Genome-wide analyses reveal widespread genetic overlap between neurological and psychiatric disorders and a convergence of biological associations related to the brain

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Abstract

Neurological and psychiatric disorders are considered to reflect distinct underlying pathogenic entities. However, the extent to which they share genetic influences remains unclear. Here, we performed a comprehensive analysis of GWAS data, involving nearly 1 million cases across ten neurological diseases and ten psychiatric disorders, to compare their common genetic risk and biological underpinnings. Using complementary statistical tools, we demonstrate extensive genetic overlap across the disorders, with varying degrees of genetic correlations. In particular, migraine, essential tremor, stroke and multiple sclerosis were genetically correlated with several psychiatric disorders. Biological interrogation indicated heterogenous biological processes associated with neurological diseases, while psychiatric disorders consistently implicated neuronal biology. Altogether, the study demonstrates that neurological and psychiatric disorders are not genetically disparate, but share key etiological aspects, which have important implications for disease classification, clinical practice, and genomic precision medicine.

Introduction

Neurological and psychiatric disorders rank among the leading causes of disability and mortality worldwide[1]. Despite their shared neural origin, the disorders are considered to reflect distinct pathogenic entities, and they are classified separately in the International Classification of Diseases[2]. The clinical division was driven by progress in brain research during the 19th and 20th century[3,4]. While neurology laid claim on the disorders with demonstrable neuropathology, such as Alzheimer's disease (ALZ), psychiatry focused on the mental disorders without recognizable pathology, such as schizophrenia (SCZ). However, findings in neuroscience over the past decades, combined with clinical and epidemiological observations, have challenged the validity of this clinical distinction[3-7].

Despite a lack of objective biomarkers, accumulating evidence indicates that psychiatric disorders have a neurobiological basis. *In vivo* neuroimaging[8] and postmortem[9] investigations show systematic brain abnormalities across different psychiatric disorders. Moreover, treatment modalities targeting neurobiological mechanisms are effective for many psychiatric disorders, including electroconvulsive therapy, transcranial magnetic stimulation and psychopharmacological agents[10-12]. Some of these interventions are used for both neurological and psychiatric illnesses, for example anticonvulsants in epilepsy and bipolar disorder (BD)[10]. Neurological and psychiatric disorders also share clinical features. Debilitating psychiatric symptoms such as hallucinations, delusions and mood disturbances are prominent across neurological disorders[13-15]. Furthermore, movement abnormalities are found in psychiatric disorders[16], and cognitive impairment is a clinical hallmark characterizing several neurological and psychiatric disorders[2,17]. Additionally, epidemiological studies reveal high comorbidity between neurological and psychiatric disorders[15,18-20], including a higher incidence of dementia among individuals with psychotic disorders[20]. Altogether, the existing clinical dichotomy inadequately reflects the interconnected nature of neurological and psychiatric disorders.

Ultimately, this may impact clinical care, whereby clinicians may fail to recognize or appropriately address all aspects of illness. To address this, various proposals have been made over the past decades calling for a more unified clinical approach to these disorders[3-7]. However, the extent to which neurological and psychiatric disorders share an etiological basis remains unclear.

The heritability of neurological and psychiatric disorders indicates that genomic research could provide new insights into their etiology[21]. This knowledge could bridge the nosological gap by forming the basis for an etiology-driven approach to disease classification, reveal novel treatment targets, and inform the development of precision medicine approaches. In recent years, genome-wide association studies (GWAS) have identified multiple common genetic variants for neurological and psychiatric disorders. Two key findings have emerged: the disorders are polygenic and genetic overlap is ubiquitous[22,23]. Genetic overlap has mainly been assessed by estimating pairwise genetic correlations using tools such as linkage disequilibrium (LD) score regression (LDSC)[24], demonstrating that the genetic risk of psychiatric disorders is highly intercorrelated[25-28]. By contrast, there are fewer significant pairwise genetic correlations among neurological disorders[25,29,30] and between neurological and psychiatric disorders[25,31]. Accordingly, neurological disorders have been considered to be genetically disparate from psychiatric disorders[25], in line with their clinical distinction[2]. However, estimates of genetic correlation are sensitive to low GWAS power and do not provide a complete picture of the genetic relationship between complex human phenotypes[22,32]. Importantly, they may conceal genetic overlap involving a mixture of concordant and discordant effect directions[33,34], and they do not account for differences in polygenicity[33], which governs the extent to which phenotypes may share genetic variants. Recent analyses using LAVA[34] and MiXeR[33] have demonstrated extensive genetic overlap across complex human phenotypes irrespective of the genetic correlations, along with differences in their polygenic

architetures[22,27,33-35]. Additionally, genetic analyses have identified overlapping risk loci and expression profiles between psychiatric and neurological disorders[31,36-41], indicative of a shared pathogenetic basis. Moreover, GWAS on psychiatric disorders implicate neurobiological pathways and neuronal cell types, suggesting that their underlying susceptibility affects brain functioning[32].

In the present study, we aimed to investigate whether the existing clinical division between neurological and psychiatric disorders is apparent at the genetic level. To this end, we conducted a comprehensive cross-disorder analysis of recent large-scale GWAS datasets using statistical tools that capture distinct forms of genetic overlap, and we biologically interpretated the genomic data.

Results

Study design (Fig.1). We curated a collection of well-powered GWAS summary statistics, resulting in data on ten psychiatric disorders (attention-deficit/hyperactivity disorder (ADHD)[42], anorexia nervosa (AN)[43], autism spectrum disorder (ASD)[44], anxiety disorders (ANX)[45], BD[46], major depressive disorder (MDD)[47], obsessive-compulsive disorder (OCD)[48], post-traumatic stress disorder (PTSD)[49], SCZ[50] and Tourette Syndrome (TS)[51]), and ten neurological disorders (ALZ[52], amyotrophic lateral sclerosis (ALS)[53], essential tremor (ET)[54], Lewy body dementia (LBD)[55], migraine (MIG)[56], multiple sclerosis (MS)[57], Parkinson's disease (PD)[58-60], stroke[61] and the epilepsy subtypes focal epilepsy (FE)[62] and genetic generalized epilepsy (GGE)[62]). Additionally, we included GWAS data on brain-related traits (general cognitive ability (COG)[63] and cortical surface area (CRT-SA) and thickness (CRT-TH)[64]), four somatic diseases (chronic kidney disease (CKD)[65], coronary artery disease (CAD)[66], inflammatory bowel disease (IBD)[67] and Type 2 Diabetes (T2D)[68]) and height[69] as comparators. All GWAS data were limited to participants of European ancestry to avoid bias due to differences in LD structure across ancestries. Ascertainment and diagnostic criteria are described in the Supplementary Note.

After data harmonization and pre-processing of the GWAS summary data, we conducted systematic cross-trait analyses and biological interrogation (Fig. 1). We first provide information on the genetic architecture characteristics distinguishing each phenotype. Next, we provide an overview of the overlapping genome-wide significant loci and genes. Third, we present the patterns of global genetic correlations across the phenotypes. Fourth, we provide estimates of genetic overlap beyond genetic correlation. Finally, we compare differentially implicated biological pathways, tissues and cell types across the included GWAS.

Individual genetic architecture characteristics. The genetic architecture of complex human phenotypes differs in terms of the heritability accounted for by single-nucleotide polymorphisms (SNP-heritability), the estimated number of SNPs influencing the phenotype (the polygenicity), and the variance of effect sizes across the associated SNPs (the discoverability)[22,32]. For each phenotype (trait or disorder), we estimated the SNP-heritability using LDSC[70] (Table 1, Fig. 2a). On average, the estimated SNP-heritability on the liability scale was almost twice as large for psychiatric disorders (14.6%, range 5.3-29.3%) compared to neurological disorders (8.2%, range 1.4-23.8%). However, regardless of disorder category, disorders with typical onset during childhood or adolescence had the highest estimated SNP-heritability, specifically OCD, GGE, SCZ and TS, all of putative neurodevelopmental origin. The average estimated SNP-heritability for non-brain related disorders was 9.8% (range 1.6-17.9%).

Using MiXeR[71], we estimated the polygenicity and discoverability for each phenotype (Fig. 2b; Supplementary Table 1), except for seven GWAS displaying poor model fit due to insufficient statistical power (ANX, PTSD, TS, OCD, FE, ET and LBD). The polygenicity estimates for all psychiatric disorders (range 7,725, sd=349 – 13,582, sd=387) and COG (11,195, sd=369) exceeded those of neurological disorders (range 464, sd=43 – 2,898, sd=220), somatic disorders (range 423, sd=55 – 1,358, sd=85), height (4,894, sd=90) and cortical imaging measures (range 1,361, sd=100 – 1,666, sd=125). For example, the least polygenic psychiatric disorder ADHD (7,725, sd=349) was estimated to be influenced by ~2.7 times more genetic variants than the most polygenic neurological disorder GGE (2,898, sd=220). In line with prior work[22,71], the most polygenic phenotypes were characterized by relatively low discoverability, indicating a larger fraction of trait-influencing variants with smaller effect sizes. In Supplementary Fig. 1, we present GWAS power plots displaying the estimated fraction of SNP-heritability explained by genome-wide significant SNPs as a function of sample size,

demonstrating that the discovery trajectories for most of the GWAS are still in the early stages, except for height.

Overlapping genome-wide significant loci and genes. We estimated the number and fraction of significantly associated loci and genes shared across the phenotype categories (Table 2) with results for each phenotypic pair provided in Supplementary Tables 2-3. For each GWAS, we identified genome-wide significant loci according to the FUMA protocol[72]. We subsequently grouped physically overlapping loci, resulting in a total number of 1,988 distinct loci. Of these, 441 loci were linked to psychiatric disorders and 227 loci to neurological disorders. In total, 41 loci were overlapping between psychiatric and neurological disorders, constituting 9.3% and 18.1% of the total number of loci linked to these categories, respectively. Additionally, we mapped GWAS associations to protein-coding genes using MAGMA[73], yielding a total number of 7,829 distinct genes. Of these, 796 genes were linked to psychiatric disorders and 497 to neurological disorders. 51 genes were shared between psychiatric and neurological disorders, constituting 6.4% and 10.3% of the total number of genes linked to these categories, respectively. Importantly, the pleiotropy across genome-wide significant loci and genes were largely driven by GWAS power, warranting cautious interpretation of these results. Almost all pleiotropy for psychiatric disorders were observed for SCZ and MDD, while the neurological GWAS were more evenly powered.

Global genetic correlations. Using bivariate LDSC[24], we estimated the global pairwise genetic correlations across all phenotypes (Supplementary Fig. 2). Our results corroborate prior findings of highly intercorrelated genetic risk among psychiatric disorders[25-28,31]. In total, 40 out of 45 genetic correlations among psychiatric disorders reached significance (FDR < 0.05). In comparison, 12 out of 45 correlations among neurological disorders reached significance

(FDR < 0.05). As recently demonstrated[29,30], the neurodegenerative disorders ALS, LBD, ALZ and PD formed a cluster of correlated disorders. Additionally, ET was correlated with both PD (r_g=0.31, p=1.80x10^{-7}) and MIG (r_g=0.17, p=3.90x10^{-3}), FE was correlated with stroke (r_g=0.30, p=1.40x10^{-3}), ALS (r_g=0.32, p=7.10x10^{-3}) and the other epilepsy subtype GGE (r_g=0.61, p=8.04x10^{-17}), while PD was negatively correlated with both MIG (r_g=-0.08, p=1.40x10^{-2}) and stroke (r_g=-0.10, p=1.57x10^{-2}).

In total, 30 out of 100 genetic correlations between neurological and psychiatric disorders reached significance at FDR < 0.05 (r_g range: -0.19 – 0.40; Fig. 3), demonstrating that genetic risk transcends the categorical boundary between these disorders. We found that MIG, ET and stroke were positively correlated with several psychiatric disorders, in particular MDD, ADHD, ANX and PTSD. The same psychiatric disorders were also correlated with CAD, consistent with a connection between mental disorders and cardiovascular illness[74]. By contrast, neither MIG or ET were significantly correlated with any somatic comparator or stroke, suggesting that their shared genetic effects with psychiatric disorders may relate to other aspects. Additionally, MS was significantly correlated with ANX (r_g=0.17, p=6.00x10^{-4}), MDD (r_g=0.11, p=1.16x10^{-5}) and SCZ (r_g=0.07, p=1.02x10^{-2}). All of these disorders were positively correlated with the immune-mediated disease IBD, indicating a common link to immunity. We also observed significant correlations between ALZ and both BD (r_g=0.14, p=1.81x10^{-2}) and SCZ (r_g=0.11, p=1.14x10^{-2}), in line with the comorbidity between dementia and psychosis[13,20,31]. Finally, we observed significant correlations between several comparators and psychiatric and neurological disorders, demonstrating body-wide effects of the involved genetic variants (Supplementary Note).

Genetic overlap beyond global genetic correlations. Using bivariate MiXeR[33], we estimated the unique and overlapping genetic architectures between pairs of phenotypes (Supplementary

Table 5). Unlike LDSC[24], MiXeR can detect genetic overlap regardless of the global genetic correlations[33]. Corroborating recent work[35], we found extensive genetic overlap across all psychiatric disorders, with a minor proportion of disorder-specific variants (Supplementary Fig. 3). MiXeR indicated varying degrees of genetic overlap between neurological disorders, with smaller proportions of shared risk compared to psychiatric disorders, suggesting that neurological disorders are more genetically distinct from each other. Despite disparate polygenicity estimates, we observed widespread genetic overlap between neurological and psychiatric disorders. This constituted a larger proportion of the genetic architectures of neurological disorders given their smaller polygenicity estimates relative to psychiatric disorders. As an example, MiXeR estimated pronounced genetic overlap between SCZ and neurological disorders PD, GGE and MIG, despite absent genetic correlations, indicative of a balanced mix of concordant and discordant effects among the shared variants (Fig. 4). Almost all genetic variants linked to PD and GGE and 70% of those linked to MIG were estimated to also influence risk of SCZ, while the overlap represented less than 30% of the SCZ variants.

Applying LAVA[34], we calculated the local genetic correlations across 2,495 genomic regions between all pairs of phenotypes. We performed local genetic correlation tests at loci where both phenotypes had heritability estimates significantly different from zero, and corrected for multiple testing using FDR. Corroborating the MiXeR findings, LAVA estimated multiple significantly correlated loci across most pairs of phenotypes, including between neurological and psychiatric disorders (Supplementary Table 6). As observed for locus and gene pleiotropy at the genome-wide significance level (Supplementary Tables 2 and 3), the number of LAVA local correlations largely reflected GWAS power. Consistent with the MiXeR findings, LAVA estimated correlated loci between SCZ and PD (14 positively correlated and 13 negatively correlated loci), GGE (six positively correlated and six negatively correlated

loci), and MIG (10 positively correlated and 15 negatively correlated loci), supporting a shared genetic basis (Fig. 4).

Tissue, cell-type and gene-set enrichment analyses. Finally, we compared GWAS enrichment with specific tissues, cell types and gene sets (Table 4), using RNA sequencing data from the Genotype-Tissue Expression (GTEx) project[75], single-cell RNA sequencing datasets from the developing and adult human brain, and predefined Gene Ontology gene sets implemented in FUMA[72,76]. We performed Bonferroni correction for the number of tested items in each analysis. The biological interrogation revealed diverse brain-related associations linked to neurological disorders. Risk genes for PD were significantly associated with various neurobiological processes, particularly concerning synaptic vesicles, and were specifically upregulated in the substantia nigra[58], central to PD pathogenesis. Risk genes for GGE were significantly associated with both GABAergic and excitatory neurons[62], in line with hyperexcitability being the main pathophysiological feature of epilepsy, but were not associated with any tissue or gene set. The only significant association observed for stroke was with the gene set 'fibrinogen', an established stroke risk factor involved in clot formation[77]. Risk genes for LBD were linked to lipid metabolism. As previously shown[52,57,76], ALZ and MS were both significantly associated with immune-enriched tissues, microglia and immunological pathways, implying a key role of the immune system. Additionally, ALZ were associated with amyloid-beta related processes.

GWAS on psychiatric disorders consistently implicated neuronal biology, corroborating previous work[26,28,32,42,46,47,50]. Risk genes for ADHD, MDD and SCZ were all upregulated in brain tissue, implicated neurobiological processes and neuronal cell types. MDD was also associated with oligodendrocyte progenitor cells. BD risk genes were significantly associated with both GABAergic and excitatory neurons, but not with any tissue or gene set. ANX was

significantly associated with several neurobiological pathways, while risk genes for AN were significantly downregulated in specific brain tissues. Apart from COG, no comparator was significantly associated with neurons. COG and CRT-TH were the only comparators whose genes were significantly upregulated in brain tissue. Further results are described in the Supplementary Note. Full results are provided in Supplementary Tables 7 and 8 and Supplementary Figs. 4 and 5.

Discussion

In the present study, we delineate the extent of common variant risk shared across major neurological and psychiatric disorders and provide new insights into their genetic relationship. Applying complementary statistical tools to massive datasets, we demonstrate widespread genetic overlap across the disorders, despite evident differences in their genetic architectures. Overall, the results advance our understanding of the shared common genetic variation underlying neurological and psychiatric disorders, suggesting that a large set of pleiotropic variants influence a range of brain functions and risk of multiple disorders, in which disorder specificity is determined by the distribution of effect sizes. While the overlapping genomic components suggest that neurological and psychiatric disorders partly share molecular genetic mechanisms, a more central role of neuronal biology was implicated in psychiatric disorders, while more diverse biological processes were associated with neurological diseases. Altogether, the findings are consistent with accumulating evidence indicating that neurological and psychiatric disorders share key etiological aspects, contrasting their clinical distinction.

To compare the genetic basis of neurological and psychiatric disorders, we analyzed GWAS summary data from 20 major disorders, representing the largest cross-disorder analysis on this subject to date (Table 1). Moreover, the application of statistical methods with different modelling assumptions and different techniques for measuring genetic overlap allowed us to interrogate their genetic relationship in a more comprehensive manner than previous work[25]. In the univariate analysis, psychiatric disorders were more polygenic than neurological disorders. Polygenicity indicates the number of additive genetic effects that may combine to yield increased trait susceptibility, providing a measure of genetic architecture complexity and possibly heterogeneity[22,78]. While both neurological and psychiatric disorders are multifactorial and clinically heterogenous, the higher levels of polygenicity of psychiatric disorders is

consistent with a hypothesis that multiple causal pathways may converge on the same mental illness, while fewer causal pathways may underlie neurological disorders. Despite similar twin-based heritability estimates across neurological and psychiatric disorders[21], the SNP-based heritability estimates appeared to negatively correlate with typical onset of illness, regardless of disorder category. This contrasts the theoretical expectation that common genetic variants might explain more variance in late-onset disorders, given their weaker impact on reproductive fitness, thereby reducing selective pressure[79]. However, current methodology may inappropriately account for the effect of age and large-effect variants such as *APOE* variants, warranting cautious interpretation of SNP-heritability estimates for late-onset disorders[80].

Expanding upon previous work based on less powerful GWAS[25,31,36-40], we demonstrate widespread genetic correlations between neurological and psychiatric disorders, most of which were positive (Fig. 3). The results indicate that neurological and psychiatric disorders partly exist on genetic continua, providing new insights into their genetic relationship. Importantly, the shared genetic components may map onto overlapping biological aspects that could be targeted therapeutically. Evidently, the pattern of correlations was not uniform across disorders, with clusters of disorders being more correlated with each other. Notably, both MIG and ET were positively correlated with several psychiatric disorders, in particular the internalizing disorders ANX, MDD and PTSD, consistent with their extensive psychiatric comorbidities[18,19]. On a cautious note, however, the GWAS on both MIG and ET were largely based on self-reports[54,56]. Although self-reported and clinically ascertained cases are shown to strongly correlate[47,56,58], we cannot exclude the possibility that some self-reports were based on underlying mental illness with somatoform symptomatology. The findings nevertheless emphasize the interconnected nature of these disorders, and may motivate further trialing of psychotherapy or antidepressants, which show beneficial effects for MIG prevention[81].

Beyond genetic correlations, we observed a more pervasive degree of genetic overlap across neurological and psychiatric disorders, involving a mixture of concordant and discordant effect sizes (Supplementary Fig. 3). As an example, MiXeR[33] indicated that a pronounced fraction of the genetic risk underlying PD, GGE and MIG overlaps with SCZ, despite absence of global genetic correlations (Fig. 4). The findings align with the discovery of multiple correlated genomic regions between these disorders using LAVA[34] (Fig. 4), and shared loci detected below the genome-wide significance level[36,37,40]. The emerging results indicate a substantial genetic basis shared across neurological and psychiatric disorders, in which multiple genetic variants are estimated to influence several disorders, but with divergent effect sizes. Accordingly, a given genetic variant may influence numerous biological pathways involved in a range of neural and behavioral systems, and thereby differently impact risk of distinct disorders. This is consistent with recent findings of highly distributed genetic effects across brain morphological, cognitive and personality traits[82-85]. From a clinical perspective, the findings are relevant to the potential implementation of genomic precision medicine in clinical psychiatry and neurology. Integrating genomic data across multiple disorders in a multivariate analytical framework may improve prediction algorithms and help identifying individuals who are more likely to experience comorbid symptoms, either endogenously or due to adverse treatment effects.

The study has some limitations. The analysis was restricted to individuals of European ancestry, given the lack of well-powered GWAS on other ancestries. Trans-ancestral follow-up studies are required to assess the generalizability of these results. The present analysis was based on common genetic variants, but rare variants likely impact the comorbidity between neurological and psychiatric disorders as well. For example, rare variants are jointly associated with epilepsy, SCZ and ASD[32]. Our study was limited by bias inherent to the original GWAS, including population stratification and ascertainment procedures. As noted above, misdiagnosis

could affect the results, in particular with more common disorders like anxiety or depression. However, prior extensive simulations did not find that misdiagnosis could explain the magnitude of correlated risk across psychiatric disorders[25,26]. Comorbid illness may also bias the assessment of genetic overlap, warranting more deeply phenotyped cohorts to assess differential genetic overlap among clinical subtypes. The results may be affected by LD, whereby a causal variant may be correlated with multiple nearby variants, leading to spurious pleiotropy. To address this, statistical fine-mapping follow-up studies are needed. Finally, there was uneven power among the included GWAS, which limit cross-disorder comparison at the present stage. This particularly affects the biological interpretation of the mapped genes, which only represent a minor fraction of the genetic risk architectures underlying these disorders. As GWAS samples get larger, cross-trait analyses based on more diverse datasets, additional disorders, and specific subtypes, should be conducted.

In conclusion, we leverage recent large-scale GWAS datasets and demonstrate widespread genetic overlap across neurological and psychiatric disorders and a convergence of biological associations related to the brain, contrasting their historically defined distinction. Incorporating these complex and interconnected illnesses into a more unified framework may help accelerate progress in these fields and potentially lead to a more coherent and productive clinical approach[3-7].

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Competing interests

O.A.A. has received speaker's honorarium from Lundbeck, Sunovion and Janssen and is a consultant for Cortechs.ai. A.M.D. is a founder of and holds equity interest in CorTechs Labs and serves on its scientific advisory board. He is also a member of the Scientific Advisory Board of Healthlytix and receives research funding from General Electric Healthcare (GEHC). The terms of these arrangements have been reviewed and approved by the University of

California, San Diego in accordance with its conflict of interest policies. Remaining authors have nothing to disclose.

References

1. Whiteford, H.A., Ferrari, A.J., Degenhardt, L., Feigin, V. & Vos, T. The global burden of mental, neurological and substance use disorders: an analysis from the Global Burden of Disease Study 2010. *PLoS One* **10**, e0116820 (2015).
2. World Health Organization. International Classification of Diseases for Mortality and Morbidity Statistics (Eleventh Revision). (2018).
3. Kandel, E.R. A new intellectual framework for psychiatry. *Am J Psychiatry* **155**, 457-69 (1998).
4. Price, B.H., Adams, R.D. & Coyle, J.T. Neurology and psychiatry: closing the great divide. *Neurology* **54**, 8-14 (2000).
5. Keshavan, M.S., Price, B.H. & Martin, J.B. The Convergence of Neurology and Psychiatry: The Importance of Cross-Disciplinary Education. *JAMA* **324**, 554-555 (2020).
6. Insel, T.R. & Quirion, R. Psychiatry as a clinical neuroscience discipline. *JAMA* **294**, 2221-4 (2005).
7. White, P.D., Rickards, H. & Zeman, A.Z. Time to end the distinction between mental and neurological illnesses. *BMJ* **344**, e3454 (2012).
8. Thompson, P.M. *et al.* ENIGMA and global neuroscience: A decade of large-scale studies of the brain in health and disease across more than 40 countries. *Transl Psychiatry* **10**, 100 (2020).
9. Leung, E. *et al.* Alterations in brain synaptic proteins and mRNAs in mood disorders: a systematic review and meta-analysis of postmortem brain studies. *Mol Psychiatry* **27**, 1362-1372 (2022).
10. Huhn, M. *et al.* Efficacy of pharmacotherapy and psychotherapy for adult psychiatric disorders: a systematic overview of meta-analyses. *JAMA Psychiatry* **71**, 706-15 (2014).
11. Espinoza, R.T. & Kellner, C.H. Electroconvulsive Therapy. *N Engl J Med* **386**, 667-672 (2022).
12. Levkovitz, Y. *et al.* Efficacy and safety of deep transcranial magnetic stimulation for major depression: a prospective multicenter randomized controlled trial. *World Psychiatry* **14**, 64-73 (2015).
13. Ismail, Z. *et al.* Psychosis in Alzheimer disease - mechanisms, genetics and therapeutic opportunities. *Nat Rev Neurol* **18**, 131-144 (2022).
14. Ffytche, D.H. *et al.* The psychosis spectrum in Parkinson disease. *Nat Rev Neurol* **13**, 81-95 (2017).
15. Gaitatzis, A., Trimble, M.R. & Sander, J.W. The psychiatric comorbidity of epilepsy. *Acta Neurol Scand* **110**, 207-20 (2004).
16. Peralta, V. & Cuesta, M.J. Motor Abnormalities: From Neurodevelopmental to Neurodegenerative Through "Functional" (Neuro)Psychiatric Disorders. *Schizophr Bull* **43**, 956-971 (2017).
17. Millan, M.J. *et al.* Cognitive dysfunction in psychiatric disorders: characteristics, causes and the quest for improved therapy. *Nat Rev Drug Discov* **11**, 141-68 (2012).
18. Minen, M.T. *et al.* Migraine and its psychiatric comorbidities. *J Neurol Neurosurg Psychiatry* **87**, 741-9 (2016).
19. Shanker, V. Essential tremor: diagnosis and management. *BMJ* **366**, l4485 (2019).
20. Richmond-Rakerd, L.S., D'Souza, S., Milne, B.J., Caspi, A. & Moffitt, T.E. Longitudinal Associations of Mental Disorders With Dementia: 30-Year Analysis of 1.7 Million New Zealand Citizens. *JAMA Psychiatry* **79**, 333-340 (2022).

21. Polderman, T.J. *et al.* Meta-analysis of the heritability of human traits based on fifty years of twin studies. *Nat Genet* **47**, 702-9 (2015).
22. Watanabe, K. *et al.* A global overview of pleiotropy and genetic architecture in complex traits. *Nat Genet* **51**, 1339-1348 (2019).
23. Abdellaoui, A., Yengo, L., Verweij, K.J.H. & Visscher, P.M. 15 years of GWAS discovery: Realizing the promise. *Am J Hum Genet* **110**, 179-194 (2023).
24. Bulik-Sullivan, B. *et al.* An atlas of genetic correlations across human diseases and traits. *Nat Genet* **47**, 1236-41 (2015).
25. Brainstorm, C. *et al.* Analysis of shared heritability in common disorders of the brain. *Science* **360**(2018).
26. Cross-Disorder Group of the Psychiatric Genomics Consortium. Genomic Relationships, Novel Loci, and Pleiotropic Mechanisms across Eight Psychiatric Disorders. *Cell* **179**, 1469-1482 e11 (2019).
27. Romero, C. *et al.* Exploring the genetic overlap between twelve psychiatric disorders. *Nat Genet* **54**, 1795-1802 (2022).
28. Grotzinger, A.D. *et al.* Genetic architecture of 11 major psychiatric disorders at biobehavioral, functional genomic and molecular genetic levels of analysis. *Nat Genet* **54**, 548-559 (2022).
29. Wightman, D.P. *et al.* The genetic overlap between Alzheimer's disease, amyotrophic lateral sclerosis, Lewy body dementia, and Parkinson's disease. *Neurobiology of Aging* (2023).
30. Qiao, J. *et al.* Genetic correlation and gene-based pleiotropy analysis for four major neurodegenerative diseases with summary statistics. *Neurobiol Aging* **124**, 117-128 (2023).
31. Wingo, T.S. *et al.* Shared mechanisms across the major psychiatric and neurodegenerative diseases. *Nat Commun* **13**, 4314 (2022).
32. Andreassen, O.A., Hindley, G.F.L., Frei, O. & Smeland, O.B. New insights from the last decade of research in psychiatric genetics: discoveries, challenges and clinical implications. *World Psychiatry* **22**, 4-24 (2023).
33. Frei, O. *et al.* Bivariate causal mixture model quantifies polygenic overlap between complex traits beyond genetic correlation. *Nat Commun* **10**, 2417 (2019).
34. Werme, J., van der Sluis, S., Posthuma, D. & de Leeuw, C.A. An integrated framework for local genetic correlation analysis. *Nat Genet* **54**, 274-282 (2022).
35. Hindley, G. *et al.* Charting the Landscape of Genetic Overlap Between Mental Disorders and Related Traits Beyond Genetic Correlation. *Am J Psychiatry* **179**, 833-843 (2022).
36. Bahrami, S. *et al.* Dissecting the shared genetic basis of migraine and mental disorders using novel statistical tools. *Brain* **145**, 142-153 (2022).
37. Smeland, O.B. *et al.* Genome-wide Association Analysis of Parkinson's Disease and Schizophrenia Reveals Shared Genetic Architecture and Identifies Novel Risk Loci. *Biol Psychiatry* **89**, 227-235 (2021).
38. Pickrell, J.K. *et al.* Detection and interpretation of shared genetic influences on 42 human traits. *Nat Genet* **48**, 709-17 (2016).
39. Ahangari, M. *et al.* Genome-wide analysis of schizophrenia and multiple sclerosis identifies shared genomic loci with mixed direction of effects. *Brain Behav Immun* **104**, 183-190 (2022).
40. Karadag, N. *et al.* Identification of novel genomic risk loci shared between common epilepsies and psychiatric disorders. *Brain* (2023).
41. Zeighami, Y. *et al.* A comparison of anatomic and cellular transcriptome structures across 40 human brain diseases. *PLoS Biol* **21**, e3002058 (2023).

42. Demontis, D. *et al.* Genome-wide analyses of ADHD identify 27 risk loci, refine the genetic architecture and implicate several cognitive domains. *Nat Genet* (2023).
43. Watson, H.J. *et al.* Genome-wide association study identifies eight risk loci and implicates metabo-psychiatric origins for anorexia nervosa. *Nat Genet* **51**, 1207-1214 (2019).
44. Grove, J. *et al.* Identification of common genetic risk variants for autism spectrum disorder. *Nat Genet* **51**, 431-444 (2019).
45. Purves, K.L. *et al.* A major role for common genetic variation in anxiety disorders. *Mol Psychiatry* **25**, 3292-3303 (2020).
46. Mullins, N. *et al.* Genome-wide association study of more than 40,000 bipolar disorder cases provides new insights into the underlying biology. *Nat Genet* **53**, 817-829 (2021).
47. Levey, D.F. *et al.* Bi-ancestral depression GWAS in the Million Veteran Program and meta-analysis in >1.2 million individuals highlight new therapeutic directions. *Nat Neurosci* **24**, 954-963 (2021).
48. International Obsessive Compulsive Disorder Foundation Genetics, C. & Studies, O.C.D.C.G.A. Revealing the complex genetic architecture of obsessive-compulsive disorder using meta-analysis. *Mol Psychiatry* **23**, 1181-1188 (2018).
49. Nievergelt, C.M. *et al.* International meta-analysis of PTSD genome-wide association studies identifies sex- and ancestry-specific genetic risk loci. *Nat Commun* **10**, 4558 (2019).
50. Trubetskoy, V. *et al.* Mapping genomic loci implicates genes and synaptic biology in schizophrenia. *Nature* **604**, 502-508 (2022).
51. Yu, D. *et al.* Interrogating the Genetic Determinants of Tourette's Syndrome and Other Tic Disorders Through Genome-Wide Association Studies. *Am J Psychiatry* **176**, 217-227 (2019).
52. Wightman, D.P. *et al.* A genome-wide association study with 1,126,563 individuals identifies new risk loci for Alzheimer's disease. *Nat Genet* **53**, 1276-1282 (2021).
53. van Rheenen, W. *et al.* Common and rare variant association analyses in amyotrophic lateral sclerosis identify 15 risk loci with distinct genetic architectures and neuron-specific biology. *Nat Genet* **53**, 1636-1648 (2021).
54. Liao, C. *et al.* Association of Essential Tremor With Novel Risk Loci: A Genome-Wide Association Study and Meta-analysis. *JAMA Neurol* **79**, 185-193 (2022).
55. Chia, R. *et al.* Genome sequencing analysis identifies new loci associated with Lewy body dementia and provides insights into its genetic architecture. *Nat Genet* **53**, 294-303 (2021).
56. Hautakangas, H. *et al.* Genome-wide analysis of 102,084 migraine cases identifies 123 risk loci and subtype-specific risk alleles. *Nat Genet* **54**, 152-160 (2022).
57. International Multiple Sclerosis Genetics, C. Multiple sclerosis genomic map implicates peripheral immune cells and microglia in susceptibility. *Science* **365**(2019).
58. Nalls, M.A. *et al.* Identification of novel risk loci, causal insights, and heritable risk for Parkinson's disease: a meta-analysis of genome-wide association studies. *Lancet Neurol* **18**, 1091-1102 (2019).
59. Chang, D. *et al.* A meta-analysis of genome-wide association studies identifies 17 new Parkinson's disease risk loci. *Nat Genet* **49**, 1511-1516 (2017).
60. Nalls, M.A. *et al.* Large-scale meta-analysis of genome-wide association data identifies six new risk loci for Parkinson's disease. *Nat Genet* **46**, 989-93 (2014).
61. Mishra, A. *et al.* Stroke genetics informs drug discovery and risk prediction across ancestries. *Nature* **611**, 115-123 (2022).

62. Berkovic, S.F., Cavalleri, G.L. & Koeleman, B.P.C. Genome-wide meta-analysis of over 29,000 people with epilepsy reveals 26 loci and subtype-specific genetic architecture. *medRxiv*, 2022.06.08.22276120 (2022).
63. Savage, J.E. *et al.* Genome-wide association meta-analysis in 269,867 individuals identifies new genetic and functional links to intelligence. *Nat Genet* **50**, 912-919 (2018).
64. Smith, S.M. *et al.* An expanded set of genome-wide association studies of brain imaging phenotypes in UK Biobank. *Nat Neurosci* **24**, 737-745 (2021).
65. Wuttke, M. *et al.* A catalog of genetic loci associated with kidney function from analyses of a million individuals. *Nat Genet* **51**, 957-972 (2019).
66. Nelson, C.P. *et al.* Association analyses based on false discovery rate implicate new loci for coronary artery disease. *Nat Genet* **49**, 1385-1391 (2017).
67. de Lange, K.M. *et al.* Genome-wide association study implicates immune activation of multiple integrin genes in inflammatory bowel disease. *Nat Genet* **49**, 256-261 (2017).
68. Mahajan, A. *et al.* Fine-mapping type 2 diabetes loci to single-variant resolution using high-density imputation and islet-specific epigenome maps. *Nat Genet* **50**, 1505-1513 (2018).
69. Yengo, L. *et al.* A saturated map of common genetic variants associated with human height. *Nature* **610**, 704-712 (2022).
70. Bulik-Sullivan, B.K. *et al.* LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nat Genet* **47**, 291-5 (2015).
71. Holland, D. *et al.* Beyond SNP heritability: Polygenicity and discoverability of phenotypes estimated with a univariate Gaussian mixture model. *PLoS Genet* **16**, e1008612 (2020).
72. Watanabe, K., Taskesen, E., van Bochoven, A. & Posthuma, D. Functional mapping and annotation of genetic associations with FUMA. *Nat Commun* **8**, 1826 (2017).
73. de Leeuw, C.A., Mooij, J.M., Heskes, T. & Posthuma, D. MAGMA: generalized gene-set analysis of GWAS data. *PLoS Comput Biol* **11**, e1004219 (2015).
74. Colton, C.W. & Manderscheid, R.W. Congruencies in increased mortality rates, years of potential life lost, and causes of death among public mental health clients in eight states. *Prev Chronic Dis* **3**, A42 (2006).
75. The GTEx Consortium. The Genotype-Tissue Expression (GTEx) project. *Nat Genet* **45**, 580-5 (2013).
76. Watanabe, K., Umicevic Mirkov, M., de Leeuw, C.A., van den Heuvel, M.P. & Posthuma, D. Genetic mapping of cell type specificity for complex traits. *Nat Commun* **10**, 3222 (2019).
77. Wilhelmsen, L. *et al.* Fibrinogen as a risk factor for stroke and myocardial infarction. *N Engl J Med* **311**, 501-5 (1984).
78. Smeland, O.B., Frei, O., Dale, A.M. & Andreassen, O.A. The polygenic architecture of schizophrenia - rethinking pathogenesis and nosology. *Nat Rev Neurol* **16**, 366-379 (2020).
79. Zuk, O. *et al.* Searching for missing heritability: designing rare variant association studies. *Proc Natl Acad Sci U S A* **111**, E455-64 (2014).
80. Lambert, J.C., Ramirez, A., Grenier-Boley, B. & Bellenguez, C. Step by step: towards a better understanding of the genetic architecture of Alzheimer's disease. *Mol Psychiatry* (2023).
81. Ashina, M. *et al.* Migraine: integrated approaches to clinical management and emerging treatments. *Lancet* **397**, 1505-1518 (2021).
82. van der Meer, D. *et al.* Understanding the genetic determinants of the brain with MOSTest. *Nat Commun* **11**, 3512 (2020).

83. van der Meer, D. *et al.* The genetic architecture of human cortical folding. *Sci Adv* **7**, eabj9446 (2021).
84. Bahrami, S. *et al.* Distributed genetic architecture across the hippocampal formation implies common neuropathology across brain disorders. *Nat Commun* **13**, 3436 (2022).
85. Hindley, G. *et al.* Multivariate genetic analysis of personality and cognitive traits reveals abundant pleiotropy. *Nat Hum Behav* (2023).

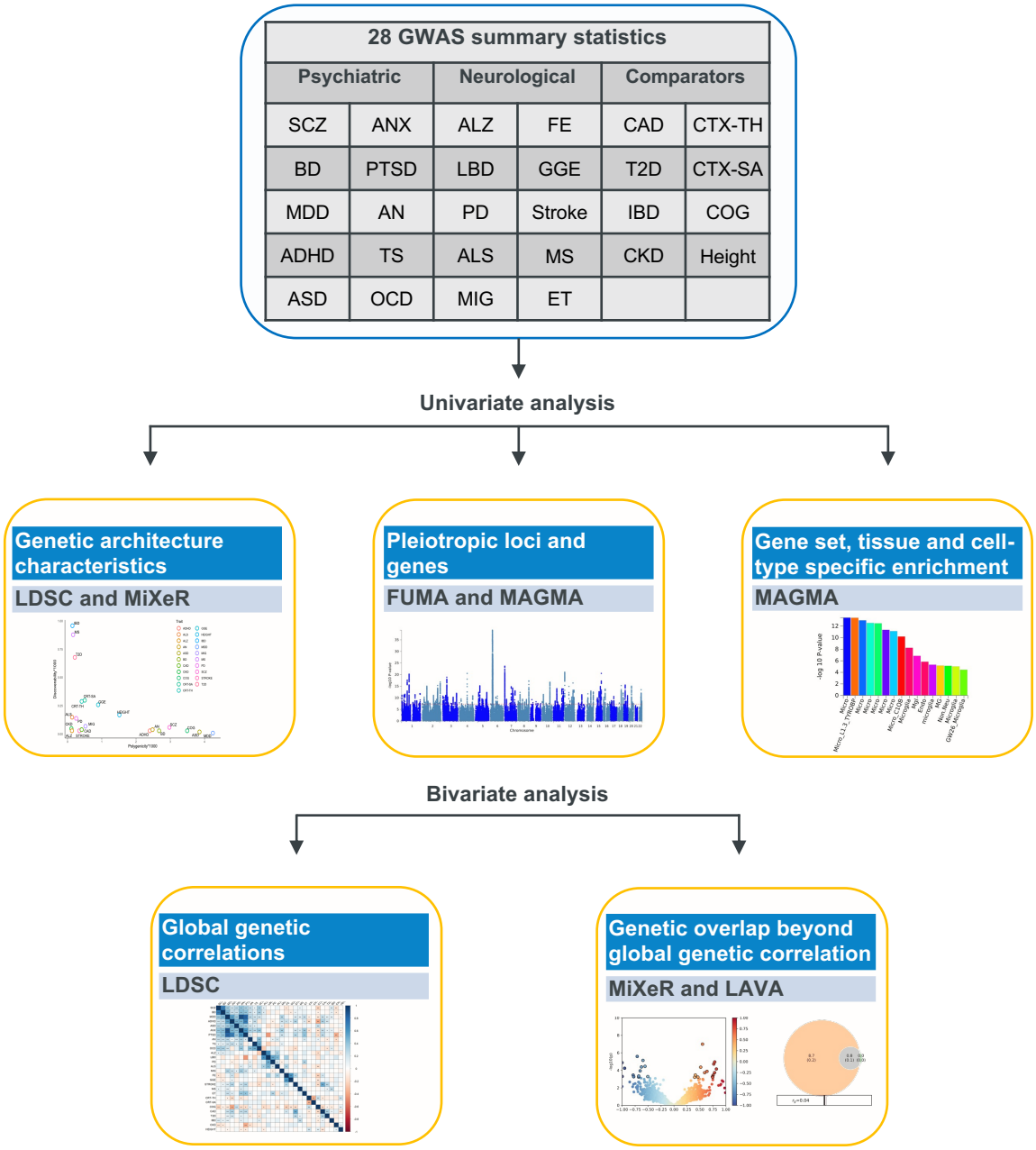
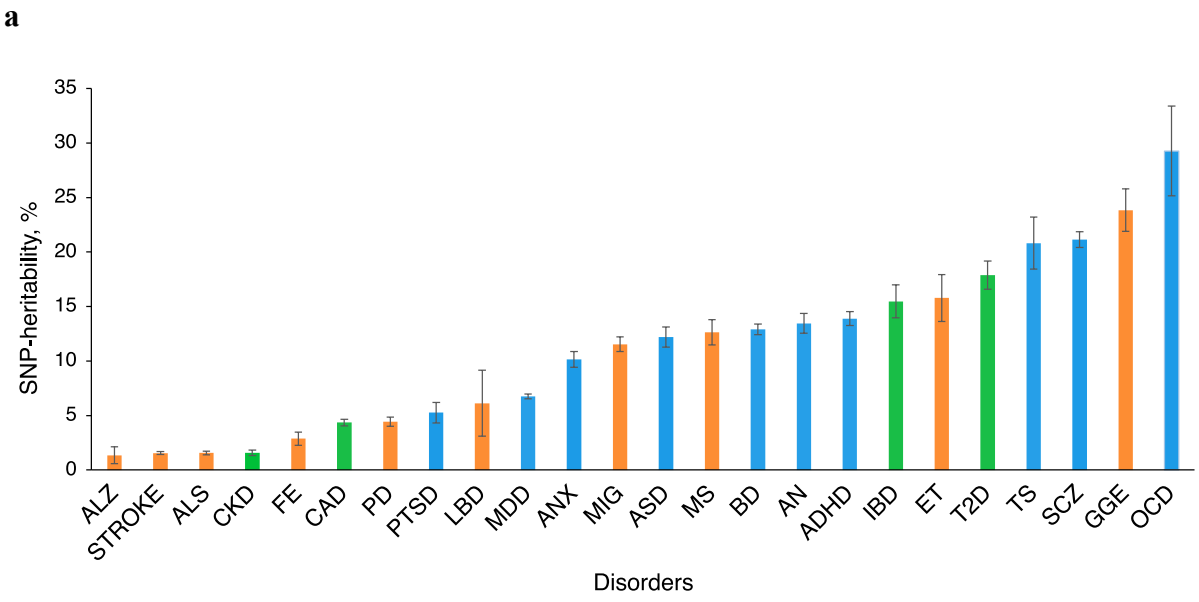


Fig. 1 | Study design. Overview of the GWAS summary statistics and analyses performed in the study. Abbreviations psychiatric disorders: Attention-deficit/hyperactivity disorder (ADHD), anorexia nervosa (AN), autism spectrum disorder (ASD), anxiety disorders (ANX), bipolar disorder (BD), major depressive disorder (MDD), obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), schizophrenia (SCZ), Tourette syndrome (TS); neurological disorders: Alzheimer's disease (ALZ), amyotrophic lateral sclerosis (ALS),

Essential Tremor (ET), Lewy body dementia (LBD), migraine (MIG), multiple sclerosis (MS), Parkinson disease (PD), focal epilepsy (FE), genetic generalized epilepsy (GGE); comparators: general cognitive ability (COG), total cortical surface area (CRT-SA) and average cortical thickness (CRT-TH), coronary artery disease (CAD), chronic kidney disease (CKD), inflammatory bowel disease (IBD) and Type 2 Diabetes (T2D); methods: linkage disequilibrium score regression (LDSC).



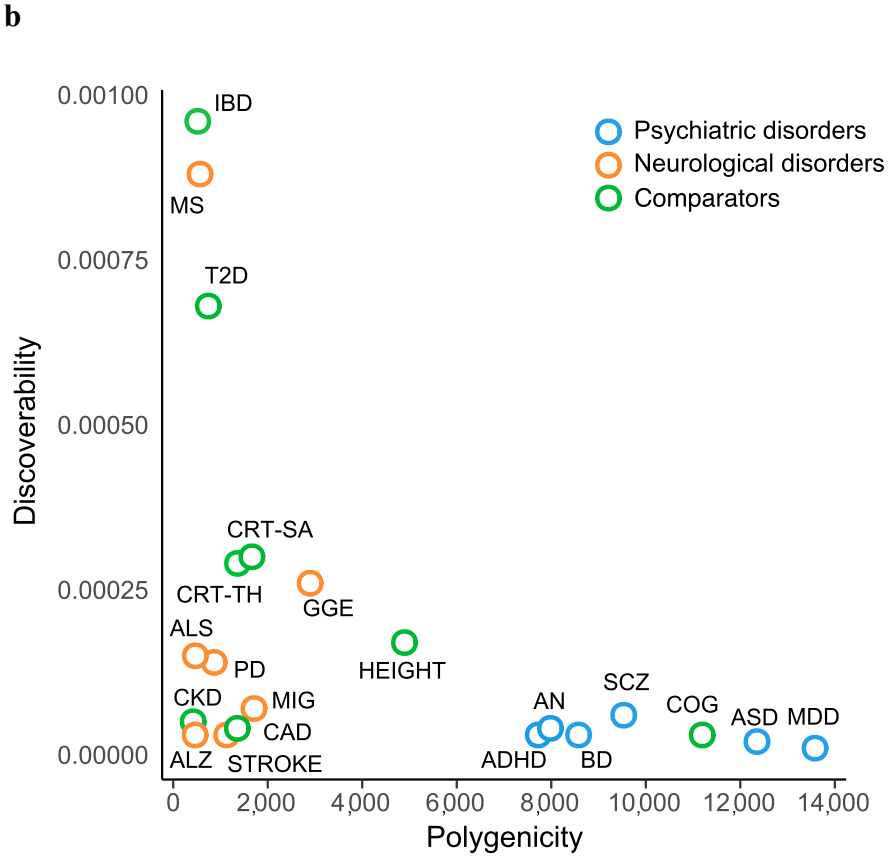


Fig. 2 | Individual genetic architecture characteristics. a, SNP-based heritability on the liability scale for all disorders estimated using LD score regression[70]. **b,** Polygenicity and

discoverability of all phenotypes estimated using MiXeR[71], excluding GWAS with poor model fit. For full univariate MiXeR results, see Supplementary Table 1.

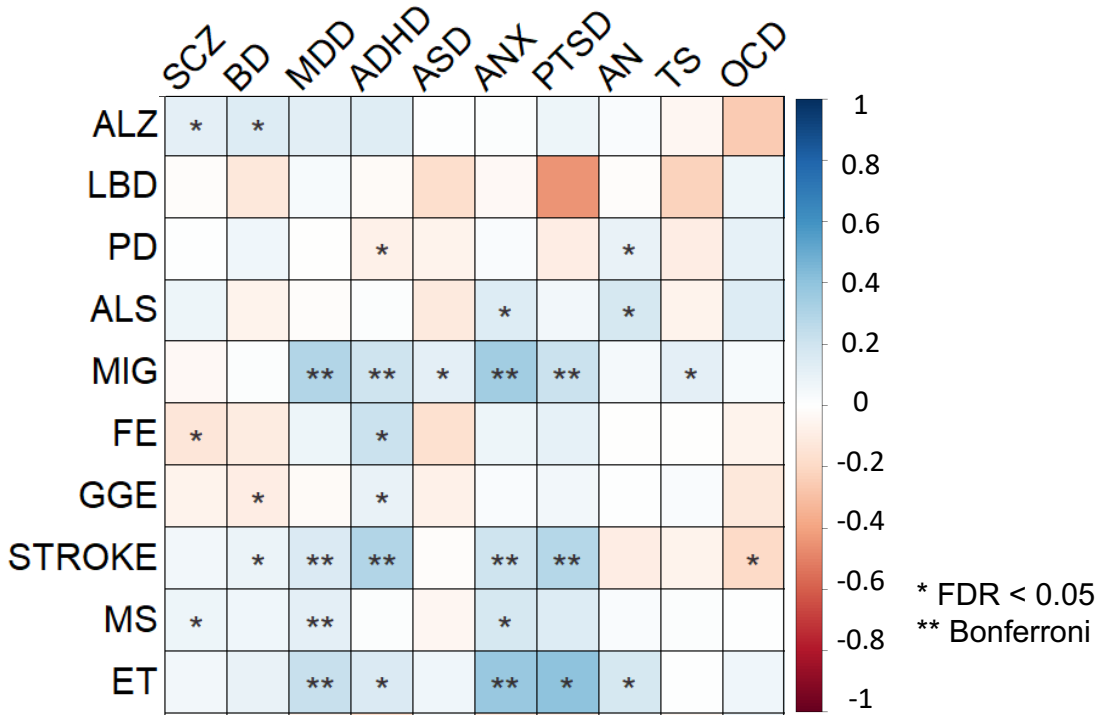


Fig. 3 | Genetic correlations. Global pairwise genetic correlations across neurological and psychiatric disorders estimated using linkage disequilibrium score regression[24]. One asterisk denotes statistical significance at FDR < 0.05, two asterisks denote statistical significance after Bonferroni correction. The color denotes the magnitude and direction of correlation.

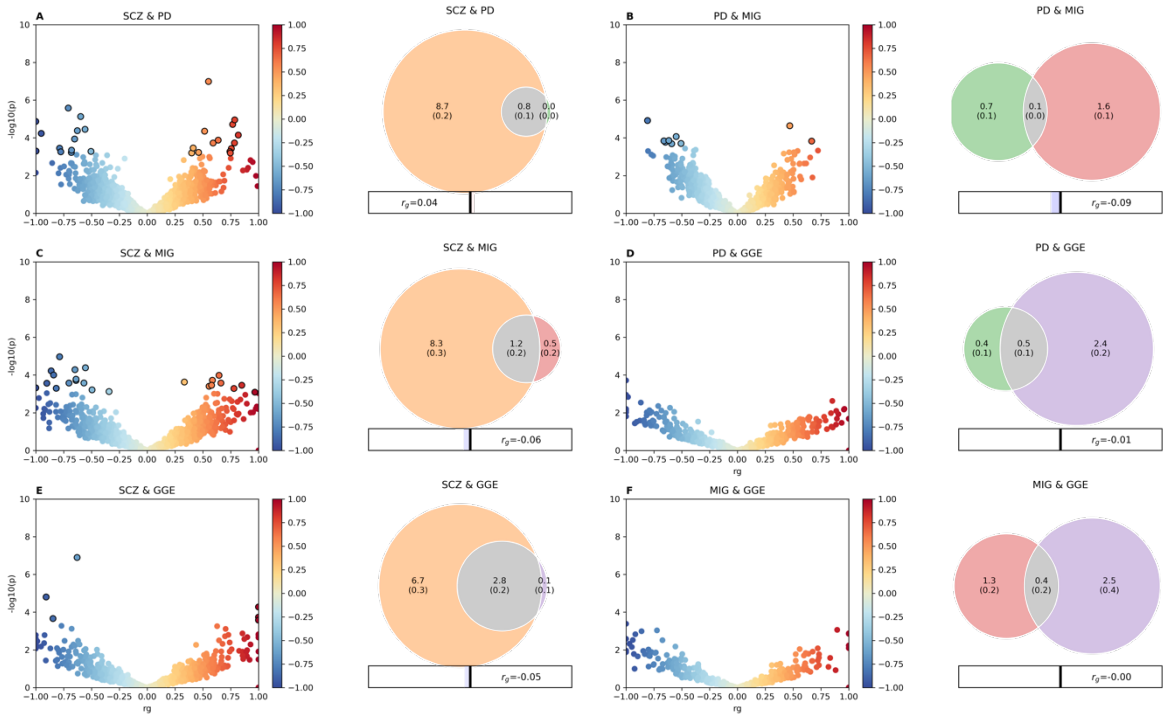


Fig. 4 | Genetic overlap beyond global genetic correlations. LAVA local correlations and MiXeR-modeled genome-wide genetic overlap for selected disorders schizophrenia (SCZ), Parkinson's disease (PD), migraine (MIG) and genetic generalized epilepsy (GGE). To the left, volcano plots of local genetic correlation coefficients (rho) against -$\log_{10}$ p-values for each pairwise analysis per locus estimated using LAVA[34] (See Supplementary Table 6 for full results). Dots encircled in black represent significantly correlated loci after false discovery rate correction. To the right, Venn diagrams showing the number (in thousands) of shared and disorder-specific variants and the global genetic correlation (r_g) estimated using MiXeR[33] (See Supplementary Fig. 3 and Supplementary Table 5 for full results). The total polygenicity for each disorder represents the estimated number of variants required to explain 90% the SNP-based heritability.

Table 1 | Overview of the GWAS contributing to the study

Phenotypes	Abbreviation	Population prevalence	SNP-heritability (se.)	GWAS loci	Cases/controls	SNPs in dataset	PubMed ID
Psychiatric disorders							
Anorexia nervosa	AN	0.009	0.135 (0.01)	7	16,992/55,525	6,173,547	31308545[43]
Anxiety disorders	ANX	0.20	0.101 (0.007)	2	31,977/82,114	4,757,986	31748690[45]
Attention deficit hyperactivity disorder	ADHD	0.05	0.139 (0.006)	25	38,691/186,843	5,746,721	36702997[42]
Autism spectrum disorder	ASD	0.012	0.122 (0.009)	2	18,381/27,969	6,783,844	30804558[44]
Bipolar disorder	BD	0.02	0.129 (0.005)	57	41,917/371,549	6,449,398	34002096[46]
Major depressive disorder	MDD	0.15	0.068 (0.002)	263	412,305/1,588,397	10,933,226	34045744[47]
Obsessive-compulsive disorder	OCD	0.025	0.293 (0.041)	0	2,699/7,037	7,101,923	28761083[48]
Post-traumatic stress disorder	PTSD	0.30	0.053 (0.009)	2	20,329/124,440	7,281,726	31594949[49]
Schizophrenia	SCZ	0.01	0.211 (0.007)	173	53,386/77,258	6,493,147	35396580[50]
Tourette syndrome	TS	0.008	0.208 (0.024)	1	4,819/9488	6,988,485	30818990[51]
Neurological disorders							
Alzheimer's disease	ALZ	0.05	0.014 (0.008)	33	86,531/676,386	10 670 851	34493870[52]
Amyotrophic lateral sclerosis	ALS	0.0000625	0.016 (0.002)	10	27,205/110,881	8 872 927	34873335[53]
Essential tremor	ET	0.01	0.158 (0.022)	1	3,408/65,772	5 194 059	34982113[54]
Focal epilepsy	FE	0.003	0.029 (0.006)	0	14,939/42,436	4 121 250	medRxiv[62]
Genetic generalized epilepsy	GGE	0.002	0.238 (0.020)	22	6,952/42,436	4 123 711	medRxiv[62]
Lewy body dementia	LBD	0.001	0.061 (0.030)	5	2,591/4,027	6 119 431	33589841[55]
Migraine	MIG	0.16	0.115 (0.007)	35	48,975/540,381	8 484 427	35115687[56]
Multiple sclerosis	MS	0.002	0.126 (0.012)	75	14,802/26,703	6 979 613	31604244[57]
Parkinson's disease	PD	0.005	0.044 (0.004)	52	53,858/846,380	8 955 805	25064009[60], 28892059[59], 31701892[58]
Stroke	Stroke	0.01	0.016 (0.001)	24	73,652/1,234,808	6 372 181	36180795[61]
Comparators							
Cognitive ability	COG	-	0.183 (0.006)	201	269,867	8,002,023	29942086[63]
Cortical surface area	CRT-SA	-	0.383 (0.034)	28	32,877	12,322,316	33875891[64]
Cortical thickness	CRT-TH	-	0.310 (0.025)	26	32,877	12,322,316	33875891[64]
Chronic kidney disease	CKD	0.15	0.016 (0.002)	21	41,395/439,303	7,767,542	31152163[65]
Coronary artery disease	CAD	0.082	0.044 (0.003)	48	71,602/260,875	7,161,097	28714975[66]
Inflammatory Bowel Disease	IBD	0.0054	0.155 (0.015)	117	25,042/34,915	7,969,489	28067908[67]
Type 2 Diabetes	T2D	0.10	0.179 (0.013)	145	74,124/824,006	18,317,551	30297969[68]
Height	Height	-	0.371 (0.017)	1405	4,080,687	1,265,438	36224396[69]

Overview of included GWAS summary datasets on psychiatric disorders, neurological disorders and comparators contributing to the study. The table displays the abbreviations used in Tables and Figures, the reported population prevalence used to estimate SNP-heritability on the liability scale for disorders, the estimated SNP-heritability calculated using LD score regression[70] (observed scale for continuous traits), the total number of genome-wide significant loci after merging any physically overlapping lead SNPs (LD blocks <250 kb apart), the number of cases and controls or participants, the number of SNPs in the GWAS summary statistics and the associated PubMed IDs. Note that for PTSD, the prevalence estimate is based on the reported prevalence after trauma exposure, rather than the prevalence estimate in the whole population[49].

Table 2 | Overview of pleiotropic loci and genes linked to psychiatric or neurological disorders at the genome-wide significant level

	Loci		Genes	
Psychiatric disorders	**Count**	**Fraction (%)**	**Count**	**Fraction (%)**
Total	441		796	
Pleiotropic with				
Psychiatric disorders	60	13.6%	148	18.6%
Neurological disorders	41	9.3%	51	6.4%
Cognitive ability	64	14.5%	136	17.1%
Cortical thickness and surface area	16	3.6%	23	2.9%
Somatic disorders	46	10.4%	72	9.0%
Height	162	36.7%	463	58.2%
Neurological disorders				
Total	227		497	
Pleiotropic with				
Psychiatric disorders	41	18.1%	51	10.3%
Neurological disorders	16	7.0%	16	3.2%
Cognitive ability	19	8.4%	35	7.0%
Cortical thickness and surface area	10	4.4%	19	3.8%
Somatic disorders	53	23.3%	58	11.7%
Height	109	48.0%	256	51.5%

Count and fraction of pleiotropic genome-wide significant loci and genes linked to psychiatric and neurological disorders across the phenotype categories. After identifying genome-wide significant loci, physically overlapping loci were merged into grouped loci. Protein-coding genes were identified using MAGMA[73]. Across all phenotypes, 1,988 grouped loci and 7,829 genes were identified. The extended MHC-region (chr6: 25–37 Mb) was excluded from these analyses. Supplementary Tables 2-3 present the number of overlapping loci and genes for each pair of phenotypes.

Table 3 | Summary of tissue and cell type specificity analyses

	Tissue specific associations	Human brain cell type associations
Neurological disorders		
ALZ	Upregulated in the spleen, terminal ileum of the small intestine and whole blood	Microglia
GGE	-	GABAergic and excitatory neurons
MS	Upregulated in EBV-transformed lymphocytes, the spleen, whole blood and the terminal ileum of the small intestine	Microglia and endothelial cells
PD	Upregulated in the substantia nigra	-
Psychiatric disorders		
ADHD	Upregulated in the cerebral cortex	GABAergic and excitatory neurons
AN	Downregulated in the putamen and hippocampus	-
BD	-	GABAergic and excitatory neurons
MDD	Upregulated in multiple brain tissues	GABAergic neurons and oligodendrocyte progenitor cells
SCZ	Upregulated in multiple brain tissues	GABAergic and excitatory neurons
Comparators		
COG	Upregulated in multiple brain tissues Downregulated in the renal cortex	GABAergic and excitatory neurons
CAD	-	Vascular cells
CRT-SA	-	Oligodendrocytes, astrocytes, stem cells, and microglia
CRT-TH	Upregulated in the cerebellar hemisphere	-
IBD	Upregulated in the spleen and whole blood Downregulated in multiple central nervous tissues	Microglia and endothelial cells
Height	Up- and downregulated in multiple tissues body-wide	Vascular cells, endothelial cells, astrocytes, oligodendrocytes, and microglia
T2D	Downregulated in multiple central nervous tissues	Vascular cells, endothelial cells, astrocytes, oligodendrocytes, and microglia

Summary of tissue and cell type specific analyses using FUMA[72,76], only significant associations after Bonferroni correction are described. Tissue analysis was based on GTEx data[75], while cell type analysis was based on 24 single-cell RNA sequencing data sets from the developing and adult human brain[76]. For full results, see Supplementary Results, Supplementary Figures 4-5, Supplementary Tables 7-8.

Methods

GWAS summary statistics. We collated large-scale GWAS summary statistics based on available sample sizes and the quality of the phenotyping procedures (Table 1; See Supplementary Note for description of each GWAS dataset). All individuals included in the analysis were of European ancestry. Informed consent was obtained from all participants in the respective GWAS. The Regional Committee for Medical Research Ethics – Southeast Norway evaluated the current protocol and found that no additional institutional review board approval was necessary as no individual data were used. All GWAS datasets were derived from existing GWAS except the two datasets on total cortical surface area and average cortical thickness, which were generated from the UK Biobank under accession number 27412, after excluding all individuals with neurological and psychiatric disorders (Supplementary Note). For epilepsy, we chose to include its two main subtypes, focal epilepsy and genetic generalized epilepsy (GGE), rather than including the phenotype 'all epilepsies combined', due to the substantial differences in the genetic risk architectures underlying these two subtypes[62], as emphasized by their differences in estimated SNP-heritability (2.9% vs 23.8%, respectively; Table 1). Before commencing analysis, all GWAS summary statistics underwent uniform quality control and were harmonized and preprocessed into a consistent file structure with a common reference for positions, rsIDs and effect alleles using the v1.6.0 cleansumstats pipeline[86].

Genome-wide significant loci. For each GWAS, we defined independently associated genomic loci using FUMA[72]. First, we identified independent significant SNPs with a genome-wide significant p-value ($5x10^{-8}$) that were independent from each other at $r^2<0.60$. LD r^2 values were obtained from the 1000 Genomes Project European-ancestry haplotype reference panel[87].

The borders of the loci were defined by identifying all candidate SNPs in LD ($r^2 \geq 0.6$) with one of the independent significant SNPs in the locus. All loci less than 250kb apart were merged.

To evaluate locus pleiotropy, we used the procedure previously applied by Watanabe et al. (2019)[22]. After identifying genome-wide significant loci for each phenotype, we grouped any physically overlapping loci across all phenotypes. A grouped locus could therefore contain more than one independent locus for a given phenotype if several loci were combined (i.e., loci *A* and *C* could both overlap with locus *B* but not with each other, but they would be grouped into one locus resulting in a continuous genomic region). Each grouped locus was then assigned to their specific phenotypes and the following categories: psychiatric disorders, neurological disorders, COG, cortical MRI measures (CRT-SA and CRT-TH), somatic diseases and height. We then determined the number and fraction of grouped loci shared across categories and between all pairs of phenotypes. The extended MHC-region (chr6: 25–37 Mb) was excluded from this analysis due to its complex LD structure.

MAGMA gene, gene-property and gene-set analysis. For each GWAS dataset, we identified significantly associated protein-coding genes and gene-sets using MAGMA (v1.08)[73] as implemented in FUMA[72] with default settings, using the SNP-wise mean model and the European 1000 Genomes reference cohort phase 3 as reference panel. The input SNPs were mapped to 20,260 protein-coding genes, excluding the extended MHC-region (chr6: 25–37 Mb). Gene boundaries were expanded to 35 kb upstream and 10 kb downstream to include probable regulatory regions outside the transcribed region[88]. Genes were considered significant if the p-value was less than 0.05 after Bonferroni correction for the number of tested genes ($0.05/20{,}260 = 2.47 \times 10^{-6}$). MAGMA calculates an association p-value for each gene based on the aggregate of all SNPs mapped to each gene, accounting for gene-size, number of SNPs in a gene and LD between markers. We then carried out competitive gene-set analysis based on the

identified genes in each phenotype. Specifically, we focused on the Gene Ontology gene set terms: biological processes (7,350 gene sets), cellular components (1,001 gene sets) and molecular functions (1,645 gene sets) obtained from MsigDB version 7.0[89]. Gene sets were considered significant if the p-value was <0.05 after Bonferroni correction for the number of tested gene sets in each category ($0.05/7{,}350 = 6{,}80\text{x}10^{-6}$, $0.05/1{,}001 = 5{,}00\text{x}10^{-5}$, $0.05/1{,}645 = 3.04\text{x}10^{-5}$, respectively).

Based on the gene-based results above, we carried out tissue specific expression analysis in 54 adult tissue types based on RNA sequencing data GTEx v.8[75] implemented in FUMA[72]. Tissues were considered significant if the *P* value was less than 0.05 after Bonferroni correction for 54 tissues. For cell type specificity analysis, we tested for enrichment in 24 single-cell RNA sequencing data sets from the developing and adult human brain available in FUMA using MAGMA gene-property analysis[76]. The specific datasets were: Allen_Human_LGN_level1[90], Allen_Human_LGN_level2[90], Allen_Human_MTG_level1[90], Allen_Human_MTG_level2[90], DroNc_Human_Hippocampus[91], GSE104276_Human_Prefrontal_cortex_all_ages[92], GSE104276_Human_Prefrontal_cortex_per_ages[92], GSE67835_Human_Cortex[93], Linnarsson_GSE101601_Human_Temporal_cortex[94], Linnarsson_GSE76381_Human_Midbrain[95], PsychENCODE_Developmental[96] PsychENCODE_Adult[96], and GSE168408_Human_Prefrontal_Cortex datasets from level 1 to 2, spanning six developmental stages: fetal, neonatal, infancy, childhood, adolescence and adult[97]. In the cell type specific analysis, systematic stepwise conditional analysis was performed within datasets to ensure that complex batch effects did not lead to false positives, as well as Bonferroni correction for multiple testing of 379 cell types ($0.05/379 = 1.30\text{x}10^{-4}$).

All statistical tests conducted using MAGMA were one sided. We did not perform additional correction for multiple testing across the 28 phenotypes, since the aim of analysis was not to determine which of the phenotypes a specific gene, gene-set, tissue or cell type was

associated with, but to explore group level patterns of shared associations across the phenotypes.

SNP-heritability and global genetic correlations. Using LDSC[70], we estimated the SNP-based heritability in the liability scale for each disorder, using reported population prevalence estimates (Table 1), and the SNP-based heritability on the observed scale for the continuous traits. LDSC distinguishes confounding from polygenicity by regressing the association statistics of SNPs on their LD scores[70]. All analyses were based on HapMap 3 SNPs only, with the MHC region (chr6: 25–34 Mb) excluded. Precalculated LD scores from the European 1000 Genomes reference cohort were used (https://data.broadinstitute.org/alkesgroup/LDSCORE/eur_w_ld_chr.tar.bz2). Additionally, we used the bivariate extension of LDSC[24] to estimate the global genetic correlations, i.e. the covariance in the SNP-heritability, between all pairs of phenotypes. Adjusting for the number of traits tested, we applied both the FDR method of Benjamini-Yekutieli[98] given the dependence between the tests and Bonferroni-correction.

Univariate and bivariate MiXeR analysis. We first applied univariate MiXeR[71] analysis to each GWAS summary dataset to estimate the proportion of causally associated genetic variants from a reference panel (the polygenicity) and the variance of effect size per causal variant (the discoverability) using maximum likelihood estimation, and the GWAS sample size necessary to discover genetic variants that explain 90% of SNP-heritability of each phenotype. We applied a threshold of 90% SNP-heritability to avoid extrapolating model parameters into variants with infinitesimally small effects. MiXeR is based on a Gaussian mixture model, assuming that a given GWAS summary dataset can be modeled as a "mixture" of pre-defined components with causal and non-causal variants, each with its own Gaussian (normal) distribution. MiXeR

incorporates the effects of LD structure, minor allele frequency, GWAS sample size, genomic inflation due to cryptic relatedness, and sample overlap (in the bivariate extension). Before analysis, the MHC region was excluded from all GWAS, while the chromosome 19 was in addition excluded from ALZ due to the strong effects of the *APOE* region[52] and complicated LD that biases the estimates of polygenicity.

Informed by the model parameters from univariate MiXeR for each phenotype, MiXeR constructs a bivariate mixture model for pairs of phenotypes, in which a mixture of four bivariate Gaussian components is modeled: variants influencing one phenotype only, variants influencing both phenotypes, and variants that are not associated with either phenotype. Bivariate MiXeR estimates the polygenicity of the shared component irrespective of effect directions and correlation of effect sizes. Additionally, MiXeR estimates the genetic correlation of shared variants, and the global genetic correlation. Model fit is evaluated by calculating the difference between the Akaike information criterion (AIC) for best-fitting MiXeR estimates and reference models. Positive AIC differences are interpreted as evidence that the best-fitting MiXeR estimates are distinguishable from the reference model. For univariate MiXeR, an "infinitesimal model" in which all variants are assumed to be 'causal' is used as the reference. For bivariate MiXeR, AIC differences are calculated by comparing the best-fitting model to minimum possible overlap, constrained by r_g, and maximum possible overlap, constrained by the polygenicity of the least polygenic trait. We provide conditional Q-Q plots and log-likelihood plots to visualize the stability of the fitness procedure.

Estimating local genetic correlations using LAVA. For all pairs of phenotypes, we applied LAVA (v1.3.8) to estimate local genetic correlations across 2,495 semi-independent genetic loci of approximately equal size (~1 Mb). LAVA accounts for potential sample overlap using LDSC[70]. After computing local SNP-heritability estimates for each phenotype, we conducted

pairwise local genetic correlation analysis for all loci with local SNP-heritability significantly different from zero. We applied FDR correction to account for multiple comparisons. The statistical tests conducted were all two sided.

Code availability

Cleansumstats pipeline (https://github.com/BioPsyk/cleansumstats)

FUMA (https://fuma.ctglab.nl/)

LAVA (https://github.com/josefin-werme/LAVA)

LDSC (https://github.com/bulik/ldsc)

MAGMA (https://ctg.cncr.nl/software/magma)

MiXeR (https://github.com/precimed/mixer)

PLINK (https://www.cog-genomics.org/plink/2.0/)

Regenie (https://rgcgithub.github.io/regenie)

Data availability

All data are publicly available or available on request.

References

22. Watanabe, K. *et al.* A global overview of pleiotropy and genetic architecture in complex traits. *Nat Genet* **51**, 1339-1348 (2019).
24. Bulik-Sullivan, B. *et al.* An atlas of genetic correlations across human diseases and traits. *Nat Genet* **47**, 1236-41 (2015).
33. Frei, O. *et al.* Bivariate causal mixture model quantifies polygenic overlap between complex traits beyond genetic correlation. *Nat Commun* **10**, 2417 (2019).
34. Werme, J., van der Sluis, S., Posthuma, D. & de Leeuw, C.A. An integrated framework for local genetic correlation analysis. *Nat Genet* **54**, 274-282 (2022).
42. Demontis, D. *et al.* Genome-wide analyses of ADHD identify 27 risk loci, refine the genetic architecture and implicate several cognitive domains. *Nat Genet* (2023).
43. Watson, H.J. *et al.* Genome-wide association study identifies eight risk loci and implicates metabo-psychiatric origins for anorexia nervosa. *Nat Genet* **51**, 1207-1214 (2019).
44. Grove, J. *et al.* Identification of common genetic risk variants for autism spectrum disorder. *Nat Genet* **51**, 431-444 (2019).
45. Purves, K.L. *et al.* A major role for common genetic variation in anxiety disorders. *Mol Psychiatry* **25**, 3292-3303 (2020).
46. Mullins, N. *et al.* Genome-wide association study of more than 40,000 bipolar disorder cases provides new insights into the underlying biology. *Nat Genet* **53**, 817-829 (2021).
47. Levey, D.F. *et al.* Bi-ancestral depression GWAS in the Million Veteran Program and meta-analysis in >1.2 million individuals highlight new therapeutic directions. *Nat Neurosci* **24**, 954-963 (2021).
48. International Obsessive Compulsive Disorder Foundation Genetics, C. & Studies, O.C.D.C.G.A. Revealing the complex genetic architecture of obsessive-compulsive disorder using meta-analysis. *Mol Psychiatry* **23**, 1181-1188 (2018).
49. Nievergelt, C.M. *et al.* International meta-analysis of PTSD genome-wide association studies identifies sex- and ancestry-specific genetic risk loci. *Nat Commun* **10**, 4558 (2019).
50. Trubetskoy, V. *et al.* Mapping genomic loci implicates genes and synaptic biology in schizophrenia. *Nature* **604**, 502-508 (2022).
51. Yu, D. *et al.* Interrogating the Genetic Determinants of Tourette's Syndrome and Other Tic Disorders Through Genome-Wide Association Studies. *Am J Psychiatry* **176**, 217-227 (2019).
52. Wightman, D.P. *et al.* A genome-wide association study with 1,126,563 individuals identifies new risk loci for Alzheimer's disease. *Nat Genet* **53**, 1276-1282 (2021).
53. van Rheenen, W. *et al.* Common and rare variant association analyses in amyotrophic lateral sclerosis identify 15 risk loci with distinct genetic architectures and neuron-specific biology. *Nat Genet* **53**, 1636-1648 (2021).
54. Liao, C. *et al.* Association of Essential Tremor With Novel Risk Loci: A Genome-Wide Association Study and Meta-analysis. *JAMA Neurol* **79**, 185-193 (2022).
55. Chia, R. *et al.* Genome sequencing analysis identifies new loci associated with Lewy body dementia and provides insights into its genetic architecture. *Nat Genet* **53**, 294-303 (2021).
56. Hautakangas, H. *et al.* Genome-wide analysis of 102,084 migraine cases identifies 123 risk loci and subtype-specific risk alleles. *Nat Genet* **54**, 152-160 (2022).
57. International Multiple Sclerosis Genetics, C. Multiple sclerosis genomic map implicates peripheral immune cells and microglia in susceptibility. *Science* **365**(2019).

58. Nalls, M.A. *et al.* Identification of novel risk loci, causal insights, and heritable risk for Parkinson's disease: a meta-analysis of genome-wide association studies. *Lancet Neurol* **18**, 1091-1102 (2019).
59. Chang, D. *et al.* A meta-analysis of genome-wide association studies identifies 17 new Parkinson's disease risk loci. *Nat Genet* **49**, 1511-1516 (2017).
60. Nalls, M.A. *et al.* Large-scale meta-analysis of genome-wide association data identifies six new risk loci for Parkinson's disease. *Nat Genet* **46**, 989-93 (2014).
61. Mishra, A. *et al.* Stroke genetics informs drug discovery and risk prediction across ancestries. *Nature* **611**, 115-123 (2022).
62. Berkovic, S.F., Cavalleri, G.L. & Koeleman, B.P.C. Genome-wide meta-analysis of over 29,000 people with epilepsy reveals 26 loci and subtype-specific genetic architecture. *medRxiv*, 2022.06.08.22276120 (2022).
63. Savage, J.E. *et al.* Genome-wide association meta-analysis in 269,867 individuals identifies new genetic and functional links to intelligence. *Nat Genet* **50**, 912-919 (2018).
64. Smith, S.M. *et al.* An expanded set of genome-wide association studies of brain imaging phenotypes in UK Biobank. *Nat Neurosci* **24**, 737-745 (2021).
65. Wuttke, M. *et al.* A catalog of genetic loci associated with kidney function from analyses of a million individuals. *Nat Genet* **51**, 957-972 (2019).
66. Nelson, C.P. *et al.* Association analyses based on false discovery rate implicate new loci for coronary artery disease. *Nat Genet* **49**, 1385-1391 (2017).
67. de Lange, K.M. *et al.* Genome-wide association study implicates immune activation of multiple integrin genes in inflammatory bowel disease. *Nat Genet* **49**, 256-261 (2017).
68. Mahajan, A. *et al.* Fine-mapping type 2 diabetes loci to single-variant resolution using high-density imputation and islet-specific epigenome maps. *Nat Genet* **50**, 1505-1513 (2018).
69. Yengo, L. *et al.* A saturated map of common genetic variants associated with human height. *Nature* **610**, 704-712 (2022).
70. Bulik-Sullivan, B.K. *et al.* LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nat Genet* **47**, 291-5 (2015).
71. Holland, D. *et al.* Beyond SNP heritability: Polygenicity and discoverability of phenotypes estimated with a univariate Gaussian mixture model. *PLoS Genet* **16**, e1008612 (2020).
72. Watanabe, K., Taskesen, E., van Bochoven, A. & Posthuma, D. Functional mapping and annotation of genetic associations with FUMA. *Nat Commun* **8**, 1826 (2017).
73. de Leeuw, C.A., Mooij, J.M., Heskes, T. & Posthuma, D. MAGMA: generalized gene-set analysis of GWAS data. *PLoS Comput Biol* **11**, e1004219 (2015).
75. The GTEx Consortium. The Genotype-Tissue Expression (GTEx) project. *Nat Genet* **45**, 580-5 (2013).
76. Watanabe, K., Umicevic Mirkov, M., de Leeuw, C.A., van den Heuvel, M.P. & Posthuma, D. Genetic mapping of cell type specificity for complex traits. *Nat Commun* **10**, 3222 (2019).
86. Gadin, J.R., Zetterberg, R., Meijsen, J. & Schork, A.J. Cleansumstats: Converting GWAS sumstats to a common format to facilitate downstream applications. (Zenodo, 2023).
87. The 1000 Genomes Project Consortium. A global reference for human genetic variation. *Nature* **526**, 68-74 (2015).
88. Maston, G.A., Evans, S.K. & Green, M.R. Transcriptional regulatory elements in the human genome. *Annu Rev Genomics Hum Genet* **7**, 29-59 (2006).

89. Liberzon, A. *et al.* Molecular signatures database (MSigDB) 3.0. *Bioinformatics* **27**, 1739-40 (2011).
90. Hodge, R.D. *et al.* Conserved cell types with divergent features in human versus mouse cortex. *Nature* **573**, 61-68 (2019).
91. Habib, N. *et al.* Massively parallel single-nucleus RNA-seq with DroNc-seq. *Nat Methods* **14**, 955-958 (2017).
92. Zhong, S. *et al.* A single-cell RNA-seq survey of the developmental landscape of the human prefrontal cortex. *Nature* **555**, 524-528 (2018).
93. Darmanis, S. *et al.* A survey of human brain transcriptome diversity at the single cell level. *Proc Natl Acad Sci U S A* **112**, 7285-90 (2015).
94. Hochgerner, H. *et al.* STRT-seq-2i: dual-index 5' single cell and nucleus RNA-seq on an addressable microwell array. *Sci Rep* **7**, 16327 (2017).
95. La Manno, G. *et al.* Molecular Diversity of Midbrain Development in Mouse, Human, and Stem Cells. *Cell* **167**, 566-580 e19 (2016).
96. Wang, D. *et al.* Comprehensive functional genomic resource and integrative model for the human brain. *Science* **362**(2018).
97. Herring, C.A. *et al.* Human prefrontal cortex gene regulatory dynamics from gestation to adulthood at single-cell resolution. *Cell* **185**, 4428-4447 e28 (2022).
98. Benjamini, Y. & Yekutieli, D. The control of the false discovery rate in multiple testing under dependency. *The Annals of Statistics* **29**, 1165-1188 (2001).