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Individualized Structural Brain Deviations in Bipolar I Disorder: a Normative Modeling Study of 4 660 ENIGMA Participants

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Abstract

Bipolar disorder (BD) is a prevalent psychiatric condition characterized by marked clinical and neuroanatomical heterogeneity. Prior neuroimaging studies have used case-control comparisons yielding small to moderate effect sizes for group differences. Large and diverse samples are needed to map heterogeneity within BD. Here, we used individualized brain morphometry deviations derived from normative modeling for three MRI-based measures (regional cortical thickness, regional surface area, and subcortical volumes). We applied this approach to a large international sample of 4 660 individuals (1 145 with bipolar I disorder and 3 515 healthy controls) from the ENIGMA Bipolar Disorder Working Group consortium (age range = 8 - 80, female = 53.15%) and examined the distribution of deviations within the bipolar disorder group, differences between healthy controls and individuals with bipolar disorder, and associations between neuroanatomical deviations and clinical variables. We found that individuals with bipolar disorder showed a higher proportion of localized extreme deviations, notably negative cortical thickness deviations in regions consistently reported as thinner in prior studies (the left superior frontal gyrus, bilateral inferior frontal gyrus (pars opercularis), left precuneus) and subcortical volume negative deviations in the left hippocampus. In addition, ROI-level deviations in the left middle temporal gyrus and the left inferior temporal gyrus were associated with longer illness duration. This is the largest study to date exploring individualized deviations as neuroanatomical features associated with bipolar disorder. Our findings suggest that neuroanatomical heterogeneity is a core feature of bipolar disorder, with preferential left-lateralized cortical-hippocampal involvement pointing to spatially structured heterogeneity.

Introduction

Bipolar disorder (BD) is a common psychiatric disorder characterized by recurrent episodes of mania/hypomania and depression, resulting in significant functional impairment (1). Neuroimaging research has identified both structural and functional alterations across a wide range of brain regions in BD. Functional MRI studies have suggested that BD involves abnormalities in fronto-limbic circuits supporting emotion processing and regulation, including both voluntary and automatic regulatory processes, with disrupted prefrontal modulation of limbic regions contributing to emotional dysregulation (2,3). Although these functional models highlight key circuits involved in emotion regulation, structural MRI studies suggest that neuroanatomical alterations in BD are not restricted to fronto-limbic regions and are instead distributed across multiple cortical and subcortical systems. Recent large-scale studies from the ENIGMA Bipolar Disorder Working Group have found widespread patterns of thinner cortex across frontal, temporal, and parietal regions, including the left pars opercularis, fusiform gyrus, and rostral middle frontal cortex, together with smaller hippocampal and thalamic volumes and enlarged lateral ventricles (4,5).

Nevertheless, several challenges remain for improving the translational impact of neuroimaging study findings (6–8). First, the widespread pattern of thinner cortex in BD from large-scale studies does not identify specific brain regions or circuits that clearly relate to BD clinical features such as illness severity, treatment or future course (5). Second, results from large samples show that BD is associated with small to moderate effect sizes or subtle abnormalities in brain structure (5). Last, despite reproducible group-level brain signatures in BD established by large case-control neuroimaging studies, their translational potential at the individual level remains limited, potentially reflecting the marked clinical and treatment-related heterogeneity of the disorder. Differences in illness course, clinical features, and exposure to psychotropic medications may contribute to, or be associated with, heterogeneity in neuroanatomical features (9–13).

Conventional case-control analyses primarily focus on mean differences and may therefore provide limited insight into inter-individual heterogeneity (14–16). Moreover, classical linear models often rely on assumptions about variance structure, including homoscedasticity, which may be difficult to satisfy in heterogeneous psychiatric populations (17). Moving beyond mean differences may thus better capture inter-individual variability, as illustrated by recent evidence of altered brain-structure variability in schizophrenia spectrum disorders (18), and ultimately contribute to precision psychiatry (19). Examining variability beyond mean differences may therefore help identify both heterogeneous deviation patterns reflecting inter-individual differences and more stable deviation patterns shared across individuals with BD. In classical linear modeling frameworks, extreme observations are commonly interpreted as aberrant values and may be removed to satisfy model assumptions. Such extreme observations may carry clinically relevant information that is obscured by approaches focused on average group effects (14). Normative modeling can therefore complement case-control comparisons by capturing individual-level deviations that may be obscured by average group effects.

In this framework, each individual's neuroanatomical features are compared with values expected from a reference population model, after accounting for covariates such as age, sex, and site. This approach quantifies the extent to which an individual's brain measures deviate from expected normative values, yielding a personalized deviation-based metric analogous to developmental growth charts used in pediatrics. Normative modeling allows individual deviations to be quantified while accounting for biological and technical covariates and

capturing potentially nonlinear relationships between these covariates and brain features (20,21). Moreover, the Bayesian approach used in normative modeling can take into account various sources of uncertainty, enabling predictions at the individual level (15). In neuroimaging, normative modeling has demonstrated potential in psychiatric research by revealing heterogeneity in psychiatric disorders (22–24). Prior studies using normative modeling in BD remain limited. Wolfers et al. (2018) identified grey matter deviations in a transdiagnostic sample including patients with schizophrenia spectrum disorders and bipolar disorder (25). These deviations were distributed across multiple brain regions and showed limited overlap among patients, with only a few loci affected in more than 2% of patients. In the BD subgroup of the discovery sample (N = 190), deviations were mainly observed in cerebellar regions. Across the clinical groups, the study also reported associations between the overall proportion of extreme deviations and cognitive performance and illness duration. Similar results were found in two independent replication samples including 116 and 61 individuals with BD, respectively, with greater overlap in the thalamus and a maximum overlap of only 9% of participants (26). A separate study with 228 BD cases confirmed the heterogeneity of affected brain regions, showing less than 7% overlap but greater overlap when considering deviations within functional networks (27). Capturing the heterogeneity of BD in structural MRI requires large samples to ensure generalizability and to characterize inter-individual variability. However, large-scale studies systematically examining individual-level structural brain deviations specifically in BD remain scarce. Most prior work on brain heterogeneity has focused on transdiagnostic comparisons across psychiatric disorders, while the clinical relevance and generalizability of individual brain deviations within BD remain largely unexplored. This question is critical in real-world neuroimaging settings, where variability in scanners, acquisition protocols, inclusion criteria, and geographic populations poses major challenges to the generalizability of individual-level inferences.

We aimed to disentangle the heterogeneity observed in neuroimaging studies of BD by examining deviations in cortical thickness, surface area and subcortical volume compared to healthy controls. We hypothesized that individuals with BD would exhibit heterogeneous patterns of extreme structural deviations in grey matter across the brain. Specifically, we first characterized the spatial distribution and whole-brain burden of individualized extreme deviations in BD, and then compared deviation burden and ROI-level deviation status between individuals with BD and controls. Finally, we examined whether the magnitude and spatial distribution of grey matter deviations were associated with clinically relevant features of BD.

Methods

Sample

All included patients met criteria for a BD-I diagnosis. Data were initially contributed by 29 independently collected neuroimaging sites participating in ENIGMA-BD (28). One site was not retained prior to analysis after preliminary site-level diagnostic inspection identified a markedly different age-related cortical thickness pattern compared with the other cohorts, leaving 28 sites. Information on diagnostic procedures and medication data collection at each site is provided in Supplementary Table 1.

Participants with MRI data missing due to ENIGMA-standard visual quality control (see *MRI data*) were excluded using feature-specific thresholds determined from the missingness distribution in the present dataset. Specifically, individuals with more than 9% missing cortical thickness regional measures (157 subjects), 10% missing surface area regional measures (245

subjects), or 6% missing subcortical volume regional measures (1080 subjects) were excluded. For SV, this threshold effectively retained participants with at most one missing measure and excluded those with two or more missing measures. These thresholds were chosen to balance data quality and sample retention, and are broadly comparable to prior ENIGMA normative-modeling work using FreeSurfer-derived morphometric measures, which retained scans with <5% missing regional measures or intracranial volume values (29). For subjects with fewer missing values than the predefined cut-off, missing ROI values were imputed using the ROI-specific median computed across all sites, separately for the control training set, the control test set, and the BD sample. Participants with missing diagnosis, age, sex, or site information were also excluded.

For each MRI-derived measure, only sites providing enough control participants to estimate site-specific normative parameters (training set of at least 30 subjects) were retained.

Following recent work using normative modeling as an objective quality-control approach to detect extreme imaging-derived outliers, we applied an additional feature-level QC step (30). Values with an absolute normative-model Z-score ≥ 5 in the control test set and BD sample were treated as extreme non-biological values and replaced with the corresponding ROI-specific median. This step was distinct from the identification of normative deviations, which used the ±1.96 threshold and constituted the main signal of interest.

Because some cohorts did not meet these feature-specific quality-control and minimum-sample criteria, the number of contributing sites differed across measures. An overview of data processing is provided in Supplementary Figure 1.

Table 1. Sample size and demographic characteristics across MRI-derived measures

	Cortical thickness			Surface area			Subcortical volume		
	CTRL (N = 3 515)		BD-I (N = 1145)	CTRL (N = 3 504)		BD-I (N = 1 159)	CTRL (N = 2655)		BD-I (N = 1 070)
	Train (N = 2 812)	Test (N = 703)		Train (N = 2 803)	Test (N = 701)		Train (N = 2 124)	Test (N = 531)	
Age, mean (SD, range)	33.4 (12.4, 8-80)		35.5 (13, 8-80)	33.1 (12.3, 8-72)		34.6 (12.9, 8-67)	32.8 (12.4, 8-80)		35.3 (12.9, 8-80)
	33.5 (12.4, 8-80)	33.1 (12.6, 9-66)		33.2 (12.1, 8-72)	32.9 (12.8, 9-66)		32.7 (12.4, 8-80)	33.3 (12.4, 8-72)	
Female, N (%)	1885 (53.6%)		592 (51.7%)	1875 (53.5%)		600 (51.8%)	1391 (52.4%)		560 (52.3%)
	1505 (53.5%)	380 (54.1%)		1496 (53.4%)	379 (54.1%)		1115 (52.5%)	276 (52%)	

Abbreviations: BD-I, bipolar I disorder; CTRL, control; SD, standard deviation.

MRI data

Detailed acquisition information for the T1-weighted brain MRI data is available in Supplementary Table 2. The T1w images were preprocessed using standard ENIGMA protocols, available at https://github.com/ENIGMA-git. Briefly, cortical measures and subcortical volumes were obtained using FreeSurfer (31), followed by quality checks based on ENIGMA-standard procedures, including outlier detection and visual inspection of all ROIs.

Each site provided MRI-derived features for brain images segmented using the Desikan-Killiany atlas (Desikan et al, 2006) for cortical measures. The atlas includes 68 cortical regions of interest (34 per hemisphere), along with hemisphere-level mean cortical thickness (CTh) and surface area (SA). Subcortical segmentation and extraction of subcortical volumes were conducted using the automatic segmentation of subcortical volumes atlas (ASEG (31)), which included 16 regions (8 per hemisphere).

We conducted our analysis separately for three structural neuroimaging measures: CTh, SA and subcortical volume (SV).

Normative modeling

The normative modeling analyses were conducted using PCNtoolkit (v0.29), with a pipeline adapted from Rutherford et al., 2022 (32). Controls were randomly separated into a training set, containing 80% of participants from each site, and an independent test set including the remaining 20%, used to evaluate model performance. The normative model was estimated only from the control training set and then applied out-of-sample to both the control test set and the BD sample. We tested two normative modeling approaches for each neuroimaging feature: Bayesian linear regression (BLR) and hierarchical Bayesian regression (HBR). For BLR models, age, sex, and site were included as covariates, with intracranial volume additionally included for SA and SV (5). For HBR models, age was included as a covariate, with intracranial volume additionally included for SA and SV, while site and sex were specified as batch effects (33,34). Within the HBR framework, we used a SHASH likelihood for CTh and a standardized Gaussian HBR configuration for SA and SV, based on held-out SMSE and Rho.

Finally, we applied each of our unique ROI-specific normative models to the control test set and to the BD sample to compute a z-score for each subject, corresponding to the measure of the distance between the actual feature value and the expected value while controlling for the subject's covariates. For each ROI, deviation status was defined by identifying values below −1.96 or above 1.96, corresponding to negative and positive deviations from the expected normative value, respectively (i.e., the deviation status). At the whole-brain level, we defined direction-specific whole-brain deviation burden (WDB, table 2), corresponding to the number of ROIs showing either negative or positive deviations (35).

Deviation distribution

We studied the deviation status distribution across the brain for each ROI and each participant of the BD group (table 2). We focused on the percentage of participants presenting deviations at each ROI and computed a ratio of positive to negative deviations per ROI (table 2).

403 **Table 2.** Summary of normative modeling measures

Normative modeling measures	Definition	Interpretation
Deviation status (DS) per ROI	At each ROI, is the z-score < -1.96 (negative deviation) or > 1.96 (positive deviation)	At each ROI, a participant can display a negative or a positive deviation
Whole-brain deviation burden (WDB)	Negative deviation burden: number of ROIs with z-score < −1.96 Positive deviation burden: number of ROIs with z-score > 1.96	Each participant has direction-specific WDB values, corresponding to the number of negative or positive deviations across the brain (between 0 and 70 for cortical measures, and 0 and 16 for subcortical volumes)
Ratio positive / negative	$Deviation\ ratio\ per\ ROI = \frac{Count\ of\ positive\ deviations}{Count\ of\ negative\ deviations}$	Values >1 indicate that positive deviations are more frequent than negative deviations at a given ROI; values <1 indicate that negative deviations are more frequent.

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Statistical analyses

We performed group comparisons for deviation status and deviation burden. Using chi-squared tests and Welch's t-tests, we examined the association between BD diagnosis and DS for each ROI and compared WDB between BD and control groups in the test set.

Associations between normative modeling measures and clinical variables within the BD group were assessed according to the type of imaging-derived and clinical variable. For CTh, clinical association analyses focused on negative deviations, whereas both negative and positive deviations were examined for SA and SV. Clinical variables included illness duration, history of psychotic symptoms, and medication status at the time of the scan, coded as binary variables for lithium, antiepileptics, antidepressants, and second-generation antipsychotics. For ROI-level deviation status, coded as a binary variable, associations with binary clinical variables were tested using chi-squared tests, whereas associations with continuous clinical variables such as illness duration were tested using Welch's t-tests. For WDB, associations with continuous clinical variables were assessed using Spearman's rank correlations, whereas associations with binary clinical variables were assessed by comparing WDB between clinical subgroups using Welch's t-tests. Medication analyses were additionally restricted to participants with complete medication data. For these analyses, WDB was modeled using negative binomial regression to account for overdispersion, whereas ROI-level deviation status was modeled using logistic regression. The first-generation antipsychotic medication variable was not analyzed because of the relatively small number of individuals receiving this treatment (N_{CTh} = 120, N_{SA} = 112, N_{SV} = 121).

Within each MRI-derived feature, p-values from whole-brain deviation burden analyses, ROI-level group comparisons, whole-brain clinical association analyses, and ROI-level clinical association analyses were corrected together using the Benjamini–Hochberg false discovery rate procedure at q = 0.05. Effect sizes are reported as Cohen's d, computed using the original mean-difference formulation (36) when applicable, and as odds ratios otherwise. In the main text, effect sizes, odds ratios and corrected p values are reported only for results that remained significant after correction. Full results are provided in the Supplementary Materials.

Results

Our sample comprised 4 660 individuals, with variation in sample size across MRI-derived features due to the quality control procedures described in Supplementary Figure 1. For CTh, the sample consisted of 3 515 controls (mean age = 33.44 years; 1 885 females [53.63%]) and 1 145 BD (mean age = 35.50 years; 592 females [51.7%]). For SA, the sample comprised 3 504 controls and 1 159 BD, and for SV, 2 655 controls and 1 070 BD. Demographics are described in Supplementary Tables 3-8, including dataset descriptions and train/test set descriptions for each neuroimaging feature.

Normative modeling

For each neuroimaging feature, Bayesian linear and hierarchical Bayesian regressions performed similarly well. Although both algorithms showed comparable test-set performance, we used outputs from the HBR algorithm due to its better capacity to account for site effects in multisite settings (34,37). Using the HBR algorithm, average test-set performance metrics for CTh (figure 1), SA (SF2), and SV (SF3) were: SMSE (Standardized Mean Squared Error)$_{CTh}$ = 0.61 (SD = 0.12) and Rho_{CTh} = 0.62 (SD = 0.09), $SMSE_{SA}$= 0.61 (SD = 0.13) and Rho_{SA} = 0.62 (SD = 0.11), $SMSE_{SV}$= 0.53 (SD = 0.13) and Rho_{SV} = 0.68 (SD = 0.1). All

SMSE values were below 1, indicating good predictive performance of the normative models, in line with prior report (38).

Figure 1

Deviation distribution

For CTh, 62% of participants in the BD group presented at least one negative deviation from the normative model. The mean WDB per participant was 2.95 (SD = 5.03) across the brain. In comparison, 51% of control participants had at least one negative deviation, with a mean WDB of 1.77 (SD = 3.38). In the BD group, 75% of the participants had at least one positive deviation, with a mean WDB of 2.06 (SD = 3.41). In the control group, 72% of the participants had at least one positive deviation, with a mean WDB of 2.06 (SD = 3.21). Deviations were frequent, but locations were inconsistent across individuals in the BD group. The ROI with the greatest overlap in deviations was the left superior frontal gyrus, where approximately 8.5% of individuals with BD showed negative deviations (Supplementary Table 9). The ratio of positive / negative deviations was below 1 for most regions in BD, indicating a general pattern of negative deviations (Figure 2).

For SA, 58% of participants in the BD group presented at least one negative deviation, with a mean WDB of 1.86. The corresponding numbers for controls were 53% and 1.49. 82% of participants in the BD group exhibited at least one positive deviation, with a mean WDB of 2.91. 80% of participants in the control group had at least one positive deviation, with a mean WDB of 2.84. Deviation locations varied across individuals in the BD group, with a maximum overlap of almost 6% for positive deviations, on the left paracentral lobule and the left isthmus cingulate cortex. The ratio of positive / negative deviations was above 1 for most regions in BD, indicating a general pattern of positive deviations (Supplementary Table 10 and Supplementary Figure 4).

For SV, 25% of participants in the BD group presented at least one negative deviation, with a mean WDB of 0.44. 17% of participants in the control group exhibited at least one negative deviation, with a mean WDB of 0.27. 43% of participants in the BD group showed at least one positive deviation, with a mean WDB of 0.83. 39% of participants in the control group presented at least one positive deviation, with a mean WDB of 0.62. SV deviations were also inconsistent across participants, with a maximum overlap of 7% for the left lateral ventricle. Ratios were mostly above 1, indicating a predominance of positive deviations, with especially high values for the lateral ventricles due to the scarcity of negative deviations (Supplementary Table 11 and Supplementary Figure 5).

Figure 2

Association between deviations and diagnosis

For CTh, at the whole brain level, those with BD showed significantly more negative deviations, with a higher WDB compared to controls ($d = 0.26$, $p < 0.01$) (Supplementary Table 12 and Figure 3). When considering each ROI independently, diagnosis was significantly associated with a higher likelihood of a negative deviation in the left superior frontal gyrus (OR = 2.74, $p < 0.01$), pars opercularis (OR = 3.14, $p < 0.01$), and precuneus (OR = 2.88, $p = 0.02$). On the right hemisphere, we found an association, but only for the pars opercularis (OR = 3.14, $p = 0.02$) (Supplementary Table 13 and Figure 3).

For SA, we did not find any significant association between diagnosis and WDB (Supplementary Table 14 and Supplementary Figure 6). When examining deviation status for each ROI, no association remained significant after correction for multiple comparisons (Supplementary Table 15 and Supplementary Figure 6).
For SV, individuals with BD showed a significantly higher WDB than controls for both negative (d = 0.18, p = 0.02) and positive (d = 0.18, p = 0.02) deviations. When examining each ROI separately with the deviation status, we found a significant association between diagnosis and negative deviation status only for the left hippocampus, indicating increased odds of deviation in participants with BD (OR = 4.29, p = 0.018) (Supplementary Table 17 and Supplementary Figure 7).

Figure 3

Clinical variables and deviations
Within the BD group, the presence of a deviation in specific brain regions was associated with longer illness duration compared with the absence of a deviation. This association was observed in the left middle temporal gyrus (d = 0.70, p = 0.018) and the left inferior temporal gyrus (d = 0.87, p = 0.02) (Supplementary Table 18 and Figure 4). No significant association was found between any of the clinical variables, including medications, and WDB (Supplementary Table 19). No ROI-level association between medication status and deviation status survived FDR correction.
For the surface area, we found no significant association between WDB and clinical variables, nor between ROI deviation status and clinical variables (Supplementary Tables 20 and 21).
No significant association was detected between subcortical volume deviations and any of the clinical variables analyzed (Supplementary Tables 22 and 23).

Figure 4

Discussion

This study represents the largest analysis to date applying normative modeling to structural brain features in BD. We investigated individualized deviations across multiple anatomical features, including cortical thickness, cortical surface area, and subcortical volumes. Individuals with BD showed a higher whole-brain burden of negative cortical thickness deviations, and a higher burden of both negative and positive subcortical-volume deviations, compared with controls. At the regional level, negative cortical thickness deviations in frontal and parietal regions were significantly more frequent in BD, and a region-specific subcortical association was observed for the left hippocampus. In addition, the presence of deviations in the left middle temporal and left inferior temporal gyri was associated with longer illness duration.
Although we examined multiple MRI-derived features, we did not identify a single region that consistently deviated from normative models across individuals with BD. Deviations varied substantially between individuals, rarely affecting the same anatomical regions, with a maximum overlap below 10% across participants with BD. This heterogeneous spatial distribution is consistent with prior normative modeling studies showing limited regional overlap of individual deviations in BD and other psychiatric disorders, with maximum regional overlap typically below or around 10% (27,33,39,40). Future studies could apply mixture

modeling to individualized deviation profiles to identify neuroanatomical subgroups and test their clinical relevance (41).

Regional and global deviations from the norm in BD

Only four cortical regions and one subcortical region showed significant deviation differences between BD and controls. The left superior frontal gyrus has previously been implicated in structural abnormalities in BD, including smaller grey matter volumes in prefrontal subregions (42,43). This region is involved in executive functions, including working memory, and is connected to multiple large-scale networks, including cognitive control and default mode networks (44,45). Similarly, the pars opercularis, a subdivision of the inferior frontal gyrus that showed significant deviations bilaterally in our analysis, has been implicated in BD, with evidence of lower grey matter volume and hypoactivation during emotion processing tasks (42,46). It has also been implicated in cortical thinning across BD and schizophrenia, suggesting that alterations in this region may partly reflect neurobiological mechanisms shared across psychotic disorders (47). As a key component of the fronto-limbic network, alterations in this region may contribute to emotion regulation and executive dysfunction in BD (48). The precuneus has also been implicated in BD across neuroimaging modalities, with reports of altered resting-state activity and functional connectivity within the default mode network (42,49). As a central hub of the default mode network, the precuneus is involved in self-referential processes and internally oriented cognition, which may be relevant to rumination and mood dysregulation in BD (50,51). At the subcortical level, the left hippocampus was the only region showing a significant enrichment of negative deviations. As a core limbic structure supporting memory and emotion regulation, the hippocampus is also among the most stress-sensitive regions of the brain (52). Hippocampal volume reduction is one of the most consistently replicated subcortical findings in BD, being most evident in BD-I (4), and has been related to recurrent mood episodes and cumulative illness burden (53).

We propose that the heterogeneous spatial distribution of deviations observed in the BD group may partly reflect underlying clinical and biological heterogeneity, consistent with evidence that BD subphenotypes differ in their clinical and genetic profiles (11). While group-level analyses identified only a limited number of regions, this smaller set may represent recurrent points of convergence within the broader inter-individual heterogeneity of brain alterations in this BD-I sample. Although these localized findings partly overlap with regions previously identified using classical case-control approaches, normative modeling provides complementary information by identifying individuals with extreme deviations from the expected normative range rather than estimating only average group differences. Notably, fewer regions were identified compared with previous studies, but these regions showed large odds ratios, suggesting that the pipeline may highlight regions in which extreme individual deviations recur more consistently in BD. This was most marked for the left hippocampus. For this region specifically, the higher proportion of individuals showing lower-than-expected hippocampal volume suggests that the smaller average hippocampal volumes reported in case-control studies may reflect a higher prevalence of below-expected values across patients rather than a uniform downward shift of the whole group (14). Whether this prevalence reflects a discrete neuroanatomical subgroup or a continuum of increased inter-individual variability remains to be determined and could be tested using the mixture-modeling approaches outlined above (54,55).

Consistent with this interpretation, individuals with BD in our sample exhibited a higher overall number of deviations than controls. Although the effect sizes for WDB were modest, this measure provides information that is complementary to traditional case-control analyses. Rather than identifying regions that differ on average between groups, WDB summarizes, at the individual level, the number of brain regions showing extreme deviations from the expected normative range, even when the specific regions involved overlap little across individuals. Although the total number of deviations provides a quantitative index of brain alterations in BD, its direct clinical applicability remains limited compared with the identification of specific affected regions. Nevertheless, a higher burden of deviations may increase the likelihood of functional disruption within shared neural systems (27).

By examining the ratio of positive to negative deviations, we demonstrated distinct global patterns of deviation across MRI features, with predominantly negative deviations for cortical thickness and predominantly positive deviations for cortical surface area and subcortical volumes. The relative predominance of positive versus negative deviations in SA and SV should be interpreted cautiously, as it may partly reflect residual tail miscalibration. The range of deviation ratios was wider at the subcortical level, with predominantly positive ventricular and negative hippocampal deviations, both potentially consistent with reduced brain tissue volume. The divergent patterns observed between cortical features may appear counterintuitive, as some regions showed negative cortical thickness deviations but positive surface area deviations. However, visual inspection suggested only partial spatial overlap between these CT and SA patterns, with each feature showing relatively consistent directional trends. This dissociation is consistent with evidence that cortical thickness and surface area reflect partly distinct neurobiological dimensions. Surface area has been suggested to be more closely related to early neurodevelopmental and genetically influenced processes, whereas cortical thickness may be more dynamic across the lifespan and more sensitive to environmental, illness-related, and treatment-related factors (56–58). At the subcortical level, individuals with BD carried a higher burden of both negative and positive deviations than controls ($d \approx 0.18$ for each). An elevation of extreme deviations in both directions is consistent with greater inter-individual variability rather than a directional group shift, in line with reports of increased brain-structural variance in BD and related disorders (18) At the regional level, however, deviations remained structure-specific, notably including ventricular enlargement, a well-replicated feature of BD associated with recurrent episodes and illness progression (59,60). Subcortical analyses were nonetheless based on fewer regions and a smaller sample than the cortical analyses, and the subcortical deviation patterns should therefore be interpreted with corresponding caution.

Clinical associations with brain deviations

We found that the presence of deviations in the left middle temporal and the left inferior temporal gyri was associated with longer illness duration. These regions overlap with temporal areas previously implicated in BD cortical abnormalities, and may relate to higher-order visual and socio-emotional processing (5,61). These illness-duration associations may reflect neuroprogressive changes; in this context, “neuroprogressive” refers to illness-related changes that may accumulate over time through recurrent mood episodes, stress-related mechanisms, inflammation, oxidative stress, or altered neuroplasticity, although the cross-sectional design precludes direct inference about progressive brain change (53,62–64). However, results regarding temporal regions have been mixed, with some studies reporting greater grey matter volume (65). Consequently, interpretations of illness duration effects

should be approached with caution, as this variable encompasses a broad and heterogeneous range of clinical trajectories and disease courses (66,67).

We found no association between medication at the time of the scan and deviations in any of the normative modeling features we examined. This contrasts with prior evidence of medication-related structural differences in BD, particularly lithium-associated larger subcortical and grey-matter volumes, which has been interpreted as supporting potential neurotrophic or neuroprotective effects of lithium (4,5,68,69). One possible explanation is that our analyses focused solely on extreme deviations, while previously reported medication effects may arise from more subtle, non-extreme group-level differences. Finally, medication analyses were limited by the availability and granularity of treatment data: medication status at the time of the scan provides only a coarse proxy for treatment exposure, without detailed information on dose, duration, treatment history, or past medication use, and analyses were restricted to cohorts with available medication data.

This study has several key strengths. The large, multisite sample drawn from ENIGMA-BD enhances the generalizability of our findings by applying standardized processing and quality control procedures from geographically distributed MRI data. In addition, we conducted a comprehensive structural neuroimaging analysis across multiple MRI-derived features, encompassing both cortical and subcortical structures. By integrating normative modeling outputs with clinical variables, we identified associations between ROI-level cortical thickness deviations and illness duration, suggesting that individual brain deviations may capture some aspects of cumulative illness exposure, while remaining exploratory.

Several limitations should be considered when interpreting our findings. Our sample was restricted to BD-I, and the generalizability of these findings to BD-II and the broader bipolar spectrum remains to be established. Moreover, this study focused exclusively on structural neuroimaging, which captures only a subset of the neurobiological alterations associated with BD. Future work could extend normative modeling approaches to other imaging modalities, such as functional MRI, where deviations in functional connectivity may provide a complementary, network-level perspective on inter-individual heterogeneity (70). The cross-sectional design limits interpretation of illness-duration associations; longitudinal data could clarify disease-related trajectories by tracking within-individual changes in deviation scores over time (71,72). Longitudinal data would enable a more precise characterization of disease-related trajectories, and advanced methods are currently being developed to quantify dynamic changes in deviation scores and to assess intra-individual progression or normalization over time (72). Finally, effect sizes for statistically significant findings were modest. Although modest effects are common in large-scale neuroimaging studies, their clinical relevance and stability across independent cohorts remain to be established, supporting the need for replication and external validation (73). Given the exploratory scope of the study, spanning multiple MRI-derived features, brain regions, deviation directions, and clinical variables, stringent correction for multiple comparisons was necessary to limit false-positive findings. This approach may have reduced sensitivity to weaker or more distributed associations, particularly in the clinical analyses.

Taken together, our findings indicate that BD is characterized by an increased burden of extreme structural deviations, particularly negative cortical thickness deviations, together with a restricted set of recurrent abnormalities involving frontal and parietal cortical regions

and the left hippocampus. Although this study represents the largest investigation of its kind to date, replication in independent cohorts and validation against clinical outcomes will be necessary to confirm these findings. Individualized brain deviations may represent useful candidate neuroimaging features for capturing neuroanatomical heterogeneity in BD and informing future stratification-oriented research.

Author contributions

N.N. designed the study, performed all analyses, developed the normative-modeling analysis code, and drafted the manuscript. J.H. and C.L. conceived and supervised the study and revised the manuscript. P.F. and E.D. contributed to the study design, methodology, and interpretation of the results. C.R.K.C., M.J.Y.K., Y.I., N.J. and P.M.T. contributed to the ENIGMA Bipolar Disorder Working Group infrastructure and to multi-site data harmonization. All other authors contributed data and/or clinical characterization from their respective cohorts, or to data acquisition and processing. All authors critically reviewed the manuscript, provided intellectual input, and approved the final version.

Data availability

The data that support the findings of this study are not publicly available. In line with the data-sharing policy of the ENIGMA Bipolar Disorder Working Group, individual-cohort neuroimaging and clinical data remain under the control of the respective contributing sites and are governed by the ethics approvals and participant consent obtained locally, which do not permit open data sharing. Requests to access derived data can be directed to the corresponding author and to the relevant site principal investigators, and will be considered subject to the governance, ethical approvals and data-transfer agreements of each contributing cohort. The analysis code used in this study is available from the corresponding author upon reasonable request.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this manuscript, generative AI was used to assist with language editing, clarity, and refinement of manuscript structure and wording.

Conflicts of interest:

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1. Grande I, Berk M, Birmaher B, Vieta E. Bipolar disorder. The Lancet. avr 2016;387(10027):1561-72. doi:10.1016/S0140-6736(15)00241-X
2. Phillips ML, Ladouceur CD, Drevets WC. A neural model of voluntary and automatic emotion regulation: implications for understanding the pathophysiology and neurodevelopment of bipolar disorder. Mol Psychiatry. sept 2008;13(9):833-57. doi:10.1038/mp.2008.65
3. Phillips ML, Swartz HA. A critical appraisal of neuroimaging studies of bipolar disorder: toward a new conceptualization of underlying neural circuitry and a road map for future research. Am J Psychiatry. août 2014;171(8):829-43. doi:10.1176/appi.ajp.2014.13081008 PubMed PMID: 24626773; PubMed Central PMCID: PMC4119497.
4. Hibar DP, Westlye LT, van Erp TGM, Rasmussen J, Leonardo CD, Faskowitz J, et al. Subcortical volumetric abnormalities in bipolar disorder. Mol Psychiatry. déc 2016;21(12):1710-6. doi:10.1038/mp.2015.227 PubMed PMID: 26857596; PubMed Central PMCID: PMC5116479.
5. Hibar DP, Westlye LT, Doan NT, Jahanshad N, Cheung JW, Ching CRK, et al. Cortical abnormalities in bipolar disorder: an MRI analysis of 6503 individuals from the ENIGMA Bipolar Disorder Working Group. Mol Psychiatry. avr 2018;23(4):932-42. doi:10.1038/mp.2017.73 PubMed PMID: 28461699; PubMed Central PMCID: PMC5668195.
6. Savitz JB, Rauch SL, Drevets WC. Clinical application of brain imaging for the diagnosis of mood disorders: the current state of play. Mol Psychiatry. mai 2013;18(5):528-39. doi:10.1038/mp.2013.25
7. Brooks JO, Vizueta N. Diagnostic and clinical implications of functional neuroimaging in bipolar disorder. J Psychiatr Res. 1 oct 2014;57:12-25. doi:10.1016/j.jpsychires.2014.05.018
8. Parker N, Ching CRK. Mapping structural neuroimaging trajectories in bipolar disorder: neurobiological and clinical implications. Biol Psychiatry. 13 févr 2025;0(0). doi:10.1016/j.biopsych.2025.02.009 PubMed PMID: 39956253.
9. Haukvik UK, Gurholt TP, Nerland S, Elvsåshagen T, Akudjedu TN, Alda M, et al. In vivo hippocampal subfield volumes in bipolar disorder-A mega-analysis from The Enhancing Neuro Imaging Genetics through Meta-Analysis Bipolar Disorder Working Group. Hum Brain Mapp. janv 2022;43(1):385-98. doi:10.1002/hbm.25249 PubMed PMID: 33073925; PubMed Central PMCID: PMC8675404.
10. Favre P, Pauling M, Stout J, Hozer F, Sarrazin S, Abé C, et al. Widespread white matter microstructural abnormalities in bipolar disorder: evidence from mega- and meta-analyses across 3033 individuals. Neuropsychopharmacology. déc 2019;44(13):13. doi:10.1038/s41386-019-0485-6

11. Coombes BJ, Markota M, Mann JJ, Colby C, Stahl E, Talati A, et al. Dissecting clinical heterogeneity of bipolar disorder using multiple polygenic risk scores. Transl Psychiatry. 18 sept 2020;10(1):314. doi:10.1038/s41398-020-00996-y
12. Valizadeh P, Cattarinussi G, Sambataro F, Brambilla P, Delvecchio G. Neuroimaging alterations associated with medication use in early-onset bipolar disorder: An updated review. J Affect Disord. 15 oct 2023;339:984-97. doi:10.1016/j.jad.2023.07.098 PubMed PMID: 37481130.
13. Wang X, Tian F, Wang S, Cheng B, Qiu L, He M, et al. Gray matter bases of psychotic features in adult bipolar disorder: A systematic review and voxel-based meta-analysis of neuroimaging studies. Hum Brain Mapp. 1 déc 2018;39(12):4707-23. doi:10.1002/hbm.24316
14. Marquand AF, Rezek I, Buitelaar J, Beckmann CF. Understanding Heterogeneity in Clinical Cohorts Using Normative Models: Beyond Case-Control Studies. Biol Psychiatry. 1 oct 2016;80(7):552-61. doi:10.1016/j.biopsych.2015.12.023 PubMed PMID: 26927419; PubMed Central PMCID: PMC5023321.
15. Marquand AF, Kia SM, Zabihi M, Wolfers T, Buitelaar JK, Beckmann CF. Conceptualizing mental disorders as deviations from normative functioning. Mol Psychiatry. 2019;24(10):1415-24. doi:10.1038/s41380-019-0441-1 PubMed PMID: 31201374; PubMed Central PMCID: PMC6756106.
16. Maccioni L, Giacomel A, Pinamonti M, De Francisci M, Del Pup F, Giubergia A, et al. Quantitative neuroimaging meets normative modelling: the last mile for precision medicine applications. NeuroImage. 1 janv 2026;325:121637. doi:10.1016/j.neuroimage.2025.121637
17. Yang K, Tu J, Chen T. Homoscedasticity: an overlooked critical assumption for linear regression. Gen Psychiatry. oct 2019;32(5):e100148. doi:10.1136/gpsych-2019-100148
18. Omlor W, Rabe F, Fuchs S, Surbeck W, Cecere G, Huang GY, et al. Estimating Multimodal Structural Brain Variability in Schizophrenia Spectrum Disorders: A Worldwide ENIGMA Study. Am J Psychiatry. 1 avr 2025;182(4):373-88. doi:10.1176/appi.ajp.20230806 PubMed PMID: 40007253.
19. Cevoli F, Manji HK, Miller AH, Penninx BWJH, Kas M, Pariante C, et al. Implementing Precision Medicine in Psychiatry. JAMA Psychiatry. 10 déc 2025. doi:10.1001/jamapsychiatry.2025.3562
20. Fraza CJ, Dinga R, Beckmann CF, Marquand AF. Warped Bayesian linear regression for normative modelling of big data. NeuroImage. 15 déc 2021;245:118715. doi:10.1016/j.neuroimage.2021.118715 PubMed PMID: 34798518; PubMed Central PMCID: PMC7613680.
21. Rutherford S, Barkema P, Tso IF, Sripada C, Beckmann CF, Ruhe HG, et al. Evidence for embracing normative modeling. eLife. 13 mars 2023;12:e85082. doi:10.7554/eLife.85082 PubMed PMID: 36912775; PubMed Central PMCID: PMC10036120.
22. Zabihi M, Oldehinkel M, Wolfers T, Frouin V, Goyard D, Loth E, et al. Dissecting the Heterogeneous Cortical Anatomy of Autism Spectrum Disorder Using Normative Models. Biol Psychiatry Cogn Neurosci Neuroimaging. juin 2019;4(6):567-78. doi:10.1016/j.bpsc.2018.11.013 PubMed PMID: 30799285; PubMed Central PMCID: PMC6551348.
23. Zabihi M, Floris DL, Kia SM, Wolfers T, Tillmann J, Arenas AL, et al. Fractionating autism based on neuroanatomical normative modeling. Transl Psychiatry. 6 nov 2020;10:384.

doi:10.1038/s41398-020-01057-0 PubMed PMID: 33159037; PubMed Central PMCID: PMC7648836.
24. Bethlehem RAI, Seidlitz J, Romero-Garcia R, Trakoshis S, Dumas G, Lombardo MV. A normative modelling approach reveals age-atypical cortical thickness in a subgroup of males with autism spectrum disorder. Commun Biol. 4 sept 2020;3(1):486. doi:10.1038/s42003-020-01212-9 PubMed PMID: 32887930; PubMed Central PMCID: PMC7474067.
25. Wolfers T, Doan NT, Kaufmann T, Alnæs D, Moberget T, Agartz I, et al. Mapping the Heterogeneous Phenotype of Schizophrenia and Bipolar Disorder Using Normative Models. JAMA Psychiatry. 1 nov 2018;75(11):1146-55. doi:10.1001/jamapsychiatry.2018.2467 PubMed PMID: 30304337; PubMed Central PMCID: PMC6248110.
26. Wolfers T, Rokicki J, Alnaes D, Berthet P, Agartz I, Kia SM, et al. Replicating extensive brain structural heterogeneity in individuals with schizophrenia and bipolar disorder. Hum Brain Mapp. 1 juin 2021;42(8):2546-55. doi:10.1002/hbm.25386 PubMed PMID: 33638594; PubMed Central PMCID: PMC8090780.
27. Segal A, Parkes L, Aquino K, Kia SM, Wolfers T, Franke B, et al. Regional, circuit and network heterogeneity of brain abnormalities in psychiatric disorders. Nat Neurosci. sept 2023;26(9):9. doi:10.1038/s41593-023-01404-6
28. Ching CRK, Hibar DP, Gurholt TP, Nunes A, Thomopoulos SI, Abé C, et al. What we learn about bipolar disorder from large-scale neuroimaging: Findings and future directions from the ENIGMA Bipolar Disorder Working Group. Hum Brain Mapp. janv 2022;43(1):56-82. doi:10.1002/hbm.25098 PubMed PMID: 32725849; PubMed Central PMCID: PMC8675426.
29. ENIGMA Clinical High Risk for Psychosis Working Group. Normative Modeling of Brain Morphometry in Clinical High Risk for Psychosis. JAMA Psychiatry. 11 oct 2023. doi:10.1001/jamapsychiatry.2023.3850
30. Cirstian R, Forde NJ, Andersson JLR, Sotiropoulos SN, Beckmann CF, Marquand AF. Objective QC for diffusion MRI data: Artefact detection using normative modelling. Imaging Neurosci. 26 avr 2024;2:1-14. doi:10.1162/imag_a_00144
31. Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, et al. Whole Brain Segmentation. Neuron. janv 2002;33(3):341-55. doi:10.1016/S0896-6273(02)00569-X
32. Rutherford S, Kia SM, Wolfers T, Fraza C, Zabihi M, Dinga R, et al. The normative modeling framework for computational psychiatry. Nat Protoc. juill 2022;17(7):1711-34. doi:10.1038/s41596-022-00696-5 PubMed PMID: 35650452.
33. Worker A, Berthert P, Lawrence AJ, Kia SM, Arango C, Dinga R, et al. Extreme deviations from the normative model reveal cortical heterogeneity and associations with negative symptom severity in first-episode psychosis from the OPTiMiSE and GAP studies. Transl Psychiatry. 2 déc 2023;13(1):373. doi:10.1038/s41398-023-02661-6
34. Bayer JMM, Dinga R, Kia SM, Kottaram AR, Wolfers T, Lv J, et al. Accommodating site variation in neuroimaging data using normative and hierarchical Bayesian models. NeuroImage. 1 déc 2022;264:119699. doi:10.1016/j.neuroimage.2022.119699 PubMed PMID: 36272672.
35. Loreto F, Verdi S, Kia SM, Duvnjak A, Hakeem H, Fitzgerald A, et al. Alzheimer's disease heterogeneity revealed by neuroanatomical normative modeling. Alzheimers Dement Diagn Assess Dis Monit. 2024;16(1):e12559. doi:10.1002/dad2.12559

962 36. Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale, N.J:
963 L. Erlbaum Associates; 1988. 567 p.
964 37. Kia SM, Huijsdens H, Rutherford S, de Boer A, Dinga R, Wolfers T, et al. Closing the life-
965 cycle of normative modeling using federated hierarchical Bayesian regression. PloS One.
966 2022;17(12):e0278776. doi:10.1371/journal.pone.0278776 PubMed PMID: 36480551;
967 PubMed Central PMCID: PMC9731431.
968 38. Laidi C, Floris DL, Tillmann J, Elandaloussi Y, Zabihi M, Charman T, et al. Cerebellar
969 Atypicalities in Autism? Biol Psychiatry. oct 2022;92(8):674-82.
970 doi:10.1016/j.biopsych.2022.05.020
971 39. Lv J, Di Biase M, Cash RFH, Cocchi L, Cropley VL, Klauser P, et al. Individual deviations
972 from normative models of brain structure in a large cross-sectional schizophrenia cohort.
973 Mol Psychiatry. juill 2021;26(7):7. doi:10.1038/s41380-020-00882-5
974 40. Shao J, Qin J, Wang H, Sun Y, Zhang W, Wang X, et al. Capturing the Individual
975 Deviations From Normative Models of Brain Structure for Depression Diagnosis and
976 Treatment. Biol Psychiatry. 1 mars 2024;95(5):403-13.
977 doi:10.1016/j.biopsych.2023.08.005 PubMed PMID: 37579934.
978 41. Miettunen J, Nordström T, Kaakinen M, Ahmed AO. Latent variable mixture modeling
979 in psychiatric research – a review and application. Psychol Med. févr 2016;46(3):457-67.
980 doi:10.1017/S0033291715002305
981 42. Chen G, Wang J, Gong J, Qi Z, Fu S, Tang G, et al. Functional and structural brain
982 differences in bipolar disorder: a multimodal meta-analysis of neuroimaging studies.
983 Psychol Med. oct 2022;52(14):2861-73. doi:10.1017/S0033291722002392 PubMed
984 PMID: 36093787.
985 43. López-Larson MP, DelBello MP, Zimmerman ME, Schwiers ML, Strakowski SM.
986 Regional prefrontal gray and white matter abnormalities in bipolar disorder. Biol
987 Psychiatry. 15 juill 2002;52(2):93-100. doi:10.1016/s0006-3223(02)01350-1 PubMed
988 PMID: 12114000.
989 44. Boisgueheneuc F du, Levy R, Volle E, Seassau M, Duffau H, Kinkingnehun S, et al.
990 Functions of the left superior frontal gyrus in humans: a lesion study. Brain. 1 déc
991 2006;129(12):3315-28. doi:10.1093/brain/awl244
992 45. Li W, Qin W, Liu H, Fan L, Wang J, Jiang T, et al. Subregions of the human superior
993 frontal gyrus and their connections. NeuroImage. 1 sept 2013;78:46-58.
994 doi:10.1016/j.neuroimage.2013.04.011
995 46. Mesbah R, Koenders MA, van der Wee NJA, Giltay EJ, van Hemert AM, de Leeuw M.
996 Association Between the Fronto-Limbic Network and Cognitive and Emotional
997 Functioning in Individuals With Bipolar Disorder: A Systematic Review and Meta-analysis.
998 JAMA Psychiatry. 1 mai 2023;80(5):432-40. doi:10.1001/jamapsychiatry.2023.0131
999 47. Knöchel C, Reuter J, Reinke B, Stäblein M, Marbach K, Feddern R, et al. Cortical
1000 thinning in bipolar disorder and schizophrenia. Schizophr Res. avr 2016;172(1-3):78-85.
1001 doi:10.1016/j.schres.2016.02.007
1002 48. Mesbah R, Koenders MA, Van Der Wee NJA, Giltay EJ, Van Hemert AM, De Leeuw M.
1003 Association Between the Fronto-Limbic Network and Cognitive and Emotional
1004 Functioning in Individuals With Bipolar Disorder: A Systematic Review and Meta-analysis.
1005 JAMA Psychiatry. 1 mai 2023;80(5):432. doi:10.1001/jamapsychiatry.2023.0131
1006 49. Xue C, Zhang X, Cao P, Yuan Q, Liang X, Zhang D, et al. Evidence of functional
1007 abnormalities in the default mode network in bipolar depression: A coordinate-based

activation likelihood estimation meta-analysis. J Affect Disord. avr 2023;326:96-104. doi:10.1016/j.jad.2023.01.088
50. Utevsky AV, Smith DV, Huettel SA. Precuneus Is a Functional Core of the Default-Mode Network. J Neurosci. 15 janv 2014;34(3):932-40. doi:10.1523/JNEUROSCI.4227-13.2014
51. Apazoglou K, Küng AL, Cordera P, Aubry JM, Dayer A, Vuilleumier P, et al. Rumination related activity in brain networks mediating attentional switching in euthymic bipolar patients. Int J Bipolar Disord. déc 2019;7(1):3. doi:10.1186/s40345-018-0137-5
52. Brown E. Hippocampal Remodeling and Damage by Corticosteroids Implications for Mood Disorders. Neuropsychopharmacology. oct 1999;21(4):474-84. doi:10.1016/S0893-133X(99)00054-8
53. Berk M, Kapczinski F, Andreazza AC, Dean OM, Giorlando F, Maes M, et al. Pathways underlying neuroprogression in bipolar disorder: Focus on inflammation, oxidative stress and neurotrophic factors. Neurosci Biobehav Rev. janv 2011;35(3):804-17. doi:10.1016/j.neubiorev.2010.10.001
54. Mao J, Wang Z, Wang Y, Jing Y, Wang X, Wang P, et al. Distinct brain functional patterns across the entire disease course between bipolar disorder and major depressive disorder: A Gaussian mixture model analysis. J Affect Disord. déc 2026;415:122474. doi:10.1016/j.jad.2026.122474
55. Brugger SP, Howes OD. Heterogeneity and Homogeneity of Regional Brain Structure in Schizophrenia: A Meta-analysis. JAMA Psychiatry. 1 nov 2017;74(11):1104. doi:10.1001/jamapsychiatry.2017.2663
56. Panizzon MS, Fennema-Notestine C, Eyler LT, Jernigan TL, Prom-Wormley E, Neale M, et al. Distinct genetic influences on cortical surface area and cortical thickness. Cereb Cortex N Y N 1991. nov 2009;19(11):2728-35. doi:10.1093/cercor/bhp026 PubMed PMID: 19299253; PubMed Central PMCID: PMC2758684.
57. Rimol LM, Nesvåg R, Hagler DJ, Bergmann Ø, Fennema-Notestine C, Hartberg CB, et al. Cortical Volume, Surface Area, and Thickness in Schizophrenia and Bipolar Disorder. Biol Psychiatry. 15 mars 2012;Translational Neuroscience Insights into Neuroplasticity Deficits in Schizophrenia71(6):552-60. doi:10.1016/j.biopsych.2011.11.026
58. Bootsman F, Brouwer RM, Schnack HG, Baal GCM van, Schot AC van der, Vonk R, et al. Genetic and environmental influences on cortical surface area and cortical thickness in bipolar disorder. Psychol Med. janv 2015;45(1):193-204. doi:10.1017/S0033291714001251
59. Strakowski SM, DelBello MP, Zimmerman ME, Getz GE, Mills NP, Ret J, et al. Ventricular and Periventricular Structural Volumes in First- Versus Multiple-Episode Bipolar Disorder. Am J Psychiatry. 1 nov 2002;159(11):1841-7. doi:10.1176/appi.ajp.159.11.1841
60. Abé C, Ching CRK, Liberg B, Lebedev AV, Agartz I, Akudjedu TN, et al. Longitudinal Structural Brain Changes in Bipolar Disorder: A Multicenter Neuroimaging Study of 1232 Individuals by the ENIGMA Bipolar Disorder Working Group. Biol Psychiatry. 15 mars 2022;Predicting the Natural History and Treatment Response in Mood Disorders91(6):582-92. doi:10.1016/j.biopsych.2021.09.008
61. Perlman SB, Fournier JC, Bebko G, Bertocci MA, Hinze AK, Bonar L, et al. Emotional Face Processing in Pediatric Bipolar Disorder: Evidence for Functional Impairments in the Fusiform Gyrus. J Am Acad Child Adolesc Psychiatry. déc 2013;52(12):1314-1325.e3. doi:10.1016/j.jaac.2013.09.004

62. Grewal S, McKinlay S, Kapczinski F, Pfaffenseller B, Wollenhaupt-Aguiar B. Biomarkers of neuroprogression and late staging in bipolar disorder: A systematic review. Aust N Z J Psychiatry. mars 2023;57(3):328-43. doi:10.1177/00048674221091731
63. Villa LM, Colic L, Kim JA, Sankar A, Goldman DA, Lessing B, et al. Aging of the brain in bipolar disorder: Illness- and onset-related effects in cortical thickness and subcortical gray matter volume. J Affect Disord. févr 2023;323:875-83. doi:10.1016/j.jad.2022.12.026
64. Marks R, Sankar A, Colic L, Soares J, Radua J, Vieta E, et al. Cortical Thickness in Middle and Older Aged Adults With Bipolar Disorder Across Six International Sites. Bipolar Disord. sept 2026;28(6):e70166. doi:10.1111/bdi.70166
65. Lim CS, Baldessarini RJ, Vieta E, Yucel M, Bora E, Sim K. Longitudinal neuroimaging and neuropsychological changes in bipolar disorder patients: Review of the evidence. Neurosci Biobehav Rev. mars 2013;37(3):418-35. doi:10.1016/j.neubiorev.2013.01.003
66. Birmaher B, Gill MK, Axelson DA, Goldstein BI, Goldstein TR, Yu H, et al. Longitudinal Trajectories and Associated Baseline Predictors in Youths With Bipolar Spectrum Disorders. Am J Psychiatry. sept 2014;171(9):990-9. doi:10.1176/appi.ajp.2014.13121577
67. De La Fuente-Tomás L, Sierra P, Sanchez-Autet M, Arranz B, García-Blanco A, Safont G, et al. A clinical staging model for bipolar disorder: longitudinal approach. Transl Psychiatry. 29 janv 2020;10(1):45. doi:10.1038/s41398-020-0718-9
68. Hallahan B, Newell J, Soares JC, Brambilla P, Strakowski SM, Fleck DE, et al. Structural magnetic resonance imaging in bipolar disorder: an international collaborative mega-analysis of individual adult patient data. Biol Psychiatry. 15 févr 2011;69(4):326-35. doi:10.1016/j.biopsych.2010.08.029 PubMed PMID: 21030008.
69. Hozer F, Sarrazin S, Laidi C, Favre P, Pauling M, Cannon D, et al. Lithium prevents grey matter atrophy in patients with bipolar disorder: an international multicenter study. Psychol Med. mai 2021;51(7):1201-10. doi:10.1017/S0033291719004112 PubMed PMID: 31983348.
70. Oliveira-Saraiva D, Ferreira HA. Normative model detects abnormal functional connectivity in psychiatric disorders. Front Psychiatry. 15 févr 2023;14:1068397. doi:10.3389/fpsyt.2023.1068397
71. Vieta E. Neuroprogression in bipolar disorder: why right is wrong. Psychol Med. juill 2024;54(10):2344-6. doi:10.1017/S0033291724001016
72. Rehak Buckova B, Fraza C, Rehák R, Kolenič M, Beckmann CF, Španiel F, et al. Using normative models pre-trained on cross-sectional data to evaluate intra-individual longitudinal changes in neuroimaging data. eLife. 12 mars 2025;13:RP95823. doi:10.7554/eLife.95823
73. Marek S, Tervo-Clemmens B, Calabro FJ, Montez DF, Kay BP, Hatoum AS, et al. Reproducible brain-wide association studies require thousands of individuals. Nature. 24 mars 2022;603(7902):654-60. doi:10.1038/s41586-022-04492-9

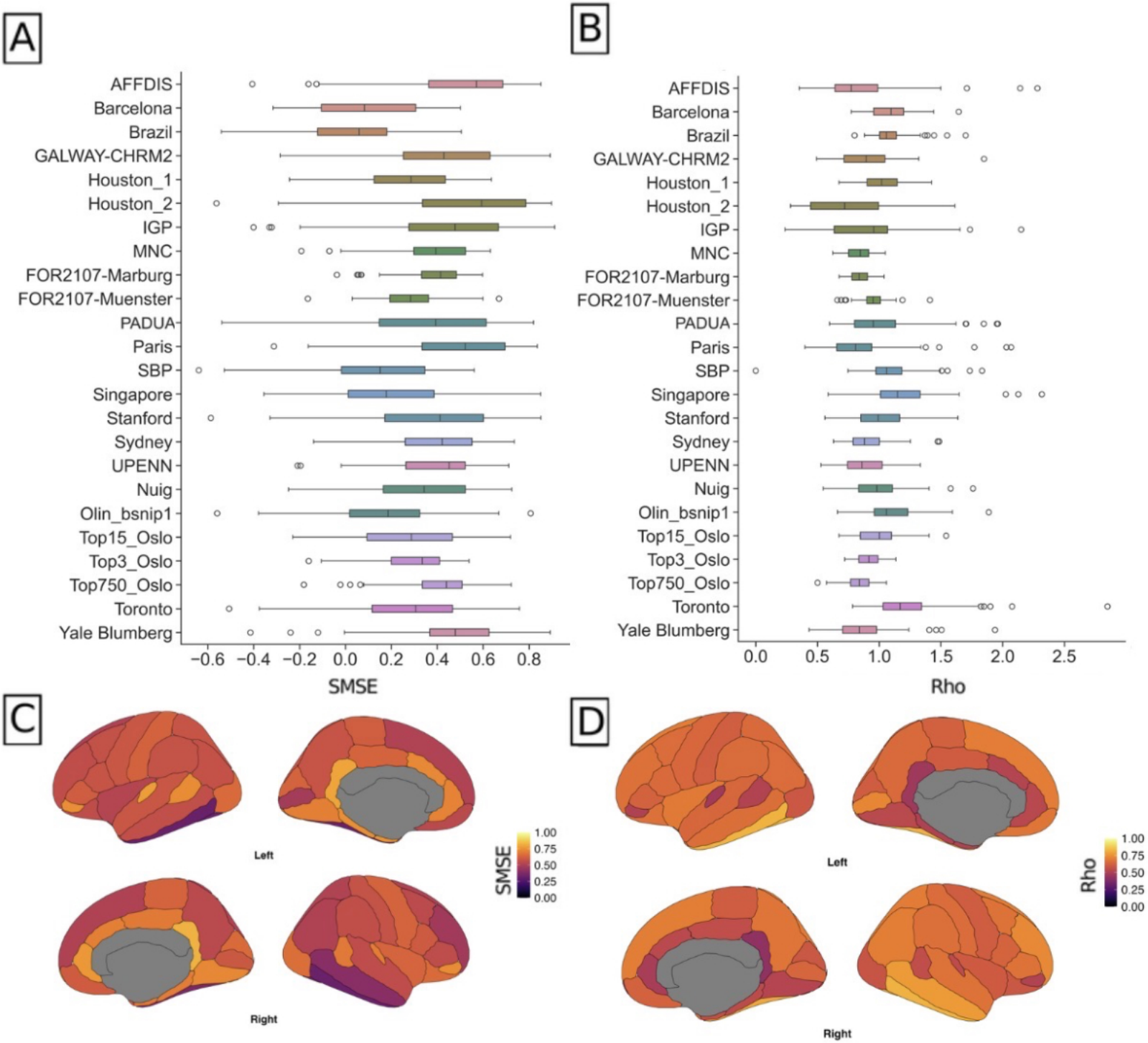
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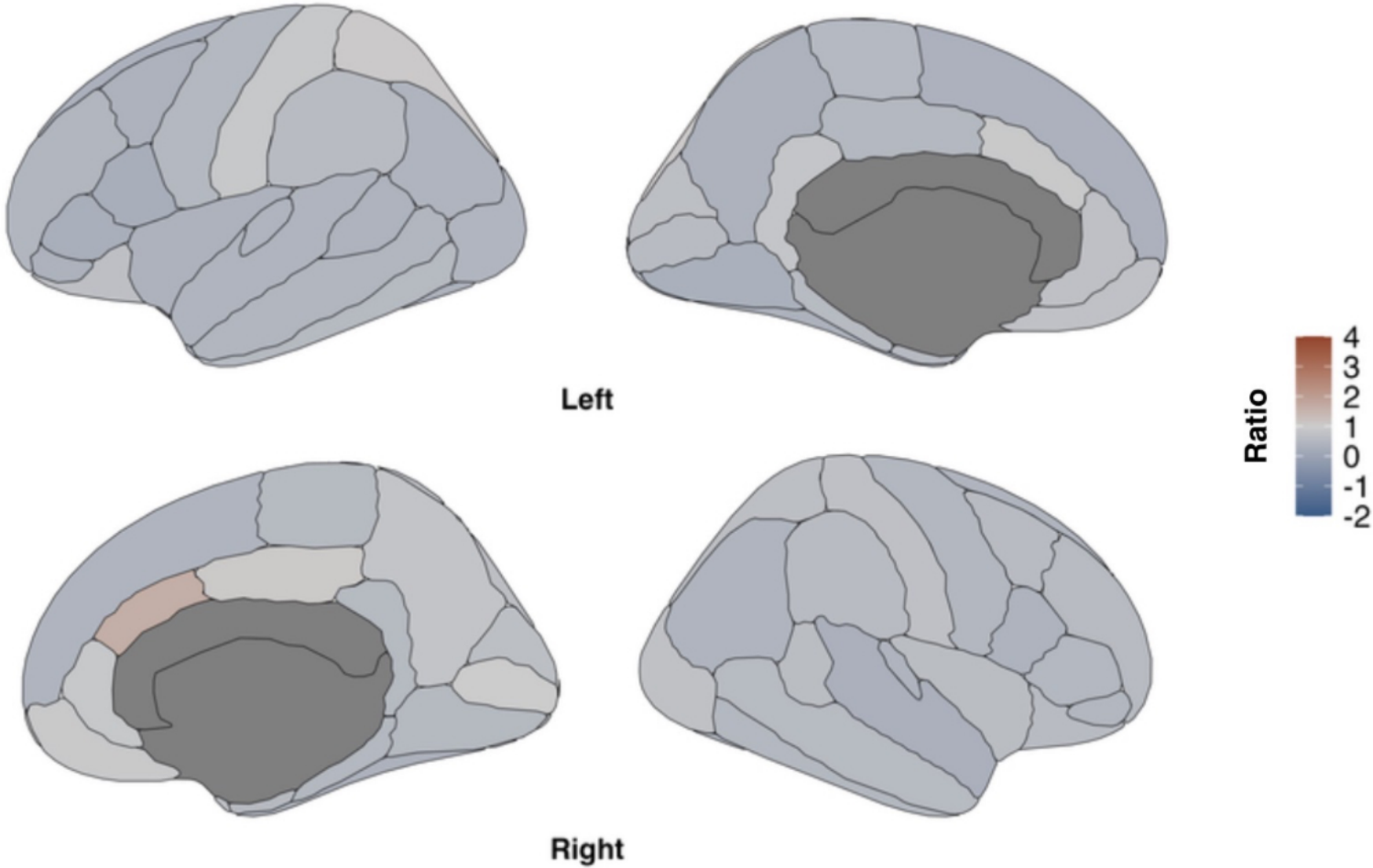
Figure 1. Distribution of HBR model performance metrics for cortical thickness. A and B: distribution across sites for SMSE (A) and Rho (B). C and D: cortical distribution of SMSE (C) and Rho (D).
Abbreviations: HBR, Hierarchical Bayesian Regression; SMSE, Standardized Mean Squared Error.

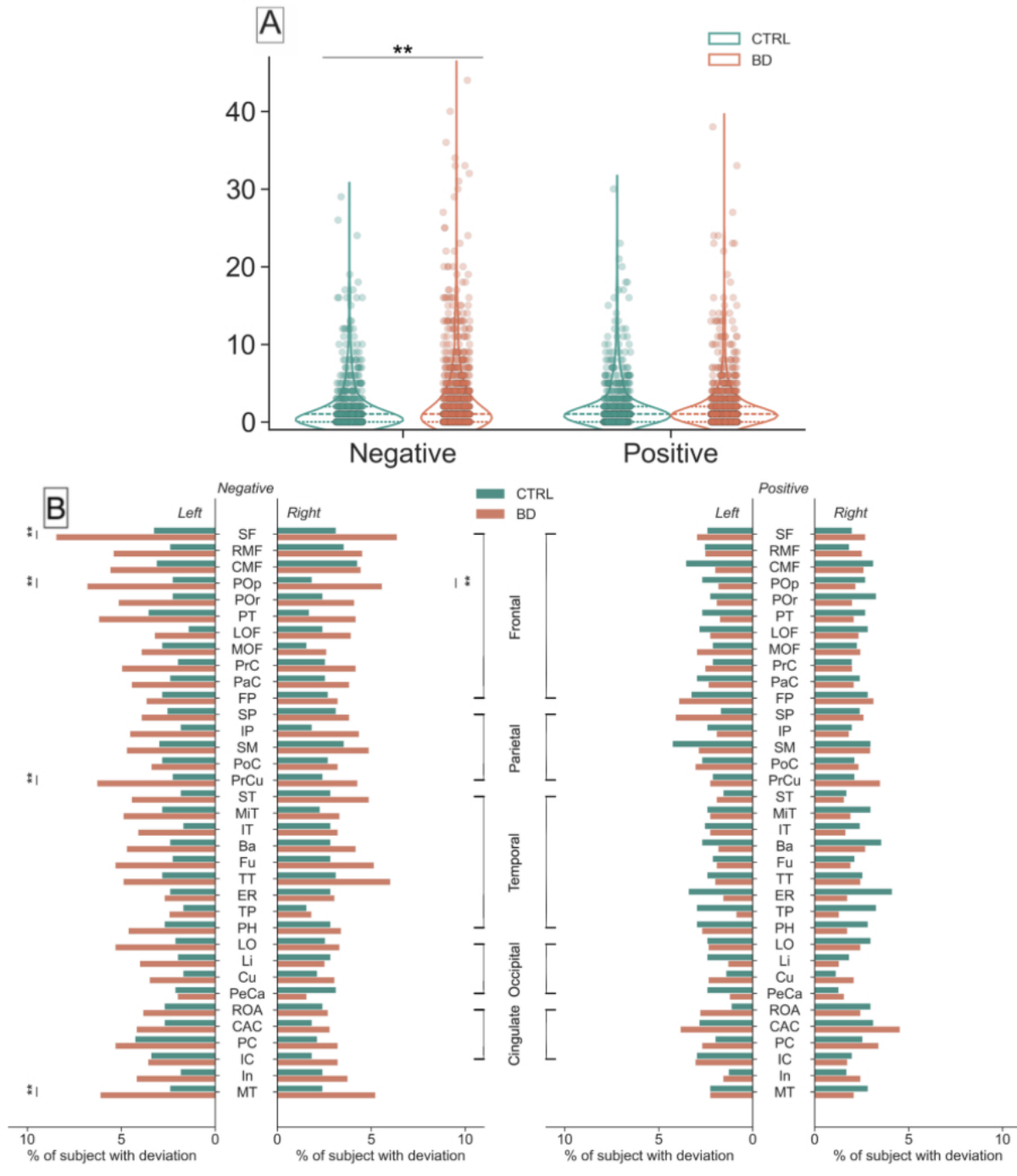
Figure 2. Cortical thickness ratio of positive to negative deviations per ROI for participants in the BD group.

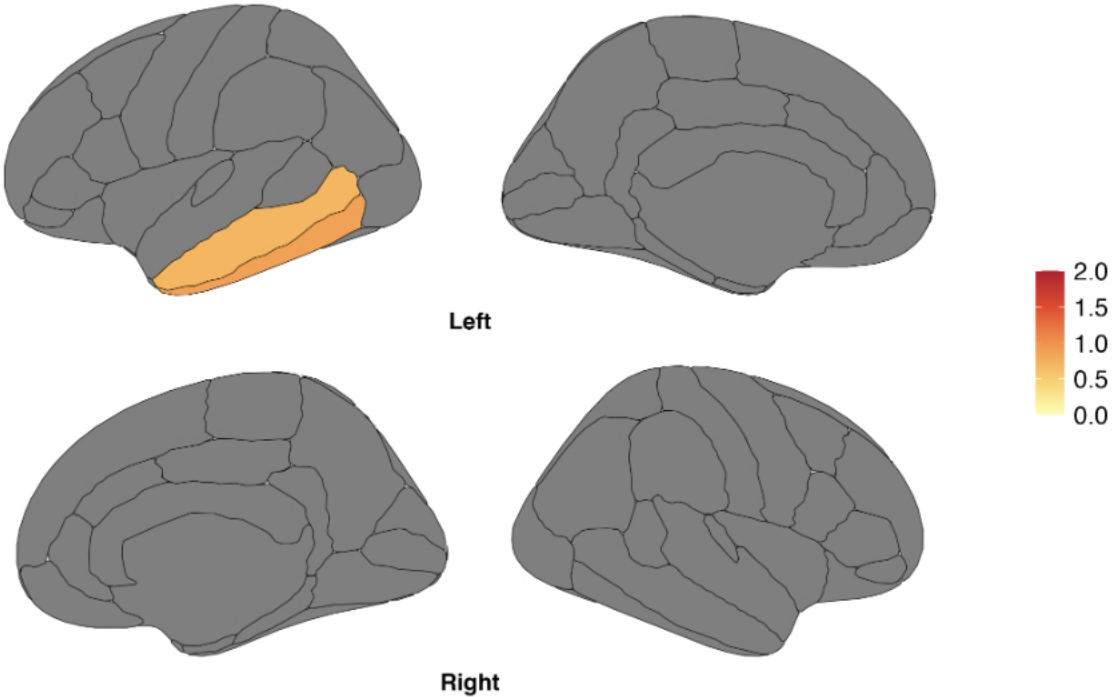
Figure 3. Group comparison of cortical thickness deviations. ** indicates FDR-corrected $p < 0.05$. A. Group comparison for the whole-brain deviation burden across cortical brain regions. B. Group comparison for deviation status at each ROI with the left side of the chart corresponding to the left hemisphere and the right side corresponding to the right hemisphere (left chart for negative deviations and right chart for positive deviations).
Abbreviations: for frontal lobe: SF, superior frontal gyrus; RMF, rostral middle frontal gyrus; CMF, caudal middle frontal gyrus; the three parts of the inferior frontal gyrus with POp, pars opercularis, POr, pars orbitalis and PT, pars triangularis; LOF, lateral orbitofrontal cortex; MOF, medial orbitofrontal; PrC, precentral gyrus; PaC, paracentral lobule; FP, frontal pole. For parietal lobe: SP, superior parietal cortex; IP, inferior parietal cortex; SM, supramarginal gyrus; PoC, postcentral gyrus; PrCu, precuneus cortex. For temporal lobe: ST, superior temporal gyrus; MiT, middle temporal gyrus; IT, inferior temporal gyrus; Ba, banks of the superior temporal sulcus; Fu, fusiform gyrus; TT, transverse temporal cortex; ER, entorhinal cortex; TP, temporal pole; PH, parahippocampal gyrus. For occipital lobe: LO, lateral occipital cortex; Li, lingual gyrus; Cu, cuneus cortex; PeCa, pericalcarine cortex. For cingulate cortex: ROA, rostral anterior cingulate cortex; CAC, caudal anterior cingulate cortex; PC, posterior cingulate cortex; IC, isthmus cingulate cortex. In, insula; MT, mean thickness.

Figure 4. Association between ROI-level deviation status and illness duration in the BD group. Absolute Cohen's d (|d|) is displayed only for regions surviving FDR correction.


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Singapore
Stanford
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UPENN
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Top3_Oslo
Top750_Oslo
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POp
POr
PT
LOF
MOF
PrC
PaC
FP
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ROA
CAC
PC
IC
In
MT
Frontal
Parietal
Temporal
Occipital
Cingulate
10
5
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% of subject with deviation


2.0
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Supplementary Files

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- Supplementaryfigure7.jpg
- Supplementaryfigure1.jpg
- Supplementaryfigure3.jpg
- Supplementaryfigure5.jpg
- Supplementaryfigure4.jpg
- Supplementarymaterial.docx
- Supplementaryfigure6.jpg
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