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Longitudinal Cortical Thickness Changes in Bipolar Disorder and the Relationship to Genetic Risk, Mania, and Lithium Use

Christoph Abé, Benny Liberg, Jie Song, Sarah E. Bergen, Predrag Petrovic, Carl Johan Ekman, Carl M. Sellgren, Martin Ingvar, and Mikael Landén

ABSTRACT

BACKGROUND: Bipolar disorder (BD) is a highly heritable psychiatric disorder characterized by episodes of manic and depressed mood states and associated with cortical brain abnormalities. Although the course of BD is often progressive, longitudinal brain imaging studies are scarce. It remains unknown whether brain abnormalities are static traits of BD or result from pathological changes over time. Moreover, the genetic effect on implicated brain regions remains unknown.

METHODS: Patients with BD and healthy control (HC) subjects underwent structural magnetic resonance imaging at baseline (123 patients, 83 HC subjects) and after 6 years (90 patients, 61 HC subjects). Cortical thickness maps were generated using FreeSurfer. Using linear mixed effects models, we compared longitudinal changes in cortical thickness between patients with BD and HC subjects across the whole brain. We related our findings to genetic risk for BD and tested for effects of demographic and clinical variables.

RESULTS: Patients showed abnormal cortical thinning of temporal cortices and thickness increases in visual/somatosensory brain areas. Thickness increases were related to genetic risk and lithium use. Patients who experienced hypomanic or manic episodes between time points showed abnormal thinning in inferior frontal cortices. Cortical changes did not differ between diagnostic BD subtypes I and II.

CONCLUSIONS: In the largest longitudinal BD study to date, we detected abnormal cortical changes with high anatomical resolution. We delineated regional effects of clinical symptoms, genetic factors, and medication that may explain progressive brain changes in BD. Our study yields important insights into disease mechanisms and suggests that neuroprogression plays a role in BD.

Keywords: Bipolar disorder, Cortical thickness, Lithium, Longitudinal study, Mania, Polygenic risk score

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Bipolar disorder (BD) is a chronic psychiatric disorder characterized by recurrent episodes of depression and hypomania or mania with interspersed euthymia (1,2). Patients with bipolar I disorder (BDI) experience full-blown manic episodes, whereas patients with bipolar II disorder (BDII) have only hypomanic episodes. BD entails alterations in sensory perception, emotional processing, and cognitive functioning (3,4). Cross-sectional brain imaging studies of BD show structural abnormalities in brain regions implicated in emotional regulation, including alterations in cortical thickness (CT) and cortical volume in neocortical prefrontal and temporal regions and the cingulate gyrus, and volumetric abnormalities in mesial temporal areas (e.g., amygdala and hippocampus) (5–8) and less consistently in insula and visual cortex (5,7–16). The largest study on BD to date found the most pronounced CT abnormalities in the pars opercularis, rostral middle frontal cortex, and fusiform gyrus, but no abnormalities in surface area (5).

BD is highly heritable, with a large number of common alleles contributing to an increased genetic risk to develop BD (17,18). This accumulated genetic risk of BD can be expressed as a polygenic risk score (PRS) (19). However, no studies have found associations between genetic risk variants and brain structure in BD (20,21). Hence, the association between the genetic risk for BD and alterations in brain structure remains elusive.

BD symptoms progressively worsen for some patients, and the term neuroprogression was coined to label this phenomenon and the conjectured accompanying neuroanatomical changes (22–25). However, it has not been unambiguously established that brain structure actually changes during the course of BD. This is because most studies are cross-sectional and cannot determine whether observed brain abnormalities result from pathological changes over time or represent static and/or premorbid conditions. In a small longitudinal study of patients with BDI, we found changes in prefrontal cortex

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associated with the occurrence of mania (26). Although this study and recent reviews suggest progressive features in prefrontal and temporal cortices (27), along with medication-induced cortical normalization (28), the few available longitudinal brain imaging studies are hampered by various limitations that range from small sample sizes, lack of control groups, and short follow-up times, over the use of large region-of-interest approaches and limited statistical models, to lack of a statistical control over potential confounders, such as psychiatric comorbidity. Additionally, most studies have focused on cortical volume, which is a function of two phenotypically and genetically distinct measures: cortical surface area and CT (29,30). CT is related to the size and number of cells in a cortical column (31) and is increasingly being used as a marker for the integrity of the cerebral cortex in control subjects and pathological conditions (32–35) including BD (5,7,8,36). Therefore, and because the largest cross-sectional study on BD to date specifically found abnormalities in CT and not surface area (5), we use CT as primary outcome measure in this study.

The primary aim of this longitudinal study was to elucidate whether progressive alterations in CT occur in BD. To this end, we significantly extended our previous longitudinal analysis (26) by including additional patients with BDI, patients with BDII, and, importantly, healthy control (HC) subjects. We analyzed brain imaging data from individuals scanned at 2 time points, 6 years apart, and investigated case-control differences in cortical thinning over time. A total number of 357 scans (including baseline and follow-up) were analyzed in a linear mixed effects (LME) model on vertex-level with high anatomical resolution. We hypothesized that BD cases would show abnormal thinning in frontotemporal brain areas. The secondary aim was to investigate whether the genetic risk for bipolar disorder (PRS-BD) predicts progressive cortical changes and to correlate PRS-BD to the observed structural brain changes. We also tested the effects of subdiagnosis, clinical characteristics, comorbidity, and medication use.

METHODS AND MATERIALS

Participants

Patients with BD were recruited at the Northern psychiatric clinic in Stockholm, Sweden. Details on inclusion criteria and diagnostic tools can be found elsewhere (37,38) and in the Supplement. In brief, a diagnosis of BD was established at baseline (time point 1 [T1]) according to DSM-IV (Structured Clinical Interview for DSM) included in the structured interview instrument Affective Disorder Evaluation (39). Patients were euthymic at scan day. HC subjects were randomly selected by Statistics Sweden. See Supplement for details.

After 6 years, cases and controls were recontacted for a follow-up investigation (time point 2 [T2]). The time interval was chosen to allow sufficient time to capture recurrent mood episodes based on the natural course of BD and to study associated brain alterations, but also to strike a balance between feasibility (e.g., increasing sample size) and low attrition rate. The same interview protocol was used. The number of mood episodes that occurred between T1 and T2 was assessed by clinical psychiatrists. All subjects consented in writing to participate in the study, which was approved by the Ethics Committee of Karolinska Institutet, Stockholm, Sweden. As in our previous study on baseline abnormalities, patients with BDI and BDII were included (7). To maximize sample size and to avoid any dropout-related bias, individuals were included regardless of whether they had completed brain scans at both time points or only at T1 or T2.

Magnetic Resonance Imaging Acquisition and Processing

Magnetic resonance imaging (MRI) scans were acquired at the MR Research Center, Karolinska University Hospital, Stockholm. Coronal three-dimensional T1-weighted images were acquired using a 1.5T MRI scanner (Signa Excite; GE Healthcare AB, Stockholm, Sweden). Participants underwent a baseline and follow-up investigation using the same protocol and scanner, which was tested for signal stability and geometric consistency 4 times per year by a local physicist and GE Healthcare personnel, ensuring a stable signal over time. Participants were scanned in random order during each time point. CT maps were obtained from structural T1-weighted images using the cortical surface reconstruction methods provided by FreeSurfer (https://surfer.nmr.mgh.harvard.edu/) (40–44). CT was calculated as the closest distance from the gray and white matter to the pial surface at each vertex on the reconstructed surfaces. Reconstructions were visually inspected and, where necessary, corrected manually. After cross-sectional processing, images were processed with the longitudinal stream implemented in FreeSurfer v5.3. Specifically, an unbiased within-subject template space and image was created to overcome asymmetry-related processing bias using inverse consistent registration methods. Following processing steps were initialized with common information from the within-subject template, increasing accuracy and statistical power (45). After longitudinal processing, surface reconstructions of the template and of images at T1 and T2 were inspected, corrected, and reprocessed where necessary. Images of participants with only one time point scan were also processed with the longitudinal stream to avoid processing bias. The resulting CT maps were smoothed with a Gaussian kernel of 15 mm.

Polygenic Risk Scores

Participants provided blood samples for genotyping conducted at the Broad Institute of MIT and Harvard (Cambridge, MA). For each individual, PRS-BD was generated with PLINK 1.9 (https://www.cog-genomics.org/plink/1.9/) using the largest genome-wide association study on BD to date (46). See Supplement for details.

Statistical Analyses

Patient Characteristics. Differences between groups and time points were tested with *t* tests or Fisher's exact χ^2 tests.

Main Analysis: Group-by-Time Interaction. To determine differences in CT changes over time between patients and HC subjects, we modeled our data using LME models, using MATLAB (The MathWorks, Inc., Natick, MA) tools developed by Bernal-Rusiel *et al.* (47,48) designed for longitudinal FreeSurfer data. We applied a spatiotemporal novel

mass-univariate analysis with CT as dependent variable and modeled a random intercept defining subject as random factor. Time between scans in years (baseline defined as 0), sex, age at baseline, group, and group-by-time interaction (variable of interest) were additional regressors. See Supplement for more methodological details. Significance maps for group-by-time interactions were false discovery rate corrected and visualized in Freeview (https://surfer.nmr.mgh.harvard.edu/fswiki/FreeviewGuide).

Follow-up Analysis: Percent Change Measures. To follow up on significant group-by-time interactions, post hoc analyses were performed to determine the direction of CT changes. We extracted average CT from anatomical regions that correspond to the clusters in which significant group-by-time interactions were found, using automated parcellation procedures implemented in FreeSurfer [see (43,49,50) for technical details]. For each participant with T1 and T2 data, we calculated the relative CT change in percent, where negative values reflect a decrease and positive values an increase in CT between T1 and T2. Final regions analyzed were total middle temporal cortex, central sulcus, medial occipital cortex (combining pericalcarine, cuneus, and lingual cortex), posterior cingulate cortex, and left inferior insula cortex. More details can be found in the Supplement. Multiple comparison correction was performed using Bonferroni Dubey Armitage-Parmar/Sidak adjustment of α level considering the number of tests and the intercorrelation between the dependent variables (51).

Follow-up Analyses on Effects of Demographic and Clinical Variables. We tested whether the observed group differences in percent change measures are affected by demographic or clinical variables (at either time point) listed in Table 1 by entering those variables separately as additional covariates and/or by excluding corresponding individuals. More details are presented in the Supplement.

Correlations With PRS-BD. Correlations between PRS-BD and CT change measures were calculated using Pearson correlations in IBM SPSS Version 21 software (IBM Corp., Armonk, NY). To increase statistical power, the primary analysis was done in the combined cohort. Correlations were also computed within BD and HC cohorts separately. Additional partial correlations were computed to test if the observed correlations in the combined cohort hold when correcting for patient status (group). Finally, as it is standard practice in genome-wide association analysis and polygenic risk scoring to include principal components (PCs) derived from linkage disequilibrium–pruned genome-wide data as covariates to account for population substructure (52), partial correlations were also performed adjusting for PCs to limit the possibility that differences in ancestry could influence the results. See Supplement for more details.

Exploratory Analysis on the Effect of Lithium Use. As lithium use has been associated with increased cortical volume (53–56), we performed additional tests for interpretational purposes. We compared the percent change in CT 1) between patients who used and did not use lithium (at T1 and T2) and 2) between patients who used lithium at both time points, only at T2, only at T1, and at neither time point. We also performed multiple regression analyses with cortical change measures as dependent variable and both lithium and PRS-BD as regressors.

Exploratory Analysis on the Effect of Hypomania and Mania. Given our previous findings on mania-related cortical decline in BDI (26), we tested if the occurrence of manic symptoms between time points was related to CT decline by comparing patients with BDI who experienced manic symptoms with patients who did not experience manic symptoms using a vertexwise LME model and follow-up analyses on percent change measures (described above). We explored the difference in percent change in inferior frontal CT of patients with BDII who experienced hypomanic episodes between time points with patients with BDII who did not experience hypomanic episodes between time points. More methodological details can be found in the Supplement.

Differences Between Diagnostic Subtypes. As evidence for subtype-related differences in brain structure is emerging (7,15,36,38,57), we tested if BDI and BDII differ with respect to cortical changes over time. We tested for differences in extracted change measures and for subtype (BDI vs. BDII)-by-time interactions using a vertexwise LME model.

RESULTS

Patient Characteristics

Table 1 displays group demographics and clinical characteristics. PRS-BD was higher in patients with BD than HC subjects. Patients had higher Montgomery–Åsberg Depression Rating Scale and Young Mania Rating Scale scores than HC subjects at both time points. Patients had accumulated mood episodes throughout life and experienced episodes between time points. Comorbid conditions and medication did not change between baseline and follow-up, with the exception that the number of patients diagnosed with attention-deficit/hyperactivity disorder increased, in line with the increase in stimulant use. At follow-up, fewer patients had a substance use disorder, and no patients had additional diagnosis of panic disorder or social phobia. The time between brain scans was approximately 6 years in both groups, with a group difference of 0.4 year. This difference was short but nevertheless accounted for in our analyses.

Main Analysis: Group-by-Time Interaction

We found statistically significant group-by-time interactions (Figure 1A) in bilateral medial occipital cortex, comprising the lingual, pericalcarine, and cuneus cortices, following a BD $>$ HC pattern with respect to thickness changes over time. The same pattern was observed in bilateral central sulci, posterior cingulate cortex, and the anterior part of left inferior insula. In addition, we found bilateral differences with a BD $<$ HC pattern in middle temporal cortex.

Follow-up on Percent Change Measures. Follow-up analyses of extracted percentage change measures revealed

Table 1. Demographics and Clinical Variables

	HC Subjects	BD Patients	*p* Value
n at T1 (T2)	83 (61)	123 (90)	
Sex, M/F, at T1 (T2)	40/43 (28/33)	44/73 (32/58)	.81 (NS)
Age, Years, at T1 (T2)	39 ± 15 (46 ± 14)	40 ± 13 (45 ± 13)	NS (NS)
Time Difference, T1 − T2	5.6 ± 0.4	6.0 ± 0.9	.008
Education Categorized	3 ± 1	3 ± 1	NS
BMI at T1 (T2)	24.1 ± 3.9 (24.1 ± 4.5)	25.6 ± 4.6 (26.1 ± 5.2)	.019 (.019)
MADRS at T1 (T2)	1.2 ± 2.1 (1.4 ± 2.4)	6.5 ± 6.9 (3.8 ± 3.6)[a]	< .001 (< .001)
YMRS at T1 (T2)	0.3 ± 1.1 (0.4 ± 1.1)	1.0 ± 1.9 (0.9 ± 1.8)	.003 (.061)
ICV in Liters	1.62 ± 0.16	1.60 ± 0.19	NS
Smokers at T1 (T2)	15 (3)[a]	39 (16)[a]	.006 (.023)
Moist Snuff Users at T1 (T2)	11 (8)	18 (19)	NS (NS)
PRS-BD	−6.1 ± 4.0	−3.1 ± 3.1	< .001
Age at Onset, Years	NA	19.3 ± 11.6	–
Diagnosis BDI/BDII at T1 (T2)	NA	69/54 (48/42)	NS
MEs Between T1 and T2	NA	1.2 ± 5.7	–
Lifetime MEs at T1	NA	1.8 ± 3.3	–
DEs Between T1 and T2	NA	3.4 ± 7.1	–
Lifetime DEs at T1	NA	12.0 ± 16.6	–
HMEs between T1 and T2	NA	1.2 ± 4.0	–
Lifetime HMEs at T1	NA	7.6 ± 13.6	–
MXEs between T1 and T2	NA	0.5 ± 2.1	–
Lifetime MXEs at T1	NA	0.8 ± 3.5	–
Li Use at T1 (T2)	NA	60 (47)	NS
AD Use at T1 (T2)	NA	43 (41)	NS
AE Use at T1 (T2)	NA	38 (20)	NS
AP Use at T1 (T2)	NA	23 (21)	NS
CS Use at T1 (T2)	NA	1 (19)[a]	< .001
Anx Use at T1 (T2)	NA	21 (20)	NS
ADHD at T1 (T2)	NA	8 (25)[a]	< .001
OCD at T1 (T2)	NA	8 (4)	NS
GAD at T1 (T2)	NA	14 (4)	.079
Panic Disorder at T1 (T2)	NA	36 (0)[a]	< .001
PTSD at T1 (T2)	NA	3 (0)	NS
Social Phobia at T1 (T2)	NA	15 (0)[a]	< .001
Alcohol Use Disorder at T1 (T2)	NA	12 (5)	NS
Substance Use Disorder at T1 (T2)	NA	11 (2)[a]	.044
Eating Disorder at T1 (T2)	NA	12 (3)	.100
History of Psychosis at T1 (T2)	NA	53 (41)	NS
CGI Improvement at T2	NA	4.8 ± 1.3	–

Mean ± SD or number of participants are listed for both groups and both time points. Data at T2 are in parentheses.

AD, antidepressants; ADHD, attention-deficit/hyperactivity disorder; AE, antiepileptics; Anx, anxiolytics; AP, antipsychotics; BD, bipolar disorder; BDI, bipolar I disorder; BDII, bipolar II disorder; BMI, body mass index; CGI, Clinical Global Impressions; CS, central stimulants; DE, depressive episodes; F, female; GAD, generalized anxiety disorder; HC, healthy control subjects; HME, hypomanic episodes; ICV, intracranial volume; Li, lithium; M, male; MADRS, Montgomery–Åsberg Depression Rating Scale; ME, manic episodes; MXE, mixed episodes; NA, not applicable; NS, not significant; OCD, obsessive-compulsive disorder; PRS, polygenic risk score; PTSD, posttraumatic stress disorder; T1, time point 1; T2, time point 2; YMRS, Young Mania Rating Scale.

[a]Significance T1 vs. T2: smoking in HC subjects, $p = .022$, BD patients, $p = .006$; MADRS in BD patients, $p = .001$.

that HC subjects showed significant cortical thinning in all tested brain regions (Table 2 and Figure 1A, C). In middle temporal cortex, patients with BD displayed greater cortical thinning than HC subjects. This pattern was reversed in other lobes: patients with BD displayed an increase of CT in medial occipital cortex and central sulci and no significant change in thickness of posterior cingulate and left insular cortices over time (Table 2 and Figure 1A, B).

Effects of Demographic and Clinical Variables. Our tests did not indicate that our results were affected by demographic and/or clinical variables, including psychiatric

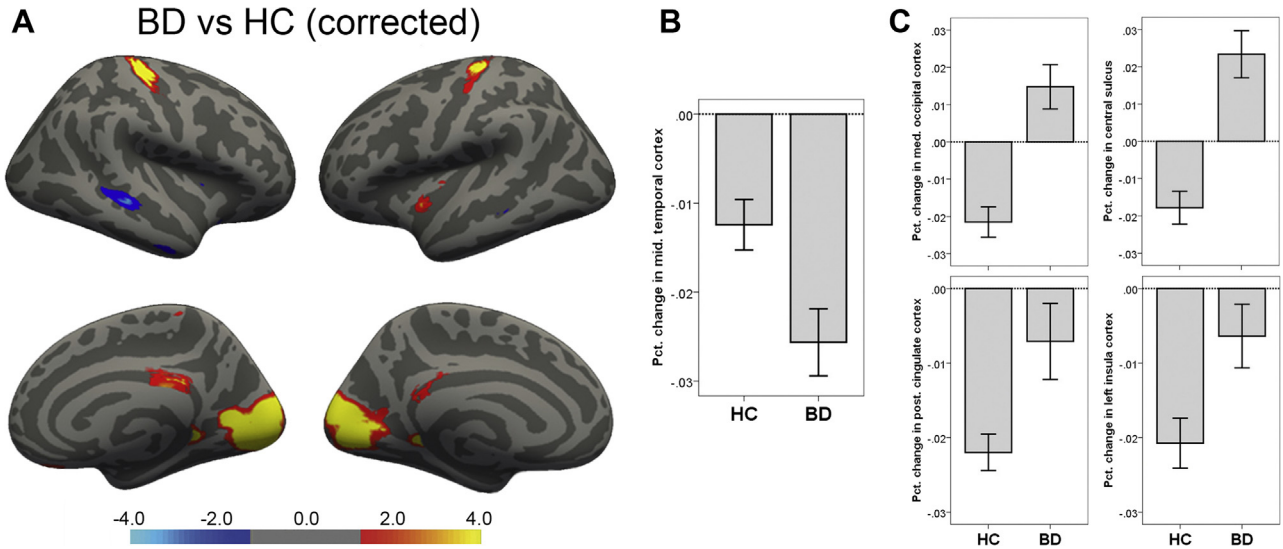

Figure 1. Main analysis (linear mixed effect). **(A)** Clusters depict significant group-by-time interactions. Significance levels are on a −log(*p*) scale. Positive values reflect bipolar disorder (BD) > healthy control (HC) patterns with respect to thickness changes over time (warm colors); negative values reflect BD < HC patterns (cold colors). Results are false discovery rate corrected. See Supplemental Figure S9 for uncorrected results. Follow-up analysis on percent change measures. **(B)** Faster decrease in BD patients compared with HC subjects. **(C)** Thickness increase (top bar plots) and less decrease in BD patients compared with HC subjects (bottom bar plots). Corresponding statistics are presented in Table 2. Pct., percent/100.

comorbidity, substance use, or medication use. See Supplement for details.

Correlations With PRS-BD

We found a significant positive correlation between PRS-BD and percent change in medial occipital cortex, central sulcus, and posterior cingulate cortex in the combined cohort (Table 3). The last-mentioned did not survive correction for multiple comparisons. Scatter plots are shown in Figure 2. When correcting for group status, the correlations in medial occipital cortex (p = .020, r = .24) and central sulcus (p = .032, r = .23) remained significant. Weak and nonsignificant correlations in the same direction were observed in both groups separately (Table 3). No other correlations were observed.

PCs that control for population substructure were nonsignificant predictors, and the correlations remained significant when correcting for PCs, with the exception that the correlation between PRS-BD and changes in posterior cingulate cortex was no longer statistically significant (r = .19, p = .080). The latter might be explained by a significant reduction of degrees of freedom when correcting for PCs (6 additional covariates). Overall, this indicates that the observed correlations were not confounded by population stratification.

Effect of Lithium Use

Although patients who used lithium at T2 (n = 25) did not significantly differ from patients who did not use lithium (n = 22), the patients who used lithium showed a significant increase in medial occipital thickness (p = .023, mean ± SD: 0.023 ± 0.047), whereas patients who did not use lithium showed no change in CT (p = .317, mean ± SD: 0.009 ± 0.040). Results obtained when further dividing these groups can be found in the Supplement. At T1 and T2, lithium users and nonusers did not differ in PRS-BD. Multiple regression analyses revealed that both PRS-BD and lithium use

Table 2. Percent Change Analysis

	HC Subjects			BD Patients			BD vs. HC	
Region	Mean ± SD	*p*	*t (df)*	Mean ± SD	*p*	*t (df)*	*p*	ES
Middle Temporal	−0.012 ± 0.019	< .001	−4.4 (45)	−0.026 ± 0.027	< .001	−6.8 (52)	.006[a]	0.6
Medial Occipital	−0.022 ± 0.028	< .001	−5.3 (45)	0.015 ± 0.043	.016	2.5 (52)	< .001[a]	1.0
Central Sulcus	−0.018 ± 0.029	< .001	−4.1 (45)	0.023 ± 0.046	.001	3.7 (52)	< .001[a]	1.1
Posterior Cingulate	−0.022 ± 0.017	< .001	−9.0 (45)	−0.007 ± 0.037	NS	−1.4 (52)	.017[a]	0.5
Left Insula	−0.021 ± 0.023	< .001	−6.2 (45)	−0.006 ± 0.031	NS	−1.5 (52)	.014[a]	0.5

Results of follow-up analyses on thickness change measures in anatomical regions of interest corresponding to the clusters obtained in the main analysis. For each group, mean ± SD of the percent change in cortical thickness (*p* value, *t* statistic, *df*) of one-sample *t* tests are given. Right column shows group comparison between BD patients (n = 53) and HC subjects (n = 46) *p* value and Cohen's *d* ES.

BD, bipolar disorder; ES, effect size; HC, healthy control.

[a]Results significant after multiple comparisons correction (adjusted α = .020).

Table 3. PRS-BD Correlations

PRS-BD Correlations	Combined (N = 91)	BD Patients (n = 46)	HC Subjects (n = 45)
Middle Temporal	$r = -.12$, $p = .269$	$r = .06$, $p = .699$	$r = -.10$, $p = .508$
Medial Occipital	$r = .37^b$, $p < .001$	$r = .27$, $p = .075$	$r = .24$, $p = .108$
Central Sulcus	$r = .37^b$, $p < .001$	$r = .25$, $p = .100$	$r = .23$, $p = .136$
Insula	$r = .18$, $p = .088$	$r = .16$, $p = .302$	$r = .02$, $p = .902$
Posterior Cingulate	$r = .22^a$, $p = .040$	$r = .12$, $p = .446$	$r = .23$, $p = .138$

Regional correlations between percent change of cortical thickness and PRS-BD were computed in the combined cohort and within BD and HC cohorts separately.

BD, bipolar disorder; HC, healthy control; PRS, polygenic risk score.

[a]Statistically significant $p < .05$.

[b]Statistically significant after multiple comparison correction (adjusted $\alpha = .010$).

significantly and uniquely predict thickness change in medial occipital and central gyrus (Supplemental Table S2).

Effect of Hypomania and Mania

We found that both mania in BDI and hypomania in BDII were associated with greater cortical thinning in inferior frontal cortex (Figure 3 and Supplement).

Differences Between Bipolar Subtypes

No differences between BDI and BDII in any cortical change measure were observed. The vertexwise LME analysis did not reveal any significant subtype-by-time interaction (Supplemental Figure S8).

DISCUSSION

Longitudinal studies assessing cortical changes are essential to elucidate the neuroprogressive nature of BD (22,58,59). We prospectively investigated CT changes over a 6-year period in a large cohort of patients with BD and HC subjects, testing the hypothesis that patients with BD show abnormal cortical thinning over time. We related our findings to genetic risk scores for BD (PRS-BD) and tested for effects of demographic and clinical variables. Our main findings were that longitudinal changes in CT differed between BD and HC cohorts. Patients with BD showed abnormal cortical thinning in temporal cortices, with increased CT in visual/somatosensory brain regions, which was partly accounted for by both genetic risk and lithium use.

Abnormal Cortical Thinning in BD

Patients with BD showed a greater decrease in CT of bilateral middle temporal cortices compared with normal age-related cortical thinning in HC subjects. This finding supports that neuroprogression occurs in BD and is in line with previous suggestions (27). Thus, temporal lobe abnormalities as observed in cross-sectional studies of BD (5,7–16) may partly result from abnormal cortical thinning over time.

It has been suggested that pathological gray matter loss may be involved in the clinical progression of BD. Underlying mechanisms may include increased neurodegeneration, neuronal apoptosis, neurotoxic susceptibility, and altered neuroplasticity, influenced by neuroinflammatory processes and/or oxidative stress during mood episodes (27,58).

Middle temporal cortices are also involved in perceptual memory and visual/sensory integration (60), and patients with BD have shown alterations in sensory-perceptual and verbal working memory during functional MRI (61). In addition, abnormalities in middle temporal cortices have been linked to depression and psychotic symptoms (62–64). However, the relationship between temporal cortical thinning, BD symptoms, and cognitive decline and the detailed mechanisms underlying the accelerated cortical thinning cannot be derived from this study.

Abnormal Increase in CT in BD

Unexpectedly, patients with BD displayed an increase of CT in medial occipital cortex and central sulcus and no CT changes in posterior cingulate and left insular cortices. By contrast, HC subjects showed an age-related decline in all of those regions.

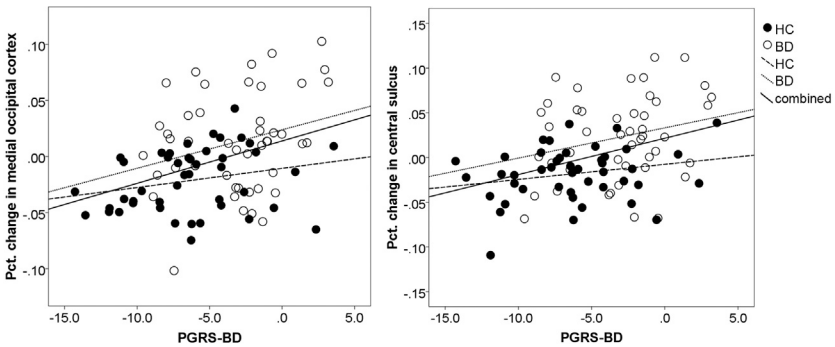

Figure 2. Correlations between polygenic risk score for bipolar disorder (BD) and percent change in medial occipital cortex (left graph) and central sulcus (right graph). Black dots and dashed lines correspond to healthy control (HC) subjects; circles and dotted lines correspond to BD patients. The regression line of the combined group is displayed as a solid line. Statistics are presented in Table 3. Pct., percent/100; PGRS, polygenic risk score.

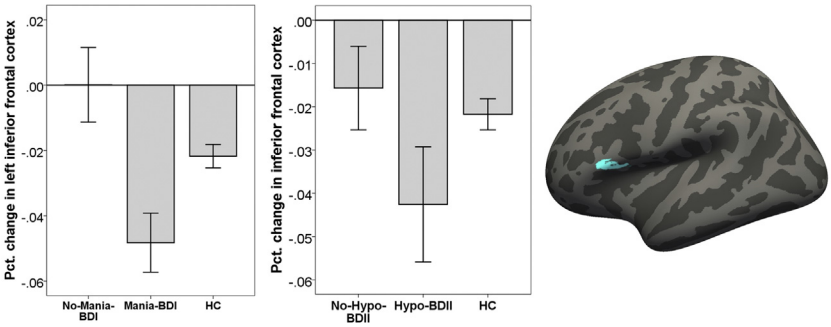

Figure 3. (Right panel) Significant cluster observed after false discovery rate correction of results shown in Supplemental Figure S1. Clusters depict significant group (patients with bipolar disorder I who experienced manic symptoms [Mania-BDI] vs. patients who did not experience manic symptoms [No-Mania-BDI])-by-time interactions observed using a linear mixed effect model (false discovery rate corrected). Significance levels are on a $-\log(p)$ scale. Cluster reflects Mania-BDI < No-Mania-BDI patterns with respect to thickness changes over time. No significant clusters of opposite contrast were observed. See Supplement for uncorrected results. Bar plots show means and SE of the percent change extracted from the left inferior frontal cortex in BDI (left plot) with respect to mania and BDII with respect to hypomania (right plot). Mania-BDI showed significantly greater decreases in inferior frontal cortex compared with both healthy control (HC) subjects ($p = .003$) and No-Mania-BDI ($p < .001$). No-Mania-BDI did not differ from HC subjects. Patients with BDII who experienced hypomanic episodes between time points (Hypo-BDII) tended toward greater decreases in inferior frontal cortex compared with patients with BDII who did not experience hypomanic episodes between time points (No-Hypo-BDII) ($p = .039$) and HC subjects ($p = .067$), which became more significant when controlling for depressive episodes. See Supplement for details. No-Hypo-BDII did not differ from HC. Pct., percent.

Intriguingly, changes in central sulci and medial occipital cortex correlated strongly with each other and with change measures in posterior cingulate cortex and insula (Supplemental Table S1).

The medial occipital (visual) cortex and the central sulcus (somatosensory cortex) form a bimodal visual/somatosensory network (65–67). The posterior cingulate cortex is highly connected to the default mode network (68–70), and the anterior insula plays a role in self-awareness, interoceptive information processing, and perception of touch and pain (71). In line with that, somatosensory-related neuroanatomy and function (5,7,72), perception and emotion recognition (73–75), visual (affect) processing (76–79), and self-referential cognitive processes (80) have been implicated in BD, and alterations in the identification and evaluation of emotions are a hallmark of BD (81). Thus, our findings tentatively suggest that networks involved in sensory perception and emotion processing may play a role in progressive features of BD.

In the present study, we observed cortical thickening in visual/somatosensory areas. Given that greater CT is commonly interpreted as better cortical integrity and has been positively related to cognitive function (33,35,38,82–91), it is tempting to speculate that cortical thickening reflects a structural normalization process. This line of reasoning is supported by results from our secondary analyses indicating that the increase of CT in visual/somatosensory areas may be related to lithium use. Lithium was linked to gray matter volume increases (53–56) and has been associated with neuroprotective effects (92,93). Intriguingly, medial occipital CT of patients with BD using lithium was abnormal at baseline, but similar to medial occipital CT of HC subjects at follow-up (Supplemental Figure S6). Normalizing effects of lithium on brain structure in BD have also been suggested in a recent review (28).

A recent meta-analysis of postmortem studies in BD suggests cortical tissue alterations in several brain areas as detected by staining of calcium-binding proteins (94). Lithium has been shown to attenuate calcium dysregulation, possibly underlying its neuroprotective effects (28,92,95). However, we had limited power to reliably test the effects of lithium use, and our study design did not allow conclusions about causal effects. Note, however, that lithium use did not fully explain the increases in thickness observed. Moreover, increased thickness does not necessarily reflect a beneficial effect but may be related to neuroinflammatory processes suggested to occur in BD (96).

Additionally, we found positive correlations between PRS-BD and relative CT change in medial occipital and central sulcus, which hold when accounting for lithium use. Thus, apart from lithium, genetic factors may contribute to the observed thickness changes in visual/somatosensory regions. Although not statistically significant, there were weak correlations present in lithium-free HC subjects. Hence, one may speculate that thickness increases in sensory areas could be part of the natural course of BD. The complex genetic architecture of BD involves many genetic variants influencing different neurobiochemical mechanisms (97,98). The identification of those variants and how the observed changes relate to visual/sensory improvements should be a subject of future research.

Static Frontal Cortical Abnormalities in BD

Contrary to our hypothesis, the cortical decline in frontal brain areas of patients with BD did not differ from that of HC subjects, indicating that frontal abnormalities observed in BD may be a static trait. Speculatively, the absence of progressive features in the frontal lobe may, in some patients, be due to medical neuroprotective effects. BDI and BDII did not differ with respect to cortical thinning over time, indicating that subtype-related cortical differences may not result from different neuroprogressive trajectories, but rather reflect static/premorbid conditions. Future studies are needed to clarify this.

Frontocortical Changes in Relation to Hypomania and Mania

Cortical thinning in frontal areas might be limited to a subgroup of patients who experience mania (26). In line with our previous study, we found that patients with BDI who experienced manic symptoms between time points showed greater thinning in the left inferior frontal cortex compared with patients with BDI who remained well. In the current study, patients with BDI who experienced manic symptoms also showed greater thinning than HC subjects. Interestingly, we

observed the same pattern in patients with BDII in relation to hypomania. This complements our previous study (26) by providing a more detailed picture of how mania and hypomania in BDI and BDII relate to frontocortical thinning and renders these changes as abnormal. Inferior frontal cortical changes correlated with changes in middle temporal cortex, which indicated mania-related decline (although only at trend level) (Supplemental Figures S1 and S3). Our findings indicate that the occurrence of both mania and hypomania is associated with accelerated cortical thinning in inferior frontal and possibly middle temporal cortex, and mania and hypomania may be associated with similar neurotoxic effects (26,27,58). This, however, remains to be clarified.

Limitations

Although cortical thinning is often interpreted as neuronal loss, the imaging method we used cannot reveal what biological mechanisms underlie changes in CT. Furthermore, potential signal drifts of MRI scanners are a common problem in longitudinal studies. However, the same MRI scanner was used for baseline and follow-up investigations and was frequently tested for signal stability. This as well as the fact that a signal drift would similarly affect HC subject and patient data makes it unlikely that possible scanner drifts would explain the observed group differences.

Although there was no indication that our results were affected by demographic and clinical variables, the results of those follow-up tests should be treated with caution, as they were performed on subsamples (e.g., excluding participants using a specific medication). Correlation analyses on PRS-BD were also performed on a subsample, as not all participants included in the imaging analysis provided genetic data. Also, questions of whether and how cortical changes relate to medication use can be better addressed in randomized clinical trials. Given the number of variables tested and the computational demand of vertexwise LME analyses, some follow-up analyses were performed by averaging thickness measures over parcellated cortical regions. Although this approach provides better comparability to previous studies that used the same parcellation method, and the patterns observed in follow-up analyses were perfectly in line with patterns in the main analysis, high anatomical resolution effects of, e.g., psychiatric comorbidity and medication use in BD, can be addressed in future studies designed to answer this scientific question. Moreover, investigations at higher field strengths (e.g., 3T or 7T) could potentially reveal cortical changes of smaller scale that remained undetected. Also, the inclusion of additional time points may improve fitting accuracy and can potentially detect nonlinear relationships between CT and time. As in all longitudinal studies over long time periods, high attrition rates are a common problem, especially in psychiatric research (in this study, moderate—approximately 40%). Thus, it is unknown if cortical changes are of the same nature in unmedicated patients or patients who were lost to follow-up. Finally, the use of polygenic scores does not allow pinpointing for particular genes influencing cortical changes. However, our findings may prompt future research to further investigate how genetic factors exert their influence.

Conclusions

We suggest that BD is associated with abnormal longitudinal changes in neocortical temporal brain areas. Abnormal frontocortical integrity in frontal brain regions of patients with BD may reflect a static trait but may be further impacted by the incidence of mania or hypomania. Lithium treatment may have neuroprotective/recovering effects noticeable in cortical regions belonging to visual/somatosensory networks, where cortical changes may be influenced by genetic factors. Combining longitudinal structural neuroimaging with polygenic approaches in the largest longitudinal study to date, we provide new important insights into factors underlying the clinical course of patients with BD receiving treatment. Our study also highlights the significance of lithium medication and the prevention of hypomanic and manic episodes in the treatment of BD and its subtypes.

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ARTICLE INFORMATION

From the Departments of Clinical Neuroscience (CA, BL, PP, CJE, MI, ML), Medical Epidemiology and Biostatistics (JS, SEB, ML), and Physiology and Pharmacology (CMS), Karolinska Institutet, Stockholm; Centre for Psychiatry Research (ML), Department of Clinical Neuroscience, Karolinska Institutet and Stockholm County, Stockholm; and Institute of Neuroscience and Physiology (ML), the Sahlgrenska Academy at the Gothenburg University, Gothenburg, Sweden.

Address correspondence to Christoph Abé, Ph.D., Department of Clinical Neuroscience, Karolinska Institutet, Nobels väg 9, Stockholm 17177, Sweden; E-mail: christoph.abe@ki.se.

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