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ORIGINAL ARTICLE

Cortical abnormalities in bipolar disorder: an MRI analysis of 6503 individuals from the ENIGMA Bipolar Disorder Working Group

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Despite decades of research, the pathophysiology of bipolar disorder (BD) is still not well understood. Structural brain differences have been associated with BD, but results from neuroimaging studies have been inconsistent. To address this, we performed the largest study to date of cortical gray matter thickness and surface area measures from brain magnetic resonance imaging scans of 6503 individuals including 1837 unrelated adults with BD and 2582 unrelated healthy controls for group differences while also examining the effects of commonly prescribed medications, age of illness onset, history of psychosis, mood state, age and sex differences on cortical regions. In BD, cortical gray matter was thinner in frontal, temporal and parietal regions of both brain hemispheres. BD had the strongest effects on left pars opercularis (Cohen's $d = -0.293$; $P = 1.71 \times 10^{-21}$), left fusiform gyrus ($d = -0.288$; $P = 8.25 \times 10^{-21}$) and left rostral middle frontal cortex ($d = -0.276$; $P = 2.99 \times 10^{-19}$). Longer duration of illness (after accounting for age at the time of scanning) was associated with reduced cortical thickness in frontal, medial parietal and occipital regions. We found that several commonly prescribed medications, including lithium, antiepileptic and antipsychotic treatment showed significant associations with cortical thickness and surface area, even after accounting for patients who received multiple medications. We found evidence of reduced cortical surface area associated with a history of psychosis but no associations with mood state at the time of scanning. Our analysis revealed previously undetected associations and provides an extensive analysis of potential confounding variables in neuroimaging studies of BD.

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INTRODUCTION

Bipolar disorder (BD) is among the most debilitating psychiatric disorders and affects 1–3% of the adult population worldwide.^{1,2} BD is known to be highly heritable with individual risk depending partially on genetics.^{3,4} However, the underlying neurobiological mechanism of the disorder remains unclear. The prognosis for individuals with BD is mixed: currently approved medications are ineffective for many patients.^{5–8} Treatment regimens for patients with BD include several different medication types, including lithium, antiepileptics, antipsychotics and antidepressants.² Some of the most commonly prescribed medications for patients with BD—including lithium^{9–12} and antiepileptics¹³—have also been associated with structural brain differences, but the scope of these effects have not been systematically investigated. Many individuals with BD are initially misdiagnosed¹⁴ and may receive inappropriate treatments^{15–17} before presenting symptoms distinguishable from those of related disorders, such as major depressive disorder.

Examinations of consistently detected, BD-specific structural brain abnormalities will increase our neurobiological understanding of the illness. Relative to matched controls, BD patients show alterations in cortical thickness, surface area and the overall gray matter volume^{18,19} measures that relate to functional impairments in cognition, behavior and symptom domains.^{20,21} Cortical thickness and surface area are highly heritable^{22,23} and may be affected by largely distinct sets of genes.^{24,25} By examining regional cortical thickness and surface area differences in individuals with BD relative to healthy controls, we may identify biologically meaningful markers of disease.

Brain abnormalities associated with BD are challenging to identify, as BD is notoriously heterogeneous in symptom profile and cycles.¹⁴ A retrospective literature-based meta-analysis of cortical thickness²⁶ found that the most consistent differences between individuals with BD and healthy controls were reduced thickness in the left anterior cingulate,^{27–32} left paracingulate,^{27–30,32,33} left superior temporal gyrus^{27,28,32–35} and prefrontal regions bilaterally.^{27–29,32–34,36,37} Reports of surface area abnormalities associated with BD are mixed, and the largest study to date ($N = 346$) failed to detect surface area differences between BD cases versus controls.³³ Overall, there remains considerable

uncertainty about the direction and anatomical profile of effects: many studies report no effect in specific cortical regions or significant effects in brain regions inconsistent with prior studies. Therefore, our understanding of BD cortical changes could be improved through a large-scale coordinated and harmonized analysis of the vast amounts of existing data to map brain differences in heterogeneous patient populations worldwide.

We formed the Bipolar Disorder Working Group within the ENIGMA Consortium^{38,39} with the overarching goal of identifying consistent brain alterations associated with BD and elucidating and controlling for moderating factors that may affect the pathophysiology of BD. This new effort builds upon our previous effort looking at subcortical differences associated with BD⁴⁰ and examines structural brain magnetic resonance imaging (MRI) and clinical data from 6503 individuals (2447 of which were BD patients) with the aim of identifying differences in cortical regions consistently associated with BD with unprecedented power. In this large sample, we sought to examine effects of: (1) diagnosis, (2) age and sex, (3) subtype diagnosis, (4) duration of illness, (5) medication differences, (6) history of psychosis, and (7) mood state in adults and adolescents/young adults.

MATERIALS AND METHODS

Samples

The ENIGMA BD Working Group includes 28 international groups with brain MRI scans and clinical data from BD patients and healthy controls. Overall, we analyzed data from 6503 people, including 2447 BD patients and 4056 healthy controls (including 1837 unrelated adult patients with BD compared with 2582 unrelated adult healthy controls). Each cohort's demographics are detailed in Supplementary Table S1. Supplementary Table S2 gives the instrument used to obtain diagnosis and medication information and Supplementary Table S3 lists exclusion criteria for study enrolment. All participating sites obtained approval from their local institutional review boards and ethics committees, and all study participants provided written informed consent.

Image processing and analysis

Structural T1-weighted MRI brain scans were acquired at each site and analyzed locally using harmonized analysis and quality-control protocols

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from the ENIGMA consortium that have previously been applied in large-scale studies of major depression.⁴¹ Image acquisition parameters and software descriptions are given in Supplementary Table S4. Cortical segmentations and parcellations for each cohort were created with the freely available and validated segmentation software, FreeSurfer.⁴² Segmentations of 68 (34 left and 34 right) cortical gray matter regions were created based on the Desikan–Killiany atlas⁴³ (as well as the hemispheric total surface area and average cortical thickness). Segmented regions were visually inspected and statistically evaluated for outliers following standardized ENIGMA protocols (<http://enigma.ini.usc.edu/protocols/imaging-protocols>). Individual sites were provided with examples of good/poor segmentation across the cortex. Diagnostic histogram plots were generated for each site and outlier subjects were flagged for further review (shared with DPH).

Statistical models of cortical differences

We examined group differences in cortical thickness and pial surface area between patients and controls using mixed-effect models, accounting for site as a random effect. Our focus was to examine differences in adults (defined as ≥ 25 years at the time of scanning) and separately cortical differences in adolescents/young adults (defined as < 25 years at the time of scanning). In the analysis of adults, the outcome measures were from each of the 70 cortical region of interests (ROIs; 68 regions and two whole-hemisphere average thickness or total surface area measures). A binary indicator of diagnosis (0=controls, 1=patients) was the predictor of interest. All cortical thickness models were adjusted for age and sex; all cortical surface area models were corrected for intracranial volume, age, sex, age-by-sex, age-squared and age-squared-by-sex to account for any higher-order effects on cortical surface area of age and sex as well as head size, which do not appear to be detectable for cortical thickness measures.⁴⁴ Effect size estimates were calculated using the Cohen's d metric computed from the t -statistic of the diagnosis indicator variable from the regression models. Similarly, for models testing interactions the predictor of interest was the product of two variables (that is, sex-by-diagnosis and age-by-diagnosis), with the main effect of each predictor included in the model. The effect size was calculated using the same procedure. In cases where the predictor of interest was a continuous variable (for example, duration of illness), we calculated the Pearson's r effect size from the t -statistic of the predictor in the regression model. Throughout the manuscript, we report uncorrected P -values, with a significance threshold over all tests in the study determined by the false discovery rate procedure at $q=0.05$.⁴⁵

We further examined patient-specific clinical characteristics, including diagnosis subtype, medication, duration of illness, history of psychosis and mood state at the time of scanning for effects on cortical thickness and surface area. Patients with a subtype diagnosis of BD type 1 or type 2 were compared with each other using the same statistical framework detailed above. Information on the instrument used for subtype diagnosis is available in Supplementary Table S2. Medications at the time of scanning (not including past medication exposure) were grouped into five major categories (lithium, antidepressants, antiepileptics, atypical and typical antipsychotics) and were jointly examined for effects on cortical thickness and surface area, within the same model. More specifically, we created a series of binary indicator variables for each medication type where a given subject was either 1—taking the medication—or 0—not taking the medication. All medication variables were included as predictors in a model (in addition to the confounding variables listed previously) with a cortical thickness or surface area measure as the outcome of interest. From this model, we were able to examine each medication predictor for its effect on a given cortical trait after accounting for all other medications. We also examined the effect of duration of illness, defined as the difference between age at the time of scan and age at first diagnosis. To minimize the likelihood of spurious correlations due to the high correlation between duration of illness and age at scan, while still being able to examine brain differences associated with illness duration, we performed a hierarchical regression with two levels. First, we used a multiple linear regression model with all potential confounding variables included and a given cortical thickness or surface area trait as the outcome. Next, we used a mixed-effect model with the residuals of the first model included as the outcome of interest, duration of illness as the predictor of interest and site as a random effect. We calculated effect-size estimates for each cortical trait from the t -statistics in this second model. We examined patient-specific differences in the cortex of BD patients with a lifetime history of psychosis. Patients with a history of psychosis were coded as 1 and those

without were coded as 0. Mood state at the time of scanning, either euthymic or depressed (other mood states such as manic, hypomanic and mixed had insufficient numbers to perform a comparison), was examined for differential effects on the cortices of BD patients. In the comparison, euthymic patients were coded as 0 and depressed patients were coded as 1. Effect-size statistics were calculated as stated previously. Finally, we examined potential sources of bias based on imaging acquisition and analysis parameters, including field strength, voxel volume and FreeSurfer version. Field strength and FreeSurfer version were assessed for significance using a partial F -test where the full model included a factor with the imaging parameters in addition to the full set of covariates described above and the reduced model contained only the full set of covariates. Voxel volume was assessed directly for effect on cortical thickness and surface area and effect sizes were estimated based on the Pearson's r of the voxel volume predictor in a model including the full set of covariates mentioned above.

RESULTS

Widespread cortical thinning associated with BD in adults

We found a significant and widespread pattern of reduced cortical thickness associated with BD (1837 BD patients, 2582 controls; Figure 1) with the largest effects in the left pars opercularis (Cohen's $d = -0.293$; $P = 1.71 \times 10^{-21}$), left fusiform gyrus ($d = -0.288$; $P = 8.25 \times 10^{-21}$) and left rostral middle frontal cortex ($d = -0.276$; $P = 2.99 \times 10^{-19}$). Large effects on average thickness over the left and right hemispheres were also present ($d = -0.325$; $P = 2.86 \times 10^{-25}$; $d = -0.303$; $P = 3.35 \times 10^{-22}$, respectively). Full results for the analysis of cortical thickness are presented in Table 1. We did not detect significant differences in cortical surface area ROIs associated with BD in adults (Supplementary Table S5). Further, we did not detect significant differences in cortical thickness or surface area ROIs (Supplementary Tables S7 and S8) for the sex-by-diagnosis interaction. We found evidence of an age-by-diagnosis interaction showing reduced surface area of the left posterior cingulate cortex ($d = -0.100$; $P = 0.00112$) with increasing age. No other significant differences in cortical thickness or surface area for the age-by-diagnosis interaction were detected (Supplementary Tables S9 and S10).

No significant cortical thickness or surface area differences between BD subtypes

We compared 1275 unrelated, adult patients diagnosed with BD type 1 with 345 unrelated, adult patients diagnosed with BD type 2. We did not detect significant differences in cortical thickness or surface area ROIs associated with subtype (Supplementary Tables S11 and S12).

Significant association of duration of illness on cortical thickness but not surface area

We found a broad pattern of reduced cortical thickness significantly associated with longer illness duration with the strongest effects in the left and right pericalcarine gyrus (Pearson's $r = -0.129$; $P = 1.35 \times 10^{-6}$; $r = -0.123$; $P = 3.96 \times 10^{-6}$), left rostral anterior cingulate gyrus ($r = -0.091$; $P = 6.09 \times 10^{-4}$) and right cuneus ($r = -0.090$; $P = 7.44 \times 10^{-4}$) and evidence of significantly increased thickness in the right entorhinal gyrus ($r = 0.089$; $P = 9.19 \times 10^{-4}$; Figure 2; Supplementary Table S13). Cortical surface area ROIs in adult BD patients were not significantly associated with illness duration (Supplementary Table S14).

Widespread effects on cortical thickness and surface area associated with commonly prescribed medications in adults diagnosed with BD

We examined cortical thickness and surface area differences associated with five major medication families: lithium, antiepileptics, antidepressants, and typical and atypical antipsychotics in

adult patients with BD. We found significant evidence of increased cortical thickness associated with taking lithium ($n=700$; compared with those not taking lithium $n=892$), with the largest effects in the left paracentral gyrus ($d=0.211$; $P=7.96 \times 10^{-5}$) and the left and right superior parietal gyrus ($d=0.202$; $P=1.60 \times 10^{-4}$; $d=0.188$; $P=4.39 \times 10^{-4}$) (Figure 3; Supplementary Table S15). We also found evidence of increased surface area in the left paracentral lobule ($d=0.17$; $P=0.0015$; Supplementary Table S16).

In the patient group, reduced cortical thickness was associated with antiepileptic treatment ($n=576$ compared with patients not taking antiepileptics $n=932$), with the largest effects in the left and right lateral occipital gyrus ($d=-0.360$; $P=5.35 \times 10^{-11}$; $d=-0.357$; $P=7.24 \times 10^{-11}$) and right paracentral gyrus ($d=-0.326$; $P=2.57 \times 10^{-9}$) (Figure 4; Supplementary Table S17). Cortical surface area was not significantly associated with antiepileptic treatment for any ROI (Supplementary Table S18).

Increased cortical surface area was associated with typical antipsychotic treatment ($n=78$ compared with patients not taking typical antipsychotics $n=1419$) in the left middle temporal gyrus ($d=0.439$; $P=2.83 \times 10^{-4}$), left inferior parietal gyrus ($d=0.366$; $P=0.00213$) and right temporal pole ($d=0.382$; $P=0.00147$; Supplementary Table S20). We did not detect any significant associations between cortical thickness and typical antipsychotic treatment (Supplementary Table S19).

We found significant evidence of reduced cortical surface area associated with atypical antipsychotic treatment ($n=504$ compared with patients not taking atypical antipsychotics $n=994$) in the right rostral middle frontal gyrus ($d=-0.199$; $P=4.00 \times 10^{-4}$) and right superior frontal gyrus ($d=-0.187$; $P=8.61 \times 10^{-4}$; Supplementary Table S22). We did not detect significant associations between cortical thickness and atypical antipsychotic treatment (see Supplementary Table S21).

We did not detect any significant association between in cortical thickness (Supplementary Table S23) or surface area (Supplementary Table S24) and antidepressant treatment.

Association of cortical surface area with history of psychosis and mood state findings at the time of scanning

When comparing 768 adult BD patients with a history of psychosis with 619 patients without a history of psychosis, we found evidence of reduced surface area in the right frontal pole of BD patients with a history of psychosis ($d=-0.167$; $P=0.0023$). We did not detect differences in cortical thickness or surface area in any other regions of interest (Supplementary Tables S25 and S26). Further, we did not detect differences in cortical thickness or surface area when comparing patients who were depressed at the time of scanning ($n=210$) with patients who were euthymic at the time of scanning ($n=819$) (Supplementary Tables S27 and S28). Comparisons with other mood states such as hypomanic, manic and mixed were not possible due to small sample sizes.

Association of cortical thickness and surface area with BD in adolescents/young adults/young adults

We compared cortical thickness and surface area between 411 adolescent/young adult patients diagnosed with BD and 1035 healthy adolescents/young adults/young adults (mean age: 21.1 years ± 3.1 s.d.; age of onset: 20.3 ± 9.5 years; and age range: 8–24.9 years). We found significantly reduced thickness in the right supramarginal gyrus ($d=-0.195$; $P=0.00102$) and reduced surface area in the left insula ($d=-0.184$; $P=0.00196$) (Supplementary Tables S29 and S30) measures. We found a broad pattern of significant interactions between age and diagnosis whereby older BD patients had reduced cortical thickness beyond the effects of age and diagnosis, with the strongest effect observed in the left rostral middle frontal gyrus ($d=-0.264$; $P=8.83 \times 10^{-6}$). We further found evidence of an interaction between sex and diagnosis in the frontal and temporal lobe gyri whereby adolescent/young adult female BD patients showed less thinning than could be explained by sex and diagnosis with the strongest effect in the right pars triangularis ($d=0.264$; $P=8.56 \times 10^{-6}$). Fully tabulated results for the age-by-diagnosis and sex-by-diagnosis comparison with cortical thickness are available in Supplementary

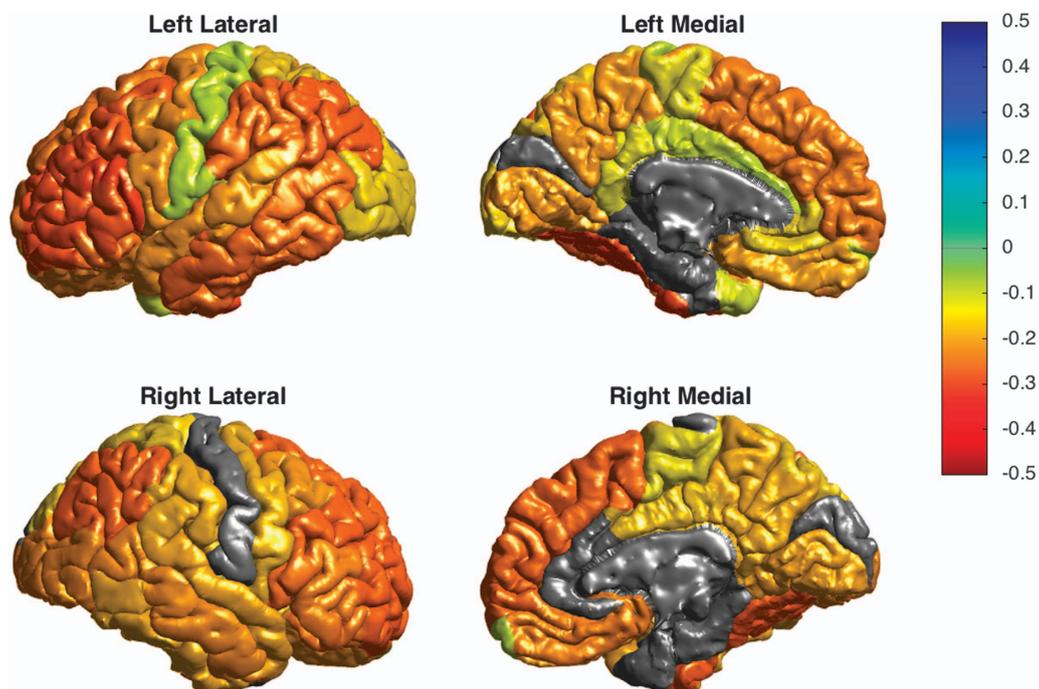


Figure 1. Cortical thinning in adult patients with bipolar disorder compared with healthy controls. Cohen's d effect sizes are plotted for each region of interest on the cortical surface of a template image. Only significant regions are shown; non-significant regions are colored in gray.

Table 1. Cortical thickness differences associated with bipolar disorder in adults (age ≥ 25 years)

	Cohen's d (BD versus CTL)	S.e.	95% CI	% Difference	P-value	FDR P-value	# Controls	# Patients
Left hemisphere average thickness	-0.325	0.031	(-0.386 to -0.264)	-1.800	2.86×10^{-25}	1.08×10^{-21}	2559	1769
Right hemisphere average thickness	-0.303	0.031	(-0.364 to -0.242)	-1.707	3.35×10^{-22}	6.33×10^{-19}	2554	1768
Left pars opercularis of inferior frontal gyrus	-0.293	0.031	(-0.354 to -0.233)	-2.251	1.71×10^{-21}	2.16×10^{-18}	2581	1837
Left fusiform gyrus	-0.288	0.031	(-0.349 to -0.228)	-2.579	8.25×10^{-21}	7.80×10^{-18}	2580	1835
Left rostral middle frontal gyrus	-0.276	0.031	(-0.336 to -0.216)	-2.114	2.99×10^{-19}	2.26×10^{-16}	2579	1837
Left pars triangularis of inferior frontal gyrus	-0.270	0.031	(-0.33 to -0.21)	-2.258	1.65×10^{-18}	1.04×10^{-15}	2581	1837
Right fusiform gyrus	-0.267	0.031	(-0.327 to -0.207)	-2.431	4.77×10^{-18}	2.58×10^{-15}	2570	1833
Left caudal middle frontal gyrus	-0.266	0.031	(-0.326 to -0.206)	-2.074	5.85×10^{-18}	2.76×10^{-15}	2581	1835
Left inferior parietal cortex	-0.265	0.031	(-0.326 to -0.205)	-1.889	6.84×10^{-18}	2.87×10^{-15}	2580	1834
Right rostral middle frontal gyrus	-0.264	0.031	(-0.324 to -0.204)	-2.048	1.21×10^{-17}	4.57×10^{-15}	2572	1832
Right inferior parietal cortex	-0.258	0.031	(-0.318 to -0.198)	-1.911	5.19×10^{-17}	1.78×10^{-14}	2574	1834
Right superior frontal gyrus	-0.256	0.031	(-0.316 to -0.196)	-1.887	9.09×10^{-17}	2.86×10^{-14}	2574	1833
Left supramarginal gyrus	-0.253	0.031	(-0.313 to -0.192)	-1.852	2.30×10^{-16}	6.70×10^{-14}	2580	1837
Left middle temporal gyrus	-0.252	0.031	(-0.312 to -0.192)	-1.940	2.77×10^{-16}	7.47×10^{-14}	2579	1831
Left inferior temporal gyrus	-0.250	0.031	(-0.31 to -0.19)	-2.606	5.01×10^{-16}	1.26×10^{-13}	2576	1824
Right pars opercularis of inferior frontal gyrus	-0.248	0.031	(-0.308 to -0.188)	-1.925	7.95×10^{-16}	1.88×10^{-13}	2574	1834
Left pars orbitalis of inferior frontal gyrus	-0.246	0.031	(-0.306 to -0.186)	-2.236	1.34×10^{-15}	2.98×10^{-13}	2580	1837
Right pars orbitalis of inferior frontal gyrus	-0.241	0.031	(-0.301 to -0.181)	-2.154	4.85×10^{-15}	1.02×10^{-12}	2572	1835
Left superior frontal gyrus	-0.233	0.031	(-0.293 to -0.173)	-1.720	3.97×10^{-14}	7.91×10^{-12}	2581	1835
Right pars triangularis of inferior frontal gyrus	-0.231	0.031	(-0.291 to -0.171)	-1.913	6.79×10^{-14}	1.28×10^{-11}	2574	1835
Right medial orbitofrontal cortex	-0.230	0.031	(-0.29 to -0.17)	-2.177	9.15×10^{-14}	1.65×10^{-11}	2567	1823
Right middle temporal gyrus	-0.219	0.031	(-0.279 to -0.159)	-2.008	1.15×10^{-12}	1.97×10^{-10}	2572	1833
Right lateral occipital cortex	-0.219	0.031	(-0.279 to -0.159)	-1.613	1.24×10^{-12}	2.03×10^{-10}	2571	1832
Left lateral orbitofrontal cortex	-0.216	0.031	(-0.276 to -0.156)	-1.747	1.97×10^{-12}	3.11×10^{-10}	2581	1835
Left precentral gyrus	-0.211	0.031	(-0.271 to -0.151)	-1.695	7.37×10^{-12}	1.12×10^{-9}	2580	1833
Left precuneus	-0.209	0.031	(-0.269 to -0.149)	-1.528	1.04×10^{-11}	1.51×10^{-9}	2581	1837
Left superior temporal gyrus	-0.209	0.031	(-0.269 to -0.149)	-1.480	1.08×10^{-11}	1.51×10^{-9}	2574	1829
Left lingual gyrus	-0.208	0.031	(-0.268 to -0.148)	-1.563	1.26×10^{-11}	1.71×10^{-9}	2580	1835
Right caudal middle frontal gyrus	-0.208	0.031	(-0.268 to -0.148)	-1.639	1.32×10^{-11}	1.72×10^{-9}	2573	1835
Left banks of superior temporal sulcus	-0.207	0.031	(-0.267 to -0.147)	-1.682	1.61×10^{-11}	2.03×10^{-9}	2579	1830
Right lateral orbitofrontal cortex	-0.207	0.031	(-0.267 to -0.147)	-1.705	1.85×10^{-11}	2.26×10^{-9}	2573	1833
Left medial orbitofrontal cortex	-0.199	0.031	(-0.259 to -0.139)	-1.919	1.01×10^{-10}	1.12×10^{-8}	2572	1826
Left insula	-0.198	0.031	(-0.258 to -0.138)	-1.379	1.14×10^{-10}	1.23×10^{-8}	2578	1836
Right lingual gyrus	-0.197	0.031	(-0.257 to -0.137)	-1.470	1.40×10^{-10}	1.47×10^{-8}	2574	1835
Right superior temporal gyrus	-0.194	0.031	(-0.255 to -0.134)	-1.496	2.87×10^{-10}	2.93×10^{-8}	2564	1823
Right inferior temporal gyrus	-0.189	0.031	(-0.249 to -0.129)	-2.101	8.29×10^{-10}	8.25×10^{-8}	2572	1827
Right precuneus	-0.188	0.031	(-0.248 to -0.128)	-1.432	1.03×10^{-9}	1.00×10^{-7}	2574	1835
Right supramarginal gyrus	-0.184	0.031	(-0.245 to -0.124)	-1.379	2.12×10^{-9}	2.00×10^{-7}	2565	1828
Right isthmus cingulate cortex	-0.183	0.031	(-0.243 to -0.123)	-1.664	2.49×10^{-9}	2.30×10^{-7}	2573	1834
Right precentral gyrus	-0.179	0.031	(-0.239 to -0.119)	-1.450	6.14×10^{-9}	5.40×10^{-7}	2569	1830
Right insula	-0.168	0.031	(-0.228 to -0.108)	-1.166	4.64×10^{-8}	3.58×10^{-6}	2567	1832
Right posterior cingulate cortex	-0.166	0.031	(-0.226 to -0.106)	-1.282	6.20×10^{-8}	4.60×10^{-6}	2574	1834
Left posterior parietal cortex	-0.161	0.031	(-0.221 to -0.102)	-1.259	1.46×10^{-7}	1.01×10^{-5}	2580	1837
Right superior parietal cortex	-0.158	0.031	(-0.218 to -0.098)	-1.357	2.53×10^{-7}	1.70×10^{-5}	2574	1834
Left lateral occipital cortex	-0.156	0.031	(-0.216 to -0.096)	-1.103	3.63×10^{-7}	2.36×10^{-5}	2577	1832
Left rostral anterior cingulate cortex	-0.153	0.031	(-0.213 to -0.093)	-1.523	5.97×10^{-7}	3.82×10^{-5}	2578	1834
Right paracentral lobule	-0.140	0.031	(-0.2 to -0.08)	-1.164	5.24×10^{-6}	2.91×10^{-4}	2574	1834
Left paracentral lobule	-0.137	0.031	(-0.197 to -0.077)	-1.170	7.71×10^{-6}	4.10×10^{-4}	2581	1836
Right isthmus cingulate cortex	-0.132	0.031	(-0.192 to -0.073)	-1.194	1.60×10^{-5}	7.36×10^{-4}	2580	1836
Right banks of superior temporal sulcus	-0.125	0.031	(-0.185 to -0.065)	-1.037	5.00×10^{-5}	2.05×10^{-3}	2574	1832
Left transverse temporal gyrus	-0.120	0.031	(-0.18 to -0.06)	-1.280	9.06×10^{-5}	3.64×10^{-3}	2579	1837
Left frontal pole	-0.118	0.031	(-0.178 to -0.058)	-1.401	1.18×10^{-4}	4.71×10^{-3}	2578	1836

Table 1. (Continued)

	Cohen's d (BD versus CTL)	S.e.	95% CI	% Difference	P-value	FDR P-value	# Controls	# Patients
Left temporal pole	-0.116	0.031	(-0.176 to -0.056)	-1.745	1.70×10^{-4}	6.22×10^{-3}	2572	1812
Left posterior cingulate cortex	-0.112	0.031	(-0.172 to -0.052)	-0.824	2.74×10^{-4}	9.24×10^{-3}	2580	1837
Right transverse temporal gyrus	-0.109	0.031	(-0.169 to -0.049)	-1.182	3.76×10^{-4}	0.012	2574	1834
Right frontal pole	-0.102	0.031	(-0.162 to -0.042)	-1.212	9.41×10^{-4}	0.024	2570	1832
Left postcentral gyrus	-0.096	0.031	(-0.156 to -0.036)	-0.782	1.79×10^{-3}	0.040	2580	1830
Left caudal anterior cingulate cortex	-0.095	0.031	(-0.155 to -0.035)	-1.007	1.88×10^{-3}	0.042	2580	1836
Right rostral anterior cingulate cortex	-0.087	0.031	(-0.147 to -0.027)	-0.858	4.84×10^{-3}	0.086	2570	1833
Right parahippocampal gyrus	-0.086	0.031	(-0.146 to -0.026)	-1.018	5.36×10^{-3}	0.091	2573	1824
Right entorhinal cortex	-0.084	0.031	(-0.144 to -0.024)	-1.246	6.59×10^{-3}	0.105	2567	1797
Right postcentral gyrus	-0.075	0.031	(-0.135 to -0.015)	-0.638	0.014	0.178	2570	1828
Right caudal anterior cingulate cortex	-0.063	0.031	(-0.123 to -0.003)	-0.663	0.039	0.329	2571	1834
Right temporal pole	-0.059	0.031	(-0.119 to 0.001)	-0.912	0.057	0.391	2563	1810
Left cuneus	-0.056	0.031	(-0.116 to 0.004)	-0.526	0.068	0.429	2579	1835
Left entorhinal cortex	-0.036	0.031	(-0.096 to 0.024)	-0.492	0.244	0.691	2569	1803
Right cuneus	-0.029	0.031	(-0.089 to 0.031)	-0.266	0.352	0.774	2572	1833
Left parahippocampal gyrus	-0.022	0.031	(-0.082 to 0.038)	-0.271	0.479	0.839	2581	1820
Left pericalcarine cortex	0.020	0.031	(-0.04 to 0.08)	0.236	0.510	0.843	2578	1836
Right pericalcarine cortex	0.015	0.031	(-0.045 to 0.075)	0.173	0.626	0.896	2574	1832

Abbreviations: BD, bipolar disorder; CI, confidence interval; CTL, control; FDR, false discovery rate.

Tables S34 and S32, respectively. We did not detect significant differences in cortical surface area for the sex-by-diagnosis interaction (Supplementary Table S33) or the age-by-diagnosis interaction (Supplementary Table S35). When comparing 104 adolescent/young adult BD patients with a history of psychosis with 143 patients without a history of psychosis, we found evidence of reduced surface area in the left inferior temporal gyrus ($d = -0.489$; $P = 0.000513$) and right caudal anterior cingulate cortex ($d = -0.433$; $P = 0.00204$) of BD patients with a history of psychosis. We did not detect differences in cortical thickness (Supplementary Tables S50 and S51). Further, we did not detect differences in cortical thickness or surface area when comparing patients who were depressed at the time of scanning ($n = 53$) with patients who were euthymic at the time of scanning ($n = 133$) (Supplementary Tables S52 and S53). Comparisons with other mood states such as hypomanic, manic and mixed were not possible due to small sample sizes. Further examinations of diagnosis subtype, duration of illness and medication effects in our adolescent/young adult sample are detailed in Supplementary Note S1. We did not find evidence of bias in cortical thickness and surface area estimates by field strength, FreeSurfer version or voxel volume in adults or adolescents/young adults (Supplementary Note S2).

DISCUSSION

Here we present a highly powered study on structural brain differences in the cortex of patients with BD using the largest sample to date. Relative to healthy controls, adults with BD had widespread bilateral patterns of reduced cortical thickness in frontal, temporal and parietal regions. In adolescents/young adults/young adults, we found reduced thickness and surface area in the supramarginal gyrus and insula (respectively) associated with BD.

In addition, we found evidence of significant age-by-diagnosis effects whereby older adolescent/young adult patients with BD had additional cortical thinning beyond what could be explained by the effects of age and diagnosis alone. This interaction may capture the accelerated thinning associated with age-related brain changes and the pathophysiology of BD. We also found evidence of significant sex-by-diagnosis effects whereby adolescent/young adult female BD patients have less thinning than would be expected based on sex and diagnosis effects alone. The dampened cortical thinning of adolescent/young adult female patients with BD may reflect the sexual dimorphism in cortical development in which females, in general, have a thicker cortex than males.⁴⁶ However, this interaction effect was not detected in our comparisons of adults and therefore appears to not be present at later stages in life. However, these findings should be confirmed in independent samples and ideally in longitudinal studies.

Interestingly, even in the current highly powered sample, only one of the analyses of diagnosis showed evidence of effects on cortical surface area (reduced surface area in the insula of adolescents/young adults). When reanalyzing the surface area differences without head size as a covariate (that is, with the intracranial volume covariate removed), an additional region of interest (right entorhinal gyrus) showed a significantly increased surface area in adults with BD (Supplementary Tables S6 and S31). In general, BD appears to be associated with reduced cortical thickness but not surface area. Cortical thickness is thought to be a localized measure of neuron numbers within a cortical layer while surface area is a measure of cortical column layer numbers and overall size of the cortex.^{18,19,47} It is therefore possible that the neurobiological mechanisms associated with BD reduce neuron numbers but do not affect overall size of the cortex or cortical columnar organization.

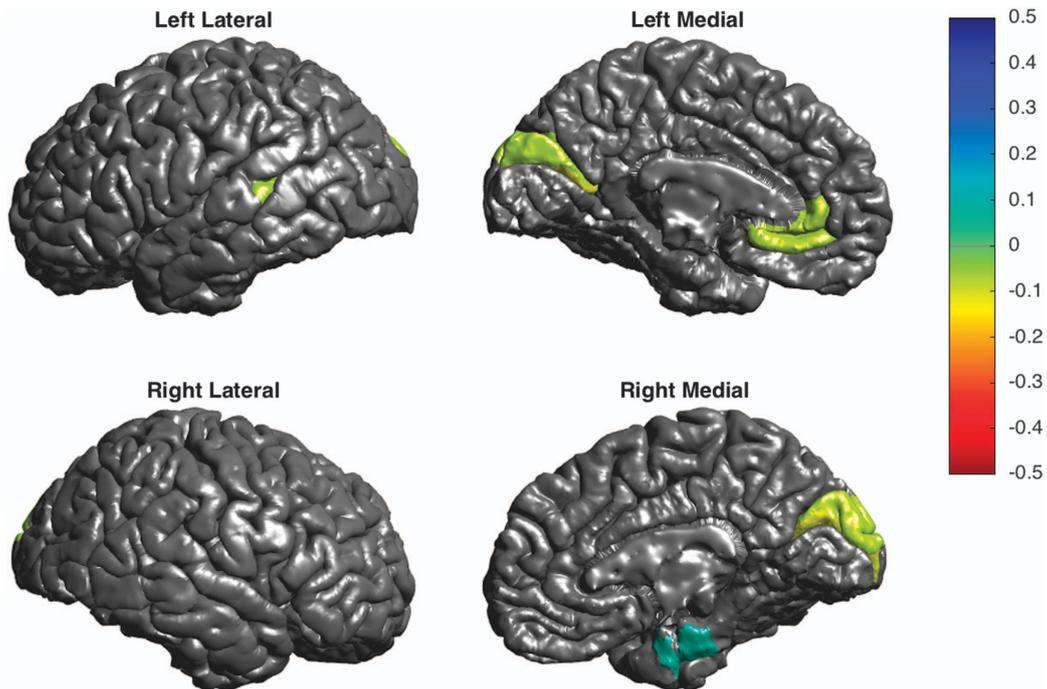


Figure 2. Cortical thinning in adult patients with bipolar disorder associated with duration of illness. Pearson's correlation r effect sizes are plotted for each region of interest on the cortical surface of a template image. Only significant regions are shown; non-significant regions are colored in gray.

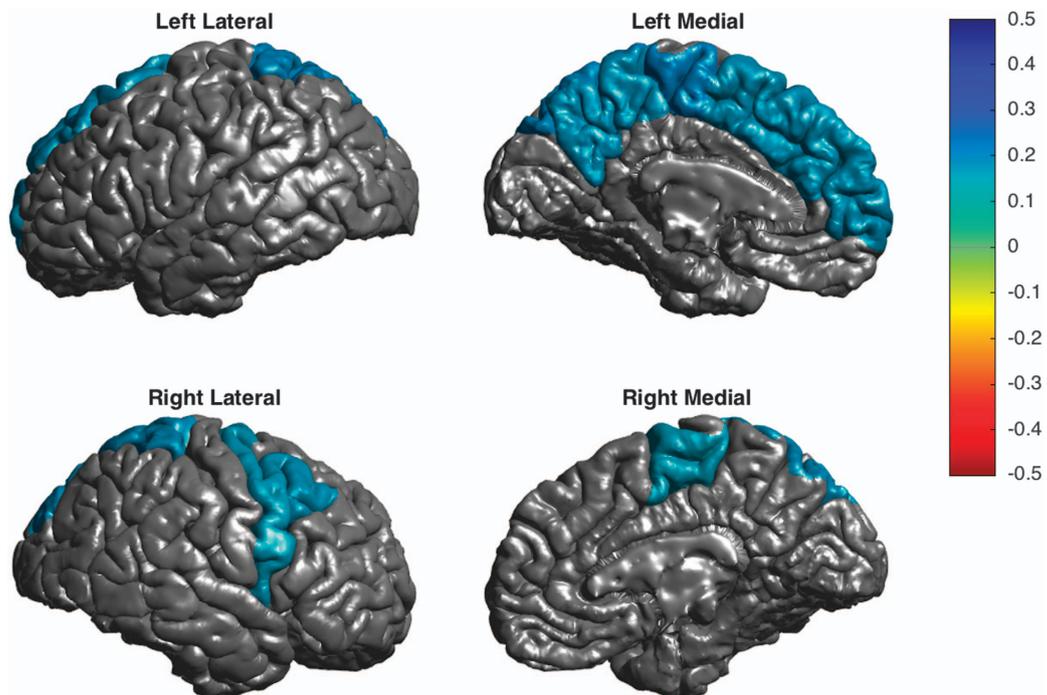


Figure 3. Cortical thickening in adult patients with bipolar disorder associated with lithium treatment. Cohen's d effect sizes are plotted for each region of interest on the cortical surface of a template image. Only significant regions are shown; non-significant regions are colored in gray.

We examined the effects of five major drug families (lithium, antiepileptics, antidepressants, atypical and typical antipsychotics) on cortical thickness and surface area in BD patients. Our statistical model accounted for different drug combinations across individuals. In adults and adolescents/young adults, treatment with lithium or antiepileptics showed significant evidence of effect on

cortical thickness (whereas lithium was positively associated with cortical thickness, antipsychotics showed a negative relationship). Prior studies of these medication types found a similar pattern of effects on surface area and thickness throughout the brain.^{9–13} The increased cortical thickness associated with lithium treatment is hypothesized to be driven by a neurotrophic effect of lithium on

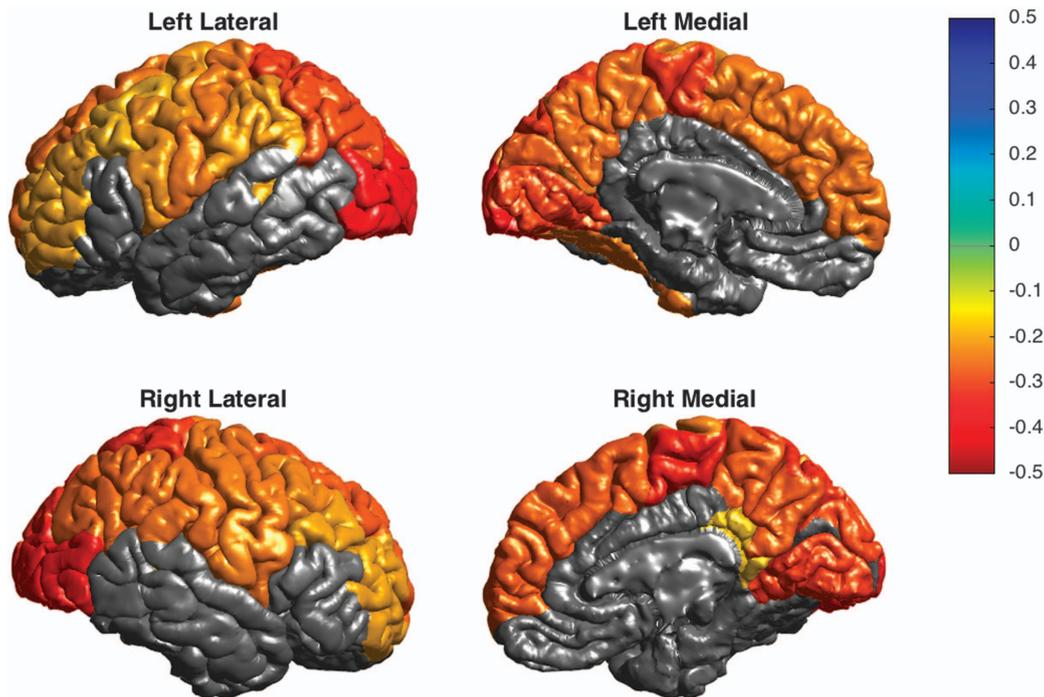


Figure 4. Cortical thinning in adult patients with bipolar disorder associated with antiepileptic treatment. Cohen's *d* effect sizes are plotted for each region of interest on the cortical surface of a template image. Only significant regions are shown; non-significant regions are colored in gray.

gray matter.^{11,48} Interestingly, the regions with the lowest thickness associated with antiepileptic treatment were the primary visual processing areas, in the occipital lobe. Treatment with antiepileptics has previously been reported to be associated with visual deficits.⁴⁹ We found evidence of reduced cortical surface area with atypical antipsychotics, which is in line with previous prospective longitudinal studies in schizophrenia.^{50,51} Our finding of increased cortical surface area associated with typical antipsychotics is difficult to interpret. The total number of patients in our sample taking typical antipsychotics was quite small (about 5%). Further efforts are needed with larger sample sizes to examine this effect more definitively. Our findings highlight the importance of accounting and controlling for medications when assessing brain differences in patients with BD.

We did not detect thickness or surface area differences between adult patients diagnosed with BD type 1 versus type 2. This is consistent with our prior work examining subcortical structural alterations in BD, where we also did not find significant volumetric differences between BD subtypes.⁴⁰ Several previous studies have identified differences in cortical thickness and surface area associated with BD type 1 that do not appear to be apparent in type 2.^{13,33} However, most large meta-analyses have failed to detect a difference between disorders subtypes.^{52,53} Despite the differences in clinical presentation of patients with BD type 1 and type 2, analyses of brain structure and genetics indicate that there are few detectable differences between the subtypes.^{13,33,53,54} It appears then that the current measures of cortical and subcortical structures are not sensitive to differences in subtype. It is possible that the subtype differences are more focal and remain undetected in this ROI-based analysis. Efforts that examine vertexwise data can help examine these issues with a greater resolution across the cortex. In addition, it should be noted that the number of adult patients diagnosed with BD type 2 ($n = 345$) was lower than those with BD type 1 ($n = 1275$). A larger (better balanced) sample size in both groups would help determine the differences more definitively.

We investigated the effect of mood state at the time of scanning as well as patient history of psychosis for effects on the cortex. In adult and adolescent/young adult patients with BD, we did not find evidence of significant differences in cortical thickness or surface area associated with a euthymic or depressed mood state at the time of scanning. The total sample size for other additional mood states (that is, manic, hypomanic, mixed) were too small to allow for comparisons across groups. This suggests that mood state at the time of scanning, at least for euthymic and depressed patients, does not influence cortical thickness and surface area measurements. However, different aspects of mood such as length of time in a given mood state or number of episodes are potential areas for further study though those measures were either unavailable or unreliable in the majority of site participating in this analysis. When we examined adult and adolescent/young adult BD patients with at least one previous episode of psychosis within or outside of an affective episode compared with patients without a history of psychosis, we found evidence of reduced cortical surface area associated with a history of psychosis in the frontal pole of adults and the inferior temporal gyrus and caudal anterior cingulate cortex in adolescents/young adults with a history of psychosis. However, the periodic nature of psychotic symptoms and the heterogeneity in collection across sites in this study limit our interpretation. In addition, the overall sizes of the effects on the cortex, while significant, are quite low. Future work should characterize psychotic symptoms in a prospectively designed and ideally large, cohort study.

Duration of illness has previously been suggested to have effects on cortical thickness in BD.^{55,56} Our study is cross-sectional, that is, we are not observing changes in thickness over time but instead evaluating patients with varying durations of illness. We did find significant evidence of reduced cortical thickness associated with longer duration of illness in adults with BD in the occipital cortex, left parietal and right frontal cortex. However, our current cross-sectional model limits the interpretation of effects that depend on the duration of illness. Large-scale,

longitudinal studies of BD are needed to specifically examine how illness duration and treatment over time affects the brain. Several such efforts are underway,^{57–59} but greater resources are needed in this area to increase power to identify robust effects.

Strengths of this study include a large sample size and harmonized analysis of the cortex, but there are several limitations: (1) samples come from heterogeneous sources—from centers around the world. Although we explicitly model differences between sites (including imaging parameters, such as field strength, FreeSurfer version and voxel volume), sources of heterogeneity (such as treatment response, stage of illness, ethnicity/race) in our estimates still remain. BD itself is quite heterogeneous, and while we attempt to model sources of heterogeneity both in the clinic and at the level of the patient, the overall effect sizes observed in this study are quite small. This suggests that the value of cortical thickness and surface area as a biomarker will likely be strongest when examined in combination with risk gene variants and additional biomarkers that reflect variation in other aspects of the disorder; (2) we examined the moderating effects of commonly prescribed medications, but our cross-sectional data represent only a snapshot of the medication history of a given subject. Although we believe that our medication models do reveal distinct and biologically meaningful patterns of effects on the cortex, we acknowledge that a large, prospective and longitudinal study of BD is the best way to disentangle these effects; (3) several moderating factors (for example, alcohol dependence,⁶⁰ smoking,^{61,62} substance abuse⁶³) may influence cortical structure but were not included in this study as these data were not available in a large portion of the data sets; (4) we examined subjects with a diagnosis of BD excluding patients with head trauma or neurological disorders; however, many sites enrolled patients with co-morbid psychiatric disorders, including anxiety and personality disorders. It therefore remains possible that the effects described here are affected by comorbid diagnoses; and (5) these data are focused on the structure of the cortex including thickness and surface area. Patterns of effects (and lack of effects) may differ when examining other brain imaging modalities (for example, white matter tracts⁶⁴ and resting state networks⁶⁵). Integrating multimodal information on BD will likely improve our understanding of the disorder and help the development of biomarkers. However, large-scale, mono-modality analyses are necessary to first determine the effectiveness of a given modality and its suitability for inclusion in future multi-modal study designs.

In general, our findings are consistent with prior reports of a thinner frontal and temporal cortex in BD.²⁶ The brain regions associated with the largest reductions in cortical thickness in adult patients diagnosed with BD were located in the ventrolateral prefrontal cortex (VLPFC), which has been an area of considerable focus and study in the BD literature.⁶⁶ Functional brain imaging studies have shown increased activity in the VLPFC in remitted BD during emotion regulation⁶⁷ and increased activity in depressed BD during a cognitive task (planning) compared with depressed major depressive disorder.⁶⁸ Functional and structural abnormalities in the VLPFC of unaffected first-degree relatives have also been observed.^{69,70} The findings in this study not only confirm the most consistent effects from prior studies but also provide novel evidence of effects showing that: (1) inferior parietal regions are associated with significantly reduced thickness in adults with BD; and (2) inferior temporal regions (including the fusiform gyrus and middle temporal gyrus) are associated with reduced cortical thickness in adults with BD. The inferior parietal lobe is involved in sensorimotor integration of the mirror neuron system⁷¹ and language tasks.⁷² Structural deficits in these brain regions may be implicated in changes in emotion perception associated with BD, which in turn are suggested to explain fluctuating or rapid changes in mood.^{73,74} The inferior temporal lobe—comprised of the middle and inferior temporal gyri and the fusiform gyrus—

has a major role in the ventral stream of visual processing and spatial awareness. Further, the inferior temporal lobe receives dense neuronal projections from the amygdala and is hypothesized to feed visual perceptions into the emotion processing circuit.⁷⁵ Our analysis of a family-based cohort enriched for BD (UCLA-BP; $n = 527$) shows a similar pattern of effects in the frontal and temporal lobes. However, regional differences in the occipital lobe were not associated with BD in the UCLA-BP cohort. We previously showed that limbic subcortical structures (including the hippocampus and thalamus), which receive dense connections with frontal and temporal lobe regions, showed evidence of volumetric reductions in BD.⁴⁰ A prior analysis of heritability in the UCLA-BP cohort shows that frontal and temporal lobe differences are both partially heritable and attributable to BD pathophysiology.⁷⁶ It should be noted that decreased cortical thickness in general is not specific to BD; it has been shown in other related disorders such as schizophrenia³³ and major depression.⁴¹ Future efforts should examine the value of cortical thickness and surface area as a pattern of effects across the cortex for distinguishing major psychiatric disorders. While we demonstrate a clear pattern of cortical thinning associated with BD, future endeavors should examine the value of these measures for improving the lives of patients including in studies of quality of life, patient outcomes and early detection and intervention.

CONFLICT OF INTEREST

AMM has received funding from Lilly, Janssen and Pfizer. It is unconnected with the current work. TvE has a contract with Otsuka Pharmaceutical Inc. The contract is not related to this work. UFM participated in the speaker's bureau for Lundbeck Norway and was a consultant for Takeda Pharmaceuticals. ACB has received salaries from P1vital Ltd, which is unrelated to this work. PGR trained personnel for Janssen Pharmaceuticals. It is unconnected with the current work. DPH and WCD are employed by Janssen Research and Development, LLC. MB has received grant/research support from Deutsche Forschungsgemeinschaft (DFG), Bundesministerium für Bildung und Forschung (BMBF), American Foundation of Suicide Prevention. MB is/has been a consultant for AstraZeneca, Bristol Myers Squibb, Ferrer International, Janssen, Lilly, Lundbeck, Merz, Neuraxpharm, Novartis, Otsuka, Servier, Takeda, and has received speaker honoraria from AstraZeneca, GlaxoSmithKline, Lilly, Lundbeck, Otsuka and Pfizer, which is all unrelated to this work. OAA has received speaker's honorarium from Lundbeck, Otsuka and Lilly. The remaining authors declare no conflicts of interest. All authors have contributed to and approved the contents of this manuscript.

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