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Identifying genetic differences between bipolar disorder and major depression through multiple genome-wide association analyses

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Background

Accurate diagnosis of bipolar disorder (BPD) is difficult in clinical practice, with an average delay between symptom onset and diagnosis of about 7 years. A depressive episode often precedes the first manic episode, making it difficult to distinguish BPD from unipolar major depressive disorder (MDD).

Aims

We use genome-wide association analyses (GWAS) to identify differential genetic factors and to develop predictors based on polygenic risk scores (PRS) that may aid early differential diagnosis.

Method

Based on individual genotypes from case–control cohorts of BPD and MDD shared through the Psychiatric Genomics Consortium, we compile case–case–control cohorts, applying a careful quality control procedure. In a resulting cohort of 51 149 individuals (15 532 BPD patients, 12 920 MDD patients and 22 697 controls), we perform a variety of GWAS and PRS analyses.

Results

Although our GWAS is not well powered to identify genome-wide significant loci, we find significant chip heritability and demonstrate the ability of the resulting PRS to distinguish BPD from MDD, including BPD cases with depressive onset (BPD-D). We replicate our PRS findings in an independent Danish cohort (iPSYCH 2015, $N = 25\,966$). We observe strong genetic correlation between our case–case GWAS and that of case–control BPD.

Conclusions

We find that MDD and BPD, including BPD-D are genetically distinct. Our findings support that controls, MDD and BPD patients primarily lie on a continuum of genetic risk. Future studies with larger and richer samples will likely yield a better understanding of these findings and enable the development of better genetic predictors distinguishing BPD and, importantly, BPD-D from MDD.

Keywords

Bipolar disorder; major depressive disorder; genome-wide association analysis; polygenic risk scoring; early differential diagnosis.

Bipolar disorder (BPD) affects more than 1% of the world's population irrespective of nationality, ethnic origin or socioeconomic status.[1,2] In the World Health Organization's (WHO's) World Mental Health surveys, BPD was ranked as the illness with the second greatest effect on days out of role.[3,4] Accurate diagnosis of BPD is difficult in clinical practice: mean delay between symptom onset and diagnosis is around 7 years.[5] One of the main reasons for this delay is that onset is often characterised by a depressive episode and, until the onset of mania, it is difficult to distinguish patients with BPD from patients with unipolar major depressive disorder (MDD).[6–12] For example, in studies that have followed up on patients with an initial MDD diagnosis, approximately between 10 and 20% demonstrate conversion to BPD over follow-up periods of about 5–10 years.[13,14] The misdiagnosis of BPD can have significant detrimental consequences, including prescription of antidepressants in the absence of mood-stabilising drugs, which can lead to mania,[15] poor clinical outcomes and high healthcare costs. Family-based studies[8,16] and our recent genome-wide association analyses (GWAS)[17] demonstrate independent patterns of inheritance for mania and depression and initial presentation of BPD.[10] Several recent studies identified BPD genetic liability as a predictor of conversion to BPD.[18,19] Together, these findings suggest that scrutinising the genetic relationship between these two core phenotypes will be valuable in understanding risk for

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BPD. Although several summary-statistics-based genetic studies have evaluated genetic similarities and differences between BPD and MDD,[19] no study has yet been performed directly assessing the genetic differences between these two phenotypes by using a systematic approach of combining individual-level genetic data from different cohorts.

Here, we aim to characterise genetic differences between patients with BPD and patients with MDD by using data from the Psychiatric Genomics Consortium ((PGC) total $N = 68\,612$ participants),[20,21] with a replication in the iPSYCH case–control study (total $N = 25\,966$).[22,23] In a follow-up analysis, we focus specifically on patients with a first onset of depression, 'depression-first BPD', who are most difficult to differentiate from MDD in clinical settings.

Method

Sample description

Our analyses are based on 17 673 BPD and 14 346 MDD cases of European ancestry from Europe, North America and Australia from the PGC BPD and MDD Working Group, which comprised our discovery data.[20,21] For a list of included cohorts, their sample sizes and case control breakdown (see Supplementary Tables 1 and 2 available at https://doi.org/10.1192/bjp.2024.125). The individual studies were approved by the respective local ethics committees and all participants provided written informed consent.

Additionally, summary statistics of GWAS based on ICD-10 secondary care contacts from national health registers[24,25] for both disorders were provided for the iPSYCH case–cohort study,[22,23] which were used for replication. All individuals were born in Denmark between 1981 and 2008, and enrolled based on a secondary care contact recorded in national health registers for BPD (ICD-10 codes: F30–F31) or MDD (ICD-10 codes: F32–F33) before 2016. Individuals with a schizophrenia (ICD-10 code: F20) diagnosis were excluded. For iPSYCH samples retrieved from the Danish Neonatal Screening Biobank, parents were informed at the time of sampling and given the option to withdraw the sample from inclusion in research studies.[22]

Polarity at onset (PAO) was available for a subset of participants with a BPD diagnosis in the PGC cohorts. For these patients, as in our previous study,[17] PAO was determined by selecting the earliest age between the onset of mania/hypomania and depression, or as provided by the cohorts. Patients for whom PAO was available were categorised into two subgroups: depression before mania/hypomania (depression-first), and mania before depression of a mixed onset (mania-first). The latter category includes both participants whose onset was marked by an episode with mixed features and participants who had their first manic and depressive episode within the same year.

For the iPSYCH data, depression-first PAO was indirectly inferred based on the presence of a registered MDD contact before first registered BPD contact.

Genotype data merge, quality control and imputation

All PGC cohorts in our analysis ascertained patients with a single main diagnosis, either MDD or BPD. To perform direct case–case genetic analyses at the genotype level, the first step is to combine multiple independent cohorts into unified cohorts including both MDD and BPD case participants. To do so, great care needs to be taken to avoid introducing population stratification and technical artifacts when combining distinct data sources. We developed and applied an iterative procedure for merging, quality control and imputation in Ricopili (version 2019_Oct_15.001 for Linux, developed by Stephan Ripke at the Broad Institute and Massachusetts General Hospital, Boston, USA; see https://sites.google.com/a/broadinstitute.org/ricopili/download-installation),[26] described in detail in Supplementary Appendix A. We thereby compiled 13 grouped case–case cohorts including 15 532 BPD cases and 12 920 MDD cases in total.

We created a similar set of 13 grouped cohorts, adding 40 160 control participants from the original merged cohorts, performing a similar quality control procedure. The resulting 13 pairs of case–control cohorts contained 14 513 BPD cases versus 22 697 controls and 12 259 MDD cases versus 17 463 controls, after additional outlier and overlap exclusions.

We also leveraged available information about BPD POA (manic episode first or depressive episode first) to compile seven case–case cohorts with 2597 depression-first BPD cases and 9217 matching MDD cases. For the manic episode first cohorts, the sample size was too small (1300 cases) and the overall observed heritability did not meet the recommended significance criteria ($z = 2.45$, $P > 0.01$),[27] so we have not included the BPD manic episode first stratification in further analyses.

GWAS

To evaluate genetic differences between BPD and MDD, we performed three primary GWAS analyses and one replication analysis.

Genotype-based case–case GWAS meta-analysis

To identify genetic risk factors differentiating BPD and MDD, we first compared BPD and MDD cases directly, similar to a previous comparison of schizophrenia and BPD.[28] Specifically, we performed GWAS on each of the 13 grouped case–case cohorts based on dosage genotypes, followed by standard inverse-s.e. weighted meta-analysis across all grouped cohorts, whereby individuals with BPD were coded as cases and individuals with MDD were coded as controls. The first 20 principal components were used as covariates. We refer to this primary GWAS analyses as BPDvsMDD GWAS. We repeated this analysis using only depression-first BPD cases and matched MDD cases (seven case–case cohorts), and refer to it as BPD-DvsMDD GWAS.

Meta-regression analysis

For the second GWAS analysis, we introduced control individuals and aimed to identify genetic differences between BPD and MDD relative to controls. To do so, for each of the 13 cohorts, we first generated summary statistics for two GWAS: one of BPD versus controls and one of MDD versus controls, where the controls for each group have been split between BPD and MDD cases proportionally (see previous section). We then used a meta-regression approach to model the effect size of each single nucleotide polymorphism (SNP) as a function of a single fixed covariate: a binary indicator of phenotype (BPD or MDD, see also Supplementary Appendix B). This GWAS is referred to as MetaRegr GWAS.

We also performed separate random-effects meta-analyses of the BPD and MDD GWAS summary statistics, to evaluate which phenotype appeared to have more heterogeneity in SNP effect sizes, using the respective meta-regression estimates.

Case–case GWAS

We also performed a third GWAS based on the case–case GWAS (CC-GWAS) method,[29] using BPD versus controls and MDD versus controls summary statistics. To do so, we compiled a version of our grouped cohorts based on a set of completely overlapping controls, as CC-GWAS covariance matrix estimation benefits from control overlap (see Supplementary Appendix C).

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Inverse-weighted meta-analysis

Since our matched case–case–control sample is based on a set of non-overlapping individuals, it permits a regular inverse-weighted meta-analysis of BPD versus controls and MDD versus controls data-sets. Although not aiming to detect differences between BPD and MDD, this analysis provides a comparison for our case–case-based analyses, and enables the distinction between loci that appear to be strictly differential between the two disorders against those that are also identified as common loci by the meta-analysis.

For all GWAS, we performed positional and expression quantitative trait loci-based annotation for all SNPs in loci with $P < 1 \times 10^{-4}$, as well as MAGMA gene-set analysis implemented in FUMA (version 1.5.2 for Linux, developed by Kyoko Watanabe at the Department of Complex Trait Genetics, Center for Neurogenomics and Cognitive Research, VU University Amsterdam, The Netherlands; see https://fuma.ctglab.nl/) (see Supplementary Appendix D). To further evaluate whether the observed signal is shared or driven by either one of the two phenotypes, we performed colocalization (see Supplementary Appendix E) for each locus with $P < 1 \times 10^{-4}$.

Multi-trait-based conditional and joint analysis

Based on the most well powered BPD and MDD GWAS summary statistics data available from Stahl et al[20] and Wray et al,[21] respectively, we performed a conditional GWAS, conditioning BPD signal on MDD signal (multi-trait-based conditional and joint analysis (mtCOJO); see Supplementary Appendix F), to determine whether this summary statistics-based method would be able to retrieve most loci identified by our GWAS methods, thus testing the balance between increased sample size and individual-level data availability.

Reverse GWAS

In Coleman et al,[30] summary statistics were used to identify loci with differential signals between the two disorders ('reverse-effect' analysis). We evaluated concordance between loci identified through this analysis and our results, by evaluating the genome-wide significant hits in the reverse-effect analysis (three in total) in our three GWAS.

Replication analysis with iPSYCH

To replicate our findings from the BPDvsMDD GWAS, we performed a similar case–case association analysis in the iPSYCH 2015 case–cohort study (2524 BPD cases and 23 442 MDD cases). GWAS was performed using Plink2 (version 2.00a2 for Linux, Mac and Windows, developed by Christopher Chang at the California Institute of Technology, Pasadena, USA, with support from Human Longevity, Inc. in 2016–2017, and input from Stanford's Department of Biomedical Data Science; see https://www.cog-genomics.org/plink/2.0/)[31] in two independent samples (iPSYCH-2012: 1452 BPD cases, 15 920 MDD cases; and additional iPSYCH-2015i: 1072 BPD cases, 7522 MDD cases) and meta-analysed.

For our onset analysis, we also utilised a constrained set of 976 individuals who had an MDD diagnosis registered on the same day or before their BPD diagnosis (depression-first BPD), against the set of 23 442 individuals with MDD diagnosis.

To evaluate the degree of replication of independent SNPs (index SNPs of independent linkage disequilibrium blocks) from our primary GWAS, we performed a sign test, grouping variants with P-value $<1 \times 10^{-5}$, to determine whether the percentage of variants in the original analysis retaining their direction of effect in the replication analysis was significantly higher than chance.

Heritability and genetic correlation

For all GWAS, heritability and genetic correlations were estimated with LD Score Regression (LDSC).[32] In addition, we estimated genetic correlations between our GWAS and well-powered (SNP heritability z-score >5 and >10 000 cases) psychiatric GWAS made publicly available by the PGC (https://pgc.unc.edu/for-researchers/download-results/). The following traits were included: schizophrenia, attention-deficit hyperactivity disorder (ADHD), cannabis use disorder, alcohol dependence, alcohol use disorder, anorexia nervosa, autism spectrum disorder and post-traumatic stress disorder (PTSD). Since our analysis is currently limited to European ancestry, we used summary statistics limited to the European population subset.

Polygenic score analyses

To evaluate whether our GWAS can help distinguish between patients with MDD and those with BPD on an individual level, we computed polygenic risk scores (PRS). We calculated leave-one-out summary statistics based on our set of GWAS, and used SBayesR (from GCTB software version 2.5.2 for Linux, developed by Jian Zeng with contributions from Luke Lloyd-Jones, Zhili Zheng and Shouye Liu at the Institute for Molecular Bioscience, The University of Queensland, Brisbane, Australia; see https://cnsgenomics.com/software/gctb/)[33] to calculate polygenic scores for each of the 13 grouped cohorts. We thus created a number of different polygenic predictors, including combinations of those using multiple regression. We report the area under the curve (AUC) score as a metric for performance, as well as the percentage of variance explained, expressed in terms of Nagelkerke's R^2, adjusted for population covariates (see Supplementary Appendix G).

Specifically, we calculated polygenic scores based on summary statistics of four different GWAS: (a) BPDvsMDD GWAS, (b) BPD versus controls GWAS (BPD GWAS), (c) MDD versus controls GWAS (MDD GWAS) and (d) MetaRegr GWAS. We compared the ability of each of these scores, based on different GWAS designs, as well as a combination of (a), (b) and (c) (combined using multiple regression), to predict the target phenotype – namely, to classify BPD versus MDD status.

To further quantify the impact of sample size, we compared our predictors to the BPD GWAS of the Psychiatric Genetics Consortium.[34] As each of our grouped cohorts contains multiple BPD and MDD studies, it is an involved process to create leave-one-out summary statistics while removing overlap; we therefore limited this comparison to one cohort ('grp5_neth').

Since we are most interested in distinguishing patients with BPD with an onset of depression from those with unipolar MDD, we repeated the above analysis, using depression-first BPD versus MDD cohorts as target data-sets.

Finally, we tested the reproducibility of our PRS results on the iPSYCH cohort.

PRS based on other psychiatric traits

Using SBayesR, we also calculated polygenic scores based on public summary statistics for each of the psychiatric GWAS included in our genetic correlation analysis. We report mean weighted AUC calculated across our 13 cohorts.

Results

GWAS does not identify significant loci

Results from the three different GWAS methods are reported in Supplementary Tables 5(a)–(e) and summarised in Fig. 1. In

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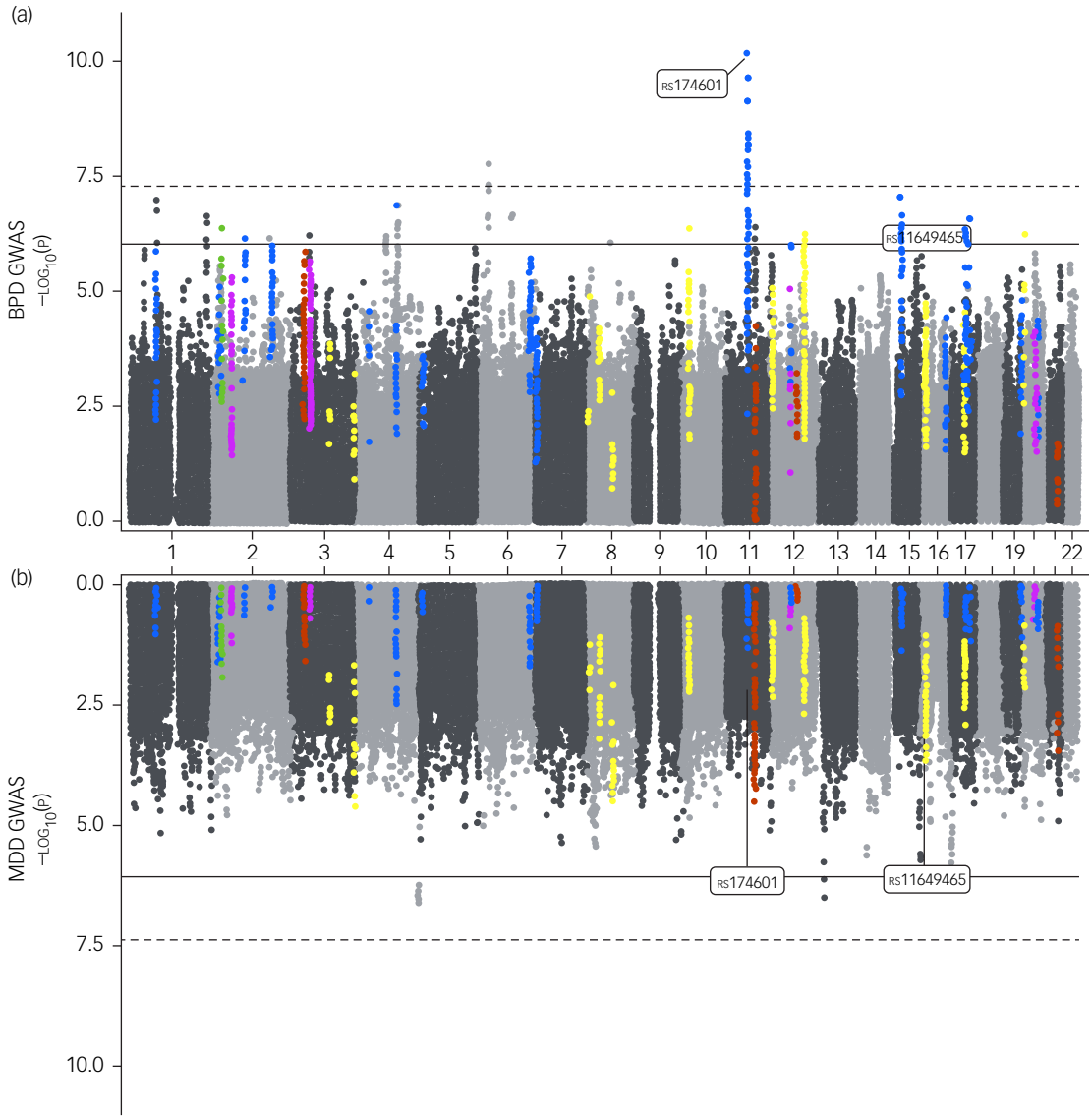

Fig. 1 Miami plot depicting our (a) BPD GWAS and (b) MDD GWAS based on our non-overlapping sample, overlaying loci with $P < 1 \times 10^{-6}$ from different GWAS, as well as common loci: red – BPDvsMDD GWAS, blue – CC-GWAS, yellow – meta-analysis, green – common locus between meta-analysis and CC-GWAS (one in total), purple – common loci between case–case GWAS and CC-GWAS (three in total), orange – common loci between all three methods (one in total). Within each locus, only SNPs in linkage disequilibrium ($R^2 > 0.1$) with the index SNP are coloured, to accurately display the underlying signal in both the top and bottom panels. The two genome-wide significant loci (for the meta-analysis and CC-GWAS) are labelled with their index SNP. The BPDvsMDD GWAS (red) column on chromosome 11 consists of two neighbouring but non-overlapping loci. MetaRegr GWAS was excluded from this figure because of its low power.

BPD GWAS, case–control GWAS of bipolar disorder; MDD GWAS, case–control GWAS of major depression; BPDvsMDD GWAS, case–case GWAS of bipolar disorder versus major depression; CC-GWAS, case–case GWAS of bipolar disorder versus major depression, based on the CC-GWAS tool; SNP, single nucleotide polymorphism; MetaRegr GWAS, case–case–control GWAS based on a meta-regression framework. Region plots for all highlighted loci are shown in Supplementary Fig. 6(a)–(f). SNPs within common loci are coloured accordingly in Supplementary Tables 6 and 7.

summary, we observed no genome-wide significant hits for BPD versus MDD or MetaRegr, but one locus passed the genome-wide threshold for CC-GWAS. Although our primary GWAS (BPDvsMDD) did not yield significant loci, we observed significant heritability (observed $h^2 = 0.23$ (s.e. 0.02), intercept 1.001 (s.e. 0.01)), with similar heritability estimated for the BPD-DvsMDD GWAS (observed $h^2 = 0.18$ (s.e. 0.04), intercept 1.01 (0.01)). Our two secondary GWAS (MetaRegr, CC-GWAS) were strongly correlated with BPDvsMDD and with each other (rg 0.91–1; Fig. 1(a)), but seemed less powered than BPD versus MDD (MetaRegr: $h^2 =$ 0.05 (s.e. 0.01) with intercept 0.96 (0.01), CC-GWAS: $h^2 = 0.17$ (s.e. 0.01) with intercept 0.98 (0.01)). Below, we elaborate on the results of individual GWAS, the suggestive genome-wide significant loci (loci with index variant reaching $P < 1 \times 10^{-6}$) identified by each one and those identified by multiple methods.

In the BPDvsMDD GWAS (Supplementary Table 5(a), Supplementary Figs 2(a) and (b), 3(a) and (b), 4(a) and 5), a total of eight suggestive loci were identified, four of which are uniquely identified by this method. Two of these, marked in boldface, fall within known BPD loci.[34] The Manhattan, quantile–quantile (Q–Q), region and region forest plots for this analysis, as well as the corresponding Manhattan and Q–Q plots for the BP-DvsMDD GWAS, can be found in Supplementary Figs 2(a), 2(b), 3(a), 3(b), 4(a) and 5.

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With CC-GWAS (Supplementary Table 5(c), Supplementary Figs 2(d), 3(d) and 4(c)), we obtain a single genome-wide significant hit (rs174601 on chromosome 11, $P = 6.4 \times 10^{-9}$, with an odds ratio of 0.99), for which we also report results from BPDvsMDD GWAS, BPD GWAS, MDD GWAS and MetaRegr GWAS, as well as meta-analysis (Supplementary Table 5(e)). For both BPDvsMDD and MetaRegr GWAS, we observe a similar effect $P < 1.0 \times 10^{-5}$ and a larger effect size (odds ratio of 0.93 for BPDvsMDD GWAS and 0.89 for MetaRegr GWAS), whereas for BPD GWAS, this SNP is genome-wide significant with $P = 8.0 \times 10^{-10}$, and maps onto a known BPD locus, close to the *FADS1*, *FADS2*, *FADS3* and *TMEM258* genes.[34] For MDD, the signal is in the same direction, although the effect is not significant ($P > 0.1$). For the meta-analysis, the same SNP has $P = 2.07 \times 10^{-6}$, likely resulting from a strong BPD signal (as also indicated by colocalization with a posterior probability for BPD of >90% for all analyses).

In the meta-regression (Supplementary Table 5(b), Supplementary Figs 2(c), 3(c) and 4(b)), four loci reached suggestive significance, none of which overlap with those of the BPDvsMDD GWAS. The phenotype-specific meta-regression analysis (see Supplementary Appendix B) further allowed us to compare effect size heterogeneity between MDD and BPD cohorts. We observed a slightly elevated effect size heterogeneity in MDD cohorts compared with BPD, indicating that across all SNPs tested, MDD cohorts are slightly more heterogeneous; however, the observed difference is minimal (mean values of 3.0×10^{-2} for MDD *v.* 2.6×10^{-2} for BPD; $P < 1 \times 10^{-16}$ paired *t*-test in all 6.9 million SNPs).

In Fig. 1, notably, BPD (top) has the greatest contribution to the signal in most loci identified by all different GWAS methods (displayed in red, blue and yellow), whereas, as expected, the contribution from MDD (bottom) is more prominent in the regions identified by the meta-analysis (in green). As an exception to this pattern, one of the two loci uniquely identified by the BPDvsMDD GWAS on chromosome 11 (chr11:84.6–85.0 Mb) reaches $P < 1 \times 10^{-4}$ significance in MDD, but not in BPD (see also Supplementary Fig. 6). Our BPDvsMDD GWAS and CC-GWAS identified five suggestive loci in common, whereas two loci (chr11:36.8–37.3 Mb and chr2:28.3–28.5 Mb) were common between the meta-analysis and either one of the case–case GWAS.

By performing colocalization analysis of our meta-analyses, we further explored whether the signal in each locus was shared or specific to a single trait (summarised in Supplementary Tables 6(a)–(d) and 7(a)–(d)). Colocalization identified two loci (out of 331 loci with $P < 1 \times 10^{-4}$ in the meta-analysis) with a high posterior probability (>75%) (see Supplementary Appendix D) of containing a shared causal variant, 12 loci as likely BPD-specific and one as likely MDD-specific. For the two loci likely containing a shared causal variant, we also report the credible set (posterior probability >90% for containing the causal variant). Out of the two, one locus in particular, overlapping the *GRIN2A* gene, has very high evidence (posterior probability for both: 93.4%).

Using summary statistics alone, 18 out of the 27 suggestive loci identified by either the BPDvsMDD GWAS or CC-GWAS were identified through conditional analysis with mtCOJO (see also Supplementary Table 8). Notably, neither the top BPDvsMDD GWAS locus nor the two top CC-GWAS loci were identified by mtCOJO, suggesting that our approach of genotype-level analyses is able to disentangle signals not detectable from using summary-level data alone. In Supplementary Tables 5(a)–(d), mtCOJO results are available for all loci identified as 'disorder-specific'. Our MAGMA-based enrichment analysis, implemented in FUMA, did not yield any gene-sets that survived Bonferroni correction. Nominally significant pathways ($P < 0.001$) are listed in Supplementary Tables 9(a)–(d).

Finally, in none of the four different GWAS (including the meta-analysis) did we observe genetic signal (at $P < 1 \times 10^{-4}$) for the three SNPs reported to differentiate BPD and MDD in the reverse GWAS of Coleman et al[30] (Supplementary Table 9).

Heritability and genetic correlation indicate a strong correlation with PGC BPD GWAS

We observe a strong genetic correlation between the BPDvsMDD GWAS summary statistics and the GWAS of PGC BPD: rg = 0.95 with BPD[20] (Fig. 2(a) and (b)), primarily BPD type 1 (Fig. 2(b)); note that genetic correlation estimates above 1 between PGC analyses occur, which may be due to overlapping individuals in the studies involved. The correlation between BPDvsMDD GWAS and our BPD GWAS, using only matched individuals, is also strong: rg = 0.88 (s.e. 0.03). On the other hand, the correlation estimate with PGC MDD[21] is negative (rg = −0.05 (s.e. 0.06)), but the s.e. overlaps with zero. The negative direction of effect is expected, given that MDD cases were coded as 'controls' in our case–case analyses (where 'cases' correspond to individuals with BPD).

Genetic correlations with other psychiatric traits tracks are presented in Fig. 1(b), alongside BPD and MDD (see also Supplementary Table 11). Mostly, the observed genetic correlations follow an expected pattern that matches the observations above: when a trait is strongly correlated with BPD, and less so with MDD (e.g. schizophrenia), the genetic correlation of BPDvsMDD falls in between. When a trait is strongly correlated with MDD, and less so with BPD (e.g. PTSD, ADHD), the genetic correlation of BPDvsMDD is driven toward zero (or a negative correlation) because of the relative strength of the MDD signal. An exception to this 'rule' is alcohol use, which is more strongly correlated with BPDvsMDD (rg = 0.19, s.e. = 0.05) than with PGC BPD (rg = 0.09, s.e. = 0.04), indicating that genetic risk factors for alcohol use could represent additional independent risk for conversion from MDD to BPD.

PRS can distinguish between MDD and BPD, including depression-first BPD

Figure 3(a) shows the classification score in terms of AUC (see also Supplementary Fig. 7 for Nagelkerke's R^2) for all 13 grouped cohorts, for polygenic scores based on BPDvsMDD GWAS, BPD GWAS, MDD GWAS and a combination of these three predictors. The mean AUC (over 100 bootstrapped samples per cohort), weighted by cohort sample size, is 0.62 (2.29% adjusted Nagelkerke R^2), 0.63 ($R^2 = 4\%$), 0.59 ($R^2 = 0.29\%$) and 0.64 ($R^2 = 4.56\%$), respectively. Similar results are shown on Fig. 3(b) for depression-first BPD, as discussed later. For all cohorts in both plots, it can be deduced from the s.e. bars that the AUC is significantly higher than the bootstrapped model using principal components only (null model AUC of 0.58), with the exception of the MDD; here, the confidence intervals overlap the null model (for AUC) or zero (for adjusted R^2) in seven cohorts. However, using paired *t*-tests, weighted by effective sample size, we show that the weighted mean across all 13 cohorts is significantly higher than that of the covariates-only 'null' model (see Supplementary Table 12).

Interestingly, the BPD predictor outperforms the predictor built on BPDvsMDD cohorts. However, this is likely because of differences in sample size of the underlying GWAS: when we compare the BPDvsMDD predictor to a version of the BPD predictor based on a GWAS of equal sample size (see Supplementary Appendix H, Supplementary Fig. 8), the performance difference initially observed is no longer significant ($P = 0.28$ for equal sample size, paired weighted *t*-test).

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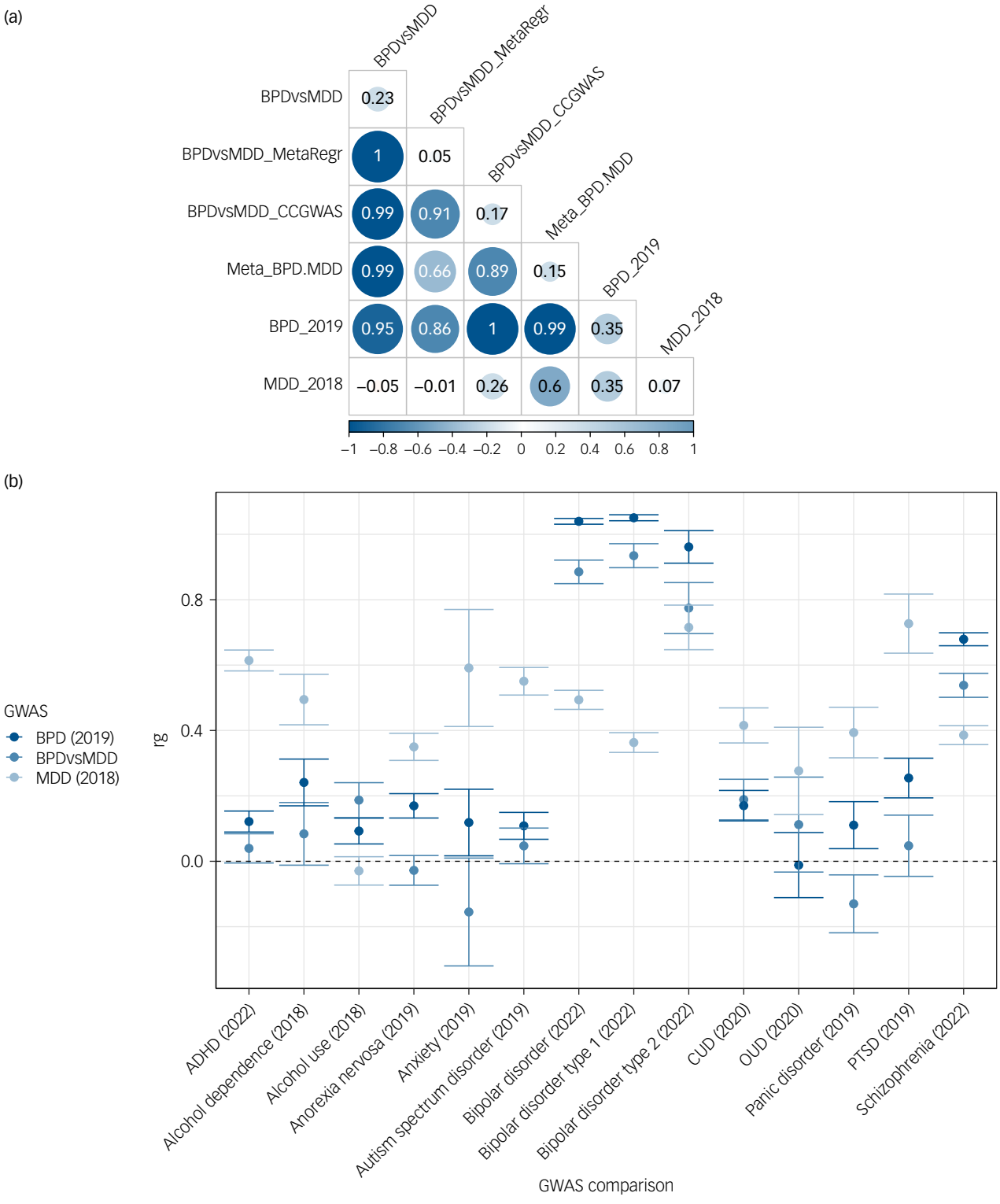

Fig. 2 (a) Genetic correlations between the different GWAS methods performed. (b) Genetic correlations between the case–case GWAS (BPDvsMDD purple), our BPD case–control GWAS (blue) and our MDD case–control GWAS (red) on the *y*-axis, and GWAS of other psychiatric traits from the PGC on the *x*-axis.

GWAS, genome-wide association analyses; MDD, major depressive disorder; BPDvsMDD, bipolar disorder versus major depressive disorder; PGC, Psychiatric Genomics Consortium; ADHD, attention-deficit hyperactivity disorder; CUD, cannabis use disorder; OUD, opioid use disorder; PTSD, post-traumatic stress disorder.

Our comparison of the BPD and BPDvsMDD predictors with a more recent PGC BPD collection,[34] including 41 917 cases and 371 549 controls, was attempted only for cohort 'grp5_neth' and demonstrates the power advantage of the PGC BPD GWAS-based predictor in classification performance (13.15% R^2 for the PGC BPD predictor, compared with 7.16% for the BPDvsMDD predictor and 10.98% for our combined BPDvsMDD + BPD + MDD GWAS predictor; Supplementary Fig. 9). However, combining our

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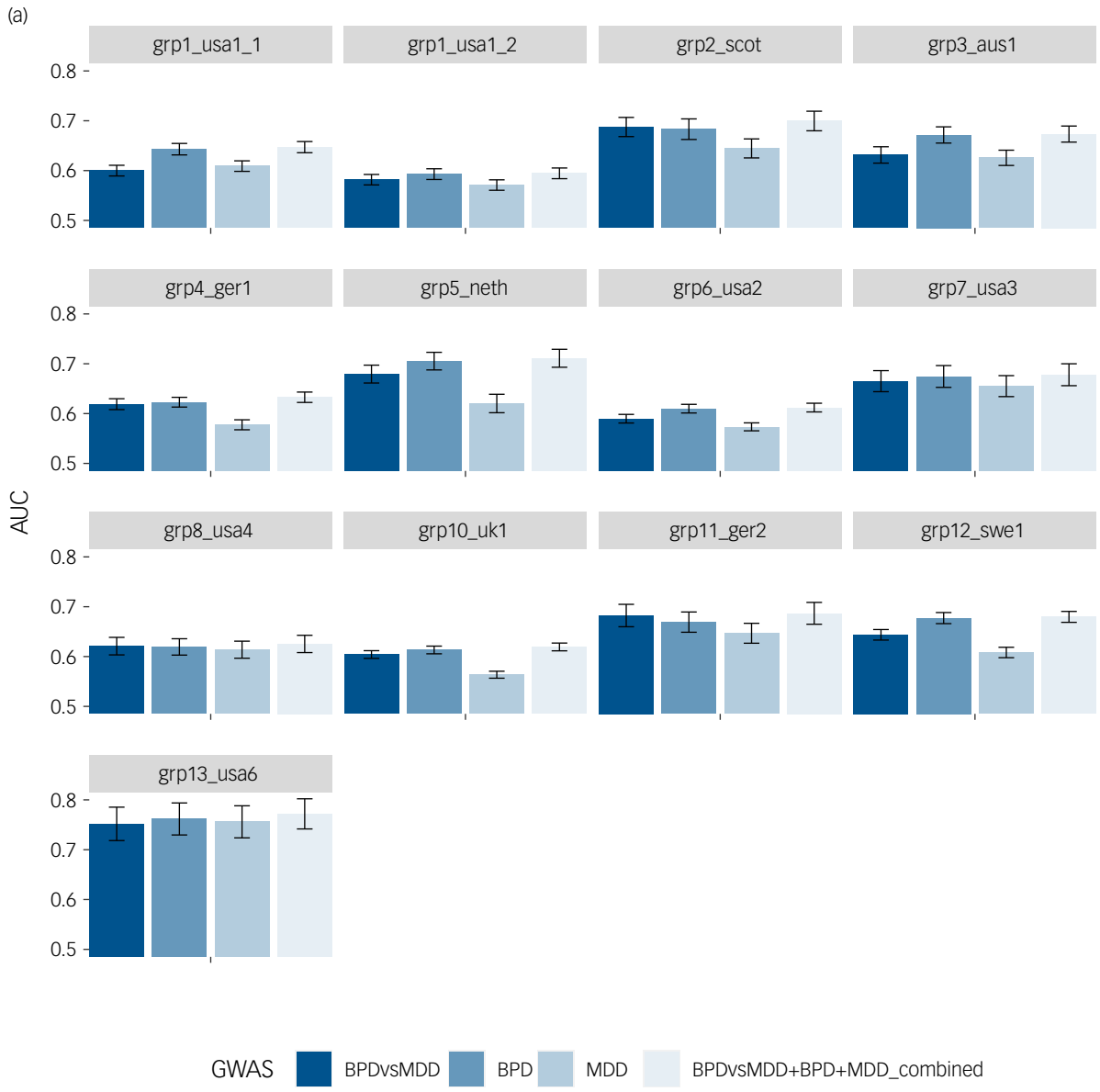

Fig. 3 Ability of our GWAS to distinguish BPD versus MDD status in our cohorts: area under the ROC curve (AUC) of PRS analysis, using SBayesR for the BPDvsMDD GWAS, (a) using all BPD versus MDD cohorts as target and (b) using BPD with depressive onset (BPD-D) versus MDD cohorts as target. (c) Ability of different psychiatric traits from the PGC to classify BPD versus MDD status in our cohorts (mean AUC weighted by cohort effective sample size is reported).

GWAS, genome-wide association analyses; MDD, major depressive disorder; ROC, receiver operating characteristic; PRS, polygenic risk scores; BPDvsMDD, bipolar disorder versus major depressive disorder; PGC, Psychiatric Genomics Consortium; ADHD, attention-deficit hyperactivity disorder; AUD, alcohol use disorder; CUD, cannabis use disorder; PTSD, post-traumatic stress disorder.

BPDvsMDD predictor with the PGC BPD predictor yields even better performance ($R^2 = 14.81\%$), thus confirming the value of utilising a predictor based on case–case GWAS.

Using a paired weighted *t*-test (one-tailed), we observed significantly increased performance of the combined predictor relative to each of the individual predictors: mean weighted AUC of 0.60 for the BPDvsMDD GWAS, 0.62 for the BPD GWAS, 0.5 for the MDD GWAS and 0.63 for all three combined (*P*-value of 3.5×10^{-5} (BPDvsMDD), 1.9×10^{-3} (BPD) and 6.5×10^{-7} (MDD)).

To delineate the contribution of the signals attributable to each disorder, we further broke down the combined predictor to two-way combinations and found that the MDD predictor contributes little over and above the BPDvsMDD + BPD GWAS combination: mean AUC 0.62 for BPDvsMDD + BPD GWAS (compared with 0.63 for all three combined, as mentioned above, with $P = 0.04$) (see Supplementary Fig.10(a) and (b)).

We next limited our analysis to the subgroup of patients with depression onset, testing the ability of BPDvsMDD (and BPD and MDD) PRS to distinguish between depression-first BPD cases and MDD cases. We found that the classification accuracy is similar to that including all BPD cohorts (Fig. 3(b) and Supplementary Fig. 10(c) and (d)). Our available sample size did not permit a similar analysis for manic-first episode BPD (heritability *z*-score of 2.4).

Finally, Fig. 3(c) shows the classification performance of all different psychiatric traits listed above (see the 'Method' section), with respect to differentiating between BPD and MDD cases. Only schizophrenia is able to provide substantial differentiation between BPD and MDD, comparable to our BPDvsMDD GWAS

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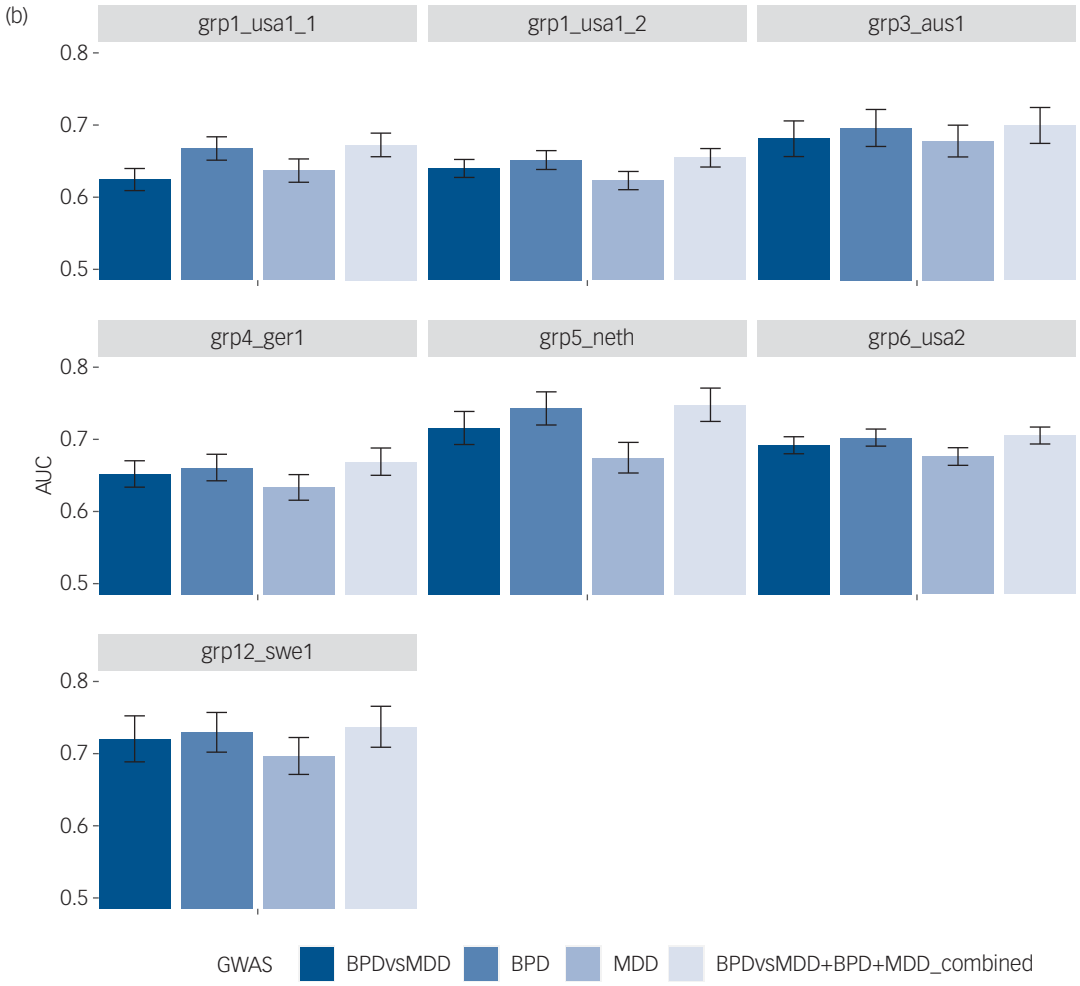

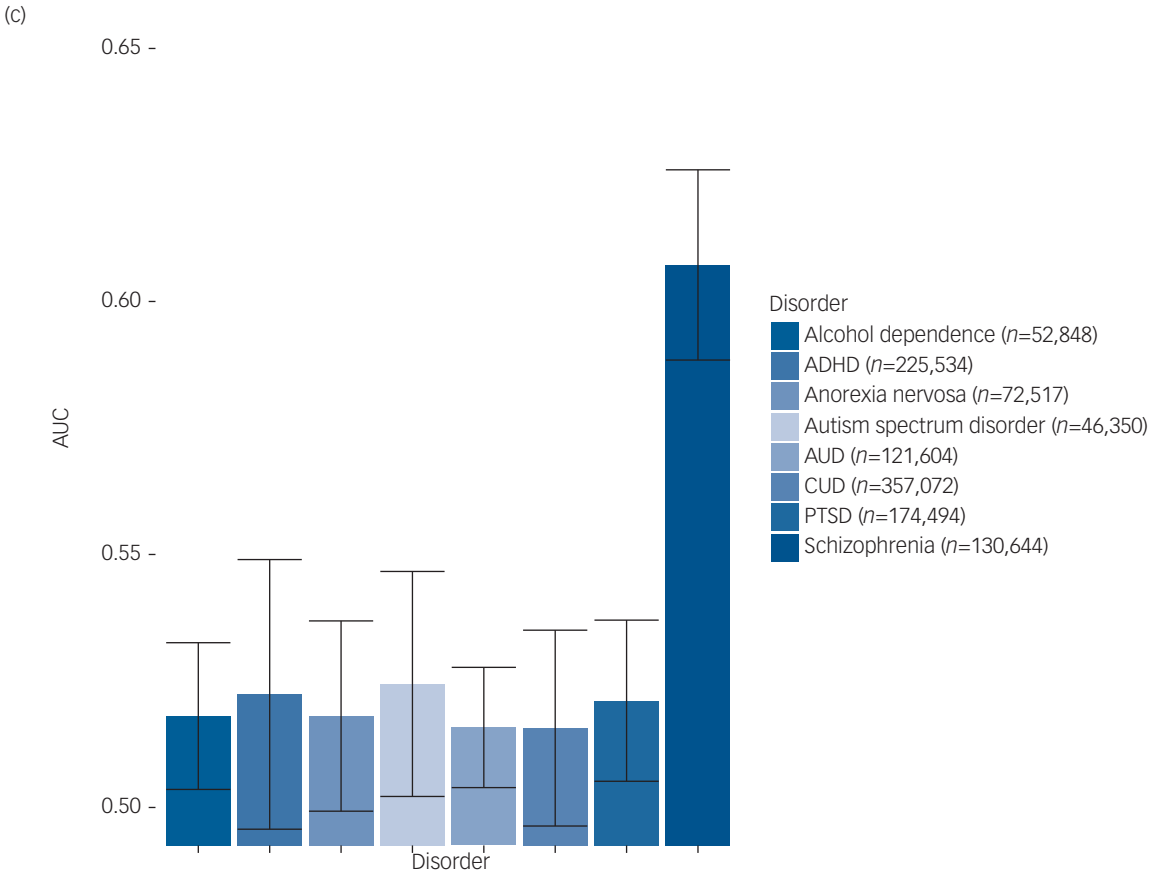

Fig. 3 (Continued)

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Table 1 Replication results of PRS analysis, using iPSYCH as the target cohort

Target cohort		Null model (predicted by ten principal components)	Full model (predicted by BPDvsMDD plus ten principal components)	Full model combined predictor (predicted by BPDvsMDD, BPD MDD and ten principal components)
All patients with a BPD diagnosis versus all patients with an MDD diagnosis	AUC	0.563	0.578	0.587
	Nagelkerke R^2	0.99%	1.39%	1.83%
	Nagelkerke R^2 adjusted	–	0.40%	0.84%
Patients with an MDD diagnosis prior to a BPD diagnosis versus patients with an MDD diagnosis and no BPD diagnosis	AUC	0.547	0.562	0.578
	Nagelkerke R^2	0.33%	0.65%	1.02%
	Nagelkerke R^2 adjusted	–	0.32%	0.69%

Nagelkerke R^2 adjusted = (Nagelkerke R^2 full model) – (Nagelkerke R^2 null model). AUC and Nagelkerke's R^2 achieved by each model (i.e. null model – principal components only, full model – BPDvsMDD GWAS and full model with combined predictor) for BPD versus MDD status classification, and for depression-first BPD versus MDD status. PRS, polygenic risk score; BPD, bipolar disorder; MDD, major depressive disorder; BPD GWAS, case–control GWAS of bipolar disorder; MDD GWAS, case–control GWAS of major depression; BPDvsMDD GWAS, case–case GWAS of bipolar disorder versus major depression.

(AUC = 0.61, s.e. = 0.02), whereas for the rest of the available psychiatric traits, the performance is very poor.

Replication with iPSYCH

Sign tests

We tested 39 independent SNPs ($P < 1.0 \times 10^{-5}$) from BPDvsMDD, of which 22 (56%) had the same direction of effect in discovery and replication samples, indicating an accumulation of the same direction of effect in our replication sample, although this test does not reach nominal significance. We observe minimal SNP heritability of BPDvsMDD in the iPSYCH cohort ($h^2 = 0.02$ (s.e. = 0.02), with intercept 1.003 (0.01)), which may account, in part, for this lack of replication.

Polygenic risk scoring

Polygenic scores based on our full PGC BPDvsMDD GWAS, calculated using SBayesR, yielded an AUC of 0.58 and an incremental Nagelkerke R^2 score of 0.40% on iPSYCH, after adjusting for population covariates in the regression model. Although it displays limited power, the PRS predictor is highly significant ($P < 1.0 \times 10^{-16}$), and an analysis of variance (ANOVA) between the full PRS model against the null model using covariates only is significant ($P = 1.9 \times 10^{-12}$), confirming the additional classification accuracy conferred by the PRS predictor.

Using our combined predictor in a multiple regression setting yields improved results, with an AUC of 0.59 and adjusted Nagelkerke R^2 of 0.84%. After examination of the individual predictors, we see that the BPD predictor has the strongest contribution ($P = 3.3 \times 10^{-7}$), whereas the BPDvsMDD and MDD predictors are not statistically significant in the presence of the BPD predictor ($P > 0.1$). As before, the full model using BPD, MDD and BPDvsMDD outperforms the null model using only covariates (ANOVA, $P < 1.0 \times 10^{-16}$) (see Table 1) and the model outperforms the model using the BPDvsMDD predictor only (ANOVA, $P = 2.8 \times 10^{-12}$).

Constrained to individuals with an MDD diagnosis before BPD diagnosis, our models have similar classification performance, with an AUC of 0.56 and adjusted Nagelkerke R^2 of 0.33% for the BPDvsMDD, and an AUC of 0.58 and adjusted Nagelkerke R^2 of 0.69% for the combined predictor.

Discussion

With the goal of identifying genetic differences between MDD and BPD, we performed three GWAS: a direct comparison between cases of both disorders, a meta-regression testing whether effect sizes differ between BPD versus controls and MDD versus controls across cohorts, and CC-GWAS using case–control summary statistics. Our analysis between these two disorders was enabled by our approach to combine individual-level case-case-control cohorts, adopted for the first time on a large scale. Specifically, we introduce a pipeline to carefully match and compile case-case-control cohorts from existing case-control cohorts. Although this approach limits the individuals that can be included, it enables direct case–case GWAS and meta-analysis and obviates the need to account for inflation owing to sample overlap.

We found that MDD and BPD are genetically distinct, with an estimated heritability of 23% on the observed scale in the direct comparison GWAS (5% by meta-regression, and 17% by CC-GWAS), thus potentially distinguishable using genetic predictors. Our primary GWAS yielded no genome-wide significant loci, likely because of a lack of power. Although we were able to include 76% of PGC participants available for these analyses, with the resulting sample sizes they are still relatively underpowered to yield genome-wide significant hits for psychiatric traits, given their polygenicity and sizes of underlying effects, among other factors.[35]

Using CC-GWAS, one of our secondary analysis approaches, we identified one genome-wide significant hit, which has support from both BPDvsMDD and meta-regression, as well as the BPD GWAS. The lack of signal in MDD highlights the BPD-specificity of this locus. In addition, we observe convergence of the different GWAS methods in a few other loci with suggestive genome-wide significance. However, increased sample sizes are needed to enable the discovery of novel loci and the identification of convergent pathways through pathway enrichment analysis.

Somewhat surprisingly, but in line with the locus-specific signal described above, we observed that the BPDvsMDD GWAS was strongly genetically correlated with BPD GWAS (ranging between 0.88 and 0.95). Relatedly, for traits that are strongly correlated with MDD, but not with BPD (e.g. PTSD, ADHD, anorexia nervosa), their genetic correlation with BPDvsMDD is driven toward zero, whereas traits strongly correlated with BPD also correlate with BPDvsMDD.

Our leave-one-out polygenic risk scoring analysis confirms the ability of our BPDvsMDD GWAS to differentiate between BPD and MDD status, which is enhanced when adding multiple predictors from the corresponding case–control GWAS in a multiple regression setting (combined BPDvsMDD, BPD and MDD predictor). Although it is possible that this is attributable to the increased effective sample size, we found that the BPD and MDD predictors (of similar sample size) contribute differently. Consistent with the observation that the BPDvsMDD GWAS has a high genetic correlation with BPD, we found that including the MDD predictor (based

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on the MDD versus controls GWAS) did not have a substantial contribution over and above the BPDvsMDD and BPD predictors.

Our BPDvsMDD and combined predictors had lower performance than a predictor built on the latest BPD GWAS,[34] which is derived from a much larger sample size, although this comparison was limited to one combined cohort because of the extensive sample overlap between the GWAS being compared. In this cohort, the BPD GWAS does not saturate classification accuracy: using our BPDvsMDD in conjunction with the well-powered latest BPD GWAS from the PGC yielded the highest estimated PRS accuracy. This is expected, since the overall variance explained by PRS is not yet close to the observed heritability, and underlines the potential for improvement.

Finally, we tested the ability of PRS to differentiate between patients with unipolar depression and patients with BPD who are most difficult to diagnose: patients with BPD with a depressive onset. Given that depression-first BPD cases have stronger depressive features than those with a manic POA,[17,36] one may hypothesise that the ability of PRS to distinguish between depression-first BPD cases and MDD cases is lower than that including all BPD cases. To the contrary, we observe that the classification accuracy of PRS is statistically indistinguishable to that including all patients with BPD, in all cohorts. This finding is encouraging, as it opens the possibility of future genetic studies being able to aid in precision psychiatry efforts, including the differential diagnosis of mood disorders.

Although our analysis demonstrates the potential of genetic predictors to distinguish BPD from MDD, including patients with a depressive onset, we stress the fact that the reported predictive ability is still very low – larger sample sizes are essential in making such predictors useful in clinical practice. However, we additionally show here that the combination of predictors from different GWAS can help in this area.

Our replication effort in iPSYCH did not show strong replication. This may be because of a lack of power, but also may be affected by the differences in ascertainment strategies. Patients in the iPSYCH samples are ascertained in secondary care hospitals, where only around 15% of MDD cases in Denmark are treated,[37] which may mean the PGC MDD cases, comprising our discovery sample, may be less representative of them. This is consistent with previous work,[38] showing that the genetic correlation between iPSYCH PGC for MDD is lower than for BPD and that the MDD–BPD cross-disorder genetic correlation is higher in iPSYCH than in prior PGC studies, potentially limiting the power to identify discriminating genetic signals. In the PGC data available to us, 83% of BPD case participants have BPD type 1, indicating a selection for severity, whereas this number is not known in iPSYCH. Despite these differences, PRS effects were replicated in iPSYCH, an independent sample.

Taken together, our results support the hypothesis that controls, patients with MDD and patients with BPD primarily lie on a continuum of genetic risk, with little specific MDD versus BPD signal detectable at the current sample sizes. Our analysis yields substantial heritability estimates; however, since disease prevalence and heritability differ between BPD and MDD (BPD has higher heritability and lower prevalence compared with MDD), relatively larger sample sizes are needed to detect MDD-specific signals.[39]

A limitation of our study is the cross-sectional nature of our phenotypic data; in particular, we expect a proportion of MDD patients to have converted to BPD since recruitment. Unfortunately, insufficient phenotypic information on age and time-since-onset was available to perform an analysis including only likely stable MDD cases in a well-powered way.

In addition to larger sample sizes, future studies with richer longitudinal phenotypic information and multi-diagnostic cohorts, as well as more direct case–case analyses, will likely yield a better understanding of our findings and enable the development of better genetic predictors distinguishing BPD from MDD, and more specifically, depression-first BPD from MDD, that may in the future be utilisable in a clinical setting.

To this end, the collection of the 13 case-case-control cohorts compiled here will be a valuable resource for the research community in psychiatric genomics. Information on accessing these data from studies shared with the PGC will be available on the PGC website. Summary statistics data from case–case GWAS analysis will also become available upon publication.

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Supplementary material

Supplementary material is available online at https://doi.org/10.1192/bjp.2024.125.

Data availability

GWAS summary statistics from our case–case GWAS of BPDvsMDD are available in the PGC Data Access Portal: https://pgc.unc.edu/for-researchers/download-results/. Individual-level data of case–case cohorts are available upon request from the PGC BPD and MDD Working Groups.

Author contributions

L.O.L., S.R., R.A.O., G.B., G.P., J.R.I.C. and J.K. made substantial contributions to the conception and design, as well as the interpretation of the work. G.P., K.-L.G.H., A.J.S., D.S., S.R. and L.O.L. made a substantial contribution in the designing and conducting the analysis of the data. G.P., K.-L.G.H., A.J.S., J.R.I.C., C.M.L., R.A.O., G.B., S.R. and L.O.L. were responsible for drafting the work or reviewing it critically for important intellectual content. P.B.M., P.R.S., A.J.F., M.B., L.J.S., C.N.P., M.T.P., Q.S.L., G.K., M.L., L. Jonsson, B.M.-M., J.W.S., E.B.B., T.M.B., D.C., S.V.d.A., H.J.G., G.H., C.O.S., J.B.P., J.R.D., F.S.G., D.F.M., F.M.M., M.M.W., J.S., M.A.F., J.M.B., A.R., S.H.W., R.R.K., M.M.B., M.J.O., K.G.-S., B.L.M., N.G.M., S.E.M., L. Jones, J.A.K., D.F.L., M.C.O., C.M.L., G.B., T.W., A.J.S. and R.A.O. made a critical contribution to the acquisition of data for this work. All authors provided final approval of the version to be published and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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