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Bipolar disorder type I and II show distinct relationships between cortical thickness and executive function

Abé C, Rolstad S, Petrovic P, Ekman C-J, Sparding T, Ingvar M, Landén M. Bipolar disorder type I and II show distinct relationships between cortical thickness and executive function.

Objective: Frontal cortical abnormalities and executive function impairment co-occur in bipolar disorder. Recent studies have shown that bipolar subtypes differ in the degree of structural and functional impairments. The relationships between cognitive performance and cortical integrity have not been clarified and might differ across patients with bipolar disorder type I, II, and healthy subjects.
Method: Using a vertex-wise whole-brain analysis, we investigated how cortical integrity, as measured by cortical thickness, correlates with executive performance in patients with bipolar disorder type I, II, and controls (N = 160).
Results: We found focal associations between executive function and cortical thickness in the medial prefrontal cortex in bipolar II patients and controls, but not in bipolar I disorder. In bipolar II patients, we observed additional correlations in lateral prefrontal and occipital regions.
Conclusions: Our findings suggest that bipolar disorder patients show altered structure–function relationships, and importantly that those relationships may differ between bipolar subtypes. The findings are line with studies suggesting subtype-specific neurobiological and cognitive profiles. This study contributes to a better understanding of brain structure–function relationships in bipolar disorder and gives important insights into the neuropathophysiology of diagnostic subtypes.

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Key words: bipolar disorder; bipolar subtypes; cortical thickness; executive functioning; neuroimaging

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Significant outcomes

- Frontal cortical thickness is positively related to executive function
- Brain structure–function relationships differ between patients with bipolar disorder and healthy controls
- Bipolar disorder subtypes demonstrate distinct structure–function relationships

Limitations

- The cross-sectional study design cannot distinguish between cortical changes over time and static traits.
- Correlations between structure and function might suggest, but cannot directly demonstrate, that the discussed brain regions are recruited in cognitive processes.

Introduction

Bipolar disorder is a psychiatric disorder characterized by recurrent episodes of mania, hypomania, and depression interspersed by euthymic periods (1). There are two established subtypes of bipolar disorder: type I (BDI) and type II (BDII). BDII is distinguished from BDI mainly by the absence of full-blown manic episodes. Cognitive impairment has been demonstrated in bipolar disorder even during euthymic periods (2–6), especially deficits in executive functions that mainly, but not exclusively, recruit frontal brain areas (3, 5–11). In line with this, brain-imaging studies have demonstrated cortical abnormalities and progressive gray matter loss primarily in frontal brain regions (7, 12–18). This co-occurrence of frontal cortical abnormalities and impaired executive function in bipolar disorder suggests that cortical integrity in frontal brain regions might be coupled to executive cognitive performance.

It has previously been suggested that relationships between prefrontal cortical *volume* and executive function differ between healthy controls and patients with bipolar disorder, which might reflect cortical dysfunction related compensation mechanisms (19, 20). Cortical volume is, however, a function of cortical surface area and cortical thickness. Cortical thickness is increasingly being used to study brain–behavior relationships and has also been associated with cognitive functioning (9, 21–24). More specifically, a recent meta-analysis reported that thicker prefrontal cortices are commonly associated with better executive performance (11), which is of particular interest for bipolar disorder research. Importantly, relationships between regional cortical thickness and functional patterns of brain activation have been demonstrated (9, 25, 26). For example, during response inhibition, which requires executive control, patients with bipolar disorder showed both hypoactivation and reduced thickness in (medial) prefrontal brain regions compared to controls, suggesting that abnormal neural activation underlies structural etiology (25). Thus, cortical thickness correlates of executive function can provide important insights into brain structure–function relationships.

Studies of the relationship between cortical thickness and cognitive function in bipolar disorder are scarce (27–30). Most studies were hampered by small sample sizes, and analyses have typically been restricted to regions where case–control differences have been found, providing only a limited picture. In addition, cortical measures have been averaged over large predefined brain areas, which might facilitate the investigation of diffuse effects, but might not detect focal structure–function associations. Moreover, most previous studies have investigated BDI, or BDI and BDII indiscriminately combined. But BDI and BDII differ with respect to symptomatology and severity (31, 32). Some (5, 6, 33, 34) but not all (2, 3) studies have observed differences between bipolar subtypes also with respect to cognitive functioning. In line with that, evidence for subtype-related differences in brain structure is emerging (17, 35–38). In a previous study, we suggested that BDII exhibits a cortical integrity in between that of healthy individuals and BDI (17). Hence, these limitations might contribute to the reason why most previous studies failed to detect correlations between executive function and prefrontal cortical thickness in patients with bipolar disorder.

However, given the importance of prefrontal cortical thickness for core executive functions, and the well-documented co-occurrence of frontal cortical abnormalities and executive performance deficits in BD, we expected to find positive associations between executive function performance and prefrontal cortical thickness. Based on studies suggesting cortical dysfunction and related compensation mechanisms, and on the emerging evidence for bipolar subtype specific structural and functional profiles, we expected that these correlations would differ between BDI, BDII, and controls.

Aims of the Study

Here, we combined two modalities (neuroimaging and neuropsychological testing) obtained from our large clinical cohort of patients with bipolar disorder type I, type II, and healthy controls ($N = 160$). The aim was to investigate the relevance of cortical thickness for executive function in order to elucidate structure–function relationships in BDI and BDII subtypes respectively. Contrasting most previous studies, we used correlation approaches with high regional resolution within the whole brain.

Methods

Participants

The sample was drawn from 225 participants that provided MRI data in a previous study, where we investigated cortical differences between BDI, BDII, and controls (17). Those participants, who also provided cognitive test data, were included in this study, resulting in 160 participants: 49 patients with BDI, 28 patients with BDII, and 83 controls.

Patients were recruited from a follow-up program at the bipolar outpatient unit Northern Stockholm psychiatric clinic, Stockholm, Sweden. Details on exclusion and inclusion criteria, diagnostic tools, and methods can be found elsewhere (39, 40), and in the Supplementary Material. In brief, the key clinical assessment instrument was a Swedish version of the Affective Disorder Evaluation (ADE), which is a standardized interview protocol developed for the Systematic Treatment Enhancement Program of Bipolar Disorder (STEP-BD). The clinical diagnosis of bipolar disorder was made according to DSM-IV criteria as per the Structured Clinical Interview for DSM-IV (SCID). In addition, the Mini International Neuropsychiatric Interview (M.I.N.I.) was completed to screen for other psychiatric diagnoses. The ADE and M.I.N.I. interviews were conducted by board-certified psychiatrists working at the tertiary bipolar outpatient unit, or residents in psychiatry completing their training at this unit. A best-estimate diagnostic decision was made based on all information available at admission by a consensus panel of experienced board-certified psychiatrists specialized in bipolar disorder. All available sources of information, encompassing patient interview, case records and, if available, interview with the next of kin, were utilized in the diagnostic assessment. Patients were not remunerated for participation.

Age- and sex-matched healthy, population-based controls were randomly selected by Statistics Sweden and contacted by mail. Details of the recruitment, and inclusion and exclusion criteria can be found elsewhere (39, 40) and in the Supplementary Material. Eligible persons were scheduled for a personal examination and investigated to exclude mental illness by a psychiatrist using the Mini International Neuropsychiatric Interview (M.I.N.I.) and selected parts of the ADE. Exclusion criteria were as follows: any current psychiatric disorder, a family history of schizophrenia or bipolar disorder in first-degree relatives, drug or alcohol abuse (based on DUDIT, AUDIT and serum levels of carbohydrate-deficient transferrin), and neurological conditions except mild migraines, pregnancy, untreated endocrine disorders, dementia, and personality disorder. All study subjects consented orally and in writing to participate in the study. The study was approved by the Ethics committee of the Karolinska Institutet, Stockholm, Sweden. The authors assert that all procedures contributing to this work comply with the ethical standards of the national and institutional committees on human experimentation, in accordance with the Declaration of Helsinki of 1975.

MRI acquisition

MRI scans were acquired at the MR Research Center, Karolinska University Hospital, Stockholm. Coronal 3D T1-weighted images were acquired with a spoiled gradient echo recall sequence (3D-SPGR, TR = 21.0 ms, TE = 6 ms, FOV = 18 cm, flip angle = 30°, acquisition matrix = 256 × 256 × 128, voxel size: 0.7 × 0.7 × 1.8 mm^3) using a 1.5-Tesla MRI medical scanner (General Electric Signa Excite 1.5T) equipped with an eight channel head coil. Axial fluid attenuation inversion recovery T2-weighted scans were acquired for examination by a senior radiologist to exclude for clinically significant anatomical abnormalities and neuropathology. Patients were in euthymic state at scan day (<14 on both MADRS and YMRS), and participants were scanned in random order.

Image processing

Measures for cortical thickness were obtained from T1-weighted images using the semi-automated segmentation and cortical surface reconstruction methods provided by FreeSurfer v5.1. Methodological details are described in (41–44) and in our previous study (17). All cortical surface reconstructions were visually inspected by the same investigator blind to diagnosis, and manually corrected if necessary, using editing tools provided by FreeSurfer. Reconstructed surfaces were smoothed (FWHM=10 mm), transformed, and resampled onto a common standard space (fsaverage).

Neuropsychological testing

Details of the full neuropsychological test battery can be found in (3). Here, we focused on core executive functions including inhibition, set shifting, and working memory-processes (45) using the following subtests of the Delis-Kaplan Executive Function System (D-KEFS): Color-Word Interference Test (CWIT, condition 1, 2, 3, and 4), Trail Making Test (TMT, condition 1, 2, 3, 4, and 5), and Design Fluency Test (DFT, condition 1, 2, and 3). The Tower and Verbal Fluency Task were omitted due to weak associations with inhibition and control (core executive functions) (46, 47), and because they rely highly on either verbal knowledge and letter fluency (confounding by education), or higher order executive functions, for example, planning and reasoning (45). We calculated an executive function domain measure as follows. First, we omitted the subtests serving as control conditions, such as color/word reading ability, processing/motor speed, etc., and only

considered conditions demanding executive functions: CWIT conditions 3 and 4 (CWIT-3, CWIT-4), TMT condition 4 (TMT-4), and DFT condition 3 (DFT-3). The raw scores of those tests were transformed into z-scores based on the performance of healthy controls. In case of CWIT and TMT, the z-scores were multiplied by −1 as higher raw scores reflect worse performance. The obtained z-scores were then averaged to an overall executive function performance measure, with higher scores indicating better overall executive performance. All individual tests strongly correlated with the domain score (correlation coefficients between 0.72 and 0.80), and with each other (all $P < 0.001$, see Table S3). The main correlation analyses with cortical thickness were performed on the domain-specific measure. The purpose of analyzing executive functions as a domain was to communicate the underlying measuring entity (48, 49), decrease the test-specific associations, and to reduce the potential alpha inflation resulting from a larger battery of tests.

Statistical analysis

Tests for group differences in demographic and descriptive variables were performed with Chi^2 and/or pairwise *t*-tests using SPSS v23. To investigate regional associations between executive performance and cortical thickness within groups, statistical maps were computed using a general linear model approach tesing for the effects of cognitive performance (covariate of interest) on cortical thickness (dependent variable) at each vertex point of the cortical surface model. The analyses were performed vertex-wise on the whole brain within each group using QDEC provided by FreeSurfer. To quantify group differences, group-by-executive function interactions were performed pairwise using the DODS model (different offset, different slopes) with group as fixed factor, and the cognitive test score as covariate of interest. Correction for multiple comparisons was performed using a Monte Carlo cluster-wise simulation approach (threshold $P = 0.05$) (50). Although BDI and BDII did not significantly differ in male to female ratio, the BDII group contained more females. Therefore, and because of possible sex related cortical thickness differences (51), we adjusted for sex in all analyses. As suggested by Mungas et al., we did not correct for age in our main analysis (10, 52). Age correction is not advisable when investigating brain structural relationships to cognitive performance, because age and brain pathology/disease progress (7, 16) are highly correlated, especially in an older patient cohort. Adjusting for age would thus correct for brain pathology, obscuring potential relationships of interest between MRI-related measures and cognitive performance. However, we provide age-corrected results in the Supplementary Material.

In additional follow-up analyses, we tested for effects of demographic and clinical variables, such as comorbidity and medication use, which were set up as continuous or categorical/discrete variables. Each variable was tested in a separate analysis, and in each group separately, to detect potential effects on the primary outcome measures (regional correlations between thickness and executive function). Further sensitivity analyses testing for effects of those variables were also performed by excluding corresponding individuals from the analysis. Specifically, we re-ran the main analysis while separately correcting for body mass index (BMI), education, moist snuff or smoking status, intracranial volume (ICV), time difference between MRI and test date, age of onset, years ill, number of depressive episodes, number of manic episodes (in BDI), use of medication type, presence of any comorbid disorder; and after excluding cases using antiepileptic and antipsychotic drugs, with comorbid social phobia, obsessive–compulsive disorder, generalized anxiety disorder, eating disorders, post-traumatic stress disorder, alcohol/drug abuse, participants not using lithium medication, and with a history of psychosis in BDII.

Results

Patient characteristics

Characteristics and demographic variables of the study participants, as well as information on their medical use, can be found in Table 1. Groups did not differ in age, BMI, ICV, or level of education. There were significantly more smokers and moist snuff users in both patient groups compared with controls. The bipolar subtype groups did not differ in age of onset, years ill, percentage of patients using antiepileptic drugs or antidepressants, or ratio of patients with or without any comorbidities. BDI had a higher percentage of patients with a history of psychosis, more often used lithium or antipsychotics, had fewer depressive episodes, and fewer cases with eating disorders. Although not statistically significant, BDII had a higher percentage of females than BDI. BDI scored significantly worse than controls on the overall executive functioning measure, while BDII tended to scored worse than controls but better than BDI.

Table 1. Demographic and clinical characteristics

Group (N = 160)	Controls (n = 83)	BDI (n = 49)	BDII (n = 28)	Controls vs. BDI	Controls vs. BDII	BDI vs. BDII
Age	39.0 ± 14.8	39.9 ± 12.0	38.14 ± 11.9	NS	NS	NS
Females	43	24	19	NS	NS	0.085
BMI	24 ± 4	26 ± 4	25 ± 5	0.014	NS	NS
Executive function	0.0 ± 0.7	−1.1 ± 1.8	−0.6 ± 0.9	<0.001	0.038	0.047
MRI vs. cognitive test time difference (month)	0.3 ± 1.0	8.4 ± 8.0	9.3 ± 9.5	<0.001	<0.001	NS
CGI-S	N/A	4.5 ± 1.3	3.7 ± 1.4	N/A	N/A	0.019
ICV	1.57 ± 0.14	1.61 ± 0.16	1.53 ± 0.17	NS	NS	NS (0.061)
Education	3 ± 1	3 ± 1	3 ± 1	NS	NS	NS
Age of onset	N/A	21 ± 7	19 ± 10	N/A	N/A	NS
Illness duration	N/A	19 ± 10	19 ± 11	N/A	N/A	NS
Depressive episodes	N/A	15 ± 14	30 ± 27	N/A	N/A	0.003
Manic episodes	N/A	3.4 ± 4.6	N/A	N/A	N/A	N/A
Lithium	N/A	36	12	N/A	N/A	0.009
Antiepileptics	N/A	14	7	N/A	N/A	NS
Antipsychotics	N/A	19	3	N/A	N/A	0.008
Antidepressants	N/A	22	16	N/A	N/A	NS
Smoker	13	16	9	0.013	0.041	NS
Moist snuff user	9	13	4	0.012	NS	NS
ADHD	N/A	9	10	N/A	N/A	NS
Alcohol	N/A	7	2	N/A	N/A	NS
Drugs	N/A	4	4	N/A	N/A	NS
Panic disorder	N/A	15	10	N/A	N/A	NS
Social phobia	N/A	7	4	N/A	N/A	NS
OCD	N/A	5	6	N/A	N/A	NS
GAD	N/A	6	4	N/A	N/A	NS
Eating disorder	N/A	3	7	N/A	N/A	0.017
PTSD	N/A	4	1	N/A	N/A	NS
History of psychosis	N/A	39	4	N/A	N/A	<0.001
MADRS	N/A	3 ± 3	4 ± 8	N/A	N/A	NS
YMDRS	N/A	1 ± 2	2 ± 3	N/A	N/A	NS

Demographic and clinical characteristics of controls, BDI, and BDII. Group means ± SD and number of participants are listed respectively. Results of pairwise group comparisons (P-values of t-tests or Fisher's exact Chi^2) are given in the right panels. ADHD, attention-deficit/hyperactivity disorder; BMI, body mass index; CGI-S, Clinical Global Impression Scale; GAD, generalized anxiety disorder; ICV, intracranial volume; OCD, obsessive–compulsive disorder; PTSD, posttraumatic stress disorder; MADRS, Montgomery Åsberg Depression Rating Scale; YMDRS, Young Mania Depression Rating Scale. N/A, not applicable, NS, not significant.

Correlation between cortical thickness and executive function

Controls showed positive correlations between executive function performance and cortical thickness in the right medial superior frontal cortex, and in the left and right inferior precentral cortex extending into the right caudal middle frontal cortex (Fig. 1). Patients with BDII showed corresponding correlations in the right medial superior frontal and bilateral inferior precentral cortex, but also demonstrated positive relationships in bilateral medial occipital regions, as well as in lateral prefrontal cortex. In contrast, BDI showed a positive association with cognitive performance only in a small cluster in the left lateral superior frontal cortex. Overall, no negative correlations were observed.

We observed the same patterns in follow-up and sensitivity analyses where we corrected for demographic and clinical variables. Although this significantly reduced the size of the sample, results and conclusions did not change after excluding cases with a specific medication use or comorbidity type (see Methods for variables tested). Likewise, results remained when we excluded smokers and snuff users from the healthy control group. The results as obtained in Fig. 1 before multiple comparison correction and when correcting for age or education are shown in the Supplementary Material (Figure S1, S2, and S4).

Significant group-by-executive function interactions were observed, revealing clusters in which the correlation between executive function and cortical thickness differed between groups (Fig. 2). Controls and BDII showed greater correlations than BDI in right medial prefrontal regions (see Fig. 2). The positive correlation in left medial occipital regions observed in BDII also differed significantly from that of BDI, where no correlation was found (Figs 2 and S7 for a representative scatter plot). In addition, a BDII>BDI cluster was detected in the right lateral prefrontal area, located in the rostral middle frontal cortex (Fig. 2). We found significant interactions for other regions, but these did not survive the Monte Carlo cluster-wise approach (see Supplementary Material for uncorrected results), for example, clusters in precentral gyrus.

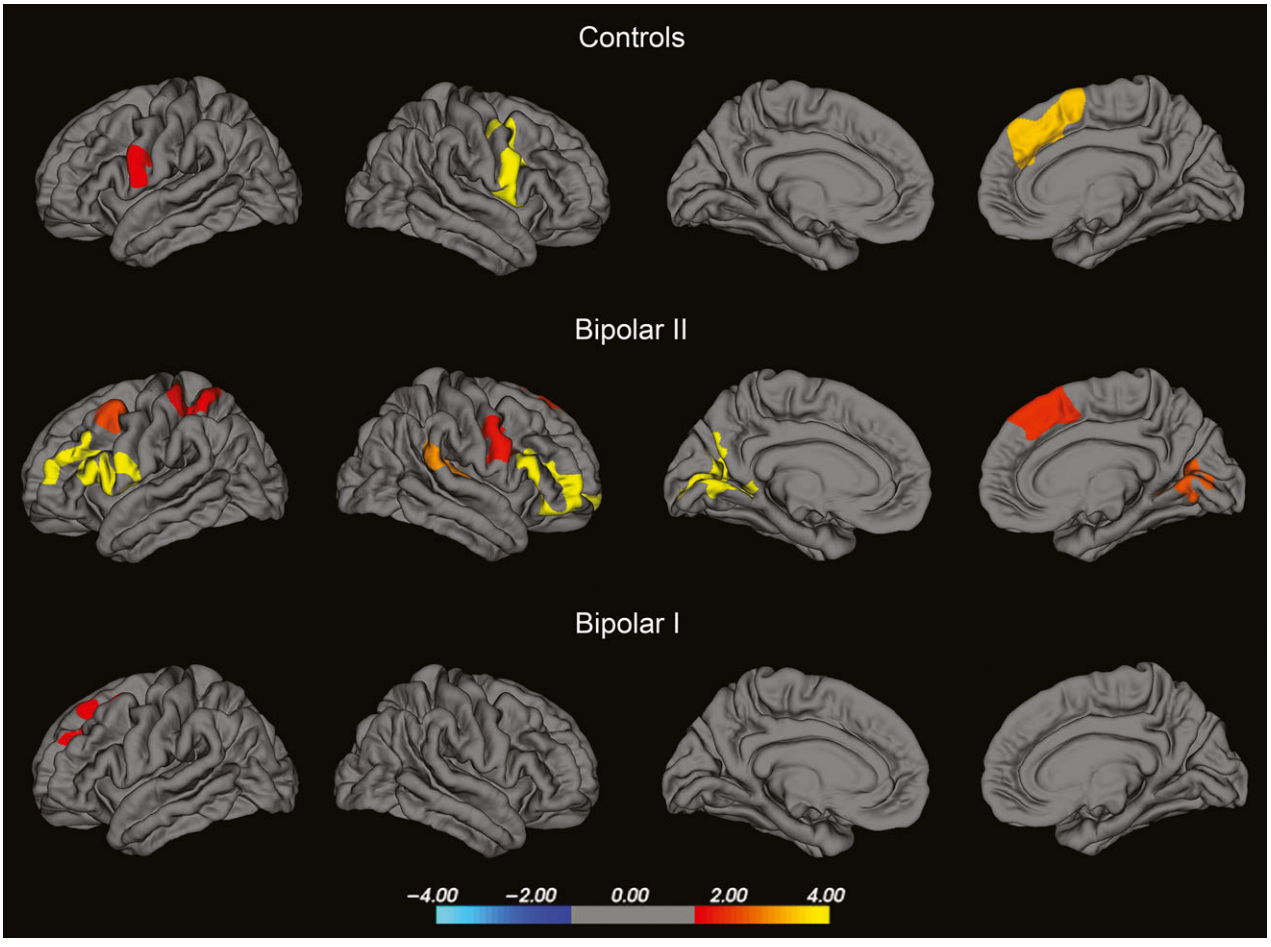

Figure 1. Significant clusters obtained after Monte Carlo cluster-wise simulation in which positive correlations between cortical thickness and executive function performance were found in controls (top), BDII (middle), and patients with BDI (bottom). Significance is represented on a log(*P*-value) scale, where positive values (warm colors) are assigned to positive correlations, and negative values (cold colors) to negative correlations. The latter was not observed. Detailed cluster statistics and corresponding Brodmann areas are given in Table S4. [Colour figure can be viewed at wileyonlinelibrary.com]

Also, the correlations in the precentral gyrus almost diminish when correcting for age and should therefore be treated with caution. Comparing BDII and controls, a significant cluster in left medial occipital regions was observed when correcting for education (see Supplementary Material).

Discussion

In this large clinical study of patients with BDI, BDII, and healthy controls, we investigated the associations between executive function and MRI-derived measures of cortical thickness on a vertex level throughout the whole brain. Better cortical integrity of prefrontal brain regions, as reflected by thicker cortices, was associated with better performance in tasks involving executive functions. This "bigger is better" hypothesis is also supported by a recent meta-analysis demonstrating that thicker cortices of prefrontal brain regions are commonly associated with better executive function performance (11). We found that patients with BDII and controls demonstrated significant associations between executive functioning and cortical thickness in the right medial prefrontal cortex. In patients with BDII, additional regional correlations were observed in lateral prefrontal and medial occipital regions. By contrast, those relationships were not present in patients with BDI, who instead showed a less pronounced association only in a small portion of the left lateral superior frontal cortex. Thus, our results indicate that brain structure–function relationships are altered in bipolar disorder and that the functional relevance of cortical thickness differs regionally between bipolar subtypes.

Studies investigating the relationship between executive function and regional cortical thickness in bipolar disorder and its subtypes are scarce, and

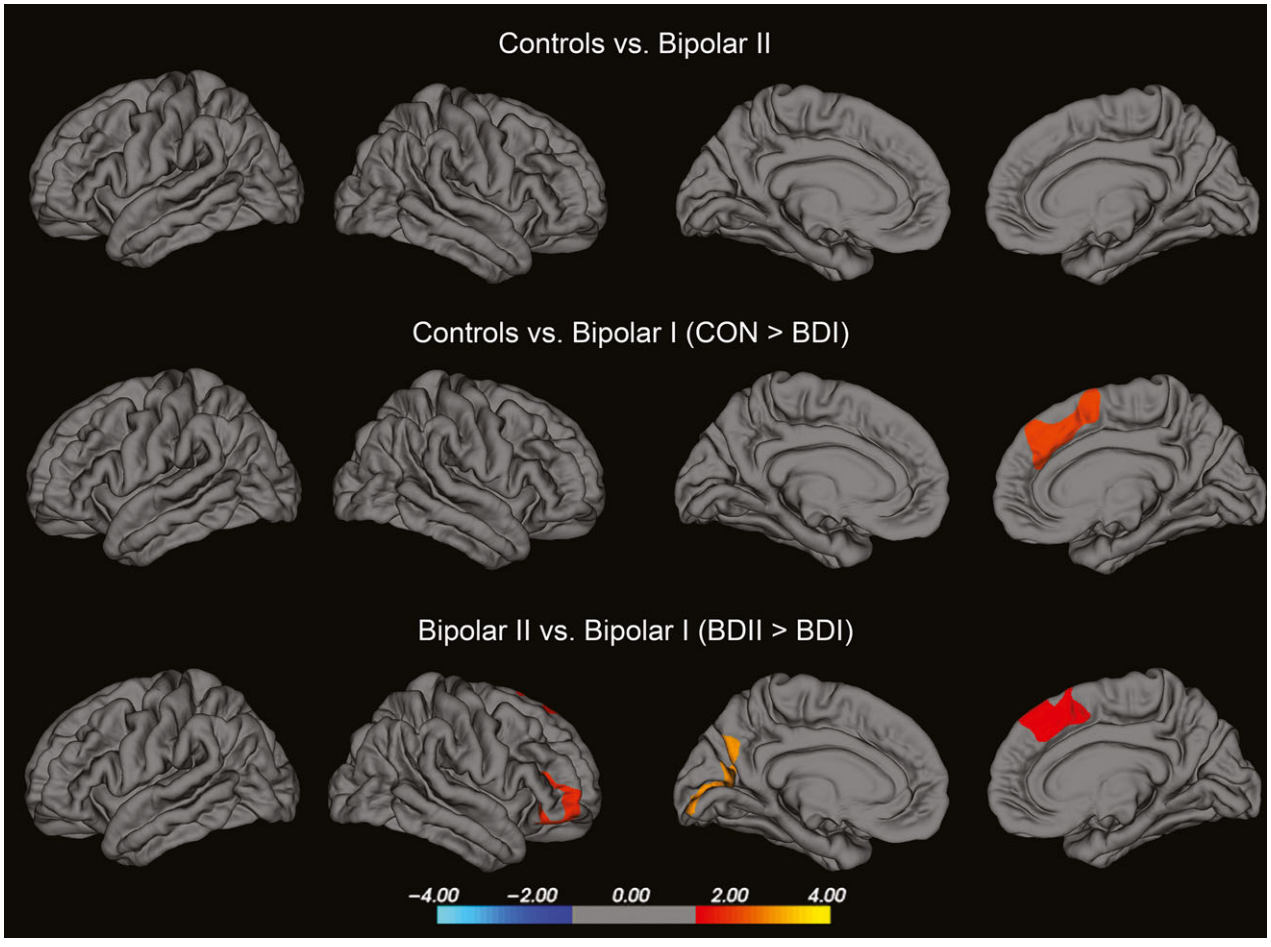

Figure 2. Clusters indicate significant group-by-executive function interactions, where group moderated the relationships between cortical thickness and executive function. Significance is represented on a log(*P*-value) scale, where positive values (warm colors) are assigned to BDII > BDI, controls > BDI, or controls > BDII contrasts. The inverted contrasts were represented by cold colors, however, that was not observed. [Colour figure can be viewed at wileyonlinelibrary.com]

most studies were not able to detect correlations between cortical thickness and executive function (27–30). A common limitation in previous studies has been the use of region of interest (ROI) approaches, in which cortical thickness measures were represented as an average over large predefined brain regions hampering the detection of focal associations. Other limitations include small samples sizes, the combination of bipolar type I and type II patients (27), genetically predisposed control groups (29), or the absence of a healthy control group (30). One study reported a correlation between the outcome of the Tower of London test and cortical thickness in a temporal brain region of patients with BDI, which was not present in controls (28). Although this study supports the idea that regional structure–function relationships differ between patients and controls, the analysis was restricted only to those brain areas in which case–control differences were observed. The results were also specific to one single test, which had an additional mental planning component. Differences in patient characteristics (e.g., shorter illness duration compared to the present study) might have been another reason for discrepancies.

In contrast to previous studies, the here applied vertex-wise whole-brain analysis provided a larger regional resolution, while considering diagnostic subtypes in a large clinical cohort. Not only could this approach reveal focal structure–function relationships in BD where most previous studies failed to detect associations, we were also able to control for demographic variables, comorbid disorders, medication use, and other important clinical variables.

The most striking finding in the present study is that structure–function relationships differed between bipolar disorder subtypes BDI and BDII. Interestingly, the cluster in right medial prefrontal cortex, where we found structure–function relationships in controls and BDII, but not in BDI, corresponds well to areas where previous studies

have shown structural abnormalities in BDI but not BDII (17, 53). The medial prefrontal cortex is a substantial part of the default mode network, and studies investigating its' functional connectivity to other brain areas reported abnormal connectivity patterns in bipolar disorder, suggesting a decoupling between regions of the default mode network (internal/emotional processes) and the task-positive (executive/cognitive processes) network in BD (54, 55). Hence, due to structural impairments, BDI might not fully recruit medial prefrontal areas or networks relying on its' integrity. This could explain why no correlations were observed in medial prefrontal regions of patients with BDI. The distinct correlation patterns are also in line with a functional MRI study that focused on executive function (stroop interference) where bipolar disorder patients failed to activate brain regions associated with task performance in controls (56). Furthermore, we (17) and others (35–38) have found less pronounced cortical abnormalities in BDII than in BDI. To support this notion, we extracted the average cortical thickness from the right medial prefrontal cortex and found that the mean cortical thickness in BDII was in between that of controls and BDI (Table S1). In line with that, the mean executive function score of BDII (Table 1) was also in between that of controls and patients with BDI, which agrees with previous observations that BDII's performance scores were in between those of controls and BDI for some cognitive tasks (2, 3, 5, 33, 34).

The medial prefrontal cortex has been shown to be involved in response inhibition, inhibitory control, and task switching (11, 57–59). Patients with bipolar disorder showed both hypoactivation during response inhibition and reduced thickness in (medial) prefrontal brain regions compared to controls (25). Interestingly, our explorative post hoc analyses of individual D-KEFS subtests indicates that CWIT and TMT (i.e., tasks with a strong inhibition component) may be the tasks driving to the associations with medial prefrontal brain areas in controls and BDII (Figure S9). However, these explorative findings should be regarded as preliminary until replicated in larger samples.

Emerging hypothesis

Leaning on observations of previous studies providing important links between cortical thickness and neural activity in task relevant brain regions (9, 25, 26), the correlations observed could potentially reflect functional involvements, and the observed clusters might overlap with areas of regional activation. One could speculate that if a specific level of structural impairment is reached in a task relevant region (here medial prefrontal cortex), other brain regions might take a compensatory role (as possible in BDII). The additional structure–function relationships observed in lateral prefrontal as well as medial occipital regions of BDII, which were not present in controls, might potentially reflect a compensatory involvement stemming from a failure to recruit medial prefrontal brain regions. Similar cortical dysfunction-related compensation mechanisms in bipolar disorder have also previously been suggested (20). Under the condition that task relevant prefrontal areas are compromised, the integrity of medial occipital (e.g., visual) areas might become more important for task performance given that visual scanning and color processing play important roles in some of the performed cognitive tasks. This might explain the observed structure–function correlations in medial occipital regions of patients with BDII. Intriguingly, in the fMRI study by Strakowski et al., bipolar subjects demonstrated relatively greater activation in the medial occipital cortex compared with controls during a stroop interference task (56), indicating an additional functional involvement as suggested here. Medial occipital areas are also known to be involved in other cognitive domains, such as working memory or mental imagery (60), which might be partly engaged in the test solving strategies of BDII. However, the level of prefrontal impairment at which a compensation could be operative might be exceeded in BDI. At this level of impairment, the compensation could be suspended or interrupted leading to further functional impairment, where cortical thickness is of no functional relevance (no correlation observed). Figure S8 summarizes the here hypothesized relationship between executive function and cortical thickness. Mania-related cortical loss in prefrontal brain regions of patients with BDI (16) could be one possible explanation for a higher cortical impairment in BDI compared with BDII. However, it remains to be elucidated how differences in severity of (hypo)mania or other symptoms are related to the observed differences, or how progressive worsening accompanied by compensation mechanisms explain the different structure–function relationships. Alternatively, previously reported subtype related cortical characteristics could in turn influence how cognitive tasks are processed. Thus, the groups might involve different brain regions to solve the same task without plastic changes being involved. However, the origin of the observed differences remains to be investigated.

In conclusion, our results suggest a positive relationship between prefrontal cortical integrity and executive performance. BDI and BDII

demonstrated regionally distinct structure–function relationships, and corresponding brain areas associated with executive function partly deviated from those showing associations in controls. Our findings are line with previous studies suggesting cortical dysfunction-related compensation mechanisms, and subtype-related neurobiological and cognitive profiles. However, the origin of our observations needs to be elucidated.

The present study contributes to a better understanding of brain structure–function relationships and the neuropathophysiology of bipolar disorder and its' subtypes. Moreover, our conclusions might not be specific to bipolar disorder. Interpreting controls, BDII and BDI as different stages of structural and functional integrity, our results could give important insights into related mechanisms in other psychiatric disorders.

Limitations and outlook

This was a structural MRI study, and thus, the results might suggest, but cannot directly demonstrate, that the discussed regions are recruited in executive function processes. A limitation of the imaging method used is that it cannot reveal mechanisms that underlie individual differences in cortical thickness. The thickness measure per se may depend on the size and number of cells in a column (61), but may also be influenced by other microstructural properties of brain tissue, such as myelination, iron, and water content affecting image contrasts and thereby the derived measures (62). Further, the cross-sectional design cannot distinguish between cortical changes over time or static/premorbid conditions. A clear strength of our study is that we were able to control for demographic variables, comorbid disorders, medication use, and other clinical variables. However, some of the follow-up tests could only be performed after excluding participants using a specific medication or with a specific comorbidity. Thus, the results of those secondary tests should be treated with caution as they were performed on smaller subsamples. Although it is unlikely that our results were confounded by psychiatric comorbidities or pharmacological treatment (63), the question if and how structure–function relationships are affected by medication use can be better addressed in a randomized clinical trial. It is not recommended to adjust for age in structure-function analyses, especially in a clinical sample, where age is related to disease progress and pathology (10, 52). This is because both normal and pathological aging related changes of the cortex resulting in worsening of executive function are important parts of the variance reflecting structure–function relationships. The flip side is that it cannot be excluded that our observations were partly mediated by age (e.g., the associations observed in precentral gyrus). This, however, is unlikely for two reasons: First, we observed correlations with high regional specificity and focal characteristics. This speaks against age as a confounder, as age commonly shows associations widespread over the cerebral cortex. Second, the groups did not differ in age, and no group-by-age interactions were observed. Another facet of this study is that the time difference between MRI scan and cognitive test date was shorter in controls than in patients. However, it is unlikely that the observed group differences, especially between BDI and BDII, are influenced by this. Within this short time range, we do not expect structural brain or cognitive changes to be of a magnitude that significantly influenced structure-function relationships in adult patients with a mean illness duration of 20 years. This is also supported by the fact that the two patient groups did not differ in the time difference, and controlling for it did not change the results.

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Declarations of interest

None.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Uncorrected correlation analysis
Figure S2. Correlations obtained when correcting for education
Figure S3. Group-by-executive function interactions (uncorrected)
Figure S4. BDII vs. controls when correcting for education
Figure S5. Correlations obtained when using age as additional covariate
Figure S6. Correlation in BDII after Monte Carlo correction (age as covariate)
Figure S7. Illustrative scatter plots of pre-frontal structure function relationships
Figure S8. Hypothesized relationship between executive function and cortical thickness
Figure S9. Explorative analysis of correlations between cortical thickness and the D-KEFS subtests CWIT-3, CWIT-4, DFT-3, and TMT-4 in controls, BDII, and BDI
Table S1. Mean differences in cortical thickness
Table S2. Number of participants who completed DKEFS
Table S3. Inter-correlations between DKEFS subtests
Table S4. Cluster summary statistics obtained after Monte Carlo cluster-wise correction and Brodmann areas