

Specificity of polygenic signatures across symptom dimensions in bipolar disorder: an analysis of UK Bipolar Disorder Research Network data



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Summary

Background Current definitions and clinical heterogeneity in bipolar disorder are major concerns as they obstruct aetiological research and impede drug development. Therefore, stratification of bipolar disorder is a high priority. To inform stratification, our analysis aimed to examine the patterns and relationships between polygenic liability for bipolar disorder, major depressive disorder (MDD), and schizophrenia with multidimensional symptom representations of bipolar disorder.

Methods In this analysis, data from the UK Bipolar Disorder Research Network (BDRN) were assessed with the Operational Checklist for Psychotic Disorders. Individuals with bipolar disorder as defined in DSM-IV, of European ancestry (self-reported), aged 18 years or older at time of interview, living in the UK, and registered with the BDRN were eligible for inclusion. Psychopathological variables obtained via interview by trained research psychologists or psychiatrists and psychiatric case notes were used to identify statistically distinct symptom dimensions, calibrated with exploratory factor analysis and validated with confirmatory factor analysis (CFA). CFA was extended to include three polygenic risk scores (PRSs) indexing liability for bipolar disorder, MDD, and schizophrenia in a multiple indicator multiple cause (MIMIC) structural equation model to estimate PRS relationships with symptom dimensions.

Findings Of 4198 individuals potentially eligible for inclusion, 4148 (2804 [67·6%] female individuals and 1344 [32·4%] male individuals) with a mean age at interview of 45 years (SD 12·03) were available for analysis. Three reliable dimensions (mania, depression, and psychosis) were identified. The MIMIC model fitted the data well (root mean square error of approximation 0·021, 90% CI 0·019–0·023; comparative fit index 0·99) and suggests statistically distinct symptom dimensions also have distinct polygenic profiles. The PRS for MDD was strongly associated with the depression dimension (standardised β 0·125, 95% CI 0·080–0·171) and the PRS for schizophrenia was strongly associated with the psychosis dimension (0·108, 0·082–0·175). For the mania dimension, the PRS for bipolar disorder was weakly associated (0·050, 0·002–0·097).

Interpretation Our findings support the hypothesis that genetic heterogeneity underpins clinical heterogeneity, suggesting that different symptom dimensions within bipolar disorder have partly distinct causes. Furthermore, our results suggest that a specific symptom dimension has a similar cause regardless of the primary psychiatric diagnosis, supporting the use of symptom dimensions in precision psychiatry.

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Introduction

More than 60% of people with bipolar disorder relapse within 2 years of a first episode, despite contemporary treatments.¹ Residual symptoms, recurrent episodes, pervasive comorbidity, and peak incidence in early adulthood lead to considerable functional impairment and reduced quality of life, making bipolar disorder one of the leading causes of disability worldwide.² Effective treatment is an area of vast unmet need.³

Although mania or hypomania are necessary for a diagnosis of bipolar disorder, there are no pathognomonic symptoms or signs and currently no biomarkers for bipolar disorder. Instead, diagnosis is based on an

individual passing a threshold count of symptoms from a heuristically established list of core criteria, which results in substantial heterogeneity. Further variability occurs due to the presence, absence, or quantity of other clinically significant features, such as psychosis, which frequently accompany bipolar disorder but are not part of the diagnostic criteria.

Poor understanding of the pathophysiology of bipolar disorder has hindered drug discovery and might, in large part, be the corollary of study designs that implicitly assume the diagnosis is a mechanistically homogeneous, discrete, and natural entity.^{4,5} However, there is increasing evidence to suggest that clinical

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Research in context

Evidence before this study

Bipolar disorder is symptomatically heterogeneous and highly polygenic. Its core symptoms and polygenic architecture overlap with other psychiatric disorders, particularly schizophrenia and major depressive disorder (MDD). Family studies suggest that the core symptom subdomains of bipolar disorder are independently transmitted.

We searched MEDLINE, PsychINFO, and Web of Science to systematically identify relevant studies published in English that used modern multivariate approaches in the genomic stratification of mood disorders published between Jan 1, 2006 (ie, the date of the earliest genome-wide association studies) and Sept 15, 2022, using combinations of the search terms “bipolar” and “polygenic” and “symptom dimension” or “subphenotype” or “symptom cluster” and “multivariate” or “structural equation model” or “latent variable” or “supervised machine learning”. There were several papers suggesting clinical heterogeneity was present in bipolar disorder, but there was only weak evidence for biologically validated symptom or patient subsets. 11 studies examined polygenic associations with single-variable phenotypes in individual regression analysis that suggest clinical heterogeneity might be indexing differential underlying genetics. However, these studies are difficult to interpret due to symptoms being highly correlated, which impedes the development of clinically useful stratification.

Added value of this study

To the best of our knowledge, this is the first study to use a unified modelling framework to stratify the bipolar phenotype

into multidimensional symptom domains in a genomically informed sample. This framework has allowed us to investigate the patterns of associations and complex relationships between polygenic liability indexed by polygenic risk scores, symptoms, and their dimensions.

Implications of all the available evidence

Our findings that mania, depression, and psychosis dimensions have differential patterns of genetic risk provide genomic support for family studies of bipolar disorder that show familial specificity for the transmission of mania, MDD, and psychosis. They also support the hypothesis that genetic heterogeneity underpins clinical heterogeneity, suggesting that within bipolar disorder, distinct symptom dimensions, at least in part, are genetically and possibly aetiologically distinct. Moreover, our results suggest that a symptom dimension might have similar causes irrespective of the primary psychiatric diagnosis. Although this needs to be tested in other samples, if true, the finding supports the use of symptom dimensions in precision psychiatry.

Our results challenge current diagnostic systems that emphasise a distinction between unipolar and bipolar depression, conceptualise mania and depression as the opposite ends of a single aetiological dimension, and poorly explain mixed states, which are a common presentation in bipolar disorder. The development of dimensional stratification could increase the precision and specificity of current classification systems and facilitate aetiological research.

variation reflects aetiological variation, making stratification a priority.⁶ Bipolar disorder is highly heritable;⁷ results from family-based studies suggest there is specific, independent transmission of the core symptom dimensions of mania, depression, and psychosis,^{8–11} which, in turn, suggests they are, at least in part, aetiologically distinct, despite their clinical concordance. Genome-wide association studies (GWAS) show that bipolar disorder is highly polygenic,¹² with a large proportion of the genetic variance of the disorder explained by common alleles shared with schizophrenia¹³ or major depressive disorder (MDD).¹⁴ As the symptom subdomains of bipolar disorder are also found in schizophrenia and MDD, we and others have postulated that genetic and phenotypic overlaps are causally related (ie, the causal heterogeneity hypothesis). More specifically, we suggest the genetic architecture of each disorder includes variants present across disorders, which influence specific shared clinical dimensions.⁸ If this hypothesis is true, then this polygenic overlap could be used to stratify bipolar disorder. Although the same symptom dimensions occur across both affective and non-affective disorders, people with schizophrenia, on average, score higher on

a reality distortion and positive psychosis dimension, people with MDD score higher on a depression dimension, and people with bipolar disorder score higher on affective domains, particularly mania.¹⁵ According to the causal heterogeneity hypothesis, on average, schizophrenia GWAS would be expected to be relatively enriched for alleles selectively influencing the psychosis dimension, MDD GWAS would be expected to be relatively enriched for alleles selectively influencing the depression dimension, and bipolar disorder GWAS would be expected to be relatively enriched for alleles selectively influencing the manic dimension.

There is some support for this proposition. In bipolar disorder, schizophrenia-related polygenic liability is associated with psychosis, particularly mood-incongruent psychosis,¹⁶ whereas in schizophrenia, bipolar disorder-related polygenic risk scores (PRSs) are associated with factor scores for mania.¹⁷ The associations, however, are not completely understood as genetic and phenotypic data are highly correlated. Early work was not based on detailed phenotypic data, but rather used a single-variable measure of an individual symptom or broad clinical characteristic that can have

strong unmeasured correlations, making interpretation difficult.¹⁸ To address this issue, genomic structural equation modelling (SEM) was used to derive specific and shared components of genetic liability of bipolar disorder, schizophrenia, and MDD and to examine their associations across a series of analyses with categorical single-variable measures of psychosis, mania, and depression.¹⁹ However, there remained a strong correlation between mania and psychosis measures, with a monotonic increase in the proportion of people with psychosis present across each category of mania. 88% of people who were classified as having severe mania also had psychosis, and the phenotypic landscape was further complicated by mixed-state presentations being included in the mania measure.¹⁹ These complications make the pattern of associations between symptoms and genetic liability complex and difficult to deconstruct.

To deal with these methodological limitations, we aimed to examine the patterns and relationships of polygenic liability for bipolar disorder, schizophrenia, and MDD with multidimensional symptom representations of bipolar disorder using a unitary SEM framework that allows adjustment for correlations between genetic liabilities and psychopathological symptoms.

Methods

Study design and participants

For this analysis, data for individuals with bipolar disorder as defined in DSM-IV, of European ancestry (self-reported), aged 18 years or older at time of interview, and living in the UK were obtained from the UK Bipolar Disorder Research Network (BDRN) database. Individuals were asked to participate in the BDRN via community mental health teams, media campaigns, and patient support groups across the UK.

The BDRN research programme has UK National Health Service Research Authority ethical approval (MREC/97/7/01) and local research and development approval in all participating trusts and health boards. All participants provided written informed consent using the Participant Information Sheet and Consent Form approved by West Midlands National Health Service Research Ethics Committee.

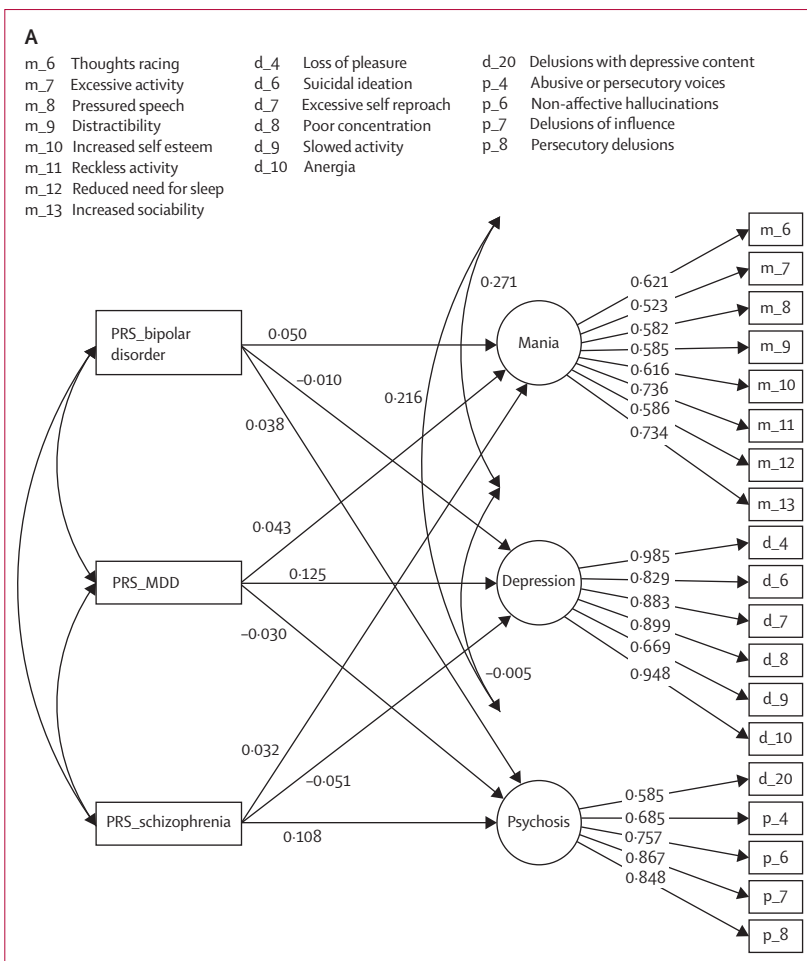
Procedures

The Operational Checklist for Psychotic Disorders (OPCRIT)²⁰ was completed by trained research psychologists or psychiatrists, data from which were extracted during a Schedules for Clinical Assessment in Neuropsychiatry (SCAN) interview²¹ and via psychiatric case notes. This interview had already been conducted with individuals in the BDRN; all raters were formally trained SCAN interviewers. Ongoing supervision and inter-rater reliability assessments were conducted to ensure consistency and accuracy in OPCRIT ratings. If only one source of information (ie, interview or case

	Total sample (n=4148)
Sex	
Female	2804 (67.6%)
Male	1344 (32.4%)
Age at clinical impairment, years	23.1 (9.5)
Completed higher education	1509 (36.4%)
Lifetime clinical characteristics	
Known contact with child services	303 (7.3%)
Probable or definite family history of bipolar disorder	363 (8.6%)
No history of psychosis	1299 (31.3%)
First presentation of bipolar disorder was a manic episode	860 (20.7%)
DSM-IV diagnosis	
Bipolar disorder type 1	2751 (66.3%)
Bipolar disorder type 2	1193 (28.8%)
Schizoaffective disorder (bipolar subtype)	137 (3.3%)
Bipolar disorder (not otherwise specified)	67 (1.6%)

Data are n (%) or mean (SD).

Table 1: Demographic and lifetime clinical characteristics of the UK Bipolar Disorder Research Network sample



(Figure 1 continues on next page)

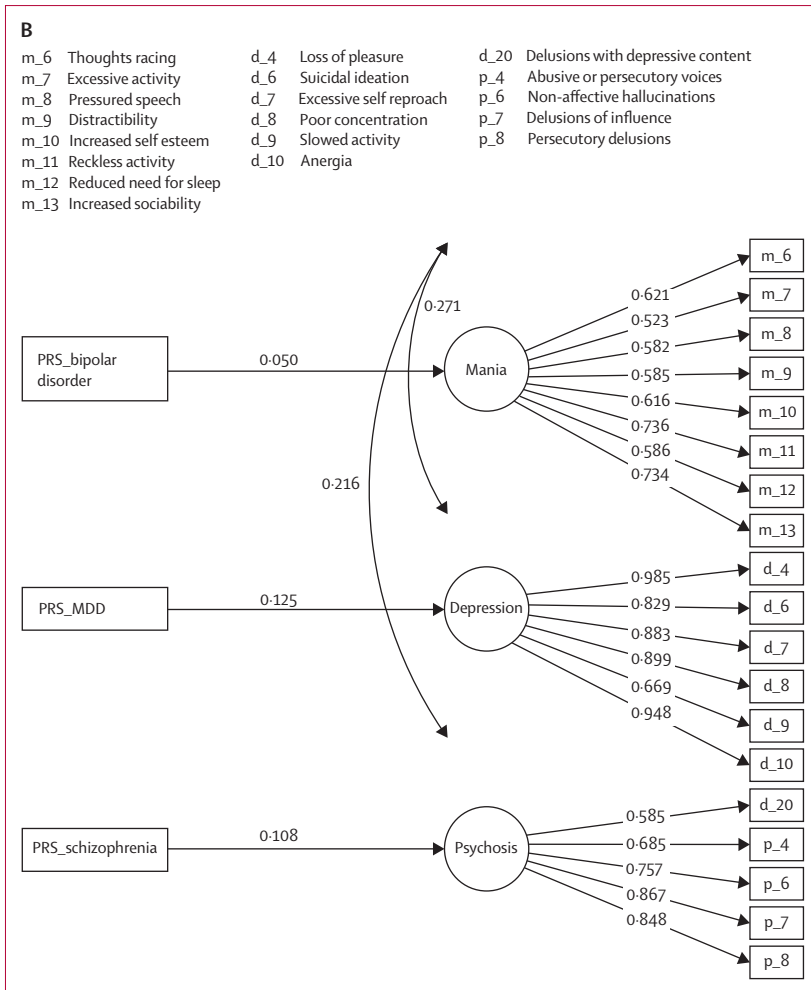


Figure 1: Multiple indicator and multiple causes model
 (A) Path diagram of associations between PRS, symptom dimensions, and symptom indicators. (B) Path diagram showing statistically significant parameters. Root mean square error of approximation 0.021 (90% CI 0.019–0.023); comparative fit index 0.985; Tucker-Lewis index 0.980. MDD=major depressive disorder. PRS=polygenic risk score.

notes) corroborated the criterion, this corroboration was sufficient to endorse the OPCRIT item. However, if information was contradictory or unclear within or between sources, the item was rated as unknown. When a rater had doubts about how to rate an item, ratings were made independently by at least two members of the team of psychologists or psychiatrists and consensus was reached through discussion. OPCRIT rating had very good to excellent inter-rater reliability (appendix p 3).

Sex data were collected via genetic testing.

Psychologists or psychiatrists also collected blood used for genotypic data at time of SCAN interview. These data were generated in three batches: GeneChip Mapping 500K Array Set (Affymetrix, Santa Clara, CA, USA), OmniExpress-24 Kit (Illumina, San Diego, CA, USA), and Infinium PsychArray-24 Kit (Illumina). Quality control was conducted for each platform separately before imputation. Single nucleotide polymorphisms

(SNPs) were excluded if the genotyping call rate was less than 95%, the minor allele frequency (MAF) was less than 0.01, or alleles deviated from Hardy-Weinberg equilibrium (HWE) at p value less than 1×10^{-6} . Individuals with 5% or more of their genotypes missing were excluded. Genome Harmonizer software (GitHub, San Francisco, CA, USA) was used to align SNPs to the Haplotype Reference Consortium (HRC) reference panel before imputation on the Michigan Imputation server. SNPs that passed initial quality control with an imputation information metric (R^2) of more than 0.8 were retained. When imputed genotypes could be given with a genotype probability of more than 0.9, the most probable genotype was allocated before the three platforms were merged. After merging, SNPs with call rates of less than 98%, MAF of less than 0.01, and HWE p value less than 1×10^{-6} were excluded. 2946888 SNPs were retained. Individuals were excluded if genotypic rates of missingness were more than 2%, if there were low or high levels of mean heterozygosity (ie, deviated 3 SD from the sample mean), or when sex inferred by genotype was discordant with data from interview. When pairs of individuals were related (identity by state > 0.1875), one person was randomly retained in the study. Ancestry-specific principal components were generated with PLINK version 2²² from both imputed and genotyped, linkage-disequilibrium pruned SNPs ($R^2 < 0.1$, window 100 kb) as the platform overlap with only genotyped markers was too small to assess ancestry correctly (appendix p 4).

PRSs were calculated with weights derived via continuous-shrinkage PRS (PRS-CS) software,²³ a high dimensional Bayesian regression framework that adjusts SNP effect sizes via a continuous shrinkage prior informed by multivariate modelling of the underlying genetic architecture. We applied the PRS-CS autotuning, allowing the algorithm to learn the global shrinkage (tuning) parameter from the discovery GWAS data; therefore, no external tuning or validation sample was needed and only one set of weights was generated for each PRS. Summary statistics from the largest available GWAS meta-analyses were used to train PRS-CS (ie, schizophrenia,¹³ MDD,²⁴ and bipolar disorder¹²) through the 1000 Genomes Project, a European phase 3 linkage-disequilibrium reference panel. PRSs for both schizophrenia and bipolar disorder were generated with summary statistics derived from GWAS that did not include any BDRN participants. PRSs were generated with PLINK²² with weights obtained from PRS-CS. The effects of 12 principal components and genotyping platform were partialled out and the PRSs were standardised.

59 OPCRIT items relating to psychopathology were examined in the exploratory component of the analysis. Items were excluded if they were outside the domains of interest (as defined by published psychopathological reviews),^{25–27} if they had low minor endorsement rates, or

See Online for appendix

if they had high degrees of missingness, all issues that make factor analysis computationally unstable. Individual Schneiderian First Rank symptoms had low frequency and were combined to create a composite variable in which the presence of any one First Rank symptom was sufficient to endorse the item. Similarly, delusions with depressive content were combined. 24 OPCRIT items with good conceptual underpinning and psychometrics (most included items had a minor endorsement rate of 10–25% and missingness of 4–8%) were entered into the initial exploratory factor analysis (EFA; appendix pp 9–10, 12–13).

Statistical analysis

The sample was randomly split into two subsamples. A calibration set used EFA to identify the underlying common factor structure and refine the OPCRIT item pool and a validation set was used to test the reproducibility of the identified factor structure in a confirmatory factor analysis (CFA).

Weighted least squares mean and variance adjusted (WLSMV) EFA with oblique (goemin) rotation was conducted sequentially across models with one to five factors, a robust estimator that does not assume normally distributed variables and is the best option for binary data. Factor retention was guided by parallel analysis, examination of the scree plot, root mean square error of approximation (RMSEA) differences across models, and the interpretability and clinical meaningfulness of the extracted factors. The set of OPCRIT items was refined by removing poorly fitting items and rerunning the analyses with the reduced item set (appendix pp 9–12). Robust WLSMV CFA was conducted in the validation set to assess reproducibility of the EFA-derived solution, evaluated with global fit indices indicating very good model fit including RMSEA (cutoff ≤ 0.05), comparative fit index (CFI; cutoff ≥ 0.95), Tucker-Lewis index (TLI; cutoff ≥ 0.95), and inspection of standardised residuals to detect localised misspecification (appendix pp 20–22).

To test the specified measurement model derived from the validation CFA, we used multigroup CFA to quantitatively test measurement invariance (equivalence) across the calibration and validation subsamples. Measurement invariance (equivalence) across sex and diagnostic categories of bipolar disorder type 1 and bipolar disorder type 2 was also evaluated as these subgroups might respond differently when questioned about psychopathology, which would make any CFA solution unstable. We tested configural invariance and scalar invariance as OPCRIT items were binary. Support for measurement invariance is provided when no significant difference in model fit is found between the configural and the scalar model, measured with the change in CFI and the change in RMSEA (appendix p 24).

After the factor structure was reproduced by CFA and measurement invariance was tested, multiple indicator

and multiple causes (MIMIC), a special case of structural equation modelling, was used to explore patterns of PRSs (derived from bipolar disorder, MDD, and schizophrenia GWAS) and associations with bipolar disorder symptom dimensions in the total sample. MIMIC is a one-step statistical approach that models all parameters estimated simultaneously. Model fit was assessed with the same indices and criterion cutoffs as the CFA (appendix p 26).

There was low frequency of missingness in the OPCRIT items (appendix pp 13–15) and missing at random was assumed.

Post-hoc analyses were conducted with robust marginal maximum likelihood estimators with categorical variables that allow missingness to be handled via full maximum likelihood methods.

Mplus version 8.6 was used for all multivariate analyses.²⁸ Data were downloaded and safely stored on a computing system maintained by Cardiff University (Cardiff, UK).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Of 4198 individuals potentially eligible for inclusion, 4148 individuals of European ancestry (self-reported) and living in the UK with a mean age at interview of 45 years (SD 12.03) were available for analysis. 2804 (67.6%) were female and 1344 (32.4%) were male (table 1).

MIMIC structural equation modelling found the expected correlations between the PRSs for schizophrenia, bipolar disorder, and MDD in the total sample (appendix p 6). MIMIC models account for these correlations when estimating path coefficients between PRS and symptom dimension. This model fits the data

	Standardised β^*	95% CI	p value
Manic symptom dimension regressed on			
PRS for bipolar disorder	0.050	0.002 to 0.097	0.040
PRS for MDD	0.043	-0.002 to 0.089	0.060
PRS for schizophrenia	0.032	-0.020 to 0.099	0.23
Depressive symptom dimension regressed on			
PRS for bipolar disorder	-0.010	-0.058 to 0.039	0.070
PRS for MDD	0.125	0.080 to 0.171	<0.0001
PRS for schizophrenia	-0.051	-0.104 to 0.002	0.059
Psychotic symptom dimension regressed on			
PRS for bipolar disorder	0.038	-0.006 to 0.078	0.092
PRS for MDD	-0.030	-0.081 to 0.002	0.146
PRS for schizophrenia	0.108	0.082 to 0.175	<0.0001

Influence of polygenic risk scores on symptom dimensions. MDD=major depressive disorder. PRS=polygenic risk score.
*Standardised path (regression) coefficient.

Table 2: Multiple indicator and multiple cause model path (regression) coefficients

well ($\chi^2=501.17$; RMSEA 0.021, 90% CI 0.019–0.023; CFI 0.99; TLI 0.98). The path (regression) coefficients were estimated jointly in the MIMIC model (figure 1). The PRS for schizophrenia was the strongest and only statistically significant predictor of the psychosis factor.

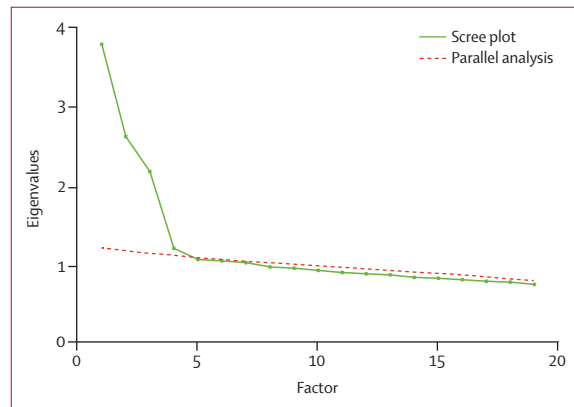


Figure 2: Scree plot and parallel analysis in exploratory factor analysis (calibration sample)

Similarly, the PRS for MDD was the strongest and only statistically significant predictor of depressive factor. Only the PRS for bipolar disorder was significantly associated with the manic factor (table 2; standardised β 0.050, 95% CI 0.002 to 0.097). All PRS effects on the manic dimension were weaker than the specific association of the PRS for schizophrenia with the psychosis dimension and the association of the PRS for MDD with the depression dimension.

The calibration subsample (2648 [63.8%] of 4148 participants) was used to explore the underlying structure and inter-relationships among OPCRIT items to identify sets of strongly correlated symptoms, known as common factors, via EFA. A three-factor solution (mapping on to mania, depression, and psychosis) made most substantive sense and was empirically supported by the parallel analysis, scree plot (figure 2), and relative change in the RMSEA across factor solutions with different numbers of specified factors (appendix pp 17–19). After removing poorly fitting items via a priori refinement criteria (appendix pp 9–10), 19 of the original 24 symptoms remained in the EFA solution (table 3). This revised set of OPCRIT items was then tested via CFA with the validation sample (1500 [36.2%] of 4148 participants) to measure reproducibility of the EFA identified. CFA found the 19-item, three-factor structure fitted the data well ($\chi^2=297.15$; RMSEA 0.03, 90% CI 0.02–0.03; CFI 0.994; TLI 0.993). There were weak correlations between factors (mania and depression 0.21; mania and psychosis 0.23; appendix p 23).

To test the model further, we examined measurement equivalence and invariance across the calibration and validation subsamples with multigroup CFA. The factor structure, factor loadings, and thresholds were similarly measured across the two subsamples, supported by observing no change in RMSEA or CFI between configural (ie, same number and pattern of factors) and scalar (ie, constrains factor loadings and item thresholds to be equal across groups) models. A CFA with the total sample was then conducted. Model fit remained very good and the factor loadings stayed strong and statistically significant (figure 3). Scalar measurement invariance was also shown between male participants and female participants and between bipolar subtypes (appendix p 25); the dimensions seemed to be measuring the same construct across subgroups.

Discussion

This analysis stratified bipolar disorder by statistically identifying distinct dimensions of psychopathology and found these dimensions were also genetically distinct. Each dimension had a distinct polygenic liability signature. The depression dimension was strongly associated with the PRS for MDD and the psychosis dimension was strongly associated with the PRS for schizophrenia. The mania dimension was most strongly associated with the PRS for bipolar disorder; however,

	Operational Checklist for Psychotic Disorders	Study label	Factor 1 (mania)	Factor 2 (depression)	Factor 3 (psychosis)
Thoughts racing	31	m_6	0.719	0.155	0.043
Excessive activity	19	m_7	0.530	0.220	-0.015
Pressured speech	30	m_8	0.512	0.171	0.107
Distractibility	21	m_9	0.595	0.277	0.108
Increased self esteem	56	m_10	0.650	0.320	0.134
Reckless activity	20	m_11	0.718	0.310	0.117
Reduced need for sleep	22	m_12	0.564	0.067	0.201
Increased sociability	53	m_13	0.711	0.266	0.057
Loss of pleasure	39	d_4	0.252	0.815	-0.110
Suicidal ideation	43	d_6	0.212	0.713	-0.041
Excessive self-reproach	42	d_7	0.357	0.753	0.026
Poor concentration	41	d_8	0.318	0.703	-0.067
Slowed activity	24	d_9	0.220	0.523	-0.014
Anergia	25	d_10	0.246	0.851	-0.260
Delusions with depressive content	69, 70, and 71	d_20	0.128	0.147	0.607
Abusive, accusatory, or persecutory voices	75	p_4	0.233	0.247	0.621
Non-affective hallucinations in any modality	77	p_6	0.109	0.072	0.751
Delusions of influence	58	p_7	0.319	-0.002	0.854
Persecutory delusions	54	p_8	0.170	-0.111	0.872
Factor correlations in exploratory factor analysis					
Factor 1	0.000
Factor 2	0.336*	0.000	..
Factor 3	0.176	-0.064	0.000

Data are factor loadings, unless otherwise stated. All factor loadings >0.4 are statistically significant. Root mean square error approximation 0.018 (90% CI 0.017–0.02). *Statistically significant at 5%.

Table 3: Exploratory factor analysis with data from the calibration subsample

associations of PRS for bipolar disorder were the most difficult to interpret as the admixture of symptom dimensions in the PRS discovery samples is currently unknown.²⁹ These findings are consistent with the clinical heterogeneity hypothesis and suggest that the common symptom dimensions of bipolar disorder have, at least in part, distinct causal components.

These results challenge current diagnostic systems, which emphasise a distinction between unipolar and bipolar depression, conceptualise mania and depression as the opposite ends of a single aetiological dimension, and poorly explain mixed states that are a common presentation, perhaps the most common presentation, in bipolar disorder. Dimensional representations can accommodate these problems. The findings of this analysis will inform new approaches to bipolar disorder (and related disorders) stratification, a necessary stage in the development of our understanding of causal mechanisms.

To our knowledge, this is the first study to use a joint modelling framework to stratify multidimensional representations of bipolar disorder in a genomically informed sample. Previous PRS studies of bipolar disorder subphenotypes have relied on minimal phenotyping.^{16,17,19} Higher PRSs for schizophrenia in people with bipolar disorder and psychosis than in control individuals is a replicated finding.^{16,17} Few studies have investigated the PRS profiles of symptoms related to the other symptom domains. The PRS for MDD has been shown to be associated with severity of depression,¹⁹ and individuals with a history of suicide attempt have a higher burden of MDD risk alleles than individuals without a history of suicide attempt in multiple psychiatric disorders, including bipolar disorder.³⁰ However, these early studies, which used single-variable measures, did not consider known correlations between symptoms, which makes the interpretation of individual regression analyses and the synthesis of evidence difficult.

This analysis is based on two premises. First, the premise that core psychopathological experiences can be represented by continuous latent variables (dimensions), each of which is likely to reflect different underlying causes. The use of factor analysis meant we did not need to use all candidate indicators of symptom dimensions because each additional indicator of a specific factor provides progressively less incremental power. This incremental power does not mean other variables of the factor are less important or have less effect, but that they are already well represented by included variables. Second, the premise that dimensions are quantitatively rather than qualitatively distributed across bipolar disorder, MDD, and schizophrenia diagnoses and that the co-occurrence of dimensions in different combinations partly explains clinical variability. Under the causal heterogeneity model, we would predict a pattern of PRS associations in which the PRS for bipolar

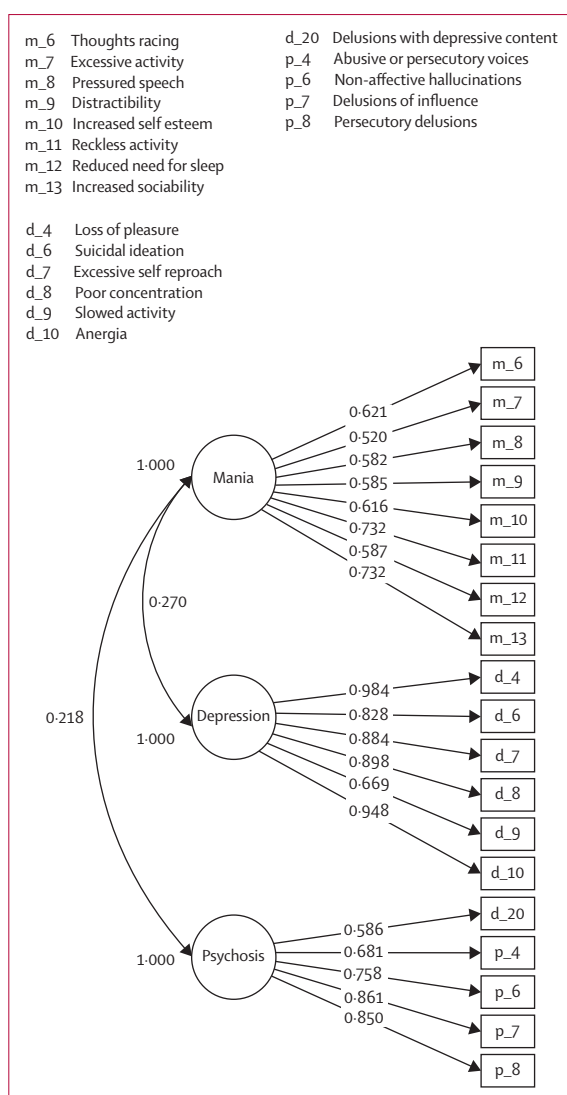


Figure 3: Confirmatory factor analysis (total sample)

disorder is most strongly associated with the mania dimension, the PRS for MDD is most strongly associated with the depression dimension, and the PRS for schizophrenia is most strongly associated with the psychosis dimension. Our findings are in keeping with this expected pattern. Although the PRS for MDD association with the mania dimension did not reach significance, it suggests there is potentially a weak association. These findings, in turn, suggest that the symptom dimensions identified in this sample might index domains of pathophysiology present across disorders, but with different prominence in each diagnostic category. We are not suggesting the dimensions identified here are the best or only dimensional stratifiers for bipolar disorder, but they provide genetically validated phenotypic markers to investigate underlying mechanisms.

Our finding that mania, depression, and psychosis dimensions have differential patterns of genetic risk is supported by family-based studies that show familial specificity for mania, MDD, and psychosis transmission.^{9–11} These results, as well as follow-up studies showing differential impairment, course, and outcome across mania and depression, highlight the importance of distinguishing between these symptom subdomains in aetiological research in the development of targeted treatments and precision psychiatry.

MIMIC provides a unitary analytical approach in which patterns and relationships between symptoms, factors, and PRSs are simultaneously and consistently estimated in a single statistical model. This method reduces potential bias due to measurement error, confounding by correlation, uncertainty from factor indeterminacy, and multiple testing. Nevertheless, CFA measurement models can vary depending on the symptom indicators entered. Although OPCRIT includes a broad range of psychopathology, it has relatively low coverage for anxiety, negative symptoms, and psychomotor activity. For this analysis, we used a minimum of five reliable and relevant indicators that provide good coverage for the identification of manic, depression, and psychosis dimensions. More indicators are not necessarily better, as increasing the number can result in a sample-specific subfactor, particularly when the boundaries of the theoretical constructs are not well elaborated. The three-factor model presented here reflected acceptable average variance extracted measures for each factor, although the average variance extracted for mania was lower than for the depression or psychosis dimensions, making it the least well characterised dimension and consequently the outcome with the least measurement precision, shown via weaker association estimates. This finding might, in part, be due to our sampling frame. Being included in a sample of people with bipolar disorder is conditional on having experienced a hypomanic or manic episode, with a single manic episode sufficient to warrant a diagnosis. This definition reduces the variation in the range of mania-related indicators and, consequently, their correlations, which could theoretically result in the mania factor being less well defined. However, our findings suggest that the PRS for bipolar disorder might be more strongly associated with the mania dimension than the PRS for MDD and the PRS for schizophrenia.

This suggestion is consistent with the association between the PRS for bipolar disorder and a mania dimension in schizophrenia.¹⁷ However, the weaker-than-expected association might also be due to the PRS for bipolar disorder currently having less predictive power than the PRS for schizophrenia or the PRS for MDD. As large GWAS focused on bipolar disorder become available, PRS prediction power is also likely to increase. PRS associations with subphenotypes are most

interpretable when they are cross-disorder (ie, examining the associations of PRS for one disorder with subphenotypes of another disorder). Associations between PRS for one disorder and the subphenotypes of that one disorder are more difficult to interpret as detailed interpretation depends on the distribution of dimensions in the discovery sample, which is currently unknown.²⁹ The inherent variability in broadly defined bipolar disorder means current PRSs for bipolar disorder include clinical heterogeneity. However, as large GWAS become available, future research might be able to construct PRS from GWAS of more homogeneous subsamples, such as bipolar disorder type 1 or in samples of genetically determined ancestral groups. This increased specificity should facilitate the exploration of more specific causes in psychiatry.

Our findings should be interpreted in the context of several limitations. First, potential recruitment bias in the BDRN sample of people with bipolar disorder might have reduced the representativeness of the sample. Second, OPCRIT is unlikely to have indexed all relevant symptomatology, so other clinically relevant dimensions might exist. Third, the predictive accuracy of PRSs is affected by both the discovery set and the methods used to train them. For example, a GWAS of people with bipolar disorder has relatively less power compared with discovery GWAS of people with schizophrenia or people with MDD. This differential power might have affected our findings. Fourth, we only examined the effect of common variants. Rare variants and environmental exposures are also likely to influence phenotypic expression. Fifth, our analysis was based on a single sample of people with bipolar disorder and self-reported European ancestry and might not generalise to populations with other ancestral backgrounds. Replication is required in samples of people with other disorders and at the population level.

Overall, our findings support the hypothesis that genetic heterogeneity underpins clinical heterogeneity, suggesting that within bipolar disorder, different symptom dimensions have partly distinct causes. Furthermore, our results suggest that a symptom dimension might have a similar cause irrespective of the primary psychiatric diagnosis, supporting the use of symptom dimensions in precision psychiatry.

Contributors

JA conceptualised the study and developed the study design and primary analytical strategy with input from MCO'D, VE-P, PAH, AGC, MJO, LJ, and IJ throughout the course of the study. JA and JTRW had access to the raw data and acquired, accessed, and verified the genetic data. KG-S, LJ, JA, and VE-P had access to the raw data and verified the phenotypic data. NJC, IJ, KG-S, and LJ ascertained and phenotyped the bipolar disorder sample. JA drafted this Article and MCO'D edited this Article. All authors had full access to all data in this study, aided in the interpretation of the findings, critically reviewed the manuscript for intellectual content, approved the final draft for submission, and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

We have complete control of the research data. Requests to access de-identified datasets, data dictionaries, and other information from the study should be sent to the corresponding author or LJ. Accessing anonymised data will require approval of a research proposal and analysis plan and a signed data access agreement from the principal investigators of the UK Bipolar Disorder Research Network. The analysis plan is available in the appendix (pp 9–12, 20–26).

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