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Cortical thickness differences between bipolar depression and major depressive disorder

Martin J Lan[a,b], **Binod Thapa Chhetry**[a,b], **Maria A Oquendo**[a,b], **M Elizabeth Sublette**[a,b], **Gregory Sullivan**[a,b], **J John Mann**[a,b,c], and **Ramin V Parsey**[d]

[a]Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York, NY

[b]Division of Molecular Imaging and Neuropathology, New York State Psychiatric Institute, New York, NY

[c]Department of Radiology, Columbia University College of Physicians and Surgeons, New York, NY

[d]Presently at Department of Psychiatry and Behavioral Health Sciences and Department of Radiology, Stony Brook University Medical Center, Stony Brook, NY, USA

Abstract

Objectives—Bipolar disorder (BD) is a psychiatric disorder with high morbidity and mortality that cannot be distinguished from major depressive disorder (MDD) until the first manic episode. A biomarker able to differentiate BD and MDD could help clinicians avoid risks of treating BD with antidepressants without mood stabilizers.

Methods—Cortical thickness differences were assessed using magnetic resonance imaging in BD depressed patients (n = 18), MDD depressed patients (n = 56), and healthy volunteers (HVs) (n = 54). A general linear model identified clusters of cortical thickness difference between diagnostic groups.

Results—Compared to the HV group, the BD group had decreased cortical thickness in six regions, after controlling for age and sex, located within frontal and parietal lobes, and posterior cingulate cortex. Mean cortical thickness changes in clusters ranged from 7.6–9.6% (cluster wise p-values from 1.0 e−4 to 0.037). When compared to MDD, three clusters of lower cortical thickness in BD were identified that overlapped with clusters that differentiated the BD and HV groups. Mean cortical thickness changes in the clusters ranged from 7.5–8.2% (cluster wise p-values from 1.0 e−4 to 0.023). The difference in cortical thickness was more pronounced when the subgroup of subjects with bipolar I disorder (BD-I) was compared to the MDD group.

Conclusions—Cortical thickness patterns were distinct between BD and MDD. These results are a step toward developing an imaging test to differentiate the two disorders.

Corresponding author: Martin J. Lan, M.D., Ph.D., Department of Psychiatry, Columbia University College of Physicians and Surgeons, 1051 Riverside Drive, Unit 42, New York, NY 10032, USA, Fax: 212-543-6017, mal9151@nyp.org.

Disclosures

The authors of this paper declare no conflicts of interest in connection with the present manuscript.

Keywords

bipolar disorder; cortical thickness; magnetic resonance imaging; major depressive disorder; neuroimaging

Bipolar disorder (BD) affects 1–2% of the population worldwide; it is a leading cause of disability and carries an elevated risk for suicide (1–3). Although mania or hypomania are the defining features of the disorder, depression is the most common presenting state and accounts for the most lifetime disability in the disorder. BD depressive episodes cannot reliably be distinguished from those of major depressive disorder (MDD) besides by patient history, and if the patient has not had a manic or hypomanic episode, the two disorders remain indistinguishable. Differentiating between MDD and BD depression is important clinically because treatment with antidepressants in the absence of a mood stabilizer carries the risk of precipitating mania and may increase rates of cycling between mood states (4). Developing a reliable test to distinguish the two conditions is therefore an important research goal (5). Disorder specific neuroimaging findings may be useful as a biomarker for BD.

Changes in cortical thickness can reflect differences in neuroplasticity, degeneration or neurotoxicity. Several studies have found less cortical thickness in BD compared to healthy volunteers in a number of regions, including several subregions of the frontal cortex and the anterior cingulate cortex (6–10). However, one study reported no cortical thickness differences in BD (11).

One potential confound in most studies published to date has been inclusion of patients taking medications. Although the effects of medication on cortical thickness have not been fully elucidated, lithium is associated with increased grey matter density (12). Antidepressant medications have also been shown to have neurotrophic effects in cell culture and within the hippocampus of mouse models (13). To limit this potential complication, we included only depressed patients who were off of all psychiatric medications at the time of scanning.

To our knowledge, no previous studies have directly compared cortical thickness differences between MD and BD subtypes of depression, the primary aim of this study. In fact, only a handful of neuroimaging studies have ever been published comparing bipolar and unipolar depression (14). As this is the first study to evaluate this question, whole cortex cluster-wise analyses were performed to examine the entire cortical mantle in an exploratory manner. As more previous studies have shown cortical thickness changes in subjects with BD, we hypothesized that the BD group would demonstrate less cortical thickness relative to the MDD group in a region specific manner.

Methods and materials

Participants

Eighteen patients with DSM-IV BD and 56 patients with MDD were diagnosed based on the Structured Clinical Interview for Axis I disorders (SCID-I/P) (15), psychiatric interview, and

chart review, as well as a consensus conference employing all sources of information. Patients with BD and MDD met criteria for a major depressive episode at the time of recruitment, with a 17-item Hamilton Depression Rating Scale (HAM-D) score > 16 (16). Fifty-four healthy volunteers (HVs) were also enrolled after a SCID-NP demonstrated no Axis I pathology, and interview revealed no history of mood disorders, psychotic disorders, or suicide in first-degree relatives. Diagnostic evaluations were performed by masters or doctoral level psychologists and were confirmed by a research psychiatrist. Participant ages ranged between 18–65 years. All patients taking psychotropic medications were tapered off medications before magnetic resonance imaging (MRI) scanning, and none were receiving fluoxetine or depot antipsychotics. Benzodiazepines were permitted in small doses. For all participants, exclusion criteria was (i) active medical conditions, (ii) positive urine toxicology screen, (iii) positive pregnancy test or planned pregnancy, and (iv) lifetime exposure to 3,4-methylenedioxymethamphetamine (MDMA). Subjects with past MDMA use were excluded because these scans had been obtained as part of another experiment that focused on the serotonin signaling system. Depressed patients were excluded if they had a history of alcohol or substance use disorder in the previous six months. HVs were excluded if they had any history of alcohol or substance use disorder. Manic symptoms were assessed with the Young Mania Rating Scale (YMRS) (17). The Institutional Review Board of the New York State Psychiatric Institute approved the study, and the procedures were in accordance with the Helsinki Declaration of 1975. All participants gave written informed consent. Participants were recruited for the study between March 2006 and August 2012. This is a secondary analysis of MRI data that were acquired for ongoing positron emission tomography studies.

MRI acquisition

High-resolution anatomical T1-weighted MRI images were acquired from a 3-T GE Signa HDx scanner using a three-dimensional spoiled gradient echo sequence: 1 mm sagittal slices with repetition time (TR): 5.0–7.5 msec, echo time (TE): 1.3–3.0 msec, flip angle 9–11°, acquisition matrix of 256 ×256, number of axial slices: 180, voxel size 1 mm^3. All scans were inspected to check for motion artifacts and to rule out gross neuropathology.

Magnetic resonance scan processing and calculations of cortical thickness

Freesurfer package 5.1.0, a freeware set of automated sequences (http://surfer.nmr.mgh.harvard.edu) was used for cortical surface reconstruction and thickness measurement (18, 19). A more detailed explanation of the procedure can be found in (19–22), and at the Freesurfer website listed above. Briefly, the T1 anatomical volume was registered to the Talairach atlas (23) and corrected for intensity variations due to magnetic field homogeneities. The normalized intensity image was then skull-stripped (22) using a deformable template model. The voxels in the brain were classified as white matter or non-white matter based on intensity and neighbor constraints. Cutting planes were computed, which separate the cerebral hemispheres and remove the cerebellum and brain stem. Any interior holes in the components representing white matter were filled. The initial triangular tessellation was formed on the surface of this white matter mass to create a surface mesh representation, and then smoothed using a deformable surface algorithm to form the gray/white surface. The algorithm was further used to expand the surface to obtain the gray

matter-CSF surface (18, 20). Since expanding the inner white matter surface generates the outer cortical surface, there is a one-to-one correspondence between mesh nodes. Finally, the images were registered to a spherical atlas and thickness at any given node was calculated by finding the closest point on the opposite surface, performing the same calculation for the corresponding node on the opposite surface, and averaging the two values (19). The cortical thickness surface map was prepared for statistical analysis by performing a smoothing using a Gaussian Kernel with full-width half maximum of 10 mm.

Statistical analysis

Freesurfer's Qdec (http://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/QdecGroupAnalysis) application was used to obtain cortical thickness difference maps between groups. Qdec uses a general linear model (GLM) to model thickness at each surface vertex as a linear combination of effects related to variables of interests, incorporating the effects of potential confounds. The main effect between each pair of diagnostic groups was evaluated with age and sex as covariates of no interest. Both age and sex have been associated with cortical thickness changes (24–26). Because the rate of past substance use disorder history was different between patients with MDD and BD, and patients with BD had a trend longer course of illness, subsequent analyses included these variables as covariates of no interest. To further characterize cortical thickness in the patients with MDD, a subgroup of patients with a positive family history of mood disorders and a subgroup of patients that were medication naïve were compared to the HV group. Statistical thickness difference maps were constructed using $-\log_{10}$(p value). Monte Carlo permutation cluster analysis with 10,000 iterations was performed to correct for multiple comparisons. Cluster-wise probabilities (CWP) were reported. Clusters were mapped on a Desikan–Killiany atlas based on gyral and sulcal structure (27, 28).

Regions-of-interest were defined based on the clusters that were significantly different between groups. These regions of interest were mapped on each brain in the study in order to obtain a quantitative measure of the average cortical thickness in that region. The region-of-interest analysis was used to evaluate potential confounds in the data and to measure the fold change in cortical thickness between groups.

Statistical differences between categorical groups were compared using a two-tailed Student's *t*-test or one-way ANOVA with Bonferroni post-hoc tests. Linear regression analyses were used to evaluate correlations between two sets of data. We used SPSS, 2012, version 20.

Results

Participants

Demographic and clinical characteristics are summarized in Table 1. The three groups were matched for sex and handedness, but differed in age. Post-hoc testing showed no pair-wise differences between the groups in age, however. The BD group had higher HAM-D scores and higher rates of lifetime substance use disorders than patients with MDD, including higher rates of remitted alcohol dependence and alcohol abuse. Twelve of the 18 patients

with BD were diagnosed with BD-I, and the rest (n = 6) were diagnosed with bipolar II disorder (BD-II). One patient with BD was in a mixed episode as determined by a YMRS > 25 and clinical determination at the time of screening. All patients were not taking medications for more than 14 days, other than two subjects with BD who had finished their medication taper less than seven days before scanning. Rates of lifetime exposure to psychiatric medications are included in Table 1.

BD group comparison to HVs

Whole brain cluster-wise analysis of patients with BD and HVs, co-varying for age and sex, demonstrated six clusters that were significantly thinner in the BD group (Fig. 1 and Table 2). On average, these regions were between 7.6–9.6% thinner than that of the HV group.

BD comparison to MDD

Whole brain cluster-wise analysis of subjects with BD and subjects with MDD, co-varying for age and sex, demonstrated three clusters that were thinner in subjects with BD (Fig. 1 and Table 2). These clusters had significant spatial overlap with clusters that were thinner when the BD group was compared to the HV group. The average cortical thickness differences in these regions ranged from 7.5–8.2%.

MDD group comparison to HVs

Whole brain cluster-wise analysis of subjects with MDD and HVs, co-varying for age and sex, demonstrated no significant clusters that differed between the two groups (Fig. 1).

Analysis of potential confounds

To assess whether the cortical thickness differences in BD were associated with illness characteristics, we studied correlations between clinical characteristics and average cortical thickness measurements of subjects with BD and subjects with MDD (n = 74). Cortical thickness correlated with age within regions that were found to differ between the two groups as expected, but was not correlated with the HAM-D, age at onset of first mood episode, or total brain volume (Table 3).

When the subset of subjects with BD-I (n = 12) was compared to the MDD group (n = 56), the regions of less cortical thickness were more expansive than with the combined BD-I and BD-II group (Fig. 2 and Table 4). Previous reports have demonstrated less cortical thickness with alcohol use disorders in HVs (73–75) and patients with BD (11). When past substance use history and current age were included as covariates of no interest, the right dorsal lateral frontal cluster remained thinner in the BD group when compared to the MDD group (Supplementary Fig. 1). To assess the effect of medication history, subjects with MDD that were medication naïve were compared to medication-exposed subjects with MDD; no clusters were found to have significantly different cortical thickness between the groups. Only three subjects with BD were medication naïve, precluding any group wise comparisons.

A previous study demonstrated less cortical thickness in subjects who were at high risk for depression based on a strong family history of major depression (29). We therefore assessed

the effect of family history in our cohort of subjects with MDD on cortical thickness. Whole brain cluster-wise analysis was performed in a combined group of subjects with BD and subjects with MDD who had a first-degree relative with MDD (n = 24) compared to HVs (n = 54), co-varying for age and sex. One cluster was identified with greater cortical thickness (Fig. 3 and Table 4).

Discussion

Significance of right caudal middle frontal result

Less cortical thickness in the right dorsal lateral frontal region in BD is the most robust finding of this study. The region was thinner in subjects with BD when compared to HV and MDD groups and could not be explained by age, sex, or substance use disorder history. A recent meta-analysis of past voxel-based morphometry studies identified the right prefrontal cortex and temporal lobe grey matter as the most robust differences between BD and HV groups (30). Our results indicate this finding to be a BD-specific phenomenon, as we did not find it in MDD. Using magnetic resonance spectroscopy, one study identified a lower N-acetyl aspartate/total creatinine ratio in the dorsolateral prefrontal cortex of patients with BD when compared to controls, implying a deficit in neuronal viability in the region (31). Postmortem brain studies also have identified lower neuronal density and glial abnormalities in individuals with BD in the region, and have provided evidence for a functional shift from excitatory to inhibitory neurotransmission (32, 33). Several functional MRI studies have shown alterations during behavioral tasks in the right dorsolateral prefrontal cortex of patients with BD, such as processing affect in images of faces (34, 35) and performing tasks of executive function (36, 37). Also, there is evidence of benefit with transcranial magnetic stimulation applied to the right dorsolateral prefrontal cortex in BD (38, 39), adding further convergent data implicating the region in the pathophysiology and treatment of the disorder.

The right dorsal lateral prefrontal cortex is implicated in a number of executive functions including working memory (40, 41), decision making (42, 43) and attentional control (44, 45). Indeed, deficits in executive function in BD are an important prognostic factor (46, 47). This region is part of the cortico-thalamic-insular circuit thought to be involved in the pathophysiology of mood disorders. In this neural circuitry model, a deficit in dorsolateral prefrontal cortex would result in decreased cortical regulation of emotional processing driven by insular cortex. This dysregulation is hypothesized to manifest as symptoms of mania and depression (48, 49).

Structural changes beyond the right dorsolateral prefrontal region in BD

Other regions we identified as having less cortical thickness in BD have been reported to have lower cortical thickness in BD in previous studies. For example, the precuneus, a region found thinner here in BD, has been found to have less activation using functional MRI when euthymic patients with BD were exposed to negatively valenced stimuli (50), less deactivation when euthymic patients with BD performed a verbal fluency task (51), and less activation when manic patients performed a continuous performance task (52). Using fluorodeoxyglucose positron emission tomography (FDG PET), the region had less metabolism during mania (53). This region has been implicated in a number of cognitive

functions including self- and external-agency attribution and theory of mind (54, 55). It is also activated during the resting state of the brain (56).

We found less cortical thickness bilaterally in inferior parietal lobe of subjects with BD compared to HVs which is consistent with decreased activation in the inferior parietal lobe reported in subjects with BD compared to HVs during tasks of selective attention using functional MRI (57, 58). Also, a resting state FDG PET study and a voxel-based morphometry study found alterations in the inferior parietal lobe in patients with BD (59, 60). This region, along with the caudal middle frontal region, has been associated with working memory tasks (40, 41) and linked with attention, particularly spatial attention (61, 62).

We found lower cortical thickness in the left posterior cingulate of subjects with BD compared to HVs. Work from our group using voxel-based morphometry analyses comport with this, showing lower volume in the posterior cingulate cortex (PCC) when compared to HVs (63–65). The PCC has also been differentially activated in individuals with BD during tasks with functional MRI tasks where subjects process positive- or negative-valenced cues (50, 66, 67) or perform cognitive tasks (51, 52, 68). The PCC has been found to be part of the default mode network (69) and is involved with consciousness (70). The pathophysiological relevance of this observation requires further work.

Previous MRI studies have reported other structural changes in BD including increased rates of white matter hyperintensities, primarily in the periventricular region, and enlarged lateral ventricles (71, 72). How our findings of less cortical thickness in BD relate to widespread changes to the structure of the brain implicated in the pathophysiology of BD requires further investigation. More extensive differences in cortical thickness were found in BD-I than the combined BD-I and BD-II population, indicating that severity of manic symptomatology is related to this biological process.

Family history in MDD

Subjects with MDD with a family history of a mood disorder showed greater cortical thickness in the orbitofrontal cortex when compared to the HV group. Greater cortical thickness in the medial aspect of the right orbitofrontal lobe has also been reported in subjects at high familial risk for major depression (29). This cortical difference may therefore be a familial marker of MDD or the risk to develop MDD.

Study limitations

Changes to cortical thickness by medications cannot be ruled out as a confounder in this study. The patients with BD had more lifetime exposure to antidepressant, antipsychotic, and mood-stabilizer medications, including lithium, compared with patients with MDD. The groups were also not matched for the number of subjects with a history of substance use disorders. Further studies are needed to evaluate the individual contributions of substance use disorders and BD to cortical thickness changes.

Future directions

Cortical thickness may prove to be a useful tool to distinguish BD from MDD, and may contribute to the pathophysiology of manic episodes. A prospective, hypothesis-driven study in a larger sample could determine predictive properties of this index of cortical thickness. Determining whether patients show differences in cortical thickness at their first symptoms of BD could determine the use of this finding for diagnostic purposes. Such an experiment would enable a calculation of the predictive capacity of this measure. Future studies may combine measures of cortical thickness with other imaging modalities for the purpose of differentiating BD from MDD. Postmortem brain studies focusing on molecular and cellular differences between the two disorders in the cortical regions found altered here are also warranted. Localization of deficits in cortical thickness associated with both alcohol use disorders and BD may lead to a better understanding of the high rates of comorbidity between these conditions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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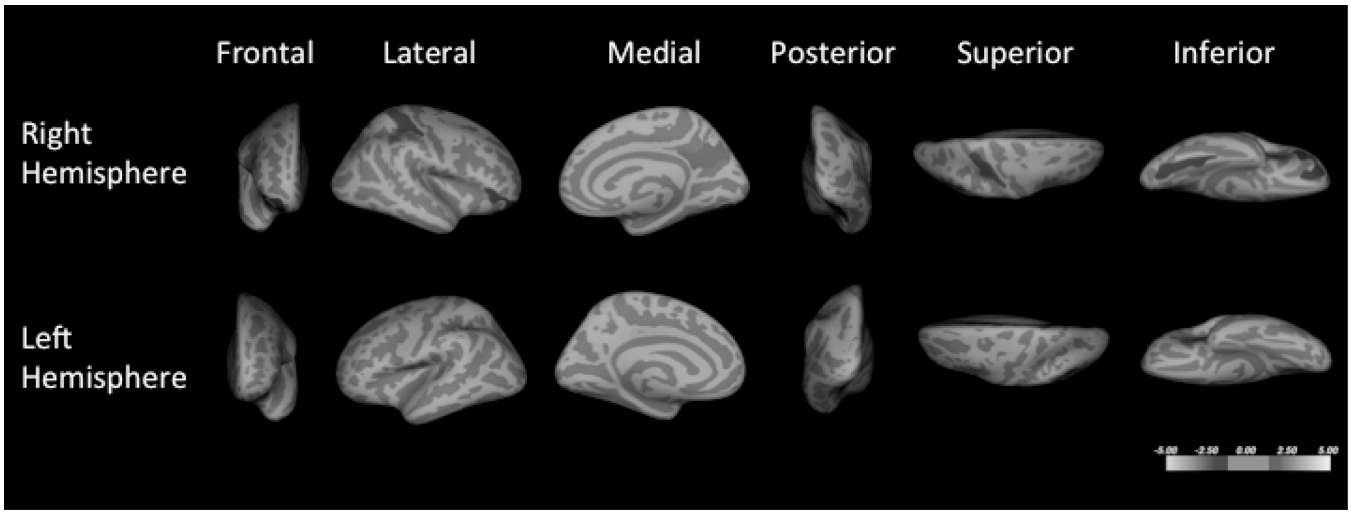


Fig. 1.

Cortical thickness comparisons of subjects with bipolar disorder (BD), major depressive disorder (MDD), and healthy volunteers (HVs) in the right **(A)** and left hemispheres **(B)**. Six regions were thinner in patients with BD when compared to HVs, including those in the left inferior parietal, the right caudal middle frontal, the left superior parietal, the right posterior cingulate, the right inferior parietal, and the right supramarginal. Three regions with significant spatial overlap with the regions of BD and HV comparison were found when subjects with BD were compared to subjects with MDD, including the right caudal middle frontal region, the left inferior parietal, and the right precuneus regions. No regions were found altered between the MDD and HV groups. Blue coloration indicates significance threshold of p-value < 0.05. Clusters are overlaid on average inflated images with sulci displayed as darker than gyri.

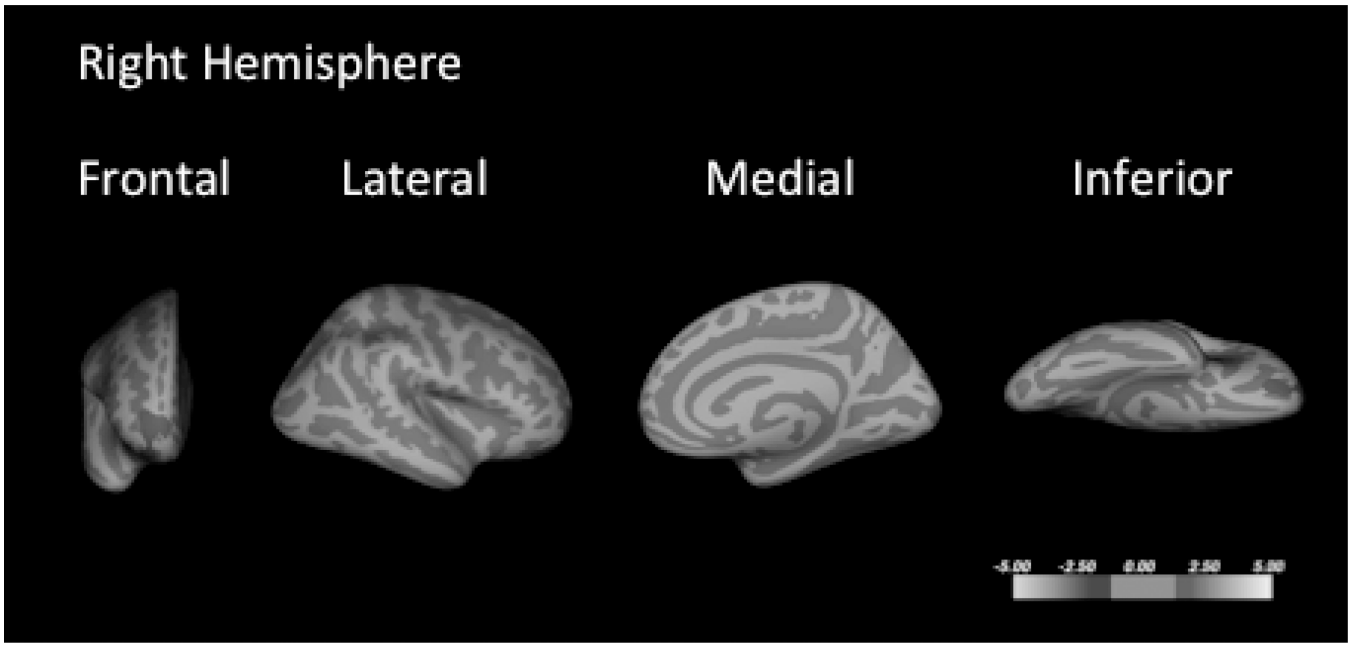
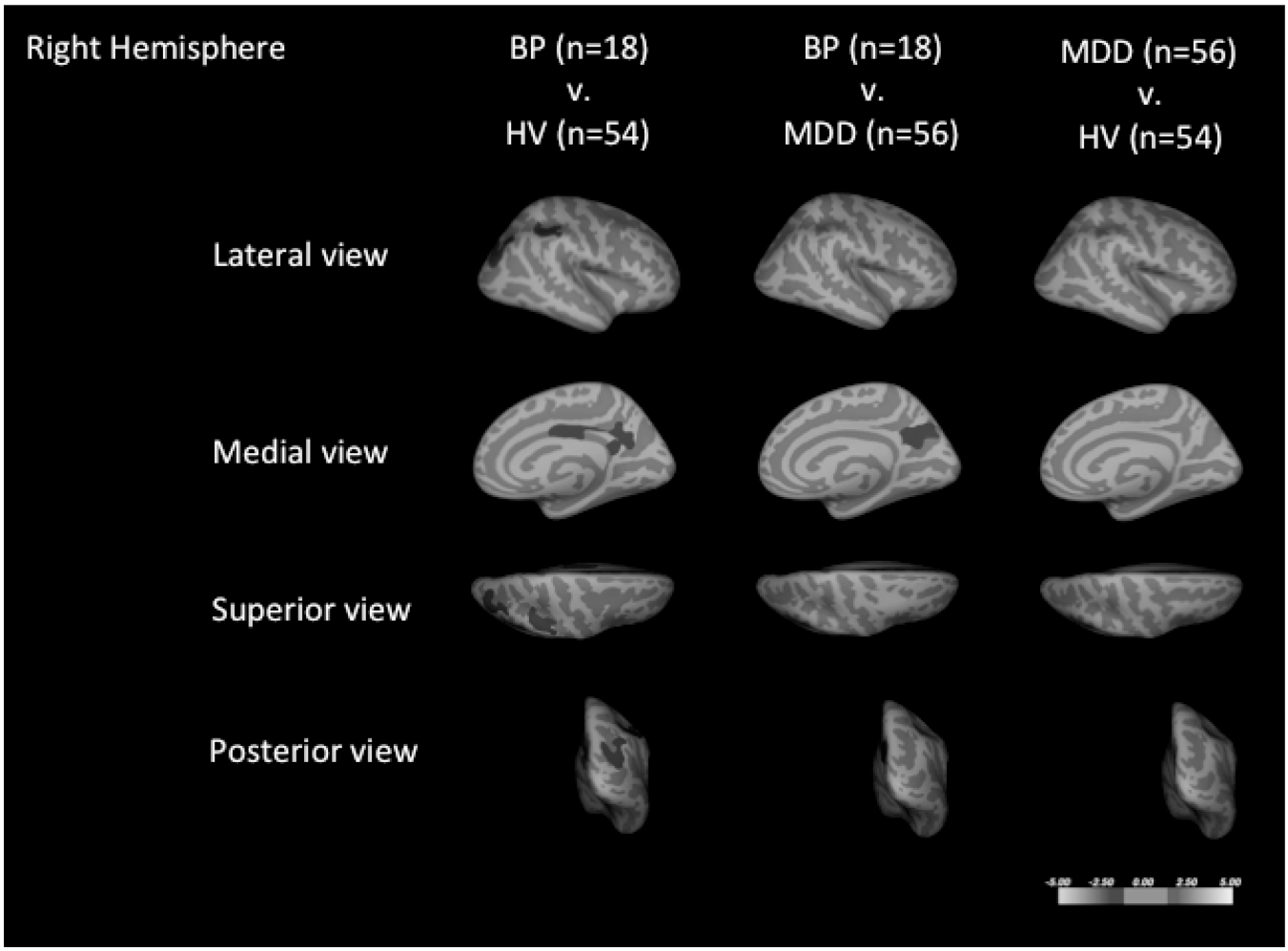


Fig. 2.

Whole brain cluster-wise comparison of cortical thickness of subgroups of the primary comparisons with age and sex as covariates. Whole brain cluster-wise comparison of cortical thickness of subjects with bipolar I disorder (n = 12) when compared to subjects with major depressive disorder (n = 56). The pattern of cortical thickness decreases was more extensive in this subgroup of patients than the combined bipolar disorder population.



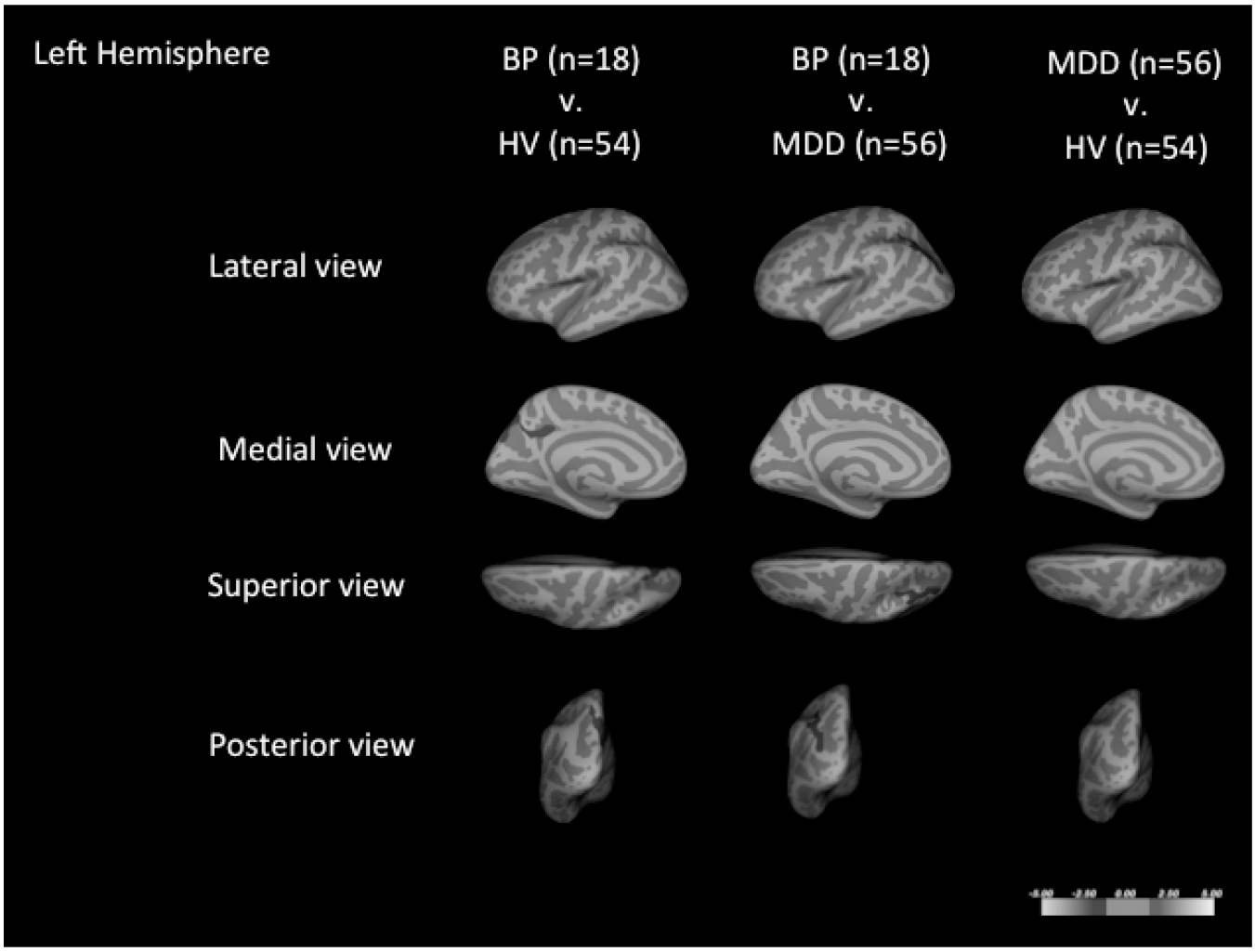


Fig. 3.

Whole brain cluster-wise comparison of cortical thickness of subjects with major depressive disorder (MDD) with a first-degree relative with a history of mood disorder (n = 24) and healthy volunteers (n = 54). One cluster in the lateral orbital frontal region was found to be thicker in patients in the MDD group.

Table 1

Demographic and clinical information for participants in the study

	BD (n = 18)	MDD (n = 56)	HV (n = 54)	p-value
General demographics				
				ANOVA; p = 0.033[c]
				BD versus HV; p = 0.174
				BD versus MDD; p = 1.00
Age, years, mean (SD)	37.6 (9.4)	36.9 (12.2)	31.8 (10.5)	MDD versus HV; p = 0.055
Sex, female, n (%)	9 (50.0)	32 (57.1)	26 (48.1)	0.65[d]
Handedness, left, n (%)	0 (0)	6 (10.7)	4 (7.4)	0.44[d]
Disorder characteristics				
Weeks of current episode, median (SD)	14.5 (194.0)	67.0 (350.8)	N/A	0.15[e]
Years of illness, mean (SD)	20.1 (10.9)	13.6 (12.9)	N/A	0.06[e]
Age of onset, years, mean (SD)	17.5 (5.6)	23.4 (12.3)	N/A	0.06[e]
HAM-D score, mean (SD)	29.4 (5.9)	23.8 (6.0)	N/A	9.0 e−4[e]
Family history, n (%)[a]	10 (55.6)	24 (42.9)	N/A	0.42[d]
Lifetime comorbid psychiatric disorders, n (%)				
Anxiety disorder	9 (50.0)	26 (46.4)	N/A	1.0[d]
Eating disorder	1 (5.6)	1 (1.8)	N/A	0.43[d]
ADHD	2 (11.1)	1 (1.8)	N/A	0.14[d]
Any substance use disorder	11 (61.1)	7 (12.5)	N/A	1.1 e−4[d]
Alcohol dependence	6 (33.3)	4 (7.1)	N/A	0.01[d]
Alcohol abuse	4 (22.2)	2 (3.6)	N/A	0.03[d]
Marijuana use disorder	1 (5.6)	1 (1.8)	N/A	0.43[d]
Cocaine abuse	1 (5.6)	0 (0)	N/A	0.24[d]
Polysubstance	1 (5.6)	0 (0)	N/A	0.24[d]
Lifetime medication history, n (%)				
Lithium	5 (27.7)	3 (5.4)	N/A	0.02[d]
Other mood stabilizer	8 (44.4)	8 (14.3)	N/A	0.02[d]
Antidepressant	14 (77.8)	29 (51.8)	N/A	0.06[d]
Antipsychotic[b]	6 (33.3)	3 (5.4)	N/A	5.1 e−3[d]

BD = bipolar disorder; MDD = major depressive disorder; HV = healthy volunteers; SD = standard deviation; HAM-D = Hamilton Depression Rating Scale; ADHD = attention-deficit hyperactivity disorder; N/A = not applicable.

[a] Number of patients with at least one first-degree relative with a history of mania or depression.

[b] All antipsychotics listed were atypical besides thioridazine that had been taken by one patient with MDD.

[c] One-way ANOVA with Bonferroni post-hoc comparisons.

[d] Fisher's Exact test.

[e] Two-tailed Student's *t*-test.

Table 2

Results of whole brain cluster-wise analysis of cortical thickness comparing subjects with bipolar disorder (BD) (n = 18), healthy volunteers (n = 54), and subjects with major depressive disorder (MDD) (n = 56)

	Size		Talairach coordinates[b]			
	(mm^2)	% change[a]	x	y	z	CWP
BD versus HV[c]						
L inferiorparietal	2069.3	9.5	−35.7	−67.6	44.9	1.0 e−4
R caudalmiddlefrontal	1369.9	9.1	39.7	13.8	47.5	1.2 e−3
L superiorparietal	1073.5	9.3	−11.3	−70.8	42.7	8.0 e−3
R posteriorcingulate	1011.2	9.6	4.8	−11.2	27.8	0.015
R inferiorparietal	964.8	8.8	36.9	−79.0	24.2	0.022
R supramarginal	881.6	7.6	42.9	−41.8	34.8	0.037
BD versus MDD[c]						
R caudalmiddlefrontal	1750.1	7.5	38.6	14.4	48.3	1.0 e−4
L inferiorparietal	924.3	8.2	−35.5	−65.2	45.9	0.021
R precuneus	941.2	7.5	4.7	−56.0	26.1	0.023

No significant results were identified when MDD was compared to HV. CWP = cluster-wise p-value; R = right; L = left.

[a] % change: the percent difference in means in cortical thickness; all regions were thinner in BD. This value was derived from the region-of-interest data of each cluster that was found to be statistically different between the two groups.

[b] Coordinates of the maximum voxel for the cluster.

[c] Age and sex as covariates.

Table 3

Effect of disease severity and total brain volume on the cortical thickness findings

Cluster annotation	HAM-D	Age at first episode	Current age	Total brain volume
	R^2 = 9.4 e−3	R^2 = −9.4 e−3	R^2 = 0.11	R^2 = 5.9 e−3
R caudalmiddlefrontal	p = 0.20	p = 0.57	p = 2.5 e−3	p = 0.45
	R^2 = 0.01	R^2 = 4.3 e−4	R^2 = 0.13	R^2 = 0.02
L inferiorparietal	p = 0.18	p = 0.31	p = 8.9 e−4	p = 0.14
	R^2 = 5.5 e−3	R^2 = 5.4 e−3	R^2 = 0.13	R^2 = 8.3 e−3
R precuneus	p = 0.24	p = 0.24	p = 9.5 e−4	p = 0.53

To assess the effect of disease severity and total brain volume on the cortical thickness findings, linear regression analyses of Hamilton Depression Rating Scale (HAM-D) score age at first episode and current age of subject were performed on the average cortical thickness measurements from regions that were found to be significantly different between the bipolar disorder (BD) and major depressive disorder (MDD) groups. Correlations were based on cortical thickness measurements from both BD and MDD groups combined (n = 74). Age was correlated with cortical thickness in three brain regions as expected, but HAM-D score, age at first episode, and total brain volume were not. R = right; L = left.

Table 4

Results of whole brain cluster-wise analysis of cortical thickness comparing the subgroup of subjects with bipolar I disorder (BD-I) (n = 12) and subjects with major depressive disorder (MDD) (n = 56)

		Talairach coordinates[a]			
	Size (mm^2)	x	y	z	CWP
BD-I versus MDD[b]					
L superiorfrontal	4470.3	−6.9	29.7	46.9	1.0 e−4
L inferiorparietal	6008.4	−34.3	−65.9	45.7	1.0 e−4
R superiorfrontal	5006.7	8.5	−5.5	47.7	1.0 e−4
R superiorpareital	1804.7	22.5	−54.2	59.2	1.0 e−4
R precuneus	1314.5	4.7	−55.6	23.9	1.8 e−3
R superiorparietal	1155.9	24.7	−39.7	56.9	6.0 e−3
R rostralmiddlefrontal	951.6	26.0	49.5	−12.3	0.024
R fusiform	890.0	27.0	−76.0	2.2	0.035

CWP = cluster-wise p-value; L = left; R = right.

[a] Coordinates of the maximum voxel for the cluster.

[b] Age and sex as covariates.