Research Paper

Cortical thickness, volume and surface area in patients with bipolar disorder types I and II

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Background: Bipolar disorder (BD) is a common chronic psychiatric disorder mainly characterized by episodes of mania, hypomania and depression. The disorder is associated with cognitive impairments and structural brain abnormalities, such as lower cortical volumes in primarily frontal brain regions than healthy controls. Although bipolar disorder types I (BDI) and II (BDII) exhibit different symptoms and severity, previous studies have focused on BDI. Furthermore, the most frequently investigated measure in this population is cortical volume. The aim of our study was to investigate abnormalities in patients with BDI and BDII by simultaneously analyzing cortical volume, thickness and surface area, which yields more information about disease- and symptom-related neurobiology. **Methods:** We used MRI to measure cortical volume, thickness and area in patients with BDI and BDII as well as in healthy controls. The large study cohort enabled us to adjust for important confounding factors. **Results:** We included 81 patients with BDI, 59 with BDII and 85 controls in our analyses. Cortical volume, thickness and surface area abnormalities were present in frontal, temporal and medial occipital regions in patients with BD. Lithium and antiepileptic drug use had an effect on the observed differences in medial occipital regions. Patients with the subtypes BDI and BDII displayed common cortical abnormalities, such as lower volume, thickness and surface area than healthy controls in frontal brain regions but differed in temporal and medial prefrontal regions, where only those with BDI had abnormally low cortical volume and thickness. **Limitations:** The group differences can be explained by progressive changes, but also by premorbid conditions. They could also have been influenced by unknown factors, such as social, environmental or genetic factors. **Conclusion:** Our findings suggest diagnosis-related neurobiological differences between the BD subtypes, which could explain distinct symptoms and point to potential biomarkers that could inform the subtype diagnosis of BD.

Introduction

Bipolar disorder (BD) is a common chronic psychiatric disorder characterized by mood disturbances with recurrent episodes of mania, hypomania and depression interspersed by euthymic periods. The disorder is not only associated with premature death, significant disability and impaired psychosocial functioning,[1] but also with cognitive impairments.[2] Summarizing previous imaging studies of patients with BD, recent meta-analyses and review articles have concluded that these patients demonstrate abnormalities primarily in frontal lobe regions, such as abnormally low volumes not only in the anterior cingulate cortex (ACC), medial and inferior frontal, orbitofrontal, ventral and dorsolateral prefrontal cortices, but also in the temporal and insular cortices.[3–9]

There are 2 established subtypes of BD: type I and type II. The subtype BDII is distinguished from BDI mainly by the absence of full-blown manic episodes. This and the generally observed lower functional impairment in patients with BDII compared with BDI[10] has led some to describe BDII as a milder form of BDI. But this conclusion is not necessarily accurate, as BDII is characterized by shorter euthymic intervals, more depressive episodes, longer time spent in a state of depression, more comorbidities and greater perceived suffering than BDI.[11,12] The fact that patients with BDI and BDII manifest different symptoms and severity suggests partly different neurobiological mechanisms and pathophysiology. Despite this, most previous studies have focused on patients with BDI or on patients with BDI and BDII combined indiscriminately. The few and small studies that have investigated patients with BDI, BDII and healthy controls suggest that the subtypes are characterized by common neurobiological alterations that are less pronounced in patients with BDII.[13–15] One study reported fewer case–control differences in grey matter

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volume in the right frontal and temporal lobes in patients with BDII (n = 20) than had previously been found in patients with BDI.[13] In a study by Elvsåshagen and colleagues,[16] which investigated only cortical thickness and surface area, patients with BDII (n = 36) had thinner cortices than controls (n = 42) in the prefrontal and left temporal regions. Another study found that whereas grey matter deficits in the ventromedial prefrontal and superior frontal regions were found in both subtypes, patients with BDI demonstrated additional bilateral abnormalities in frontal, temporal, parietal and parahippocampal regions.[14] In the same study, patients with BDI (n = 23) showed indications for less grey matter in the frontal, temporal and posterior cingulate regions than those with BDII (n = 23), supporting the idea of different neurobiological characteristics and distinct pathophysiology of the 2 subtypes.[14] Furthermore, Maller and colleagues[15] showed that patients with BDI (n = 16) had thinner cortices than those with BDII (n = 15) in medial orbitofrontal and superior temporal regions. They also suggested that some cortical abnormalities may be more pronounced in patients with BDI.[15]

In addition to the fact that most imaging studies have focused on the BDI subtype, the majority of previous studies have, with very few exceptions,[15,17] solely investigated cortical volume, which is a function of cortical thickness and surface area. Thus, the measure of cortical volume is influenced by distinct genetic sources, as cortical thickness and surface area have been suggested to be genetically and phenotypically distinct from each other.[18,19] Cortical thickness serves as a proxy marker of the integrity of the cerebral cortex[20–22] and is related to the size, number and density of cells in a cortical column.[23] Cortical thickness has also been associated with cognitive functions and is a metric increasingly used to study brain–behaviour associations.[24–26] Hence, investigating cortical volume together with cortical thickness and surface area enhances the sensitivity for detecting group differences in cortical morphometry and gives more information on the mechanisms underlying potential differences.

To investigate shared and unique diagnosis-related neuroanatomical abnormalities in the 2 BD subgroups, we examined cortical thickness, volume and area in patients with BDI, BDII and healthy controls. We hypothesized that patients with BDI and BDII would have common as well as unique diagnosis-related cortical abnormalities in regions where previous studies have reported volumetric abnormalities in patients with BD (i.e., temporal and prefrontal brain regions).

Methods

Participants

We recruited patients with BD from a long-term follow-up program at the bipolar outpatient unit at the Northern Stockholm psychiatric clinic, Stockholm, Sweden. Further details on the exclusion and inclusion criteria, diagnostic tools and methods can be found in the study by Ekman and colleagues[27] and in Appendix 1, available at jpn.ca. In brief, patients at the unit were invited to participate in the study provided that they had diagnoses of BD type I, type II or BD not otherwise specified (NOS); or a diagnosis of schizoaffective disorder, manic type. The clinical diagnosis of BD was established according to the structured interview instrument Affective Disorder Evaluation (ADE), which has previously been used in the Systematic Treatment Enhancement Program for Bipolar Disorders project. The ADE includes a social anamnesis, medical history and the affective module of the Structured Clinical Interview for DSM-IV.[28] We categorized education level as pre–high school (9 yr), high school (average 12 yr), less than 3 years of university (average 2 yr), and 3 or more years of university (average 4 yr). Because our scientific question focused on BDI and BDII, we excluded persons with the diagnoses BD NOS and schizoaffective disorder, manic type.

The study also included age- and sex-matched healthy controls randomly recruited from the general population in the same catchment area as the patients with BD. Detailed exclusion criteria can be found in the study by Jakobsson and colleagues[28] or in Appendix 1.

All participants consented orally and in writing to the follow-up program. They were not remunerated for participation. The study was approved by the Ethics committee of the Karolinska Institutet, Stockholm, Sweden.

MRI acquisition

We acquired MRI scans at the MR Research Center, Karolinska University Hospital, Stockholm, Sweden. Coronal 3-dimensional T_1-weighted images were acquired with a spoiled gradient echo recall sequence (3D-SPGR) under the parameters repetition time (TR) 21.0 ms, echo time (TE) 6 ms, field of view (FOV) 18 cm, flip angle 30°, acquisition matrix $256 \times 256 \times 128$ and voxel size $0.7 \times 0.7 \times 1.8$ mm^3, using a 1.5 T Signa Excite MRI medical scanner (General Electric) equipped with an 8-channel head coil. Additional axial fluid attenuation inversion recovery T_2-weighted scans were acquired for examination by senior radiologists to assure that the investigated sample was free of clinically significant anatomic abnormalities and neuropathology.

Image processing

In order to create similar initialization conditions for Freesurfer processing, we reoriented T_1-weighted images to the anterior–posterior commissure line using Matlab version 8.1 (R2013a) and SPM8. Measures for cortical volume, cortical thickness and cortical surface area were obtained using the semiautomated segmentation and cortical surface reconstruction methods provided by Freesurfer version 5.1, as described elsewhere.[29–34] In brief, the procedure includes intensity normalization; removal of nonbrain tissue; segmentation of cortical grey, subcortical white and deep grey matter volumetric structures; and triangular tessellation of the grey/white matter interface and white matter/cerebrospinal fluid (CSF) boundary (pial surface). All surface reconstructions were visually inspected and, where necessary, corrected manually using editing tools provided by Freesurfer, including corrections of erroneous skull stripping and white matter and grey matter

segmentations. Individual reconstructed surfaces were smoothed, transformed and resampled onto a common standard space (fsaverage) using the "-qcache" command.

Statistical analyses

Tests for group differences in demographic and descriptive variables were performed using χ^2 and/or pairwise *t* tests in SPSS software version 21. Pairwise group comparisons for cortical volume, cortical surface area and cortical thickness were performed vertex-wise on the whole brain using the QDEC tool provided by Freesurfer. In the main analyses we investigated the surface area of the white–grey matter boundary (white matter surface); results of secondary tests comparing the area of the grey matter–CSF surface (pial surface) are presented in Appendix 1, Figure S4. In agreement with the findings of Fears and colleagues,[35] no age × group interactions were observed. Therefore, to avoid disguising possible age-related disease effects, we used the DOSS (different offset, same slopes) setting in the applied general linear model approach. In combination with QDEC, DOSS instabilities have been reported in the Freesufer community, but results obtained with and without using the QDEC tool were identical. To investigate more diffuse abnormalities of larger scale rather than focal differences and still avoid possible over-smoothing, we used a surface-based smoothing with a full-width at half-maximum of 15 mm. In the main analysis, we used age and sex as covariates. Correction for multiple comparison was done using a Monte Carlo cluster-wise simulation approach (threshold = 1.3 corresponding to $p = 0.05$). The Monte Carlo–corrected results were compared with those obtained using false-discovery rate (FDR)–correction, which led to the same conclusions.

In follow-up tests we also tested for effects of body mass index (BMI), years of education, intracranial volume, age at disease onset and duration of illness by entering those variables simultaneously with age and sex as covariates. We also tested for effects of smoking/snuff status; alcohol misuse; drug use; comorbid attention-deficit/hyperactivity disorder (ADHD), panic disorder, obsessive–compulsive disorder (OCD), generalized anxiety disorder (GAD), posttraumatic stress disorder (PTSD), social phobia, bulimia or anorexia; history of psychosis; and use of medications, such as lithium (Li), antiepileptics, antidepressants and antipsychotics. Those measures were set up as binary variables: "1" was assigned to patients who used a certain medication type or had a specific comorbidity, and "0" was assigned to those who did not. We performed follow-up analyses testing for effects of those variables on our outcome by using them as additional covariates of no interest, or as discrete (fixed) factors, respectively, to compare MRI measures between patients with and without a certain comorbidity or use of medication, to repeat the main analysis using the corresponding variables separately as additional covariates, and by excluding corresponding individuals from the analysis. This was done for participants with GAD, OCD, PTSD, social phobia, schizophrenia, bulimia, anorexia, alcohol use and drug use in the comparisons between patients with BDI and BDII and controls and for participants with a history of psychosis and antipsychotic use in the comparison between patients with BDII and controls.

Results

Participants

A total of 225 patients assessed had MRI data of sufficient quality for the applied analysis method; after excluding those with BD NOS and schizoaffective disorder, there were 81 patients with BDI and 59 patients with BDII available for our analyses. We also included 85 healthy controls matched for age and sex. The large sample size enabled us to control for important confounding factors, such as use of medication and psychiatric comorbidities. Detailed demographic and clinical characteristics of the study participants can be found in Table 1.

The study groups were equivalent in age and years of education. The prevalence of males was lower in patients with BDII than in those with BDI and controls; therefore, we accounted for sex in our statistical analyses (see also the sensitivity analysis on this matter described in Appendix 1). Body mass index was slightly higher in patients with BDI than controls. The percentage of smokers was lower in controls than patients with BDI and BDII. Comparing patients with BDI and BDII revealed no differences in BMI, duration of illness, age at illness onset, smoking/snuff status, alcohol or drug misuse, use of antiepileptic drugs, or psychiatric comorbidity. History of psychosis and use of Li and antipsychotic medication was more prevalent in the BDI than the BDII group, whereas antidepressant use was less prevalent. Patients with BDI had slightly more severe illness according to their Clinical Global Impression (CGI) scores, although the scores of both groups fell in the moderate category of disease/symptom severity. Patients with BDI had more lifetime manic and fewer depressive episodes than those with BDII.

Group comparisons of cortical volume, thickness and surface area

Patients with BDI versus controls

The results of the vertex-wise analyses are shown in Figure 1. Compared with controls, patients with BDI had lower cortical thickness in the left and right frontal and temporal regions, insula, pre- and postcentral regions and medial occipital lobe (including visual areas). More specifically, frontal regions included the rostral and caudal middle frontal areas; pars opercularis; pars triangularis; pars orbitalis; medial and lateral orbitofrontal cortices; dorsal anterior cingulate cortex (dACC); and medial and lateral superior frontal cortices, including the dorsomedial prefrontal cortex (dmPFC). Temporal regions included the temporal pole and the superior, inferior and middle temporal, entorhinal and fusiform cortices. Clusters in the medial occipital cortex contained the lingual, pericalcarine and cuneus cortices. Regions in which differences in cortical thickness were found also revealed differences in cortical volume and/or surface area in the same or adjacent regions (Fig. 1).

Patients with BDII versus controls

Similar to patients with BDI, patients with BDII showed thinner cortices than controls in the left and right frontal and temporal regions and in medial occipital regions. A cluster of lower insula

thickness compared with controls was present, but did not survive correction for multiple comparisons. As in the comparison of patients with BDI and controls, regions in which we observed differences in cortical thickness were similar to regions showing differences in cortical volume and/or area (Fig. 2). Although the abnormalities in patients with BDII were observed in the same regions as in patients with BDI, the observed clusters were smaller than those observed in the comparison between patients with BDI and controls. In striking contrast to patients with BDI, however, patients with BDII did not demonstrate differences compared with controls in the right temporal, dmPFC and dACC in either cortical volume or thickness (neither corrected, nor uncorrected for multiple comparisons).

Patients with BDI versus those with BDII

Patients with BDI demonstrated significantly lower cortical thickness than those with BDII in the right temporal lobe (Fig. 3). Patients with BDI also demonstrated lower cortical thickness than those with BDII in a large cluster of medial frontal regions, such as the dmPFC and dACC. But this finding did not survive correction for multiple comparisons in the main analysis (Fig. 3, right panel).

Follow-up analyses

The results of the main analyses did not change when controlling for BMI, years of education, intracranial volume, age at disease onset, duration of illness, psychiatric comorbidities, substance use, history of psychosis, or medical treatment. The only effects observed were for Li use in the comparison between patients with BDI and controls and for the use of antiepileptic drugs in the comparisons between both the BDI and BDII groups and controls. We also conducted a sensitivity analysis in women only to exclude the possibility that a larger proportion of women in the BDII group could account for the suggested lesser extent of cortical thickness abnormalities in patients with BDII (Appendix 1, Fig. S5). This analysis of women only perfectly matched the results obtained in the main analysis.

Table 1: Participants demographic and clinical characteristics and the results of pairwise group comparisons

	Group; mean ± SD or no. (%)*			Comparison; *p* value		
Characteristic	Control, *n* = 85	BDI, *n* = 81	BDII, *n* = 59	BDI v. BDII	BDII v. control	BDI v. control
Age, yr	39 ± 15	40 ± 12	40 ± 13	0.83	0.59	0.72
Male sex	41 (48)	36 (44)	16 (27)	0.036	0.011	0.63
No. manic episodes, median (IQR)†	—	2 (3)	—	—	—	—
No. depression episodes, median (IQR)†	—	10 (15)	18 (41)	0.003	—	—
BMI	24 ± 4	26 ± 5	25 ± 4	0.06	0.34	0.001
Duration of illness, yr	—	18 ± 10	21 ± 14	0.16	—	—
Age at onset, yr	—	22 ± 9	19 ± 11	0.19	—	—
Education, yr (categorized), median (IQR)†	3 (2)	3 (2)	3 (2)	0.27	0.76	0.35
CGI-S	—	4.48 ± 1.42	3.83 ± 1.17	0.005	—	—
Smoker	15 (18)	24 (30)	19 (32)	0.75	0.014	0.023
Moist snuff	9 (11)	18 (22)	7 (12)	0.13	0.62	0.02
Alcohol misuse	—	13 (16)	6 (10)	0.33	—	—
Drug misuse	—	7 (9)	6 (10)	0.74	—	—
Medication use						
Lithium	—	56 (69)	20 (34)	< 0.001	—	—
Antiepileptics	—	26 (32)	21 (36)	0.67	—	—
Antidepressants	—	32 (40)	36 (61)	0.011	—	—
Antipsychotics	—	33 (41)	6 (10)	0.001	—	—
Comorbid disorders						
ADHD	—	18 (22)	17 (29)	0.40	—	—
Panic disorder	—	24 (30)	20 (48)	0.55	—	—
Social phobia	—	13 (16)	10 (34)	0.86	—	—
OCD	—	10 (48)	8 (14)	0.81	—	—
GAD	—	13 (12)	9 (15)	0.93	—	—
PTSD	—	5 (6)	2 (3)	0.49	—	—
Anorexia	—	5 (6)	7 (12)	0.23	—	—
Bulimia	—	7 (9)	5 (8)	0.99	—	—
Psychosis	—	65 (80)	4 (7)	< 0.001	—	—
Schizophrenia	—	1 (1)	2 (3)	0.38	—	—
Intracranial volume (L)	1.57 ± 0.14	1.58 ± 0.18	1.54 ± 0.17	0.18	0.26	0.80

ADHD = attention-deficit/hyperactivity disorder; BDI/BDII = bipolar disorder subtypes I and II; BMI = body mass index; CGI-S = Clinical Global Impression; GAD = generalized anxiety disorder; ICV = intracranial volume; IQR = interquartile range; OCD = obsessive–compulsive disorder; PTSD = posttraumatic stress disorder; SD = standard deviation.
*Unless indicated otherwise.
†Significance was determined with the nonparametric Mann–Whitney *U* test.

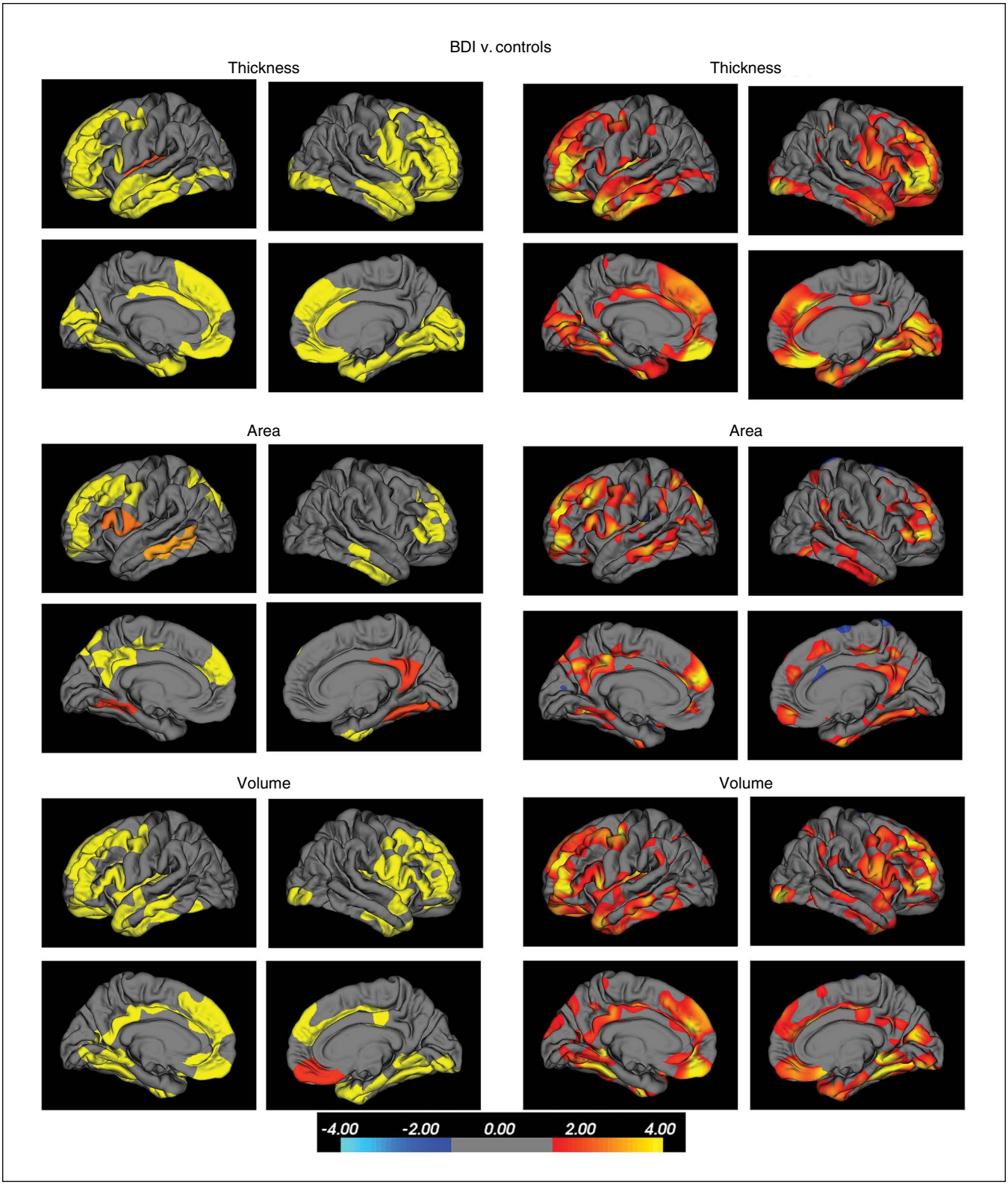

Fig. 1: Differences in cortical thickness (top), area (middle) and volume (bottom) for patients with bipolar disorder type I (BDI) versus controls. Results before (right panel) and after (left panel) corrections for multiple comparisons are shown. Significance is represented on a log(*p* value) scale, where positive values (warm colours) are assigned to the BDI < control clusters and negative values (cold colours) are assigned to the BDI > control clusters.

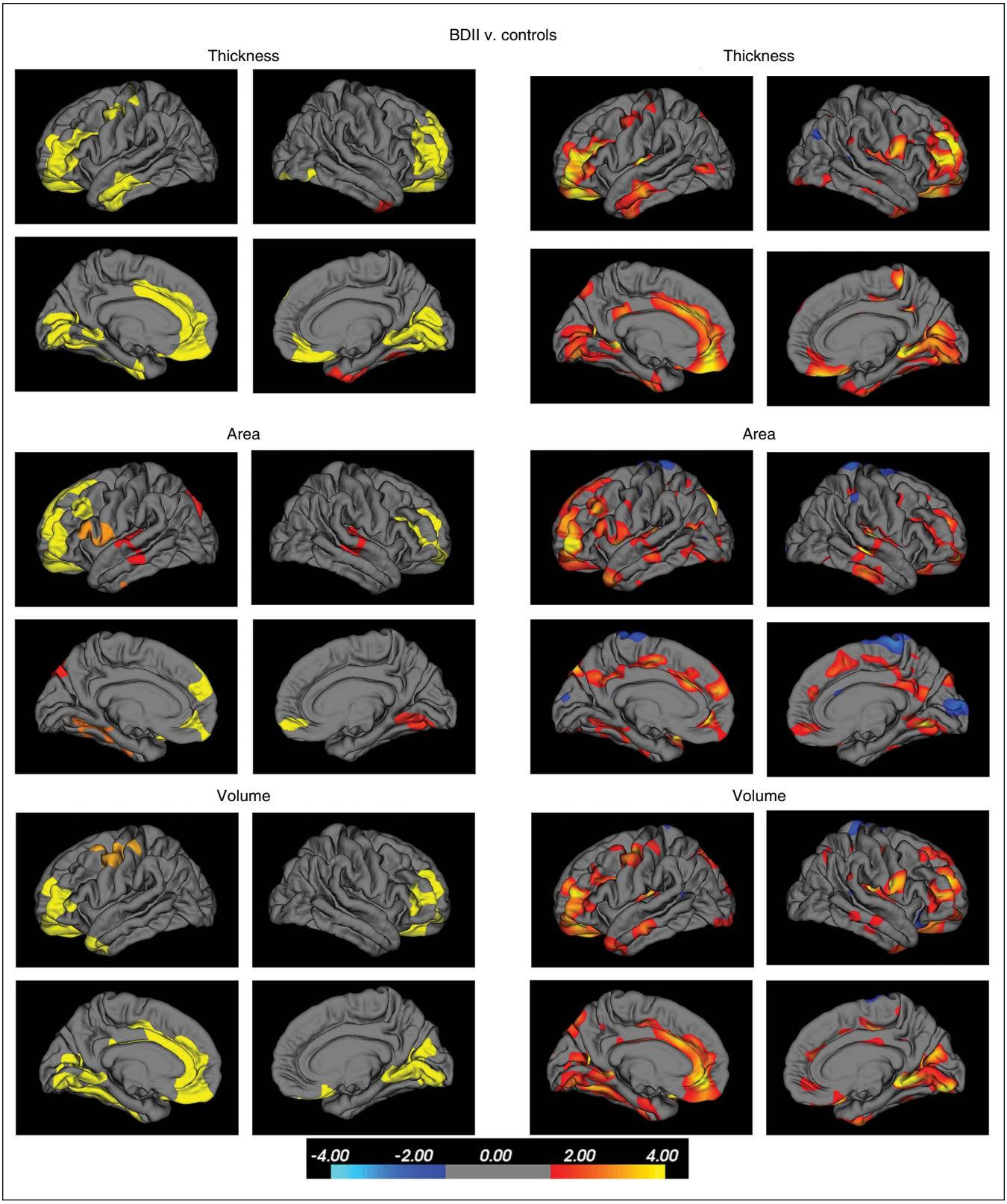

Fig. 2: Differences in cortical thickness (top), area (middle) and volume (bottom) for patients with bipolar disorder type II (BDII) versus controls. Results before (right panel) and after (left panel) corrections for multiple comparisons are shown. Significance is represented on a log(*p* value) scale, where positive values (warm colours) are assigned to the BDII < control clusters and negative values (cold colours) are assigned to the BDII > control clusters.

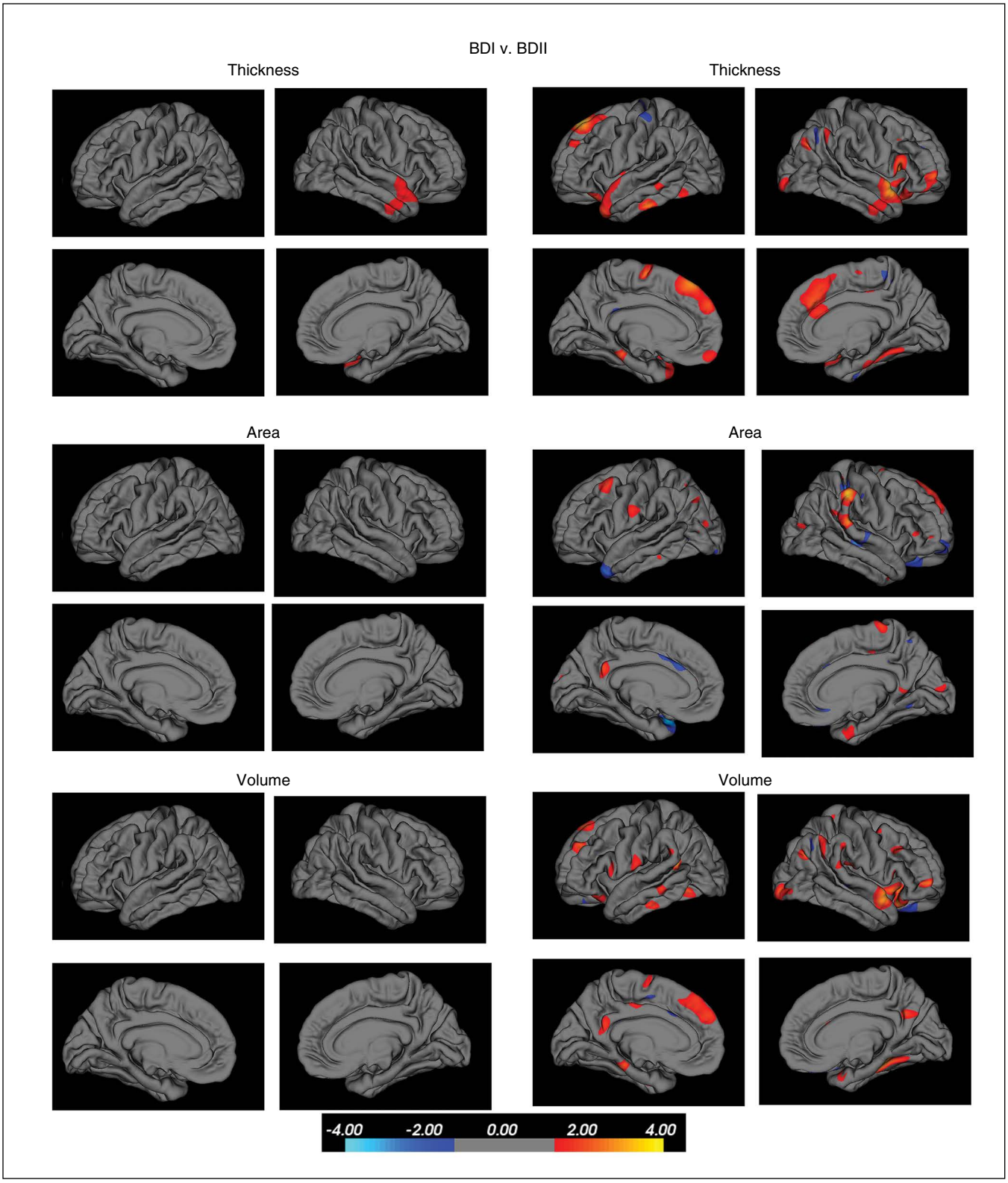

Fig. 3: Differences in cortical thickness (top), area (middle) and volume (bottom) for patients with bipolar disorder type I (BDI) versus type II (BDII). Results before (right panel) and after (left panel) corrections for multiple comparisons are shown. Significance is represented on a log(*p* value) scale, where positive values (warm colours) are assigned to the BDI < BDII clusters and negative values (cold colours) are assigned to the BDI > BDII clusters.

Correcting for use of lithium

When comparing cortical thickness, volume and area between Li users and Li nonusers in the combined patient group (correcting for diagnosis), we found significant differences in medial occipital areas, where Li users showed greater cortical thickness and volume than Li nonusers (Appendix 1, Fig. S1). This affected the comparisons between patients with BDI and controls. The unadjusted results demonstrated lower cortical thickness in medial occipital regions in patients with BDI than in controls. When correcting for Li use, additional differences in cortical volume of the medial occipital regions emerged, where patients with BDI had lower volume than controls (Appendix 1, Fig. S2).

Controlling for use of Li did not change the results of the comparison between patients with BDII and controls. However, in the comparison between patients with BDI and those with BDII, the cluster showing lower cortical thickness in the right dmPFC and dACC of patients with BDI survived correction for multiple comparisons when correcting for Li use (Appendix 1, Fig. S3B).

Correcting for antiepileptic drug use

Comparing cortical thickness, volume and area between antiepileptic users and nonusers in the combined patient cohort (corrected for diagnosis), we found significantly lower cortical thickness and volume in the left and right medial occipital regions (lingual, pericalcarine and cuneus), parts of the (medial) superior and caudal middle frontal regions, and the medial paracentral gyrus (Appendix 1, Fig. S1, right panel). In line with this, differences in cortical thickness and volume of bilateral medial occipital and right medial superior frontal regions disappeared when we adjusted for use of antiepileptics in the comparisons between both patient groups and controls (Appendix 1, Fig. S2 and Fig. S3).

Patients with BDI showed significantly lower cortical thickness than patients with BDII in the cluster containing the right dmPFC and dACC when correcting for use of antiepileptics (Appendix 1, Fig. S3C**).**

Discussion

To our knowledge, this is the largest study to date investigating differences in cortical thickness, volume and area in patients with BDI and BDII separately compared with healthy controls. We found cortical abnormalities specific for the respective subtypes, BDI and BDII. Taken together, the findings suggest partly shared, but also partly unique, neurobiological features of the 2 BD subtypes.

We also reproduced consistently reported volumetric abnormalities in bipolar disorder and revealed a co-occurrence of those with abnormalities in cortical thickness and surface area.

Cortical abnormalities in patients with BDI and BDII

Most previous studies on bipolar disorder are hampered by small sample sizes and by the fact that only cortical volume was investigated. Cortical volume is a function of genetically and phenotypically distinct measures of cortical thickness and area. In a previous study by Rimol and colleagues,[17] who investigated all 3 measures together, patients with BDI (n = 87) had lower cortical thickness in lateral and medial frontal regions, but did not differ from controls (n = 207) in cortical volume or area. Here, we reproduced the cortical thickness abnormalities found by Rimol and colleagues, but also showed that those were accompanied by abnormalities in cortical volume and area. The fact that Rimol and colleagues did not observe differences in cortical area and volume might be due to different population characteristics (e.g., older age at onset, shorter illness duration, different medication use), methodological issues, or to effects being too weak to detect. Also, although it was implied in the study by Rimol and colleagues that grey and white matter surface was investigated, it was not clearly specified whether pial or white matter surface area was compared.

A co-occurrence of abnormalities in different cortical measures was also observed in a smaller study by Maller and colleagues,[15] who investigated cortical thickness and volume in patients with BDI (n = 16) and BDII (n = 15), but omitted area. Thus, finding differences in either cortical area or volume in addition to thickness abnormalities was expected, not only because volumetric abnormalities in patients with BD have been frequently reported, but also because of the mathematical dependency of the investigated measures.

In addition to widespread abnormalities in lateral and medial frontal regions, we found that patients with BD had cortical abnormalities in the medial and lateral orbitofrontal, temporal and insular cortices, which is in line with recent reviews and meta-analyses.[3–9]

Moreover, we observed that patients with BDI and BDII had abnormally low volume and/or thickness in medial occipital brain regions, including the cuneus, pericalcarine and lingual cortices. These findings are in line with previously reported deficits in visual processing and perception[36–40] — unrelated to lithium use[41,42] — and also with deficits in working memory tasks[10,43–46] that partly engage visual areas of the medial occipital cortex.[47–50] Hence, it is not farfetched to assume that previously observed deficits in visual tasks in patients with BD might be partly related to neuroanatomical abnormalities in medial occipital brain regions.

Our results suggest that previously reported volumetric abnormalities in patients with BD might be a combination of cortical thickness and area abnormalities. The fact that volumetric abnormalities in the prefrontal regions were reflected in thickness and surface area abnormalities, whereas volumetric differences in the medial occipital regions were accompanied only by thickness abnormalities could indicate that cortical abnormalities in different brain regions in patients with BD might underlie different mechanisms. Furthermore, we found differences in white matter surface area, but comparisons of pial surface area showed no differences between groups on the whole (Appendix 1, Fig. S4). This indicates that cortical abnormalities in patients with BD might be more pronounced in the vicinity of the grey/white matter surface than closer to the pial surface.

Patients with BDI versus BDII

The observed cortical abnormalities in patients with BDII were regionally similar to those in patients with BDI. However, patients with BDII had smaller cluster sizes mainly in the frontal and temporal regions, indicating that abnormalities in patients with BDII are less widespread and more focal than those in patients with BDI. Our results are in agreement with those of Elvsåshagen and colleagues,[16] who reported thinner cortices in patients with BDII than in controls in bilateral prefrontal and left temporal regions. In their study, however, no differences in surface area were found, and a cluster of abnormally low cortical thickness in the right medial prefrontal regions of patients with BDII was observed — a result that was not found in our study. This discrepancy might arise from minor differences in applied methodology and/or from different sample characteristics, such younger age, higher Montgomery–Åsberg Depression Rating Scale scores, or different medication use. Strikingly, in our study patients with BDII demonstrated no abnormalities in the right dmPFC, right dACC or right temporal cortex, which were abnormal in patients with BDI. These findings suggest that patients with BDI and BDII differ structurally in those brain areas and point to partly shared and partly unique neurobiological characteristics the subtypes.

Patients with BDI had lower cortical thickness than patients with BDII in the right temporal cortex. This finding supports previous research suggesting that the observation that BDI patients performed worse than BDII patients in memory tasks might be related to temporal lobe abnormalities unique to BDI.[10] Furthermore, patients with BDI have lower cortical thickness than patients with BDII in a cluster comprising the right dmPFC and dACC, which was even more pronounced when controlling for medication use. The dmPFC has been related to depression[51] as well as BD.[52] The dmPFC and dACC have also been associated with regulation of emotional and cognitive processes (e.g., executive functions) and their interplay.[9,53–61] Thus, our results support the idea that previously observed differences between patients with BDI and BDII in some cognitive domains, emotional regulation and mood symptoms could partly be related to neuroanatomical differences between the bipolar subtypes, such as those reported here.

Effect of medication on the medial occipital cortex

When comparing patients with BD who took Li or antiepileptic drugs with those who did not, we detected differences in medial occipital regions. Yet, the effect of those 2 types of medication had opposite directionality: Li use was associated with larger and antiepileptic drugs with lower cortical volume/thickness in the medial occipital cortex. In accordance, the observed differences between patients and controls in the medial occipital areas become more pronounced when controlling for Li use. This is in agreement with other studies that found Li to be associated with increased cortical volumes[62–64] and could be related to neuroprotective mechanisms, as suggested for Li effects on hippocampal volumes.[65] In contrast, the observed abnormalities in medial occipital areas disappeared when controlling for antiepileptic drug use. This suggests that those abnormalities could be partly attributed to drug use. However, our cross-sectional study design cannot determine if a certain drug caused a change in cortical structure. An alternative explanation is that premorbid low cortical volume or thickness in medial occipital brain areas is associated with symptoms requiring corresponding medical treatment. In addition, other unknown environmental, social, or genetic factors might have influenced the results. Regardless, our results disagree with those of Hafeman and colleagues,[62] who suggested that anticonvulsants have generally no influence on structural neuroimaging findings. It is noteworthy that use of antiepileptic drugs has been associated with visual impairments,[66] which is in agreement with our observed alterations of the medial occipital cortex, and with aforementioned deficits in visual processing and perception in patients with BD. It is therefore important to further elucidate the underlying mechanism of the abnormalities in medial occipital brain areas observed here and how these abnormalities are influenced by medication.

Limitations

Even though our study is, to our knowledge, one of the largest MRI studies of BD and its subtypes to date, there are some important limitations to consider. The study was cross-sectional. Thus, it cannot be determined which abnormalities are progressive during the course of illness and which would be better described as premorbid conditions. A longitudinal study with repeated scans is needed to answer this question. Because we controlled for sex and our results were maintained when performing the analyses in women only, it is unlikely that our findings were influenced by sex differences and the larger ratio of women to men in the BDII group. However, it still needs to be ascertained whether sex-related cortical thickness differences in BDI and BDII are of the same nature as those observed in healthy controls.[67–71] As commonly observed, the percentage of smokers was higher in patients than controls,[72] and smoking has been shown to have effects on cortical structure.[73–77] Although our results were maintained when controlling for smoking status, it cannot be excluded that smoking could have had an impact on the outcome. Also, controlling for medication use in our cross-sectional study design might have disguised disease effects, and the observed medication effects might have influenced nontrivial interactions between morphology and different medication types. Ideally placebo-controlled clinical trials would be needed to identify the degree to which those factors play out. Furthermore, the percentage of Li users and of patients with a history of psychosis was high in the BDI group, thus it is unclear if cortical abnormalities are of different nature in unmedicated patients without a history of psychosis. Although we were able to control for important demographic and clinical variables, we could not control for social, environmental or genetic factors or for nutrition, physical exercise and sexual orientation,[69] which might have had an impact on our findings. Thus, there is a need for future

research focusing on the extent to which those factors might have contributed to the observed group differences. Finally, we focused on cortical abnormalities; the investigation of subcortical abnormalities and their associations with cortical measures in patients with BD is an important future perspective, as is the investigation of behavioural and cognitive measures and their neurobiological correlates in extension to previous findings of Fears and colleagues.[35]

Conclusion

We demonstrated neurobiological characteristics of patients with BDI and BDII, showing partly shared but also distinct abnormalities. This could explain distinct symptoms and/or symptom severity, serve as potential biomarkers to assist with diagnosis of bipolar subtypes and could provide potential targets for treatment and interventions. We also reproduced volumetric abnormalities in patients with BD that were previously reported in a large, clinical, single-centre cohort. Finally, our study revealed that abnormalities in cortical thickness, volume and area in patients with BD co-occur and that some of them probably are influenced by Li or antiepileptic medication use.

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