650	1.84×10 ⁻⁵
L Middle occipital gyrus	2.372±0.040	2.406±0.033	2.593±0.022	18.026	8.16×10 ⁻⁸
L Lateral occipito-temporal gyrus	2.427±0.069	2.489±0.058	2.813±0.038	17.980	8.48×10 ⁻⁸
L Lingual gyrus	2.155±0.061	2.138±0.051	1.905±0.034	10.559	4.81×10 ⁻⁵
L Parahippocampal gyrus	2.787±0.048	2.824±0.040	3.006±0.026	11.776	1.64×10 ⁻⁵
L Angular gyrus	2.630±0.027	2.626±0.023	2.736±0.015	10.876	3.63×10 ⁻⁵
L Supramarginal gyrus	2.594±0.036	2.600±0.030	2.804±0.020	23.257	1.23×10 ⁻⁹
L Superior parietal lobule	2.255±0.033	2.293±0.028	2.430±0.018	14.924	1.09×10 ⁻⁶
L Precentral gyrus	2.680±0.040	2.693±0.033	2.880±0.022	16.250	3.56×10 ⁻⁷
L Subcallosal gyrus	2.206±0.070	2.261±0.059	2.493±0.039	9.247	1.55×10 ⁻⁴
L Anterior transverse temporal gyrus	2.362±0.050	2.460±0.042	2.255±0.027	8.560	2.89×10 ⁻⁴
L Planum polare	3.036±0.064	3.104±0.053	3.437±0.035	22.392	2.43×10 ⁻⁹
L Middle temporal gyrus	2.731±0.056	2.758±0.046	3.074±0.030	24.043	6.66×10 ⁻¹⁰
Right hemisphere					
R Frontomarginal gyrus	2.284±0.034	2.296±0.028	2.421±0.018	10.278	6.17×10 ⁻⁵
R Inferior occipital gyrus	2.505±0.046	2.485±0.038	2.695±0.025	13.434	3.89×10 ⁻⁶
R Subcentral gyrus	2.590±0.036	2.574±0.030	2.785±0.019	22.776	1.79×10 ⁻⁹
R Transverse frontopolar gyrus	2.477±0.033	2.507±0.027	2.675±0.018	21.157	6.46×10 ⁻⁹
R Anterior cingulate gyrus	2.682±0.027	2.627±0.023	2.825±0.015	29.606	9.88×10 ⁻¹²
R Anterior mid-cingulate gyrus	2.671±0.026	2.626±0.022	2.830±0.014	35.687	1.25×10 ⁻¹³
R Dorsal posterior cingulate gyrus	2.770±0.039	2.739±0.032	2.952±0.021	18.680	4.77×10 ⁻⁸
R Ventral posterior cingulate gyrus	2.348±0.073	2.366±0.061	2.653±0.040	11.337	2.42×10 ⁻⁵
R Cuneus	1.945±0.061	2.028±0.051	1.792±0.033	8.203	4.00×10 ⁻⁴
R Pars opercularis	2.661±0.030	2.735±0.025	2.881±0.017	25.036	3.09×10 ⁻¹⁰
R Pars orbitalis	2.667±0.041	2.747±0.034	2.844±0.023	7.898	5.28×10 ⁻⁴
R Pars triangularis	2.540±0.029	2.656±0.024	2.756±0.016	22.921	1.60×10 ⁻⁹
R Middle frontal gyrus	2.653±0.028	2.665±0.024	2.767±0.016	9.946	8.30×10 ⁻⁵
R Middle occipital gyrus	2.467±0.039	2.436±0.033	2.626±0.022	14.116	2.17×10 ⁻⁶
R Lateral occipito-temporal gyrus	2.454±0.062	2.517±0.051	2.806±0.034	18.349	6.26×10 ⁻⁸
R Lingual gyrus	2.187±0.055	2.201±0.046	1.957±0.030	12.929	6.02×10 ⁻⁶

Table 2. Comparison of cortical thickness between patients with BD I and BD II and HCs (continued)

Cortical regions	BD I (N=30)	BD II (N=44)	HC (N=100)	All groups	
	Mean±SD	Mean±SD	Mean±SD	F	p
R Parahippocampal gyrus	2.889±0.054	2.885±0.045	3.073±0.030	8.241	3.86×10 ⁻⁴
R Orbital gyrus	2.610±0.032	2.687±0.026	2.774±0.017	11.481	2.13×10 ⁻⁵
R Angular gyrus	2.573±0.026	2.609±0.022	2.716±0.014	15.359	7.53×10 ⁻⁷
R Supramarginal gyrus	2.576±0.036	2.602±0.030	2.811±0.020	25.634	1.96×10 ⁻¹⁰
R Superior parietal lobule	2.260±0.033	2.284±0.028	2.411±0.018	11.888	1.49×10 ⁻⁵
R Precentral gyrus	2.664±0.039	2.701±0.032	2.838±0.021	10.919	3.49×10 ⁻⁵
R Planum polare	2.974±0.063	3.016±0.052	3.222±0.034	8.890	2.14×10 ⁻⁴
R Middle temporal gyrus	2.759±0.051	2.779±0.043	3.059±0.028	21.714	4.15×10 ⁻⁹

The general linear model (GLM) was adjusted for age, sex, educational level, and intracranial volume as covariates. Regions that remained significant after Bonferroni correction are listed: 76 regions of cortex, corrected $p=(0.05/76)=6.58\times 10^{-4}$. BD I, bipolar disorder type I; BD II, bipolar disorder type II; HC, healthy controls; SD, standard deviation

(TICV) as covariates to prevent potential confounding effects. For cortical regions indicated to have significant alterations in our main analysis, post-hoc analyses were performed to determine significant pairwise comparisons after Bonferroni tests. For multiple comparisons, Bonferroni corrections were applied to minimize the type I error risk: $p<0.05/76$ (number of comparisons in bilateral hemispheres) $=6.58\times 10^{-4}$.

In an additional analysis, we performed a two-tailed Pearson's partial correlation test to examine the correlation of illness duration and HDRS scores with CT or SA in the BD groups. Cortical regions with significant differences among the three groups in the main analyses were included in the additional analysis. Correlation analysis was performed with age, sex, educational level, and TICV as covariates.

To analyze group differences in demographic and clinical variables, we performed analysis of variance³⁸ for continuous variables (i.e., age, TICV, and HDRS scores) and chi-squared tests for categorical variables (i.e., sex, educational level, family history, mood state, and drug treatment). We also performed t-tests to compare illness duration and psychiatric scale scores, including the YMRS, Korean version of the Mood Disorder Questionnaire, Hamilton Anxiety Rating Scale, and Barratt Impulsiveness Scale scores, between the BD I and BD II groups. All statistical analyses were performed using SPSS (version 24.0; IBM Corp., Armonk, NY, USA).

RESULTS

Demographic and clinical characteristics

The demographic and clinical variables of 30 patients with BD I, 44 patients with BD II, and 100 HCs, including age, sex, educational levels, TICV, mood state, and psychotropic medications, are presented in Table 1. No significant differences were found in age, sex, educational level, and TICV. There were significant differences in the HDRS score among the BD I, BD

II, and HC groups ($F=53.940$, $p<0.001$). For the mood state, seven patients with BD I and 21 patients with BD II were in a depressive episode, while the rest of the patients were in a euthymic state ($p<0.05$). Although the YMRS scores in the BD I group were significantly higher than those in the BD II group ($p<0.05$), none of the patients with BD I or BD II showed a minimum score for manic symptom severity of 13 points.^{28,39} The illness duration in the BD I group was significantly longer than that in the BD II group. All patients with BD I and 43 patients with BD II were taking psychotropic medications at the time of enrollment. Detailed information about psychotropic medications used by BD patients is described in Table 1.

CT analysis

Cortical thinning in patients with BD compared to that in HCs

We detected significant and widespread cortical thinning in diverse regions along the bilateral frontal, temporal, parietal, and occipital regions; cingulate gyrus; and left insula in both patients with BD I and BD II. Forty-nine cortical regions of the 76 cortical gyri demonstrated significant differences, and the results of CT analysis are presented in Tables 2 and 3. Notably, the regions with the largest differences on comparison between patients with BD I and BD II and HCs involved the bilateral cingulate gyrus, including the left anterior cingulate gyrus ($p=1.09\times 10^{-14}$), right anterior mid-cingulate gyrus ($p=1.25\times 10^{-13}$), and right anterior cingulate gyrus ($p=9.88\times 10^{-12}$). Patients with BD I showed more widespread cortical thinning than patients with BD II and HCs. Some areas of the VLPFC (including the pars triangularis, left pars opercularis, and right pars orbitalis of the inferior frontal gyrus) and the OFC (including the right orbital gyrus) showed significant cortical thinning only in patients with BD I but not in patients with BD II, compared to that in HCs; however, the left pars orbitalis showed significant

Table 3. Post-hoc comparison of cortical thickness between patients with BD I and BD II and HCs

Cortical regions	BD I vs. HC	BD II vs. HC	BD I vs. BD II	Comparison
	P	P	P	
Left hemisphere				
L Frontomarginal gyrus	2.38×10^{-5}	2.36×10^{-6}	0.971	BD I & BD II < HC
L Inferior occipital gyrus	1.73×10^{-6}	8.94×10^{-4}	0.085	BD I < HC
L Subcentral gyrus	1.01×10^{-4}	5.90×10^{-5}	0.758	BD I & BD II < HC
L Transverse frontopolar gyrus	3.14×10^{-4}	0.018	0.169	BD I < HC
L Anterior cingulate gyrus	1.84×10^{-8}	2.79×10^{-13}	0.344	BD I & BD II < HC
L Anterior mid-cingulate gyrus	8.79×10^{-5}	2.11×10^{-7}	0.512	BD I & BD II < HC
L Dorsal posterior cingulate gyrus	1.06×10^{-6}	3.39×10^{-10}	0.474	BD I & BD II < HC
L Ventral posterior cingulate gyrus	8.33×10^{-5}	8.33×10^{-5}	0.388	BD I & BD II < HC
L Cuneus	0.008	3.13×10^{-4}	0.633	BD II > HC
L Pars opercularis	1.33×10^{-5}	0.007	0.067	BD I < HC
L Pars orbitalis	0.003	3.08×10^{-4}	0.833	BD II < HC
L Pars triangularis	2.34×10^{-5}	0.004	0.124	BD I < HC
L Short insular gyrus	5.33×10^{-5}	6.07×10^{-4}	0.350	BD I & BD II < HC
L Middle occipital gyrus	2.45×10^{-6}	5.82×10^{-6}	0.509	BD I & BD II < HC
L Lateral occipito-temporal gyrus	2.31×10^{-6}	6.55×10^{-6}	0.488	BD I & BD II < HC
L Lingual gyrus	4.97×10^{-4}	2.3×10^{-4}	0.837	BD I & BD II > HC
L Parahippocampal gyrus	1.05×10^{-4}	2.4×10^{-4}	0.560	BD I & BD II < HC
L Angular gyrus	8.2×10^{-4}	1.01×10^{-4}	0.928	BD II < HC
L Supramarginal gyrus	6.74×10^{-7}	5.85×10^{-8}	0.887	BD I & BD II < HC
L Superior parietal lobule	8.43×10^{-6}	6.9×10^{-5}	0.382	BD I & BD II < HC
L Precentral gyrus	1.87×10^{-5}	6.15×10^{-6}	0.798	BD I & BD II < HC
L Subcallosal gyrus	4.71×10^{-4}	1.29×10^{-3}	0.551	BD I < HC
L Anterior transverse temporal gyrus	0.063	7.58×10^{-5}	0.137	BD II > HC
L Planum polare	1.52×10^{-7}	6.56×10^{-7}	0.418	BD I & BD II < HC
L Middle temporal gyrus	2.32×10^{-7}	6.79×10^{-8}	0.715	BD I & BD II < HC
Right hemisphere				
R Frontomarginal gyrus	5.02×10^{-4}	3.22×10^{-4}	0.784	BD I & BD II < HC
R Inferior occipital gyrus	3.87×10^{-4}	1.04×10^{-5}	0.737	BD I & BD II < HC
R Subcentral gyrus	3.69×10^{-6}	2.27×10^{-8}	0.737	BD I & BD II < HC
R Transverse frontopolar gyrus	4.15×10^{-7}	9.49×10^{-7}	0.492	BD I & BD II < HC
R Anterior cingulate gyrus	9.39×10^{-6}	2.03×10^{-11}	0.124	BD I & BD II < HC
R Anterior mid-cingulate gyrus	3.34×10^{-7}	8.25×10^{-13}	0.186	BD I & BD II < HC
R Dorsal posterior cingulate gyrus	6.24×10^{-5}	1.65×10^{-7}	0.573	BD I & BD II < HC
R Ventral posterior cingulate gyrus	3.24×10^{-4}	1.34×10^{-4}	0.842	BD I & BD II < HC
R Cuneus	0.029	1.58×10^{-4}	0.295	BD II > HC
R Pars opercularis	2.24×10^{-9}	4.15×10^{-6}	0.064	BD I & BD II < HC
R Pars orbitalis	2.56×10^{-4}	0.022	0.138	BD I < HC
R Pars triangularis	7.15×10^{-10}	7.18×10^{-4}	0.002	BD I < HC
R Middle frontal gyrus	5.63×10^{-4}	4.35×10^{-4}	0.756	BD I & BD II < HC
R Middle occipital gyrus	5.61×10^{-4}	3.78×10^{-6}	0.543	BD I & BD II < HC
R Lateral occipito-temporal gyrus	1.53×10^{-6}	6.51×10^{-6}	0.440	BD I & BD II < HC
R Lingual gyrus	3.50×10^{-4}	1.98×10^{-5}	0.847	BD I & BD II > HC

Table 3. Post-hoc comparison of cortical thickness between patients with BD I and BD II and HCs (continued)

Cortical regions	BD I vs. HC	BD II vs. HC	BD I vs. BD II	Comparison
	P	P	P	
R Orbital gyrus	1.10×10^{-5}	0.007	0.062	BD I<HC
R Angular gyrus	4.64×10^{-6}	7.84×10^{-5}	0.307	BD I & BD II<HC
R Supramarginal gyrus	5.92×10^{-8}	4.55×10^{-8}	0.582	BD I & BD II<HC
R Superior parietal lobule	1.02×10^{-4}	2.14×10^{-4}	0.572	BD I & BD II<HC
R Precentral gyrus	1.31×10^{-4}	5.71×10^{-4}	0.473	BD I & BD II<HC
R Middle temporal gyrus	9.34×10^{-7}	2.28×10^{-7}	0.766	BD I & BD II<HC

The general linear model (GLM) was adjusted for age, sex, educational level, and intracranial volume as covariates. Regions that remained significant after Bonferroni correction are listed: 76 regions of cortex, corrected $p=(0.05/76)=6.58 \times 10^{-4}$. BD I, bipolar disorder type I; BD II, bipolar disorder type II; HC, healthy controls; SD, standard deviation

cortical thinning in patients with BD II but not in patients with BD I.

No significant differences in CT between BD subtypes

In our post-hoc analysis comparing CT between BD I and II patients (Table 3), there were no significant regions showing differences between patients with BD I and BD II after correction for multiple comparisons. Although BD I patients demonstrated lower CT than BD II patients in the right pars triangularis ($p=0.002$), this difference did not remain significant after Bonferroni correction.

Cortical SA analysis

Mixed results for cortical SA in patients with BD I and BD II compared to that in HCs

Diverse regions with significantly different SA in patients with BD compared to that in HCs are shown in Tables 4 and 5. We detected various regions with significantly decreased SA in both BD I and II patients compared to that in HCs, with the largest differences noted in the left long insula ($p=1.80 \times 10^{-14}$), right straight gyrus ($p=2.18 \times 10^{-9}$), left pars orbitalis ($p=2.28 \times 10^{-9}$), right anterior cingulate gyrus ($p=8.77 \times 10^{-9}$), right posterior mid-cingulate gyrus ($p=6.36 \times 10^{-7}$), right lateral superior temporal gyrus ($p=6.83 \times 10^{-7}$), right subcentral gyrus ($p=6.83 \times 10^{-7}$), right cuneus ($p=1.37 \times 10^{-6}$), right superior frontal gyrus ($p=1.44 \times 10^{-5}$), and right lingual gyrus ($p=2.17 \times 10^{-5}$). Cortices showing increased SA in both patients with BD I and II included the right pars triangularis ($p=2.76 \times 10^{-6}$), right ventral posterior cingulate ($p=1.73 \times 10^{-5}$), right middle frontal gyrus ($p=2.37 \times 10^{-5}$), and right anterior temporal gyrus ($p=3.06 \times 10^{-5}$).

In the present analysis, the SA of the right pars opercularis was significantly smaller in patients with BD II but not patients with BD I than in HCs ($p=3.27 \times 10^{-6}$). Conversely, there were cortical areas showing a significantly increased SA in BD II patients but not in BD I patients compared to that in HCs, including the right frontomarginal gyrus ($p=2.25 \times 10^{-5}$), right

parahippocampal gyrus ($p=4.96 \times 10^{-5}$), and right superior occipital gyrus ($p=5.29 \times 10^{-5}$).

Right long insula as a significant region for differentiating BD subtypes

The right long insula was shown to be a significant region for differentiating BD subtypes in the SA analysis, even after correcting for multiple comparisons. BD II patients demonstrated a significantly smaller SA in the right long insula ($p=6.57 \times 10^{-4}$) than BD I patients. In the left long insula, BD II patients showed a smaller SA than BD I patients, but this difference did not remain significant after Bonferroni correction ($p=0.003$).

Association of CT and SA with illness duration and HDRS scores

The results of the correlations of illness duration with CT and SA after the adjustment for age, sex, educational level, and TICV are shown in Tables 6 and 7. We found a significant positive correlation between CT in the right dorsal posterior cingulate and illness duration, but it was not significant after correction ($p=0.031$). We also explored the correlation of HDRS score with CT and SA. Negative correlations were found for SA in the left long insula ($r=-0.250$, $p=0.037$) and right long insula ($r=-0.292$, $p=0.014$) with HDRS scores, but these correlations did not remain significant after Bonferroni correction.

We also performed correlation analyses between illness duration or HDRS score and cortical abnormalities in patients with BD I and BD II, respectively (Supplementary Tables 1-4 in the online-only Data Supplement). In the correlation analyses, illness duration showed a positive correlation with CT in the left pars triangularis in BD II patients ($r=0.361$, $p=0.022$) and a negative correlation with SA in the left insula in BD I patients ($r=-0.425$, $p=0.030$); however, these results did not persist after Bonferroni correction. Similarly, in BD I patients, HDRS score showed negative correlations with CT in the left inferior occipital gyrus ($r=-0.434$, $p=0.027$), left dorsal posterior cingulate gy-

Table 4. Comparison of cortical surface area between patients with BD I and BD II and HCs

Cortical regions	BD I (N=30)	BD II (N=44)	HC (N=100)	All groups	
	Mean±SD	Mean±SD	Mean±SD	F	p
Left hemisphere					
L Pars orbitalis	915.8±23.9	898.6±19.9	900.4±13.1	22.469	2.28×10 ⁻⁹
L Long insular gyrus	425.4±15.0	367.0±12.5	496.3±8.2	38.484	1.80×10 ⁻¹⁴
Right hemisphere					
R Frontomarginal gyrus	705.1±25.6	754.5±21.3	635.1±14.0	11.417	2.25×10 ⁻⁵
R Subcentral gyrus	899.8±24.8	903.3±20.7	1,017.1±13.6	14.884	1.13×10 ⁻⁶
R Transverse frontopolar gyrus	1,068.9±64.8	1,032.0±54.0	814.7±35.5	8.992	1.96×10 ⁻⁴
R Anterior cingulate gyrus	1,658.5±59.4	1,591.3±49.5	1,941.8±32.5	20.774	8.77×10 ⁻⁹
R Posterior mid-cingulate gyrus	852.6±38.3	822.0±31.9	1,015.3±21.0	15.560	6.36×10 ⁻⁷
R Ventral posterior cingulate gyrus	512.2±67.5	512.5±56.2	234.5±36.9	11.718	1.73×10 ⁻⁵
R Cuneus	1,338.9±48.5	1,326.5±40.4	1,555.0±26.6	14.654	1.37×10 ⁻⁶
R Pars opercularis	734.9±42.4	668.8±35.3	874.5±23.2	12.943	5.94×10 ⁻⁶
R Pars orbitalis	421.4±35.9	379.9±30.0	280.0±19.7	7.721	6.21×10 ⁻⁴
R Pars triangularis	1,221.0±119.2	1,236.5±99.3	696.8±65.2	13.835	2.76×10 ⁻⁶
R Middle frontal gyrus	3,192.5±125.4	3,180.9±104.5	2,677.2±68.7	11.359	2.37×10 ⁻⁵
R Superior frontal gyrus	3,328.3±242.8	3,340.1±202.3	4,344.1±132.9	11.929	1.44×10 ⁻⁵
R Long insular gyrus	436.9±13.9	374.1±11.6	437.4±7.6	11.022	3.19×10 ⁻⁵
R Short insular gyrus	771.4±69.1	753.3±57.6	526.7±37.8	7.953	5.02×10 ⁻⁴
R Superior occipital gyrus	1,121.4±29.5	1,202.4±24.6	1,067.0±16.2	10.452	5.29×10 ⁻⁵
R Lingual gyrus	1,694.2±74.0	1,716.7±61.7	2,008.5±40.5	11.459	2.17×10 ⁻⁵
R Parahippocampal gyrus	988.8±60.8	1,056.8±50.7	795.4±33.3	10.523	4.96×10 ⁻⁵
R Precuneus	1,388.7±83.4	1,424.0±69.5	1,730.0±45.7	10.249	6.33×10 ⁻⁵
R Straight gyrus	444.7±22.2	417.6±18.5	554.5±12.2	22.527	2.18×10 ⁻⁹
R Anterior transverse temporal gyrus	566.5±60.1	544.2±50.1	313.1±32.9	11.069	3.06×10 ⁻⁵
R Lateral superior temporal gyrus	1,020.4±44.7	1,011.9±37.3	1,227.2±24.5	15.476	6.83×10 ⁻⁷
R Planum temporale	959.4±81.3	951.9±67.8	650.0±44.5	9.720	1.02×10 ⁻⁴

The general linear model (GLM) was adjusted for age, sex, educational level, and intracranial volume as covariates. Regions that remained significant after Bonferroni correction are listed: 76 regions of cortex, corrected $p=(0.05/76)=6.58\times 10^{-4}$. BD I, bipolar disorder type I; BD II, bipolar disorder type II; HC, healthy controls; SD, standard deviation

rus ($r=-0.439$, $p=0.025$), left middle occipital gyrus ($r=-0.421$, $p=0.032$), and right pars orbitalis ($r=-0.470$, $p=0.015$), and with SA in the right anterior cingulate gyrus ($r=-0.414$, $p=0.036$), and right straight gyrus ($r=-0.415$, $p=0.035$). However, the significance did not persist after controlling for multiple comparisons.

Association of SA in the right long insula with YMRS score

We performed additional correlation analyses to explore whether the decrease in SA in the right long insular gyrus was related to the lower YMRS score (Supplementary Tables 5 and 6 in the online-only Data Supplement). A positive correlation between YMRS score and SA in the right insula was found in all BD patients ($r=0.244$, $p=0.042$), but this result did not remain significant when the analysis was limited to BD II patients and

after a correction for multiple comparisons was performed.

DISCUSSION

In the present study, we investigated differences in CT and SA between patients with BD I and BD II. In addition to common cortical abnormalities, we also found differences specific to BD subtype. We aimed to explore the neurobiological mechanisms of BD based on these differences and identify neuroimaging markers that differentiated BD subtypes. To our knowledge, ours is the first study to identify cortical regions with significantly different SA values, which can be used for distinguishing BD subtypes.

Table 5. Post-hoc comparison of cortical surface area between patients with BD I and BD II and HCs

Cortical regions	BD I vs. HC	BD II vs. HC	BD I vs. BD II	Comparison
	P	P	P	
Left hemisphere				
L Pars orbitalis	5.29×10^{-4}	1.23×10^{-9}	0.063	BD I & BD II < HC
L Long insular gyrus	5.57×10^{-5}	6.86×10^{-15}	0.003	BD I & BD II < HC
Right hemisphere				
R Frontomarginal gyrus	0.018	7.36×10^{-6}	0.141	BD II > HC
R Subcentral gyrus	5.76×10^{-5}	1.04×10^{-5}	0.915	BD I & BD II < HC
R Anterior cingulate gyrus	4.86×10^{-5}	2.44×10^{-8}	0.387	BD I & BD II < HC
R Posterior mid-cingulate gyrus	2.77×10^{-4}	1.38×10^{-6}	0.541	BD I & BD II < HC
R Ventral posterior cingulate gyrus	4.22×10^{-4}	6.73×10^{-5}	0.997	BD I & BD II > HC
R Cuneus	1.43×10^{-4}	6.11×10^{-6}	0.845	BD I & BD II < HC
R Pars opercularis	0.005	3.27×10^{-6}	0.234	BD II < HC
R Pars triangularis	1.71×10^{-4}	1.30×10^{-5}	0.921	BD I & BD II > HC
R Middle frontal gyrus	4.31×10^{-4}	1.01×10^{-4}	0.944	BD I & BD II > HC
R Superior frontal gyrus	3.41×10^{-4}	6.35×10^{-5}	0.970	BD I & BD II < HC
R Long insular gyrus	0.977	1.12×10^{-5}	6.57×10^{-4}	BD II < BD I & HC
R Superior occipital gyrus	0.109	1.01×10^{-5}	0.037	BD II > HC
R Lingual gyrus	2.80×10^{-4}	1.33×10^{-4}	0.816	BD I & BD II < HC
R Parahippocampal gyrus	0.006	3.35×10^{-5}	0.392	BD II > HC
R Precuneus	4.58×10^{-4}	3.65×10^{-4}	0.746	BD I & BD II < HC
R Straight gyrus	2.68×10^{-5}	6.72×10^{-9}	0.352	BD I & BD II < HC
R Anterior transverse temporal gyrus	3.11×10^{-4}	1.93×10^{-4}	0.777	BD I & BD II > HC
R Lateral superior temporal gyrus	8.15×10^{-5}	3.95×10^{-6}	0.885	BD I & BD II < HC
R Planum temporale	1.08×10^{-3}	3.10×10^{-4}	0.943	BD II > HC

The general linear model (GLM) was adjusted for age, sex, educational level, and intracranial volume as covariates. Regions that remained significant after Bonferroni correction are listed: 76 regions of cortex, corrected $p=(0.05/76)=6.58 \times 10^{-4}$. BD I, bipolar disorder type I; BD II, bipolar disorder type II; HC, healthy controls; SD, standard deviation

Common cortical abnormalities in BD patients

Our main findings were as follows: patients with BD I and II share widespread cortical thinning in the bilateral frontal, temporal, parietal, and occipital regions; cingulate gyrus; and left insula; decreased SA in the left insula, right ACC, middle cingulate cortex, left pars orbitalis, and right superior frontal gyrus; and increased SA in the right pars triangularis, right posterior cingulate cortex, right middle frontal gyrus, and right anterior temporal gyrus compared to HCs. Our results of widespread cortical thinning are consistent with those of previous studies.^{10,11,15,40} Alternatively, our significant findings regarding cortical SA are contrary to those of previous studies,^{11,17-20} which failed to detect significant differences in SA between BD patients and HCs; however, there are a few studies that have reported results supporting our findings.^{8,13,21,22}

The largest decrease in CT in patients with BD was found in the bilateral ACC, consistent with the findings of previous studies.^{10,11,15,40} Contrary to previous null findings,^{11,16-20} we found

significantly decreased SA in the right ACC. Considering that the ACC is a critical region that integrates cognitive and emotional functions, shifts attention, and supports goal-directed behavior,^{16,41-44} we postulate that structural changes in the ACC could result in impaired cognitive control and emotion dysregulation in patients with BD.^{34,45,46}

Distinct cortical abnormalities between BD subtypes

We found no significant differences in CT between patients with BD I and BD II, which is supported by the findings of a previous study.¹¹ However, we found that in patients with BD I, more regions showed cortical thinning in the ventral prefrontal cortex (vPFC), including the VLPFC and OFC, which have long been studied as a critical focus in the pathophysiology of BD.⁴⁷⁻⁵⁰ While cortical thinning involved more areas in patients with BD I, wide areas with significant alterations in SA were observed in patients with BD II. Hibar et al.¹¹ suggested that BD may be associated with reduced neuron numbers, but this does

Table 6. Correlation of illness duration and HDRS score with cortical thickness in patients with BD

Cortical regions	Illness duration (months)		HDRS	
	R	P	R	P
	Left hemisphere			
L Frontomarginal gyrus	-0.153	0.207	-0.221	0.729
L Inferior occipital gyrus	-0.014	0.911	-0.234	0.198
L Subcentral gyrus	0.049	0.687	-0.203	0.860
L Transverse frontopolar gyrus	-0.094	0.437	-0.109	0.600
L Anterior cingulate gyrus	-0.034	0.782	-0.390	0.138
L Anterior mid-cingulate gyrus	0.008	0.950	-0.294	0.235
L Dorsal posterior cingulate gyrus	0.020	0.871	-0.362	0.193
L Ventral posterior cingulate gyrus	0.047	0.702	-0.350	0.115
L Cuneus	-0.082	0.498	0.240	0.502
L Pars opercularis	0.045	0.712	-0.181	0.621
L Pars orbitalis	-0.050	0.679	-0.199	0.334
L Pars triangularis	0.068	0.578	-0.147	0.810
L Short insular gyrus	0.096	0.432	-0.235	0.609
L Middle occipital gyrus	0.094	0.437	-0.323	0.123
L Lateral occipito-temporal gyrus	0.141	0.244	-0.272	0.319
L Lingual gyrus	-0.088	0.469	0.246	0.445
L Parahippocampal gyrus	0.021	0.865	-0.298	0.088
L Angular gyrus	0.066	0.588	-0.192	0.711
L Supramarginal gyrus	0.122	0.313	-0.310	0.152
L Superior parietal lobule	0.166	0.169	-0.181	0.820
L Precentral gyrus	0.100	0.411	-0.266	0.135
L Subcallosal gyrus	-0.120	0.323	-0.281	0.108
L Anterior transverse temporal gyrus	-0.090	0.458	0.268	0.159
L Planum polare	0.058	0.633	-0.252	0.748
L Middle temporal gyrus	0.061	0.617	-0.277	0.413
Right hemisphere				
R Frontomarginal gyrus	0.144	0.234	0.107	0.378
R Inferior occipital gyrus	0.034	0.778	-0.077	0.527
R Subcentral gyrus	0.036	0.769	-0.161	0.184
R Transverse frontopolar gyrus	0.001	0.996	0.161	0.183
R Anterior cingulate gyrus	-0.027	0.825	-0.010	0.937
R Anterior mid-cingulate gyrus	0.101	0.404	-0.228	0.058
R Dorsal posterior cingulate gyrus	0.258	0.031	-0.030	0.804
R Ventral posterior cingulate gyrus	0.022	0.853	-0.089	0.464
R Cuneus	-0.064	0.599	0.106	0.382
R Pars opercularis	-0.084	0.491	-0.032	0.790

Table 6. Correlation of illness duration and HDRS score with cortical thickness in patients with BD (continued)

Cortical regions	Illness duration (months)		HDRS	
	R	P	R	P
	Right hemisphere (continued)			
R Pars orbitalis	-0.006	0.959	-0.063	0.603
R Pars triangularis	-0.115	0.344	0.108	0.373
R Middle frontal gyrus	0.007	0.957	0.027	0.827
R Middle occipital gyrus	0.109	0.367	-0.121	0.320
R Lateral occipito-temporal gyrus	0.040	0.740	-0.138	0.255
R Lingual gyrus	-0.070	0.563	0.136	0.263
R Parahippocampal gyrus	0.132	0.277	-0.176	0.144
R Orbital gyrus	0.016	0.895	0.002	0.985
R Angular gyrus	-0.055	0.650	-0.075	0.540
R Supramarginal gyrus	0.028	0.815	-0.171	0.157
R Superior parietal lobule	0.154	0.202	-0.110	0.366
R Precentral gyrus	0.031	0.801	-0.075	0.539
R Planum polare	0.058	0.631	-0.171	0.156
R Middle temporal gyrus	0.071	0.557	-0.055	0.652

A two-tailed Pearson's partial correlation analysis was performed that controlled for age, sex, educational level, and intracranial volume. The 49 cortical regions that remained significant after Bonferroni correction are listed (corrected $p=[0.05/49]=1.02 \times 10^{-3}$). BD, bipolar disorder; HDRS, Hamilton Depression Rating Scale

not lead to changes in overall cortical size from the result that BD showed significant changes only in CT, not in SA, in their study. However, our study showed that investigating both CT and SA enhanced the sensitivity for distinguishing BD subtypes. As previous research¹¹ focused on the comparison of cortical abnormalities between patients with BD and HCs, comparisons between patients with BD I and HCs and between patients with BD II and HCs were not performed, although post-hoc analyses were performed for differences according to subtype.¹¹ Therefore, we speculate that the difference of our study may be a result of considering BD subtypes as different disease entities and performing three-group comparisons, which helped to elucidate subtype-specific morphological parameters.

Interestingly, the right long insula was found to be a significant region for differentiating BD subtypes even after Bonferroni correction. Patients with BD II demonstrated a smaller SA than patients with BD I in the right long insula, which is posterior part of the insula. Similarly, a smaller SA in the left posterior insula was detected in patients with BD II compared to that in patients with BD I, but this did not remain significant after correction for multiple comparisons. Although the anterior insula has been suggested as a critical multimodal hub within the cingulo-opercular system (i.e., the salience network) involved in detecting emotional salience and integrating sensorimotor,

Table 7. Correlation of illness duration and HDRS score with cortical surface areas in patients with BD

Cortical regions	Illness duration (months)		HDRS	
	R	P	R	P
Left hemisphere				
L Pars orbitalis	-0.002	0.990	-0.111	0.359
L Long insular gyrus	-0.076	0.531	-0.250	0.037
Right hemisphere				
R Frontomarginal gyrus	-0.174	0.149	-0.007	0.956
R Subcentral gyrus	0.098	0.419	0.085	0.483
R Transverse frontopolar gyrus	-0.065	0.593	-0.008	0.945
R Anterior cingulate gyrus	-0.009	0.938	-0.164	0.174
R Posterior mid-cingulate gyrus	0.035	0.774	-0.195	0.106
R Ventral posterior cingulate gyrus	-0.071	0.561	0.043	0.725
R Cuneus	0.066	0.586	-0.020	0.868
R Pars opercularis	0.204	0.091	-0.162	0.181
R Pars orbitalis	-0.152	0.210	0.098	0.420
R Pars triangularis	-0.080	0.510	0.096	0.430
R Middle frontal gyrus	-0.118	0.329	0.161	0.184
R Superior frontal gyrus	0.079	0.517	-0.071	0.559
R Long insular gyrus	-0.064	0.596	-0.292	0.014
R Short insular gyrus	-0.123	0.310	0.044	0.718
R Superior occipital gyrus	-0.001	0.991	0.104	0.393
R Lingual gyrus	0.102	0.399	-0.006	0.959
R Parahippocampal gyrus	-0.114	0.349	0.115	0.344
R Precuneus	0.050	0.678	0.026	0.829
R Straight gyrus	0.037	0.758	-0.145	0.232
R Anterior transverse temporal gyrus	-0.084	0.489	0.084	0.490
R Lateral superior temporal gyrus	0.108	0.373	-0.116	0.337
R Planum temporale	-0.108	0.375	0.071	0.557

A two-tailed Pearson's partial correlation analysis was performed that controlled for age, sex, educational level, and intracranial volume. The 24 cortical regions that remained significant after Bonferroni correction are listed (corrected $p=[0.05/24]=2.08 \times 10^{-3}$). BD, bipolar disorder; HDRS, Hamilton Depression Rating Scale

emotional, and cognitive information,^{51,52} relatively little research has been conducted on the posterior insula. Three insular subregions, the posterior, ventral anterior, and dorsal anterior regions,⁵³ showed different connectivity patterns in functional MRI studies.^{52,54} Deen et al.⁵⁴ suggested the possibility that the dorsal anterior insula/dorsal ACC network creates a pathway through which inputs, such as somatosensory and interoceptive information from the posterior insula or affective information from the ventral anterior insula, can affect decision-making and be-

havior. Therefore, we speculate that prominent deformities in the posterior insula contribute to dysfunction in the integration of emotional and cognitive signals through impaired somatosensory and interoceptive input in patients with BD II.

To our knowledge, no previous studies have suggested that the right posterior insula can be used to differentiate between BD subtypes; however, several functional MRI studies^{52,55} have focused on the insular region to distinguish bipolar depression from unipolar depression. Ambrosi et al.⁵² found that functional connectivity between the left posterior insula and right frontopolar prefrontal cortex could be a biomarker distinguishing between bipolar and unipolar depression, as functional connectivity was found to be lower in bipolar depression than in unipolar depression. Although such previous studies have been conducted on patients with BD I or BD II indiscriminately, we suggested that connectivity with the posterior insula could be more prominent in those with BD II; however, further investigations are needed to elucidate its role in the pathophysiology of BD.

Additionally, we explored the correlation of clinical states and illness duration with CT and SA but did not find any significant findings after Bonferroni correction. A previous study reported findings consistent with our results, showing no association between a euthymic or depressive state and cortical abnormalities.¹¹ Although there was no association between illness duration and cortical abnormalities in our study, a previous study reported that a longer illness duration in BD patients was positively associated with CT in the occipital, parietal, and right frontal cortices, but not with SA.¹¹ Therefore, further studies are required to address this issue.

There are several limitations to our study. First, due to the cross-sectional design, we could not prove causality between cortical abnormalities and BD subtypes. Second, the BD groups were heterogeneous in terms of medications used, including lithium, antiepileptic drugs (AEDs), atypical antipsychotics (AAs), and antidepressants (ADs). To overcome this limitation, we analyzed the effect of lithium, AEDs, and AAs on cortical abnormalities in our additional analyses (Supplementary Tables 7–12 in the online-only Data Supplement). We found that the use of AAs was significantly associated with cortical thinning in the right pars triangularis (AA users: 2.57 ± 0.17 ; AA nonusers: 2.80 ± 0.14 ; $F=15.858$, $p=1.69 \times 10^{-4}$), but the other results were insignificant (lithium or AED use with respect to CT or SA; AA use with respect to SA). Contrarily, a meta-analysis found evidence of increased CT or SA with the use of lithium, cortical thinning with the use of AEDs, and reduced SA with the use of AAs in several regions.^{11,15} This suggests that the effect of medication on cortical abnormalities may vary and is dependent on sample size. As we did not control for the dosage and combination effects of various medications, we could

not overlook the possible confounding effects of medications. Third, our sample was heterogeneous with regard to mood state as more patients with BD II were in a depressive state than those with BD I. This could lead to the misconception that our differences in SA in the right long insula may be due to the depressive state. However, large-scale studies, such as the ENIGMA consortium, have investigated cortical SA in adult patients with major depressive disorder but showed no SA abnormalities, including in the insular gyrus, when compared with controls.⁵⁶ Fourth, although we suggested that a decreased SA in the right long insula is crucial for differentiating between the BD subtypes, we failed to prove the correlation of SA in the right long insula with clinical states and illness duration after Bonferroni correction. However, our result was consistent with that reported by a previous study that found no significant correlation between clinical state and illness duration with SA. CT and SA are genetically independent. Unlike cortical thinning, which begins at 2–4 years and gradually progresses throughout lifetime, cortical SA expands until 12 years and remains relatively stable.^{56–60} Therefore, we hypothesized that SA is less affected by environmental factors, such as disease state and duration, because it might be determined earlier in the neurodevelopmental period.^{12,14}

Despite several limitations, our study is one of the few that explored common and unique cortical abnormalities in patients with BD I and BD II. Our finding of cortical thinning in patients with BD is consistent with previous findings involving the bilateral frontal, temporal, and occipital regions; cingulate gyrus; and insula. We found alterations in SA in BD patients, including increase SA in the pars triangularis and decreased SA in the insula. Our study confirms previous results and provides novel findings for comparing BD subtypes. Cortical thinning involved more areas, including the vPFC, in patients with BD I, while changes in SA were more extensive in patients with BD II.

In conclusion, our finding of decreased SA in the right long insula could be crucial for differentiating between BD subtypes. Further large-scale and longitudinal investigations regarding the association between BD subtypes and cortical abnormalities are necessary for confirmation.

Supplementary Materials

The online-only Data Supplement is available with this article at <https://doi.org/10.30773/pi.2021.0074>.

Availability of Data and Material

All data generated or analyzed during the study are included in this published article (and its supplementary information files).

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Byung-Joo Ham. Data curation: Wooyoung Kang, Youbin Kang, Aram Kim. Formal analysis: Kyu-Man Han, Woo-Suk Tae. Funding acquisition: Byung-Joo Ham. Investigation: Byung-Joo Ham. Methodology: Kyu-Man Han, Woo-Suk Tae. Project administration: Byung-Joo Ham. Resources: Byung-Joo Ham. Software: Woo-Suk Tae. Supervision: Byung-Joo Ham. Validation: Kyu-Man Han. Visualization: Kyu-Man Han. Writing—original draft: Yoonmi Woo. Writing—review & editing: Byung-Joo Ham, Kyu-Man Han.

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Supplementary Table 1. Correlation of illness duration and HDRS score with cortical thickness in patients with BD I

Cortical regions	Illness duration (months)		HDRS	
	R	p	R	p
Left hemisphere				
L Frontomarginal gyrus	-0.390	0.049	-0.031	0.881
L Inferior occipital gyrus	-0.133	0.517	-0.434	0.027
L Subcentral gyrus	-0.082	0.690	0.048	0.815
L Transverse frontopolar gyrus	0.079	0.702	0.131	0.523
L Anterior cingulate gyrus	-0.316	0.116	-0.158	0.442
L Anterior mid-cingulate gyrus	-0.180	0.380	-0.158	0.440
L Dorsal posterior cingulate gyrus	-0.041	0.841	-0.439	0.025
L Ventral posterior cingulate gyrus	-0.090	0.662	-0.337	0.092
L Cuneus	0.047	0.819	0.268	0.186
L Pars opercularis	0.050	0.808	-0.185	0.365
L Pars orbitalis	0.048	0.814	-0.169	0.410
L Pars triangularis	-0.064	0.756	-0.153	0.456
L Short insular gyrus	0.075	0.716	-0.313	0.119
L Middle occipital gyrus	0.083	0.688	-0.421	0.032
L Lateral occipito-temporal gyrus	0.077	0.709	-0.325	0.106
L Lingual gyrus	-0.071	0.729	0.232	0.254
L Parahippocampal gyrus	-0.152	0.457	-0.109	0.596
L Angular gyrus	0.059	0.773	0.023	0.912
L Supramarginal gyrus	0.117	0.569	-0.307	0.128
L Superior parietal lobule	0.230	0.259	-0.188	0.357
L Precentral gyrus	0.048	0.816	-0.248	0.222
L Subcallosal gyrus	-0.380	0.055	-0.135	0.511
L Anterior transverse temporal gyrus	0.086	0.676	0.224	0.270
L Planum polare	-0.040	0.844	-0.309	0.125
L Middle temporal gyrus	-0.003	0.989	-0.321	0.110
Right hemisphere				
R Frontomarginal gyrus	0.298	0.139	0.035	0.865
R Inferior occipital gyrus	-0.118	0.566	-0.262	0.197
R Subcentral gyrus	0.032	0.875	-0.260	0.199
R Transverse frontopolar gyrus	-0.028	0.893	0.146	0.476
R Anterior cingulate gyrus	0.013	0.948	0.057	0.781
R Anterior mid-cingulate gyrus	0.157	0.444	-0.101	0.624
R Dorsal posterior cingulate gyrus	0.245	0.227	-0.189	0.354
R Ventral posterior cingulate gyrus	-0.097	0.637	-0.324	0.106
R Cuneus	0.072	0.728	0.273	0.177
R Pars opercularis	-0.224	0.272	-0.056	0.788
R Pars orbitalis	0.084	0.683	-0.470	0.015
R Pars triangularis	-0.100	0.627	0.010	0.960
R Middle frontal gyrus	0.079	0.700	0.123	0.548
R Middle occipital gyrus	-0.028	0.893	-0.312	0.120
R Lateral occipito-temporal gyrus	-0.062	0.763	-0.369	0.063
R Lingual gyrus	-0.044	0.830	0.362	0.069
R Parahippocampal gyrus	-0.025	0.904	-0.139	0.498
R Orbital gyrus	0.058	0.777	-0.150	0.465
R Angular gyrus	-0.071	0.729	-0.134	0.512
R Supramarginal gyrus	-0.056	0.788	-0.255	0.210
R Superior parietal lobule	0.192	0.346	-0.245	0.229
R Precentral gyrus	0.009	0.966	-0.018	0.930
R Planum polare	-0.082	0.690	-0.278	0.170
R Middle temporal gyrus	-0.074	0.720	-0.300	0.136

A two-tailed Pearson's partial correlation analysis was performed that controlled for age, sex, educational level, and intracranial volume. The 49 cortical regions that remained significant after Bonferroni correction are listed (corrected $p=[0.05/49]=1.02\times 10^{-3}$). BD, bipolar disorder; HDRS, Hamilton Depression Rating Scale

Supplementary Table 2. Correlation of illness duration and HDRS score with cortical thickness in patients with BD II

Cortical regions	Illness duration (months)		HDRS	
	R	p	R	p
Left hemisphere				
L Frontomarginal gyrus	0.003	0.983	-0.097	0.550
L Inferior occipital gyrus	0.090	0.580	-0.018	0.910
L Subcentral gyrus	0.171	0.292	-0.096	0.556
L Transverse frontopolar gyrus	-0.158	0.330	-0.125	0.442
L Anterior cingulate gyrus	0.095	0.560	0.004	0.980
L Anterior mid-cingulate gyrus	0.118	0.467	-0.072	0.659
L Dorsal posterior cingulate gyrus	0.012	0.943	0.064	0.696
L Ventral posterior cingulate gyrus	0.096	0.557	-0.005	0.975
L Cuneus	-0.163	0.316	-0.088	0.588
L Pars opercularis	0.140	0.390	-0.088	0.588
L Pars orbitalis	-0.117	0.472	-0.046	0.779
L Pars triangularis	0.361	0.022	-0.047	0.772
L Short insular gyrus	0.153	0.345	0.093	0.570
L Middle occipital gyrus	0.105	0.519	-0.015	0.927
L Lateral occipito-temporal gyrus	0.212	0.190	0.074	0.648
L Lingual gyrus	-0.099	0.543	-0.069	0.674
L Parahippocampal gyrus	0.172	0.289	-0.131	0.422
L Angular gyrus	0.052	0.751	-0.071	0.664
L Supramarginal gyrus	0.108	0.505	-0.051	0.753
L Superior parietal lobule	0.173	0.286	0.073	0.653
L Precentral gyrus	0.120	0.459	-0.091	0.577
L Subcallosal gyrus	0.166	0.306	-0.251	0.118
L Anterior transverse temporal gyrus	-0.156	0.336	-0.005	0.974
L Planum polare	0.165	0.309	0.177	0.276
L Middle temporal gyrus	0.149	0.359	0.053	0.746
Right hemisphere				
R Frontomarginal gyrus	0.060	0.714	0.084	0.605
R Inferior occipital gyrus	0.154	0.342	0.131	0.421
R Subcentral gyrus	0.014	0.933	-0.063	0.699
R Transverse frontopolar gyrus	0.032	0.846	0.204	0.207
R Anterior cingulate gyrus	-0.156	0.337	0.123	0.450
R Anterior mid-cingulate gyrus	-0.007	0.964	-0.205	0.204
R Dorsal posterior cingulate gyrus	0.257	0.109	0.212	0.190
R Ventral posterior cingulate gyrus	0.109	0.502	0.114	0.483
R Cuneus	-0.126	0.439	-0.091	0.576
R Pars opercularis	0.154	0.341	-0.116	0.477
R Pars orbitalis	0.019	0.910	0.077	0.638
R Pars triangularis	-0.007	0.965	-0.003	0.983
R Middle frontal gyrus	-0.012	0.941	-0.127	0.436
R Middle occipital gyrus	0.209	0.196	0.094	0.564
R Lateral occipito-temporal gyrus	0.159	0.326	0.043	0.795
R Lingual gyrus	-0.074	0.648	-0.102	0.532
R Parahippocampal gyrus	0.226	0.160	-0.029	0.857
R Orbital gyrus	0.125	0.441	-0.034	0.835
R Angular gyrus	-0.046	0.778	-0.042	0.795
R Supramarginal gyrus	0.103	0.527	-0.089	0.583
R Superior parietal lobule	0.131	0.419	0.027	0.870
R Precentral gyrus	0.029	0.858	-0.016	0.922
R Planum polare	0.168	0.299	-0.059	0.716
R Middle temporal gyrus	0.215	0.184	0.170	0.295

A two-tailed Pearson's partial correlation analysis was performed that controlled for age, sex, educational level, and intracranial volume. The 49 cortical regions that remained significant after Bonferroni correction are listed (corrected $p=[0.05/49]=1.02\times 10^{-3}$). BD, bipolar disorder; HDRS, Hamilton Depression Rating Scale

Supplementary Table 3. Correlation of illness duration and HDRS score with cortical surface area in patients with BD I

Cortical regions	Illness duration (months)		HDRS	
	R	p	R	p
Left hemisphere				
L Pars orbitalis	-0.298	0.140	-0.271	0.180
L Long insular gyrus	-0.425	0.030	-0.252	0.214
Right hemisphere				
R Frontomarginal gyrus	-0.072	0.728	0.258	0.203
R Subcentral gyrus	-0.069	0.739	-0.163	0.427
R Transverse frontopolar gyrus	0.022	0.916	0.270	0.182
R Anterior cingulate gyrus	-0.093	0.651	-0.414	0.036
R Posterior mid-cingulate gyrus	-0.022	0.914	-0.331	0.099
R Ventral posterior cingulate gyrus	0.048	0.817	0.208	0.307
R Cuneus	0.017	0.934	-0.257	0.205
R Pars opercularis	0.066	0.749	-0.302	0.134
R Pars orbitalis	-0.142	0.488	0.351	0.079
R Pars triangularis	0.018	0.929	0.378	0.057
R Middle frontal gyrus	-0.018	0.931	0.343	0.086
R Superior frontal gyrus	-0.039	0.851	-0.331	0.099
R Long insular gyrus	-0.339	0.090	-0.188	0.358
R Short insular gyrus	-0.043	0.833	0.236	0.245
R Superior occipital gyrus	0.178	0.385	0.135	0.512
R Lingual gyrus	-0.012	0.954	-0.254	0.210
R Parahippocampal gyrus	0.020	0.924	0.361	0.070
R Precuneus	-0.030	0.883	-0.209	0.304
R Straight gyrus	-0.107	0.602	-0.415	0.035
R Anterior transverse temporal gyrus	-0.005	0.981	0.292	0.148
R Lateral superior temporal gyrus	0.090	0.662	-0.361	0.070
R Planum temporale	-0.029	0.888	0.219	0.282

A two-tailed Pearson's partial correlation analysis was performed that controlled for age, sex, educational level, and intracranial volume. The 24 cortical regions that remained significant after Bonferroni correction are listed (corrected $p=[0.05/24]=2.08\times 10^{-3}$). BD, bipolar disorder; HDRS, Hamilton Depression Rating Scale

Supplementary Table 4. Correlation of illness duration and HDRS score with cortical surface area in patients with BD II

Cortical regions	Illness duration (months)		HDRS	
	R	p	R	p
Left hemisphere				
L Pars orbitalis	0.143	0.379	0.135	0.405
L Long insular gyrus	-0.035	0.830	0.013	0.937
Right hemisphere				
R Frontomarginal gyrus	-0.168	0.299	-0.202	0.211
R Subcentral gyrus	0.249	0.121	0.264	0.100
R Transverse frontopolar gyrus	-0.142	0.381	-0.208	0.198
R Anterior cingulate gyrus	0.021	0.899	0.081	0.620
R Posterior mid-cingulate gyrus	0.061	0.708	-0.030	0.856
R Ventral posterior cingulate gyrus	-0.167	0.302	-0.126	0.437
R Cuneus	0.111	0.496	0.168	0.301
R Pars opercularis	0.280	0.080	0.031	0.848
R Pars orbitalis	-0.180	0.268	-0.083	0.611
R Pars triangularis	-0.149	0.358	-0.110	0.500
R Middle frontal gyrus	-0.209	0.196	-0.038	0.817
R Superior frontal gyrus	0.165	0.310	0.161	0.320
R Long insular gyrus	-0.174	0.283	-0.013	0.935
R Short insular gyrus	-0.195	0.227	-0.121	0.456
R Superior occipital gyrus	-0.049	0.765	0.000	1.000
R Lingual gyrus	0.215	0.183	0.205	0.205
R Parahippocampal gyrus	-0.193	0.232	-0.133	0.412
R Precuneus	0.140	0.389	0.212	0.190
R Straight gyrus	0.096	0.557	0.139	0.391
R Anterior transverse temporal gyrus	-0.170	0.294	-0.091	0.578
R Lateral superior temporal gyrus	0.108	0.506	0.083	0.610
R Planum temporale	-0.168	0.301	-0.093	0.569

A two-tailed Pearson's partial correlation analysis was performed that controlled for age, sex, educational level, and intracranial volume. The 24 cortical regions that remained significant after Bonferroni correction are listed (corrected $p=[0.05/24]=2.08\times 10^{-3}$). BD, bipolar disorder; HDRS, Hamilton Depression Rating Scale

Supplementary Table 5. Correlation of YMRS score with cortical surface area in patients with BD

Cortical regions	YMRS score	
	R	p
Left hemisphere		
L Pars orbitalis	0.071	0.559
L Long insular gyrus	0.142	0.242
Right hemisphere		
R Frontomarginal gyrus	-0.184	0.127
R Subcentral gyrus	0.077	0.525
R Transverse frontopolar gyrus	-0.123	0.312
R Anterior cingulate gyrus	0.117	0.337
R Posterior mid-cingulate gyrus	0.114	0.346
R Ventral posterior cingulate gyrus	-0.097	0.423
R Cuneus	0.066	0.588
R Pars opercularis	0.190	0.116
R Pars orbitalis	-0.072	0.551
R Pars triangularis	-0.105	0.388
R Middle frontal gyrus	-0.173	0.152
R Superior frontal gyrus	0.077	0.524
R Long insular gyrus	0.244	0.042
R Short insular gyrus	-0.132	0.277
R Superior occipital gyrus	-0.119	0.328
R Lingual gyrus	0.040	0.741
R Parahippocampal gyrus	-0.090	0.461
R Precuneus	0.135	0.264
R Straight gyrus	0.097	0.423
R Anterior transverse temporal gyrus	-0.085	0.484
R Lateral superior temporal gyrus	0.122	0.315
R Planum temporale	-0.112	0.355

A two-tailed Pearson's partial correlation analysis was performed that controlled for age, sex, educational level, and intracranial volume. The 24 cortical regions that remained significant after Bonferroni correction are listed (corrected $p=[0.05/24]=2.08\times 10^{-3}$). BD, bipolar disorder; YMRS, Young Mania Rating Scale

Supplementary Table 6. Correlation of YMRS score with cortical surface areas in patients with BD II

Cortical regions	YMRS score	
	R	p
Left hemisphere		
L Pars orbitalis	0.044	0.789
L Long insular gyrus	0.222	0.169
Right hemisphere		
R Frontomarginal gyrus	-0.274	0.087
R Subcentral gyrus	0.318	0.046
R Transverse frontopolar gyrus	-0.259	0.107
R Anterior cingulate gyrus	0.209	0.196
R Posterior mid-cingulate gyrus	0.175	0.280
R Ventral posterior cingulate gyrus	-0.206	0.203
R Cuneus	0.255	0.113
R Pars opercularis	0.286	0.074
R Pars orbitalis	-0.202	0.211
R Pars triangularis	-0.228	0.156
R Middle frontal gyrus	-0.266	0.098
R Superior frontal gyrus	0.200	0.216
R Long insular gyrus	0.078	0.631
R Short insular gyrus	-0.227	0.158
R Superior occipital gyrus	-0.084	0.605
R Lingual gyrus	0.132	0.418
R Parahippocampal gyrus	-0.161	0.320
R Precuneus	0.258	0.107
R Straight gyrus	0.280	0.080
R Anterior transverse temporal gyrus	-0.191	0.237
R Lateral superior temporal gyrus	0.291	0.068
R Planum temporale	-0.185	0.253

A two-tailed Pearson's partial correlation analysis was performed that controlled for age, sex, educational level, and intracranial volume. The 24 cortical regions that remained significant after Bonferroni correction are listed (corrected $p=[0.05/24]=2.08 \times 10^{-3}$). BD, bipolar disorder; YMRS, Young Mania Rating Scale

Supplementary Table 7. Effects of lithium on cortical thickness in BD

Cortical regions	All groups	
	F	p
Left hemisphere		
L Frontomarginal gyrus	0.546	0.463
L Inferior occipital gyrus	0.468	0.496
L Paracentral lobule	0.021	0.884
L Subcentral gyrus	1.442	0.234
L Transverse frontopolar gyrus	0.063	0.802
L Anterior cingulate gyrus	0.346	0.559
L Anterior mid-cingulate gyrus	0.244	0.623
L Posterior mid-cingulate gyrus	0.016	0.901
L Dorsal posterior cingulate gyrus	0.435	0.512
L Ventral posterior cingulate gyrus	2.814	0.098
L Cuneus	0.002	0.961
L Pars opercularis	8.577	0.005
L Pars orbitalis	0.962	0.330
L Pars triangularis	2.497	0.119
L Middle frontal gyrus	2.236	0.139
L Superior frontal gyrus	0.080	0.779
L Long insular gyrus	0.004	0.951
L Short insular gyrus	0.800	0.374
L Middle occipital gyrus	1.157	0.286
L Superior occipital gyrus	0.054	0.816
L Lateral occipito-temporal gyrus	1.283	0.261
L Lingual gyrus	0.569	0.453
L Parahippocampal gyrus	1.072	0.304
L Orbital gyrus	0.245	0.622
L Angular gyrus	4.360	0.041
L Supramarginal gyrus	2.964	0.090
L Superior parietal lobule	1.234	0.270
L Postcentral gyrus	0.039	0.845
L Precentral gyrus	0.789	0.378
L Precuneus	2.120	0.150
L Straight gyrus	0.004	0.951
L Subcallosal gyrus	0.212	0.647
L Anterior transverse temporal gyrus	0.133	0.716
L Lateral superior temporal gyrus	5.289	0.025
L Planum polare	2.149	0.147
L Planum temporale	0.106	0.746
L Inferior temporal gyrus	2.857	0.096
L Middle temporal gyrus	2.191	0.143
Right hemisphere		
R Frontomarginal gyrus	0.022	0.884
R Inferior occipital gyrus	3.120	0.082
R Paracentral lobule	1.286	0.261
R Subcentral gyrus	8.965	0.004
R Transverse frontopolar gyrus	0.000	0.998
R Anterior cingulate gyrus	0.000	0.997
R Anterior mid-cingulate gyrus	0.296	0.588
R Posterior mid-cingulate gyrus	0.430	0.514
R Dorsal posterior cingulate gyrus	2.080	0.154
R Ventral posterior cingulate gyrus	1.401	0.241
R Cuneus	0.070	0.791
R Pars opercularis	10.068	0.002
R Pars orbitalis	5.762	0.019
R Pars triangularis	7.248	0.009
R Middle frontal gyrus	2.171	0.145
R Superior frontal gyrus	0.086	0.770
R Long insular gyrus	0.314	0.577
R Short insular gyrus	1.080	0.302
R Middle occipital gyrus	0.835	0.364
R Superior occipital gyrus	0.093	0.762
R Lateral occipito-temporal gyrus	2.199	0.143
R Lingual gyrus	0.115	0.736
R Parahippocampal gyrus	0.016	0.900
R Orbital gyrus	5.042	0.028
R Angular gyrus	4.185	0.045
R Supramarginal gyrus	1.584	0.212
R Superior parietal lobule	1.955	0.167
R Postcentral gyrus	0.203	0.654
R Precentral gyrus	1.391	0.242
R Precuneus	2.637	0.109
R Straight gyrus	0.000	1.000
R Subcallosal gyrus	0.930	0.338
R Anterior transverse temporal gyrus	0.763	0.386
R Lateral superior temporal gyrus	0.865	0.356
R Planum polare	0.153	0.697
R Planum temporale	4.289	0.042
R Inferior temporal gyrus	2.281	0.136
R Middle temporal gyrus	4.223	0.044

The general linear model (GLM) included BD patients and adjusted for age, sex, educational level, and intracranial volume as covariates. Regions that remained significant after Bonferroni correction are listed: 76 regions of cortex, corrected $p=(0.05/76)=6.58 \times 10^{-4}$. BD, bipolar disorder

Supplementary Table 8. Effects of lithium on cortical surface area in BD

Cortical regions	All groups	
	F	p
Left hemisphere		
L Frontomarginal gyrus	0.296	0.588
L Inferior occipital gyrus	0.017	0.897
L Paracentral lobule	0.052	0.821
L Subcentral gyrus	0.094	0.760
L Transverse frontopolar gyrus	0.076	0.784
L Anterior cingulate gyrus	1.658	0.202
L Anterior mid-cingulate gyrus	0.050	0.823
L Posterior mid-cingulate gyrus	0.992	0.323
L Dorsal posterior cingulate gyrus	0.523	0.472
L Ventral posterior cingulate gyrus	0.085	0.772
L Cuneus	0.436	0.511
L Pars opercularis	2.976	0.089
L Pars orbitalis	0.016	0.899
L Pars triangularis	2.035	0.158
L Middle frontal gyrus	0.216	0.643
L Superior frontal gyrus	1.811	0.183
L Long insular gyrus	0.007	0.933
L Short insular gyrus	0.968	0.329
L Middle occipital gyrus	0.108	0.744
L Superior occipital gyrus	2.152	0.147
L Lateral occipito-temporal gyrus	0.666	0.417
L Lingual gyrus	0.045	0.832
L Parahippocampal gyrus	0.451	0.504
L Orbital gyrus	1.040	0.312
L Angular gyrus	0.198	0.657
L Supramarginal gyrus	0.081	0.777
L Superior parietal lobule	0.531	0.469
L Postcentral gyrus	0.002	0.967
L Precentral gyrus	1.502	0.225
L Precuneus	0.041	0.841
L Straight gyrus	0.007	0.933
L Subcallosal gyrus	0.093	0.761
L Anterior transverse temporal gyrus	1.770	0.188
L Lateral superior temporal gyrus	1.788	0.186
L Planum polare	0.786	0.378
L Planum temporale	0.049	0.825
L Inferior temporal gyrus	0.535	0.467
L Middle temporal gyrus	1.862	0.177
Right hemisphere		
R Frontomarginal gyrus	0.019	0.890
R Inferior occipital gyrus	0.000	0.991
R Paracentral lobule	2.195	0.143
R Subcentral gyrus	0.362	0.549
R Transverse frontopolar gyrus	0.779	0.380
R Anterior cingulate gyrus	2.256	0.138
R Anterior mid-cingulate gyrus	0.341	0.561
R Posterior mid-cingulate gyrus	0.687	0.410
R Dorsal posterior cingulate gyrus	0.126	0.723
R Ventral posterior cingulate gyrus	0.763	0.385
R Cuneus	0.034	0.855
R Pars opercularis	0.047	0.829
R Pars orbitalis	1.138	0.290
R Pars triangularis	0.524	0.472
R Middle frontal gyrus	0.206	0.651
R Superior frontal gyrus	0.235	0.629
R Long insular gyrus	1.187	0.280
R Short insular gyrus	0.354	0.554
R Middle occipital gyrus	0.015	0.904
R Superior occipital gyrus	1.249	0.268
R Lateral occipito-temporal gyrus	0.005	0.945
R Lingual gyrus	0.282	0.597
R Parahippocampal gyrus	0.124	0.726
R Orbital gyrus	2.205	0.142
R Angular gyrus	2.220	0.141
R Supramarginal gyrus	0.992	0.323
R Superior parietal lobule	0.001	0.972
R Postcentral gyrus	2.270	0.137
R Precentral gyrus	0.003	0.955
R Precuneus	0.042	0.838
R Straight gyrus	1.601	0.210
R Subcallosal gyrus	0.012	0.914
R Anterior transverse temporal gyrus	0.948	0.334
R Lateral superior temporal gyrus	0.135	0.714
R Planum polare	0.269	0.606
R Planum temporale	0.353	0.554
R Inferior temporal gyrus	0.122	0.728
R Middle temporal gyrus	0.227	0.635

The general linear model (GLM) included BD patients and adjusted for age, sex, educational level, and intracranial volume as covariates. Regions that remained significant after Bonferroni correction are listed: 76 regions of cortex, corrected $p=(0.05/76)=6.58 \times 10^{-4}$. BD, bipolar disorder

Supplementary Table 9. Effects of antiepileptic medication on cortical thickness in BD

Cortical regions	All groups	
	F	p
Left hemisphere		
L Frontomarginal gyrus	3.940	0.051
L Inferior occipital gyrus	0.145	0.704
L Paracentral lobule	0.555	0.459
L Subcentral gyrus	0.063	0.802
L Transverse frontopolar gyrus	0.016	0.898
L Anterior cingulate gyrus	0.503	0.481
L Anterior mid-cingulate gyrus	0.329	0.568
L Posterior mid-cingulate gyrus	0.115	0.736
L Dorsal posterior cingulate gyrus	1.096	0.299
L Ventral posterior cingulate gyrus	0.005	0.946
L Cuneus	1.647	0.204
L Pars opercularis	0.123	0.727
L Pars orbitalis	0.052	0.820
L Pars triangularis	0.252	0.617
L Middle frontal gyrus	1.279	0.262
L Superior frontal gyrus	0.195	0.660
L Long insular gyrus	0.885	0.350
L Short insular gyrus	0.566	0.454
L Middle occipital gyrus	0.711	0.402
L Superior occipital gyrus	3.576	0.063
L Lateral occipito-temporal gyrus	0.557	0.458
L Lingual gyrus	1.347	0.250
L Parahippocampal gyrus	0.181	0.672
L Orbital gyrus	0.004	0.948
L Angular gyrus	0.087	0.769
L Supramarginal gyrus	0.017	0.898
L Superior parietal lobule	1.767	0.188
L Postcentral gyrus	0.091	0.764
L Precentral gyrus	1.437	0.235
L Precuneus	1.256	0.266
L Straight gyrus	0.007	0.931
L Subcallosal gyrus	0.021	0.886
L Anterior transverse temporal gyrus	3.237	0.076
L Lateral superior temporal gyrus	2.910	0.093
L Planum polare	0.000	0.990
L Planum temporale	0.257	0.614
L Inferior temporal gyrus	0.394	0.532
L Middle temporal gyrus	0.461	0.499
Right hemisphere		
R Frontomarginal gyrus	0.016	0.901
R Inferior occipital gyrus	0.597	0.442
R Paracentral lobule	0.424	0.517
R Subcentral gyrus	0.080	0.778
R Transverse frontopolar gyrus	0.000	0.997
R Anterior cingulate gyrus	0.176	0.676
R Anterior mid-cingulate gyrus	0.347	0.558
R Posterior mid-cingulate gyrus	0.004	0.951
R Dorsal posterior cingulate gyrus	1.252	0.267
R Ventral posterior cingulate gyrus	0.374	0.543
R Cuneus	1.834	0.180
R Pars opercularis	3.004	0.088
R Pars orbitalis	0.849	0.360
R Pars triangularis	1.107	0.296
R Middle frontal gyrus	1.157	0.286
R Superior frontal gyrus	0.018	0.894
R Long insular gyrus	1.883	0.175
R Short insular gyrus	0.048	0.827
R Middle occipital gyrus	0.134	0.715
R Superior occipital gyrus	1.807	0.183
R Lateral occipito-temporal gyrus	0.204	0.653
R Lingual gyrus	1.789	0.186
R Parahippocampal gyrus	0.946	0.334
R Orbital gyrus	0.125	0.725
R Angular gyrus	0.374	0.543
R Supramarginal gyrus	0.184	0.669
R Superior parietal lobule	2.402	0.126
R Postcentral gyrus	0.139	0.710
R Precentral gyrus	0.690	0.409
R Precuneus	0.433	0.513
R Straight gyrus	1.887	0.174
R Subcallosal gyrus	0.447	0.506
R Anterior transverse temporal gyrus	1.821	0.182
R Lateral superior temporal gyrus	0.089	0.766
R Planum polare	0.758	0.387
R Planum temporale	1.811	0.183
R Inferior temporal gyrus	0.221	0.639
R Middle temporal gyrus	0.363	0.549

The general linear model (GLM) included BD patients and adjusted for age, sex, educational level, and intracranial volume as covariates. Regions that remained significant after Bonferroni correction are listed: 76 regions of cortex, corrected $p=(0.05/76)=6.58 \times 10^{-4}$. BD, bipolar disorder

Supplementary Table 10. Effects of antiepileptic medication on cortical surface area in BD

Cortical regions	All groups	
	F	p
Left hemisphere		
L Frontomarginal gyrus	0.625	0.432
L Inferior occipital gyrus	0.396	0.531
L Paracentral lobule	0.985	0.325
L Subcentral gyrus	2.325	0.132
L Transverse frontopolar gyrus	0.015	0.902
L Anterior cingulate gyrus	0.009	0.924
L Anterior mid-cingulate gyrus	1.779	0.187
L Posterior mid-cingulate gyrus	1.281	0.262
L Dorsal posterior cingulate gyrus	0.682	0.412
L Ventral posterior cingulate gyrus	2.524	0.117
L Cuneus	0.558	0.458
L Pars opercularis	0.083	0.774
L Pars orbitalis	0.180	0.673
L Pars triangularis	0.552	0.460
L Middle frontal gyrus	0.936	0.337
L Superior frontal gyrus	0.270	0.605
L Long insular gyrus	1.915	0.171
L Short insular gyrus	2.163	0.146
L Middle occipital gyrus	0.569	0.453
L Superior occipital gyrus	1.418	0.238
L Lateral occipito-temporal gyrus	0.202	0.654
L Lingual gyrus	0.072	0.789
L Parahippocampal gyrus	0.204	0.653
L Orbital gyrus	0.501	0.481
L Angular gyrus	0.011	0.916
L Supramarginal gyrus	0.369	0.545
L Superior parietal lobule	1.826	0.181
L Postcentral gyrus	0.014	0.907
L Precentral gyrus	3.653	0.060
L Precuneus	0.220	0.640
L Straight gyrus	0.236	0.628
L Subcallosal gyrus	0.004	0.951
L Anterior transverse temporal gyrus	0.225	0.637
L Lateral superior temporal gyrus	0.119	0.731
L Planum polare	0.401	0.529
L Planum temporale	0.179	0.674
L Inferior temporal gyrus	0.332	0.566
L Middle temporal gyrus	0.351	0.556
Right hemisphere		
R Frontomarginal gyrus	4.265	0.043
R Inferior occipital gyrus	0.084	0.772
R Paracentral lobule	0.051	0.822
R Subcentral gyrus	0.279	0.599
R Transverse frontopolar gyrus	0.526	0.471
R Anterior cingulate gyrus	0.876	0.352
R Anterior mid-cingulate gyrus	1.094	0.299
R Posterior mid-cingulate gyrus	0.801	0.374
R Dorsal posterior cingulate gyrus	0.483	0.489
R Ventral posterior cingulate gyrus	0.567	0.454
R Cuneus	1.059	0.307
R Pars opercularis	1.894	0.173
R Pars orbitalis	1.199	0.277
R Pars triangularis	1.115	0.295
R Middle frontal gyrus	2.739	0.103
R Superior frontal gyrus	0.432	0.513
R Long insular gyrus	0.516	0.475
R Short insular gyrus	0.409	0.525
R Middle occipital gyrus	1.159	0.285
R Superior occipital gyrus	3.854	0.054
R Lateral occipito-temporal gyrus	0.557	0.458
R Lingual gyrus	0.468	0.496
R Parahippocampal gyrus	0.894	0.348
R Orbital gyrus	0.276	0.601
R Angular gyrus	0.157	0.693
R Supramarginal gyrus	0.009	0.926
R Superior parietal lobule	1.444	0.234
R Postcentral gyrus	0.222	0.639
R Precentral gyrus	0.979	0.326
R Precuneus	0.630	0.430
R Straight gyrus	1.737	0.192
R Subcallosal gyrus	0.060	0.807
R Anterior transverse temporal gyrus	0.770	0.383
R Lateral superior temporal gyrus	1.434	0.235
R Planum polare	0.134	0.715
R Planum temporale	0.957	0.331
R Inferior temporal gyrus	5.089	0.027
R Middle temporal gyrus	0.947	0.334

The general linear model (GLM) included BD patients and adjusted for age, sex, educational level, and intracranial volume as covariates. Regions that remained significant after Bonferroni correction are listed: 76 regions of cortex, corrected $p=(0.05/76)=6.58 \times 10^{-4}$. BD, bipolar disorder

Supplementary Table 11. Effects of atypical antipsychotics on cortical thickness in BD

Cortical regions	All groups	
	F	p
Left hemisphere		
L Frontomarginal gyrus	5.016	0.028
L Inferior occipital gyrus	2.662	0.107
L Paracentral lobule	1.028	0.314
L Subcentral gyrus	0.467	0.497
L Transverse frontopolar gyrus	2.044	0.157
L Anterior cingulate gyrus	1.937	0.169
L Anterior mid-cingulate gyrus	2.010	0.161
L Posterior mid-cingulate gyrus	0.075	0.785
L Dorsal posterior cingulate gyrus	2.309	0.133
L Ventral posterior cingulate gyrus	1.495	0.226
L Cuneus	0.186	0.667
L Pars opercularis	6.509	0.013
L Pars orbitalis	2.241	0.139
L Pars triangularis	3.777	0.056
L Middle frontal gyrus	2.085	0.153
L Superior frontal gyrus	0.805	0.373
L Long insular gyrus	0.298	0.587
L Short insular gyrus	1.116	0.294
L Middle occipital gyrus	1.473	0.229
L Superior occipital gyrus	0.042	0.838
L Lateral occipito-temporal gyrus	0.613	0.437
L Lingual gyrus	0.133	0.717
L Parahippocampal gyrus	1.710	0.195
L Orbital gyrus	1.515	0.223
L Angular gyrus	3.663	0.060
L Supramarginal gyrus	3.945	0.051
L Superior parietal lobule	0.601	0.441
L Postcentral gyrus	0.010	0.921
L Precentral gyrus	0.947	0.334
L Precuneus	0.225	0.637
L Straight gyrus	0.396	0.531
L Subcallosal gyrus	0.849	0.360
L Anterior transverse temporal gyrus	0.486	0.488
L Lateral superior temporal gyrus	0.662	0.419
L Planum polare	1.976	0.164
L Planum temporale	2.912	0.093
L Inferior temporal gyrus	1.992	0.163
L Middle temporal gyrus	5.027	0.028
Right hemisphere		
R Frontomarginal gyrus	1.090	0.300
R Inferior occipital gyrus	5.099	0.027
R Paracentral lobule	2.045	0.157
R Subcentral gyrus	1.217	0.274
R Transverse frontopolar gyrus	1.080	0.302
R Anterior cingulate gyrus	0.592	0.444
R Anterior mid-cingulate gyrus	1.112	0.295
R Posterior mid-cingulate gyrus	0.495	0.484
R Dorsal posterior cingulate gyrus	0.966	0.329
R Ventral posterior cingulate gyrus	1.717	0.195
R Cuneus	0.058	0.810
R Pars opercularis	4.331	0.041
R Pars orbitalis	1.990	0.163
R Pars triangularis	15.858	1.69×10^{-4}
R Middle frontal gyrus	1.870	0.176
R Superior frontal gyrus	0.461	0.499
R Long insular gyrus	0.262	0.610
R Short insular gyrus	0.907	0.344
R Middle occipital gyrus	0.814	0.370
R Superior occipital gyrus	0.004	0.953
R Lateral occipito-temporal gyrus	2.303	0.134
R Lingual gyrus	0.140	0.710
R Parahippocampal gyrus	0.297	0.587
R Orbital gyrus	4.073	0.048
R Angular gyrus	2.216	0.141
R Supramarginal gyrus	3.984	0.050
R Superior parietal lobule	3.059	0.085
R Postcentral gyrus	0.394	0.532
R Precentral gyrus	1.941	0.168
R Precuneus	0.002	0.967
R Straight gyrus	1.633	0.206
R Subcallosal gyrus	0.017	0.896
R Anterior transverse temporal gyrus	0.950	0.333
R Lateral superior temporal gyrus	0.054	0.817
R Planum polare	1.235	0.270
R Planum temporale	0.000	0.999
R Inferior temporal gyrus	2.130	0.149
R Middle temporal gyrus	3.561	0.063

The general linear model (GLM) included BD patients and adjusted for age, sex, educational level, and intracranial volume as covariates. Regions that remained significant after Bonferroni correction are listed: 76 regions of cortex, corrected $p=(0.05/76)=6.58 \times 10^{-4}$. BD, bipolar disorder

Supplementary Table 12. Effects of atypical antipsychotics on cortical surface area in BD

Cortical regions	All groups	
	F	p
Left hemisphere		
L Frontomarginal gyrus	2.308	0.133
L Inferior occipital gyrus	1.672	0.200
L Paracentral lobule	0.098	0.755
L Subcentral gyrus	0.464	0.498
L Transverse frontopolar gyrus	2.080	0.154
L Anterior cingulate gyrus	3.521	0.065
L Anterior mid-cingulate gyrus	0.032	0.859
L Posterior mid-cingulate gyrus	0.045	0.833
L Dorsal posterior cingulate gyrus	0.163	0.688
L Ventral posterior cingulate gyrus	1.441	0.234
L Cuneus	0.008	0.930
L Pars opercularis	0.093	0.762
L Pars orbitalis	0.970	0.328
L Pars triangularis	0.028	0.868
L Middle frontal gyrus	0.490	0.486
L Superior frontal gyrus	1.018	0.317
L Long insular gyrus	1.420	0.237
L Short insular gyrus	0.248	0.620
L Middle occipital gyrus	1.765	0.188
L Superior occipital gyrus	0.000	0.983
L Lateral occipito-temporal gyrus	0.046	0.831
L Lingual gyrus	0.160	0.691
L Parahippocampal gyrus	0.214	0.645
L Orbital gyrus	0.996	0.322
L Angular gyrus	0.002	0.963
L Supramarginal gyrus	5.487	0.022
L Superior parietal lobule	3.602	0.062
L Postcentral gyrus	0.109	0.742
L Precentral gyrus	0.376	0.542
L Precuneus	4.706	0.034
L Straight gyrus	0.097	0.756
L Subcallosal gyrus	0.222	0.639
L Anterior transverse temporal gyrus	0.326	0.570
L Lateral superior temporal gyrus	2.345	0.130
L Planum polare	1.554	0.217
L Planum temporale	0.030	0.862
L Inferior temporal gyrus	2.856	0.096
L Middle temporal gyrus	0.798	0.375
Right hemisphere		
R Frontomarginal gyrus	2.455	0.122
R Inferior occipital gyrus	0.164	0.687
R Paracentral lobule	0.002	0.969
R Subcentral gyrus	0.297	0.587
R Transverse frontopolar gyrus	0.524	0.471
R Anterior cingulate gyrus	0.491	0.486
R Anterior mid-cingulate gyrus	0.006	0.937
R Posterior mid-cingulate gyrus	0.284	0.596
R Dorsal posterior cingulate gyrus	0.065	0.799
R Ventral posterior cingulate gyrus	0.779	0.381
R Cuneus	2.310	0.133
R Pars opercularis	0.620	0.434
R Pars orbitalis	0.453	0.503
R Pars triangularis	0.896	0.347
R Middle frontal gyrus	1.577	0.214
R Superior frontal gyrus	0.733	0.395
R Long insular gyrus	2.905	0.093
R Short insular gyrus	1.214	0.274
R Middle occipital gyrus	0.012	0.914
R Superior occipital gyrus	0.954	0.332
R Lateral occipito-temporal gyrus	2.112	0.151
R Lingual gyrus	1.259	0.266
R Parahippocampal gyrus	0.736	0.394
R Orbital gyrus	1.144	0.289
R Angular gyrus	0.002	0.963
R Supramarginal gyrus	0.583	0.448
R Superior parietal lobule	0.175	0.677
R Postcentral gyrus	0.874	0.353
R Precentral gyrus	0.019	0.890
R Precuneus	0.169	0.682
R Straight gyrus	0.490	0.486
R Subcallosal gyrus	0.068	0.795
R Anterior transverse temporal gyrus	0.555	0.459
R Lateral superior temporal gyrus	0.247	0.621
R Planum polare	3.056	0.085
R Planum temporale	0.572	0.452
R Inferior temporal gyrus	1.715	0.195
R Middle temporal gyrus	0.050	0.825

The general linear model (GLM) included BD patients and adjusted for age, sex, educational level, and intracranial volume as covariates. Regions that remained significant after Bonferroni correction are listed: 76 regions of cortex, corrected $p=(0.05/76)=6.58 \times 10^{-4}$. BD, bipolar disorder