Article

Mapping the genetic landscape across 14 psychiatric disorders

https://doi.org/10.1038/s41586-025-09820-3

Received: 5 December 2024

Accepted: 28 October 2025

Published online: 10 December 2025

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Psychiatric disorders display high levels of comorbidity and genetic overlap[1,2], challenging current diagnostic boundaries. For disorders for which diagnostic separation has been most debated, such as schizophrenia and bipolar disorder[3], genomic methods have revealed that the majority of genetic signal is shared[4]. While over a hundred pleiotropic loci have been identified by recent cross-disorder analyses[5], the full scope of shared and disorder-specific genetic influences remains poorly defined. Here we addressed this gap by triangulating across a suite of cutting-edge statistical and functional genomic analyses applied to 14 childhood- and adult-onset psychiatric disorders (1,056,201 cases). Using genetic association data from common variants, we identified and characterized five underlying genomic factors that explained the majority of the genetic variance of the individual disorders (around 66% on average) and were associated with 238 pleiotropic loci. The two factors defined by (1) Schizophrenia and bipolar disorders (SB factor); and (2) major depression, PTSD and anxiety (Internalizing factor) showed high levels of polygenic overlap[6] and local genetic correlation and very few disorder-specific loci. The genetic signal shared across all 14 disorders was enriched for broad biological processes (for example, transcriptional regulation), while more specific pathways were shared at the level of the individual factors. The shared genetic signal across the SB factor was substantially enriched in genes expressed in excitatory neurons, whereas the Internalizing factor was associated with oligodendrocyte biology. These observations may inform a more neurobiologically valid psychiatric nosology and implicate targets for therapeutic development designed to treat commonly occurring comorbid presentations.

Half of the population will meet criteria for at least one psychiatric disorder during their lifetime[7], with many meeting criteria for multiple disorders[1]. High levels of psychiatric comorbidity complicate efforts to differentiate among psychiatric disorders. These challenges are heightened because psychiatric disorders are defined by signs and symptoms, as the underlying pathophysiologies remain largely unclear. Rapid progress in psychiatric genomics has identified hundreds of associated loci (genetic variants), many of which exhibit pleiotropic (shared) associations across disorders, and revealed high correlations in genetic liability across disorders[8].

The present analyses represent the third major study from the Psychiatric Genomics Consortium Cross-Disorder working group[9] (CDG3). Here we examined the shared and unique influences of common genetic variants across 14 psychiatric disorders. Triangulating across multiple, complementary analytic approaches, we dissected the genetic architecture across disorders at the genome-wide, regional, functional and individual genetic variant levels. Our results have implications for refining clinical nosology and repurposing and developing novel treatments.

GWAS data for 14 psychiatric disorders

A summary of the datasets is provided in Extended Data Table 1. Psychiatric disorders were included if described in a psychiatric diagnostic manual[10,11] and power was sufficient to interpret genetic correlations[4]. This reflects a major update relative to previous CDG1 (ref. 12) and CDG2 (ref. 5) analyses (average case increase of around 165% above CDG2; Supplementary Fig. 1), with new genome-wide association studies (GWASs) for all eight disorders from CDG2: attention-deficit/hyperactivity disorder (ADHD), anorexia nervosa (AN), autism spectrum disorder (ASD), bipolar disorder (BIP), major depression (MD), obsessive–compulsive disorder (OCD), schizophrenia (SCZ) and Tourette's syndrome (TS)[13–20]. We added six additional disorders: alcohol-use disorder (AUD)[21], anxiety disorders (ANX)[22], post-traumatic stress disorder (PTSD)[23], nicotine dependence assessed using the Fagerström test for nicotine dependence (NIC)[24], opioid-use disorder (OUD)[25] and cannabis-use disorder (CUD)[26]. The three substance-use disorders (SUDs) are novel relative to a more recent cross-disorder analysis[27], and sample size increases were significant for previously included disorders (average case increase of around 287%). The sample sizes, and therefore the power of the disorder GWAS, differed (Extended Data Table 1 ($N_{effective}$)).

Owing to an uneven representation of ancestral groups, the full set of cross-disorder analyses was restricted to GWAS summary statistics from a single genetic ancestry group—European-like (EUR-like)—defined on the basis of genetic similarity to European descent in global reference panels[28]. We also report bivariate results for MD[29] and SCZ[30] in East-Asian-like (EAS-like) genetic ancestry groups and AUD[31], CUD[26],

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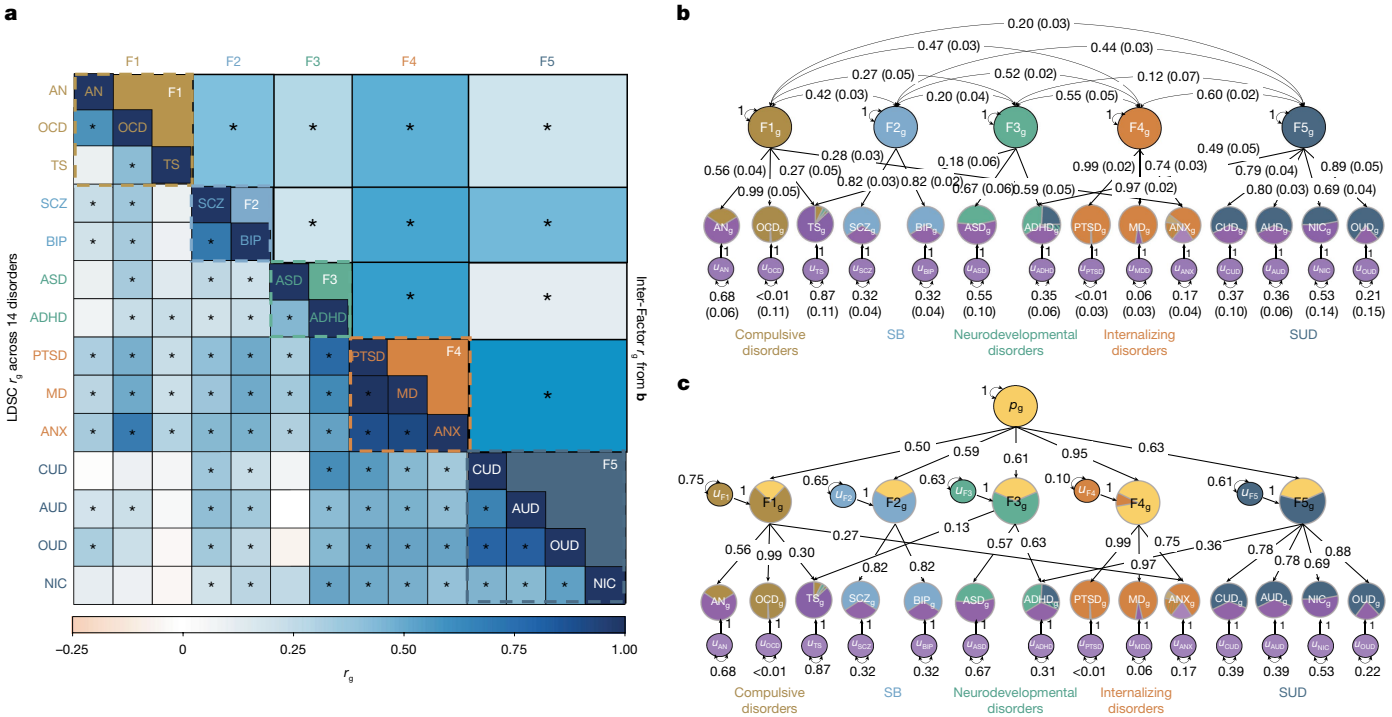


Fig. 1 | Genome-wide structural models. a, Heatmap of r_gs across the 14 disorders as estimated using LDSC on the lower diagonal and the correlations among the psychiatric factors as estimated using GenomicSEM above the diagonal. Two-sided *P* values were derived from the *Z*-statistics, calculated as the point estimate of the r_g divided by its s.e. Cells depicted with an asterisk reflect values that were significant at a Bonferroni-corrected threshold for multiple comparisons. Exact values are reported in Supplementary Table 1. Disorders that load on the same factor are shown in the same colour. Per the legend at the bottom of the panel, darker blue shading indicates larger, positive r_gs. LDSC estimates were used as the input to genomic SEM to produce the results in **b** and **c**. **b**, Estimates from the five-factor model along with standard errors in parentheses. Estimates are standardized relative to SNP-based heritabilities, where this is equal to the sum of the squared factor loading (the single-headed arrow(s) from the factor to the disorder) and the residual variance (the values on the double-headed arrows on the single-colour circles with text labels that begin with u). Disorders are shown as pie charts; the proportion of residual variance is shaded in purple and the variance explained by the psychiatric factors is shaded in the colour of the corresponding factor. **c**, Standardized estimates from the *p*-factor model. The disorders are colour coded as in **b**, and the first-order factors (F1–F5) are also colour coded to show variance explained by the second-order *p*-factor in yellow.

OUD[25] and PTSD[23] in African-like (AFR-like) genetic ancestry groups similarly defined based on reference panels.

Genome-wide genetic correlations

Genetic correlations (r_gs) estimated using linkage disequilibrium (LD) score regression (LDSC)[4] revealed pervasive genetic overlap across disorders at the genome-wide level, with clusters of disorders demonstrating particularly high genetic overlap in individuals of EUR-like genetic ancestry (Fig. 1; Supplementary Table 1; see Supplementary Figs. 2–4 for consideration of high r_g across PTSD and MD). The LDSC estimates within AFR-like participants were not significant, due to limited power (Supplementary Table 4). The r_g between MD and SCZ in EAS-like participants (r_g = 0.45, s.e. = 0.09) was double that observed in EUR-like participants (r_g = 0.22, s.e. = 0.04), which has been shown[29] to be driven by a single cohort of severe and recurrent MD[32].

As the majority of analyses were restricted to participants of EUR-like genetic ancestry, we sought to gauge how generalizable our findings were across ancestral groups. We achieved this using Popcorn[33], which can estimate r_gs for the same trait across ancestral groups. We estimated the genetic impact correlation (ρ_{gi}), which considers different allele frequencies across populations by calculating the correlation between the population-specific, allele-variance-normalized single-nucleotide polymorphism (SNP) effect sizes. The results were underpowered for many comparisons, but included a strong EAS–EUR correlation for SCZ (ρ_{gi} = 0.85, s.e. = 0.04), followed by lower correlations between EAS-like and EUR-like for MD (ρ_{gi} = 0.67, s.e. = 0.16) and for AFR-like and EUR-like PTSD (ρ_{gi} = 0.59, s.e. = 0.27; Supplementary Table 4). While these results suggest that the findings that follow for EUR-like ancestry groups may generalize better for some disorders (such as SCZ) than for others (for example, PTSD and MD), that conclusion awaits replication in more highly powered analyses.

MiXeR reveals pervasive genetic overlap

Genome-wide r_gs from LDSC indicate shared genetic risk across psychiatric disorders. However, LDSC may underestimate the extent of genetic overlap if shared causal variants reflect a mixture of directionally concordant and discordant associations. We applied bivariate causal mixture modelling (MiXeR) to quantify the degree of genome-wide polygenic overlap reflecting the total number of shared causal variants regardless of magnitude or directionality[6]. Cross-trait analyses were limited to MD, SCZ, BIP, ANX, ADHD, PTSD, AUD and AN, because other disorders were underpowered (Methods; results for univariate MiXeR are reported in Supplementary Table 5 and Extended Data Fig. 1). Supplementary Fig. 5 displays cross-trait MiXeR results for pairwise overlap across four particularly well-powered disorder samples: ADHD, SCZ, BIP and MD (complete results are shown in Supplementary Figs. 6–9 and Supplementary Table 6). There was greater polygenic overlap across psychiatric disorders than suggested by the r_gs from LDSC. Overall, MiXeR results suggested that the shared genetic signal for psychiatric disorders primarily reflects variants with concordant effects across disorders, while differentiation in genetic risk is driven by fewer shared discordant or unique variants.

Genomic SEM identifies five factors

We used genomic structural equation modelling (genomic SEM)[27,34] in the EUR-like genetic ancestry datasets to model genetic overlap from LDSC across 14 disorders as latent factors representing dimensions of shared genetic risk (Methods). A five-factor model (Supplementary Tables 2 and 3) provided the best fit to the data (comparative fix index (CFI) = 0.971, standard root mean square residual (SRMR) = 0.063). These five latent genomic factors (capitalized throughout, to distinguish them from the psychiatric disorders that define them) (Fig. 1) comprised: F1, a Compulsive disorders factor defined by AN, OCD and, more weakly, TS and ANX; F2, a SB factor defined by SCZ and BIP; F3, a Neurodevelopmental factor defined by ASD, ADHD and, more weakly, TS; F4, an Internalizing disorders factor defined by PTSD, MD and ANX; and F5, a SUD factor defined by OUD, CUD, AUD, NIC and, to a lesser extent, ADHD.

Within this five-factor model, Internalizing disorders and SUD factors displayed the highest interfactor correlation (r_g = 0.60; s.e. = 0.02). The median residual genetic variance unexplained by the latent factors was 33.5%, indicating that most genetic risk was shared among disorder subsets. TS displayed the most unique genetic signal, with 87% of its genetic variance unexplained by the factors. The structure of the first four factors was similar to that found by genomic SEM applied to subsets of these disorders in previous work[5,27], indicating stability in the underlying factor structure, even as sample sizes and the number of disorders have increased. The newly added SUD traits formed the fifth factor.

Evidence of moderate r_g between factors suggests that a higher-order factor may explain common variance across the correlated factors. Consistent with this observation, a hierarchical model also fit the data well (CFI = 0.959, SRMR = 0.074). We refer to this as the *p*-factor model, which included a higher-order general psychopathology factor defined by the five lower-order psychiatric factors (such as SUD). Internalizing loaded most strongly on *p* (0.95), with the other 4 factors having moderate loadings (0.50–0.63).

As some of the underlying data were obtained using brief, self-reported diagnoses, we performed a sensitivity analysis in which those data were excluded (Supplementary Note 1, Supplementary Tables 7–11 and Supplementary Figs. 10–18). The r_g matrix was largely unchanged; the five-factor model identified in the full sample continued to provide good fit to the data and produced similar point estimates, and downstream GWAS analyses (detailed below) identified similar loci.

Genetic correlations with factors

We estimated r_gs between the five correlated factors, hierarchical *p*-factor and 31 complex traits (Supplementary Table 12) to place shared genetic liability indexed by the factors in a broader clinical context. These factors vary in their use for capturing shared genetic signal; accordingly, we used the Q_{Trait} heterogeneity statistic to assess this use at the genome-wide level. When Q_{Trait} is significant, this indicates a trait's r_g deviates from the factor structure. For example, if trait *X* is negatively correlated with SCZ but unrelated to BIP, Q_{Trait} would probably be significant, suggesting that trait *X* lies outside the shared signal captured by the factor. Significant correlations were defined at a Bonferroni-corrected threshold of $P < 2.68 \times 10^{-4}$, while not significant for Q_{Trait} at this same threshold. This Q_{Trait} exclusion criteria was relaxed for the *p*-factor if that trait was significantly associated with the majority (≥3) of the five correlated factors, as this indicates the trait is capturing transdiagnostic associations the *p*-factor is intended to index.

The Internalizing disorders and SUD factors were the only factors associated with household income ($r_{g\_Internalizing}$ = −0.40, s.e. = 0.02; r_{g_SUD} = −0.41, s.e. = 0.03; Fig. 2) and were the most pervasively associated with different cognitive outcomes, including childhood intelligence ($r_{g\_Internalizing}$ = −0.27, s.e. = 0.05; r_{g_SUD} = −0.40, s.e. = 0.07). Only the SUD factor was associated with adult intelligence (r_{g_SUD} = −0.40, s.e. = 0.03) and verbal numerical reasoning (r_{g_SUD} = −0.41, s.e. = 0.03). This was compared to more circumscribed cognitive associations for the Compulsive disorders and SB factors, including a large negative correlation with the pairs matching test (potentially indexing memory; $r_{g\_Compulsive}$ = −0.33, s.e. = 0.03; r_{g_SB} = −0.34, s.e. = 0.03). The SB and SUD factors were the only ones associated with risk tolerance (r_{g_SB} = 0.31, s.e. = 0.03; r_{g_SUD} = 0.38, s.e. = 0.03). The Neurodevelopmental factor was uniquely associated with childhood BMI ($r_{g\_Neurodevelopmental}$ = 0.26, s.e. = 0.06) and showed high genetic overlap with childhood aggression ($r_{g\_Neurodevelopmental}$ = 0.94, s.e. = 0.10). As would be expected, the five traits significantly associated with all five correlated factors were also among the top correlations for the *p*-factor, reflecting stress sensitivity (r_{g_p} = 0.50, s.e. = 0.02), loneliness (r_{g_p} = 0.62, s.e. = 0.02), neuroticism (r_{g_p} = 0.64, s.e. = 0.02), self-harm (r_{g_p} = 0.74, s.e. = 0.04) and suicide attempts (r_{g_p} = 0.87, s.e. = 0.03). The full set of correlations is shown in Supplementary Table 13; comparison across factors is shown in Extended Data Fig. 2; and comparison across traits within each factor is shown in Extended Data Fig. 3.

LAVA finds regional hotspots of overlap

Global estimates of pleiotropy, such as the genome-wide r_gs from LDSC, provide an average of the degree of shared signal across the genome. However, as genetic overlap is unlikely to be constant across genomic regions, we segmented the genome into 1,093 LD-independent regions, and applied local analysis of (co)variant association (LAVA[35]; Methods) to assess the r_g between disorders within these regions. In addition to capturing heterogeneity in genetic overlap and pinpointing relevant regions, LAVA identifies potential r_g hotspots shared among several disorders, thereby providing further insight into genetic architecture.

We restricted analyses to loci with sufficient SNP-based heritability for the disorders analysed ($P < 4.6 \times 10^{-5}$ = 0.05/1,093; Methods). Correcting for the number of bivariate tests performed across all regions and disorder pairs, we detected 458 significant pairwise local r_gs ($P < 2.1 \times 10^{-6}$ = 0.05/24,273). The pairs of disorders with the greatest number of local r_g hits were MD and ANX (113 regions), MD and PTSD (88 regions), and BIP and SCZ (40 regions), accounting for over half of all significant local r_gs detected (Fig. 3a). This is consistent with the genome-wide levels of overlap indicated through the LDSC global r_g (Fig. 1), the polygenic overlap estimated with MiXeR (Supplementary Figs. 5–9), and the multivariate genetic structure identified by genomic SEM. Both global and local r_gs tended to be positive, with significant negative r_gs identified in only three instances (Supplementary Fig. 19). This indicates that the genetic risk for one disorder typically increases the risk for another (Supplementary Fig. 20).

We detected 101 regions that contained significant local r_gs between several disorder pairs, which we call r_g hotspots (see Supplementary Tables 14–23 for local r_gs across disorders in the top 10 hotspots). The most pleiotropic of these hotspots was on chromosome 11, which contained 17 positive and significant local r_gs involving 8 of the 14 analysed disorders (Fig. 3b). This region also stands out as the most significantly associated with 8 of these 17 disorder pairs, while ranking in the top 25% of associated loci for 12 of them (Supplementary Fig. 21). Notably, this region contains the *NCAM1–TTC12–ANKK1–DRD2* gene cluster that has been frequently associated with psychiatric phenotypes[36–39], and flagged as a likely pleiotropy hotspot for a range of cognitive and behavioural outcomes related to, for example, intelligence, personality, substance use and sleep[35,40–42].

Risk loci for psychiatric factors

We used multivariate GWAS within genomic SEM[34] to identify SNPs associated with the factors from the five-factor model or the *p*-factor

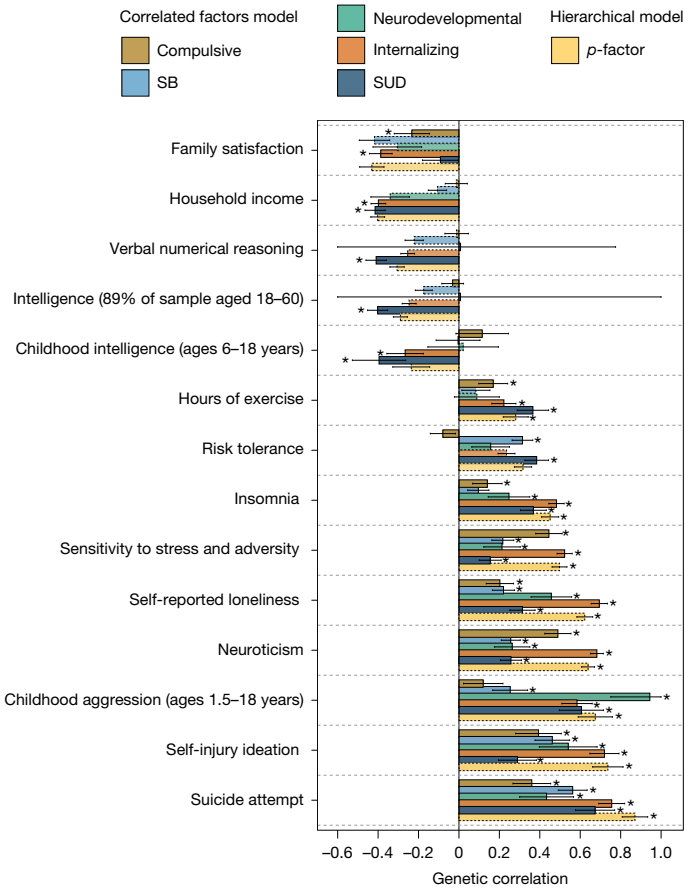


Fig. 2 | External trait genetic correlations for psychiatric factors. Point estimates for the r_gs between 14 external traits and the 5 psychiatric factors from the correlated factors model and the *p*-factor from the hierarchical model. These traits were selected as they were significantly correlated with at least one factor at >0.35 or <−0.35. Bars depicted with a dashed outline were significant for the Q_{Trait} heterogeneity statistic, which indicates that the pattern of r_gs for that trait did not fit the factor structure. Bars depicted with an asterisk reflect values that were significant at a Bonferroni-corrected threshold for multiple comparisons, that were also not significant at this same Bonferroni corrected threshold for Q_{Trait}. This is with the exception that the *p*-factor is depicted with an asterisk even if it is significant for the Q_{Trait}, provided that the same trait was significantly correlated with the majority (at least three) of the five other factors. The two-sided *P* values used to evaluate significance were derived from the *Z*-statistics, calculated as the point estimate of the r_g divided by its s.e. Error bars are ±1.96 s.e., centred around the point estimate of the r_gs. Traits are ordered by the point estimate for the *p*-factor. The implied sample size for the psychiatric factors was: Compulsive ($\hat{n}$ = 54,100), SB ($\hat{n}$ = 127,202), Neurodevelopmental ($\hat{n}$ = 84,760), Internalizing ($\hat{n}$ = 1,637,337), SUD ($\hat{n}$ = 313,395) and *p*-factor ($\hat{n}$ = 2,168,621). Sample sizes for the external traits are reported in Supplementary Table 12 and exact *P* values are reported in Supplementary Table 13.

in the hierarchical model. Similar to the Q_{Trait} metric, we estimated factor-specific Q_{SNP} heterogeneity statistics. This indexes SNPs that deviate strongly from the factor structure, due to either disorder-specific or directionally discordant effects. We defined genomic hits for the factors as those that were significant after Bonferroni correction ($P < 5 \times 10^{-8}/6$ genomic factors) and did not overlap with Q_{SNP} hits for that factor (Methods). Most hits were identified for the SB (n = 102) and Internalizing (n = 150) factors. After merging overlapping loci across the five correlated factors, 238 unique hits remained, including 27 broadly pleiotropic loci associated with two or more factors. The hierarchical model identified 160 hits for the *p*-factor (Fig. 4, Supplementary Fig. 22 and Supplementary Tables 24–36), 57 of which were not identified in the five-factor model (295 unique hits across both models). Forty-eight hits were novel relative to the univariate GWAS, of which 38 have been described in previous GWAS for a broad range of outcomes, and 10 are entirely novel (Supplementary Table 37).

We identified 33 unique hits with significant Q_{SNP} effects across the factors from the five-factor model. By comparison, we identified 117 Q_{SNP} hits from the *p*-factor model that showed significantly divergent effects across the five, lower-order psychiatric factors (Supplementary Table 36). These *p*-factor Q_{SNP} hits also included the chromosome 11 LAVA hotspot, where this region was found not to confer transdiagnostic risk due to an absence of signal for the Neurodevelopmental factor. For the SUD factor, highly significant Q_{SNP} hits were driven by variants in the genes involved in biological pathways specific to particular psychoactive substances, including the alcohol dehydrogenase genes (*ADH1A*, *ADH1B* and *ADH1C*) for AUD and the *CHRNA3–CHRNA5–CHRNB4* nicotinic receptor subunit gene cluster for NIC. More Q_{SNP} loci for the *p*-factor model relative to the five-factor model indicates that many shared genetic relationships are better captured by the five factors (Supplementary Figs. 23 and 24).

A phenome-wide association study conducted in the Mayo Clinic Biobank revealed that factor hits were associated with multiple psychiatric disorders, especially those that loaded on the factor (Supplementary Table 38 and Supplementary Fig. 25). The Internalizing disorders (Supplementary Fig. 25d) and *p*-factor (Supplementary Fig. 25f) loci were also associated with a range of medical outcomes (for example, chronic pain and hypertension).

Divergent loci across disorders

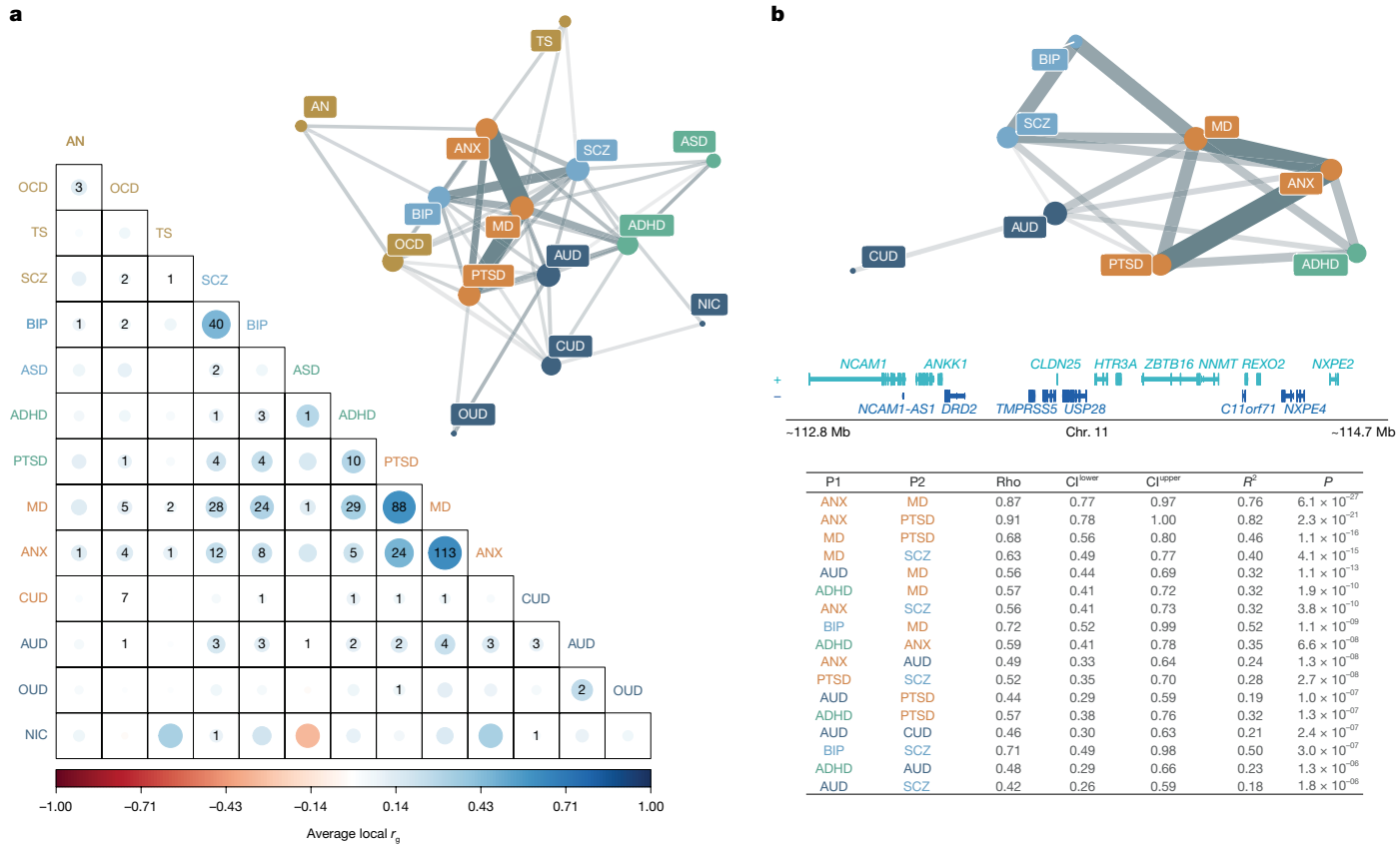
In more fine-grained analyses of disorder pairs, case–case GWAS (CC-GWAS)[43] was used to identify loci with different allele frequencies across cases of different disorders. Such loci may reflect distinctive genetic effects across disorder pairs. CC-GWAS was applied to 75 disorder pairs, comparing 13 disorders. NIC was excluded because it is a continuous trait, and the pairs ANX–MD, ANX–PTSD and MD–PTSD were excluded because all had an r_g estimate of >0.8, thereby risking an inflated type I error rate (Methods). The genome-wide significance threshold was defined at 5.5×10^{-10} (that is, $5 \times 10^{-8}/91$ pairwise comparisons). An overview of CC-GWAS input parameters is provided in Supplementary Table 39.

In total, 412 loci showed significantly different effects across the 75 disorder pairs (Supplementary Tables 40 and 41); most (294 out of 412) were in comparisons that included SCZ, possibly reflecting either greater power for the SCZ GWAS or more distinctive biology for this disorder. Owing to overlap among the hits, the 412 loci comprised 109 LD-independent loci (Supplementary Table 42). Five of these were CC-GWAS specific, implying that they were not significantly associated with case–control status in either of the disorders in the respective disorder pair. CC-GWAS also computes a genome-wide genetic distance between the cases of two disorders ($F_{ST,causal}$), indicating how genetically dissimilar the cases are on average. As expected, these genetic distances were inversely correlated (r = −0.79, s.e. = 0.07) with r_g (Supplementary Table 43). In support of the five-factor model, >99% of the CC-GWAS hits were identified for disorder pairs that loaded on separate factors (Supplementary Tables 44 and 45). Disorders that cluster on the same factor from the five-factor model are, apparently, largely indistinguishable at the level of individual genetic variants.

Functional annotation

Enrichment analyses

To understand biological functions influenced by the risk loci, we prioritized candidate risk genes implicated by the multivariate GWAS loci using expression quantitative trait loci (eQTL)[44,45] and Hi-C[44,46] datasets collected from fetal and adult brain samples (Methods and Supplementary Tables 46 and 47). Owing to the limited number of



P1	P2	Rho	CI^{lower}	CI^{upper}	R^2	P
ANX	MD	0.87	0.77	0.97	0.76	6.1×10^{-27}
ANX	PTSD	0.91	0.78	1.00	0.82	2.3×10^{-21}
MD	PTSD	0.68	0.56	0.80	0.46	1.1×10^{-16}
MD	SCZ	0.63	0.49	0.77	0.40	4.1×10^{-15}
AUD	MD	0.56	0.44	0.69	0.32	1.1×10^{-13}
ADHD	MD	0.57	0.41	0.72	0.32	1.9×10^{-10}
ANX	SCZ	0.56	0.41	0.73	0.32	3.8×10^{-10}
BIP	MD	0.72	0.52	0.99	0.52	1.1×10^{-09}
ADHD	ANX	0.59	0.41	0.78	0.35	6.6×10^{-08}
ANX	AUD	0.49	0.33	0.64	0.24	1.3×10^{-08}
PTSD	SCZ	0.52	0.35	0.70	0.28	2.7×10^{-08}
AUD	PTSD	0.44	0.29	0.59	0.19	1.0×10^{-07}
ADHD	PTSD	0.57	0.38	0.76	0.32	1.3×10^{-07}
AUD	CUD	0.46	0.30	0.63	0.21	2.4×10^{-07}
BIP	SCZ	0.71	0.49	0.98	0.50	3.0×10^{-07}
ADHD	AUD	0.48	0.29	0.66	0.23	1.3×10^{-06}
AUD	SCZ	0.42	0.26	0.59	0.18	1.8×10^{-06}

Fig. 3 | Local genetic correlations. a, An overview of the average patterns of local r_gs across the genome for all pairs of disorders, shown as a heatmap (below diagonal) and a network plot (above diagonal). The colours of the heatmap represent the average local r_gs across all evaluated loci, with darker red and blue shading indicating more negative and positive r_g, respectively; the dot size reflects the strengths of average associations; and the numbers indicate how many of the local r_gs were significant. These results are mirrored in the network plot, where the width or the edges reflect the number of significant associations, meaning that only disorders with at least one significant local r_g are connected, and the edge opacity reflects the strength of the average local r_g across tested loci. Note that label colours are concordant with the genomic SEM factor structure from Fig. 1 and, as shown, disorders of similar colours also tend to be proximally located within the network. **b**, The local r_g structure within the top r_g hotspot on chromosome (chr.) 11 (112755447–114742317, GRCh37 reference genome), that is, the region where the greatest number of significant r_gs were found across all disorder pairs. Here, the network plot illustrates all significant r_gs detected in this region, with both edge width and opacity reflecting the strength of the association. The region plot in the middle displays the genes contained within the hotspot, and the table below shows the r_g estimates (Rho), 95% confidence intervals (CI^{lower}, CI^{upper}), variance explained (R^2) and P values for all significant pairwise local r_gs in this region. Label colours are again concordant with those used for the genomic SEM factor structure in Fig. 1.

variants associated with other factors, analyses were restricted to the *p*-factor, the SB and Internalizing disorders factors and Q_{SNP} for these latter two factors. We first compared the target gene expression along the temporal trajectory of human brain development, finding that genes associated with the three factors were expressed at higher levels than Q_{SNP} target genes across the lifespan, with the largest difference observed at fetal stages and early life (Fig. 5 and Supplementary Fig. 26). This suggests that pleiotropic variants are involved in early, fundamental neurodevelopmental processes. We next examined biological processes using Gene Ontology (GO) enrichment analysis[47]. The target genes of the *p*-factor were primarily enriched in broader biological processes related to gene regulation (Fig. 5). To enhance the specificity of the gene sets, we removed Internalizing disorders and SB target genes that also appeared for the *p*-factor. SB (minus *p*-factor) target genes were enriched in more specific terms related to neuron development. No significant results were identified for the Internalizing disorders factor, probably reflecting the large proportion of target genes overlapping with the *p*-factor. Results from MAGMA[48] (Supplementary Methods) provided convergent support for the role of early neurodevelopmental processes in transdiagnostic psychiatric risk. Specifically, genetic signal for the five correlated factors and *p*-factor showed enrichment in genes identified from rare variant studies of ASD[49–51], neurodevelopmental delay[49] or both (Supplementary Fig. 27).

Averaged results across expression-weighted cell type enrichment (EWCE)[52] and MAGMA were used to evaluate enrichment within neuronal cell types in fetal and adult single-cell datasets[53–57] (Supplementary Tables 48 and 49). Genes associated with the SB factor were significantly enriched in fetal data in interneurons and seven excitatory neuron subtypes, the strongest of which was for excitatory maturing neurons[53,54] (Fig. 5). The SB factor was also uniquely enriched for deep-layer excitatory neurons in the adult brain[57]. Internalizing disorder genes were enriched within four excitatory neuron subtypes in fetal data[53], although the signal was not as strong or pervasive as for the SB factor. In adult data, the Internalizing factor was enriched for medial ganglionic eminence (MGE) interneurons[56] and different glial cells, specifically oligodendrocytes and Bergmann glia[56,57]. The *p*-factor was enriched for five excitatory neuron subtypes in fetal data and oligodendrocyte precursor cells in adult data[56]. A significant proportion of these genes is expressed during both fetal and adult stages; cell type enrichment was largely driven by genes that are not expressed in a particular developmental stage (Supplementary Fig. 28). We also tested enrichment for loci specific to MD and SCZ identified from CC-GWAS. MD-specific signal was enriched for cycling and intermediate progenitors in fetal brain. SCZ-specific signal was enriched for endothelial, vascular and upper rhombic lip cells in adult brain (Supplementary Fig. 28).

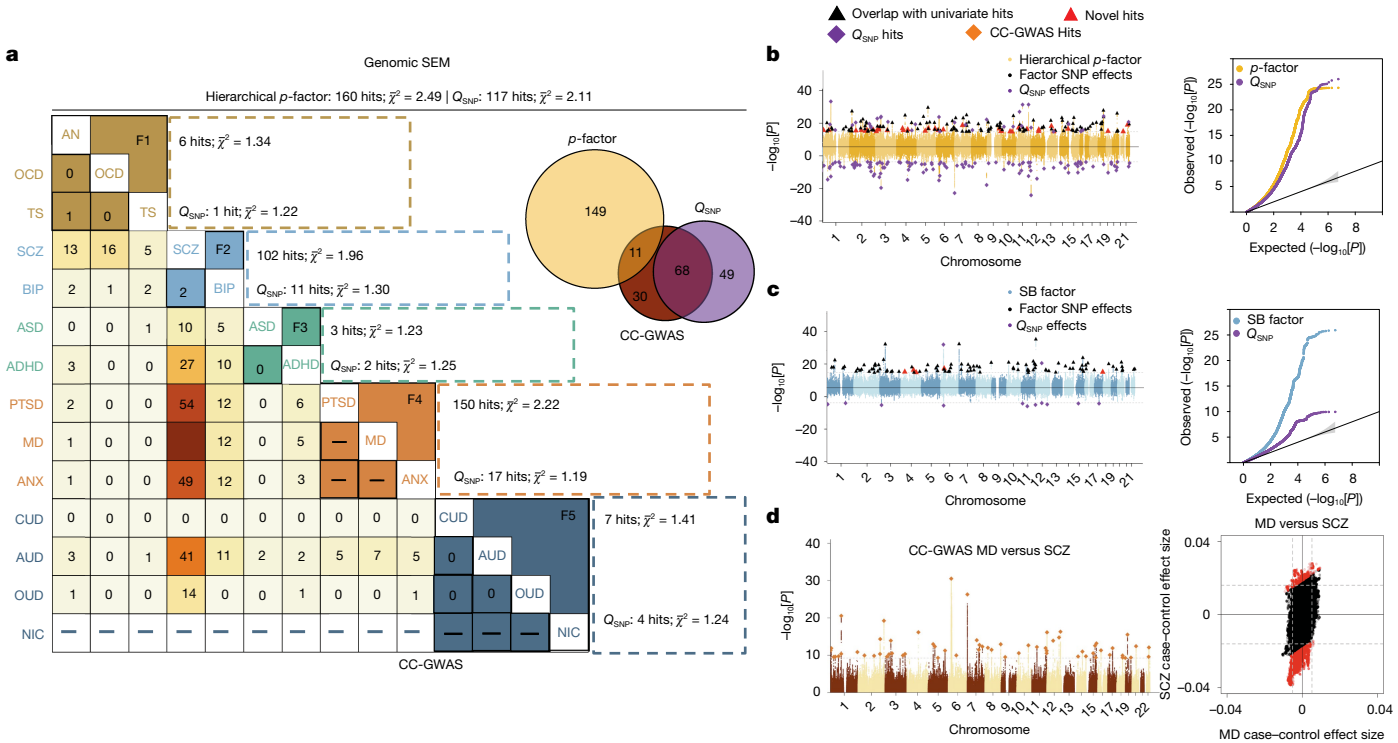


Fig. 4 | Locus-level results. a, Heatmap of CC-GWAS loci below the diagonal across pairwise combinations of disorders; the darker orange shading indicates a higher number of CC-GWAS hits. CC-GWAS results are not shown for the Internalizing disorders as their r_gs were too high, or for nicotine dependence as this is a continuously measured trait. Genomic SEM results (number of hits and mean χ^2 for each factor and factor-specific Q_{SNP} estimate) are reported above the diagonal. Results for the *p*-factor are shown above the plot along with a Venn diagram of the overlap between *p*-factor, *p*-factor Q_{SNP} and overall CC-GWAS hits. The disorders are ordered and coloured according to the genomic SEM factor structure from Fig. 1. **b**,**c**, The Miami and *QQ*-plots for the *p*-factor (**b**) and SBs factors (**c**), respectively. These panels show the results for the $-\log_{10}$-transformed two-tailed *P* values for the factor on the top half of the Miami plot and the $\log_{10}$-transformed one-tailed *P* values for Q_{SNP} on the bottom half. Factor hits that were within 100 kb of univariate hits are shown as black triangles, novel hits for the factors that were not within 100 kb of a univariate or Q_{SNP} hit are shown as red triangles and Q_{SNP} hits are shown as purple diamonds. **d**, The two-tailed $-\log_{10}[P]$ in a Manhattan plot for the CC-GWAS comparison across MD and SCZ, which produced the most hits (orange diamonds), as well as the scatterplot of standardized case–control effect sizes of MD (*x* axis) versus SCZ (*y* axis), with CC-GWAS significant SNPs labelled in red. For **b**–**d**, the grey dashed lines indicate the significance threshold, which was defined using Bonferroni correction for multiple comparisons.

Stratified genomic SEM

We used stratified genomic SEM[27], a multivariate corollary of partitioned LDSC[58], to characterize the functional signals captured by the psychiatric factors in the five-factor and *p*-factor models, estimating enrichment for 162 functional annotations that passed quality control (Methods and Supplementary Table 50). Enrichment of the factor variances in the five-factor or *p*-factor models reflects groups of genetic variants that index a disproportionate concentration of genetic risk sharing. For the *p*-factor model, we also examined the enrichment of the residual (unique) variances of the five lower-order factors. Annotations significant for a factor in the *p*-factor model are therefore likely to capture signal specific to that factor. Enrichment was also calculated for a recent GWAS of height[59] to evaluate the specificity of the psychiatric findings. We used a Bonferroni-corrected significance threshold of $P < 2.81 \times 10^{-5}$ (Methods). We focus here on results for the better-powered SB, Internalizing and *p*-factor, and do not discuss annotations that lacked psychiatric specificity, as indicated by significant enrichment for height (for example, evolutionarily conserved annotations).

We identified 34 annotations that were significant for the SB factor in both models and are thereby likely to be specific to the neurobiology of the SB factor. This included the intersection between protein-truncating-variant-intolerant (PI) genes and several neuronal subtypes, including excitatory CA1 and CA3 hippocampal neurons (Extended Data Fig. 4 and Supplementary Table 50). In total, 51 significant annotations were identified for the Internalizing disorders factor, including PI-oligodendrocyte precursor annotations. We also found strong enrichment for an annotation reflecting neural progenitor biology[60], further implicating early neurobiological processes in shared psychiatric risk. No annotations remained significant for the Internalizing disorders factor's residual variance (that is, independent of the *p*-factor), as would be expected given that only 10% of the genetic variance in the Internalizing disorders factor was separate from *p*. Finally, 64 significant annotations were detected for the *p*-factor, the strongest of which were fetal male brain H3K4me1 histone mark and PI-GABAergic neuron annotations.

Discussion

Our analyses characterized the landscape of shared and divergent genetic influences of common variants on 14 psychiatric disorders. At the genome-wide level, we confirmed pervasive genetic overlap across 14 clinically distinguished psychiatric disorders, as indicated by large pairwise r_g within the EUR-like genetic ancestry group and even greater overlap when including loci that are shared, but have divergent directional effects. This overlap was parsimoniously captured by five genomic factors (Compulsive, SB, Neurodevelopmental, Internalizing and SUD), which explained the majority of the genetic variance of the individual disorders. We identified 101 regions with correlated effects, including a hotspot on chromosome 11 with associations for 8 disorders. We found that broadly pleiotropic variants are primarily involved in early neurobiological processes, while also identifying different

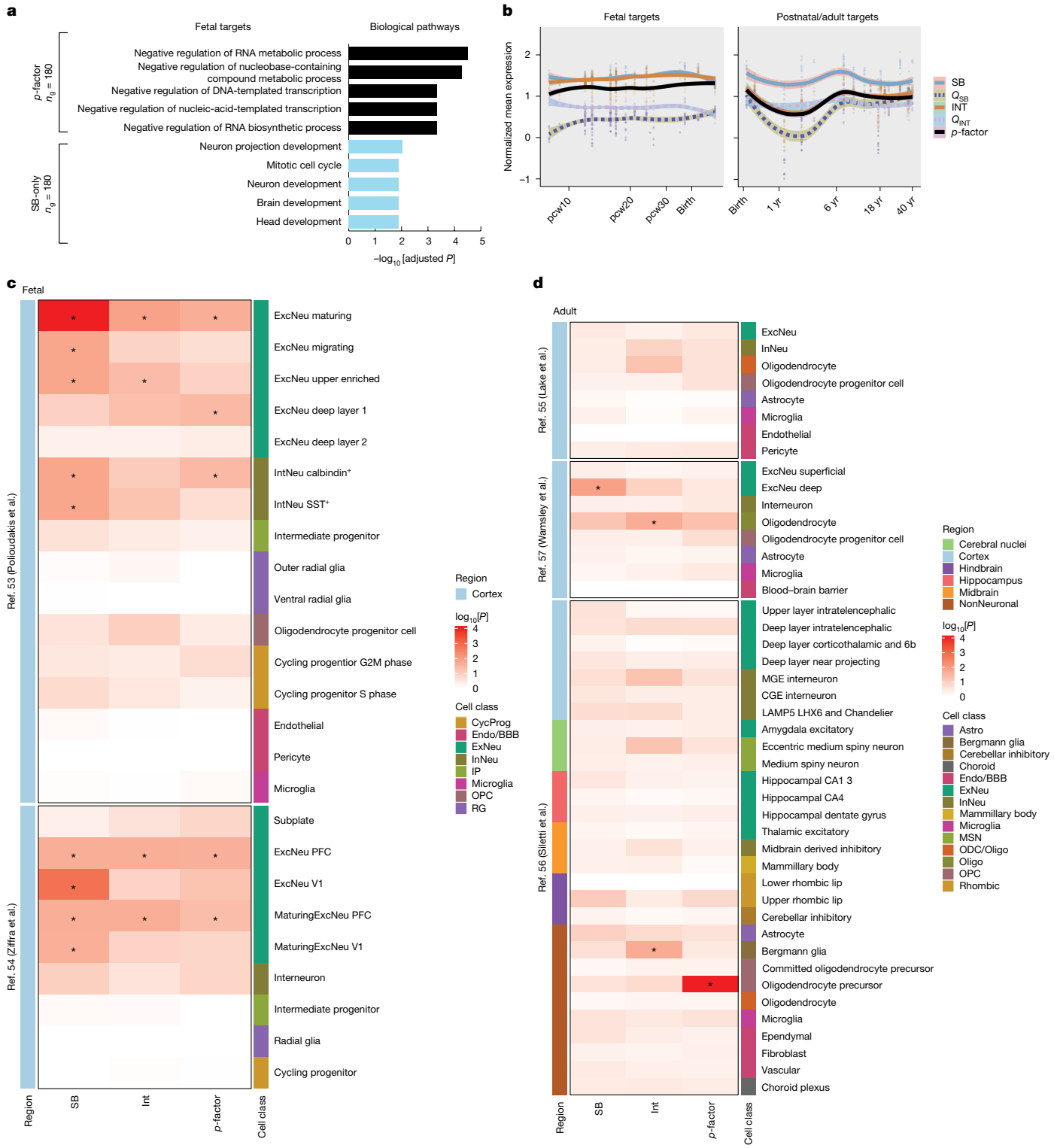


Fig. 5 | Functional annotation of factor variants. a, GO enrichment analysis of predicted target genes with transdiagnostic associations (that is, variants associated with the *p*-factor), or those target genes associated with the SB factor that were not overlapping with *p*-factor target genes. Depicted $-\log_{10}$-transformed *P* values are one-sided, calculated using a χ^2 test; false-discovery rate (FDR) correction was applied for multiple comparisons. **b**, The averaged and normalized expression levels of target genes of the indicated classes along the temporal trajectory of human brain development. Shading around the lines reflects 95% CIs. pcw10, post-conception week 10. **c**,**d**, Average $\log_{10}[P]$ values across EWCE and MAGMA enrichment for genes associated with the indicated factors in fetal brain cell types using two independent single-cell RNA-sequencing (scRNA-seq) datasets[53,54] (**c**) or adult brain cell types using three independent single-nucleus RNA-seq (snRNA-seq) datasets[55–57] (**d**). The *P* values from EWCE and MAGMA were two-sided and each had an FDR correction applied for multiple comparisons before averaging the two sets of results. EWCE *P* values were empirically derived using a permutation test; MAGMA *P* values were calculated using an *F*-test. Int, Internalizing disorders factor. The implied sample size for the three depicted psychiatric factors was: SB ($\hat{n}$ = 127,202), Internalizing ($\hat{n}$ = 1,637,337) and *p*-factor ($\hat{n}$ = 2,168,621). CycProg, cycling progenitor; Endo/BBB, endothelial/blood brain barrier; ExNeu, excitatory neuron; InNeu, interneurons; IP, intermediate progenitor; OPC, oligodendrocyte progenitor cell; RG, radial glia; Astro, astrocyte; MSN, medium spiny neuron; ODC/Oligo, oligodendrocyte.

brain cell types that uniquely confer risk to more circumscribed subsets of disorders. At the individual-variant level, we identified 238 loci associated with at least one of the five correlated psychiatric factors, along with 412 loci that distinguished disorders that primarily belong to different factors.

The SB (defined by SCZ and BIP) and Internalizing disorders (defined by major depression, PTSD and anxiety) factors offered a particularly useful way to understand shared risk across sets of disorders. For these factors, a diverse set of methods produced convergent results across genome-wide, regional and locus-level results, indicating that the disorders within these factors are characterized by overlapping genetic signal. A replicated finding across functional methods reflected enrichment for the SB factor in excitatory neuron annotations, including CA1 and CA3 hippocampal neurons, deep-layer neurons from adult data, and maturing, migrating, prefrontal and visual cortex excitatory neurons in fetal data. The Internalizing factor also showed enrichment in excitatory neurons, but was more consistently enriched in different glial cells in adult data, including oligodendrocytes and their precursor cells and Bergmann glia.

At the genome-wide level, the *p*-factor was strongly related to the Internalizing disorders factor and evinced the largest r_gs with external traits reflecting broad clinical characteristics, such as neuroticism, stress sensitivity and loneliness. These results are consistent with conceptualizations of the *p*-factor as reflecting a general tendency towards negative emotionality[61]. In support of the *p*-factor, LAVA identified pleiotropic hotspots characterized by widespread local r_g across disorders and multivariate GWAS yielded 160 hits for this factor alone. However, the *p*-factor also had more hits for the Q_{SNP} heterogeneity metric (117) than all five-factors from the correlated factors model (33), indicating that the *p*-factor alone is insufficient for explaining cross-disorder risk. The *p*-factor was largely enriched for broad biological categories, such as gene regulation. These results suggest a conceptual model in which there is a partial, broadly transdiagnostic component of genetic vulnerability to psychiatric disorders that primarily captures Internalizing genetic signals, with subsequent levels of more canalized and neurobiologically meaningful subdomains of psychopathology captured by the five factors.

Our study has several limitations. Analyses were restricted primarily to EUR-like genetic ancestry populations due to the limited availability of GWAS data for other groups and the limitations of methods requiring more genetically homogeneous groups[62]. The sample sizes for GWASs of non-EUR-like populations are still orders of magnitude smaller and not currently powered for more precise cross-ancestry assessments; this emphasizes the need for future research including the generation of additional ancestrally representative data, which will enable well-powered studies and the examination of cross-disorder genetic architecture across regional and cultural differences. Cross-ancestry r_gs should be interpreted in light of findings that show considerably smaller within-disorder, within-ancestry r_gs across cohorts for PTSD ($r_g = 0.73$, s.e. = 0.21)[63] and MD ($r_g = 0.76$, s.e. = 0.03)[64] relative to SCZ ($r_g = 0.95$, s.e. = 0.03)[65]. This suggests that cross-ancestry r_gs for PTSD and MD could drop below 1 for reasons independent of ancestry-specific signal, such as environmental moderation of genetic effects or increased phenotypic heterogeneity. Another limitation reflects potential inflation in r_g estimates by cross-trait assortative mating[66], diagnostic misclassification[67] or the use of super-normal controls[68]. However, the high genetic overlap observed among subclusters of psychiatric disorders is unlikely to be explained by cross-trait assortment alone[69] and current sensitivity analyses using stricter case definitions suggested that impact of diagnostic misclassification was modest. Wide ranges in sample sizes across the univariate psychiatric GWAS used as input should also be considered when evaluating relative levels of significant findings, particularly for locus discovery.

The current investigation into the genetic structure of psychopathology reflects a comprehensive genomic examination of cross-disorder psychiatric risk. It extends previous cross-disorder psychiatric genetics analyses[5,27] using updated datasets, new disorders and triangulation across different methodological approaches to produce a robust set of findings[70]. We identified subsets of disorders with particularly high genetic overlap and characterized the biological processes implicated by their shared risk. This evidence should contribute substantially to the ongoing debates regarding diagnostic boundaries between disorders such as BIP and SCZ. Certain pharmacological interventions have proven to be effective across a range of disorders (for example, selective serotonin reuptake inhibitors)[71], indicating that future work could build on our findings to identify new or repurposed therapeutics that target the shared signal captured by the factors. While much remains to be done, cross-disorder genetics continues to fill in critical gaps in our understanding of shared and unique psychiatric risk factors with implications for the future of psychiatric research, therapeutics and nosology.

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/s41586-025-09820-3.

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Methods

Quality control of summary statistics

A standard set of quality-control filters was applied to all univariate GWAS summary statistics before conducting cross-disorder analyses. Any additional quality-control filters applied by a method are noted in its corresponding section below. These quality-control filters included removing strand ambiguous SNPs, restricting to SNPs with an imputation score (INFO) > 0.6 and with a minor allele frequency > 1% when this information was available in the GWAS data. We also restricted analyses to SNPs with an SNP-specific sum of the effective sample that is >50% of the total sum of the effective sample or, when this SNP-specific information was not available, to SNPs for which >50% of the cohorts contributed information, as indexed by the direction column in the GWAS summary statistics. The MHC region was excluded from all summary statistics before the analysis. Base pair location is given in genome build GRCh37/hg19 throughout the Article and its Supplementary Information.

Genomic SEM

Genome-wide models. All GWAS summary statistics were run through the munge function before running the multivariable version of LDSC used as input to genomic SEM[7]. The munge function aligns GWAS effects to the same reference allele and restricts to HapMap3 SNPs and SNPs with INFO > 0.9. LDSC was estimated using these munged summary statistics, applying a liability threshold model for all case–control psychiatric disorders (that is, all disorders except for the NIC outcome, which reflects a GWAS of the continuous Fagerström test for nicotine dependence[24]). For comparability, population prevalence was chosen to match what was used in the corresponding manuscript that introduced the GWAS of each trait. The ascertainment correction was performed using the sum of effective sample sizes across contributing cohorts for each disorder[72]. We note that, for CUD[26], we used the recently described formula[72] for estimating the sum of effective sample size directly from the GWAS data. This is because, in this instance, we found that the implied sum of effective sample size was much smaller than the value computed from the reported sample sizes, which is probably attributable to the complex familial structure in the included deCODE sample.

The two primary estimates from multivariable LDSC are the genetic covariance matrix and the corresponding sampling covariance matrix. The genetic covariance matrix contains SNP-based heritabilities on the diagonal and the co-heritabilities (genetic covariances) across every pairwise combination of included disorders on the off-diagonal. The sampling covariance matrix contains squared standard errors (sampling variances) on the diagonal, which allows genomic SEM to appropriately account for differences in the precision of GWAS estimates for disorders with unequal power. The off-diagonal contains sampling dependencies, which will arise in the presence of sample overlap across GWAS phenotypes. As these sampling dependencies are estimated directly from the data, summary statistics can be included with varying and unknown levels of sample overlap. We note that study overlap between disorders is not expected to affect the findings, as study overlap affects only the covariance of error terms of the GWASs resulting in increased intercepts of cross-trait LDSC with no expected impact on the estimates of r_g[4,43]. To guard against model overfitting, an exploratory factor analysis (EFA) was performed on even chromosomes and used to inform the fitting of an confirmatory factor analysis (CFA) in odd chromosomes. The EFA was performed using the factanal R package for 2–5 factors using both promax (correlated) and varimax (orthogonal) rotations. Disorders were specified to load on a factor in the CFA when the standardized EFA loadings were >0.3, with disorders allowed to cross-load (for example, TS on the Compulsive and Neurodevelopmental factors) if this was the case for multiple factors. Models specified based on varimax EFA results still allowed for interfactor correlations, as allowing only subsets of disorders to load on each factor will induce genetic overlap. A common-factor model was also modelled to test a single-latent-factor model predicting all 14 disorders. We did not evaluate models with more than five factors as these caused issues with model convergence. Results revealed that a five-factor model specified based on the promax EFA results (Supplementary Table 3) fit the data best in odd chromosomes (CFI = 0.973, SRMR = 0.073; Supplementary Table 2). This model also fit the data well in all autosomes, and was subsequently carried forward for all analyses, along with the *p*-factor model described in the main text. Considering the high r_g across PTSD and MD, we also evaluated a model (in odd autosomes) that estimated the residual genetic covariance across these two disorders; however, we found that this did not significantly improve model fit (model χ^2_1 difference = 2.86, $P = 0.094$).

Stratified genomic SEM. Stratified genomic SEM proceeds in two stages[27]. In stage 1, the s_ldsc function in genomic SEM, a multivariable implementation of stratified LDSC (S-LDSC)[58], was used to estimate the stratified genetic covariance and sampling covariance matrices within each functional annotation. We specifically used the zero-order estimates for these analyses. In stage 2, the enrich function was used to estimate the enrichment of the factor variances and residual genetic variances unique to the indicators. This is achieved by first estimating the model in the genome-wide annotation including all SNPs. The factor loadings from these genome-wide estimates are then fixed and the (residual) variances of the factors and disorders are freely estimated within each annotation. These reflect the within-annotation estimates for each variance component that are scaled to be comparable to the genome-wide estimates. This cumulative set of results is used to calculate the enrichment ratio of ratios. The numerator reflects the ratio of the estimate of the factor variance within an annotation over the genome-wide estimate. The denominator is the ratio of SNPs in the annotation over the total number of SNPs examined. Enrichment estimates greater than the null of 1 are therefore observed when an annotation explains a disproportionate level of genetic variance relative to the annotation's size.

Functional annotations used to estimate the stratified matrices were obtained from a variety of data resources. This included: (1) the baseline annotations from the 1000 Genomes Phase 3 BaslineLD (v.2.2)[73] from the S-LDSC developers[58]; (2) tissue-specific gene expression annotation files created using data from GTEx[74] and DEPICT[75]; (3) tissue-specific histone marks from the Roadmap Epigenetics project[76]; (4) annotations that we created[27] from data in GTEx[74] and the Genome Aggregate Database (gnomAD)[77] that index protein-truncating-variant-intolerant (PI) genes, genes expressed in different types of brain cells in the human hippocampus and prefrontal cortex, and their intersection; (5) 11 neuronal cell type annotations defined by peaks from single-cell assay for transposase accessibility by sequencing (scATAC–seq) in the human forebrain[54]; (6) an annotation defined by peaks from ATAC–seq data with greater accessibility in neural progenitor enriched regions encompassing the ventricular, subventricular and intermediate zones (GZ) over neuron-enriched regions within the subplate, marginal zone and cortical plate (CP; GZ > CP), and a second CP > GZ annotation reflecting the converse[60]; and (7) a fetal and an adult annotations defined by eQTLs identified using high-throughput RNA-seq[45]. We excluded 22 annotations that produced stratified genetic covariance matrices that were highly non-positive definite to examine a total of 162 annotations. We corrected for multiple testing by using a strict Bonferroni correction for the 162 annotations analysed that passed quality control across the 11 factors examined (the factors from the five-factor factor model and the *p*-factor and residuals of the five factors from the *p*-factor model) of $P < 2.81 \times 10^{-5}$.

Multivariate GWAS. The sumstats function in genomic SEM was used to align SNP effects across traits to the same reference allele and

standardize the effects and their corresponding s.e. values relative to the total variance in the predicted phenotype. The s.e. values were additionally corrected for uncontrolled confounds by taking the product of s.e. values and the LDSC univariate intercept when this value was >1. After removing 136 SNPs that produced highly non-positive definite matrices when combined with the genetic covariance matrix, the final listwise deleted set consisted of 2,795,800 SNPs present across all 14 disorders. The userGWAS function was used to estimate the multivariate GWAS for SNP effects on the five factors from the five-factor model and the *p*-factor. We used a significance threshold of $P < 8.33 \times 10^{-9}$, reflecting the standard genome-wide threshold of 5×10^{-8} with a Bonferroni correction for the six factors. As a quality-control check, we confirmed that the attenuation ratio[32] was near 0 for all factors (Supplementary Table 17), suggesting that the factor signal is not due to uncontrolled confounds (such as population stratification).

The Q_{SNP} heterogeneity metric is a χ^2-distributed test statistic produced through a nested-model comparison of a common pathway model, in which the SNP predicts a latent factor, to an independent pathways model, where the SNP directly predicts the factor indicators. Factor-specific Q_{SNP} estimates for the five-factor model were estimated using five independent pathways models that consisted of the SNP predicting both the indicators for one factor and the remaining four factors. For the *p*-factor model, the SNP predicted the five, first-order factors to obtain Q_{SNP} estimates for the second-order, *p*-factor.

Cross-ancestry analyses

We applied the cross-ancestry Popcorn[33] method to estimate genetic impact correlation (ρ_{gi} metric) across EUR-like, EAS-like and AFR-like genetic ancestry groups. Six disorders were included in the analysis, including EAS-like summary statistics for MD and SCZ and AFR-like summary statistics for OUD, AUD, PTSD and CUD. The reference panel for the EAS dataset was based on 504 individuals from EAS population of the 1000 Genomes Phase3 data[78]. For AFR-like genetic ancestry, we performed the Popcorn analysis using three alternative references from 1000 Genomes Phase3 data: (1) the African Ancestry in the southwest United States subgroup ($n = 61$); (2) the African population ($n = 661$); and (3) a reference panel created to capture the admixed ancestral background of some AFR-like individuals reflecting the combination across the EUR-like and AFR-like sample ($n = 1{,}164$). Cross-ancestry results and within-ancestry LDSC results for the AFR-like and EAS-like populations are reported in Supplementary Table 4. We acknowledge that using LDSC with admixed ancestry may violate its assumptions; thus, our results for AFR-like ancestry should be interpreted with caution. With this in mind, we performed LDSC for AFR-like datasets using two different LD reference panels for AFR-like ancestry or admixed American ancestry from Pan UK Biobank to assess their impact on results (Supplementary Table 4). The results in Extended Data Table 1 report liability-scale heritabilities for AFR-like datasets using the admixed LD scores, as these produced more sensible results.

MiXeR

MiXeR (v.1.3) was applied using the procedure outlined in the original publication[6]. We performed additional simulations to evaluate appropriate threshold for inclusion of a GWAS study in cross-trait MiXeR analysis. In previous simulations, we demonstrated that MiXeR cannot produce reliable estimates for analyses using low-powered input[79]. Specifically, as statistical power increases, the Akaike information criterion (AIC) differences indicate that MiXeR-modelled estimates become increasingly more distinguishable from the minimum and maximum overlap, corresponding to the increasing precision of MiXeR estimates. This demonstrates that AIC differences are sensitive to the input power of the summary statistics and can be used to support the reliability of MiXeR estimates. On the basis of these previous simulations, psychiatric disorders were brought forward for cross-trait MiXeR analysis when the product of N_{Eff} and MiXeR h^2_{SNP} estimates were >12,000, where this cut point reflects the product of $N_{Eff} \geq 100{,}000$ and $h^2_{SNP} \geq 0.12$. As a result, we excluded OUD, TS, NIC, OCD, ASD and CUD. As AN was very close to this threshold and had a high AIC in univariate analysis, it was brought forward for cross-trait analyses along with the seven remaining psychiatric disorders. For the NIC summary statistics, we excluded two loci defined as a 2 Mb window around either the *CHRNA3–CHRNA5–CHRNB4* gene cluster or the *CHRNA4* gene, which is known to have such a large effect on the phenotype that it would skew results. We note that, for PTSD, ANX and MD, the r_gs were so high that there was little room for additional overlap beyond correlation, given MiXeR's modelling assumptions. Specifically, the range in size of the putative shared component is too small to allow for an accurate model fit in this situation, as demonstrated by the range on the respective *x* axes (Supplementary Fig. 7). There is also a considerable uncertainty of polygenicity estimates for PTSD and ANX. Thus, cross-trait MiXeR results for PTSD, ANX and MD should be interpreted with caution.

LAVA

Local r_g analyses were conducted using LAVA v.0.1.0[35]. To avoid evaluating local r_gs in regions in which there is a low amount of genetic signal (which could lead to unstable or uninterpretable estimates) for all phenotype pairs and loci separately, we used the univariate test in LAVA as a filtering step, computing bivariate local r_gs only in loci where both analysed phenotypes have a h^2_{SNP} significant at $P < 4.6 \times 10^{-5} = 0.05/1{,}093$ (where 1,093 represents the total number of analysed loci). Given this filtering step, we performed 24,273 local r_g tests across all loci and phenotype pairs, resulting in a Bonferroni corrected *P* value threshold of $P < 2.1 \times 10^{-6} = 0.05/24{,}273$ for the bivariate, local r_g analyses.

Genomic loci used for the regional r_g analyses were defined by segmenting the genome into approximately equal-sized, semi-independent blocks using the LAVA partitioning algorithm (https://github.com/cadeleeuw/lava-partitioning). This algorithm works by iteratively splitting the chromosomes into smaller chunks, creating break points at regions where the LD between SNPs is the lowest (see the program manual for more details). To achieve a balance between block size and correlations between adjacent blocks, we ran the algorithm with the default parameters, changing only the minimum size requirement (in the number of SNPs) to 5,000, based on the 1,000 genomes data. Sample overlap was accounted for by obtaining the estimated intercepts from bivariate LDSC and providing these to LAVA.

CC-GWAS

CC-GWAS[43] was applied to identify loci with different allele frequencies across cases of different disorders, contrasting cases one disorder pair at a time. CC-GWAS is based on estimating a weighted difference of the CC-GWAS results of the disorders considered, thereby avoiding the necessity to match cases across disorders at individual level. CC-GWAS combines two components. The first component ($CC\text{-}GWAS_{OLS}$) optimizes power and protects against type I error rate at null–null SNPs (SNPs that affect neither of both disorders), based on analytical expectations of genetic differences between cases and controls of both diseases. The second component ($CC\text{-}GWAS_{Exact}$) controls type I error rate at 'stress test' SNPs (SNPs affecting both disorders resulting in no allele frequency difference across cases of both disorders). A SNP is significantly associated with case–case status when the *P* value of the OLS component reaches genome-wide significance and when the *P* value of the exact-component is $<10^{-4}$ (there is an upper bound on the number of stress test SNPs as these are causal SNPs). Importantly, CC-GWAS also filters false-positive associations that may arise due to (subtle) differential tagging of a stress test SNP in the respective CC-GWAS, which are present even in within-ancestry analysis[43]. CC-GWAS excludes analyses of any disorder pair with an $r_g > 0.8$ because these have a small genetic distance between cases with increased risk of type-I error at stress test SNPs.

Locus definition and cross-locus overlap

The same locus definition (also referred to as a hit in the main text) was used for CC-GWAS and genomic SEM. Significant loci were identified using the clumping functionality in PLINK v.1.9 with an r^2 threshold of 0.1 and a 3,000 kb window. Physically proximal loci (including when comparing loci both within and across factors from genomic SEM and for CC-GWAS and univariate GWAS results), were additionally collapsed into a single locus when the locus windows were within 100 kb of one another on either side. For the univariate results, we use the same locus definition applied to the complete GWAS summary statistics for each disorder (that is, without our quality-control filters applied), along with a more liberal genome-wide significance threshold of $P < 5 \times 10^{-8}$ without a Bonferroni correction. These more liberal quality-control and significance thresholds were used for univariate loci to benchmark whether genomic SEM and CC-GWAS loci could be considered strictly novel. The 1000 Genomes Phase 3 reference files[78] were used for LD pruning for each respective genetic ancestry group (that is, EUR-like, EAS-like, AFR-like).

Functional annotation

To predict the target genes of the variants (Supplementary Fig. 17), we first expanded the variants by including any variants within the LD block ($r^2 > 0.6$) based on the EUR population using LDProxy from the LDlink R package[80]. We began by curating the genes of which the promoters (±500 bp from the transcription start site) or exons overlap with the variants of interest. Conversely, to map target genes that are not near the variants, we first filtered the variants for those localized in either human fetal brain open-chromatin regions[60] or human adult brain H3K27ac ChIP–seq regions[44], both of which indicate enhancer activity, but during different stages of brain development. Next, we assigned target genes to each filtered variant using eQTL[44,45] or HiC loops[44,46] generated from samples from the corresponding stages. We also assigned variants present in promoter or exonic regions to the corresponding genes (Supplementary Fig. 17). Finally, we filtered all of the target genes for those expressed (RNA-seq count > 0) in the corresponding tissues. In this way, we obtained 715 and 572 target genes in fetal and adult brains, respectively (Supplementary Tables 40 and 41). Notably, there is a prominent overlap between the two sets of genes, which is a result of the shared, positional mapping of genes to promoters or exons (Supplementary Fig. 17). Both the fetal and adult target genes were enriched in GO terms related to neuron or brain development, suggesting the biological relevance of the genetic variants.

To plot the temporal expression trends of the predicted target genes, we used gene expression datasets from the BrainSpan. We plotted the averaged gene expression (reads per million kb) of the selected genes over all samples collected from the cortex at the available stages of development, then generated a smoothened curve with the loess method. We performed GO enrichment analysis using the ToppGene suite[36]. We filtered the enriched terms by containing at least 10% of the input list of genes, then displayed up to top 5 terms by adjusted *P* values under the indicated category.

EWCE[52] was used to assess the cell type enrichment of target genes for the variants using a size-biased averaging method. This method uses single-cell datasets to compute the average expression of a set of genes (in this case, genes assigned to variants for each factor) and compares this to the average expression levels for 100,000 permuted gene lists of the same size that are randomly sampled from a background set of genes. Annotations were taken from publicly available datasets[53–57], but simplified to provide cell-type-level instead of cluster-level enrichments. For example, several upper-layer clusters in the dataset of ref. 57 were combined into 'ExcNeu superficial' and so on. For the ref. 56 dataset, EWCE objects were processed for each brain region separately. This included the hippocampal formation, cortex, cerebral nuclei (dissections including basal nuclei, amygdaloid complex, basal forebrain, claustrum), midbrain (including tissues from thalamic complex, hypothalamus, and midbrain) and hindbrain (including tissues from spinal cord, pons, myelencephalon and cerebellum) and non-neuronal cells across regions. For superclusters that were present in multiple regions, enrichment was tested only for regions with the highest abundance of that supercluster (for example, MGE interneuron supercluster is most abundant in cortex, so this cell type was dropped from enrichment analyses in the midbrain) to prevent excess multiple comparisons. *P* values were FDR-corrected based on the number of cell types × gene lists within brain region and dataset.

MAGMA gene-set enrichment analyses were performed using the MAGMA.Celltyping package in R[81]. Rather than considering only the top associated genes, as done in EWCE, MAGMA relies on the genome-wide signals to competitively evaluate enrichment through linear regression[48]. We used the European subset of the 1000 Genomes[78] as LD reference data, and mapped SNPs to genes based on their genomic location (GRCh37/hg19). To allow the inclusion of nearby regulatory variants, we considered all SNPs within a 35 kb upstream and 10 kb downstream window of the gene transcription region. As signed effect-size estimates are not available for the Q_{SNP} results, these analyses were restricted to the factors. The FDR corrected *P* values from MAGMA and EWCE were averaged together to produce the results reported in the main text (but see Supplementary Tables 48 and 49 for *P* values from the individual methods).

Reporting summary

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

Data availability

The data supporting the findings of this study are all publicly available or can be requested for access. Specific download links for various datasets are directly below. Psychiatric disorder GWAS summary statistics for data from the PGC can be downloaded or requested online (https://www.med.unc.edu/pgc/download-results/). Links to the LD scores and reference panel data for GenomicSEM analyses can be found at GitHub (https://github.com/GenomicSEM/GenomicSEM/wiki). Links to the BaselineLD v.2.2 annotations can be found online (https://data.broadinstitute.org/alkesgroup/LDSCORE). Gene expression datasets from Brainspan can be found online (https://brainspan.org/static/download.html). Multivariate GWAS summary statistics for the latent psychiatric factors in GenomicSEM, including the sensitivity GWAS results, are available online (https://www.med.unc.edu/pgc/download-results/).

Code availability

Genomic SEM analyses were implemented using publicly available code (v.0.5.0, https://github.com/GenomicSEM/GenomicSEM). Factanal was conducted using publicly available code within the stats R package (v.3.6.2, https://www.rdocumentation.org/packages/stats/versions/3.6.2). MiXeR was conducted using publicly available code (v.1.3; https://github.com/precimed/mixer). LAVA was conducted using publicly available code (v.0.1.0, https://github.com/josefin-werme/LAVA). CC-GWAS was conducted using publicly available code (v.0.1.0, https://github.com/wouterpeyrot/CCGWAS). LDlink was conducted using publicly available code (v.1.4.0, https://cran.r-project.org/web/packages/LDlinkR/vignettes/LDlinkR.html). ToppGene suite was conducted using publicly available code (v.0.1.0, https://toppgene.cchmc.org/). EWCE was conducted using publicly available code (v.1.16.0, https://nathanskene.github.io/EWCE/). MAGMA was conducted using publicly available code (v.2.0.15, https://neurogenomics.github.io/MAGMA_Celltyping/index.html).

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Acknowledgements We acknowledge the work of the members of individual Psychiatric Genomics Consortium working groups, the iNDiGO consortium and the MVP who contributed summary statistics to these analyses. GWAS summary statistics for the MVP used in this study were obtained from the database of Genotypes and Phenotypes (dbGaP) under accession number phs001672.v9.p1.c1 under approved project 30159. We thank the MVP staff, researchers and volunteers, who have contributed to MVP, and especially participants who previously served their country in the military and now agreed to enrol in the study (https://www.research.va.gov/mvp/). This work was made possible by the contributions of the many investigators who comprise these working groups and the numerous grants from governmental and charitable bodies, as well as philanthropic donation. We acknowledge the Mayo Clinic Biobank (MCB) research team, as well as the patient participants who consented to participate in this research program; the Mayo Clinic Center for Individualized Medicine for support of the MCB, and Regeneron Genetics Center for providing genetic data for MCB participants for the analysis. In particular, we thank the research participants worldwide who shared their life experiences and biological samples to make work like this possible. The PGC has been supported by the following grants: MH085508, MH085513, MH085518, MH085520, MH094411, MH094421, MH094432, MH096296, MH109499, MH109501, MH109514, MH109528, MH109532, MH109536, MH109539, MH124871, MH124851, MH124839, MH124847, MH124873, MH124875 and DA054869. Specific investigators were supported by the following grants: R01MH120219 and R01AG073593 (A.D.G.); European Union Horizon 2020 grant agreement 964874 (RealMent) (J.W.); The Amsterdam Cohort Hub, which is part of the Sector Plan 'Accelerating Health' of the Dutch Ministry of Education, Culture and Science (W.J.P.); Autism Speaks Postdoctoral Fellowship (Q.G.); DP1DA054394 and T32IR5226 (S.S.S.-R.); ERC-2018-ADG 834057 (C.d.L.); European Union Horizon grant agreement 965381, U01AR076092, R01MH116037, 1R01NS128535, R01MH131685, 1R01MH130899, U01MH135970 and Supernus (S.V.F.); F30MH135712 (M.P.M.); K08MH135343 (T.T.M.); Lundbeck Foundation (R102-A9118, R155-2014-1724, and R248-2017-2003), NIH/NIMH (1R01MH124851-01) and EU's Horizon Europe program under grant agreement no. 101057385 (R2D2-MH) (A.D.B.); R01MH124839-02, Research Council of Norway (RCN) 334920 (K.S.O.); U54GM115516 (S.L.S.); R01MH124847 (J.M.H.); R01DA054869 (H.J.E.); R01MH106595 (A.X.M.); R01MH106595 (K.C.K., C.M.N. and M.B.S.); R01MH124847 (C.M.N.); R01MH112904, R01MH123775, U24MH068457, R01MH104964 and R01MH123451 (J.A.K.); R01MH119243 and R01GM148494 (P.H.L.); R01MH120219, R01AG073593, P30AG066614 and P2CHD042849 (E.M.T.-D.); R01MH121924 (B.J.C., A.B., V.P. and J.M.B.); R01MH123922 and R01MH121521 (M.J.G.); R01MH124851 (B.F.); R01MH136149 and R01120170 (L.M.T.); R21MH123908 and K08MH122673 (K.G.J.); the Novo Nordisk Foundation (NNF20OC0065561, NNF21SA0072102), the Lundbeck Foundation (R344-2020-1060), the European Union's Horizon 2020 research and innovation program under grant agreement no. 965381 (TIMESPAN) (D.D.); R01NS102371, R01NS105746 and R01MH124851 (J.M.S.); U01MH125050 (CIHR) and PJT-180339 (M.M.); NIHR Biomedical Research Centre (IS-BRC-1215-20018) (G.B.); K01DA051759 (E.C.J.); AA030083 (A.S.H.); and R01MH125938, R01MH137208, P50AA022537 and The Brain & Behavior Research Foundation NARSAD grant 28632P&S Fund (R.E.P.).

Author contributions Note that the lists of working group members are organized alphabetically by last name. We also highlight that these lists are not exhaustive with respect to the members of the working groups; rather, they reflect individual members of the working groups who approved the contents of this Article. A.D.G., J.W., W.J.P. and O.F. conducted the primary analyses presented in the paper for GenomicSEM, LAVA, CC-GWAS and MiXeR, respectively. L.K.B., Q.G., M.P.M. and J.W. ran the functional follow-up analyses. O.F. and R.E.P. ran and provided feedback on cross-ancestry and diverse ancestry genome-wide analyses. B.J.C., A.B., V.P. and J.M.B. conducted the phenome-wide association study analyses. C.d.L., E.M.T.-D. and P.H.L. provided additional feedback on the analyses and included data. A.D.G., J.W., W.J.P., O.F., K.S.K. and J.W.S. wrote the initial draft of the manuscript. K.S.K. and J.W.S. jointly supervised the research. All of the named authors provided iterative feedback on the manuscript, including O.A.A., V.A., A.D.B., G.B., N.C., D.D., H.J.E., S.V.F., B.F., M.J.G., J.G., A.S.H., J.M.H., E.C.J., T.T.M., M.M., K.S.M., B.M.N., C.M.N., J.I.N., K.S.O., E.B.R., S.S.S.-R., S.L.S., J.M.S., H.S., K.S., M.B.S., N.I.S., L.M.T., B.V., I.D.W., G.B.W., N.R.W. and D.Y. All of the collaborators within the listed working group banners approved the contents of the manuscript.

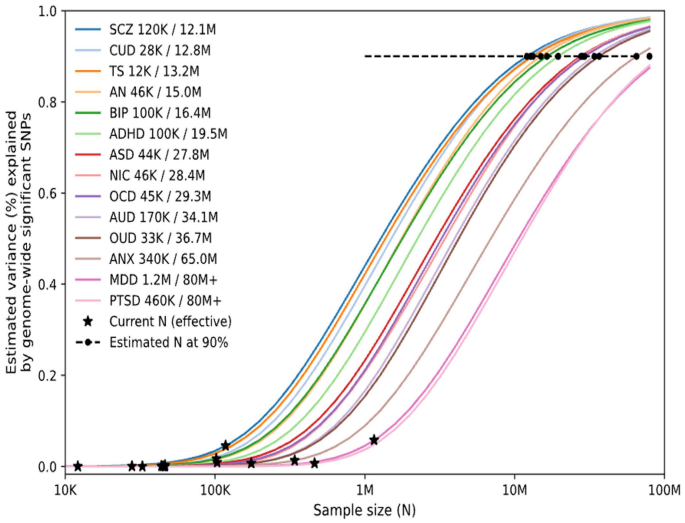
Competing interests J.W.S. is a member of the scientific advisory board of Sensorium Therapeutics (with stock options) and has received grant support from Biogen. K.G.J. is a consultant for Allia Health. A.D.B. has received a speaker fee from Lundbeck. In the past year, S.V.F. received income, potential income, travel expenses continuing education support and/or research support from Aardvark, Aardwolf, AIMH, Akili, Atentiv, Axsome, Genomind, Ironshore, Johnson & Johnson/Kenvue, Kanjo, KemPharm/Corium, Noven, Otsuka, Sky Therapeutics, Sandoz, Supernus, Tris and Vallon. With his institution, S.V.F. has US patent US20130217707 A1 for the use of sodium-hydrogen exchange inhibitors in the treatment of ADHD. S.V.F. also receives royalties from books published by Guilford Press (*Straight Talk about Your Child's Mental Health*), Oxford University Press (*Schizophrenia: The Facts*) and Elsevier (*ADHD: Non-Pharmacologic Interventions*) and is program director of www.ADHDEvidence.org and www.ADHDinAdults.com. The other authors declare no competing interests.

Additional information

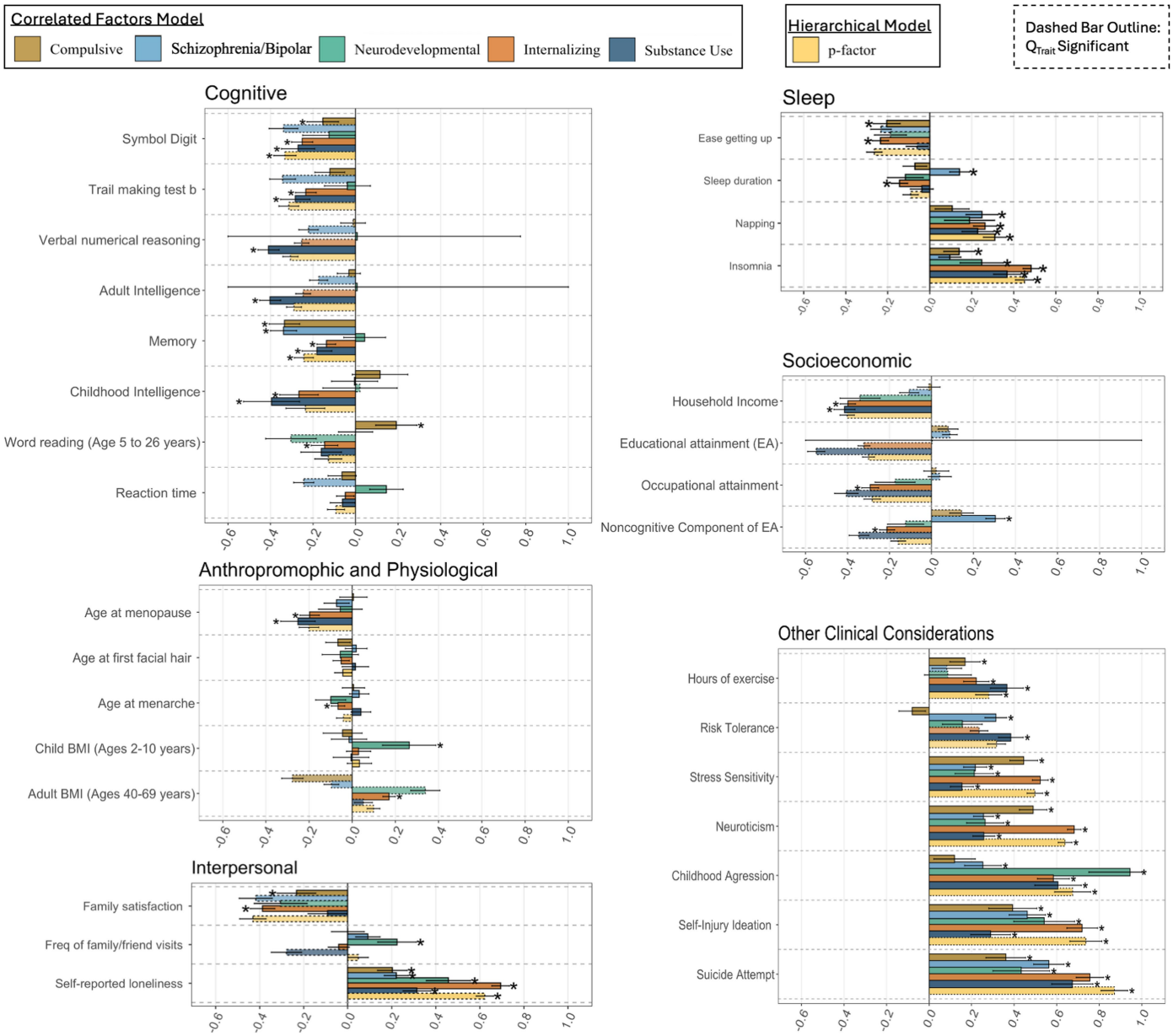
Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41586-025-09820-3.

Correspondence and requests for materials should be addressed to Andrew D. Grotzinger or Jordan W. Smoller.

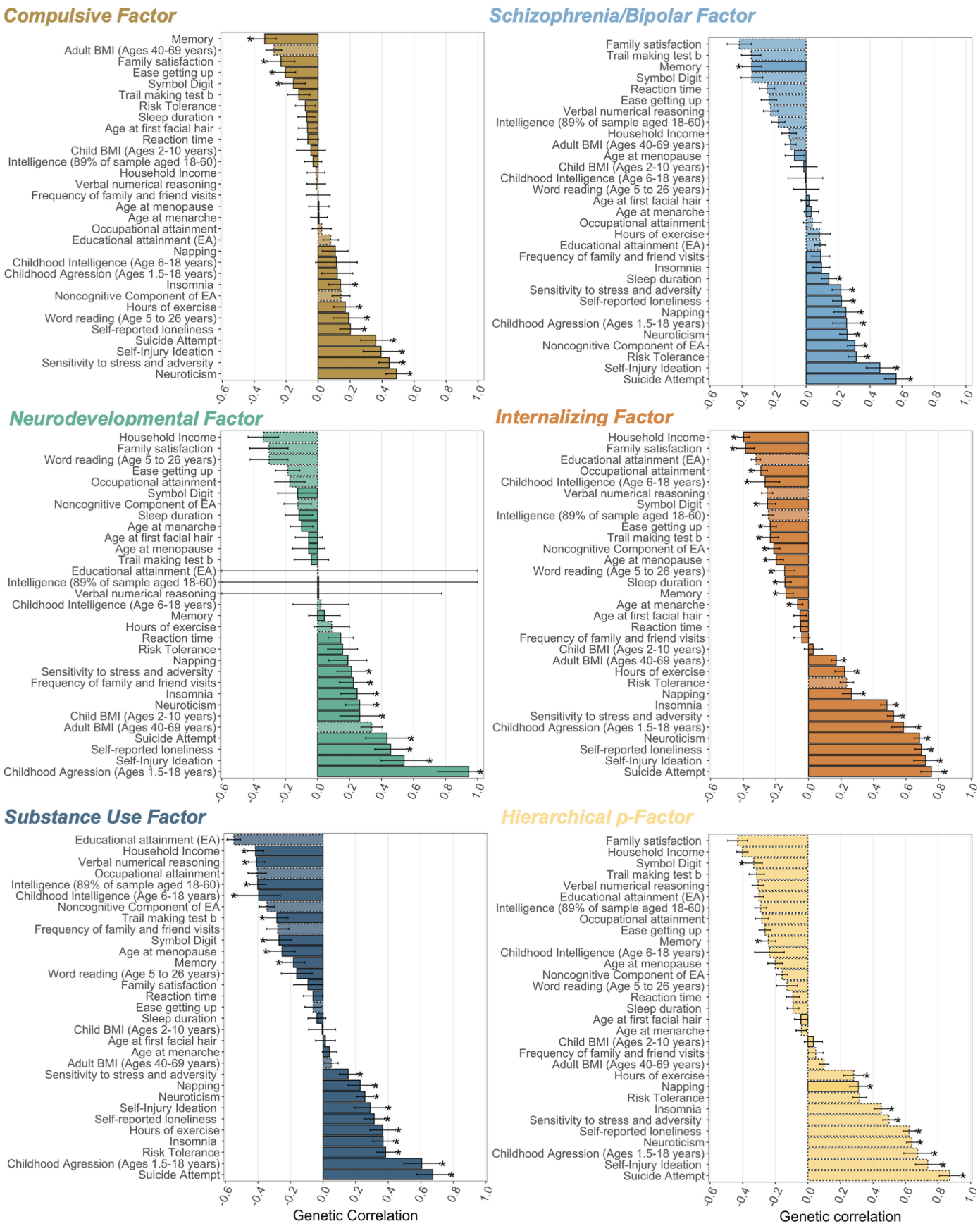
Peer review information *Nature* thanks Karoline Kuchenbaecker and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. Peer reviewer reports are available.



Extended Data Fig. 1 | Univariate MiXeR Results. Power curves estimating the sample size of a GWAS study are needed to saturate the yield of genome-wide significant loci. The legend shows the current effective sample size of today's GWAS, followed by the projected effective sample size needed for the GWAS yield to saturate.

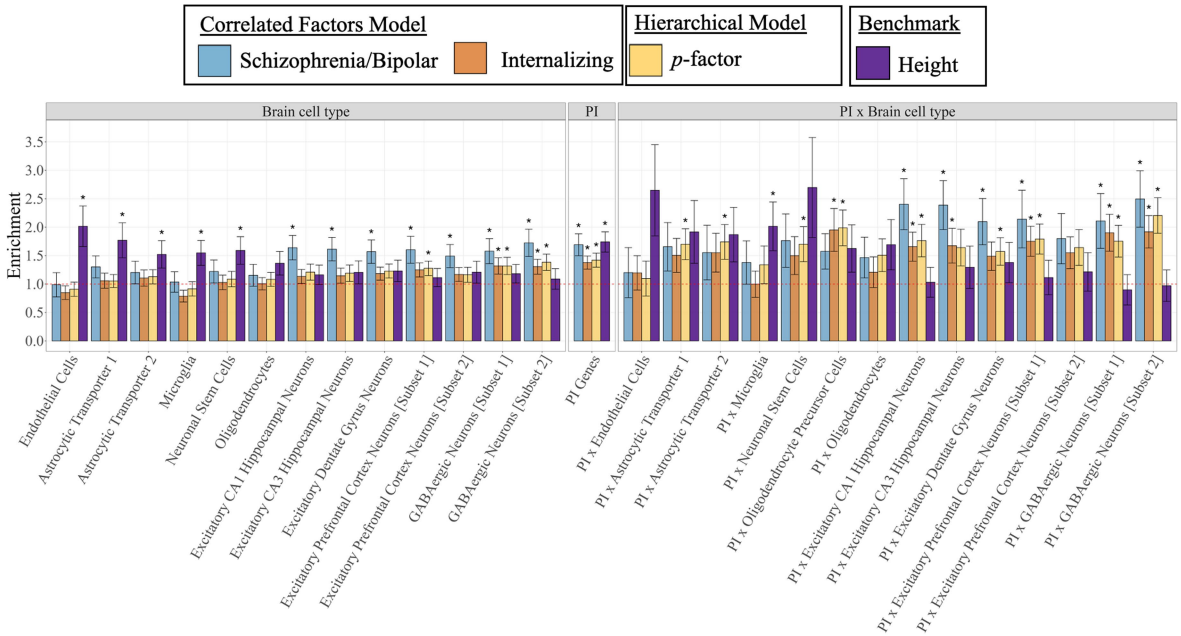


Extended Data Fig. 2 | External trait genetic correlations: Comparison across psychiatric factors. Bar graphs depict genetic correlations with the 31 complex traits for the five psychiatric factors from the correlated factors model and the second-order, *p*-factor from the hierarchical model. Panels are separated by the different groupings of traits (e.g., cognitive; socioeconomic). Bars depicted with a dashed outline were significant at a Bonferroni-corrected threshold for the Q_{Trait} heterogeneity metric that flags traits whose patterns of genetic correlations from LDSC do not conform to those implied by the factor model. Error bars are +/−1.96 *SE* that are centred around the point estimate of the genetic correlations. Bar depicted with a * reflect values that were significant at a Bonferroni corrected threshold for multiple comparisons, that were also not significant at this same Bonferroni corrected threshold for $Q_{Trait.}$ This is with exception of the *p*-factor, which is depicted with a '*' even if it is significant for the Q_{Trait}, as long as that same trait was significantly correlated with the majority (at least three) of the five other factors. The two-sided *P*-values used to evaluate significance were derived from the *Z*-statistics, calculated as the point estimate of the genetic correlation divided by its standard error. Correlations are ordered according to the point estimate for the *p*-factor. The implied sample size for the psychiatric factors was: Compulsive ($\hat{n}$ = 54,100); Schizophrenia/Bipolar ($\hat{n}$ = 127,202); Neurodevelopmental ($\hat{n}$ = 84,760); Internalizing ($\hat{n}$ = 1,637,337); Substance Use ($\hat{n}$ = 313,395); *p*-factor ($\hat{n}$ = 2,168,621). See Suppl. Table 12 for sample sizes for the external traits and Suppl. Table 13 for exact *P*-values.



Extended Data Fig. 3 | See next page for caption.

Extended Data Fig. 3 | External trait genetic correlations: Comparison within factors. Bar graphs depict genetic correlations with the 31 complex traits that are ordered by magnitude within each factor for the five psychiatric factors from the correlated factors model and the second-order, *p*-factor from the hierarchical model. Bars depicted with a dashed outline for the Q_{Trait} heterogeneity metric. Bar depicted with a * reflect values that were significant at a Bonferroni corrected threshold for multiple comparisons, that were also not significant at this same Bonferroni corrected threshold for $Q_{Trait.}$ This is with exception of the *p*-factor, which is depicted with a '*' even if it is significant for the Q_{Trait}, as long as that same trait was significantly correlated with the majority (at least three) of the five other factors. The two-sided *P*-values used to evaluate significance were derived from the *Z*-statistics, calculated as the point estimate of the genetic correlation divided by its standard error. Error bars are +/− 1.96 *SE* that are centred around the point estimate of the genetic correlations. The implied sample size for the psychiatric factors was: Compulsive ($\hat{n}$ = 54,100); Schizophrenia/Bipolar ($\hat{n}$ = 127,202); Neurodevelopmental ($\hat{n}$ = 84,760); Internalizing ($\hat{n}$ = 1,637,337); Substance Use ($\hat{n}$ = 313,395); *p*-factor ($\hat{n}$ = 2,168,621). See Suppl. Table 12 for sample sizes for the external traits and Suppl. Table 13 for exact *P*-values.



Extended Data Fig. 4 | Stratified Genomic SEM results. Bar graph depicts the enrichment results for different brain cell types, protein-truncating variant intolerant (PI) genes, and the intersection across PI genes and brain cell types. Results are shown only for the SB, Internalizing, and *p*-factor due to the limited signal for the other factors. Enrichment for height is depicted in purple to benchmark results and evaluate specificity in signal for the psychiatric factors relative to another human complex trait. Error bars are +/- 1.96 *SE* that are centred around the enrichment point estimate. Enrichment estimates that were significant at a strict Bonferroni corrected threshold for multiple comparisons are shown with a *. The one-sided *P*-values used to evaluate significance were derived from the *Z*-statistics, calculated as the enrichment point estimate divided by its standard error. Exact *P*-values are reported in Suppl. Table 50. The implied sample size for the psychiatric factors was: Compulsive ($\hat{n}$ = 54,100); Schizophrenia/Bipolar ($\hat{n}$ = 127,202); Neurodevelopmental ($\hat{n}$ = 84,760); Internalizing ($\hat{n}$ = 1,637,337); Substance Use ($\hat{n}$ = 313,395); *p*-factor ($\hat{n}$ = 2,168,621).

Extended Data Table 1 | Summary of Psychiatric Disorder Datasets

Psychiatric Disorders	Sample Size			Lifetime Prevalence	Liability Scale Heritability	GWAS loci
	Cases	*Controls*	$N_{effective}$			
European (EUR)-Like Genetic Ancestry						
Tourette's Syndrome	4,819	9,488	12,140	0.8%	.22 (.03)	1
Schizophrenia	53,386	77,258	117,498	1.0%	.22 (.01)	177
Cannabis Use Disorder	14,808	343,726	26,789	4.8%	.19 (.02)	2
Bipolar Disorder	41,917	371,549	101,963	2.0%	.19 (.01)	58
Attention-Deficit/Hyperactivity Disorder	38,691	186,843	99,252	5%	.18 (.01)	27
Anorexia Nervosa	16,992	55,525	46,322	0.9%	.16 (.01)	8
Obsessive Compulsive Disorder	14,688	656,901	32,706	2.5%	.16 (.01)	1
Alcohol Use Disorder	57,564	256,399	179,186	15.9%	.12 (.01)	25
Autism Spectrum Disorder	18,381	27,969	43,778	1.2%	.12 (.01)	3
Anxiety Disorders	117,401	699,243	329,323	2.0%	.11 (.01)	47
Nicotine Dependence	46,213		-	-	.09 (.01)	2
Major Depression	412,305	1,588,397	1,105,086	15.0%	.06 (.01)	230
Opioid Use Disorder	10,544	72,163	45,543	1.0%	.06 (.01)	1
Post-traumatic Stress Disorder	141,479	1,113,329	451,034	12.5%	.05 (.01)	25
African-Like Genetic Ancestry						
Alcohol Use Disorder	3,335	2,945	*4,053*	15.9%	.22 (.09)	1
Cannabis Use Disorder	3,848	5,897	*9,044*	4.8%	.10 (.03)	0
Post-traumatic Stress Disorder	11,560	39,474	*32,940*	12.5%	.03 (.01)	0
Opioid Use Disorder	5,212	26,876	*15,935*	1.0%	.01 (.02)	0
East Asian (EAS)-Like Genetic Ancestry						
Schizophrenia	22,778	35,362	11,532	1.0%	.69 (.04)	19
Major Depression	13,893	155,912	42,011	15%	.05 (.01)	1

The table is ordered with respect to the liability scale heritabilities (within each genetic ancestry). The $N_{effective}$ column reports the sum of effective sample sizes across contributing cohorts. Nicotine dependence includes a single value for the sample size columns as this was the one continuous measure, defined using the Fagerström Test for Nicotine Dependence. The reported population prevalences were taken from the corresponding univariate publication when possible and were used for liability scale conversions (possible scale = 0–100%). The numbers in parentheses in the liability scale heritability column reflect the corresponding standard errors. The GWAS loci column reports the number of independent significant hits. A genome-wide significance threshold of $P<5\times10^{-8}$ was employed to correct for multiple statistical comparisons, and significance was evaluated using two-sided *P* values obtained from *Z*-statistics, which reflected the estimated univariate GWAS beta over its estimated standard error. Results are shown for: Tourette's Syndrome[18], Schizophrenia[17,30], Cannabis Use Disorder[26], Bipolar Disorder[13], Attention-Deficit/Hyperactivity Disorder[15], Anorexia Nervosa[14], Obsessive Compulsive Disorder[19], Alcohol Use Disorder[21,31], Autism Spectrum Disorder[16], Anxiety Disorders[22], Nicotine Dependence[24], Major Depression[20,29], Opioid Use Disorder[25], and Post-traumatic Stress Disorder[23].

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☐	☒	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒	A description of all covariates tested
☐	☒	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
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☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
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☐	☒	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	No software was used for data collection.
Data analysis	Genomic SEM analyses were implemented using the publicly available code here for v0.5.0: https://github.com/GenomicSEM/GenomicSEM Factanal was conducted using publicly available code here within the stats R package for v3.6.2: https://www.rdocumentation.org/packages/stats/versions/3.6.2 MiXeR was conducted using publicly available code here for v1.3: https://github.com/precimed/mixer LAVA was conducted using publicly available code here for v.0.1.0: https://github.com/josefin-werme/LAVA CC-GWAS was conducted using publicly available code here for v0.1.0: https://github.com/wouterpeyrot/CCGWAS LDlink was conducted using publicly available code here for v1.4.0: https://cran.r-project.org/web/packages/LDlinkR/vignettes/LDlinkR.html ToppGene suite was conducted using publicly available code here for v0.1.0: https://toppgene.cchmc.org/ EWCE was conducted using publicly available code here for v.1.16.0: https://nathanskene.github.io/EWCE/ MAGMA was conducted using publicly available code here for v.2.0.15: https://neurogenomics.github.io/MAGMA_Celltyping/index.html

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Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

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Psychiatric disorder GWAS summary statistics for data from the PGC can be downloaded or requested here:
https://www.med.unc.edu/pgc/download-results/
Links to the LD-scores and reference panel data for GenomicSEM analyses can be found here: https://github.com/GenomicSEM/GenomicSEM/wiki
Links to the BaselineLD v2.2 annotations can be found here:
https://data.broadinstitute.org/alkesgroup/LDSCORE
Gene expression datasets from Brainspan can be found here:
https://brainspan.org/static/download.html

Multivariate GWAS summary statistics for the latent psychiatric factors in GenomicSEM, including the sensitivity GWAS results, are available at:
https://www.med.unc.edu/pgc/download-results/

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Biological sex (as determined by the sex chromosomes) was used as a covariate in the original GWAS analyses for all included traits. All included GWAS summary statistics included both male and female subjects, with the exact split across males and females provided in the original papers describing this univariate GWAS data.
Reporting on race, ethnicity, or other socially relevant groupings	This study includes GWAS summary statistics for genetic ancestry groups that can be approximately described, based on genetic similarity to global reference panels, as reflecting European-like, East Asian-like, and African/African American-like genetic ancestries. The sample sizes are separately reported for each of these genetic ancestry groups in Extended Data Table 1.
Population characteristics	In order to achieve adequate power for GWAS analyses, the psychiatric disorders that are used as the primary data input in this paper include data from multiple cohorts, each with different population characteristics. The supplementary materials of the corresponding univariate GWAS papers include information on the different cohorts that went into their analyses. Our current manuscript reports sample sizes (case/control) and diagnosis for each disorder.
Recruitment	As described directly above, this study was not involved in recruitment of study participants. Rather, the individual cohorts that made-up the univariate GWAS for psychiatric disorders employed different recruitment strategies. This recruitment strategies ranged from volunteer basis, population-level surveys, and convenience sampling from hospital settings. As no single recruitment strategy was used for a psychiatric disorder this should ideally reduce bias induced by any one form of recruitment.
Ethics oversight	Primary data collection was not conducted for this study. As the data was used was already collected and deidentified, ethics oversight was not applicable.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	The current study reflects the largest and most comprehensive cross-disorder psychiatric genetic analysis to-date. This study makes use of the largest psychiatric disorder GWAS currently available. Sample sizes for each of the included 14 disorders are provided in Table 1 of the main text.
Data exclusions	We employed strict quality control of the GWAS summary statistics prior to running analyses. These QC filters included removing strand ambiguous SNPs, restricting to SNPs with an imputation score (INFO) > 0.6 and with a minor allele frequency (MAF) > 1% when this information was available in the GWAS summary stats. Finally, we restrict to SNPs with a SNP-specific sum of the effective sample that is >

50% of the total sum of the effective sample or, when this SNP-specific information was not available, to SNPs for which > 50% of the cohorts contributed information, as indexed by the direction column in the GWAS summary stats. The MHC region was excluded from all summary statistics prior to the analysis.

Replication

We examined how genetic correlations in European-like genetic ancestry individuals compared to results from East Asian-like and African/ African American-like genetic ancestry individuals. The genetic correlation (rg) between major depression and schizophrenia in East Asian-like participants (rg = 0.45; SE = 0.09) was double that observed in European-like participants (rg = 0.22; SE = 0.04), though this discrepancy was previously shown to be driven by a single cohort of severe and recurrent major depression. Genetic correlations across disorders using African-like genetic ancestry GWAS did not produce any significant results due to lower power reflective of smaller participants sample sizes in these GWAS. Genetic correlations across genetic ancestry groups within a disorder were generally underpowered, but included a strong East Asian-like and European-like genetic correlation for schizophrenia.

Functional analyses using MAGMA, Expression-Weighted Cell Type Enrichment, and Stratified Genomic SEM replicated certain key findings, including the enrichment of excitatory neuron pathways for the Schizophrenia/Bipolar factor and oligodendrocyte biology for the Internalizing factor.

We also evaluated replication of results when utilizing more strictly ascertained samples of psychiatric cases. We find that the general pattern of results replicates for this ascertainment sensitivity analysis, with similar patterns of genetic correlations across disorders, multivariate genetic architecture, and genetic variants associated with the psychiatric factors.

Randomization

As this is a study of genetic risk for psychiatric disorders, and not a study of treatment effects as might be evaluated in a randomized control trial, randomization is not relevant as a study consideration. This is because participants cannot be randomized by the experimenter to have a psychiatric disorder or not.

Blinding

Blinding does not apply to this type of study design as the study participants are not randomly assigned to have a psychiatric disorder or not. In addition, there is no bias that can be introduced by the scientists running the genetic association analyses being aware of their psychiatric case status.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Plants

Seed stocks

Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.

Novel plant genotypes

Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.

Authentication

Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.