

Larger putamen in individuals at risk and with manifest bipolar disorder

Original Article

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Abstract

Background: Individuals at risk for bipolar disorder (BD) have a wide range of genetic and non-genetic risk factors, like a positive family history of BD or (sub)threshold affective symptoms. Yet, it is unclear whether these individuals at risk and those diagnosed with BD share similar gray matter brain alterations.

Methods: In 410 male and female participants aged 17–35 years, we compared gray matter volume (3T MRI) between individuals at risk for BD (as assessed using the EPIbipolar scale; $n = 208$), patients with a DSM-IV-TR diagnosis of BD ($n = 87$), and healthy controls ($n = 115$) using voxel-based morphometry in SPM12/CAT12. We applied conjunction analyses to identify similarities in gray matter volume alterations in individuals at risk and BD patients, relative to healthy controls. We also performed exploratory whole-brain analyses to identify differences in gray matter volume among groups. ComBat was used to harmonize imaging data from seven sites.

Results: Both individuals at risk and BD patients showed larger volumes in the right putamen than healthy controls. Furthermore, individuals at risk had smaller volumes in the right inferior occipital gyrus, and BD patients had larger volumes in the left precuneus, compared to healthy controls. These findings were independent of course of illness (number of lifetime manic and depressive episodes, number of hospitalizations), comorbid diagnoses (major depressive disorder, attention-deficit hyperactivity disorder, anxiety disorder, eating disorder), familial risk, current disease severity (global functioning, remission status), and current medication intake.

Conclusions: Our findings indicate that alterations in the right putamen might constitute a vulnerability marker for BD.

Introduction

Bipolar disorder (BD) is a severe and recurrent mental disorder (Pfennig *et al.*, 2020). People with BD are often diagnosed years after the first onset of subsyndromal depressive or manic symptoms (Pfennig *et al.*, 2011). Treatment delay is associated with poorer social and occupational outcome and increased risk for suicide (Joslyn, Hawes, Hunt, & Mitchell, 2016; McCraw, Parker, Graham, Synnott, & Mitchell, 2014; Miller, Dell'Osso, & Ketter, 2014; Post *et al.*, 2010). Improved diagnostic instruments and guidelines for targeted interventions may assist in the prevention and overall disease management of BD (Pfennig *et al.*, 2020).

Potential early risk factors for BD have been identified that predispose the development of the disorder (Marangoni, Faedda, & Baldessarini, 2018; Pfennig *et al.*, 2017), in particular, a positive family history of BD, subsyndromal manic symptoms, or increased cyclothymic mood swings with increased activity (Bechdolf *et al.*, 2012; Duffy *et al.*, 2014; Hafeman *et al.*, 2016). Further risk factors are (sub)threshold affective symptoms, changes in sleep and circadian rhythm, recurrent anxiety, specific personality traits (e.g. heightened creativity), substance abuse (e.g. cannabis), or reduced psychosocial functioning (Duffy, Vandeleur, Heffer, & Preisig, 2017; Faedda *et al.*, 2019). Attention-deficit hyperactivity disorder (ADHD) and major depressive disorder (MDD) are also considered risk factors as they may precede the onset of BD (Faedda *et al.*, 2014; Faedda *et al.*, 2019; Pfennig *et al.*, 2017).

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Depression is more likely to precede BD when additional features, like a positive family history of BD or subclinical manic symptoms, are present (Leopold et al., 2012; Marangoni et al., 2018). Clinical risk assessment tools have been developed to facilitate early identification and intervention for those at risk of developing BD, such as the Bipolar Prodrome Symptom Interview and Scale prospective version (BPSS-P) (Correll et al., 2014), the Early Phase Inventory for Bipolar Disorders (EPI*bipolar*) (Leopold et al., 2012), or the Semistructured Interview for Bipolar At Risk States (SIBARS) (Fusar-Poli et al., 2018).

Using structural magnetic resonance imaging (MRI), patients diagnosed with BD show reduced gray matter volumes (GMVs) of the insula, thalamus, anterior cingulate cortex, inferior frontal gyrus, middle frontal gyrus, superior temporal gyrus, and superior frontal gyrus, and increased volumes of the putamen, precuneus, and posterior cingulate cortex relative to healthy controls (HCs), as evidenced by recent meta-analyses (Gong et al., 2021; Lu et al., 2019b; Yu et al., 2019). Relatives with a positive family history of BD (without a psychiatric diagnosis) have increased volumes of the inferior frontal gyrus, supramarginal gyrus, gyrus rectus, lingual gyrus, and superior temporal gyrus, and decreased volumes of the cerebellum and superior frontal gyrus compared to HCs, according to recent meta-analyses (Cattarinussi, Di Giorgio, Wolf, Balestrieri, & Sambataro, 2019; Zhang et al., 2020). Both relatives with a positive family history of BD and BD patients showed smaller volumes of the orbitofrontal cortex and cerebellum and larger volumes of the inferior frontal gyrus (Eker et al., 2014; Sarıççek et al., 2015); yet, the sample sizes of these studies were small and only familial risk was investigated. Non-genetic risk factors, like subthreshold depressive or manic symptoms or ADHD, are crucial to investigate because only a minority of individuals with a positive family history of BD will eventually develop BD (5–17%) (Craddock & Jones, 1999; Hafeman et al., 2016; Mikolas et al., 2021; Post et al., 2018). To date, no study has investigated shared brain alterations in people at risk with both genetic and non-genetic risk factors as well as patients diagnosed with BD, relative to HCs.

Therefore, we aimed to investigate whether individuals at risk for BD have structural brain alterations that are similar to those observed in patients with BD, relative to HCs. We assessed whole-brain GMV using 3 Tesla MRI in a large sample of young adults, comprising HCs, BD patients, and individuals at risk with various genetic and non-genetic risk factors. These factors included a positive family history of BD, subsyndromal manic symptoms, a lifetime diagnosis of depression or ADHD, and other clinical hints as defined by the EPI*bipolar* scale. We hypothesized that individuals at risk would show the same structural gray matter alterations as patients diagnosed with BD when compared to HCs.

Methods

Participants

In this cross-sectional, case-control study, we analyzed structural MRI data from 410 participants (218 female [53.17%]) aged 17–35 years (mean [s.d.] age, 25.9 [4.3] years) including 208 people at risk for BD, as assessed by the EPI*bipolar* instrument (Leopold et al., 2012), 87 patients with a DSM-IV-TR diagnosis of BD, and 115 HCs, from a total of seven sites.

Participants were included from three cohorts: first, the *Improving early recognition and intervention in people at-risk for development of bipolar disorder* cohort (BMBF BIPOLIFE,

Early-BipoLife; Pfennig et al., 2020; $n = 208$); second, the *Adjuvant psychotherapy in early-stage bipolar disorder* (BMBF BIPOLIFE, study A2; Ritter et al., 2016; $n = 37$); third, the *Marburg-Münster Affective Disorder Cohort Study* (FOR2107/MACS; Kircher et al., 2019; $n = 165$). The first two cohorts stemmed from the BIPOLIFE project, a prospective-longitudinal, naturalistic observational cohort study that focuses on unresolved questions concerning early recognition, diagnosis, treatment, and prognosis of BD (Ritter et al., 2016). MACS is part of the FOR2107, a consortium that investigates the neurobiology of major psychiatric disorders (Kircher et al., 2019).

Both BIPOLIFE studies (Early-BipoLife and study A2) received approval from the Ethics Committee of the Medical Faculty of the Technische Universität Dresden (No: EK290082014) and all local ethics committees. All participants provided written informed consent and obtained financial compensation. Early-BipoLife is registered with www.clinicaltrials.gov under NCT02456545, and study A2 is registered with www.clinicaltrials.gov under NCT02506322 and with German Register of Clinical Studies under DRKS00006013. The FOR2107/MACS study was approved by the local Ethics Committees of Münster (2014-422-b-S) and Marburg (07/14), Germany, in accordance with the Declaration of Helsinki. All participants provided written informed consent before participation and were given financial compensation.

BIPOLIFE cohorts

MRI data were acquired at eight German universities and teaching hospitals with early detection centers and specialized in- and out-patient care in Germany (Berlin, Bochum, Dresden, Frankfurt, Göttingen, Hamburg, Marburg, and Tübingen). Prior to MRI scanning, participants were comprehensively phenotyped with the German version of the structured clinical interview (SCID-I) for the DSM-IV-TR by trained staff (Wittchen, Wunderlich, Gruschwitz, & Zaudig, 1997). In a semi-structured interview, clinical variables were assessed, such as course of illness (i.e. number of lifetime manic and depressive episodes, number of hospitalizations), remission status (using SCID-I), measurements of symptomatology (e.g. Hamilton Depression Scale, HAM-D; Young Mania Rating Scale, YMRS; Hamilton, 1960; Young, Biggs, Ziegler, and Meyer, 1978), and social functioning (Global Assessment of Functioning, GAF; Hall, 1995). BD risk was assessed using EPI*bipolar* (Leopold et al., 2012), which requires the BPSS-P (Correll et al., 2014), the SCID-I, and the assessment of participants' family history of BD. This semi-structured interview assesses a wide range of early and late risk factors for BD and categorizes participants into no-risk, low-risk, and high-risk groups based on main and secondary factors. Primary risk factors of the EPI*bipolar* scale include familial genetic predisposition for BD, elevated cyclothymic mood swings with increased activity, or subthreshold manic symptoms. Secondary risk factors consist of specific sleep and circadian rhythm disturbances, cyclothymic mood swings without activity changes, substance misuse, ADHD, psychosocial impairment, or non-bipolar affective disorder. Low-risk individuals have at least one risk factor but lack a main risk factor, or they have a family history of BD as the only main factor. High-risk individuals have either one main risk factor along with one or more secondary risk factors, or they have more than one main risk factor (for details, see online Supplementary Table S1). For this study, we pooled the low- and high-risk groups into one risk group (i.e. BD-RISK) to test our

hypothesis of shared GMV alterations among individuals at risk and BD patients, relative to HCs.

Participants recruited from the Early-BipoLife study included: (a) help-seeking young individuals without a BD diagnosis who consulted early detection centers and specialized facilities with at least one proposed risk factor for BD, such as family history of BD, (sub)threshold affective symptomatology/depressive syndrome, hypomanic/mood swings, sleep/circadian rhythm disturbances, or other clinical indicators; (b) in-/outpatients diagnosed with depression; or (c) in-/outpatients with a clinically confirmed ADHD diagnosis. At-risk individuals were excluded if they had a diagnosis of BD, schizoaffective disorder, or schizophrenia; anxiety, obsessive-compulsive, or substance dependence disorder that fully accounted for the symptomatology; limited understanding of the study; a minor's implied or expressed negative intent to participate; or acute suicidality (for details, see Pfennig et al., 2020).

A2 study participants were patients diagnosed with BD I or II who had experienced at least one episode in the previous 2 years, were in current stable remission, and received regular medical care, including mood-stabilizing medication. Exclusion criteria were current rapid cycling, acute suicidality, schizoaffective and schizophrenic disorders, ADHD diagnosis, substance use disorder within the past 6 months, antisocial and borderline personality disorders, ongoing psychotherapy, and psychotherapy within the last 6 months (for details, see Ritter et al., 2016).

FOR2107/MACS cohort

BD and HC participants of the FOR2107 study were recruited from the Department of Psychiatry at the University of Marburg, the Institute for Translational Psychiatry Münster, local psychiatric hospitals (Vitos Marburg, Gießen, Herborn, and Haina, LWL Münster, Germany), and through local newspaper ads and flyers. A semi-structured interview was conducted by trained staff using the German version of the SCID-I. Clinical variables were obtained, like the number of episodes, duration of illness, and remission status (according to SCID-I; Wittchen et al., 1997), and psychopathological scales and other rater-based scales were applied (Kircher et al., 2019). Exclusion criteria were a history of neurological or general medical conditions, benzodiazepine use, current substance dependence, and verbal intelligence quotient (IQ) ≤ 80 . Additional exclusion criteria for the HC group involved current or past mental disorders per DSM-IV-TR and lifetime intake of psychotropic medication (for details, see Kircher et al., 2019).

To ensure that the HC group did not share variance with the BD-RISK group, HCs were excluded from this study with subsyndromal depressive or manic symptoms, cyclothymic symptoms, familial risk, and childhood trauma. Depressive and manic symptoms were assessed with the HAM-D and the YMRS; HCs must have had a HAM-D score below 8 and a YMRS score below 3 to be eligible (Hamilton, 1960; Young, Biggs, Ziegler, & Meyer, 2000). Cyclothymic symptoms were assessed with the Temperament Evaluation of Memphis, Pisa, Paris and San Diego – Münster translation (TEMPS-M; Erfurth et al., 2005); HCs must have scored less than four (out of seven) items on the cyclothymic temperament scale. Familial risk was gathered via a questionnaire asking if a first-degree relative had been treated for BD. Environmental risk was evaluated using the childhood trauma questionnaire (Wingenfeld et al., 2010); HCs were not allowed to score above the cut-offs in any of the five scales (Walker et al., 1999). For descriptive statistics of the study participants, see Table 1.

MRI data acquisition and preprocessing

All MRI data were obtained from 3 Tesla MRI scanners with standardized pulse sequence parameters and extensive quality assurance protocols (for an overview, see Vogelbacher et al., 2018, 2021). All participants underwent neuroimaging assessments including high-resolution structural T1-weighted images. MRI data of the BIPOLIFE cohorts were collected using Siemens scanners (Trim Trio, Skyra, Prisma; Siemens Healthineers, Erlangen, Germany), and MRI data of the FOR2107 cohort were collected using Siemens Tim Trio (Marburg) and Siemens Prisma (Münster) scanners, all with standardized procedures (Vogelbacher et al., 2018, 2021). A detailed description of the scanning parameters can be found elsewhere (Stein et al., 2022; Vogelbacher et al., 2021).

We preprocessed data using the Computational Anatomy Toolbox for SPM (CAT12; v1720, Jena University Hospital, Germany) within SPM12 (v7771, Statistical Parametric Mapping, Institute of Neurology, London, UK), running under MATLAB (v2017a, The MathWorks). Default settings (https://neuro-jena.github.io/cat12-help/#major_process) were applied throughout the preprocessing process, which included segmentation, bias correction, affine registration, and tissue classification into gray matter, white matter, and cerebrospinal fluid. Total intracranial volume (TIV) was estimated, and advanced segmentation techniques, such as skull-stripping, brain parcellation, and detecting subtle brain abnormalities, were employed. Spatial normalization was performed using the high-dimensional DARTEL registration algorithm (Ashburner, 2007), and data were normalized to Montreal Neurological Institute (MNI) space. GMV was calculated by modulating gray matter tissue probability maps with the non-linear deformation fields from the DARTEL normalization. For data smoothing, an 8 mm full-width half-maximum Gaussian kernel was used. We conducted individual quality control through the check homogeneity function in CAT12, ensuring that images were free from artifacts and abnormalities.

As recommended by the ENIGMA consortium, the ComBat tool (v1.0.1; <https://github.com/Jfortin1/ComBatHarmonization>) was used in MATLAB (R2017a) to harmonize imaging data from a total of seven sites and two body coil changes performed in June 2016 and August 2018 at the Marburg site. ComBat is an effective tool to harmonize data from different imaging protocols to remove unwanted variation induced by site (Fortin et al., 2017; Mahon, Ghita, Hugo, & Weiss, 2020). This approach estimates the site-related statistical variance using Empirical Bayes, while preserving known or suspected biological or clinical variation in the data, which has been validated by previous large-scale studies. The number of scans per site in the included sites ranged from 19 to 161, adhering to the rule of thumb for the minimum number of participants per site (Fortin et al., 2017). Quality control on all images before harmonization ensured that registration errors had no impact on the harmonization outcomes (Vogelbacher et al., 2018, 2021).

Statistical analyses

Voxel-based morphometry

To identify structural similarities and differences among the three groups (HC, BD-RISK, BD), we compared smoothed GMVs using a 1×3 design in SPM (v7771) operating under MATLAB (R2017a). For these analyses, we adopted the three-way procedure by Brosch et al. (2022). First, we ran analysis of covariance

Table 1. Descriptive statistics of study participants

	HC (<i>n</i> = 115)	BD-RISK (<i>n</i> = 208)	BD (<i>n</i> = 87)	<i>P</i>
Age	27.01 (3.79)	24.71 (4.42)	27.64 (4.17)	<0.001 ^a
Sex, <i>n</i>	F = 67, M = 48	F = 107, M = 101	F = 44, M = 43	0.432
TIV	1540.82 (145.36)	1521.44 (139.87)	1548.25 (144.94)	0.274
Education, years	15.12 (2.27)	13.05 (2.18)	13.17 (2.01)	<0.001 ^b
Remission status	-	a = 69, r = 90	a = 31, r = 50	0.446
Duration of illness, years	-	NA	9.68 (6.22)*	-
Number of depressive episodes	-	4.17 (5.91)	6.15 (7.00)	<0.001
Number of manic episodes	-	-	4.64 (6.02)	-
Number of hospitalizations	-	1.00 (1.27)	2.98 (2.44)*	<0.001
MDD diagnosis, <i>n</i> (%)	-	178 (85.57%)	-	-
ADHD diagnosis, <i>n</i> (%)	-	56 (26.92%)	-	-
Antipsychotic medication, <i>n</i> (%)	-	35 (17.16%)	34 (39.54%)	<0.001
Antidepressant medication, <i>n</i> (%)	-	95 (46.57%)	28 (32.56%)	0.027
Lithium, <i>n</i> (%)	-	7 (3.37%)	29 (33.72%)	<0.001
Stimulants, <i>n</i> (%)	0 (0%)	16 (7.77%)	4 (4.60%)	0.326
HAM-D	0.63 (1.15)	NA	7.02 (5.31)*	<0.001
IDS-C	NA	14.85 (12.09)	7.94 (10.11)**	<0.001
YMRS	0.21 (0.54)	2.61 (3.62)	3.00 (5.24)	<0.001 ^c
GAF	92.82 (6.47)	61.39 (15.66)	64.63 (13.06)	<0.001 ^d
First-degree relative with BD, <i>n</i> (%)	0 (0%)	18 (8.65%)	2 (4%)*	0.270
First-degree relative with MDD, SCZ, or SZA, <i>n</i> (%)	0 (0%)	72 (34.61%)	16 (32%)*	0.680
Comorbidities, lifetime				
Alcohol abuse, <i>n</i> (%)	-	21 (10.09%)	10 (11.49%)	0.741
Cannabis abuse, <i>n</i> (%)	-	26 (12.50%)	2 (2.29%)	0.006
Anxiety disorder, <i>n</i> (%)	-	84 (40.38%)	21 (24.13%)	0.008
Eating disorder, <i>n</i> (%)	-	26 (12.50%)	5 (5.74%)	0.077

Note. All values are given as mean (s.d.) unless otherwise specified. ADHD, attention-deficit hyperactivity disorder; BD, bipolar disorder; BD-RISK, help-seeking individuals at risk for bipolar disorder as defined by the EP**i**bipolar instrument (Leopold et al., 2012); GAF, Global Assessment of Functioning; HAM-D, Hamilton Depression Rating Scale; HC, healthy control; IDS-C, Inventory for Depressive Symptomatology-Clinician; MDD, major depressive disorder; NA, not available (in respective cohort); TIV, total intracranial volume; SCZ, schizophrenia; SZA, schizoaffective disorder; YMRS, Young Mania Rating Scale; a, acute; r, partially or fully remitted (according to SCID-I/DSM-IV-TR); F, female; M, male. *Data were missing for 37 participants in the BD group. **Data were missing for 50 participants in the BD group. *p* Values stem from the χ^2 , non-parametric Mann-Whitney *U*, or Kruskal-Wallis test. Significant post-hoc Dwass-Steel-Critchlow-Fligner pairwise comparisons emerged: aHC > BD-RISK, BD > BD-RISK, HC > BD-RISK and BD; bHC > BD-RISK, HC > BD, HC > BD-RISK and BD; cHC > BD-RISK, HC > BD, HC > BD-RISK and BD; dHC > BD-RISK, HC > BD, HC > BD-RISK and BD.

(ANCOVA) to identify significant differences in GMV between HC, BD-RISK and BD participants using *F*-test in SPM12. Second, in post-hoc *t* test analyses, differences between groups were explored; *p*-values were adjusted for multiple comparisons using Holm-Bonferroni correction. Third, we performed conjunction analyses to test our hypotheses of similarities between individuals at risk and BD patients relative to HCs; conjunction analyses identify an overlap in GMV alterations in two or more respective groups *v.* a control group, using minimum *t*-statistics (Brett, Nichols, Andersson, Wager, & Poline, 2004). For this analysis, we used a region of interest (ROI)-based approach because conjunction analyses tend to be statistically conservative (Brett et al., 2004). For the selection of ROIs, we relied on three recent meta-analyses of BD patients *v.* HCs – the highest level of evidence. We selected these meta-analyses because they employed

different meta-analytic approaches, to ensure a comprehensive coverage of regions associated with BD. According to these meta-analyses, BD patients had decreased volumes of the insula, thalamus, anterior cingulate cortex, inferior frontal gyrus, middle frontal gyrus, superior frontal gyrus, and superior temporal gyrus, and increased volumes of the putamen, precuneus, and posterior cingulate cortex, relative to HCs (Gong et al., 2021; Lu et al., 2019b; Yu et al., 2019). Using these ROIs, we created two masks in the Dartel space Neuromorphometrics atlas using CAT12. One mask for reduced GMVs and one mask for increased GMVs for one-tailed analyses, to test our hypotheses of shared GMV alterations, either decreased or increased (for visualization of selected ROIs, see online Supplementary Fig. S1). In accordance with the CAT12 guideline (<https://neuro-jena.github.io/cat/>), we applied a threshold mask of 0.1 to exclude areas not

pertaining to the brain. We considered results significant if they met $p < 0.05$ peak-level family-wise error correction (FWE) for multiple comparisons, with a threshold of $k \geq 10$ voxels after an initial $p < 0.05$ FWE correction. We labelled significant clusters using the Dartel space Neuromorphometrics atlas. We used the covariates age, sex, and TIV in all analyses (Crowley et al., 2018; Hyatt et al., 2020). Effect sizes were obtained from the t - and F -values and degrees of freedom as provided by SPM12 (Lakens, 2013).

Secondary analyses

In the event we found structural differences among groups, we extracted the weighted means of intensity values of significant clusters of the t test and conjunction analyses as an approximation of GMV. We used these values to assess their relationship with psychiatric diagnoses (i.e. ADHD, MDD, anxiety disorder, eating disorder, alcohol abuse, cannabis abuse), remission status, familial risk (i.e. having a first-degree relative with BD, or MDD, schizophrenia, or schizoaffective disorder), and current medication intake (i.e. antipsychotic, antidepressant, lithium, stimulants) using ANCOVA in Jamovi software (*The Jamovi Project*, 2021). We also investigated the relationship between the weighted means of intensity values of significant clusters and the number of lifetime manic and depressive episodes (both separately), number of hospitalizations, duration of illness, and GAF as a proxy for course of illness and disease severity, respectively, using partial Pearson correlations, or Spearman's rho, for non-normal data. These analyses were run to account for the potential influence of current or past disease severity, familial risk, and medication intake on brain structure (Haukvik et al., 2022; Hozer et al., 2021; Zhang et al., 2020). Additionally, to explore the potential influence of the risk classification of the EPIbipolar scale on our results, we performed exploratory ROI-based conjunction analyses on low- and high-risk groups, separately, and BD patients, compared to HCs. We also assessed the relationship between the significant cluster values and each individual risk factor of the EPIbipolar scale and the cumulative impact of risk factors (i.e. the EPIbipolar sum score) using ANCOVAs and multiple linear regression, respectively. All secondary analyses were accounted for age, sex, and TIV. A two-sided $p < 0.05$ was considered statistically significant. p -Values were adjusted for multiple testing using Holm–Bonferroni correction.

Results

Global effects of GMV among groups

Whole-brain analyses

Two significant clusters emerged comparing GMV differences across groups (i.e. HC, BD-RISK, BD) using F -statistics (see online Supplementary Fig. S2). The first cluster included the left Supplementary motor cortex, $k = 179$, $x/y/z = -10/3/51$, $F_{2,404} = 16.94$, $\eta_p^2 = 0.077$, $p = 0.002$ FWE peak-level, while the second cluster included parts of the right inferior occipital gyrus and right occipital fusiform gyrus, $k = 77$, $x/y/z = 40/-72/-15$, $F_{2,404} = 15.81$, $\eta_p^2 = 0.072$, $p = 0.006$ FWE peak-level.

Distinct GMV alterations among groups

Whole-brain analyses

To identify individual whole-brain differences among groups, we performed post-hoc t test comparisons of GMVs between each

group. Significant differences in GMV between groups emerged. BD patients showed larger GMV in the left precuneus relative to HCs, and individuals at risk for BD showed smaller GMV in the right inferior occipital gyrus, amongst others, relative to HCs. Table 2 shows the post-hoc t test results and Fig. 1 the corresponding significant brain areas.

Shared GMV alterations in BD-RISK and BD groups

ROI analyses

To identify commonly altered structural brain alterations in people at risk for BD and patients with BD relative to HCs, we ran conjunction analyses of the risk and BD groups $v.$ HCs ($HC < BD-RISK \cap HC < BD$) using the ROIs derived from recent meta-analyses (Gong et al., 2021; Lu et al., 2019b; Yu et al., 2019). Conjunction analyses revealed that individuals at risk and patients with BD both had larger GMV in the right putamen relative to HCs, $k = 10$, $x/y/z = 30/-10/0$, $t_{1,404} = 3.93$, $d = 0.391$, $p = 0.036$ FWE peak-level (see Fig. 2; for visualization of significant cluster within the selected ROIs, see online Supplementary Fig. S3). Exploratory whole-brain conjunction analyses revealed a similar pattern (see online Supplementary material 1). No significant shared GMV reductions emerged. For comprehensiveness, FWE cluster-level significant results from exploratory whole-brain analyses are presented in the online Supplementary Table S2. Split-half cross-validation for effect size reliability estimation can be found in online Supplementary Table S3.

Secondary analyses

Using ANCOVAs, we found no significant influence of a lifetime psychiatric diagnosis (i.e. MDD, ADHD, anxiety disorder, eating disorder, alcohol abuse, cannabis abuse), remission status, familial risk, and current medication intake on the extracted means of the identified clusters (see online Supplementary Tables S4 and S5). Applying partial correlations, there was no significant association between the extracted means of the significant clusters and course of illness (i.e. the number of lifetime manic and depressive episodes, number of hospitalizations, duration of illness) and current disease severity (i.e. GAF; see online Supplementary Table S6). Furthermore, main results were not influenced by the high- or low-risk classification (see online Supplementary material 2), the cumulative impact of risk factors (see online Supplementary material 3), nor a specific risk factor of the EPIbipolar scale (see online Supplementary Table S7).

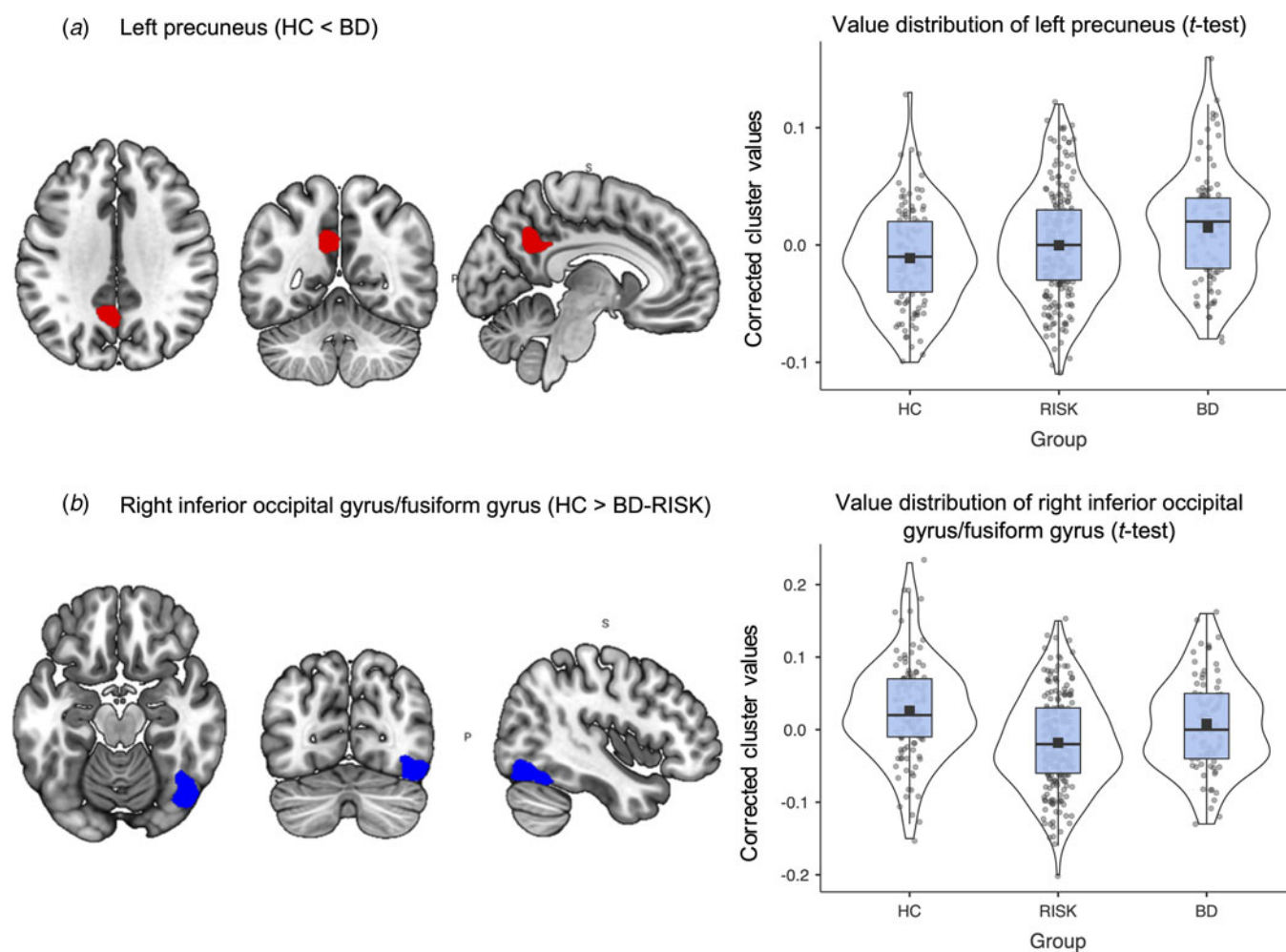
Discussion

In this study, we compared, for the first time, brain structural alterations among individuals at risk for BD, BD patients, and HCs, going beyond the traditional approach of assessing only first-degree relatives as a risk factor. We assessed shared and distinct brain structural alterations in young individuals (aged 17–35 years) with a wide range of genetic and non-genetic risk factors for BD and patients diagnosed with BD, relative to HCs. We found larger GMV in the right putamen in both individuals at risk and patients with BD relative to HCs. Exploratory analyses revealed that individuals at risk for BD had smaller volumes in the right inferior occipital gyrus relative to HCs, while BD patients had larger GMV in the left precuneus relative to HCs. These findings were independent of course of illness, comorbid diagnoses of MDD and ADHD (in individuals at risk) as well

Table 2. Results of FWE peak-level significant post-hoc *t* tests of exploratory whole-brain analyses

	MNI coordinates				<i>T</i>	<i>k</i> cluster	Cohen's <i>d</i>	<i>p</i> FWE peak-level
	H	<i>x</i>	<i>y</i>	<i>z</i>				
HC<BD								
100% Precuneus	L	-12	-57	36	4.99	18	0.497	0.009*
HC>BD-RISK								
86% Inferior occipital gyrus; 14% Occipital fusiform gyrus	R	40	-72	-15	5.27	121	-0.524	0.003*
100% Supplementary motor area	L	-3	2	56	5.14	265	-0.511	0.005*
BD-RISK<BD								
100% Supplementary motor area	L	-12	4	50	4.85	16	0.483	0.016*

Note. R, right; L, left; H, hemisphere; *k*, number of significant voxels per cluster after initial $p < 0.05$ FWE adjustment for multiple testing (i.e. FWE peak-level correction). Only areas $k \geq 10$ voxels are included. Percentages show to what extent the identified clusters lie in the brain regions of the Dartel space Neuroinformatics atlas. *Results were significant after adjustment for multiple testing using Holm-Bonferroni correction.

**Figure 1.** Distinct gray matter volume alterations (whole-brain analyses).

Note. Post-hoc *t* test comparisons revealed (A) larger GMV in the left precuneus in BD patients relative to HCs ($k = 18$, $x/y/z = -12/-57/36$, $t_{1,404} = 4.99$, $d = 0.497$, $p = 0.009$ FWE peak-level), depicted in red, and (B) smaller GMV in the right inferior occipital gyrus/occipital fusiform gyrus in individuals at risk relative to HCs ($k = 121$, $x/y/z = 40/-72/-15$, $t_{1,404} = 5.27$, $d = -0.524$, $p = 0.003$ FWE peak level), depicted in blue. Violin plots depict the jittered distribution of corrected mean intensity values of clusters for each group. For visualization, we show uncorrected clusters at an initial threshold of $p < 0.001$.

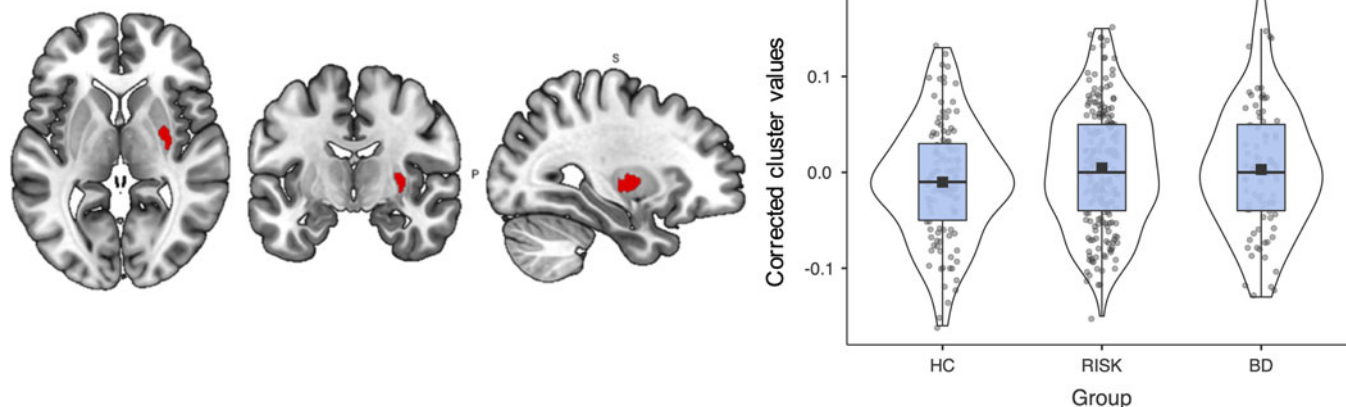
A. Right putamen (HC < BD-RISK \cap HC < BD)

Figure 2. Shared gray matter volume alterations (ROI analyses).

Note. Conjunction analysis (HC < BD-RISK \cap HC < BD) revealed (A) larger GMV in the right putamen in both individuals at risk and with manifest BD relative to HCs ($k=10$, $x/y/z=30/-10/0$, $t_{1,404}=3.93$, $d=0.391$, $p=0.036$ FWE peak-level), depicted in red. Violin plots show the jittered distribution of corrected mean intensity values of clusters within ROIs for each group. For visualization, we show uncorrected clusters at an initial threshold of $p < 0.001$.

as anxiety disorder, eating disorder, alcohol abuse, and cannabis abuse, disease severity, familial risk, and current medication intake.

This study offers three new insights. First, the finding that both individuals at risk and patients with BD had larger GMVs in the right putamen might constitute a vulnerability marker for BD (Gong et al., 2019; Strakowski, DelBello, and Adler, 2005). Together with the caudate nucleus, the putamen forms the dorsal striatum. The putamen receives input from cortical regions that together, with the thalamus, form cortico-striato-thalamic loops (Gong et al., 2019; Haber, 2016). These loops are involved in cognitive, emotional, learning, and motor processes (Ghandili & Munakomi, 2022; Gong et al., 2019; Luo, Mao, Shi, Wang, & Li, 2019; Mulders et al., 2022; Whitton, Treadway, & Pizzagalli, 2015). Alterations of the putamen might lead to an increased liability for cognitive deficits, emotion dysregulation, and impulsive behavior, some of the typical features of BD (Luo et al., 2019; Strakowski et al., 2005; Whitton et al., 2015). Altered putamen volume has been consistently shown in BD (Lu et al., 2019b; Yu et al., 2019), but also in other psychiatric disorders, like MDD, ADHD, anxiety disorder, schizophrenia, post-traumatic stress disorder, or obsessive-compulsive disorder (Gong et al., 2019; Liu et al., 2023; Luo et al., 2019). Gong et al. (2019) found increased putamen volume across patients with MDD, schizophrenia, obsessive-compulsive disorder, and post-traumatic stress disorder, as well as in unaffected relatives with a positive family history of these disorders, relative to HCs. The authors concluded that an increased putamen volume might constitute a transdiagnostic feature of (familial) vulnerability to general psychopathology. However, since our putamen finding was independent of the diagnoses of MDD, ADHD, anxiety disorder, and eating disorder (see online Supplementary Table S5), we can speculate that putamen alterations might be a vulnerability marker specific to BD. This notion is also supported by the evidence that diagnoses of MDD, ADHD, and anxiety disorder were more frequently associated with decreased rather than increased putamen volumes (Liu et al., 2023; Lu et al., 2016; Lu et al., 2019a; Luo et al., 2019; Pan et al., 2023; Sacchet, Camacho, Livermore, Thomas, & Gotlib, 2017; Talati et al., 2022). Since our putamen finding was also independent of familial risk of BD, MDD, schizophrenia,

and schizoaffective disorder (see online Supplementary Table S5), this potential vulnerability marker likely occurred due to a combination of both genetic and non-genetic risk factors for BD. Given the complex and overlapping nature of psychiatric disorders, the risk factors identified in our study could also indicate a susceptibility to a wider spectrum of severe mental illnesses, similar to psychosis risk (Mennigen & Bearden, 2020). However, since our selection of risk factors is specifically tailored to BD, including a family history of BD, specific sleep and rhythm disturbances, and previous depressive episodes, our putamen finding might be a neuroanatomical marker for BD.

Second, the finding that BD patients had increased GMV in the left precuneus relative to HCs might constitute a feature of the current manifest psychiatric disease. Only BD patients had increased volumes of this area but not individuals at risk (Gong et al., 2019). Increased volumes of the precuneus have consistently been shown in BD, as evidenced by a recent meta-analysis (Lu et al., 2019b). The precuneus is part of the superior parietal lobule and is the core node of the default mode network (DMN), which is activated during resting state (Lu et al., 2014). The DMN and particularly the precuneus are related to the recollection of past experiences and self-referential processes, like thinking about oneself and others (Acosta, Straube, & Kircher, 2019; Cabanis et al., 2013; Cavanna & Trimble, 2006; Kircher et al., 2000; Sugiura, 2013; Zhang, Opmeer, Ruhé, Aleman, & van der Meer, 2015). Volumetric alterations of this structure may result in functional imbalances of the DMN that could lead, in part, to the deficits observed in patients with BD (Long, Qin, Wu, Li, & Zhou, 2022), like increased rumination (Zhao et al., 2021), poor cognitive performance (e.g. difficulties in staying focused on a given task) (Long et al., 2022; Whitfield-Gabrieli & Ford, 2012), and reduced social functioning (i.e. interpersonal, social, and workplace-related dysfunction) (Espinós, Fernández-Abascal, & Ovejero, 2019; Whitfield-Gabrieli & Ford, 2012; Zhang et al., 2015). In contrast to our study, the ENIGMA studies, which focused on subcortical volume and cortical thickness changes in BD compared to HCs, did not find alterations of the precuneus (Hibar et al., 2018, 2016). This discrepancy may be due to several methodological differences. First, Hibar et al. (2016, 2018) used a less stringent false discovery rate correction, which may have

identified more widespread but less focal changes across the brain, which is in contrast to our more stringent approach of localized differences. Second, their focus on specific ROIs of cortical thickness and subcortical structures contrasts with our whole-brain GMV analysis using voxel-based morphometry. Third, the older participant age in the ENIGMA study (HC: mean = 36.79, s.d. = 12.26; BD: mean = 39.97, s.d. = 11.89) compared to ours (HC: mean = 27.01, s.d. = 3.79; BD: mean = 27.64, s.d. = 4.17) may have led to the observed differences in brain alterations, given the progressive nature of BD (Abé et al., 2022). Lastly, the pooling of many studies from different countries in the ENIGMA analyses may have increased the variability of the data compared to our study.

Third, individuals at risk for BD showed reduced GMV in the right inferior occipital gyrus. In functional MRI studies, neocortical visual areas, like the inferior occipital gyrus, and limbic regions, like the amygdala, have been linked to the visual processing of faces (Sato et al., 2017). Abnormal activation of these areas has been found in patients with BD and was linked to impaired processing of emotional faces (Gong et al., 2020; Miola et al., 2022; Phillips, Drevets, Rauch, and Lane, 2003). Abnormalities of this structure may be, in part, associated with impaired social functioning in patients with BD (Brotman et al., 2008; Gong et al., 2020; Phillips et al., 2003). To date, only one MRI study of bipolar risk assessed structural brain alterations in people at risk for BD beyond the approach of assessing only first-degree relatives (Mikolas et al., 2021). In an ROI-based approach using Freesurfer, Mikolas et al. (2021) showed that help-seeking individuals with more concurrent genetic and non-genetic risk factors for BD had a thinner cortex in the left pars opercularis of the inferior frontal gyrus relative to help-seeking individuals with fewer risk factors. Yet, this study did not assess shared structural GMV alterations among individuals at risk and patients with BD relative to HCs using voxel-based morphometry, which our study is the first to investigate.

A potential limitation of this study is the combined analysis of data from different cohorts. Unwanted systematic differences in data collection between the three cohorts and seven sites might have introduced variance in our results despite standardized data collection practices (Vogelbacher et al., 2018, 2021) and harmonization of scanner differences using ComBat (Fortin et al., 2017); however, large participant numbers are only possible with multi-centric studies and combination of cohorts. Second, the thorough screening of the HC group may limit the generalizability of our results; yet, this approach ensured that HCs and individuals at risk shared only minimal variance, enabling the detection of potentially true differences in GMV associated with BD risk. Third, because of the cross-sectional nature of the present study, we cannot make inferences about the causality of the observed findings. Fourth, since we analyzed MRI data cross-sectionally, sampling variability might obscure future results (Marek et al., 2022). Future studies should assess the data longitudinally to enable inferences about the direction, functionality, and robustness of the observed findings.

Conclusion

Our work indicates that increased putamen volume might be a vulnerability marker for BD. Our study provides data from a large sample of young people with a wide range of genetic and non-genetic risk factors and BD patients, at an age when transition to BD is likely (Solmi et al., 2022). Our findings provide new insights into the neural pathomechanisms of BD.

Supplementary material. The supplementary material for this article can be found at <https://doi.org/10.1017/S0033291724001193>.

Data availability statement. The data that support the findings of this study are available from the corresponding author (F. T.-O.) upon reasonable request.

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Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and

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