Contribution of common genetic variants to disease status and symptom dimensions in affective and psychotic disorders

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From the Institute of Human Genetics

This work is dedicated to anyone struggling with affective or psychotic disorders.

And to my mother, Eva David, for her unshakeable faith in my ability to succeed.

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List of Abbreviations

BD	Bipolar disorder
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
GWAS	Genome-wide association study
GWS	Genome-wide significant
h^2_{SNP}	SNP-based heritability
IHME	Institute for Health Metrics and Evaluation
MD	Major depression
MDD	Major depressive disorder
PGC	Psychiatric Genomics Consortium
PRS	Polygenic risk score
RDoC	Research Domain Criteria
SCZ	Schizophrenia
SNP	Single nucleotide polymorphism
SSD	Schizophrenia spectrum disorder
YLDs	Years lived with disability

1 Abstract

Affective and psychotic disorders, such as major depressive disorder (MDD), bipolar disorder (BD), and schizophrenia spectrum disorders (SSD), represent complex psychiatric conditions with a moderate to high heritability. Throughout the last decade, genome-wide association studies (GWAS) have demonstrated the association of many common genetic variants with disease risk. However, the pathophysiological mechanisms of affective and psychotic disorders are still incompletely understood and it is expected that many more disease-associated genetic loci await identification. Moreover, while the different affective and psychotic disorders are considered distinct entities by current diagnostic systems, they exhibit notable phenotypic overlaps and substantial genetic correlations. This suggests that etiological processes may be partially shared between diagnostic groups. Against this backdrop, the three studies included in this thesis were conducted to improve our understanding of the role of common genetic variation in affective and psychotic disorders. In particular, in the first and second study, the contribution of common genetic variants to symptom dimensions of acute and lifetime psychopathology observed across MDD, BD, and SSD was examined. In the third study, the largest GWAS meta-analysis of BD to date was conducted, which revealed novel disease-associated loci and provided insights into the underlying pathobiology via a plethora of GWAS downstream analyses. Altogether, the results of this research expand our knowledge on the complex relationships of common genetic variants with disease status and symptom dimensions within and across affective and psychotic disorders.

2 Introduction

According to the Global Burden of Disease 2021 Study (Institute for Health Metrics and Evaluation (IHME), 2024), mental disorders are among the top ten leading causes of health loss worldwide. Relative to the total number of years lived with disability (YLDs) across all causes in 2021, major depressive disorder (MDD) accounted for 5.1 %, schizophrenia (SCZ) for 1.7 %, and bipolar disorder (BD) for 0.9 % of total YLDs (Institute for Health Metrics and Evaluation (IHME), 2024). The high relevance of mental disorders can be explained, amongst others, by their frequent occurrence, with reported lifetime prevalences of around 14 % for MDD, around 2 % for BD, and around 0.5 % for SCZ (Kessler *et al.*, 2012; McGrath *et al.*, 2008; Merikangas *et al.*, 2011).

MDD, BD, and SCZ represent types of affective and psychotic disorders, for which diagnostic criteria are provided by classification systems such as the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5, American Psychiatric Association, 2013). As affective disorders, MDD and BD are characterized by severe disturbances in mood that cause substantial impairments in an individual's occupational or social functioning. In MDD, individuals experience one or more major depressive episodes, marked by symptoms such as low mood, loss of interest, and changes of appetite or sleep (Marx *et al.*, 2023). The main types of BD are characterized by episodes of mania, which typically alternate with major depressive episodes, (bipolar I disorder) or by hypomania in combination with at least one major depressive episode (bipolar II disorder). During manic episodes, individuals experience an abnormally elevated or irritable mood, with symptoms such as inflated self-esteem, reduced need for sleep, distractibility and excessive activity (Vieta *et al.*, 2018). In SCZ, symptoms of psychosis are prevailing, with delusions, hallucinations, disorganized thinking, disorganized or abnormal motor behavior, and negative symptoms as the five key symptom domains (Kahn *et al.*, 2015).

The etiology of MDD, BD, and SCZ is multifactorial, with a contribution of both environmental and genetic factors. Twin and family studies have estimated a heritability, i.e., proportion of phenotypic variance explained by genetic factors, of around 37 % for MDD (Sullivan *et al.*, 2000), 60 % to 85 % for BD (Johansson *et al.*, 2019; McGuffin *et al.*,

2003), and 73 % to 90 % for SCZ (Sullivan *et al.*, 2003). The underlying genetic architecture of these disorders is complex and highly polygenic. Genetic variants across the allelic spectrum have been implicated (Kendall *et al.*, 2021; Sullivan *et al.*, 2012). Recent large-scale exome sequencing studies have substantiated the role of rare variants in MDD, BD, and SCZ (Palmer *et al.*, 2022; Singh *et al.*, 2022; Tian *et al.*, 2024). An in-depth discussion of rare-variant studies is, however, beyond the scope of this introduction, as the focus of this dissertation lies on common genetic variation.

Common genetic variants, often defined based on a minor allele frequency above 1 % in the general population, and in particular single nucleotide polymorphisms (SNPs), have been shown to play an important role in affective and psychotic disorders by means of genome-wide association studies (GWAS). As the detection of small effect sizes requires large samples to obtain sufficient statistical power, a major breakthrough in understanding the contribution of common variants to disease risk could only be achieved through large-scale GWAS meta-analyses conducted by international consortia such as the Psychiatric Genomics Consortium (PGC, Sullivan, 2010; Sullivan *et al.*, 2018). The most recent GWAS meta-analyses of affective and psychotic disorders led by the PGC, including the GWAS meta-analysis of BD that is part of this dissertation, are listed in Table 1.

***Table 1**: Most recent GWAS meta-analyses of affective and psychotic disorders conducted by the PGC*

Disorder	Reference	# Cases	# Controls	# GWS SNPs
MD	Adams *et al.* (2025)	688,808	4,364,225	697
BD	O'Connell *et al.* (2025)	158,036	2,796,499	337
SCZ	Trubetskoy *et al.* (2022)	76,755	243,649	342

BD, bipolar disorder; GWAS, genome-wide association study; GWS SNPs, independent genome-wide significant (i.e., association $p < 5 \times 10^{-8}$) single nucleotide polymorphisms; MD, major depression; PGC, Psychiatric Genomics Consortium; SCZ, schizophrenia; #, number of.

Most disease-associated common variants are thought to act in an additive manner. This enables the calculation of polygenic risk scores (PRS) based on GWAS findings as weighted sums of risk alleles carried by an individual, reflecting part of the susceptibility to disease (Lewis, Vassos, 2020). PRS are a widely used research tool for studying the association of genetic risk conferred by common variants with various phenotypic and biological measures. A clinical utility of PRS in psychiatry has not been reached yet, owing

to a limited amount of variance explained as well as a low specificity and sensitivity (Andlauer, Nöthen, 2020).

While the individual affective and psychotic disorders are considered distinct entities in current nosology, they exhibit overlaps in clinical presentation and etiological factors. E.g., psychotic features are not only a hallmark of SCZ, but can also occur in severe forms of MDD or BD. In schizoaffective disorder, which is considered a schizophrenia spectrum disorder (SSD), symptoms of SCZ are observed in combination with a mood episode. On the genetic level, several loci with pleiotropic effects on multiple disorders have been identified (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019), and substantial pairwise genetic correlations between the disorders have been estimated, amounting to 68 % between BD and SCZ, 36 % between MDD and SCZ, and 34 % between MDD and BD (Grotzinger *et al.*, 2022). Moreover, phenotypic heterogeneity exists within diagnostic groups, e.g., there are more than 10,000 unique ways to meet the diagnostic criteria for MDD according to DSM-5 (Cai *et al.*, 2020). The issue of unclear boundaries and a limited alignment of symptom-based diagnostic categories with biomedical research findings has fueled transdiagnostic and dimensional perspectives in psychiatric research (e.g., Insel *et al.*, 2010; Kotov *et al.*, 2017), which are ingrained in the first two studies included in this dissertation.

2.1 Aims

Despite a large body of research investigating different aspects of affective and psychotic disorders, their genetic underpinnings remain incompletely understood. Therefore, the overarching objective of this doctoral thesis was to enhance the understanding of the complex relationships of common genetic variants with disease status and symptom dimensions within and across affective and psychotic disorders. To this end, three studies were conducted. The first and second study included in this dissertation were based on data of the German FOR2107 consortium (Kircher *et al.*, 2019), including individuals with a diagnosis of MDD, BD, or SSD. The focus of these studies was on the contribution of common genetic variants to psychopathological symptom dimensions observed across the diagnostic boundaries of MDD, BD, and SSD, using PRS analyses and exploratory GWAS. In particular, the first study (David *et al.*, 2023) represents a genetic follow-up on

the factor model of acute psychopathology previously published by Stein *et al.* (2020). In the second study (Krug *et al.*, 2024), a new factor model of lifetime psychopathology was described and the brain morphometric and genetic correlates of the three symptom dimensions were examined. The latest GWAS meta-analysis of BD by the PGC (O'Connell *et al.*, 2025), as mentioned above, constitutes the third study of this dissertation. The aim of this study was to identify novel associations of common variants with BD disease status by leveraging a considerable increase in sample size compared to the previous GWAS meta-analysis (Mullins *et al.*, 2021). Using a plethora of GWAS downstream analyses, the study further aimed to enhance and refine our understanding of the genetic architecture and biological underpinnings of BD. The findings of all three studies included in this dissertation were published in peer-reviewed journals and are presented in the following chapter.

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3 Publications

3.1 Genetic contributions to transdiagnostic symptom dimensions in patients with major depressive disorder, bipolar disorder, and schizophrenia spectrum disorders

This study was authored by David FS, Stein F, Andlauer TF, Streit F, Witt SH, Herms S, Hoffmann P, Heilmann-Heimbach S, Opel N, Repple J, Jansen A, Nenadić I, Papiol S, Heilbronner U, Kalman JL, Schaupp SK, Senner F, Schulte EC, Falkai PG, Schulze TG, Dannlowski U, Kircher T, Rietschel M, Nöthen MM*, Krug A*, and Forstner AJ*.

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In this study, we conducted a genetic follow-up investigation of five previously published symptom dimensions of acute psychopathology present in affective and psychotic disorders. As the first author, I played a major role in the planning of the scientific work and data collection, conducted the data analyses, evaluation, and interpretation, and was responsible for the primary drafting and revision of the manuscript.

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Genetic contributions to transdiagnostic symptom dimensions in patients with major depressive disorder, bipolar disorder, and schizophrenia spectrum disorders

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ABSTRACT

Major depressive disorder (MDD), bipolar disorder (BD), and schizophrenia spectrum disorders (SZ) exhibit considerable phenotypic and genetic overlap. However, the contribution of genetic factors to their shared psychopathological symptom dimensions remains unclear. The present exploratory study investigated genetic contributions to the symptom dimensions "Depression", "Negative syndrome", "Positive formal thought disorder", "Paranoid-hallucinatory syndrome", and "Increased appetite" in a transdiagnostic subset of the German FOR2107 cohort (n = 1042 patients with MDD, BD, or SZ). As replication cohort, a subset of the German/Austrian PsyCourse study (n = 816 patients with MDD, BD, or SZ) was employed. First, the relationship between symptom dimensions and common variants associated with MDD, BD, and SZ was investigated via polygenic risk score (PRS) association analyses, with disorder-specific PRS as predictors and symptom dimensions as outcomes. In the FOR2107 study sample, PRS for BD and SZ were positively associated with "Positive formal thought disorder", the PRS for SZ was positively associated with "Paranoid-hallucinatory syndrome", and the PRS for BD was negatively associated with "Depression". The effects of PRS for SZ were replicated in PsyCourse. No significant associations were observed for the MDD PRS. Second, genome-wide association studies (GWAS) were performed for the five symptom dimensions. No genome-wide significant associations and no replicable suggestive associations (p < 1e−6 in the GWAS) were identified. In summary, our results suggest that, similar to

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diagnostic categories, transdiagnostic psychiatric symptom dimensions are attributable to polygenic contributions with small effect sizes. Further studies in larger thoroughly phenotyped psychiatric cohorts are required to elucidate the genetic factors that shape psychopathological symptom dimensions.

1. Introduction

Major depressive disorder (MDD), bipolar disorder (BD), and schizophrenia spectrum disorders (SZ) such as schizophrenia and schizoaffective disorder represent major psychiatric disorders with overlapping clinical phenotypes (Kircher et al., 2019). Although considered distinct diagnostic groups in clinical practice, these disorders have several mood and psychotic features in common. Depressed mood, for example, represents the key symptom in patients diagnosed with MDD, but also occurs in patients diagnosed with BD and SZ (Cotton et al., 2012; Tondo et al., 2017; Upthegrove et al., 2017). Similarly, while psychotic features, such as delusions, typically occur in patients diagnosed with SZ, they are also observed in patients with a diagnosis of BD or MDD (Rosen et al., 2012; Toh et al., 2015; van Bergen et al., 2019; Varghese et al., 2011). Therefore, in recent years, several authors have proposed that the major psychiatric disorders should be conceptualized as a dimensional clinical spectrum, rather than as distinct diagnostic categories (Benazzi, 2005; Keshavan et al., 2011; Lynham et al., 2018). This has prompted transdiagnostic studies to investigate shared phenotypic dimensions and etiological factors.

1.1. Factor model of transdiagnostic symptoms

Factor models represent a valuable approach to the dissection of latent variables in psychiatric disorders (Baek et al., 2019; Emsley et al., 2003; Li et al., 2014). Recently, Stein et al. (2020) conducted exploratory and confirmatory transdiagnostic factor analyses of psychopathological symptoms in individuals with a DSM-IV diagnosis of MDD, BD, or SZ ($n = 1182$). The study sample consisted of a subset of the German FOR2107 cohort, a deeply phenotyped transdiagnostic psychiatric cohort that allows for a plethora of analyses (Kircher et al., 2019). Using a comprehensive set of psychopathological scales for the rating of acute psychopathology (SANS, SAPS, HAMA, HAM-D, YMRS), Stein et al. (2020) identified and validated five transdiagnostic symptom dimensions, i.e., "Depression", "Negative syndrome", "Positive formal thought disorder", "Paranoid-hallucinatory syndrome", and "Increased appetite". While some symptom dimensions exhibited higher average factor scores in specific diagnostic groups, e.g., "Depression" in MDD, distributions of factor scores overlapped between diagnoses. This concordance of the factor model with the clinical observation of heterogeneous phenotypes in the major psychiatric disorders provides a sound basis for the further investigation of shared etiological factors.

1.2. Genetic contributions to major psychiatric disorders

Research has shown that genetic factors play a substantial role in the etiology of the major psychiatric disorders. As demonstrated by twin and family studies, each of the disorders has a strong genetic component, with heritability estimates ranging from 40 % for MDD to 60–80 % for schizophrenia and 60–85 % for BD (Nöthen et al., 2019). For these disorders, genome-wide association studies (GWAS) have identified multiple risk variants that are common in the general population (Mullins et al., 2021; Trubetskoy et al., 2022; Wray et al., 2018). This, in turn, has enabled the calculation of polygenic risk scores (PRS), which summarize disorder-specific genetic risk at the individual level (Andlauer and Nöthen, 2020; Lewis and Vassos, 2020). Furthermore, cross-disorder studies have demonstrated high genetic correlations between the major psychiatric disorders, which supports the hypothesis of shared etiological factors (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019). In view of the observed genetic and phenotypic overlap between the major psychiatric disorders, the investigation of associations between genetic factors and transdiagnostic measures is becoming an increasingly valued approach (e.g., Andlauer et al., 2021b; Pelin et al., 2021).

1.3. Present study

The aim of the present study was to investigate the association of common genetic variants with the five transdiagnostic symptom dimensions identified by Stein et al. (2020). PRS association analyses were performed to determine the impact of genetic liability for MDD, BD, and SZ. Further, exploratory GWAS were performed for each of the five symptom dimensions. Results were followed up via replication analyses in an independent cohort.

2. Methods

2.1. Sample description and factor scores

All individuals from the German FOR2107 cohort (Kircher et al., 2019) who had been included in the factor analysis study of Stein et al. (2020) were selected for the present analyses. Written informed consent was obtained from all participants during the original FOR2107 recruitment process. Ethical approval was obtained from the local ethics committees of the Universities of Marburg and Münster, Germany. The sample in Stein et al. (2020) comprised 1182 individuals (465 males/717 females) with a DSM-IV diagnosis of MDD, BD, or SZ. For each of these subjects, factor scores for the transdiagnostic symptom dimensions "Depression", "Negative syndrome", "Positive formal thought disorder", "Paranoid-hallucinatory syndrome", and "Increased appetite" were provided by Stein et al. (2020) for the purposes of the present analyses. The individual items contributing to each factor are listed in Supplementary Table 1.

2.2. Genotyping, quality control, and imputation

Genotyping, quality control (QC), and imputation were previously performed as described elsewhere (Meller et al., 2019; Pelin et al., 2021) for the complete FOR2107 cohort, of which the selected sample constitutes a subset. Briefly, genomic DNA was extracted from blood samples and used for genome-wide genotyping with the Infinium PsychArray BeadChip (Illumina, San Diego, CA, USA). After initial QC and population substructure analyses in PLINK v1.90 (Chang et al., 2015), genotype data were imputed to the 1000 Genomes phase 3 reference panel (Auton et al., 2015) using SHAPEIT and IMPUTE2 (Delaneau et al., 2011; Howie et al., 2009). Post-imputation QC included removal of variants with any of the following characteristics: a minor allele frequency < 1 %; a Hardy-Weinberg equilibrium test $p < 1e{-}6$; or an INFO metric < 0.8. From the 1182 subjects for which factor scores were available, 140 individuals were excluded from the present analyses due to: a lack of high-quality genotype data ($n = 124$); a mismatch between information on phenotypic and genotypic sex ($n = 2$); or intra-sample relatedness ($n = 14$) ($\hat{\pi} \geq 0.125$). In the remaining sample ($n = 1042$), henceforth referred to as FOR2107 study sample, imputed genotype probabilities were available for 8565143 common variants.

2.3. Replication sample

For replication analyses, an independent subset of the German/Austrian PsyCourse study (Budde et al., 2019) was selected. Genotyping,

QC, and imputation were previously performed within the complete PsyCourse cohort in the same way as conducted for the FOR2107 cohort. The replication sample comprised $n = 816$ unrelated individuals with a DSM-IV diagnosis of MDD, BD, or SZ. Some of the psychopathology assessment scales applied in the PsyCourse study differed to those used by Stein et al. (2020). However, the respective scales are well correlated (e.g., Rush et al., 2006; van Erp et al., 2014), and mapping symptoms between correlated scales, e.g. SANS/SAPS and PANSS, is common practice in corsortia comprising different study sites, e.g. the ENIGMA consortium. Differing scales included the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) and the Inventory of Depressive Symptoms (IDS-C_{30}) (Rush et al., 1986). To emulate the previously established factor model by Stein et al. (2020), single symptoms included in the original model were mapped to symptoms of the scales used in the replication sample (Supplementary Table 2). For the symptom mapping, equivalent items available in the replication sample were sought for each item of the original factor model. In some cases, a 1:1 mapping of items was not possible, resulting in both 1:n (one-to-many, e.g. HAMA4 to IDS-C 1, 2, 3, and 4) and n:1 (many-to-one) mappings (e.g. both HAMA6 and HAMD1 to IDS-C 5). For few items (HAMA2, HAMD16, SAPS28) that were part of the first four factors in the original model, no corresponding item was identified in the replication sample. Due to lack of data on appetite behavior, the fifth factor "Increased appetite" was not included in the model replication step. Confirmatory factor analysis (CFA) in the replication sample was performed in accordance with Stein et al. (2020) using *MPlus* (version 8.4) (Muthén and Muthén, 1998-2017). As in Stein et al. (2020), the model was estimated using the MLR method. Goodness of fit was assessed using the chi-square significance test, the comparative fit index (CFI) (Bentler, 1990), and the root mean square error of approximation (RMSEA) (Browne and Cudeck, 1993). Latent standardized factor scores for each patient were extracted using *MPlus*.

2.4. Polygenic risk score association analyses

In the complete FOR2107 cohort, disorder-specific PRS for MDD, BD, and SZ were calculated using publicly available GWAS summary statistics (Mullins et al., 2021; Trubetskoy et al., 2022; Wray et al., 2018, meta-analysis excluding 23andMe). For PRS calculation, variant weights were estimated via the PRS-CS approach (Ge et al., 2019), using multiple pre-selected values for the global shrinkage parameter φ (1e−4, 1e−3, 1e−2). PRS were calculated in R (R Core Team, 2019), as described previously (Andlauer et al., 2021a,b). For the FOR2107 study sample, linear regression models were then fitted in R with one of the three z-scaled disorder-specific PRS as predictor and one of the five symptom dimensions as outcome. Due to non-normal distribution of factor scores within the symptom dimensions, rank-based inverse normal transformed values (McCaw et al., 2020) were used. Sex, age, and the first four ancestry components calculated via multidimensional scaling (MDS) were included as covariates (Supplementary Fig. 1). Linear models were first fitted for the complete transdiagnostic FOR2107 study sample, and then separately for each diagnostic subgroup. Adjustment of p values for multiple testing was performed using the Benjamini-Hochberg approach (Benjamini and Hochberg, 1995) for 45 tests (5 symptom dimensions × 3 PRS models × 3 values for φ). Model coefficients were considered statistically significant at $p < 0.05$. The variance explained (R^2) by each PRS was calculated as the difference between R^2 of the full model and R^2 of the null model containing the covariates only. The same analysis was conducted in the PsyCourse study sample for the four approximated symptom dimensions. As the PsyCourse sample was part of the BD GWAS by Mullins et al. (2021), the PRS for BD was calculated in the replication sample using summary statistics of the respective leave-one-out GWAS from Mullins et al. (2021), in which the PsyCourse sample had been excluded (41670 BD cases, 371261 controls).

2.5. Genome-wide association studies and downstream analyses

For each of the five symptom dimensions, a GWAS was performed in the FOR2107 study sample using the linear regression approach in PLINK. Rank-based inverse normal transformed values were used as quantitative phenotypes. Sex, age, and the first four ancestry components calculated via MDS were included as covariates. To facilitate comparisons between symptom dimensions, all variables were z-scaled via the 'standard-beta' modifier. Clumping of genetic markers was performed using a maximum p value of 1e−4 for index variants ('–clump-p1 1e−4'); a linkage disequilibrium threshold of 0.1 ('–clump-r2 0.1'); and a window size of 1000 kb ('–clump-kb 500'). Genetic associations with $p < 5e{-}8$ were considered genome-wide significant, and genetic associations with $p < 1e{-}6$ were considered suggestive of association (e.g., Forstner et al., 2021; Risch and Merikangas, 1996). FUMA (Watanabe et al., 2017) was used for basic annotation of summary statistics, and MAGMA (de Leeuw et al., 2015) as implemented in FUMA was used for gene-based analyses. LocusZoom (Pruim et al., 2010) was used to generate regional plots. Power calculations were performed in accordance with the formulas provided in Visscher et al. (2017).

2.6. Replication analysis

For variants with suggestive evidence of association in the discovery GWAS, association testing was performed in the PsyCourse study sample using PLINK. Rank-based inverse normal transformed factor scores were used as outcomes and sex, age, and the first four ancestry components calculated via MDS as covariates. For the examined variants, a sign test was performed to evaluate concordance of the directions of effect between cohorts, and combined effects and p values were calculated using inverse variance-weighted meta-analysis in METAL (Willer et al., 2010). Since all lead variants of the discovery GWAS with $p < 1e{-}6$ were present in the imputed PsyCourse genotype data, no investigation of other variants at these loci in linkage disequilibrium with the lead variants was performed.

3. Results

The distribution of the FOR2107 study sample ($n = 1042$ individuals post-QC) across diagnostic subgroups is shown in Table 1. The distribution of factor scores and PRS (Fig. 1) demonstrates the transdiagnostic nature of the psychopathological symptom dimensions and the relationships between disorder-specific PRS and diagnostic groups.

Emulation of the factor model of Stein et al. (2020) in the PsyCourse replication sample (Table 2) yielded four factors (i.e., "Depression", "Negative syndrome", "Positive formal thought disorder", "Paranoid-hallucinatory syndrome") comparable to the first four symptom dimensions in Stein et al. (2020). The dimension "Increased appetite" could not be approximated. Results of the CFA of the emulated four-factor model suggested an acceptable fit: $\chi^2 = 939.24$, $df = 187$, $p < 0.0001$, $CFI = 0.868$, $RMSEA = 0.058$.

3.1. PRS association analyses

Associations between disorder-specific PRS for MDD, BD, and SZ and the five transdiagnostic symptom dimensions were investigated in the FOR2107 study sample (Fig. 2A, Supplementary Table 3) to determine whether disorder-specific PRS explain any of the transdiagnostic variance in disorder-related symptom dimensions. A significant positive effect of the PRS for SZ was observed on "Positive formal thought disorder" (maximum $\beta = 0.102$ at $\varphi = 1e{-}3$ with $R^2 = 0.010$ and adjusted $p = 0.0087$), and "Paranoid-hallucinatory syndrome" (maximum $\beta = 0.084$ at $\varphi = 1e{-}3$ with $R^2 = 0.007$ and adjusted $p = 0.0362$). A significant negative effect of the PRS for BD was observed on "Depression" (minimum $\beta = -0.084$ at $\varphi = 1e{-}4$ with $R^2 = 0.007$ and adjusted $p = 0.0362$) as well as a significant positive effect on "Positive formal

Table 1
Characteristics of the FOR2107 study sample.

	Major depressive disorder	Bipolar disorder	Schizophrenia spectrum disorders	Total sample
n	783	134	125	1042
Sex	f = 506, m = 277	f = 70, m = 64	f = 53, m = 72	f = 629, m = 413
Age (SD)	37.1 (13.3)	42.1 (12.5)	38.4 (11.5)	37.9 (13.1)
Age at onset (SD)	26.2 (12.7)	25.4 (12.0)	22.2 (9.1)	25.6 (12.5)
Depressive episodes (SD)	4.1 (6.9)	7.7 (8.1)	6.2 (8.2)	4.6 (7.2)
Manic episodes (SD)	–	5.8 (6.9)	4.7 (9.4)	5.6 (7.4)
Psychotic episodes (SD)	–	–	5.1 (8.2)	5.1 (8.2)
Antidepressants (%)	471 (60.2 %)	52 (38.8 %)	36 (28.8 %)	559 (53.6 %)
Antipsychotics (%)	150 (19.2 %)	64 (47.8 %)	106 (84.8 %)	320 (30.7 %)
Mood stabilizers (%)	36 (4.6 %)	76 (56.7 %)	13 (10.4 %)	125 (12.0 %)
Inpatient treatment (%)	240 (30.7 %)	37 (27.6 %)	58 (46.4 %)	335 (32.2 %)
Remission (%)	308 (39.3 %)	47 (35.1 %)	37 (29.6 %)	392 (37.6 %)

Sample size (n), number of female (f) and male (m) participants, the mean age at recruitment and at onset in years as well as selected clinical characteristics are shown. The latter includes the mean number of depressive, manic, and psychotic episodes where applicable, the number and percentage of participants on different groups of medications, the number and percentage of participants undergoing inpatient treatment, and the number and percentage of participants in remission. SD, standard deviation.

thought disorder" (maximum $\beta = 0.129$ at $\varphi = 1e{-}3$ with $R^2 = 0.017$ and adjusted $p = 0.0009$). For the PRS for MDD, no significant associations were found with any of the symptom dimensions. In PsyCourse, the significant positive effects of the PRS for SZ could be replicated, while the PRS for BD did not have a significant effect on either "Depression" or "Positive formal thought disorder" (Supplementary Fig. 2).

When regression modeling was conducted in the FOR2107 study sample separately for each diagnostic subgroup, heterogeneous effects were observed (Fig. 2B). While the positive effect of PRS for SZ on "Positive formal thought disorder" and "Paranoid-hallucinatory syndrome" reached statistical significance in the total sample, no significant signal was present in any of the diagnostic subgroups. Similarly, with regard to the significant negative effect of the PRS for BD on the "Depression" dimension observed in the total sample, no significant signals were found in the analysis of diagnostic subgroups. Interestingly, PRS for BD showed some evidence for subgroup-specific effects on "Positive formal thought disorder" and "Paranoid-hallucinatory

Table 2
Characteristics of the PsyCourse replication sample.

	Major depressive disorder	Bipolar disorder	Schizophrenia spectrum disorders	Total sample
n	65	353	398	816
Sex	f = 37, m = 28	f = 175, m = 178	f = 166, m = 232	f = 378, m = 438
Age (SD)	41.9 (15.2)	45.9 (13.0)	41.3 (11.9)	43.3 (12.8)
Age at first inpatient treatment (SD)	33.2 (13.3)	33.6 (12.3)	27.5 (9.9)	30.5 (11.6)
Depressive episodes (SD)	4.5 (3.3)	9.0 (10.8)	5.2 (6.2)	7.4 (9.3)
Manic episodes (SD)	–	5.9 (6.8)	3.6 (2.8)	5.5 (6.3)
Antidepressants (%)	52 (80.0 %)	165 (46.7 %)	118 (29.7 %)	335 (41.1 %)
Antipsychotics (%)	30 (46.2 %)	238 (67.4 %)	382 (96.0 %)	650 (79.7 %)
Mood stabilizers (%)	5 (7.7 %)	245 (69.4 %)	50 (12.6 %)	300 (36.8 %)
Inpatient treatment (%)	34 (52.3 %)	102 (28.9 %)	205 (51.5 %)	341 (41.8 %)
Remission (%)	8 (12.3 %)	12 (3.4 %)	7 (1.8 %)	27 (3.3 %)

Sample size (n), number of female (f) and male (m) participants, the mean age at recruitment and at first inpatient treatment in years as well as selected clinical characteristics are shown. The latter includes the mean number of depressive and manic episodes where applicable, the number and percentage of participants on different groups of medications, the number and percentage of participants undergoing inpatient treatment, and the number and percentage of participants in remission. SD, standard deviation.

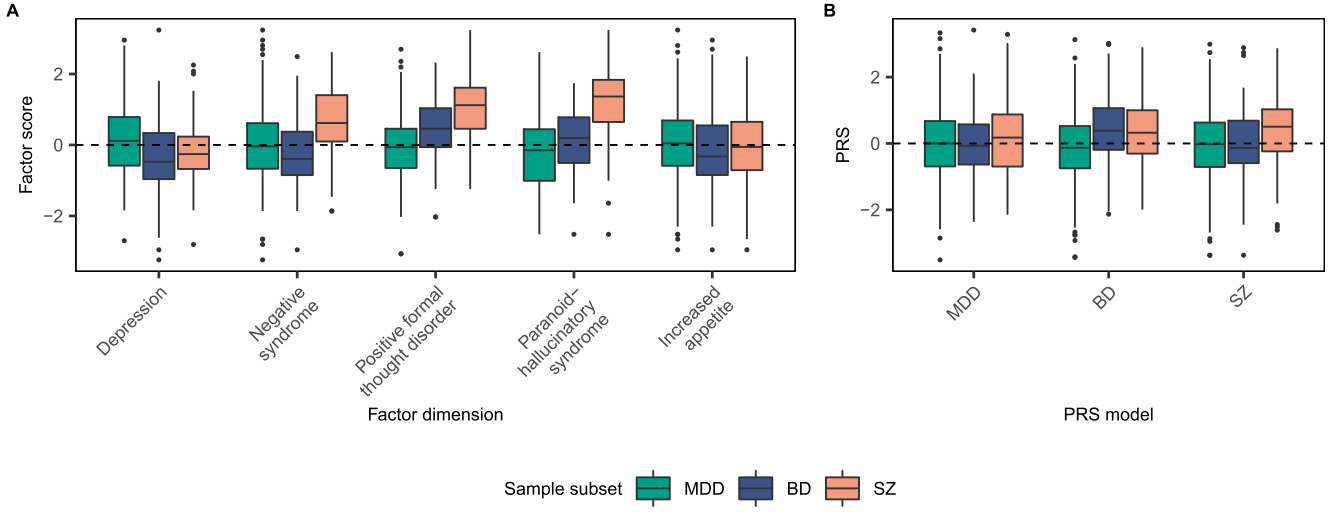

Fig. 1. Distribution of factor scores and PRS across diagnostic groups.
(A) The boxplots of factor scores from Stein et al. (2020) demonstrate overlapping distributions between diagnostic groups. Rank-based inverse normal transformed factor scores used for statistical analyses are shown. (B) Distributions of PRS for MDD, BD, and SZ at $\varphi = 0.001$ after z-scaling (mean = 0, standard deviation = 1) by PRS model. BD, bipolar disorder; MDD, major depressive disorder; PRS, polygenic risk score; SZ, schizophrenia spectrum disorders.

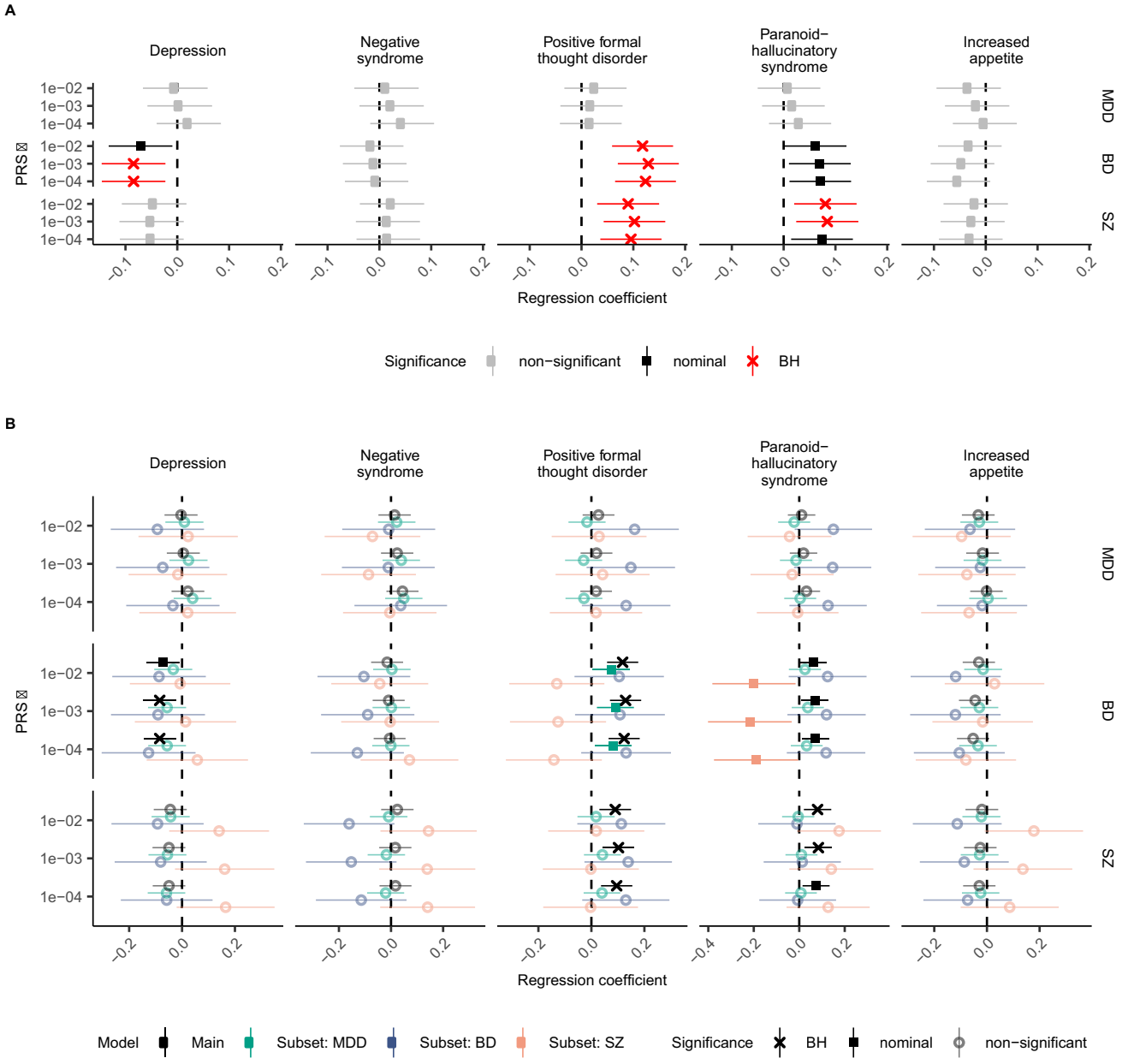

Fig. 2. PRS association analyses.
(A) Regression coefficients of the disorder-specific PRS for MDD, BD, and SZ at different PRS φ values on the transdiagnostic symptom dimensions are shown with 95 % confidence intervals for models based on the complete FOR2107 study sample. Model coefficients with $p < 0.05$ after correction for multiple testing with the Benjamini-Hochberg approach are indicated in red, while nominally significant effects (unadjusted $p < 0.05$) are indicated in black. (B) The regression analysis was repeated within each diagnostic subgroup. Regression coefficients of these subset analyses are shown in comparison to the main model presented in (A). BD, bipolar disorder; BH, Benjamini-Hochberg; MDD, major depressive disorder; PRS, polygenic risk score; SZ, schizophrenia spectrum disorders.

syndrome", albeit non-significant after correction for multiple testing, with a tendency towards negative effects in the subgroup of SZ cases and towards positive effects in the subgroup of BD cases.

3.2. Genome-wide association analyses

In the FOR2107 study sample, GWAS were performed for each of the five symptom dimensions. No evidence of genomic inflation was observed, with λ values between 0.99 and 1.01. No genome-wide significant associations were identified. However, one to three loci per symptom dimension showed suggestive evidence of association ($p <$ 1e−6; Table 3, Supplementary Figs. 3–7). The MAGMA gene analysis and gene-set analysis in FUMA yielded no statistically significant results for any of the symptom dimensions after correction for multiple testing (data not shown). Among the nine loci with association at $p <$ 1e−6, four lead variants were located in introns of protein-coding and noncoding genes and five at intergenic positions. Closer examination of the loci with suggestive evidence of association (Fig. 3, Supplementary Figs. 8–11) revealed that genes at two of the loci have been implicated previously in major psychiatric disorders, i.e., *RELN* and *NEFH*.

Table 3
Lead variants of associated loci ($p < 1e{-}6$) in FOR2107 study sample. Subsequent rows with the same shade represent genetic variants that are associated with the same factor. The respective factor for each group of rows is indicated in the first column.

Factor	CHR	RSID	BP	A1/A2	BETA	SE	P	GENE(S)
Depression	7	rs12536739	103387409	C/T	0.2231	0.0451	9.02E-07	*RELN*
Negative syndrome	1	rs2787876	48948331	A/G	0.5786	0.1091	1.37E-07	*SPATA6, AGBL4*
	4	rs6832060	173985694	A/T	-0.3247	0.0657	8.99E-07	*GALNTL6, GALNT7*
Positive formal thought	1	rs74574738	219286141	T/C	0.9628	0.1828	1.70E-07	*LYPLAL1-AS1*
disorder	11	rs11407840	23543893	G/GA	-0.5118	0.1008	4.55E-07	*MIR8054*
	22	rs420395	29851183	T/C	-0.4079	0.0820	7.72E-07	*RFPL1, NEFH*
Paranoid-hallucinatory	7	rs4726988	148326035	T/C	0.2151	0.0434	8.24E-07	*C7orf33, CUL1*
syndrome	8	rs35831749	69000845	AC/A	-0.2330	0.0469	7.81E-07	*PREX2*
Increased appetite	20	rs193035887	15947060	G/T	-1.0856	0.2142	4.76E-07	*MACROD2*

CHR, chromosome; RSID, reference variant identifier; BP, base pair position (GRCh37); A1, effect allele; A2, other allele; BETA, effect size estimate; SE, standard error; P, association *p* value; GENE(S), nearest gene(s), up- and downstream within 250 kb distance in case of intergenic variants.

3.3. Replication analysis

In the replication analysis of variants with $p < 1e{-}6$ in the discovery GWAS, none of the eight variants showed a nominally significant association ($p < 0.05$) with the respective emulated factor dimension in the PsyCourse replication sample (Supplementary Table 4). For five of the eight evaluated variants, the direction of effect was identical in the FOR2107 study sample and the PsyCourse replication sample. In a binomial sign test, the null hypothesis of random directions of effect could not be rejected ($p = 0.36$).

4. Discussion

Genetic factors play a substantial role in the development of MDD, BD, and SZ (Sullivan and Geschwind, 2019). Although multiple studies have investigated genetic associations within individual diagnostic groups, few studies analyzed genetic associations with transdiagnostic measures. Among others, McCoy et al. (2018) conducted GWAS of five dimensional phenotypes of psychopathology and successfully identified genome-wide significant loci in three dimensions, indicating the merit of this approach. In view of the observed genetic and phenotypic overlap between the major psychiatric disorders, the present study explored genetic contributions to the five transdiagnostic symptom dimensions described by Stein et al. (2020), i.e., "Depression", "Negative syndrome", "Positive formal thought disorder", "Paranoid-hallucinatory syndrome", and "Increased appetite" via PRS analyses and GWAS.

As hypothesized by previous authors (e.g. Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2018; Guzman-Parra et al., 2021), the manifestation of cross-disorder symptom dimensions may be shaped by certain sets of genetic risk variants. Thus, some associations between genetic factors and symptom dimensions may have already been captured by disorder-specific GWAS conducted by large international consortia (Mullins et al., 2021; Trubetskoy et al., 2022; Wray et al., 2018). For example, the genetic associations identified to date by GWAS of SZ may include variants that contribute to positive formal thought disorder in all major psychiatric disorders, rather than in SZ only. This hypothesis is supported by the positive, although non-significant effect of PRS for SZ on "Positive formal thought disorder" found in the present subgroup analysis of BD cases. However, the opposite direction of effects of the PRS for BD on symptom dimensions "Positive formal thought disorder" and "Paranoid-hallucinatory syndrome" in the subgroups BD and SZ might point to the existence of genetic factors with divergent effects between disorders and therefore distinct biological differences between groups. These results are consistent with previous work by the Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium (2018), who also described genetic factors with both concordant and divergent effects in BD and SZ. Thus, while transdiagnostic approaches might facilitate the identification of concordant effects due to increase in sample size, their value may be limited if effects differ between groups.

Interestingly, we identified a significant negative effect of PRS for BD on "Depression" in the transdiagnostic FOR2107 sample, which was most pronounced in the subgroup of BD cases. However, as this association was not found in the PsyCourse replication sample, additional studies in independent samples are required before definitive conclusions can be drawn about the effect of the PRS for BD on the "Depression" symptom dimension.

Surprisingly, no significant effect of the PRS for MDD on the symptom dimension "Depression" was observed in either the total transdiagnostic sample or in the MDD subgroup. These findings may reflect the lower heritability of MDD compared to the other major psychiatric disorders and its high degree of etiological heterogeneity (Cai et al., 2020; Nöthen et al., 2019). Therefore, the investigation of endophenotypes in MDD may be valuable to disentangling its genetic etiology (Kendall et al., 2021). The question whether the symptom dimension "Depression" is impacted by the same genetic risk variants in the different diagnostic groups remains to be answered.

In the present GWAS, two of the loci with suggestive evidence of association harbored genes that have been implicated previously in major psychiatric disorders. On chromosome 7, the lead variant rs12536739, suggestively associated with "Depression", mapped to an intron of *RELN*. This gene encodes the Reelin protein, which is involved in cortex development and synaptic function (Ishii et al., 2016; Jossin, 2020). Interestingly, Reelin has been associated with several psychiatric disorders, including MDD, BD, and SZ (Fatemi et al., 2001; Fatemi et al., 2000; Lussier et al., 2011). The second gene, *NEFH*, is located around 25 kb downstream of the lead variant rs420395 on chromosome 22, suggestively associated with "Positive formal thought disorder". *NEFH* encodes the neurofilament heavy polypeptide, for which altered protein levels have been observed in the dorsolateral prefrontal cortex of SZ patients (Pinacho et al., 2016). Notably, none of the present suggestive genetic associations achieved replication in the independent PsyCourse sample. These suggestive associations should thus be viewed with caution until replication is achieved in future studies.

From a clinical perspective, the present analyses generated support for the factor model of Stein et al. (2020) in the independent PsyCourse sample, after symptom mapping to take into account differences in the applied psychopathological assessment scales. These results point to a cross-disorder and cross-scale psychopathological classification into four to five factors. In line with current approaches on dimensional

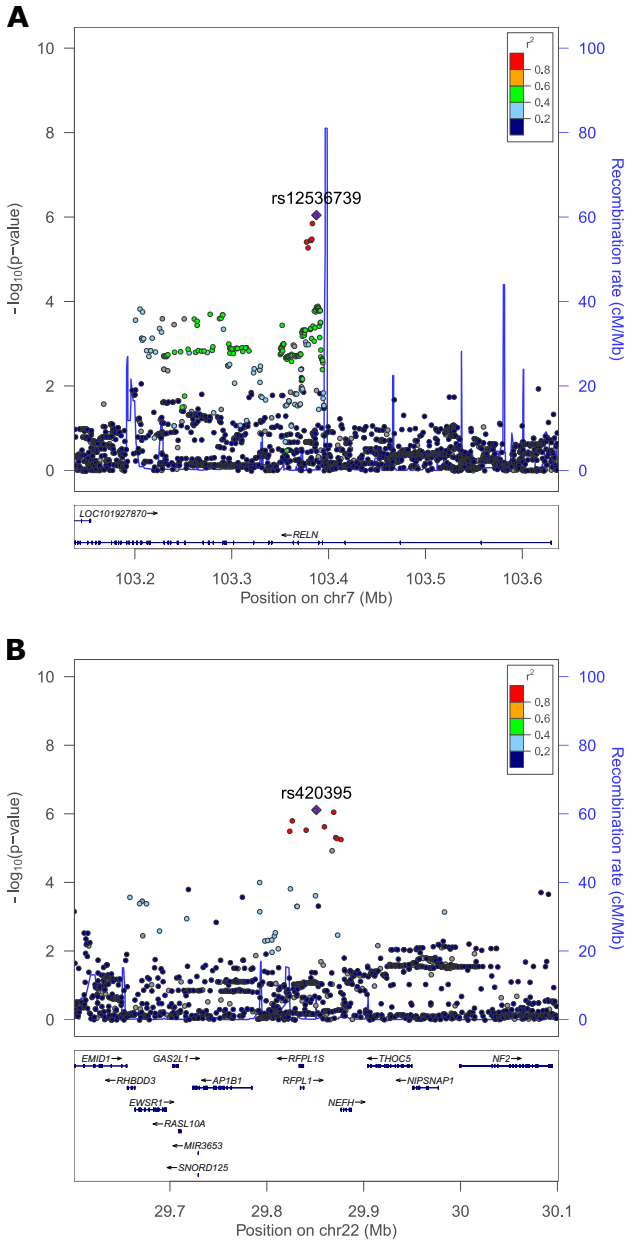

Fig. 3. Regional plots for loci with suggestive evidence of association and a link to major psychiatric disorders.
For the lead variant rs12536739, which displayed suggestive evidence of association with factor dimension "Depression" (A), and lead variant rs420395, which displayed suggestive evidence of association with factor dimension "Positive formal thought disorder" (B), regional plots with a window size of 500 kb are shown. The lead variants represent the linkage disequilibrium reference variants. Below the regional plots, annotation tracks for genes are included. Both *RELN* (A) and *NEFH* (B) have been associated with the major psychiatric disorders in previous research. cM, centimorgan; Mb, megabase.

psychiatry (Anderson et al., 2018; Conway et al., 2019; Kaczkurkin et al., 2018), this type of approach addresses the issue of cross-diagnostic heterogeneity in nosology, and might be a useful framework for studying the shared neurobiology of the major psychiatric disorders.

4.1. Limitations

The present study had four main limitations. First, since the effect sizes of individual risk alleles in complex diseases, such as psychiatric disorders, are generally low (Watanabe et al., 2019), the statistical power to detect genome-wide associations was limited at the given GWAS sample size (Supplementary Fig. 12; Visscher et al., 2017), despite the fact that the FOR2107 cohort represents one of the largest deeply phenotyped transdiagnostic psychiatric cohorts worldwide. In the replication analysis in PsyCourse ($n = 816$), however, the power to detect associations exceeded 90 % at the p value threshold of 0.05 (Supplementary Table 4). Second, due to the unavailability of some of the psychopathology scales used in the original factor model, the symptom dimensions were approximated in the PsyCourse sample via CFA. Although this resulted in a comparable factor model with reasonable fit, an identical phenotype definition would have been preferable for the genetic replication (Kraft et al., 2009). In future studies, efforts should be made to achieve uniform standards in the collection of phenotype data across psychiatric studies in order to overcome this issue. Third, the sample distribution across diagnostic groups differed both within and between the FOR2107 and the PsyCourse sample, with a higher percentage of MDD cases (75 %) in FOR2107 and a lower percentage (8 %) in PsyCourse. Despite the higher heritability of BD and SZ, the power to discover effects driven by BD and SZ cases in the FOR2107 sample may have been reduced compared to MDD. While we assume that the distribution in PsyCourse did not affect the replication of effects driven by BD and SZ cases, since they accounted for the majority of cases in PsyCourse, it is likely that the power to replicate effects driven by MDD cases was reduced. Lastly, the factor model was based on ratings of acute symptoms experienced at the time of data collection. However, factor scores do not remain stable throughout the patient's lifetime. The power of the present analyses may thus have been reduced, depending on the phase of illness that was being experienced by the participants at the time of assessment. Despite this limitation, these data can be considered as an exploratory starting point for the assessment of genetic contributions to transdiagnostic symptom dimensions. To overcome this limitation, future work by the present authors will focus on factor models that are based on lifetime psychopathological symptom dimensions and their genetic underpinnings.

4.2. Conclusion

The present study explored genetic contributions to the five transdiagnostic symptom dimensions reported by Stein et al. (2020). The PRS association analyses generated some degree of evidence for transdiagnostic effects of PRS for SZ on the symptom dimensions "Positive formal thought disorder" and "Paranoid hallucinatory syndrome". In contrast, no effect on the five symptom dimensions was found for PRS for MDD, and the effect of PRS for BD on "Positive formal thought disorder" pointed towards opposite effects in BD and SZ. The GWAS identified no genome-wide significant associations at the given sample size, which suggests that polygenic contributions with small effect sizes are implicated in the individual symptom dimensions. While the small effect sizes in psychiatric genetics studies of common variants limit the immediate clinical utility at this point in time, these studies are nevertheless essential for understanding the biological basis of the major psychiatric disorders. Further studies involving larger deeply phenotyped cohorts of multiple diagnostic subgroups and the evaluation of longitudinally stable measures are required to elucidate the genetic factors that impact the manifestation of different psychopathological symptom dimensions in the major psychiatric disorders.

CRediT authorship contribution statement

FSD, MMN, AK and AJF designed the study. FSD, FStein, TFMA, FStreit, SHW, SH, PH, SH-H, NO, JR, AJ, IN, SP, UH, JLK, SKS, FSenner, ECS, PGF, TGS, UD, TK, MR, MMN, AK, and AJF participated in data acquisition, quality control and preparation. FSD, FStein, and TFMA performed the statistical analyses. FSD, FStein, MMN, AK, and AJF

evaluated and interpreted the results. FSD wrote the first draft of the manuscript; FSD, FStein, TFMA, AK and AJF revised it. All authors contributed to and have approved the final manuscript.

Declaration of competing interest

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Role of the funding source

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2023.01.002.

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3.2 Factor analysis of lifetime psychopathology and its brain morphometric and genetic correlates in a transdiagnostic sample

This study was authored by Krug A*, Stein F*, David FS, Schmitt S, Brosch K, Pfarr J-K, Ringwald KG, Meller T, Thomas-Odenthal F, Meinert S, Thiel K, Winter A, Waltemate L, Lemke H, Grotegerd D, Opel N, Repple J, Hahn T, Streit F, Witt SH, Rietschel M, Andlauer TFM, Nöthen MM, Philipsen A, Nenadić I, Dannlowski U, Kircher T, and Forstner AJ.

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In this study, we investigated symptom dimensions of lifetime psychopathology present in affective and psychotic disorders. Frederike Stein and Axel Krug developed a new factor model comprising three symptom dimensions. In addition, they investigated the relation of the identified psychopathological factors to gray matter volume and cortical thickness, and I investigated the relation to common genetic factors. As the second author, I played a significant role in the planning of the scientific work, data collection, evaluation and interpretation, with a particular focus on the parts of the study related to genetics.

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ARTICLE OPEN

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Factor analysis of lifetime psychopathology and its brain morphometric and genetic correlates in a transdiagnostic sample

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There is a lack of knowledge regarding the relationship between proneness to dimensional psychopathological syndromes and the underlying pathogenesis across major psychiatric disorders, i.e., Major Depressive Disorder (MDD), Bipolar Disorder (BD), Schizoaffective Disorder (SZA), and Schizophrenia (SZ). Lifetime psychopathology was assessed using the OPerational CRITeria (OPCRIT) system in 1,038 patients meeting DSM-IV-TR criteria for MDD, BD, SZ, or SZA. The cohort was split into two samples for exploratory and confirmatory factor analyses. All patients were scanned with 3-T MRI, and data was analyzed with the CAT-12 toolbox in SPM12. Psychopathological factor scores were correlated with gray matter volume (GMV) and cortical thickness (CT). Finally, factor scores were used for exploratory genetic analyses including genome-wide association studies (GWAS) and polygenic risk score (PRS) association analyses. Three factors (paranoid-hallucinatory syndrome, PHS; mania, MA; depression, DEP) were identified and cross-validated. PHS was negatively correlated with four GMV clusters comprising parts of the hippocampus, amygdala, angular, middle occipital, and middle frontal gyri. PHS was also negatively associated with the bilateral superior temporal, left parietal operculum, and right angular gyrus CT. No significant brain correlates were observed for the two other psychopathological factors. We identified genome-wide significant associations for MA and DEP. PRS for MDD and SZ showed a positive effect on PHS, while PRS for BD showed a positive effect on all three factors. This study investigated the relationship of lifetime psychopathological factors and brain morphometric and genetic markers. Results highlight the need for dimensional approaches, overcoming the limitations of the current psychiatric nosology.

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INTRODUCTION

There is a long tradition of investigating the relationship between psychopathological syndromes and brain structure and function in patients suffering from schizophrenia (SZ) and schizoaffective disorder – henceforth referred to as schizophrenia spectrum disorders (SSD), as well as bipolar disorder (BD), and major depressive disorder (MDD). Several studies have linked specific symptoms such as verbal hallucinations to local brain structures, particularly the bilateral superior temporal gyri [1–3]. However, these have been either low in statistical power or variance [4], or limited to a specific diagnosis, such as SZ [5, 6]. This raises the question of generalizability across diagnostic categories: Since almost all symptoms can be present in different diagnoses (e.g., formal thought disorders are found in SZ, as well as in BD, and in MDD) [7–9], it is of major interest to study these syndromes transdiagnostically using dimensional approaches. Moreover, the

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phenotypic overlap between psychiatric disorders is also reflected at a brain structural [10–13] as well as genetic level [14].

Factor analyses of lifetime psychopathology have mostly been performed within one categorical disorder. Only a few studies are available, investigating transdiagnostic symptom dimensions of lifetime psychopathology across diagnoses: Investigating patients with DSM-IV diagnosed SZ, BD and delusional disorder, Serretti and Olgiati found that a five-factor model best described lifetime symptom dimensions [15]. In a sample consisting of patients with SZ, BD, MDD, delusional, and psychotic disorder not otherwise specified, a four-factor solution was obtained, consisting of excitement, psychotic features (hallucinations and delusions), depression and disorganization [16]. Studying the factor structure of the OPerational CRITeria (OPCRIT) system in the SZ spectrum and BD, Reininghaus and colleagues obtained a bifactor model with one transdiagnostic psychosis dimension and five specific factors comprising positive, negative, manic, disorganized and depressive symptoms [17].

Previously, most structural and functional magnetic resonance neuroimaging studies focused on categorical comparisons of one patient group (MDD, BD, or SSD) compared to a healthy control (HC) group. However, these studies failed to identify structural and functional brain correlates that separate disorders [18]. In contrast, studies and meta-analyses indicated common alterations across diagnoses [11–13, 19, 20]. Transdiagnostic studies of dimensional psychopathology might thus be more promising regarding identification of common risk factors and might especially lead to a more precise treatment of these syndromes on a transdiagnostic rather than diagnosis-based level. In addition, they should be able to take into account the heterogeneity of psychiatric disorders as well as potential comorbidities. This should also help to identify specific neurobiological markers which in turn can inform personalized treatment interventions.

Twin and family studies demonstrate that genetic factors contribute substantially to the development of MDD, BD and SZ, with heritability estimates of around 60% to 85% for SZ and BD [21–23] and around 40% for MDD [24]. Recent genome-wide association studies (GWAS) have identified numerous genome-wide significant loci for all three psychiatric disorders (e.g., refs. [25, 26]). Furthermore, transdiagnostic GWAS meta-analyses have demonstrated an extensive genetic overlap between MDD, BD and SZ [14]. Byrne et al. provided evidence that only a small subset of the genome-wide significant variants for SZ and MDD have disorder-specific effects [27]. One plausible hypothesis, therefore, is that pleiotropic genetic variants mediate their disease risk via effects on transdiagnostic symptom dimensions. In addition, an analysis of polygenic risk scores (PRS), which summarize the effects of multiple common genetic variants into an individual genetic risk profile [28], by Ruderfer et al. showed that the PRS for SZ was significantly increased in BD patients with psychotic features and SZ patients with prominent negative symptoms [29]. These results suggest that there are genetic factors underlying specific symptom dimensions within both disorders [29].

As symptom presentations can fluctuate within an individual patient over the course of life and even within a single episode, the aim of the present study was to i) assess lifetime symptoms in a transdiagnostic sample to identify underlying symptom factors; and ii) investigate the relationship of detected factors with local GMV and CT. Considering that brain structure is less variable within a short period of time, we hypothesize that this approach would yield more conclusive results than correlating GMV with psychopathology present at any given point in time. In addition, applying both GMV as well as CT measures should render a fuller picture of underlying mechanisms as we would not assume that all potential associations would be based on one measure alone. Finally, iii) it was explored if the detected factor structure can be linked to common genetic variation. Based on previous brain-morphometric and genetic studies, we hypothesized findings from specific DSM-IV diagnostic categories to be present across diagnoses, too.

MATERIAL AND METHODS

Participants

Patients were recruited as part of the FOR2107 cohort [30] (www.for2107.de). Patient recruitment took place via the in-patient facilities of the University hospitals in Marburg and Münster, Germany, through participating hospitals, and via postings in local newspapers. Written informed consent was obtained from all patients before participation. According to the Declaration of Helsinki, all procedures were approved by the local ethics committees. After study participation, all patients received financial compensation. After excluding patients with incomplete data, serious medical illnesses, neurological illnesses, and an IQ < 80, we analyzed a total of $N = 1038$ patients (see Table 1a, b, required sample size is based on [31]) suffering from MDD, BD, and SSD (aged 18–65).

Psychopathological assessment and factor score calculation

The German version of the structured interview SCID-I (DSM-IV-TR [32]) and the OPCRIT (version 4 [33]) were administered in all patients. Lifetime psychopathology was assessed as any occurrence of symptoms during the life span until data acquisition. Trained personnel assessed lifetime symptoms based on patients' reports and additional hospital records, when available. Numerous interview trainings assured data quality. Interrater-reliability was assessed with the interclass coefficient, achieving good reliability of $r > 0.86$. For the present study, only symptomatic items were included (items 17–77). Following the procedures described in Stein et al. [34], we separated the total cohort ($N = 1038$) into two samples using the "mindiff" [35] package in R [36] accounting for age, sex, and diagnostic category (i.e., same distribution of categorical diagnoses across both samples). In the first sample of $n = 520$, we performed varimax rotated principal axis factor analyses with bootstrapping (5000 permutations) using the *psych* [37] and *EFAutilities* [38] packages in R (v4.0.5.) for models with 2–5 factors. Hereof, z-transformed values were used since the data was differently scaled. For interpretation purposes, items with factor loadings <0.5 were not considered in the analysis [34]. Cronbach's alpha coefficients [39] were used to test the internal consistency of the explorative factors. Using the second sample of $n = 518$, we cross-validated the explorative models using confirmatory factor analysis in Mplus (version 8.4 [40]). Confirmatory model estimation was performed using the maximum-likelihood-method (MLM) since this estimator is robust to standard errors and is one of the most common estimators [41]. The following fit indices were used: chi-square significance test, comparative fit index (CFI [42]) and Root Mean Square Error of Approximation (RMSEA [43]). Based on these fit indices, we evaluated the different models and selected the one with best fit. After cross-validating the explorative model in the second sample, we tested the model for the whole sample ($N = 1038$).

As the DSM-IV-TR diagnostic groups were unequally distributed, we wanted to rule out potential confounding effects of formal diagnosis. Therefore, we tested the selected factorial model in an age- and sex-matched sample with an equal diagnosis distribution (each $n = 108$ of MDD, BD, SSD, total $n = 324$) (see supplement eTable1). Matching was performed using the "MatchIt" package [44] in R [36]. Furthermore, the factorial model was also tested within each of the three diagnostic categories and factor loadings were compared between DSM diagnosis using non-parametric Kruskal–Wallis tests (see supplement).

MRI assessment and preprocessing

Subjects were scanned with a 3-T MRI at the Department of Psychiatry and Psychotherapy in Marburg (Tim Trio, Siemens, Erlangen, Germany; 12-channel head coil) and the Institute for Translational Psychiatry in Münster (Prisma, Siemens, Erlangen, Germany; 20-channel head coil). MRI data were acquired according to an extensive quality assurance protocol [45]. A fast gradient echo MP-RAGE sequence with a slice thickness of 1.0 mm consisting of 176 sagittal orientated slices in Marburg and 192 in Münster and a FOV of 256 mm was used to acquire T1 weighted images. Parameters differed across sites: Marburg: TR = 1.9 s, TE = 2.26 ms, TI = 900 ms, flip angle = 9°; Münster: TR = 2.13 s, TE = 2.28 ms, TI = 900 ms, flip angle = 8°.

For a detailed description of the preprocessing of MRI data please see refs. [31, 46]. In short, both voxel-based-morphometry GMV and cortical thickness

Table 1. a: Characteristics of the explorative sample $n = 520$. b: Characteristics of the confirmatory sample $n = 518$.

	Major depressive disorder ($n = 402$)	Bipolar disorder ($n = 64$)	Schizophrenia spectrum disorders ($n = 54$)	Group comparison (F/Chi-values in brackets)
a				
Age	36.53 (13.45)	41.05 (11.96)	37.46 (11.75)	$p = 0.005$[a] (5.34)
Sex	$m = 140$ $f = 262$	$m = 30$ $f = 34$	$m = 28$ $f = 26$	$p = 0.016$ (8.15)
Years of education	13.25 (2.68)	13.5 (2.79)	12.54 (2.45)	$p = 0.213$ (1.55)
Age of onset	26.14 (12.64)	21.97 (10.66)	22.54 (10.26)	$p = 0.034$[b] (3.4)
TIV	1563.7 (160.75)	1578.16 (149.26)	1580.85 (152.16)	$p = 0.685$ (0.38)
	Major depressive disorder ($n = 401$)	**Bipolar disorder ($n = 63$)**	**Schizophrenia spectrums disorders ($n = 54$)**	**Group comparison (F/Chi-values in brackets)**
b				
Age	36.53 (12.84)	41.03 (12.31)	37.48 (11.27)	$p = 0.023$[a] (3.8)
Sex	$m = 140$ $f = 261$	$m = 30$ $f = 33$	$m = 29$ $f = 25$	$p = 0.008$ (9.67)
Years of education	13.25 (2.79)	14.47 (2.8)	12.51 (2.84)	$p = 0.001$[b] (1.55)
Age of onset	25.52 (12.28)	26.0 (11.18)	22.89 (8.27)	$p = 0.23$ (1.48)
TIV	1558.8 (148.18)	1596.85 (134.22)	1584.76 (206.19)	$p = 0.193$ (1.65)

TIV total intracranial volume.
[a]MDD < BD.
[b]MDD < BD; SSD < BD.

(CT) data were preprocessed using the default parameters as implemented in the CAT12-Toolbox (Computation Anatomy Toolbox for SPM, build 1184, Structural Brain Mapping group, Jena University Hospital, Germany) building on SPM12 (Statistical Parametric Mapping, Institute of Neurology, London, UK). We opted for GMV and CT over other MRI-derived metrics for two primary reasons. Firstly, volume and thickness measures, commonly employed in large-scale analyses such as those by the ENIGMA consortium, were selected to facilitate result comparisons. Second, recent neuroimaging research has underscored the complementary nature of GMV and CT measurements. GMV provides insight into overall gray matter volume, which can reflect global brain atrophy or neurodevelopmental factors. In contrast, CT offers information about the thickness of the cortical mantle, allowing for the detection of localized changes. By analyzing both GMV and CT, we aimed to capture both global and local structural alterations in the context of these psychiatric disorders [47, 48]. Images were spatially registered, segmented [49] and normalized [50]. CT preprocessing included fully-automated methods projecting local maxima to other GM voxels using a neighbor relationship described by the white matter distance [51]. Quality control of processed data was performed as implemented in CAT12. For GMV data, a Gaussian kernel of 8 mm FWHM was used for smoothing. For CT data, a Gaussian kernel of 20 mm FWHM was used.

Statistical analyses: gray matter volume and cortical thickness

For both GMV and CT analyses, we used separate linear regression models for each factor using CAT12 and SPM12. The following nuisance variables were included in brain structural analyses: age, sex, and two dummy-coded variables accounting for the different MRI scanners and a body coil exchange in Marburg (Marburg pre body coil: yes/no, Marburg post body coil: yes/no, Münster as reference category [30, 45]). To control for potential medication effects, we used three dummy coded (yes/no) covariates accounting for the current medication with antidepressants, mood stabilizers and antipsychotics. For GMV analyses total intracranial volume was additionally accounted as covariate of no interest and absolute threshold masking with a threshold value of 0.1 was used.

To further test confounding effects of unequally distributed diagnostic categories, we performed multiple regression analyses in the age and sex matched sample ($n = 324$) with same n per diagnosis, again. Besides this whole brain analysis, we additionally performed ROI analyses of the detected clusters from the total sample in the matched sub-sample (see supplement).

In addition to multiple regression analyses, we performed full factorial ANCOVA whole brain interaction analyses (factor x diagnosis) for each of the three factors to test whether transdiagnostic brain correlates were driven by single DSM-IV-TR diagnostic categories for both the total and the matched sample with same n per diagnosis. Moreover, post hoc interaction analyses (factor x diagnosis) were performed specifically within each detected cluster of the total sample using the "lm-function" in R.

Cluster labeling was applied using the dartel space Neuromorphometrics atlas (http://www.neuromorphometrics.com/) for GMV analyses and for CT analyses using the Desikan–Killiany atlas [52]. Results were suggested significant at $p < 0.05$ peak-level, family wise error (FWE) corrected, cluster extend $k = 35$ voxels in the total and matched sample.

GWAS and PRS association analysis

DNA extraction, genome-wide genotyping, quality control and imputation were carried out as previously described [53] in the full FOR2107 cohort. Briefly, genotyping was performed using genomic DNA from blood samples and the Infinium PsychArray BeadChip (Illumina, San Diego, CA, USA). Pre-imputation quality control (QC) was performed in GenomeStudio, PLINK v1.9 [54], and R [36], with removal of genetic variants and individuals according to standard filter criteria. Genotype data were imputed to the 1000 Genomes phase 3 reference panel [55] using SHAPEIT [56] and IMPUTE2 [57]. In post-imputation QC, variants with a minor allele frequency <1%, Hardy-Weinberg equilibrium $p < 1e{-}6$, and an INFO metric <0.8 were removed. From the total sample of the present study ($N = 1038$), high-quality genotype data were available for 951 individuals. From these, 13 individuals were excluded due to intra-sample relatedness ($\hat{\pi} > 0.125$), resulting in a sample of $n = 938$ individuals used for genetic analyses.

For each of the three factors, GWAS, which should be considered exploratory at the given sample size, were conducted via linear regression in PLINK with rank-based inverse normal transformed values [58] as quantitative phenotypes due to the non-normal distribution of factor scores. Sex, age and the first four multidimensional scaling (MDS) components were included as covariates. All variables were z-scaled via the 'standard-beta' modifier for better comparability between factor dimensions. We performed clumping of genetic markers in the GWAS results using a maximum p value of 1e−4 for index variants ('--clump-p1 1e−4'), an LD threshold of 0.1 ('--clump-r2 0.1'), and a window size of 1000 kb ('--clump-kb 500'). We considered genetic associations with $p < 5e{-}8$ to be genome-wide significant and with $p < 1e{-}6$ to be suggestive. We performed gene-based and gene-set analyses with MAGMA [59] as implemented in FUMA [60]. The resulting p values were corrected for multiple testing using the Bonferroni method taking into account the number of tested genes ($n = 18{,}846$) or gene sets ($n = 10{,}678$). We used LocusZoom [61] to generate regional plots.

Table 2. Explorative factor model of sample 1, $n = 520$.

Factor	Item	Symptom	Loading	Cronbach´s Alpha
1 (PHS)	Opcrit61	Delusions of passivity	0.711	0.910
	Opcrit64	Delusions and hallucinations last for one week	0.700	
	Opcrit68	Thought broadcast	0.697	
	Opcrit66	Thought insertion	0.681	
	Opcrit58	Delusions of influence	0.681	
	Opcrit62	Primary delusional perception	0.657	
	Opcrit55	Well organized delusions	0.650	
	Opcrit60	Widespread delusions	0.621	
	Opcrit54	Persecutory delusions	0.620	
	Opcrit74	Running commentary voices	0.602	
	Opcrit73	Third person auditory hallucinations	0.571	
	Opcrit59	Bizarre delusions	0.552	
	Opcrit67	Thought withdrawal	0.549	
	Opcrit63	Other primary delusions	0.543	
	Opcrit77	Non-affective hallucination in any modality	0.522	
2 (MA)	Opcrit35	Elevated mood	0.890	0.921
	Opcrit19	Excessive activity	0.829	
	Opcrit30	Pressured speech	0.804	
	Opcrit56	Increased self esteem	0.795	
	Opcrit20	Reckless activity	0.765	
	Opcrit22	Reduced need for sleep	0.760	
	Opcrit31	Thoughts racing	0.732	
	Opcrit21	Distractibility	0.525	
3 (DEP)	Opcrit39	Loss of pleasure	0.678	0.736
	Opcrit25	Loss of energy/tiredness	0.635	
	Opcrit37	Dysphoria	0.603	
	Opcrit41	Lack of concentration	0.507	

PRS for MDD, BD and SZ were calculated based on publicly available summary statistics from three studies [25, 26, 62]. Variant weights for PRS calculation were estimated with PRS-CS [63] using default parameters and a set of pre-defined values for the global shrinkage parameter φ (1e−4, 1e−3, 1e−2). PRS were subsequently calculated in R [36] as described previously [64]. Linear additive models with rank-based inverse normal transformed factor scores as outcome, one of the z-scaled disorder-specific PRS as predictor and sex, age and the first four MDS components as covariates were fitted in R. The PRS association analysis was conducted for both the complete set of $n = 938$ individuals as well as for each diagnostic subgroup separately. Adjustment of p values for multiple testing was performed with the Benjamini–Hochberg approach [65] within each set of 27 tests (3 factor dimensions * 3 PRS models * 3 values for φ). Model coefficients were considered to be statistically significant at $p < 0.05$. We calculated the variance explained (R^2) by each PRS as the difference between R^2 of the full model and R^2 of the null model containing only the covariates.

RESULTS

Exploratory and confirmatory factor analyses

We tested explorative models ranging from 2-5 factors. Results of these models can be found in Supplementary eTables 2a–d. In a next step, we evaluated the four explorative models using confirmatory analyses in the second sample. Model fits were as follows: a) 2 factors: $\chi^2 = 393.645$, $df = 224$, $p < 0.001$, $CFI = 0.903$, $RMSEA = 0.038$; b) 3 factors: $\chi^2 = 543.005$, $df = 316$, $p < 0.001$, $CFI = 0.904$, $RMSEA = 0.037$; c) 4 factors: $\chi^2 = 588.773$, $df = 314$, $p < 0.001$, $CFI = 0.875$, $RMSEA = 0.042$; d) 5 factors: $\chi^2 = 748.705$, $df = 391$, $p < 0.001$, $CFI = 0.884$, $RMSEA = 0.041$. Based on the fit indices, we decided to use model b) with 3 factors (Table 2) for further analyses as this model outperformed the other ones. Moreover, a 3-factor model is also in line with the Scree Plot (Supplementary eFigure 1). The model included the factors paranoid-hallucinatory syndrome (PHS) (explaining 14% of total variance), mania (MA) (explaining 11% of total variance), and depression (DEP) (explaining 5% of total variance). Furthermore, we performed a confirmatory factor analysis in the whole sample ($N = 1038$) showing a good fit $\chi^2 = 605.667$, $df = 316$, $p < 0.0001$, $CFI = 0.932$, $RMSEA = 0.03$. Results of the confirmatory analyses of the matched sample and within each diagnostic category are presented in the supplement (Supplementary eResults1 and 2). We investigated differences of the factor loadings between diagnostic categories using a non-parametric ANOVA (Kruskal–Wallis). Diagnostic groups differed significantly in all three factors identified (Supplementary eResults3 and Supplementary eFigure 2).

Brain morphometric correlates of life-time psychopathology

Results of the multiple regression analyses of the total sample are displayed in Table 3 (GMV) and 4 (CT). For the paranoid-hallucinatory syndrome (PHS), negative GMV correlations were observed in the bilateral hippocampus, amygdala, and right angular gyrus (see Fig. 1). CT was negatively correlated with the paranoid-hallucinatory syndrome (PHS) comprising left supramarginal, bilateral superior temporal, and right lateral occipital clusters (see Fig. 2). Whole-brain interaction analyses revealed no significant interaction of psychopathological factor and DSM-IV-TR diagnosis for both GMV and CT. Post hoc interaction analyses on the significant clusters in Tables 3 and 4 revealed no significant

Table 3. Results of the lifetime paranoid-hallucinatory syndrome (PHS) and its local gray matter (GMV) correlates.

		MNI coordinates				
Anatomical region	**H**	**X**	**Y**	**Z**	**t-value**	**Cluster size**
Factor I: Paranoid-hallucinatory syndrome: gray matter volume						
Entorhinal area, hippocampus, amygdala, parahippocampal gyrus, fusiform gyrus, temporal pole	L	−27	−8	−27	5.53	560
Angular gyrus, middle occipital gyrus	R	57	−64.5	22.5	5.13	150
Amygdala, hippocampus, entorhinal area	R	25.5	−4.5	−27	5.00	83
Medial frontal cerebrum	R	3	57	−10.5	4.81	64

Only negative correlations are reported as no positive correlations were detected.
H hemisphere, *L* left, *R* right.

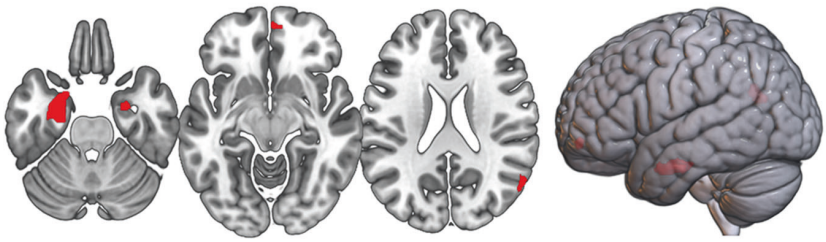

Fig. 1 Local GMV correlates of the lifetime paranoid-hallucinatory syndrome (PHS). Negative association of factor 1 paranoid-hallucinatory syndrome (PHS) and gray matter volume (GMV) comprising parts of the bilateral hippocampus, amygdala, and right angular gyrus across patients with major depressive disorder, bipolar disorder, and schizophrenia spectrum disorders. Clusters are shown at $p < 0.05$ peak-level, family-wise error-corrected.

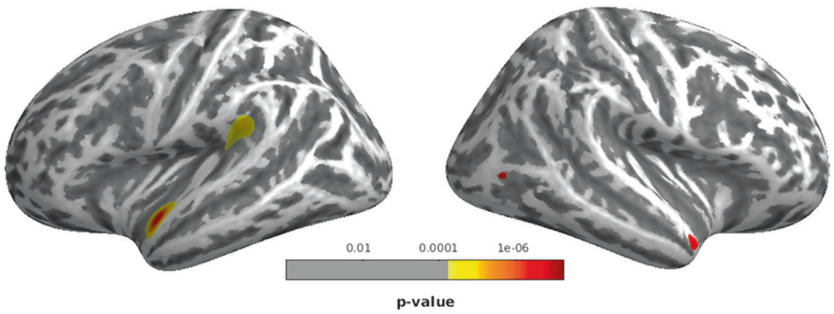

Fig. 2 CT correlates of the paranoid-hallucinatory syndrome (PHS). Negative association of factor 1 paranoid-hallucinatory syndrome (PHS) and cortical thickness (CT) comprising parts of left supramariginal, bilateral superior temporal, and right lateral occipital clusters across patients with major depressive disorder, bipolar disorder, and schizophrenia spectrum disorders. Clusters are shown at $p < 0.05$ peak-level, family-wise error-corrected.

interactions of factor x diagnosis (all *ps* > 0.05, see Supplementary eResults4 and Supplementary eFig. 3–10 for details). Results of the GMV and CT analyses in the matched sample are presented in the supplement (Supplementary eResults 5, Supplementary eTables 3 and 4). Here, results from the total sample could be replicated. We did not find any associations with the DEP and MA factors for both GMV and CT.

Genetic correlates of life-time psychopathology

Our exploratory GWAS revealed genome-wide significant associations for MA and DEP (Fig. 3, Supplementary eFigs. 11–13, Supplementary eTable 5), with intronic lead variants rs10062519 ($p = 1.10e{-}8$) located in *ADAMTS19* for MA and rs11131155 ($p = 4.12e{-}8$) located in *RAD18* for DEP. In the MAGMA gene analysis, a genome-wide significant association was identified for *SYTL1* (DEP, $p = 1.79e{-}6$). The MAGMA gene-set analysis yielded no statistically significant results for any of the three factors after correction for multiple testing (data not shown).

In the PRS association analysis of the complete sample (Fig. 4), we detected a positive effect of PRS for BD on all three factors (PHS: maximum $\beta = 0.13$ at $\varphi = 1e{-}3$ with $R^2 = 0.021$ and adjusted $p = 5.48e{-}5$; MA: maximum $\beta = 0.18$ at $\varphi = 1e{-}3$ with $R^2 = 0.031$ and adjusted $p = 1.17e{-}6$; DEP: maximum $\beta = 0.08$ at $\varphi = 1e{-}4$ with $R^2 = 0.006$ and adjusted $p = 0.038$). Further, a positive effect on PHS was observed for the PRS for MDD (maximum $\beta = 0.07$ at $\varphi = 1e{-}2$ with $R^2 = 0.006$ and adjusted $p = 0.038$) and SZ (maximum $\beta = 0.13$ at $\varphi = 1e{-}3$ with $R^2 = 0.020$ and adjusted $p = 7.06e{-}5$). In the subset analysis of each diagnostic group, none of the effects observed in the complete transdiagnostic sample reached statistical significance (Supplementary eFig. 14).

DISCUSSION

In the present study, exploratory and confirmatory factor analyses of lifetime psychopathology revealed a three-factor model with

Table 4. Results of the lifetime paranoid-hallucinatory syndrome (PHS) and its cortical thickness correlates.

		MNI Coordinates				
Anatomical region	**H**	**X**	**Y**	**Z**	**t-value**	**Cluster size**
Factor I: Paranoid-hallucinatory syndrome: Cortical thickness						
Superior temporal cortex	L	−48.3	−3.62	−12.1	5.07	657
Supramarginal cortex	L	−48.3	−38.5	25.9	4.34	777
Superior temporal cortex	R	48.6	15.6	−22.6	4.11	236
Lateral occipital cortex	R	44.6	−71.7	3.1	4.00	47

Only negative correlations are reported as no positive correlations were detected.
H hemisphere, *L* left, *R* right.

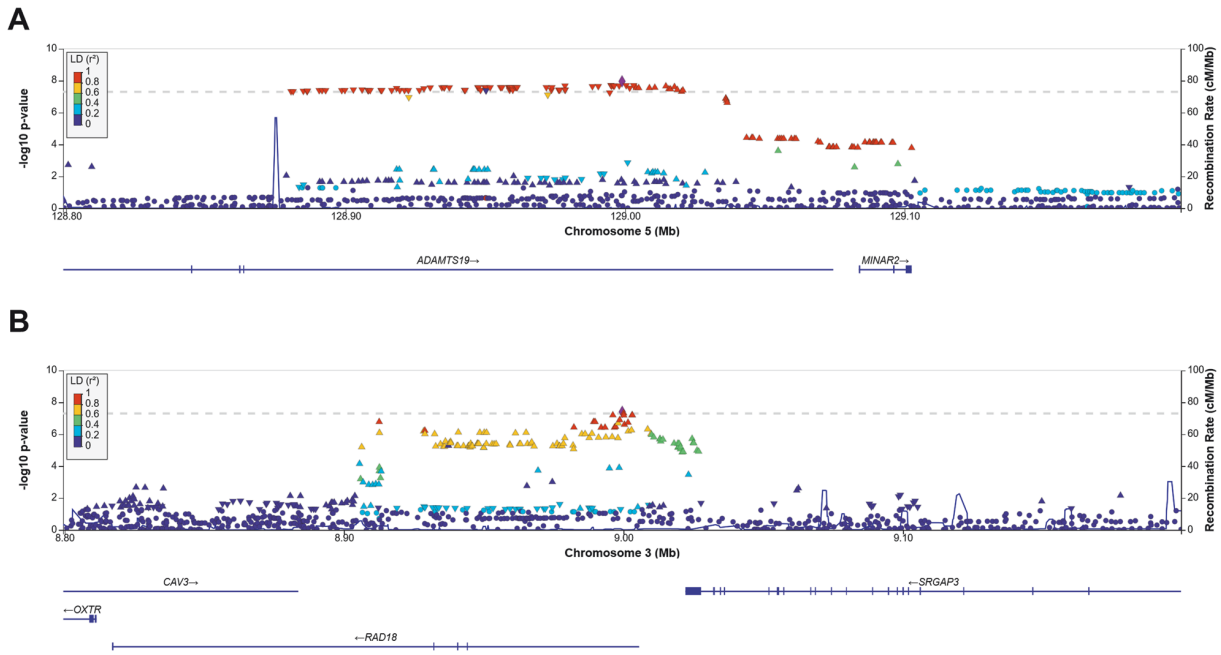

Fig. 3 Genetic loci with genome-wide significant association. Regional plots with a window size of 500 kb are shown for the genome-wide significant associations with MA "mania" (**A**), and DEP "depression" (**B**). The respective lead variants rs10062519 and rs11131155 are depicted as linkage disequilibrium reference variants (purple diamonds). cM centimorgan, LD Ref Var, linkage disequilibrium reference variant, Mb megabase.

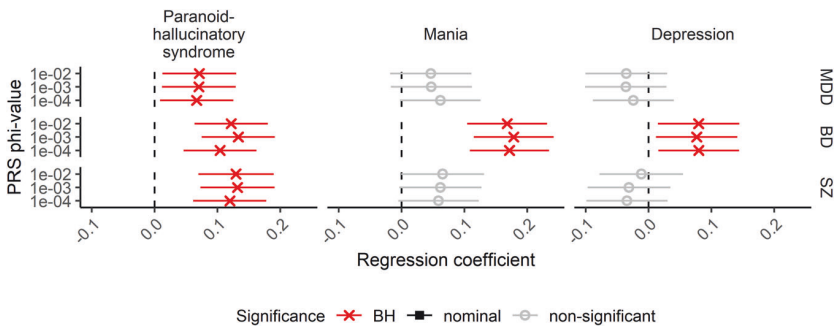

Fig. 4 PRS association analysis. Regression of the three factors on the PRS for MDD, BD, and SZ shows significant effects of PRS for MDD, BD, and SZ on PHS "paranoid-hallucinatory syndrome" and of PRS for BD on MA "mania" and DEP "depression" in the full transdiagnostic sample. BD bipolar disorder, BH Benjamini–Hochberg, MDD major depressive disorder, SZ schizophrenia.

superior fit properties compared to models with less or more factors. Factors were the paranoid-hallucinatory syndrome (PHS), mania (MA) and depression (DEP). In addition, several associations with both brain morphometry and genetics were reported. This study represents a successful advancement of previous research by Stein et al. [34] and David et al. [66] all of them part of the FOR2107 cohort, wherein five factors of acute psychopathology were described and genetically investigated.

Compared to previous factor analytical research in the three diagnoses included in our study, utilizing the OPCRIT, the present factor solution features three factors, while other studies showed an additional negative factor, which was not present in our study. Nevertheless, an overlap exists as previous models also comprised a depression factor and a mania factor (e.g., refs. [15, 67]). The often-reported factors positive and negative symptoms are split into all three factors in the present results while disorganization best fits the present second factor MA.

The derived lifetime psychopathological factors were used to investigate underlying GMV and CT correlates. We were able to detect numerous associations between the PHS and both GMV and CT in both temporal and frontal regions. We did not detect any interactions for both factor x diagnosis on a whole-brain level, nor in post hoc analyses of the significant clusters. These findings do not exclude that the severity of both brain structural alterations and psychopathological syndromes may vary by diagnosis. Our study aligns with previous studies proposing overlaps in acute psychopathology, brain structure as well as genetics across MDD, BD and SSD [11–13, 68]. Combining a data-driven approach to psychopathology with studying neuroanatomical and genetic correlates may help elucidate the biological underpinnings of complex syndromes in psychiatric disorders. Approaches such as those applied in the present study can reveal intra- and inter-disorder heterogeneity and thus could support the establishment of treatments specific to symptom or syndrome in the next step.

When comparing our results to previous dimensional studies, a recent study also identified subcortical volume reductions associated with hallucinations as well as delusions [69], but reductions of superior temporal areas have also been well established in SSD [1, 3, 70, 71]. The present findings are also in line with a recent investigation where psychotic symptoms were negatively correlated with CT in a large sample of SSD patients, relatives and healthy controls [72]. Consistent with previous studies in SSD, we found cortical thinning in the bilateral STG to be correlated with the PHS factor [73], indicating this brain structure to be a core feature of positive symptomatology.

Exploratory GWAS and PRS analyses suggest a contribution of common genetic variants to all three factor dimensions, supporting the hypothesis that symptoms observed in different diagnostic groups may be influenced by the same genetic variants across diagnostic boundaries [14, 29]. Interestingly, the genome-wide significant loci of our GWAS implicated protein-coding genes that both might be linked to psychiatric disorders. *ADAMTS19* is a member of the ADAMTS (a disintegrin and metalloproteinase with thrombospondin motif) family [74], which might be involved in neuroplasticity [75]. The *RAD18* gene encodes for a DNA damage repair protein [74, 76]. Notably, a study by Alsulami and colleagues provided evidence that RAD18 interacts with SETD1A [76], which has previously been associated with SSD at the rare variant level [77, 78]. As it is known that genome-wide significant lead variants do not necessarily exert their effects through the nearest genes (e.g., ref. [79]), the above discussed functional interpretations should be viewed with caution, as further bioinformatic and functional analyses are needed to identify the gene(s) relevant at the identified loci.

Finally, despite the associations at the genetic level, we did not detect an association between the MA or DEP factor and brain morphology. This suggests that even though aspects of lifetime psychopathology might at least be partially influenced by genetic factors, this might not necessarily be detectable on a neural level. It could thus be argued that a dimensional approach is even more important than a narrow nosology as these associations might be subtle and implications for translation into treatment options are not as clear, yet.

Limitations

There are several limitations to be considered: First, as lifetime psychopathology was assessed only at one point in this study, a bias may arise in favor of symptoms that have occurred recently or are currently present, as they could be more salient in the individual's memory. This bias could lead to an overemphasis on these symptoms during the assessment process [80]. As a result, symptoms that occurred in the past may be underreported or forgotten entirely. We tried to circumvent these biases by carefully examining every hospital record available for each patient, but these were not available for all patients included here. In addition, the used psychopathological scale did not include the full symptomatic spectrum, which restricted the identification of psychopathological factors.

Second, sample sizes of each diagnostic category were unequal. The aim of the present study was to investigate syndrome-brain structure and syndrome-genetic associations dimensionally rather than within categorical diagnoses. The presence of psychotic and manic symptoms in the MDD group might be limited, which may result in restricted variance found for the PHS factor. While results can be considered as diagnosis-shared, severity may be differing across diagnoses.

Third, MRI techniques in general might not be able to detect subtle differences in locations of effects if these occurs in close proximity. In addition, true effects between groups might be mapped onto the same neural circuit while in fact there are differences on the underlying cellular level [81].

Fourth, pharmacological treatment was considered as three dummy coded variables to account for the current intake of antidepressants, antipsychotics, and mood stabilizers. This approach does not take into account both the dosage and lifetime cumulative intake of psychotropic medication, which might have influenced our results.

Finally, the available sample size represents a limitation for the genetic analyses, as the robust detection of genetic associations with small effect sizes usually requires meta-analytical efforts involving multiple cohorts [82]. Thus, the exploratory nature of the presented GWAS should be considered in the interpretation of our findings.

CONCLUSION

This study comprehensively investigated the association of lifetime psychopathological dimensions and brain morphometric markers as well as underlying genetic factors. At the level of brain imaging, GMV and CT reductions in temporal, occipital, and limbic structures were found to be correlated with paranoid-hallucinatory symptoms in a transdiagnostic sample. On the genetic level, we identified genome-wide significant loci for MA and DEP factors, as well as positive effects of specific PRS on different factors. These findings suggest that genetic factors contribute to the identified factor dimensions. The results presented in this study highlight the importance of i) dimensional modeling and ii) transdiagnostic research gaining a better understanding of pathophysiological mechanisms underlying MDD, BD and SSD.

DATA AVAILABILITY

The data and code supporting the findings of this study can be accessed by contacting the corresponding author (FS).

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AUTHOR CONTRIBUTIONS

AK* & FS*: data collection, study design, analysis, data interpretation, literature search, writing, figures, *contributed equally; FSD: data collection, study design, genetic analysis, data interpretation, figure, literature search, writing; TFMA, SS, KB, JKP, KGR, TM, FTO, SM, KT, AW, LW, HL, DG, NO, JR, FSTR, SW: data collection and curation, review; AP: data interpretation, review; TH, MR, MMN, IN, UD, TK: funding acquisition, data collection, data curation, review; AJF: data collection, study design, genetic analysis, data interpretation, writing.

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL

Patients gave written informed consent to the study protocol. This study was approved by the local Ethics Committee Marburg (AZ:07/14) and Münster (AZ:2014-422-b-S) according to the Declaration of Helsinki.

ADDITIONAL INFORMATION

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3.3 Genomics yields biological and phenotypic insights into bipolar disorder

More than 300 authors contributed to this large study of the Bipolar Disorder Working Group of the Psychiatric Genomics Consortium. The first, shared second and shared last authors are O'Connell KS, Koromina M*, van der Veen T*, Boltz T*, David FS*, Yang JMK*, Lin K*, Wang X*, Coleman JRI*, Mitchell BL*, McGrouther CC*, Rangan AV*, Lind PA*, Koch E*, Harder A*, Parker N*, Bendl J*, McQuillin A+, Forstner AJ+, Mullins N+, Di Florio A+, Ophoff RA+, and Andreassen OA+.

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In this study, we conducted the largest GWAS meta-analysis of BD to date and performed a plethora of downstream analyses to obtain novel insights into the biology and genetic architecture of BD. As part of the analytical team, I played a significant role in the planning of the scientific work, data collection, evaluation and interpretation. Above all, I was responsible for the cell type-specific analysis and, together with Maria Koromina and Toni Boltz, for the quantitative trait loci integration analyses.

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Article

Genomics yields biological and phenotypic insights into bipolar disorder

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Bipolar disorder is a leading contributor to the global burden of disease[1]. Despite high heritability (60–80%), the majority of the underlying genetic determinants remain unknown[2]. We analysed data from participants of European, East Asian, African American and Latino ancestries (n = 158,036 cases with bipolar disorder, 2.8 million controls), combining clinical, community and self-reported samples. We identified 298 genome-wide significant loci in the multi-ancestry meta-analysis, a fourfold increase over previous findings[3], and identified an ancestry-specific association in the East Asian cohort. Integrating results from fine-mapping and other variant-to-gene mapping approaches identified 36 credible genes in the aetiology of bipolar disorder. Genes prioritized through fine-mapping were enriched for ultra-rare damaging missense and protein-truncating variations in cases with bipolar disorder[4], highlighting convergence of common and rare variant signals. We report differences in the genetic architecture of bipolar disorder depending on the source of patient ascertainment and on bipolar disorder subtype (type I or type II). Several analyses implicate specific cell types in the pathophysiology of bipolar disorder, including GABAergic interneurons and medium spiny neurons. Together, these analyses provide additional insights into the genetic architecture and biological underpinnings of bipolar disorder.

Bipolar disorder (BD) is an often lifelong mood disorder that impairs quality of life, functional ability and is associated with suicidality[5]. Symptoms typically occur in early adulthood[5], with a similar prevalence and incidence rate across the world[6]. Current treatment options include pharmacotherapies such as mood stabilizers, antipsychotics and antidepressants, preferably administered in conjunction with psychosocial interventions[1,5]. However, approximately one-third of patients relapse within the first year of treatment[7].

The heterogeneous nature of the disorder is noted in the fifth edition of *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5), which includes the category 'bipolar and related disorders', encompassing BD type I (BDI), BD type II (BDII) and cyclothymic disorders[8]. The 11th revision of *International Classification of Diseases* (ICD-11) also recognizes BDI and BDII as distinct subtypes[9]. BDI is characterized by episodes of both mania and depression, whereas BDII includes episodes of hypomania and depression. Advances in genetics and neuroimaging have begun to make inroads into the underlying pathophysiology of BD. The Psychiatric Genomics Consortium (PGC) Bipolar Disorder Working Group has spearheaded genetic discoveries in BD[10,11]. A genome-wide association study (GWAS) of 41,917 individuals with BD and 371,549 control individuals identified 64 loci and highlighted calcium channel antagonists as potential targets for drug repurposing[3]. Brain imaging studies have shown decreased cortical thickness, lower subcortical volume and disrupted white matter integrity associated with BD, as well as brain alterations associated with medication use[12]. To date, this research has been conducted almost exclusively on individuals of European (EUR) ancestry.

Here we present the largest to date multi-ancestry GWAS meta-analysis of 158,036 individuals with BD and 2,796,499 control individuals, combining clinical, community and self-reported samples. We identified 337 linkage disequilibrium-independent genome-wide significant variants that map to 298 loci. We hypothesized that differences in source of patient ascertainment, BD subtype and genetic ancestry might lead to differences in genetic architecture, thus we also analysed these groups separately. We provide new insights into the genetic architecture and neurobiological mechanisms involved in BD, with the potential to inform the development of new treatments and precision medicine approaches.

Study population

The current GWAS meta-analysis includes 79 cohorts. Case definitions were based on a range of assessment methods: (semi-)structured clinical interviews (clinical), medical records, registries and questionnaire data (community) and self-reported surveys (self-reported). Details of the cohorts, including sample size, ancestry, and inclusion or exclusion criteria for individuals, are provided in Supplementary Tables 1 and 2 and the Supplementary Note. BD subtype data were available for a subset of individuals within the clinical and community groups. Of individuals with BD (cases), 82.5% in the clinical ascertainment group had BDI, as did 68.7% of individuals in the community ascertainment group ($X^2 = 730$, $P < 2.2 \times 10^{-16}$; Supplementary Table 2). The total number of samples available for analyses included 158,036 cases with BD and 2,796,499 controls (effective n (n_{eff}) = 535,720; see Methods).

Genetic architecture of BD

Given our hypothesis that samples ascertained and assessed by different methods could lead to differences in the genetic architecture, we performed meta-analyses separately for clinical, community and

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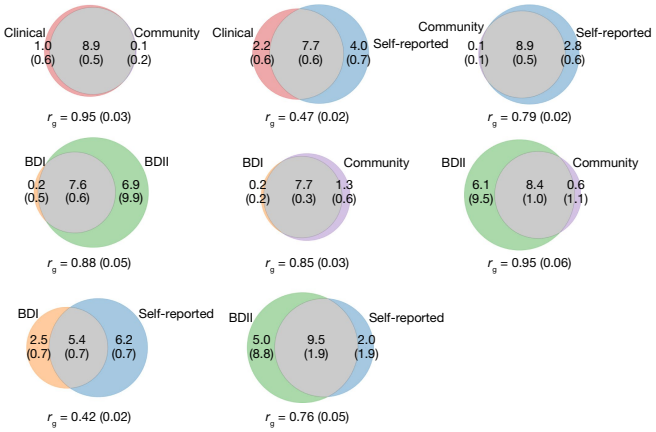

Fig. 1 | Genetic correlation and bivariate MiXeR estimates for the genetic overlap of BD ascertainment and subtypes. Trait-influencing genetic variants shared between each pair (grey) and unique to each trait (colours) are shown. The numbers within the Venn diagrams indicate the estimated number of trait-influencing variants (and standard errors; in thousands) that explain 90% of SNP-h^2 in each phenotype. The size of the circles reflects the polygenicity of each trait, with larger circles corresponding to greater polygenicity. The estimated genetic correlation (r_g) and standard error between BD and each trait of interest from LDSC are shown below the corresponding Venn diagram. Clinical and community samples were stratified into BDI and BDII subtypes if subtype data were available. Model fit statistics indicated that MiXeR-modelled overlap for bivariate comparisons including the BD subtypes (BDI and BDII) were not distinguishable from minimal or maximal possible overlap, and therefore are to be interpreted with caution (see Supplementary Table 4).

self-reported samples. Using linkage disequilibrium score regression (LDSC)[13] and assuming a population prevalence of 2%[14], BD ascertained from clinical samples was more heritable (single-nucleotide polymorphism heritability (SNP-h^2) = 0.22; s.e. = 0.01) than BD ascertained from community samples (SNP-h^2 = 0.05; s.e. = 0.003) or self-reported (SNP-h^2 = 0.08; s.e. = 0.003; Supplementary Table 3). We used genetic correlation[13] and MiXeR[15,16] analyses to further investigate the genetic architecture of BD based on assessment. Although there was a strong genetic correlation (r_g) between clinical and community samples (r_g = 0.95; s.e. = 0.03), the genetic correlation for self-reported BD was significantly greater ($P = 7.4 \times 10^{-28}$) with community samples (r_g = 0.79; s.e. = 0.02) than with clinical samples (r_g = 0.47; s.e. = 0.02; Extended Data Fig. 1).

MiXeR estimated the greatest polygenicity for BD ascertained from self-reported samples, followed by clinical and then community samples (Fig. 1 and Supplementary Table 4). BD in clinical samples was estimated to be the most discoverable, whereas self-reported BD had the lowest discoverability (Extended Data Fig. 2 and Supplementary Table 4). Almost all variants estimated to influence BD in community samples were shared with BD ascertained from clinical samples. The majority of clinical and community BD-influencing variants were also shared with self-reported BD (Fig. 1 and Extended Data Fig. 3). The mean correlation of variant effects in the shared components was high across all groups (community and self-reported r_{g_shared} = 0.95 (s.e. = 0.03), community and clinical r_{g_shared} = 0.99 (s.e. = 0.01) and clinical and self-reported r_{g_shared} = 0.74 (s.e. = 0.06; Supplementary Table 4).

To analyse BD subtypes, we used available GWAS summary statistics for BDI (25,060 individuals) and BDII (6,781 individuals)[3], which come from a subset of the clinical and community samples. Assuming a population prevalence of 1%[17], BDI was more heritable (SNP-h^2 = 0.21; s.e. = 0.01) than BDII (SNP-h^2 = 0.11; s.e. = 0.01). BDI and BDII were highly, but imperfectly, correlated (r_g = 0.88; s.e. = 0.05). The genetic correlations between both subtypes and the community samples were high (BDI r_g = 0.85; s.e. = 0.03, BDII r_g = 0.95; s.e. = 0.06). By contrast, the genetic correlation between BDI and self-reported BD (r_g = 0.42; s.e. = 0.02) was significantly lower ($P = 7.1 \times 10^{-13}$) than between BDII and self-reported BD (r_g = 0.76; s.e. = 0.05; Extended Data Fig. 1).

Given the difference in proportion of individuals with BDI and BDII within the clinical and community cohorts, we evaluated the genetic correlation between BD within clinical and community cohorts, and self-reported BD, after conditioning on the genetic risk for BDI and BDII. After conditioning, the genetic correlation between self-reported BD and BD within community cohorts (r_g = 0.92; s.e. = 0.09) was not significantly different (P = 0.10) than BD in clinical cohorts (r_g = 0.71; s.e. = 0.13).

We show that genetic architecture is different across ascertainment and subtypes, and that these differences appear to be driven by the proportion of BD subtype within the sample. Despite these observed differences, the high correlations of variant effects in the shared components across ascertainment groups support our decision to use a meta-analysis for all BD cases.

Ancestry-specific GWAS meta-analyses

We conducted separate meta-analyses in four ancestral groups. Because the self-reported data differed in genetic architecture from the clinical and community data, we performed separate meta-analyses with and without the inclusion of the self-reported data. Supplementary Table 2 provides a summary of the GWAS meta-analyses, and details of associated loci are described in Supplementary Tables 5–7. Ancestry-specific estimates of SNP heritability and cross-ancestry genetic correlations are provided in Supplementary Table 3.

We identified 261 independent genome-wide significant variants mapping to 221 loci associated with BD in EUR ancestry meta-analyses that included self-reported data, and 94 independent genome-wide significant variants mapping to 88 loci without self-reported data (Supplementary Tables 5 and 6). There were 92 of the 94 independent genome-wide significant variants available for meta-analysis in the self-reported cohorts, of which 78 (85%) were concordant for direction of effect (Supplementary Table 6).

In the East Asian (EAS) ancestry meta-analysis, we identified two BD-associated loci, one of which is novel with an ancestry-specific index variant (rs117130410, chromosome 4: 105734758, build GRCh37; Extended Data Fig. 4 and Supplementary Table 7). Although this variant had a frequency of 16% and 9% in EAS individuals with BD and controls, respectively, it is monomorphic in non-Asian populations. The second locus (rs174576, chromosome 11: 61603510, build GRCh37; Supplementary Table 7) was only identified when the self-reported data were excluded from the meta-analysis as the index variant was not available in the self-reported data. This locus has been identified previously and implicates the *FADS1* and *FADS2* genes[3,18]. No genome-wide significant loci were observed in the African American (AFR) or Latino (LAT) ancestry meta-analyses.

Multi-ancestry meta-analysis

A multi-ancestry meta-analysis of all the datasets identified 337 linkage disequilibrium-independent genome-wide significant variants mapping to 298 loci (Extended Data Fig. 4 and Supplementary Table 8). There was minimal test statistic inflation due to uncontrolled population stratification after correction for principal components in each dataset (LDSC intercept = 1.052 (s.e. = 0.016), attenuation ratio = 0.071 (s.e. = 0.013)).

Of the 298 loci identified in this multi-ancestry meta-analysis, 267 are novel for BD. Of the 64 previously reported BD-associated loci[3], 31 met genome-wide significance in the present analysis containing all samples, and of the 33 that did not, 25 met genome-wide significance in either the clinical samples or in the meta-analysis that excluded self-reported data (Supplementary Table 9). Moreover, the direction

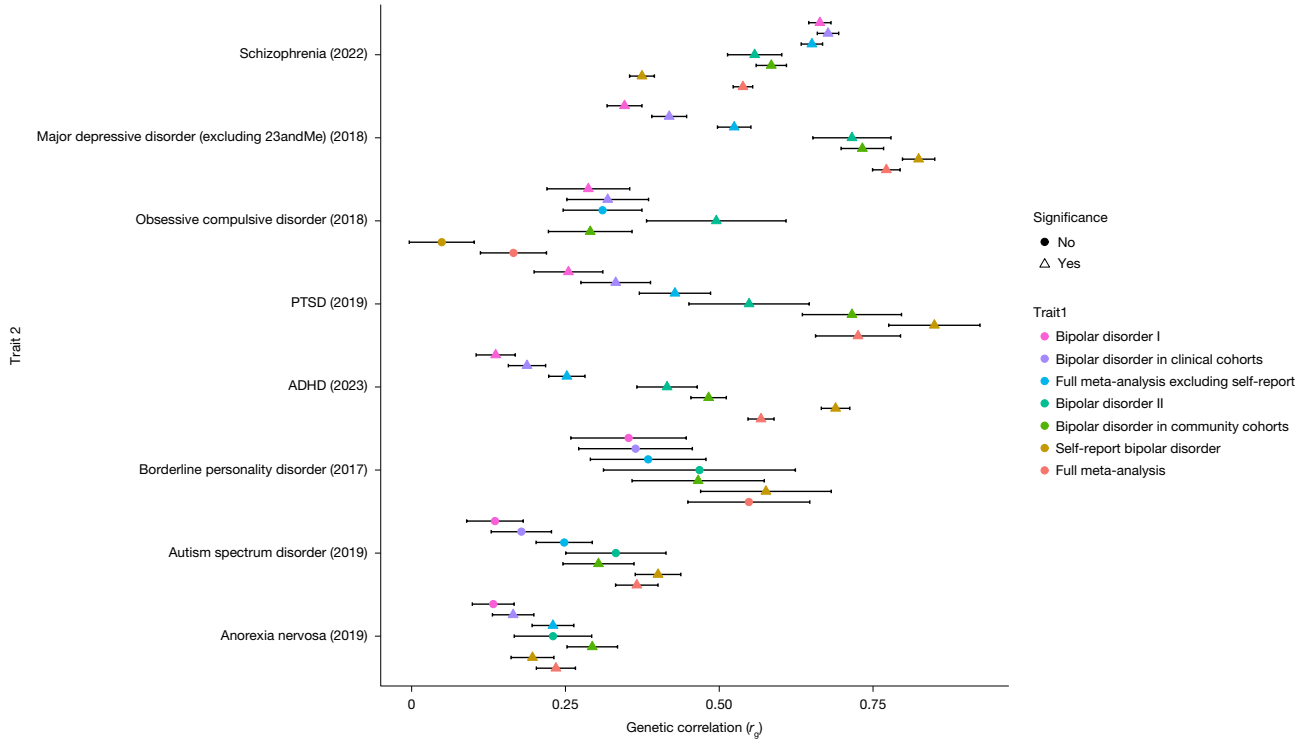

Fig. 2 | Genetic correlations (with standard errors) between BD and other psychiatric disorders. The *y* axis (trait 2) is ordered based on the significance and magnitude of genetic correlation of each trait with BDI. *P* values were calculated from the two-sided *z*-statistics computed by dividing the estimated genetic correlation by the estimated standard error, without adjustment. The standard error for a genetic correlation was estimated using a ratio block jackknife over 200 blocks. The triangles indicate significant results passing the Bonferroni-corrected significance threshold of two-sided $P < 3.6 \times 10^{-5}$. Error bars represent the standard error of the estimate. The year indicated in parentheses after each trait refers to the year in which the GWAS was published. Details are provided in Supplementary Table 13. PTSD, post-traumatic stress disorder.

of association for all top SNPs (12,151 SNPs with $P < 1 \times 10^{-5}$) from the previous GWAS was consistent with the direction of association in this multi-ancestry meta-analysis of all samples (Supplementary Table 9).

When considering the effect of ancestry on the discovery of these 298 loci, one locus (index SNP rs7248481, chromosome 19: 13079957–13122567) was most strongly associated in the EAS ancestry meta-analysis. For all other loci, the association was strongest in the EUR ancestry meta-analysis. The majority of the 298 loci were nominally significant ($P < 0.05$) within the AFR (290 of 298 loci), EAS (257 of 298 loci) and LAT (293 of 298 loci) ancestry-specific meta-analyses, highlighting consistency of signal across the ancestry groups (Supplementary Table 8).

We estimated the proportion of SNP-h^2 accounted for by SNPs within genome-wide significant loci[19]. Compared with only 8.3% accounted for by SNPs within the 64 previously identified loci[3], SNPs within the 298 loci account for 18.5% of the SNP-h^2 of BD (Supplementary Table 10). Moreover, SNPs within the 298 loci also accounted for higher proportions of SNP-h2 in the clinical (64 loci: 8.5%; 298 loci: 17.8%), BDI (64 loci: 8.3%; 298 loci: 17.5%), community (64 loci: 4.8%; 298 loci: 22.6%) and self-reported (64 loci: 2.0%; 298 loci: 21.1%) samples.

We carried out sensitivity meta-analyses excluding the self-reported samples (leaving 67,948 cases and 867,710 controls; $n_{eff} = 191{,}722$) and identified 116 independent genome-wide significant variants mapping to 105 loci (Supplementary Table 11). There was minimal test statistic inflation due to uncontrolled population stratification after correction for principal components in each dataset (LDSC intercept = 1.050; s.e. = 0.012, attenuation ratio = 0.086; s.e. = 0.018). Analysis of self-reported cohorts only (90,088 cases and 1,928,789 controls; $n_{eff} = 344{,}088$) identified 126 loci (Supplementary Table 12). Of the 116 independent genome-wide significant variants identified in the meta-analysis excluding the self-reported samples, 110 variants were available for meta-analysis in the self-reported samples, of which 96 (87%) were concordant (Supplementary Table 11).

Our multi-ancestry meta-analysis identified 298 loci, implicating 337 linkage disequilibrium-independent genome-wide significant variants.

Genetic correlations with other traits

Genome-wide genetic correlations were estimated between EUR ancestry BD GWAS (with and without self-reported data, and when stratified by ascertainment and subtypes) and human diseases and traits via the Complex Traits Genetics Virtual Lab (https://vl.genoma.io) web platform[20] (Fig. 2 and Supplementary Tables 13–15). Most psychiatric disorders, including major depressive disorder, post-traumatic stress disorder, attention deficit–hyperactivity disorder (ADHD), borderline personality disorder and autism spectrum disorder, were more strongly correlated with the full meta-analysis, BDII and BD in community and self-reported samples, than with BDI and BD in clinical cohorts (Fig. 2). By contrast, schizophrenia was more strongly genetically correlated with the full BD meta-analysis excluding self-reported data and with BDI and BD in clinical samples (Fig. 2). This pattern of correlations, together with the observed patterns of genetic architecture, suggest that the self-reported samples include a high proportion of people with BDII.

Polygenic association with BD

Polygenic risk score (PRS) analyses were performed using PRS-CS-auto[21] in 55 EUR ancestry cohorts for which individual-level genotype and phenotype data were available (40,992 cases and 80,215 controls), as well as one cohort of AFR ancestry (347 cases and 669 controls) and

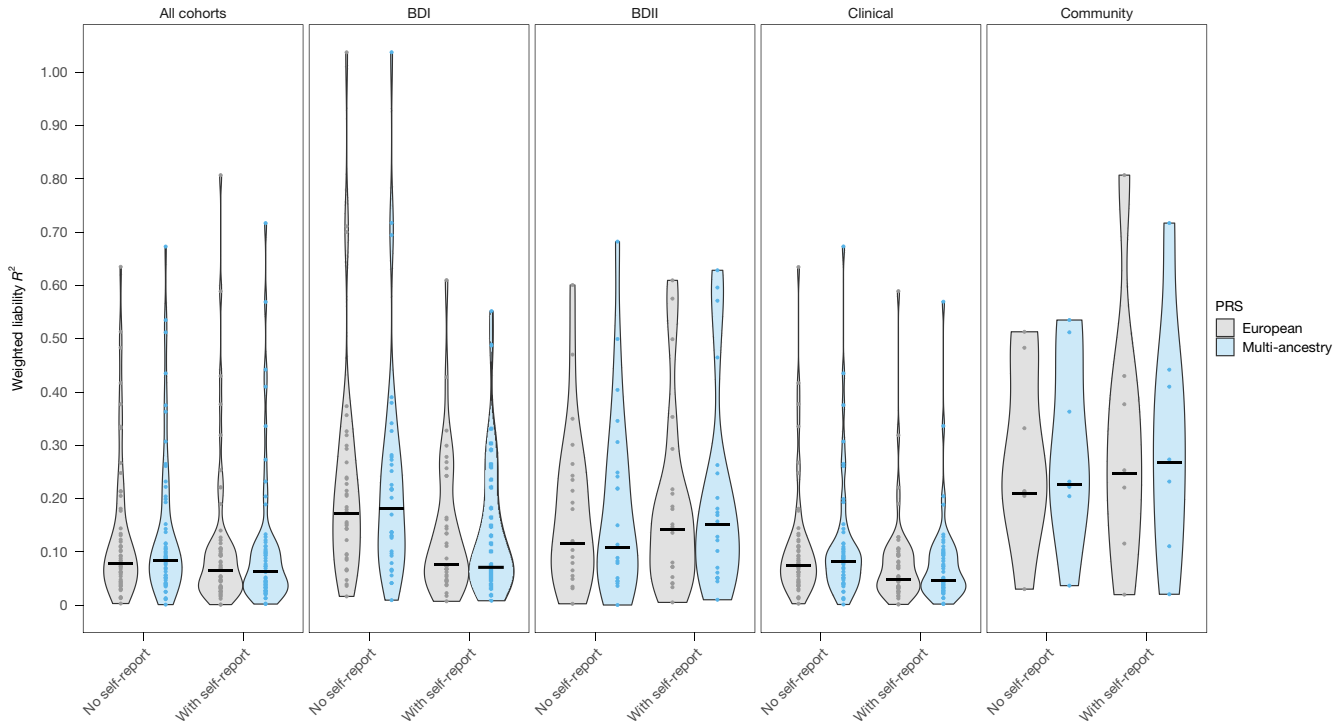

Fig. 3 | Phenotypic variance in BD in EUR cohorts explained by PRSs derived from the multi-ancestry and EUR meta-analyses (with and without self-reported data). Variance explained is presented on the liability scale, assuming a 2% population prevalence of BD. The results (all cohorts) are the median weighted liability R^2 values across all 55 EUR cohorts (40,992 cases and 80,215 controls; n_{eff} = 46,725). Similarly, BDI, BDII, clinical and community panels show the results across 36 BDI cohorts (12,419 cases and 33,148 controls; n_{eff} = 14,607), 21 BDII cohorts (2,549 cases and 23,385 controls; n_{eff} = 4,021), 48 clinical cohorts (27,833 cases and 46,623 controls; n_{eff} = 29,543) and 7 community cohorts (13,159 cases and 36,592 controls; n_{eff} = 17,178). All analyses were weighted by the effective *n* per cohort. The median liability R^2 is represented as a horizontal black line.

three cohorts of EAS ancestry (4,473 cases and 65,923 controls; Supplementary Tables 16–20). In the EUR ancestry cohorts, the variance explained by the multi-ancestry GWAS without the self-reported data (R^2 = 0.090, s.e. = 0.019) was significantly greater than that explained by both the multi-ancestry GWAS including self-reported data (R^2 = 0.058, s.e. = 0.017, $P = 2.72 \times 10^{-4}$) and the EUR ancestry GWAS excluding the self-reported data (R^2 = 0.084, s.e. = 0.018, $P = 5.62 \times 10^{-3}$; Fig. 3a and Supplementary Tables 16 and 21). Individuals in the top quintile (top 20%) for this multi-ancestry GWAS without the self-reported data PRS had an odds ratio of 7.06 (95% CI = 3.9–10.4) of being affected with BD compared with individuals in the middle quintile. The corresponding median area under the receiver operating characteristic curve was 0.70 (95% CI = 0.67–0.73). Therefore, the BD liability explained remains insufficient for diagnostic prediction in the general population.

Similarly, PRS derived from GWAS excluding self-reported data explained significantly more variance in cases of BDI (Fig. 3b and Supplementary Tables 17) and in clinical cohorts (Fig. 3d and Supplementary Tables 19) than when self-reported data were included. Conversely, inclusion of the self-reported data yielded greater median R^2 estimates for the PRS in cases of BDII (Fig. 3c and Supplementary Tables 18) and in community cohorts (Fig. 3e and Supplementary Tables 20); however, these differences were not significant. These results are probably due to increased phenotypic heterogeneity when the self-reported data were included in the PRS discovery sample (see Fig. 2).

PRS analysis of three clinically ascertained EAS cohorts revealed that the PRSs derived from GWAS excluding the self-reported data (Taiwan: EUR ancestry PRS (EUR-PRS) R^2 = 0.069, multi-ancestry PRS (multi-PRS) R^2 = 0.075; Japan: EUR-PRS R^2 = 0.027, multi-PRS R^2 = 0.025; Korea: EUR-PRS R^2 = 0.016, multi-PRS R^2 = 0.022) performed better than those that included self-reported data (Taiwan: EUR-PRS R^2 = 0.026, multi-PRS R^2 = 0.036; Japan: EUR-PRS R^2 = 0.015, multi-PRS R^2 = 0.015; Korea: EUR-PRS R^2 = 0.014, multi-PRS R^2 = 0.017; Supplementary Table 22).

In a clinically ascertained AFR target cohort, the inclusion of self-reported data increased the explained variance (R^2) by both the multi-PRS and the EUR-PRS from 0.010 to 0.23 or 0.22, respectively (Supplementary Table 22).

Pathway, tissue and cell-type enrichment

Gene set enrichment analyses were performed on the summary statistics derived from the multi-ancestry meta-analysis including self-reported data, using MAGMA[22]. We identified significant enrichment of six gene sets (Supplementary Table 23) related to synapse and transcription factor activity. The association signal was enriched among genes expressed in the brain (Supplementary Table 24), and specifically in the early-to-mid-prenatal stages of development (Supplementary Table 25). Single-cell enrichment analyses of brain cell types indicate involvement of neuronal populations from different brain regions, including hippocampal pyramidal neurons and interneurons of the prefrontal cortex and hippocampus (Supplementary Fig. 1), and were largely consistent with findings from the previous PGC-BD GWAS[3]. Similar patterns of enrichment were observed based on ascertainment and subtype (Supplementary Fig. 2). In addition, GSA-MiXeR[19] highlighted enrichment of specific dopamine-related and calcium-related biological processes and molecular functions, as well as GABAergic interneuron development, respectively (Supplementary Table 26).

A recent study[23] has analysed single-nucleus RNA sequencing data of 3.369 million nuclei from 106 anatomical dissections within 10 brain regions and divided cells into 31 superclusters and 461 clusters, respectively, based on principal component analysis of sequenced genes.

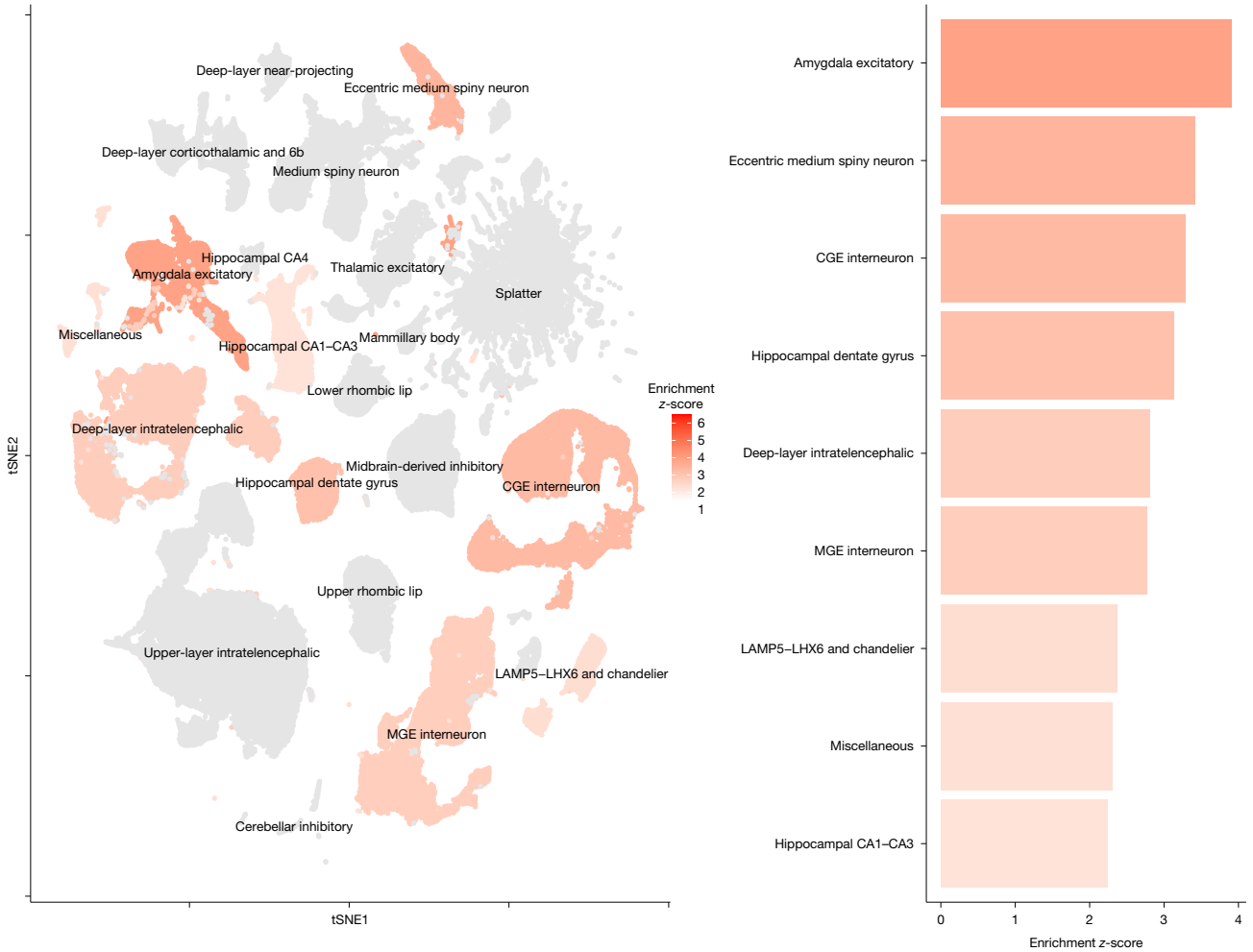

Fig. 4 | Supercluster-level SNP-h^2 enrichment for BD. The *t*-distributed stochastic neighbour embedding (tSNE) plot (naming convention and source of the single-cell data from Siletti et al.[23]; left) is coloured by the enrichment *z*-score. Grey indicates non-significantly enriched superclusters (false discovery rate > 0.05). The bar plot (right) shows the nine significantly enriched superclusters. CGE, caudal ganglionic eminence; MGE, medial ganglionic eminence.

These superclusters were then annotated based on their regional composition within the brain (Fig. 4). We used stratified LDSC[24] to estimate SNP-h^2 enrichment for the top decile of expression proportion genes in each of the 31 superclusters and 461 clusters, as previously described[25]. Heritability was significantly enriched in 9 of the 31 superclusters (Fig. 4), and 49 of the 461 clusters (Extended Data Fig. 5). No enrichment was seen in non-neuronal clusters. Two clusters within the medium spiny neurons, not observed at the supercluster level, were significantly enriched, further supporting the involvement of striatal processes in BD.

Together, these results implicate the synapse, interneurons of the prefrontal cortex and hippocampus, and hippocampal pyramidal neurons as particularly relevant in the molecular biology of BD.

Single-cell enrichment analysis in 914 cell types across 29 non-brain mouse tissues identified significant enrichment in the enteroendocrine cells of the large intestine and delta cells of the pancreas, which remained significant after cross-dataset conditional analyses with a mouse brain tissue dataset (Supplementary Table 27).

Fine-mapping

We performed functional fine-mapping using Polyfun+SuSiE[26] (Supplementary Tables 28 and 29). At a threshold of posterior inclusion probability (PIP) > 0.50, we identified 80 putatively causal fine-mapped SNPs for the multi-ancestry meta-analyses including self-reported data. At the more stringent threshold of PIP > 0.95, we identified 20 putatively causal SNPs. When comparing the number of SNPs within 95% credible sets, the inclusion of multi-ancestry and self-reported data led to smaller credible sets (that is, credible sets with fewer numbers of SNPs). For example, we identified 175 95% credible sets of less than 20 SNPs in the multi-ancestry dataset with self-reported data, compared with 122 in the EUR dataset with self-reported data (Extended Data Fig. 6). Putatively causal SNPs with a PIP > 0.5 were mapped to genes by performing variant annotation with Variant Effect Predictor (VEP; GRCh37) Ensembl release 109 (ref. 27), based on their position relative to annotated Ensembl transcripts and known regulatory features. This analysis identified 71 unique genes annotated to fine-mapped SNPs from the multi-ancestry meta-analysis including self-reported data (Supplementary Table 29).

Common and rare variation convergence

Within loci associated with BD in the multi-ancestry meta-analysis, the 71 genes annotated to putatively causal fine-mapped SNPs (Supplementary Table 29) were enriched for ultra-rare (5 or less minor allele

count) damaging missense and protein-truncating variants in cases of BD in the Bipolar Exome (BipEx) consortium dataset[4] (OR = 1.16, 95% CI = 1.05–1.28, $P = 0.002$), and in cases of schizophrenia in the Schizophrenia Exome Meta-analysis (SCHEMA) dataset[28] (OR = 1.21, 95% CI = 1.02–1.43, $P = 0.024$). This enrichment is similar to that observed for schizophrenia[28] and ADHD[29].

Credible BD-associated genes

In addition to the 71 genes annotated to the fine-mapped putatively causal SNPs as described above, we annotated a further 45 genes to the 80 fine-mapped SNPs by summary data-based Mendelian randomization using expression quantitative trait locus (eQTL) and splicing QTL (sQTL) data, as well as by proximity, that is, the nearest gene to each SNP (Extended Data Fig. 7 and Supplementary Tables 30 and 31). No genes were annotated to the CpGs identified by the methylation QTL (mQTL) analysis (Supplementary Table 30). We then determined whether any of these 116 genes were also identified through the genome-wide gene-based analysis using MAGMA[22], eQTL analyses using transcriptome-wide association study (TWAS) as implemented in FUSION[30] and isoTWAS[31], or through enhancer–promoter interactions[32,33]. This resulted in seven possible approaches by which loci could be mapped to genes, including eQTL evidence (eQTL or TWAS or FOCUS or isoTWAS), mQTL, sQTL, VEP, proximity, MAGMA and enhancer–promoter interactions.

We integrated the results from the post-GWAS analyses described above and identified a credible set of 36 genes identified by at least three of the described approaches (Supplementary Table 31). The *SP4* gene was identified by six of these approaches, and astrocyte and GABAergic neuron-specific regulation of *SP4*, by the genome-wide significant variant rs2107448, was identified from cell-type-specific enhancer–promoter interaction results (Supplementary Table 31). Moreover, the *TTC12* and *MED24* genes were identified by five of the approaches. Eight of the 36 credible genes have synaptic annotations in the SynGO database[34]. Three genes (*HTT*, *ERBB4* and *LR5NF*) were mapped to both postsynaptic and presynaptic compartments. One gene (*CACNA1B*) was mapped to only the presynapse, and four genes (*SHANK2*, *OLFM1*, *SHISA9* and *SORCS3*) were mapped to only the postsynapse (Supplementary Table 32).

On the basis of the lifespan gene expression data from the Human Brain Transcriptome project (www.hbatlas.org)[35], suggestive evidence for two clusters of credible genes was observed based on temporal expression (Extended Data Fig. 8 and Supplementary Table 31). The first cluster showed reduced prenatal gene expression, with gene expression peaking at birth and remaining stable over the life course. Conversely, the second cluster showed a peak in gene expression during fetal development with a drop-off in expression before birth. However, both clusters showed high variability in gene expression across the lifespan.

Together, these results implicate 36 credible genes in BD.

Drug target analyses

Gene set analyses were performed restricted to genes targeted by drugs, assessing individual drugs and grouping drugs with similar actions, as previously described[3,36]. Gene-level and gene set analyses of the multi-ancestry GWAS summary statistics including self-reported data were performed in MAGMA[22], and identified significant enrichment in the targets of anticonvulsant pregabalin (Supplementary Table 33). There was also significant enrichment in the targets of antipsychotics and anxiolytics (Supplementary Table 34).

Examination of the Drug Gene Interaction Database (DGIdb)[37] to identify drug–gene interactions using the credible genes as input genes showed that 15 out of 36 genes were interacting with a total of 528 drugs. Gene set enrichment analysis of these drug–gene interactions showed a significant enrichment ($P < 0.0001$) for targets of the atypical antipsychotic drugs nemonapride and risperidone (Supplementary Table 35). However, after correction for the total number of drugs ($n = 69{,}018$), the enrichment was not significant (false discovery rate > 0.05). In addition, 16 of the 36 credible genes had evidence of tractability with a small molecule in the OpenTargets dataset, including *FURIN*, *MED24*, *THRA*, *ALDH2*, *ANKK1*, *ARHGAP15*, *CACNA1B*, *ERBB4*, *ESR1*, *FES*, *GPR139*, *HTT*, *MLEC*, *MSH6*, *PSMD14* and *TOMM2*.

Among the 36 credible genes, two genes (*ALDH2* and *ESR1*) were within the list of 139 lithium target and interaction partner genes. The results of the network-based separation (S_{AB}) analysis do not indicate a general overlap between the credible genes and lithium target genes in the human protein interactome ($S_{AB} = 0.124$, $z = 1.710$, $P = 0.044$). The positive S_{AB} value indicates that the lithium target genes and the 36 credible genes are separated from each other in the network of protein–protein interactions.

As the credible gene list is primarily derived from our fine-mapping analysis, it is possible that lithium target genes (and interaction partners) are within loci for which significant fine-mapped putatively causal SNPs were not identified. The identification of evidence of tractability with small molecules for some of the credible genes indicates opportunities for novel drug development.

Discussion

We performed, to our knowledge, the largest GWAS of BD, including diverse samples of EUR, EAS, AFR and LAT ancestry, resulting in an over fourfold increase in the number of BD-associated loci: 337 linkage disequilibrium-independent genome-wide significant variants mapping to 298 loci. In the meta-analysis of EUR, the largest ancestry group, we identified over 200 genome-wide significant loci. We also found a novel ancestral-specific association in the EAS cohort. We confirmed our hypothesis that differences in ascertainment and BD subtype might lead to differences in genetic architecture. Post-GWAS analyses provide novel insights into the biological underpinnings and genetic architecture of BD and highlight differences depending on ascertainment of participants and BD subtype. We also showed that multi-ancestry data improved fine-mapping and polygenic prediction.

Enrichment of the common variant associations from this multi-ancestry meta-analysis highlights the synapse, interneurons of the prefrontal cortex and hippocampus, and hippocampal pyramidal neurons as particularly relevant. Exploratory analyses[19] suggest enrichment of dopamine-related and calcium-related biological processes and development of GABAergic interneurons. These findings were further corroborated by enrichment analyses in single-nucleus RNA sequencing data from adult post-mortem brain tissue, which highlighted specific clusters of interneurons derived from the caudal and medial ganglionic eminences and medium spiny neurons predominantly localized in the striatum. Medium spiny neurons are not enriched in depression using the same dataset[25]. Although interneurons derived from ganglionic eminences were also enriched in schizophrenia, stronger signals were observed for amygdala excitatory and hippocampal neurons[25].

A novel finding is that single-cell enrichment analysis of non-brain mouse tissues identified significant enrichment in the enteroendocrine cells of the large intestine and delta cells of the pancreas. Conditional analyses suggest that this enrichment is independent of overlapping genes between these cell types and those expressed in neurons. Stimulation of enteroendocrine cells by short-chain fatty acids promotes serotonin production in the colon, which leads to enhanced levels of serotonin in systemic circulation and in the brain, and is a proposed mechanism by which microbiota influence the gut–brain axis[38,39]. Of note, lithium treatment is shown to upregulate short-chain fatty acid-producing bacteria, highlighting a potential mechanism of action[40].

We mapped genes to the 80 putatively causal SNPs identified from fine-mapping based on seven complementary approaches

and identified a subset of 36 credible genes implicated by at least three of these approaches. The top credible gene, identified by six gene-mapping approaches, was *SP4*, which has also been implicated in schizophrenia through both rare[28] and common[41] variation. Moreover, we clustered the credible genes based on similar patterns of temporal variation in expression over the lifespan and found suggestive evidence for two clusters. Although within cluster gene expression was highly variable across the lifespan, the second cluster had a peak in expression during fetal development aligning with the neurodevelopmental hypothesis of mental disorders[42]. Genes prioritized through fine-mapping were shown to be enriched for ultra-rare damaging missense and protein-truncating variation in the BipEx[4] and SCHEMA[28] datasets, respectively, highlighting convergence of common and rare variant signals as recently shown in schizophrenia[41].

We identified differences in the genetic architecture of BD subtypes related to ascertainment. BD within clinical and community samples was highly but imperfectly correlated, with varying correlations with self-reported BD. The low genetic correlation and minimal genetic overlap between cases ascertained through clinical studies and cases with self-reported BD are driven by a greater proportion of BDI within the clinical and community samples. In line with these results, PRS derived from meta-analyses excluding the self-reported data performed better in clinical and BDI target samples, whereas the inclusion of self-reported data improved the PRS in community and BDII target samples. Moreover, the pattern of correlations between BD and other psychiatric disorders differed with the inclusion of self-reported data. Schizophrenia had the highest genetic correlation with BD without the inclusion of the self-reported data, whereas major depressive disorder was most strongly correlated with BD after the inclusion of the self-reported data. These results suggest that the self-reported samples may include a high proportion of people with BDII. Moreover, this is in line with recent findings in individuals diagnosed with BDII, which showed increasing PRS for depression and ADHD and decreasing PRS for BD over time[43]. However, BD in the outpatient setting may be overdiagnosed in people with conditions such as chronic depression or borderline personality disorder, highlighting a higher rate of comorbid disorders and potential for 'overdiagnosis' of BD within cohorts of this nature[44,45]. We showed that the differences in genetic architecture and phenotypic proportions of the clinical, community and self-reported cohorts with BD affected the replication of previous BD-associated loci. Previously associated loci that fell short of meeting genome-wide significance in the current study were genome-wide significant in the clinical samples and in the meta-analyses that excluded self-reported data, and all top SNPs (12,151 SNPs with $P < 1 \times 10^{-5}$) from the previous GWAS were consistent in direction of association in this multi-ancestry meta-analysis of all samples (Supplementary Table 9).

Investigation of the novel ancestral-specific association in the EAS ancestry meta-analysis in the GWAS Catalog[46] highlights overlaps with genome-wide significant loci for reduced sleep duration[47] and lower educational attainment[48], as well as a suggestive locus ($P < 2 \times 10^{-6}$) for the interaction between cognitive function and major depressive disorder[49]. These findings suggest a role for this genomic region in complex brain-related phenotypes.

The multi-ancestry PRS provided the greatest improvement over the EUR-PRS in two of the three EAS ancestry target cohorts (Korea and Taiwan). More subtle improvements were seen when the EUR target cohorts were analysed. Multi-ancestry training data provided little improvement in the AFR target cohort, which may be due to the genetic heterogeneity of this target cohort[50]. These results highlight the benefits of multi-ancestry representation in the PRS training data, in line with findings from other diseases[51]. The predictive power of this BD PRS shows a substantial improvement compared with previous findings[3]; however, this BD PRS alone still falls short of clinical utility[52].

One limitation is the lack of in-sample linkage disequilibrium estimates for all cohorts due to a lack of in-house raw genotype data for some cohorts. For instance, analysis of the MHC/C4 locus was not considered as the number of samples for which individual-level genotype data were accessible did not increase much since the previous analysis[3]. We used a EUR linkage disequilibrium reference panel to analyse the multi-ancestry meta-analyses[53] in which linkage disequilibrium patterns and interindividual heterogeneity within the ancestry groups are not fully captured. Another limitation is the inclusion of samples with minimal phenotyping. Although this allowed us to achieve large sample sizes, especially in under-represented non-EUR ancestry cohorts, and greatly increase the number of loci identified, minimally phenotyped samples have some shortcomings. For example, minimal phenotyping may result in low specificity association signals, as shown in major depression[54,55], and individuals in community-based biobanks may represent those less severely affected, as shown in schizophrenia[56].

In conclusion, in this large-scale multi-ancestry GWAS of BD, we identified 298 significant BD-associated loci, from which we have demonstrated convergence of common variant associations with rare variant signals and highlight 36 genes credibly implicated in the pathobiology of the disorder. We identified differences in the genetic architecture of BD based on ascertainment and subtype, suggesting that stratification by subtype will be important in BD genetics moving forwards. Several analyses implicate specific cell types in BD pathophysiology, including GABAergic interneurons and medium spiny neurons, as well as the enteroendocrine cells of the large intestine and delta cells of the pancreas. Enrichment of dopamine-related and calcium-related biological processes were also identified, further contributing to our understanding of the biological aetiology of BD.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41586-024-08468-9.

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Article

Methods

Sample description

Details of each of the cohorts, including sample size, ancestry, inclusion and exclusion criteria for cases and controls as well as citations, are provided in Supplementary Table 1 and the Supplementary Note. We included three types of samples: (1) samples in which participants were assessed using semi-structured or structured interviews (clinical), (2) samples in which participants were assessed using medical records, registries and questionnaire data (community), and (3) samples in which participants self-report a diagnosis of BD (self-reported). The clinical samples included 55 cohorts, 46 of which were included in previous PGC-BD GWAS publications[3,10,11]. The community samples included 20 cohorts, 11 of which were included in the previous PGC-BD GWAS[3]. Finally, we included four self-reported cohorts from 23andMe, in which individuals were classified as cases if they self-reported having received a clinical diagnosis or treatment for BD in responses to web-based surveys ("Have you ever been diagnosed with, or treated for, bipolar disorder?").

Individual-level genotype and phenotype data were shared with the PGC for 53 'internal' cohorts, whereas the remaining 26 'external' cohorts contributed summary statistic data.

The final multi-ancestry meta-analysis included up to 158,036 cases and 2,796,499 controls. The total n_{eff}, equivalent to an equal number of cases and controls in each cohort ($4 \times n_{cases} \times n_{controls}/(n_{cases} + n_{controls})$, was 535,720 with 82.3% of participants (proportion of n_{eff}) of EUR ancestry, 4.4% of AFR ancestry, 4.2% of EAS ancestry and 9.1% of LAT ancestry.

The majority of new cohorts included in this study were external community cohorts in which subtype definitions were more difficult to determine, and as such, the total number of BDI and BDII subtype cases does not differ remarkably from the previous PGC-BD GWAS[3] (Supplementary Table 1). Thus, the previous BDI (25,060 cases and 449,978 controls) and BDII (6,781 cases and 364,075 controls) GWAS summary statistic data were used for BDI and BDII analyses in this study.

Genotyping and imputation

Technical quality control was performed separately on each cohort for which individual-level data were provided separately according to standards developed by the PGC[57], including SNP missingness < 0.05 (before sample removal), subject missingness < 0.02, autosomal heterozygosity deviation ($F_{het} < 0.2$), SNP missingness < 0.02 (after sample removal), difference in SNP missingness between cases and controls < 0.02, SNP Hardy–Weinberg equilibrium ($P > 1 \times 10^{-10}$ in BD cases and $P > 1 \times 10^{-6}$ in controls), and mismatches between pedigree and genetically determined sex based on the F statistic of X chromosome homozygosity (female $F < 0.2$ and male $F > 0.8$). In addition, relatedness was calculated across cohorts using identity by descent, and one of each pair of related individuals (pi_hat > 0.2) was excluded, prioritizing exclusion of individuals related to the most others, controls over cases, and individuals from larger cohorts. Principal components were generated using genotyped SNPs in each cohort separately using EIGENSTRAT (v6.1.4; https://www.hsph.harvard.edu/alkes-price/software/)[58]. Genotype imputation was performed using the prephasing/imputation stepwise approach implemented in Eagle (v2.3.5; https://alkesgroup.broadinstitute.org/Eagle/)[59] and Minimac3 (https://genome.sph.umich.edu/wiki/Minimac3)[60] to the Haplotype Reference Consortium (HRC) reference panel (v1.0)[61]. Data on the X chromosome were also available for all 53 internal cohorts, and these were imputed to the HRC reference panel in males and females separately. The remaining 22 external cohorts were processed by the contributing collaborative teams using comparable procedures. Identical individuals between PGC-processed cohorts and external cohorts with suspected sample overlap were detected using genotype-based checksums (https://personal.broadinstitute.org/sripke/share_links/zpXkV8INxUg9bayDpLToG4g58TMtjN_PGC_SCZ_w3.0718d.76) and removed from the PGC cohorts.

Genome-wide association study

For internal cohorts, GWAS were conducted within each cohort using an additive logistic regression model in PLINK (v1.90; https://www.cog-genomics.org/plink2/)[62], covarying for the first five principal components and any others as required, as previously described[3]. Analyses of the X chromosome were performed in males and females separately, with males scored 0 or 2 and females scored 0, 1 or 2. X chromosome analyses were performed only in individuals of EUR ancestry for which individual-level data were available. For external cohorts, GWAS were conducted by the collaborating research teams using comparable procedures. To control test statistic inflation at SNPs with low minor allele frequency (MAF) in small cohorts, SNPs were retained only if cohort MAF was more than 1% and minor allele count was more than 10 in either cases or controls (whichever had smaller n).

Initially, meta-analysis of GWAS summary statistics was conducted using inverse-variance-weighted fixed-effect models in METAL (v2011-03-25; https://genome.sph.umich.edu/wiki/METAL_Documentation)[63] across cohorts within ancestral groups. A genome-wide significant locus was defined as the region around a SNP with $P < 5.0 \times 10^{-8}$ with linkage disequilibrium $R^2 > 0.1$, within a 3,000-kb window, based on the linkage disequilibrium structure of the ancestry-matched HRC reference panel (v1.0)[61], except LAT (EUR panel used). Multi-ancestry meta-analysis was similarly performed by combining cohorts with diverse ancestry using inverse-variance-weighted fixed-effect models in METAL[63]. Given that more than 80% of the included participants were of EUR ancestry, the linkage disequilibrium structure of the EUR HRC reference panel was used to define genome-wide significant loci.

For all meta-analyses, SNPs present in less than 75% of total effective sample size (n_{eff}) were removed from the meta-analysis results. In addition, we used the DENTIST tool (https://github.com/Yves-CHEN/DENTIST) for summary data-based analyses, which leverages linkage disequilibrium from a reference sample (ancestry-matched HRC reference panel (v1.0)[61], except LAT and multi-ancestry for which the EUR panel was used) to detect and filter out problematic variants by testing the difference between the observed z-score of a variant and a predicted z-score from the neighbouring variants[64].

To identify independent association signals ($P < 5 \times 10^{-8}$), the GCTA forward selection and backward elimination process (command 'cojo-slct') was applied using the summary statistics from the EAS, EUR and multi-ancestry meta-analysis (both including and excluding the self-report data), with the EAS and EUR HRC reference panels, respectively[65,66].

The genetic correlation between meta-analyses based on all new cohorts (118,284 cases and 2,448,096 controls) and EUR cohorts from our previous PGC-BD GWAS[3] was $r_g = 0.64$ (s.e. = 0.02), and $r_g = 0.91$ (s.e. = 0.04) when excluding self-reported cohorts. Concordance of the direction of associations in the present GWAS with associations in the previously published BD data were evaluated as previously described[67].

Heritability and genetic correlation

LDSC (https://github.com/bulik/ldsc)[13] was used to estimate the SNP-h^2 of BD from EUR GWAS summary statistics, including all cohorts as well as subgroups by ascertainment and BD subtype. Popcorn was used to estimate SNP-h^2 of BD from non-EUR GWAS summary statistics[68]. SNP-h^2 was converted to the liability scale using a lifetime BD prevalence of 2%. LDSC bivariate genetic correlations were also estimated between EUR BD GWASs (with and without self-report data) and 11 other psychiatric disorders as well, as 1,390 human diseases and traits via the Complex Traits Genetics Virtual Lab (https://vl.genoma.io) web platform[20]. Adjusting for the number of traits tested, the Bonferroni-corrected $P < 3.569 \times 10^{-5}$. Cross-ancestry bivariate genetic correlations were estimated using Popcorn (https://github.com/brielin/Popcorn)[68].

Differences in r_g between phenotype pairs were tested as a deviation from 0 using the block jackknife approach implemented in LDSC[69].

The results of the clinical and community cohort meta-analyses were conditioned on genetic risks for BDI and BDII, to account for differences in proportion of the BD subtypes within these cohorts. Conditioning was conducted using multitrait-based conditional and joint analysis using GWAS summary data (mtCOJO; https://yanglab.westlake.edu.cn/software/gcta/#mtCOJO)[70], implemented in GCTA[65]. mtCOJO is robust to sample overlap between the GWAS of the exposure and outcome. The conditioned summary statistics were evaluated for genetic correlation with self-reported BD using LDSC.

MiXeR

We applied causal mixture models (MiXeR; https://github.com/precimed/mixer)[15,16,71] to investigate the genetic architecture of BD, specifically the overlap between clinical, community and self-report samples, as well as BD subtypes. We first computed univariate analyses to estimate the polygenicity, discoverability and heritability of each trait. These were followed by bivariate analyses to compute the number of shared trait-influencing variants between pairs of traits, and finally trivariate analyses to compute the proportion of shared variants between all three traits analysed. We also determined the correlation of effect sizes of SNPs within the bivariate shared components. For trivariate MiXeR analyses, model optimization procedures were repeated 20 times (20 runs) to obtain the means and standard errors of model parameters. Estimated parameters from the 'run' with the smallest deviation from the median overlap pattern were then selected and reported.

Polygenic association with BD

We used PRS-CS-auto[21] to compute PRSs in target cohorts, using a discovery GWAS in which the target cohort was left out. Given that the majority of the individuals included in the meta-analysis were of EUR descent, we used the EUR linkage disequilibrium reference panel based on UK BioBank data as provided by PRS-CS developers (https://github.com/getian107/PRScs). Raw scores were standardised to *z*-scores, and covariates including sex, the first five principal components and any others as required (as above for each cohort GWAS) were included in the logistic regression model, via the glm() function in R[72], with family=binomial and link=logit. The variance explained by PRS (R^2) was first converted to Nagelkerke's pseudo-R^2 via the fmsb package in R (https://cran.r-project.org/web/packages/fmsb/index.html), and then converted to the liability scale to account for the proportion of cases in each cohort and the population prevalence of BD[73]. We have provided R^2 values for BD assuming a population prevalence of 2%, based on a recent multinational survey[14]. The weighted average R^2 values were then calculated using the n_{eff} for each cohort. PRS-specific medians and their confidence intervals were computed using non-parametric bootstrap replicates (10,000 resamples with replacement). The odds ratios for BD for individuals in the top quintile of PRS compared with those in the middle quintile were calculated for all cohorts. Similarly, the area under the curve (AUC) statistic was calculated via the pROC package in R (https://cran.r-project.org/web/packages/pROC/index.html), for which we performed a training and testing procedure by taking 80% of the individuals in a given cohort on which to train the model, and tested the predictability in the remaining 20% of individuals. Ten random samplings of training and testing sets were performed in all cohorts, and the median AUC after all permutations is provided Supplementary Tables 16–22. The median confidence intervals for the AUC were similarly averaged across the ten random permutations. These AUC statistics were calculated based on the logistic regression model that includes the standardized PRS as a predictor and principal component covariates. To assess the gain in AUC due to the PRS itself, we subtracted the median AUC of the model containing only the covariates from the full model, reported in Supplementary Tables 16–22 as AUC.

Gene and gene set association analysis

Gene-level, gene set and tissue set associations were performed using a SNP-wise mean model (±10-kb window) implemented in MAGMA (https://ctg.cncr.nl/software/magma)[22]. Bonferroni correction was used to control for multiple testing. In addition, we performed gene set analysis with GSA-MiXeR (https://github.com/precimed/gsa-mixer)[19], which quantifies partitioned heritability attributed to $n = 10{,}475$ gene sets from the Gene Ontology[74] and SynGO[34] databases, alongside their fold enrichment with respect to a baseline model. The GSA-MiXeR full model incorporates 18,201 protein-coding genes, using a joint model to estimate heritability attributed to each gene based on GWAS summary statistics and HRC[59] reference panel to account for linkage disequilibrium between variants. The baseline model in GSA-MiXeR accounted for a set of 75 functional annotations[75], as well as accounting for MAF-dependent and linkage disequilibrium-dependent genetic architecture. The heritability model in GSA-MiXeR was estimated using Adam (method for stochastic gradient-based optimization of the likelihood function)[76]. Standard errors of fitted parameters were estimated from the observed Fisher's information matrix (the negative Hessian matrix of the log-likelihood function).

Identified credible genes were further assessed for enrichment in synaptic processes using the SynGO tool (v1.2; https://www.syngoportal.org/) with default settings[34].

Cell-type-specific enrichment analyses

Single-cell enrichment analyses of brain cell types were performed according to Mullins et al.[3]. In brief, from five publicly available single-cell RNA sequencing datasets derived from human[77,78] and mouse[79–81] brain tissues, 10% of genes with the highest gene expression specificity per cell type were extracted. After MAGMA[22] gene analysis of the multi-ancestry GWAS summary statistics including self-reported data using an annotation window of 35 kb upstream and 10 kb downstream of the gene boundaries and the 1,000 Genomes phase 3 EUR reference panel, MAGMA gene set analyses were conducted for all cell types in each dataset, respectively. Within each dataset, false discovery rate (FDR)-adjusted $P < 0.05$ was considered statistically significant.

In addition, we performed an exploratory single-cell enrichment analysis in 914 cell types across 29 non-brain mouse tissues as implemented in FUMA[82]. Cell types with FDR-adjusted $P < 0.05$ were considered statistically significant. Moreover, to determine that identified enrichment was not due to overlapping genes with neuronal cell types, we performed cross-dataset conditional analyses of significantly enriched cell types with mouse brain tissue.

Single-nucleus RNA sequencing enrichment

We used the Human Brain Atlas single-nucleus RNA sequencing dataset[23] consisting of 3.369 million nuclei sequenced using single-nucleus RNA sequencing. The nuclei were from adult post-mortem donors, and the dissections focused on 106 anatomical locations within 10 brain regions. Following quality control, the nuclear gene expression patterns allowed the identification of a hierarchy of cell types that were organized into 31 superclusters and 461 clusters. In the current paper, we used the same naming system for the cell types and the brain regions as in Siletti et al.[23]. We estimated SNP-h^2 enrichment for the top decile of expression proportion genes (approximately 1,300 genes) in each of the 31 superclusters and 461 clusters, respectively, using stratified LDSC[24], as previously described[25]. We used FDR correction (FDR < 0.05) to account for multiple comparisons.

Fine-mapping

We performed functional fine-mapping of genome-wide significant loci via Polyfun-SuSiE[26], using functional annotations of the baseline-LF2.2 UKB model and linkage disequilibrium estimates from the HRC EUR ($n = 21{,}265$) reference panel. The maximum number of causal variants

per fine-mapped region was adjusted accordingly based on the results from the conditional analysis. We excluded loci that fell within the MHC locus (chromosome 6: 28000000–34000000, build GRCh37) due to the known complexity of the linkage disequilibrium architecture in that region. Genome-wide significant locus ranges with a linkage disequilibrium $R^2 > 0.1$ were used as fine-mapping ranges. Putatively causal SNPs (PIP > 0.50 and part of 95% credible set) were mapped to genes by performing variant annotation with VEP (GRCh37) Ensembl release 75 (https://www.ensembl.org/info/docs/tools/vep/index.html)[27].

Convergence of common and rare variation

Data from the BipEx consortium[4] (13,933 cases of BD and 14,422 controls) were used to assess the convergence of common and rare variant signals, using a similar approach as previously used for schizophrenia[41]. This dataset includes approximately 8,200 individuals with BDI and 3,400 individuals with BDII, whereas the remainder of the sample lack BD subtype information. Ultra-rare variants (5 or less minor allele count) for damaging missense (missense badness, PolyPhen-2 and regional constraint score of more than 3) and protein-truncating variants (including transcript ablation, splice acceptor variants, splice donor variants, stop gained and frameshift variants) were considered. An enrichment of rare variants in genes prioritized through fine-mapping in cases relative to controls were assessed using a Fisher's exact test. Given the genetic overlap between BD and schizophrenia, we repeated the analysis in data from the Schizophrenia Exome Meta-analysis (SCHEMA) cohort (24,248 schizophrenia cases and 97,322 controls)[28]. Using the same approach as taken in the SCHEMA[28] and BipEx[4] papers, background genes included all genes surveyed in each sequencing study, respectively. As a sensitivity analysis, we further evaluated the enrichment of synonymous variants in the credible genes in cases of BD of the BipEx cohort and found no enrichment (OR = 0.96, 95% CI = 0.935–0.985).

QTL integrative analysis

We conducted different QTL integration analyses to elucidate molecular mechanisms by which variants associated with BD might be linked to the phenotype. Summary data-based Mendelian randomization (SMR; v1.3; https://yanglab.westlake.edu.cn/software/smr/)[83] with subsequent heterogeneity in dependent instruments (HEIDI)[70] tests were performed for eQTLs, sQTLs and mQTLs. Data on eQTLs and sQTLs were obtained from the BrainMeta study (v2; $n = 2{,}865$)[84], whereas data on mQTLs were obtained from the Brain-mMeta study (v1; $n = 1{,}160$)[85]. Putatively causal SNPs identified from fine-mapping, as outlined above, were used as the QTL instruments for the SMR analyses. Using the BD GWAS and QTL summary statistics, each putative causal SNP was analysed as the target SNP for probes within a 2-Mb window on either side using the --extract-target-snp-probe option in SMR. The EUR HRC linkage disequilibrium reference panel was used for the analyses of the multi-ancestry meta-analysis. A Bonferroni correction was applied for 2,021 tests, that is, SNP-QTL probe combinations, in the eQTL analysis ($P_{SMR} < 2.47 \times 10^{-5}$), 6,755 tests in the sQTL analysis ($P_{SMR} < 7.40 \times 10^{-6}$) and 2,222 tests in the mQTL analysis ($P_{SMR} < 2.25 \times 10^{-5}$). The significance threshold for the HEIDI test was $P_{HEIDI} \geq 0.01$. Additional eQTL integration analyses were conducted using TWAS (http://gusevlab.org/projects/fusion/), FOCUS and isoTWAS (https://github.com/bhattacharya-a-bt/isotwas). Details related to these analyses are provided in the Supplementary Note.

Enhancer–promoter gene interactions

To investigate enhancer–promoter interactions influenced by BD GWAS variants, we utilized cell-type-specific enhancer–promoter maps from a multi-omics dataset, which included joint single-nucleus ATAC–single nucleus RNA sequencing and cell-specific Hi-C data from developing brains. We used the activity-by-contact (ABC) model[32,33] for this analysis. Following the authors' guidelines, we excluded enhancer–promoter interactions that (1) had an ABC score below 0.015, (2) involved ubiquitously expressed genes or genes on the Y chromosome, or (3) included genes not expressed in major brain cell types. Focusing on the BD GWAS, we selected only those enhancer–promoter links that overlapped genome-wide significant SNPs (with peaks extended by 100 bp on both sides to increase overlap) or their linkage disequilibrium buddies ($R^2 \geq 0.8$). This selection process yielded 11,023 enhancer–promoter links. We then overlapped these putative disease-relevant variants with enhancer–promoter links to prioritize causal genes. To avoid multiple associations for a single variant, we applied the ABC-Max approach[33], retaining only the enhancer–promoter links with the highest ABC score for each peak.

Credible gene identification

We have provided a set of credible genes by integrating information from various gene-mapping strategies, using a similar approach previously described[86] (Extended Data Fig. 7 and Supplementary Table 31). First, genes identified through fine-mapping, and QTL (eQTL, mQTL and sQTL) analyses using SMR and proximity (nearest gene within 10 kb) to fine-mapped putatively causal SNPs were included. The identified set of 116 genes were then further assessed based on gene-level associations (MAGMA)[22], additional integrative eQTL analyses[30,31] and enhancer–promoter gene interactions[32,33]. The criteria for filtering genes from the different eQTL methods were: (1) SMR adjusted $P < 0.05$ and HEIDI test $P > 0.01$, (2) TWAS adjusted $P < 0.05$ and colocalization probability (COLOC.PP4) > 0.7, (3) FOCUS posterior inclusion probability > 0.7 and within a credible set, and (4) isoTWAS permutation $P < 0.05$, isoTWAS poster inclusion probability > 0.7 and within a credible set (Extended Data Fig. 7). Genes annotated by at least one of these eQTL approaches were confirmed as having eQTL evidence (Supplementary Table 31). Thus, seven approaches were considered by which loci could be mapped to genes, including eQTL evidence (eQTL or TWAS or FOCUS or isoTWAS), mQTL, sQTL, VEP, proximity, MAGMA and enhancer–promoter interactions.

Temporal clustering of credible genes

Lifespan gene expression from the Human Brain Transcriptome project (www.hbatlas.org)[35] was used to cluster the list of credible genes based on their temporal variation. The gene expression and associated metadata were acquired from the Gene Expression Omnibus (GEO accession GSE25219). The data consist of 57 donors 5.7 weeks post-conception to 82 years of age with samples extracted across regions of the brain. Before filtering gene expression for the list of credible genes, gene symbols of both credible genes and the gene expression dataset were harmonized using the 'limma' package in R (https://www.bioconductor.org/packages/release/bioc/html/limma.html), which updates any synonymous gene symbols to the latest Entrez symbol. Gene expression was available for 34 of the 36 credible genes. Within a given brain region, the expression of each gene was then mean centred and scaled. Outliers in gene expression more than 4 standard deviations from the mean were removed. To generate a single gene expression profile for each gene across the lifespan, at a given age, the mean gene expression for a given gene was taken across brain regions, and in some cases across donors. This resulted in a matrix in which each gene had a single expression value for each age across the lifespan. This gene expression-by-age matrix was then used to cluster the credible genes by the lifespan expression profiles using the R package 'TMixClust' (https://www.bioconductor.org/packages/release/bioc/html/TMixClust.html). This method used mixed-effect models with non-parametric smoothing splines to capture and cluster non-linear variation in temporal gene expression. We tested $K = 2$ to $K = 10$ clusters performing 50 clustering runs to analyse stability. The clustering solution with the highest likelihood (that is, the global optimum using an expectation maximization technique) is selected as the most stable solution across the 50 runs for each of the trials testing 2–10 clusters. We compared the average silhouette width across the $K = 2$ to $K = 10$ clusters and selected that

with the maximum value as the optimal number of clusters. The highest average silhouette width was 0.24 for two clusters, whereas the lowest was 0.17 for four clusters. Overall, evidence was suggestive for a two-cluster solution for the temporal expression of credible genes.

Drug enrichment analyses

Gene set analyses were performed restricted to genes targeted by drugs, assessing individual drugs and grouping drugs with similar actions as previously described[3,36]. Gene-level and gene set analyses of the multi-ancestry GWAS summary statistics including self-reported data were performed in MAGMA (v1.10)[22], as outlined above for cell-type-specific enrichment.

Gene sets were defined comprising the targets of each drug in the Drug Gene Interaction database DGIdb (v5.0.6)[37]; the Psychoactive Drug Screening Database Ki DB[87]; ChEMBL (v27)[88]; the Target Central Resource Database (v6.7.0)[89]; and DSigDB (v1.0)[90]; all downloaded in October 2020. Multiple testing was controlled using a Bonferroni-corrected significance threshold of $P < 5.41 \times 10^{-5}$ (924 drug sets with at least 10 valid drug gene sets) for drug set analysis and $P < 5.49 \times 10^{-4}$ (91 drug classes) for drug-class analysis, respectively.

We also assessed whether any of the 36 credible genes were classified as druggable in the OpenTargets platform (https://genetics.opentargets.org/).

In addition, gene set analyses were also performed to test the enrichment of drug–gene interactions on only credible genes as described above. Moreover, we investigated whether any lithium target genes, as well as their interaction partners, were among the 36 credible genes using the latest version of the human protein interactome[91]. We calculated the S_{AB} between credible genes and lithium target genes, in which a significant overlapping network neighbourhood would be indicative of functional similarity[92].

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

Genome-wide association summary statistics for these analyses are available at https://www.med.unc.edu/pgc/download-results/. The full GWAS summary statistics for the 23andMe datasets will be made available through 23andMe to qualified researchers under an agreement with 23andMe that protects the privacy of the 23andMe participants. Please visit https://research.23andme.com/collaborate/#dataset-access for more information and to apply to access the data. After applying with 23andMe, the full summary statistics including all analysed SNPs and samples in the GWAS meta-analyses will be accessible to the approved researchers. Genotype data are available for a subset of cohorts, including dbGAP accession numbers and/or restrictions, as described in the 'Cohort descriptions' section of the supplementary materials.

Code availability

No custom code was developed for this study. All software and tools used for the analyses presented are publicly available and referenced within the respective sections in the Methods of the article.

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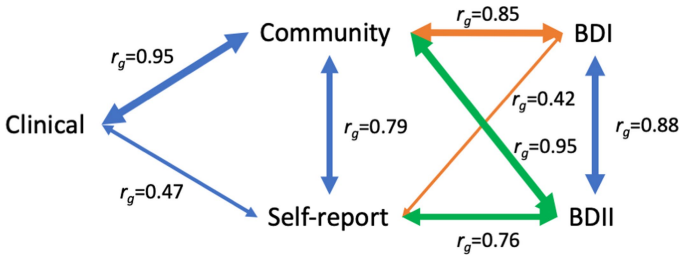
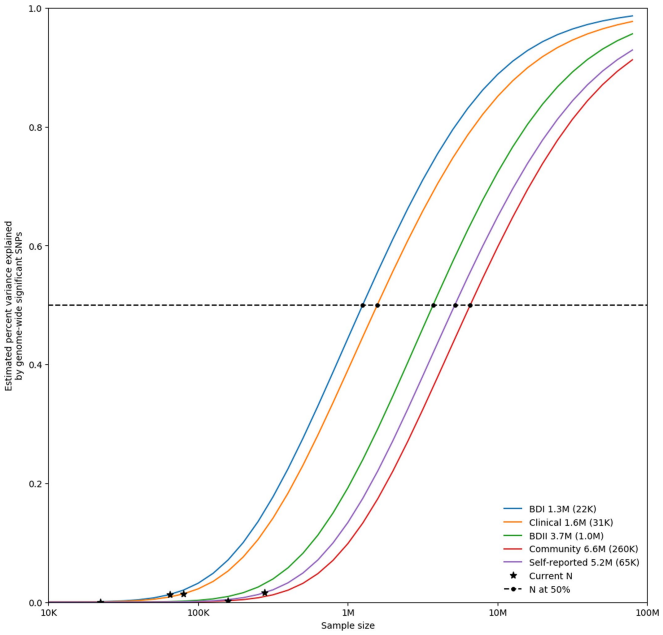
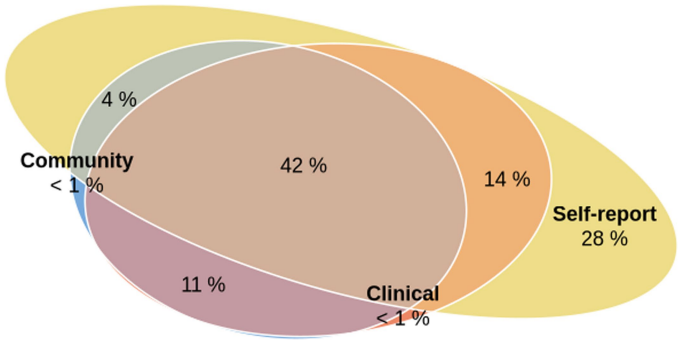


Extended Data Fig. 1 | Network diagram of the genetic correlations between BD ascertained from Clinical, Community and Self-report samples, as well as BD-subtypes (BDI and BDII). The line widths are proportional to the strength of the correlations between pairs. BDI: bipolar disorder I, BDII: bipolar disorder II.



Extended Data Fig. 2 | Univariate MiXeR estimates of the required effective sample size needed to capture 50% of the genetic variance (horizontal dashed line) associated with each BD ascertainment and subtype. N and Sample size refer to the effective sample size. The estimated effective sample size (and standard errors) are given in the legend alongside each trait name.



Extended Data Fig. 3 | Trivariate MiXeR estimates for the genetic overlap of BD from Clinical, Community and Self-report samples. The percentages show the proportion of trait-influencing variants within each section of the Venn diagram relative to the sum of all trait-influencing variants across all samples. The size of the circles reflects the polygenicity of each trait.

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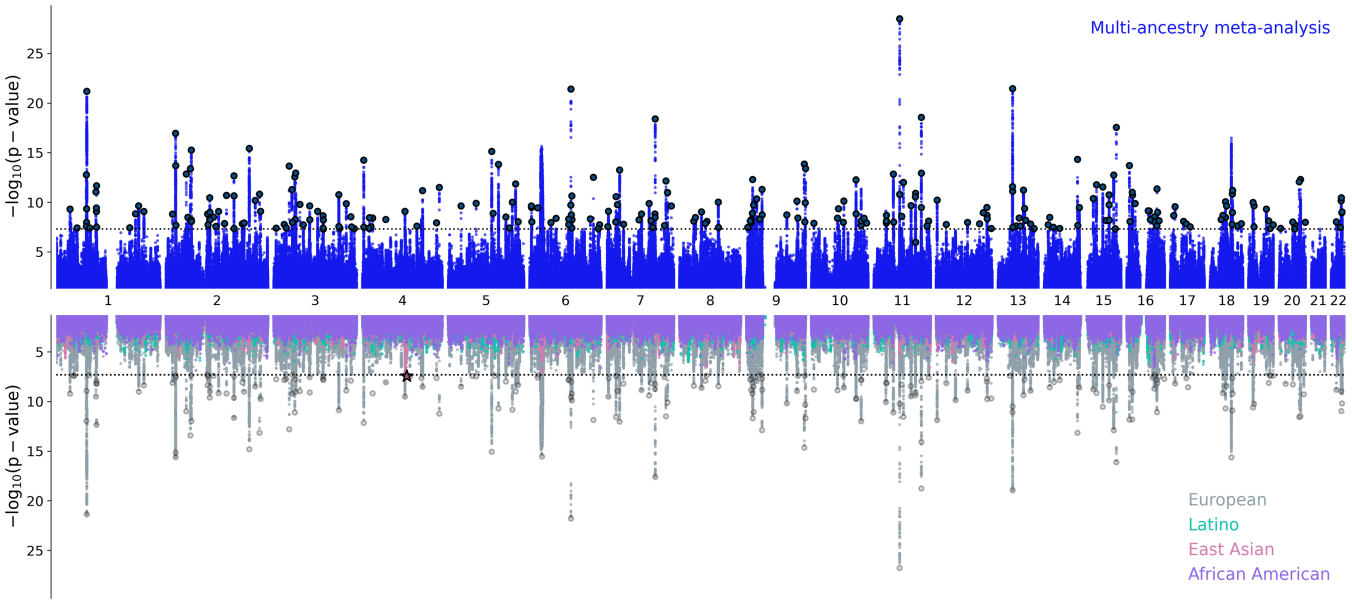
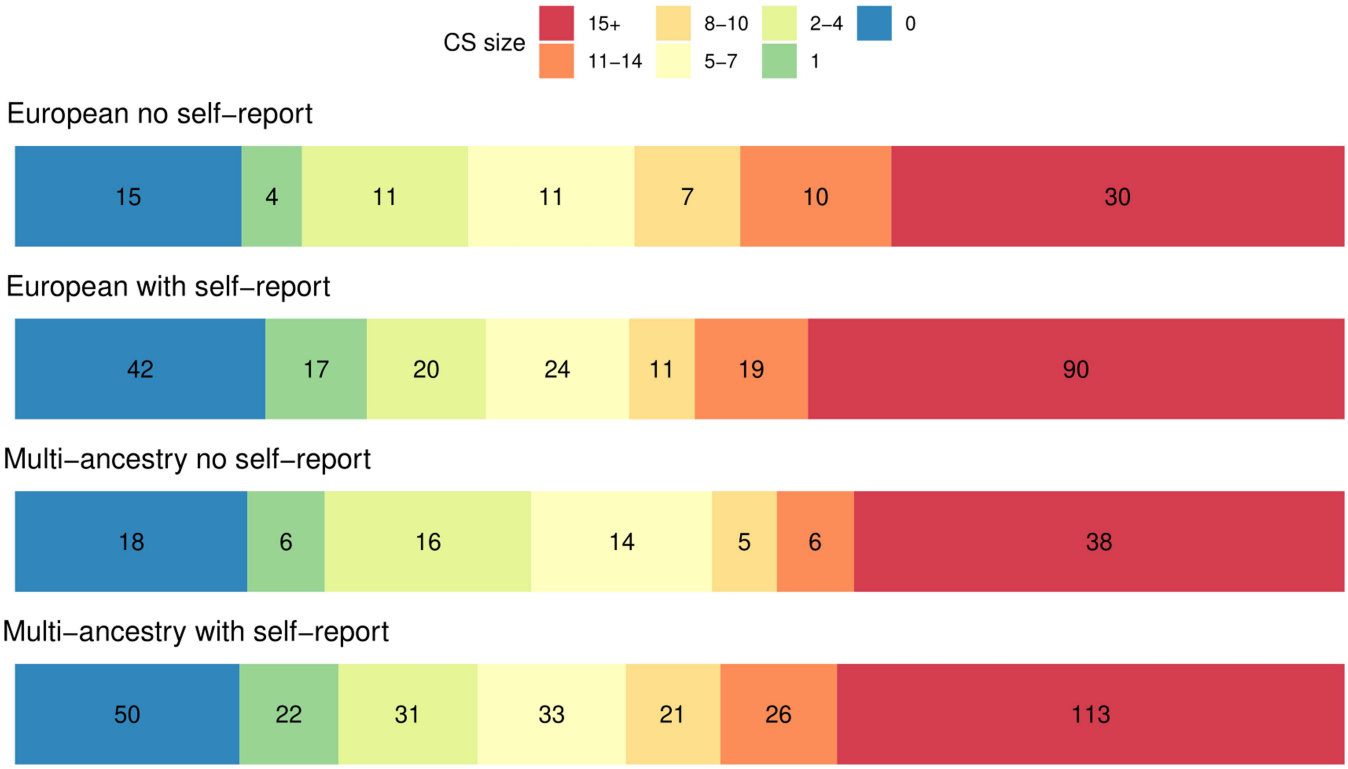
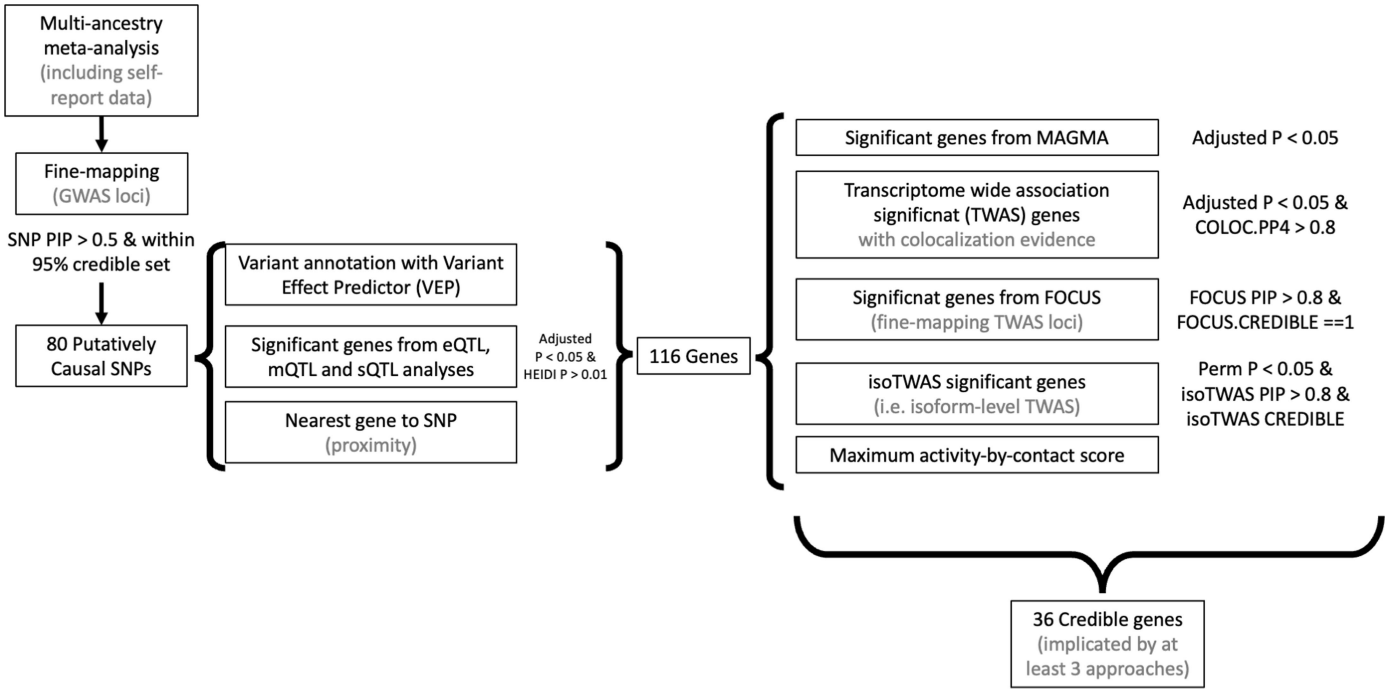


Extended Data Fig. 4 | Miami plot for BD genome-wide meta-analyses, including all cohorts. Upper panel: the multi-ancestry meta-analysis identified 298 genome-wide significant (GWS) loci. Lower panel: porcupine plot showing the results of the Latino (0 GWS loci), African American (0 GWS loci), East Asian (1 GWS locus) and European (229 GWS loci) meta-analyses. The x-axes show genomic position (chromosomes 1–22), and the y axes show statistical significance as −log10[p-value]. P-values are two-sided and based on an inverse-variance-weighted fixed-effects meta-analysis. The dashed black lines show the GWS threshold ($P < 5 \times 10^{-8}$). The star indicates the position of the East Asian GWS locus (rs117130410, 4:105734758, build GRCh37).

Extended Data Fig. 5 | Cluster-level SNP-heritability enrichment for bipolar disorder. The t-distributed stochastic neighbor embedding (tSNE) plot (left) (from Siletti et al.[23]) is coloured by the enrichment z-score. Grey indicates non-significantly enriched superclusters (FDR > 0.05). The barplot (right) shows the top 35 significantly enriched clusters. The numbers in parentheses on the y-axis indicate the cell type clusters as defined in Siletti et al.[23].



Extended Data Fig. 6 | Number of SNPs within the smallest 95% credible sets (CS) from meta-analysis of European and multi-ancestry meta-analyses when excluding and including self-report data. Colours represent CS of varying size, with blue CS containing 0 SNPs and red CS containing 15+ SNPs. All fine-mapped SNPs regardless of their PIP were used to assess the size of the 95% credible sets.



Extended Data Fig. 7 | Methods and criteria for credible gene identification.

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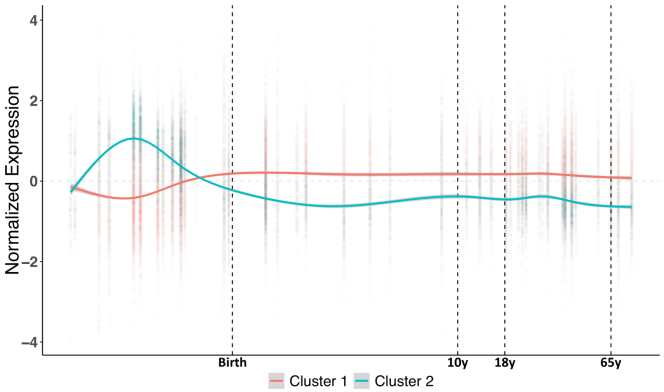

Extended Data Fig. 8 | Clustering of patterns of temporal variation in expression of 34 credible genes. Cluster 1 (n = 21 genes) shows reduced prenatal gene expression, with gene expression peaking at birth and remaining stable over the life-course. Cluster 2 (n = 13 genes) includes genes with a peak gene expression during fetal development with a drop-off in expression before birth. Genes within each cluster are described in Supplementary Table 31. To illustrate the variability in gene expression within each cluster we plot each donor expression value in each sampled brain region for the 34 credible genes as individual points. Smoothing splines used to illustrate the age trajectory for each cluster is based on generalized additive models with the predicted 95% confidence interval in grey. We use age in days to plot the variation in gene expression with the x-axis on a log2 scale and labels for birth, 10, 18, and 65 years of age as reference points.

4 Discussion

The following chapter highlights key findings from the three studies included in this doctoral thesis, briefly discusses their significance in relation to existing literature, and outlines directions for future research regarding the role of common genetic variation in affective and psychotic disorders.

In the first and second study we investigated how common genetic variants are associated with symptom dimensions of acute (David *et al.*, 2023) and lifetime (Krug *et al.*, 2024) psychopathology shared across MDD, BD, and SSD. As suggested by initiatives such as the Research Domain Criteria (RDoC) project (Cuthbert, 2014), we adopted a transdiagnostic perspective that focuses on dimensions of behavior observed across diagnostic boundaries rather than on existing diagnostic groupings. In the PRS analyses of the transdiagnostic sample we found associations of individual symptom dimensions with the polygenic liability for BD and SCZ, respectively, e.g., between the PRS for SCZ and the dimension of paranoid-hallucinatory syndrome (David *et al.*, 2023) and between the PRS for BD and the dimension of mania (Krug *et al.*, 2024). This is in line with the substantial genetic overlaps between the disorders (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019) and indicates that genetic variants identified by disorder-specific case-control GWAS of affective and psychotic disorders might comprise variants related to individual symptom dimensions shared across diagnoses. Similar findings were obtained by studies of polygenic profiles within BD (Allardyce *et al.*, 2023; Richards *et al.*, 2022), supporting this view.

While the exploratory GWAS in David *et al.* (2023) did not reveal any genome-wide significant associations, the exploratory GWAS in Krug *et al.* (2024) yielded two genome-wide significant findings for the lifetime symptom dimensions of mania and depression. This could be interpreted as lifetime measures being more suitable than acute measures of psychopathology for the investigation of genetic correlates. However, neither rs10062519, which was associated with lifetime mania, nor rs11131155, associated with lifetime depression, showed a genome-wide significant disease association (i.e., $p < 5 \times 10^{-8}$) in the latest large-scale GWAS meta-analyses of BD (O'Connell *et al.*, 2025) and major depression (Adams *et al.*, 2025), respectively. Therefore, given the

sample size of our exploratory GWAS, the findings should be interpreted with caution until replication is achieved by other studies.

In contrast to the first two studies adopting a transdiagnostic approach, the third study included in this thesis consists of a disorder-specific investigation of common genetic variants associated with BD disease status (O'Connell *et al.*, 2025). The study represents the largest GWAS meta-analysis of BD to date, encompassing over 158,000 cases and 2.7 million controls from four different ancestral groups. 298 genome-wide significant loci associated with BD were identified. In addition, the results of the meta-analysis fueled a wide variety of downstream analyses, such as quantitative trait loci integration and cell type enrichment analyses. The massive increase in sample size compared to the previous GWAS meta-analysis of BD by the PGC (Mullins *et al.*, 2021; more than 41,000 cases and 371,000 controls) was largely driven by the inclusion of samples from 23andMe, Inc. (more than 90,000 cases and 1.9 million controls), in which case status was ascertained via a single-item self-report question. In addition, over 22,000 cases and 441,000 controls were newly added from community samples, in which case ascertainment was based on medical records, health registries, and questionnaire data. Notably, the SNP-based heritability (h^2_{SNP}) of BD in the community samples (h^2_{SNP} = 0.05) and self-report samples (h^2_{SNP} = 0.08) was substantially lower than in the samples with clinical case ascertainment (h^2_{SNP} = 0.22). This observed difference in the genetic architecture of BD depending on the type of case ascertainment may reflect differences in the phenotypic composition, e.g., in regard to BD subtypes and disease severity (O'Connell *et al.*, 2025).

The three studies included in this thesis illustrate the trade-off between sample size and the depth and quality of phenotypic data in genetic studies of affective and psychotic disorders. The deep phenotyping data of the FOR2107 cohort made it possible to construct transdiagnostic dimensional phenotypes of psychopathology and, in combination with the genotyping and brain imaging data, enabled the investigation of their genetic and brain morphometric correlates in David *et al.* (2023) and Krug *et al.* (2024). However, this came at the cost of a limited sample size, impeding the detection of associated common variants that individually have small effects on highly polygenic complex conditions. The GWAS were underpowered and thus only exploratory, even though well-constructed quantitative phenotypes are known to increase statistical power

for the investigation of common variants in common diseases compared to binary phenotypes (Waszczuk *et al.*, 2023). Conversely, the minimal phenotyping strategy employed in O'Connell *et al.* (2025) resulted in a large sample size and successful discovery of novel BD-associated loci, but the depth of available phenotype data was not sufficient to resolve the observed heterogeneity. Minimal phenotyping can also come at the cost of low disease specificity of GWAS signals, as demonstrated by Cai *et al.* (2020) in the context of MDD. However, the lower heritability and higher phenotypic heterogeneity compared to other affective and psychotic disorders likely exacerbates the consequences of minimal phenotyping in MDD. For SSD, Woolway *et al.* (2024) have recently demonstrated the validity of self-reported diagnoses in genomic research. Together this indicates that the best phenotyping strategy for genetic discovery may differ between different affective and psychotic disorders and phenotypes.

One apparent limitation of both David *et al.* (2023) and Krug *et al.* (2024) is the restriction of the study sample to individuals of European ancestry. Even in O'Connell *et al.* (2025), where we investigated individuals from four different ancestral groups, the majority of individuals were of European ancestry. While ancestry-specific research designs are helpful to reduce the effect of population stratification on common variant associations, they limit the transferability and generalizability of findings, with important implications on equity in health care (Martin *et al.*, 2019). This issue has received increasing attention in the research community throughout the past years, and it should be emphasized that the global efforts towards the recruitment of more ancestrally diverse samples in psychiatric genetics research and the development of suitable methods for multi-ancestry analyses and diversity-aware modelling must continue (Peterson *et al.*, 2019).

Overall, the studies included in this dissertation enhance our understanding of the complex relationships of common genetic variants with symptom dimensions and disease status in affective and psychotic disorders. For future research, a number of directions may prove fruitful. First, standardized digital phenotyping, including ecological momentary assessments, may be used for a more cost efficient collection of detailed phenotype data (Montag, Quintana, 2023), potentially mitigating the trade-off between sample size and phenotyping depth. This may resolve some of the observed genetic heterogeneity due to the ability to define more homogeneous patient subgroups and to construct more specific

quantitative phenotypes. Second, in light of the ever increasing number of GWAS findings, the multimodal integration with rare variant data and other molecular features such as transcriptomics, proteomics, and metabolomics is expected to be of increasing relevance. The multimodal integration will strengthen the identification of genes, pathways, and cell types that are involved in the pathophysiological mechanisms of affective and psychotic disorders (Bruner, Grant, 2024). Lastly, given the growing abundance of various types of data, the application of artificial intelligence, in particular multimodal deep learning models, may lead to a breakthrough in the identification of etiologically defined groups of patients exhibiting distinct genetic and molecular profiles (Chen *et al.*, 2022). Together, these opportunities could be a significant step towards the goal of psychiatric research, which ultimately consists of a more effective prevention and treatment of mental disorders.

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