Archival Report

Longitudinal Structural Brain Changes in Bipolar Disorder: A Multicenter Neuroimaging Study of 1232 Individuals by the ENIGMA Bipolar Disorder Working Group

Christoph Abé, Christopher R.K. Ching, Benny Liberg, Alexander V. Lebedev, Ingrid Agartz, Theophilus N. Akudjedu, Martin Alda, Dag Alnæs, Silvia Alonso-Lana, Francesco Benedetti, Michael Berk, Erlend Bøen, Caterina del Mar Bonnin, Fabian Breuer, Katharina Brosch, Rachel M. Brouwer, Erick J. Canales-Rodríguez, Dara M. Cannon, Yann Chye, Andreas Dahl, Orwa Dandash, Udo Dannlowski, Katharina Dohm, Torbjørn Elvsåshagen, Lukas Fisch, Janice M. Fullerton, Jose M. Goikolea, Dominik Grotegerd, Beathe Haatveit, Tim Hahn, Tomas Hajek, Walter Heindel, Martin Ingvar, Kang Sim, Tilo T.J. Kircher, Rhoshel K. Lenroot, Ulrik F. Malt, Colm McDonald, Sean R. McWhinney, Ingrid Melle, Tina Meller, Elisa M.T. Melloni, Philip B. Mitchell, Leila Nabulsi, Igor Nenadić, Nils Opel, Bronwyn J. Overs, Francesco Panicalli, Julia-Katharina Pfarr, Sara Poletti, Edith Pomarol-Clotet, Joaquim Radua, Jonathan Repple, Kai G. Ringwald, Gloria Roberts, Elena Rodriguez-Cano, Raymond Salvador, Kelvin Sarink, Salvador Sarró, Simon Schmitt, Frederike Stein, Chao Suo, Sophia I. Thomopoulos, Giulia Tronchin, Eduard Vieta, Lars T. Westlye, Adam G. White, Lakshmi N. Yatham, Nathalia Zak, Paul M. Thompson, Ole A. Andreassen, and Mikael Landén, for the ENIGMA Bipolar Disorder Working Group

ABSTRACT

BACKGROUND: Bipolar disorder (BD) is associated with cortical and subcortical structural brain abnormalities. It is unclear whether such alterations progressively change over time, and how this is related to the number of mood episodes. To address this question, we analyzed a large and diverse international sample with longitudinal magnetic resonance imaging (MRI) and clinical data to examine structural brain changes over time in BD.

METHODS: Longitudinal structural MRI and clinical data from the ENIGMA (Enhancing Neuro Imaging Genetics through Meta Analysis) BD Working Group, including 307 patients with BD and 925 healthy control subjects, were collected from 14 sites worldwide. Male and female participants, aged 40 ± 17 years, underwent MRI at 2 time points. Cortical thickness, surface area, and subcortical volumes were estimated using FreeSurfer. Annualized change rates for each imaging phenotype were compared between patients with BD and healthy control subjects. Within patients, we related brain change rates to the number of mood episodes between time points and tested for effects of demographic and clinical variables.

RESULTS: Compared with healthy control subjects, patients with BD showed faster enlargement of ventricular volumes and slower thinning of the fusiform and parahippocampal cortex ($0.18 < d < 0.22$). More (hypo)manic episodes were associated with faster cortical thinning, primarily in the prefrontal cortex.

CONCLUSIONS: In the hitherto largest longitudinal MRI study on BD, we did not detect accelerated cortical thinning but noted faster ventricular enlargements in BD. However, abnormal frontocortical thinning was observed in association with frequent manic episodes. Our study yields insights into disease progression in BD and highlights the importance of mania prevention in BD treatment.

https://doi.org/10.1016/j.biopsych.2021.09.008

Bipolar disorder (BD) is a heritable ([1],[2]) psychiatric disorder characterized by recurrent episodes of (hypo)mania and depression ([3],[4]). Cross-sectional neuroimaging studies of BD

show structural brain abnormalities in the prefrontal and temporal cortex, cingulate gyrus, amygdala, and hippocampus ([5–8]) and less consistently in the insula and visual cortex

---

(5,7–16). In prior cross-sectional studies from the ENIGMA (Enhancing Neuro Imaging Genetics through Meta Analysis) BD Working Group, including 6503 individuals, we found the most pronounced cortical thickness alterations in pars opercularis and rostral middle frontal and fusiform cortex, albeit with small effect sizes but no abnormalities in cortical surface area (5). We also reported smaller amygdala, hippocampus, and thalamus volumes and larger ventricular volumes in patients with BD compared with healthy control (HC) subjects (6). However, the extent and heterogeneity of brain abnormalities among patients is substantial (17–19), and cross-sectional studies cannot determine whether the observed brain alterations arise from progressive changes over time.

The term neuroprogression refers to the progressive symptomatic and functional decline observed in some patients with BD that may be associated with progressive neuroanatomical changes (20–23). However, few studies have used a longitudinal design to assess brain changes during the course of BD (24–28). These single-center studies and recent reviews (29) suggest progressive features in the prefrontal and temporal cortices associated with BD. These brain changes could be part of the natural course of BD but could also reflect cortical changes influenced by medication (30,31), genetic factors (25), and the occurrence of mood episodes (24–27). The potential relationship to manic episodes, specifically, is supported by studies demonstrating associations between frontotemporal cortical decline and the occurrence of (hypo) manic episodes (25,26) as well as in first-episode mania (32). It has also been suggested that no cortical changes or even cortical thickness increases, potentially reflecting normalization processes, occur during periods without manic (24,25) or other mood (28) episodes. However, longitudinal brain imaging studies are scarce, and many of them are hampered by various limitations such as small samples, short follow-up times, lack of control groups, or lack of a statistical control for potential confounders such as psychiatric comorbidity and medication use.

The primary aim of this multicenter longitudinal brain imaging study was to overcome the limitations of prior studies, to elucidate whether progressive changes in cortical thickness, surface area, and subcortical volumes occur in BD, beyond those expected with normal aging. While cortical thickness and surface area seem to be genetically distinct measures (33,34), cortical thickness is increasingly being used as a marker for cortical integrity (35–38), also within BD (5,7,8,25,39). In view of our prior findings of abnormalities in cortical thickness but not surface area in BD, we used cortical thickness as a primary cortical measure and cortical surface area as a secondary measure. We thus significantly extend our previous cross-sectional ENIGMA-BD analyses (5,6) by investigating longitudinal changes in the same measures for patients with BD and HC subjects.

Through ENIGMA-BD, we combined data collected from 14 independent studies, including 2464 structural brain magnetic resonance imaging (MRI) scans from 1232 individuals scanned at 2 time points (0.5–9 years apart) and tested for differences in regional annualized change rates between patients with BD (n = 307) and HC subjects (n = 925). Based on the literature reviewed above, we hypothesized that patients with BD at the group level would show greater frontotemporal cortical

thinning over time; greater volume decline in the amygdala, thalamus, and hippocampus; and greater ventricular volume enlargements relative to HC subjects. Given the growing evidence for the potential involvement of mania, the second aim was to investigate whether the number of manic episodes between imaging investigations was associated with annual change rates in patients. Similar associations with hypomanic, mixed, and depressive episodes were explored. We also tested the effects of demographic and clinical variables, such as psychiatric comorbidity, bipolar subtype, and medication use.

METHODS AND MATERIALS

Participating Sites and Cohort Characteristics

Fourteen international sites from 9 countries from the ENIGMA-BD Working Group contributed individual subject longitudinal MRI and clinical data of 325 patients with BD and 978 HC subjects (mean age: 40 ± 17 years) collected at baseline (time point 1 [TP1]) and follow-up (TP2). ENIGMA-BD applies standardized processing, quality control, and analysis techniques to independently collected data samples. Further details about our standardized methods and protocols can be found in our recent review (40). Demographic and clinical data consisted of sex, age, body mass index, educational level, ethnicity, smoking status, alcohol use, substance use, age of onset, number of mood episodes, mood state, bipolar subtype, psychiatric comorbidity, history of psychotic symptoms, and medication use at the time of scan (see Supplement 1 for more details and how these variables were coded). Tables S1–S3 in Supplement 1 list the demographic and clinical details for each diagnostic instruments used to obtain diagnoses and clinical information and exclusion criteria for each center.

In the main analysis, we included centers that provided both patient and control data to reliably correct for imaging site and account for potential scanner drifts, yielding a final sample size of 1232 participants (307 patients with BD and 925 HC subjects). Data from the center that provided only HC data (n = 53) and the center that provided only BD data (n = 18) were included in secondary within-group analyses. All sites received approval from their local ethics committees, and all participants provided written informed consent.

MRI Acquisition and Processing

T1-weighted anatomical brain images were acquired at each site (Table S4 in Supplement 1 for acquisition parameters). Participants underwent baseline and follow-up investigation using the same protocol and scanner. ENIGMA-standardized image processing, quality control, and data extraction tools were applied to each of the 14 independently collected ENIGMA-BD samples. Methodological details are provided in Supplement 1. In brief, FreeSurfer (41–45) was used on-site to perform cortical reconstructions and subcortical segmentations at each imaging time point. Images were first processed cross-sectionally and then with the longitudinal stream implemented in FreeSurfer (version 5.3 or higher) (46). We investigated 68 cortical thickness (and surface area) regions of interest (ROIs), as defined by the Desikan-Killiany atlas (47). Volumetric measures of the following subcortical structures

were included: the nucleus accumbens, amygdala, hippocampus, pallidum, putamen, caudate, thalamus, and lateral ventricles. For each ROI, yearly change rates were computed according to the formula: (measure at TP2 − measure at TP1)/ (measure at TP1 × time between scans).

This yielded a time-independent relative change measure (percent per year) for each participant and each ROI, where negative values reflected a decrease and positive values an increase over time. This approach was chosen because the majority of sites provided data from 2 time points, to be consistent with previous ENIGMA projects, and to enable comparison within and across disorders (5,6,48). If participants provided data from more than 2 time points, the first and last scans were used for change rate computations.

Statistical Analyses

Cohort Characteristics. Differences in demographic and clinical variables between groups at each time point (Table S6 in Supplement 1) were tested with t tests or Fisher's exact χ^2 tests.

Group Differences in Yearly Change Rates (Main Analysis). To determine differences in yearly change rates between patients with BD and HC subjects, we used linear mixed modeling with change rates in brain phenotypes as dependent variable, group (BD vs. HC; variable of interest) as fixed factor, age and sex as covariates, and imaging site as random factor, as in our previous study (5). For each ROI, effect size (Cohen's d) and significance (p values) of group comparisons were mapped into brain space using the ENIGMA viewer (http://enigma.ini.usc.edu/research/enigma-viewer) (Figures 1 and 2).

As in our prior work (5,6), we treated the investigation of subcortical and cortical phenotypes as independent studies but here report findings of both analyses in the same manuscript. Within each phenotype, multiple-comparison correction was performed using Bonferroni's Dubey Armitage-Parmar/ Sidak's adjustment of the alpha level, considering the number of tests (68 for cortical thickness, 8 for subcortical volumes) and their intercorrelation ($r_{thickness}$ = 0.2778, α = 0.0024; $r_{subcortical}$ = 0.11463, α = 0.0047) between the dependent variables (49). Changes in surface area (r_{area} = 0.2339, α = 0.0020) were not part of the main hypothesis but are reported for completeness.

Sensitivity Analysis Testing for Potential Confounders. We tested whether the observed group differences in yearly change rates were affected by demographic or clinical variables (listed in Table S6 in Supplement 1). Methodological details are provided in Supplement 1. Corresponding results are provided in Supplemental Data DS_2.

Correlations Between Change Rates and Manic Episodes Between Time Points. Within patients with BD, correlations between change rates and the number of mood episodes between time points were calculated using nonparametric Spearman's rank correlations in SPSS (version 26; IBM Corp.), given the non-normal distributions of mood episodes (Figures S10 and S11 in Supplement 1). In addition, we constructed a second measure of interest defined as the combined number of manic, hypomanic, and mixed episodes between time points. This measure reflects the total number of elated mood episodes, as investigated in Abé *et al.* (25). Although our hypothesis focused on the effects of manic
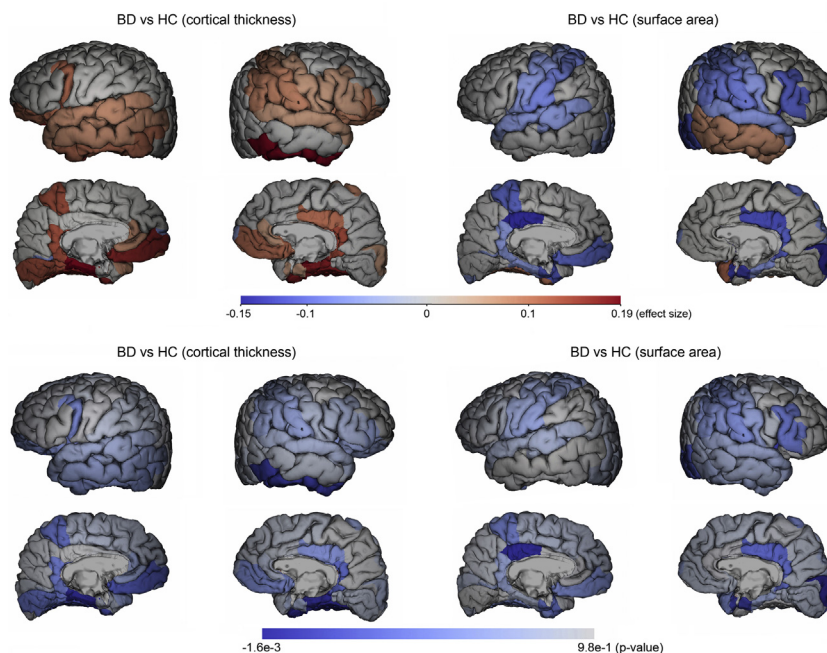

Figure 1. Effect sizes (Cohen's d) (top) and significance of group differences (p value) (bottom) between patients with bipolar disorder (BD) and healthy control (HC) subjects mapped into brain space. Cortical thickness findings (left) and surface area findings (right) are shown. The figure displays the overall pattern in the uncorrected raw results. See Figure 3 for findings after multiple comparisons correction. Numerical values and detailed statistical results are shown in Supplemental Data DS_1. Positive effect sizes (warm red colors) represent BD > HC patterns (HC declines faster). Negative effect sizes (cold blue colors) represent BD < HC patterns (BD declines faster). Corresponding change rates for each group are provided in Supplemental Data DS_3 and Figure S13 in Supplement 1.
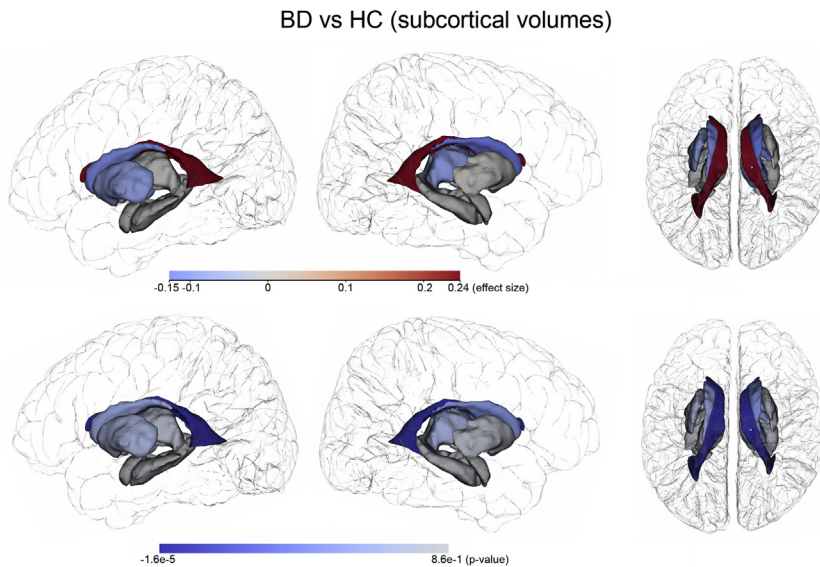
Figure 2. Subcortical volume findings. Effect sizes (Cohen's *d*) (top) and significance of group differences (*p* value) (bottom) between patients with bipolar disorder (BD) and healthy control (HC) subjects. The figure displays the overall pattern of uncorrected raw results. See Figure 3 for findings after multiple comparisons correction. Numerical values and detailed statistical results are shown in Supplemental Data DS_1. Positive effect sizes (warm red colors) represent BD > HC patterns (HC declines faster/increases less). Negative effect sizes (cold blue colors) represent BD < HC patterns (BD declines faster). Corresponding change rates for each group are provided in Supplemental Data DS_3.

episodes, we present results for depressive episodes for completeness (Supplement Data DS_2). The same correction methods as described for the main analysis were performed to account for the number of correlations tested. We performed sensitivity tests adjusting for demographic and clinical variables, including the number of depressive episodes. We also repeated the analyses when excluding the Stockholm cohort, which previously showed associations between cortical decline and manic episodes (25), and the STOP-EM cohort, which was a first-episode mania cohort. See Supplement Data DS_2 and Supplement 1 for details on sensitivity tests and for results of exploratory analyses within BD subtypes.

Intercorrelations Between Brain Phenotypes (Post Hoc Analyses). To test whether the observed cortical thickness increases related to surface area decreases in the same ROI, we calculated Pearson correlations between the corresponding phenotypes. Given the widespread albeit weak effects demonstrated in Figure 1, we also correlated global thickness with global area changes. Given the observed increases in ventricular volumes and indications for subcortical decline in patients with BD, we tested for relationships between ventricle and subcortical volume change rates. Moreover, because we observed intercorrelations between such brain phenotypes, we tested whether multivariate classification methods (partial least squares and random forest) could distinguish between patients with BD and HC subjects based on regional change rate data. Corresponding methods and results of these exploratory tests are shown in Supplement 1.

RESULTS

Cohort Characteristics

A total of 2464 brain MRI scans from 1232 individuals (307 patients and 925 HC subjects) were included in the main

analysis. Table S6 in Supplement 1 displays group characteristics. Patients with BD and HC subjects did not differ statistically in male/female ratios. Patients with BD were on average 6 years younger than HC subjects. The interscan interval was 0.9 years shorter in the HC group. Although the BD group contained fewer participants with White ethnic background, it was the most reported in both groups (83% and 90%). The BD group differed from the HC group in educational level, had higher body mass index, and was more likely to smoke than the HC group. Up to 58% of patients experienced mood episodes between time points. Lithium and antipsychotic drugs were the most frequently used medication types. Patients with BD had comorbid psychiatric diagnoses ranging from 1% (eating disorders) to 9% (attention-deficit/hyperactivity disorder). A few HC subjects (4%) reported alcohol abuse, 1 control subject had generalized anxiety disorder, and 1 control subject reported a history of psychotic symptoms. These were included in the main analysis but were excluded in tests for potential confounders. Sex, age, and interscan interval were accounted for in the main analysis. Effects of other demographic and clinical variables were tested for in additional follow-up analyses (Supplemental Data DS_1).

Case-Control Differences in Yearly Change Rates (Main Analysis)

Effect sizes and significance of group comparisons are shown in Figures 1 and 2. Overall, HC subjects showed lower cortical thickness change rates compared with patients with BD but showed both lower and higher change rates in surface area ROIs. The effect sizes were small ($-0.15 < d < 0.19$) and were predominantly observed in the frontal and temporal cortex. Cortical thickness change rates in the following ROIs displayed group differences at the $p < .05$ level (HC < BD pattern): the bilateral fusiform, left medial orbitofrontal, bilateral parahippocampal, right inferior temporal, and right isthmus cingulate cortex. For detailed statistical results and surface area

findings, see Supplemental Data DS_1. With respect to subcortical regions, change rates of bilateral caudate and lateral ventricles differed between BD and HC groups, where the BD group showed lower change rates in caudate and higher change rates in ventricle volumes than the HC group (Figure 2).

Group differences in ventricular volume (left: $F_{1206,1} = 18.7$, $p = 1.6 \times 10^{-5}$; right: $F_{1206,1} = 15.2$, $p = 1.0 \times 10^{-4}$), right fusiform ($F_{1185,1} = 10.0$, $p = .0016$), and right parahippocampal ($F_{1183,1} = 9.7$, $p = .0019$) thickness change rates remained significant after correcting for multiple comparisons. While both groups showed ventricular volume increases over time, patients with BD showed faster increases than HC subjects. Compared with HC subjects, patients with BD displayed less or no decline in fusiform and parahippocampal thickness (Figure 3). No significant differences in surface area change rates were observed (Supplemental Data DS_1). Change rates in significant ROIs for individual sites can be found in Supplement 1 (Figures S1–S4 in Supplement 1).

Effects of Demographic and Clinical Variables (Sensitivity Tests)

Overall, the sensitivity tests did not indicate that the group differences were affected by demographic and clinical variables. While adjusting for first-generation antipsychotic (FGA) use did not affect group differences, FGA use at TP1 was associated with larger increases in bilateral ventricular volume ($p_{left} = .004$, $p_{right} = .014$) and faster decrease in right fusiform thickness ($p < .001$) in patients. Note that only 14 patients used FGA; hence, these results should be treated with caution. Similarly, history of psychosis (at TP1) was related to faster decline in right parahippocampal thickness ($p = .035$). There were no differences associated with the use of other

medication types. Patients with bipolar I disorder showed a decline in right parahippocampal thickness, whereas patients with bipolar II disorder showed thickness increases in the same region (mean difference: $p = .010$). The observed effects of FGA, history of psychosis, and bipolar subtype within patients are shown in Figures S5–S9 in Supplement 1. Age was not related to changes in cortical measures but correlated positively with change rates of ventricle volumes in HC subjects (Supplement 1 and Supplemental Data DS_1). No significant effects of sex, age × age, or group × age were observed.

Correlations Between Change Rates and Manic Episodes Between Time Points

Overall, we found negative correlations between the number of mood episodes between time points and cortical change rates, indicating faster rate of cortical thinning in patients with more mood episodes. After correction for multiple tests, we found significant negative correlations between the number of manic episodes and yearly change rates of left lingual thickness and frontal pole. The combined number of (hypo)manic and mixed episodes inversely correlated with thickness changes in several (pre)frontal and temporal ROIs (Table S7 in Supplement 1; Figure 4; Supplemental Data DS_2). There were no correlations with surface area or subcortical volume change rates. In complementary tests, we found correlations with depressive episodes (Supplemental Data DS_2).

Post hoc tests for interpretational purpose revealed that those with no manic episodes ($n = 138$) between time points (or no (hypo)manic and mixed episodes) showed either no changes or increased cortical thickness, whereas patients who had one or more manic episodes ($n = 55$) showed cortical thinning over time (Supplemental Data DS_2).
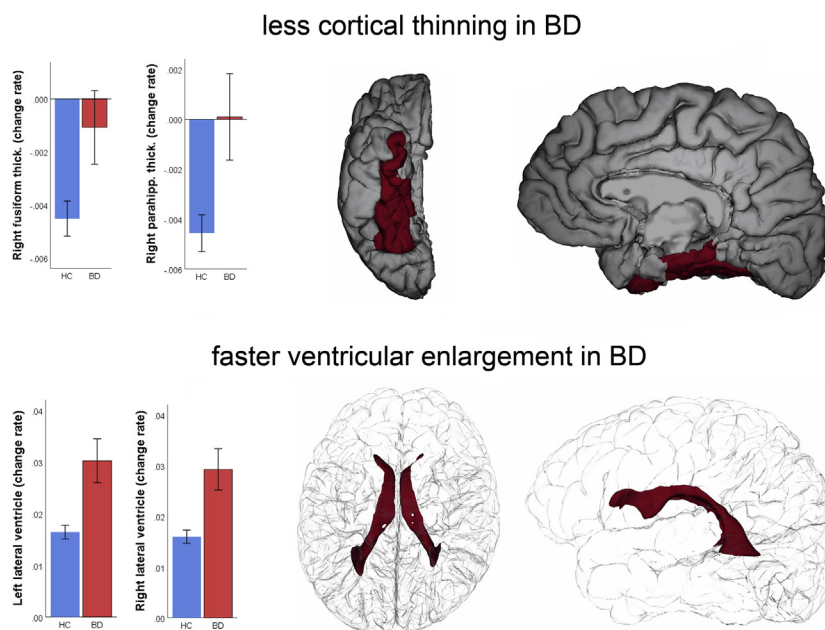

Figure 3. Main findings after multiple comparison correction. Compared with healthy control (HC) subjects, patients with bipolar disorder (BD) showed less reductions in fusiform and parahippocampal thickness (top) and more extensive ventricle enlargements over time (bottom). Means and standard errors for each group are provided on the left for significant regions of interest. Error bars represent standard error of the mean. See Table 1 for numerical values of means and standard deviations.
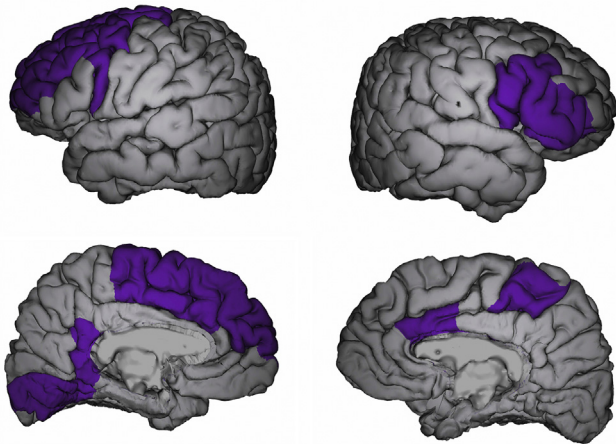
associations with (hypo)manic episodes

Figure 4. Anatomical location of brain regions listed in Table S7 in Supplement 1 (purple) in which significant negative correlations between thickness change rates and the number of (hypo)manic episodes were observed. See Table S7 in Supplement 1 for statistical details and Supplemental Data DS_2 for complementary results for other mood episodes.

The observed correlations remained robust when adjusting for age, sex, and imaging site, excluding outliers, the Stockholm and/or STOP-EM cohort, and when adjusting for the number of depressive episodes between time points (Supplemental Data DS_2). The results also remained when controlling for FGA use. The correlations with (hypo)manic and mixed episodes and thickness changes in lingual, pars orbitalis, pars opercularis, causal anterior cingulate, and caudal middle frontal ROIs remained when controlling for history of psychosis (Supplemental Data DS_2).

Intercorrelations Between Brain Phenotypes (Post Hoc Analysis)

Changes in cortical thickness and surface area were not correlated. In patients, yearly change rates of ventricular volume correlated negatively with changes in all investigated subcortical regions except the right pallidum and left accumbens (Figure 5; Table S5 in Supplement 1). Multivariate case-control classification analyses did not provide sufficient classification accuracy (Supplement 1).

DISCUSSION

To our knowledge, the present ENIGMA-BD Working Group study is the largest longitudinal neuroimaging study of BD to date. On average, patients with BD did not show accelerated decline in any cortical phenotype investigated. Instead, patients with BD showed less cortical thinning than HC subjects in some areas. We did, however, find significantly larger change rates of ventricular volumes in patients with BD than HC subjects. Importantly, more manic episodes between imaging time points were associated with a higher degree of thinning in prefrontal cortex in patients.

Cortical Changes in BD

While HC subjects indicated cortical thinning over time across the whole brain (Figure S13 in Supplement 1), patients with BD showed less or no thinning over time. With respect to surface area, patients showed both higher and lower change rates than HC subjects, indicating that surface area decreases faster in some and slower in other brain areas compared with HC subjects. However, most findings did not withstand correction for multiple comparisons. After correction, case-control differences were observed in fusiform and parahippocampal thickness change rates, where patients with BD displayed less decline compared with HC subjects.

As greater cortical thickness in adults is commonly interpreted as reflecting better cortical integrity (36,38,50–59), it is tempting to speculate that increases in cortical thickness (or a lack of thinning) reflect structural improvement processes. For example, lithium use has been linked to gray matter volume increases (5,6,60–63) and putative neuroprotective effects (31,64–66). A recent review also suggested that lithium has normalizing effects on brain structure (31). Although we did not find any relationship between lithium use and changes in cortical thickness, given our limited information on medication use, we cannot exclude that lithium use prior to baseline scan had an effect on brain change rates. Potential normalizing effects of lithium could also be one possible explanation for why we did not detect group differences in prefrontal brain areas. However, medication effects remain an area of focused investigation in future ENIGMA-BD studies with more detailed medication information such as dosage and history of use. It should be noted, however, that size increases of cortical structures do not necessarily reflect beneficial effects but may be related to neuroinflammatory processes previously suggested to occur in BD (67).

Furthermore, the observed group differences were not affected by the use of lithium, antiepileptics, antipsychotics, or antidepressants, and, except for FGA, change rates for patients with BD on medication at the time of scan did not differ from those not on such medications. However, our study
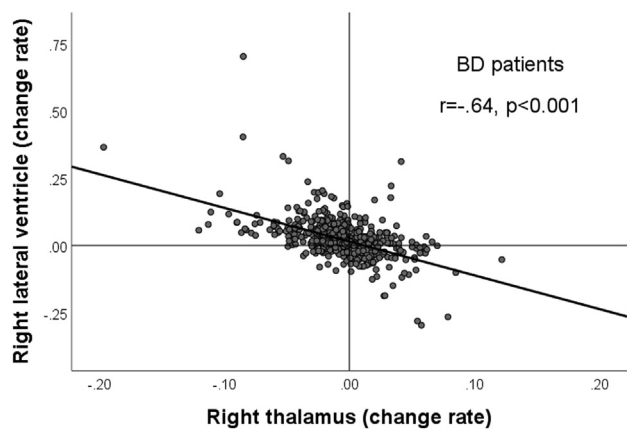

Figure 5. Representative example of intercorrelation between ventricular and subcortical volume change rates in patients. See Table S5 in Supplement 1 for results obtained for other subcortical regions. BD, bipolar disorder.

Table 1. Group Comparisons of Yearly Change Rates (Main Results)

Regional Change Rate in Region	HC, Mean (SD)	BD, Mean (SD)	p Value (BD vs. HC)	Effect Size
Right Fusiform Thickness	−0.0045 (0.0200)	−0.0011 (0.0239)	.0016	0.18
Right Parahippocampal Thickness	−0.0046 (0.0220)	0.0001 (0.0230)	.0019	0.18
Left Ventricle Volume	0.0164 (0.0401)	0.0303 (0.0740)	<.001	0.25
Right Ventricle Volume	0.0160 (0.0398)	0.0293 (0.0710)	<.001	0.22

Means and SDs for each group are listed for change rates of regions in which group comparisons were significant after correction for multiple comparisons. Statistical results of group comparisons in other brain areas and phenotypes are provided in Supplemental Data DS_1.

BD, bipolar disorder; HC, healthy control.

design did not allow conclusions about whether and how medication use affects brain changes in BD, and given the small number of patients using FGA (n = 14), such associations with medication use, along with results corrected for medication use, should be interpreted with caution (see Limitations).

Subcortical Changes in BD

The overall pattern revealed lower subcortical volume change rates and larger ventricular change rates in patients with BD compared with HC subjects, but only the ventricular findings survived correction for multiple comparisons. Given that both groups showed ventricular increases over time (positive change rates), this indicates faster bilateral ventricular enlargements in BD. However, ventricular change rates correlated negatively with those for subcortical volumes, indicating that those patients with BD who display greater ventricle enlargement also display greater subcortical decline over time. These results lend support to the notion that neuroprogression may occur in BD (29), predominantly characterized by ventricle enlargements. Thus, larger ventricle volumes as observed in cross-sectional studies of BD (5,7–16) may partly result from abnormal rates of enlargement during the course of illness.

Overall, the reported cortical and subcortical findings remained significant after correcting for potential confounds, including medication use, psychiatric comorbidity, and demographic variables. The robustness of our findings was further supported by the results from leave-one-site-out analyses (Supplement 1). Multivariate classification analyses did not provide reliable accuracy for case-control classifications. While this may indicate that ROI-based structural change rates may not follow multivariate patterns, such methods may have potential utility in future studies of other brain measures.

Cortical Thinning in Relation to Manic Episodes

Prior studies have proposed that the occurrence of manic episodes is associated with cortical decline (24–26). In this study, the number of manic episodes and the total number of elevated mood episodes (mixed and (hypo)manic episodes) between time points correlated negatively with cortical change rates, predominantly in prefrontal cortex. Effects were small (r < 0.25) but significant. These results were consistent when adjusting for the number of depressive episodes between time points, indicating that the greater the number of manic episodes, the faster the rate of prefrontal cortical thinning. Similar associations were observed in the lingual (visual) cortex. The effects of manic episodes on cortical changes were observed in the combined patient cohort but may differ regionally

between BD subtypes, as indicated by our exploratory analyses (Supplement 1).

Mechanisms underlying pathological gray matter loss may include increased neurodegeneration, neuronal apoptosis, neurotoxic susceptibility, and altered neuroplasticity influenced by neuroinflammatory processes and/or oxidative stress during mood episodes (24,29,68). Although our results are in line with these theories, the mechanisms underlying accelerated cortical thinning cannot be derived from this study. It also remains unclear if manic episodes precede gray matter loss or vice versa, or if there is another causative factor promoting both manic episodes and gray matter changes.

Moreover, our results indicate that patients experiencing mania between time points displayed prefrontal cortical thinning, whereas those who did not experience manic episodes showed no significant cortical changes or thickness increases. While this may suggest cortical normalization processes when mania is prevented, future studies are warranted. Efforts are underway to collect more detailed clinical information from ENIGMA-BD samples including behavioral, cognitive, and functional measures to empower future investigations (40). Although frontocortical abnormalities observed in cross-sectional studies of BD may in part reflect a static trait, our study suggests that some of these abnormalities could arise from progressive changes over time, which may be associated with the experience of manic symptoms. This and the commonly observed heterogeneity of patient groups (17–19) stresses the importance of identifying additional risk factors and subgroups at risk for pathological brain changes.

Limitations

A detailed discussion of the study limitations is provided in Supplement 1. In brief, the imaging method we used cannot reveal what biological mechanisms underlie the observed brain changes (69). Patients with BD were younger than HC subjects. However, age did not correlate with cortical change rates (only with ventricular volumes in HC subjects) and was used as covariate, accounting for individual age-related variation in change rates. In addition, results obtained from sensitivity analyses in age-range–matched adults did not change our conclusions (Supplemental Data DS_1). In addition, because age-related brain changes are commonly of larger magnitude in older people (70,71), we would expect group differences in ventricular volume changes to be even more pronounced if groups were of same age. However, whether and how longitudinal brain changes in BD depend on age remains to be investigated in future studies.

Moreover, how cortical changes or the number of mood episodes relate to medication effects can be better addressed using refined between time point cumulative medication use data and in randomized clinical trials. It is challenging to accurately assess the number of mood episodes, especially in cases that did not require hospitalizations or rely on self-report. Moreover, how the number of hospitalizations as well as the duration of mood episodes relate to longitudinal brain changes in BD remains to be investigated.

Although the ROI approach provides better comparability with previous studies that used the same brain parcellation method, analyses with higher regional resolution, e.g., voxelwise or surface-based vertex-wise analyses, could potentially reveal focal cortical variations that remained undetected at the ROI level. Although we attempted to parse patient groups with potential differential brain trajectories, such as those who experienced frequent manic episodes, refined data-driven analyses aimed at the identification of other potential subpopulations in even larger samples are warranted.

Finally, our findings do not allow conclusions about brain changes that occur in the natural course of BD if untreated.

Conclusions

Our findings suggest that patients with BD show less cortical decline but greater ventricular enlargements over time than HC subjects. Faster frontocortical thinning was associated with more frequent manic episodes. Although it remains to be clarified whether differential change rates in BD reflect beneficial effects from mood-stabilizing treatment, structural improvements when manic symptoms are prevented, or detrimental effects of manic episodes, our findings highlight the importance of preventing manic episodes and provide evidence for a neuroprogressive course of illness in BD.

ARTICLE INFORMATION

From the Department of Clinical Neuroscience (CA, BL, AVL, MI), Osher Center; Department of Clinical Neuroscience (IA), Centre for Psychiatric Research; Department of Medical Epidemiology and Biostatistics (ML), Karolinska Institutet; Karolinska University Hospital (MI), Department of Neuroradiology; and Center for Psychiatric Research (JR), Department of Clinical Neuroscience, Karolinska Institutet and Stockholm Health Care Services, Stockholm County Council, Stockholm; Department of Psychiatry and Neurochemistry (ML), Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; Imaging Genetics Center (CRKC, LN, SIT, PMT), Mark and Mary Stevens Institute for Neuroimaging and Informatics, University of Southern California, Los Angeles, California; University of New Mexico (RKL), Albuquerque, New Mexico; Norwegian Centre for Mental Disorders Research (IA, TE, BH, IM, LTW) and KG Jebsen Centre for Neurodevelopmental Disorders (IA, LTW, OAA), Institute of Clinical Medicine; Norwegian Centre for Mental Disorders Research (DA, AD, TE, BH, IM, LTW, NZ, OAA), Division of Mental Health and Addiction, University of Oslo; Department of Psychology (AD, LTW), Institute of Clinical Medicine (OAA), and Department of Neurology (UFM), University of Oslo; Department of Psychiatric Research (IA), Diakonhjemmet Hospital; Bjørknes College (DA); Unit of Psychosomatic and CL Psychiatry

(EB); Department of Neurology (TE), Division of Clinical Neuroscience; Department of Psychiatry and Addiction (UFM), Section for C-L Psychiatry and Psychosomatics, Oslo University Hospital, Oslo, Norway; Institute of Medical Imaging and Visualisation (TNA), Bournemouth University, Bournemouth; Early Psychosis: Interventions and Clinical-detection lab (JR), Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, United Kingdom; Centre for Neuroimaging and Cognitive Genomics (TNA, DMC, CM, LN, GT), Clinical Neuroimaging Laboratory, NCBES Galway Neuroscience Centre, College of Medicine, Nursing, and Health Sciences, National University of Ireland, Galway, Ireland; Department of Psychiatry (MA, TH, SRM), Dalhousie University, Halifax, Nova Scotia; Djavad Mowafaghian Centre for Brain Health (AGW); Department of Psychiatry (LNY), University of British Columbia, Vancouver, British Columbia, Canada; National Institute of Mental Health (MA, TH), Klecany, Czech Republic; FIDMAG Germanes Hospitalàries Research Foundation (SA-L, EJC-R, EP-C, ER-C, RS, SS); Centro de Investigación Biomédica en Red de Salud Mental (SA-L, CdMB, EJC-R, JMG, EP-C, JR, RS, SS, EV); Institut d'Investigacions Biomèdiques August Pi i Sunyer (CdMB, JMG, JR, EV); Barcelona Bipolar Disorders and Depressive Unit (CdMB, JMG, EV), Hospital Clínic, Institute of Neurosciences; Hospital general de Granollers (FP); University of Barcelona (CdMB, JMG, EV); Benito Menni CASM (FP, ER-C), Barcelona, Spain; Psychiatry and Clinical Psychobiology Unit (FB, EMTM, SP), Division of Neuroscience, IRCCS Ospedale San Raffaele; University Vita-Salute San Raffaele (FB, EMTM), Milano, Italy; Lee Kong Chian School of Medicine (KS), Nanyang Technological University; Yong Loo Lin School of Medicine (KS), National University of Singapore; West Region (KS), Institute of Mental Health, Singapore, Singapore; Orygen (MB), the National Centre of Excellence in Youth Mental Health, Centre for Youth Mental Health, Florey Institute for Neuroscience and Mental Health and the Department of Psychiatry, the University of Melbourne; the Department of Public Health and Preventive Medicine (MB); the Turner Institute for Brain and Mental Health (YC, CS), School of Psychological Science and Monash Biomedical Imaging Facility, Monash University; Department of Psychiatry (OD), The University of Melbourne, Melbourne; Deakin University (MB), the Institute for Mental and Physical Health and Clinical Translation, School of Medicine, Barwon Health, Geelong, Victoria; School of Medical Sciences (JMF) and School of Psychiatry (GR, PBM), University of New South Wales; Neuroscience Research Australia (JMF, BJO), Sydney, New South Wales, Australia; Institute for Translational Psychiatry (FB, UD, KD, LF, DG, TH, NO, JR, KS) and Clinic for Radiology (WH), University of Münster, Münster; Department of Psychiatry and Psychotherapy (KB, TTJK, TM, IN, J-KP, KGR, SS, FS), Philipps-University Marburg, Marburg; Center for Mind, Brain and Behavior (KB, TTJK, TM, IN, J-KP, KGR, SS, FS), University of Marburg and Justus Liebig, University of Giessen, Giessen; and Department of Psychiatry, Social Psychiatry and Psychotherapy (SS), Hannover Medical School, Hannover, Germany; Department of Psychiatry (RMB), University Medical Center Utrecht Brain Center, Utrecht University, Utrecht; Complex Trait Genetics (RMB), Center for Neurogenomics and Cognitive Research, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands; and Signal Processing Laboratory (EJC-R), École polytechnique fédérale de Lausanne, Lausanne, Switzerland.

Address correspondence to Christoph Abé, Ph.D., at christoph.abe@ki.se.

REFERENCES

1. Craddock N, Sklar P (2013): Genetics of bipolar disorder. Lancet 381:1654–1662.
2. Goes FS (2016): Genetics of bipolar disorder: Recent update and future directions. Psychiatr Clin North Am 39:139–155.
3. Merikangas KR, Jin R, He JP, Kessler RC, Lee S, Sampson NA, et al. (2011): Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. Arch Gen Psychiatry 68:241–251.
4. Ekman M, Granström O, Omérov S, Jacob J, Landén M (2013): The societal cost of bipolar disorder in Sweden. Soc Psychiatry Psychiatr Epidemiol 48:1601–1610.
5. Hibar DP, Westlye LT, Doan NT, Jahanshad N, Cheung JW, Ching CRK, et al. (2018): Cortical abnormalities in bipolar disorder: An MRI analysis of 6503 individuals from the ENIGMA Bipolar Disorder Working Group. Mol Psychiatry 23:932–942.
6. Hibar DP, Westlye LT, van Erp TG, Rasmussen J, Leonardo CD, Faskowitz J, et al. (2016): Subcortical volumetric abnormalities in bipolar disorder. Mol Psychiatry 21:1710–1716.
7. Abé C, Ekman CJ, Sellgren C, Petrovic P, Ingvar M, Landén M (2016): Cortical thickness, volume and surface area in patients with bipolar disorder types I and II. J Psychiatry Neurosci 41:240–250.
8. Hanford LC, Nazarov A, Hall GB, Sassi RB (2016): Cortical thickness in bipolar disorder: A systematic review. Bipolar Disord 18:4–18.
9. McDonald C, Zanelli J, Rabe-Hesketh S, Ellison-Wright I, Sham P, Kalidindi S, et al. (2004): Meta-analysis of magnetic resonance imaging brain morphometry studies in bipolar disorder. Biol Psychiatry 56:411–417.
10. Kempton MJ, Geddes JR, Ettinger U, Williams SC, Grasby PM (2008): Meta-analysis, database, and meta-regression of 98 structural imaging studies in bipolar disorder. Arch Gen Psychiatry 65:1017–1032.
11. Arnone D, Cavanagh J, Gerber D, Lawrie SM, Ebmeier KP, McIntosh AM (2009): Magnetic resonance imaging studies in bipolar disorder and schizophrenia: Meta-analysis. Br J Psychiatry 195:194–201.
12. Bora E, Fornito A, Yücel M, Pantelis C (2012): The effects of gender on grey matter abnormalities in major psychoses: A comparative voxel-wise meta-analysis of schizophrenia and bipolar disorder. Psychol Med 42:295–307.
13. Selvaraj S, Arnone D, Job D, Stanfield A, Farrow TF, Nugent AC, et al. (2012): Grey matter differences in bipolar disorder: A meta-analysis of voxel-based morphometry studies. Bipolar Disord 14:135–145.
14. Savitz JB, Price JL, Drevets WC (2014): Neuropathological and neuromorphometric abnormalities in bipolar disorder: View from the medial prefrontal cortical network. Neurosci Biobehav Rev 42:132–147.
15. Maller JJ, Thaveenthiran P, Thomson RH, McQueen S, Fitzgerald PB (2014): Volumetric, cortical thickness and white matter integrity alterations in bipolar disorder type I and II. J Affect Disord 169:118–127.
16. Eker C, Simsek F, Yılmazer EE, Kitis O, Cinar C, Eker OD, et al. (2014): Brain regions associated with risk and resistance for bipolar I disorder: A voxel-based MRI study of patients with bipolar disorder and their healthy siblings. Bipolar Disord 16:249–261.
17. McWhinney SR, Abé C, Alda M, Benedetti F, Bøen E, Del Mar Bonnin C, et al. (2021): Association between body mass index and subcortical brain volumes in bipolar disorders–ENIGMA study in 2735 individuals. Mol Psychiatry 26:6806–6819.
18. Wolfers T, Doan NT, Kaufmann T, Alnæs D, Moberget T, Agartz I, et al. (2018): Mapping the heterogeneous phenotype of schizophrenia and bipolar disorder using normative models. JAMA Psychiatry 75:1146–1155.
19. Wolfers T, Rokicki J, Alnaes D, Berthet P, Agartz I, Kia SM, et al. (2021): Replicating extensive brain structural heterogeneity in individuals with schizophrenia and bipolar disorder. Hum Brain Mapp 42:2546–2555.
20. Passos IC, Mwangi B, Vieta E, Berk M, Kapczinski F (2016): Areas of controversy in neuroprogression in bipolar disorder. Acta Psychiatr Scand 134:91–103.
21. Cardoso T, Bauer IE, Meyer TD, Kapczinski F, Soares JC (2015): Neuroprogression and cognitive functioning in bipolar disorder: A systematic review. Curr Psychiatry Rep 17:75.
22. Barbosa IG, Bauer ME, Machado-Vieira R, Teixeira AL (2014): Cytokines in bipolar disorder: Paving the way for neuroprogression. Neural Plast 2014:360481.
23. Schneider MR, DelBello MP, McNamara RK, Strakowski SM, Adler CM (2012): Neuroprogression in bipolar disorder. Bipolar Disord 14:356–374.
24. Abé C, Ekman CJ, Sellgren C, Petrovic P, Ingvar M, Landén M (2015): Manic episodes are related to changes in frontal cortex: A longitudinal neuroimaging study of bipolar disorder 1. Brain 138:3440–3448.

25. Abé C, Liberg B, Song J, Bergen SE, Petrovic P, Ekman CJ, et al. (2020): Longitudinal cortical thickness changes in bipolar disorder and the relationship to genetic risk, mania, and lithium use. Biol Psychiatry 87:271–281.

26. Moorhead TW, McKirdy J, Sussmann JE, Hall J, Lawrie SM, Johnstone EC, McIntosh AM (2007): Progressive gray matter loss in patients with bipolar disorder. Biol Psychiatry 62:894–900.

27. Zak N, Bøen E, Boye B, Andreassen OA, Doan NT, Malt UF, et al. (2019): Mood episodes are associated with increased cortical thinning: A longitudinal study of bipolar disorder type II. Bipolar Disord 21:525–538.

28. Kozicky JM, McGirr A, Bond DJ, Gonzalez M, Silveira LE, Keramatian K, et al. (2016): Neuroprogression and episode recurrence in bipolar I disorder: A study of gray matter volume changes in first-episode mania and association with clinical outcome. Bipolar Disord 18:511–519.

29. Lim CS, Baldessarini RJ, Vieta E, Yucel M, Bora E, Sim K (2013): Longitudinal neuroimaging and neuropsychological changes in bipolar disorder patients: Review of the evidence. Neurosci Biobehav Rev 37:418–435.

30. Ho BC, Andreasen NC, Ziebell S, Pierson R, Magnotta V (2011): Long-term antipsychotic treatment and brain volumes: A longitudinal study of first-episode schizophrenia. Arch Gen Psychiatry 68:128–137.

31. McDonald C (2015): Brain structural effects of psychopharmacological treatment in bipolar disorder. Curr Neuropharmacol 13:445–457.

32. Keramatian K, Chakrabarty T, Saraf G, Pinto JV, Yatham LN (2021): Grey matter abnormalities in first-episode mania: A systematic review and meta-analysis of voxel-based morphometry studies. Bipolar Disord 23:228–240.

33. Panizzon MS, Fennema-Notestine C, Eyler LT, Jernigan TL, Prom-Wormley E, Neale M, et al. (2009): Distinct genetic influences on cortical surface area and cortical thickness. Cereb Cortex 19:2728–2735.

34. Winkler AM, Kochunov P, Blangero J, Almasy L, Zilles K, Fox PT, et al. (2010): Cortical thickness or grey matter volume? The importance of selecting the phenotype for imaging genetics studies. Neuroimage 53:1135–1146.

35. Dickerson BC, Wolk DA, Alzheimer's Disease Neuroimaging Initiative (2012): MRI cortical thickness biomarker predicts AD-like CSF and cognitive decline in normal adults. Neurology 78:84–90.

36. Durazzo TC, Mon A, Gazdzinski S, Meyerhoff DJ (2013): Chronic cigarette smoking in alcohol dependence: Associations with cortical thickness and N-acetylaspartate levels in the extended brain reward system. Addict Biol 18:379–391.

37. Almeida Montes LG, Prado Alcántara H, Martínez García RB, De La Torre LB, Avila Acosta D, Duarte MG (2013): Brain cortical thickness in ADHD: Age, sex, and clinical correlations. J Atten Disord 17:641–654.

38. Burzynska AZ, Nagel IE, Preuschhof C, Gluth S, Bäckman L, Li SC, et al. (2012): Cortical thickness is linked to executive functioning in adulthood and aging. Hum Brain Mapp 33:1607–1620.

39. Elvsåshagen T, Westlye LT, Bøen E, Hol PK, Andreassen OA, Boye B, Malt UF (2013): Bipolar II disorder is associated with thinning of prefrontal and temporal cortices involved in affect regulation. Bipolar Disord 15:855–864.

40. Ching CRK, Hibar DP, Gurholt TP, Nunes A, Thomopoulos SI, Abé C, et al. (2020): What we learn about bipolar disorder from large-scale neuroimaging: Findings and future directions from the ENIGMA Bipolar Disorder Working Group. Hum Brain Mapp 43:56–82.

41. Dale AM, Fischl B, Sereno MI (1999): Cortical surface-based analysis. I. Segmentation and surface reconstruction. Neuroimage 9:179–194.

42. Fischl B, Sereno MI, Dale AM (1999): Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. Neuroimage 9:195–207.

43. Fischl B, Dale AM (2000): Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc Natl Acad Sci U S A 97:11050–11055.

44. Fischl B, van der Kouwe A, Destrieux C, Halgren E, Ségonne F, Salat DH, et al. (2004): Automatically parcellating the human cerebral cortex. Cereb Cortex 14:11–22.

45. Fischl B, Salat DH, van der Kouwe AJ, Makris N, Ségonne F, Quinn BT, Dale AM (2004): Sequence-independent segmentation of magnetic resonance images. Neuroimage 23(suppl 1):S69–S84.

46. Reuter M, Schmansky NJ, Rosas HD, Fischl B (2012): Within-subject template estimation for unbiased longitudinal image analysis. Neuroimage 61:1402–1418.

47. Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, et al. (2006): An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage 31:968–980.

48. Brouwer RM, Panizzon MS, Glahn DC, Hibar DP, Hua X, Jahanshad N, et al. (2017): Genetic influences on individual differences in longitudinal changes in global and subcortical brain volumes: Results of the ENIGMA plasticity working group. Hum Brain Mapp 38:4444–4458.

49. Sankoh AJ, Huque MF, Dubey SD (1997): Some comments on frequently used multiple endpoint adjustment methods in clinical trials. Stat Med 16:2529–2542.

50. Yuan P, Raz N (2014): Prefrontal cortex and executive functions in healthy adults: A meta-analysis of structural neuroimaging studies. Neurosci Biobehav Rev 42:180–192.

51. Choi YY, Shamosh NA, Cho SH, DeYoung CG, Lee MJ, Lee JM, et al. (2008): Multiple bases of human intelligence revealed by cortical thickness and neural activation. J Neurosci 28:10323–10329.

52. Dickerson BC, Fenstermacher E, Salat DH, Wolk DA, Maguire RP, Desikan R, et al. (2008): Detection of cortical thickness correlates of cognitive performance: Reliability across MRI scan sessions, scanners, and field strengths. Neuroimage 39:10–18.

53. Gautam P, Warner TD, Kan EC, Sowell ER (2015): Executive function and cortical thickness in youths prenatally exposed to cocaine, alcohol and tobacco. Dev Cogn Neurosci 16:155–165.

54. Schmidt EL, Burge W, Visscher KM, Ross LA (2016): Cortical thickness in frontoparietal and cingulo-opercular networks predicts executive function performance in older adults. Neuropsychology 30:322–331.

55. Joshi SH, Vizueta N, Foland-Ross L, Townsend JD, Bookheimer SY, Thompson PM, et al. (2016): Relationships between altered functional magnetic resonance imaging activation and cortical thickness in patients with euthymic bipolar I disorder. Biol Psychiatry Cogn Neurosci Neuroimaging 1:507–517.

56. Abé C, Rolstad S, Petrovic P, Ekman CJ, Sparding T, Ingvar M, Landén M (2018): Bipolar disorder type I and II show distinct relationships between cortical thickness and executive function. Acta Psychiatr Scand 138:325–335.

57. Engvig A, Fjell AM, Westlye LT, Moberget T, Sundseth Ø, Larsen VA, Walhovd KB (2010): Effects of memory training on cortical thickness in the elderly. Neuroimage 52:1667–1676.

58. Walhovd KB, Fjell AM, Dale AM, Fischl B, Quinn BT, Makris N, et al. (2006): Regional cortical thickness matters in recall after months more than minutes. Neuroimage 31:1343–1351.

59. Makris N, Biederman J, Valera EM, Bush G, Kaiser J, Kennedy DN, et al. (2007): Cortical thinning of the attention and executive function networks in adults with attention-deficit/hyperactivity disorder. Cereb Cortex 17:1364–1375.

60. Sun YR, Herrmann N, Scott CJM, Black SE, Khan MM, Lanctôt KL (2018): Global grey matter volume in adult bipolar patients with and without lithium treatment: A meta-analysis. J Affect Disord 225:599–606.

61. Hajek T, Bauer M, Simhandl C, Rybakowski J, O'Donovan C, Pfennig A, et al. (2014): Neuroprotective effect of lithium on hippocampal volumes in bipolar disorder independent of long-term treatment response. Psychol Med 44:507–517.

62. Cousins DA, Aribisala B, Nicol Ferrier I, Blamire AM (2013): Lithium, gray matter, and magnetic resonance imaging signal. Biol Psychiatry 73:652–657.

63. Monkul ES, Matsuo K, Nicoletti MA, Dierschke N, Hatch JP, Dalwani M, et al. (2007): Prefrontal gray matter increases in healthy

individuals after lithium treatment: A voxel-based morphometry study. Neurosci Lett 429:7–11.

64. Berk M, Dandash O, Daglas R, Cotton SM, Allott K, Fornito A, *et al.* (2017): Neuroprotection after a first episode of mania: A randomized controlled maintenance trial comparing the effects of lithium and quetiapine on grey and white matter volume. Transl Psychiatry 7: e1041.

65. Dwivedi T, Zhang H (2014): Lithium-induced neuroprotection is associated with epigenetic modification of specific BDNF gene promoter and altered expression of apoptotic-regulatory proteins. Front Neurosci 8:457.

66. Guo X, Liu D, Wang T, Luo X (2019): Aetiology of bipolar disorder: Contribution of the L-type voltage-gated calcium channels. Gen Psychiatr 32:e100009.

67. Muneer A (2016): Bipolar disorder: Role of inflammation and the development of disease biomarkers. Psychiatry Investig 13:18–33.

68. Vieta E, Berk M, Schulze TG, Carvalho AF, Suppes T, Calabrese JR, *et al.* (2018): Bipolar disorders. Nat Rev Dis Primers 4:18008.

69. Weinberger DR, Radulescu E (2021): Structural magnetic resonance imaging all over again. JAMA Psychiatry 78:11–12.

70. Scahill RI, Frost C, Jenkins R, Whitwell JL, Rossor MN, Fox NC (2003): A longitudinal study of brain volume changes in normal aging using serial registered magnetic resonance imaging. Arch Neurol 60:989–994.

71. Storsve AB, Fjell AM, Tamnes CK, Westlye LT, Overbye K, Aasland HW, Walhovd KB (2014): Differential longitudinal changes in cortical thickness, surface area and volume across the adult life span: Regions of accelerating and decelerating change. J Neurosci 34:8488–8498.