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Transcriptome-informed brain cartography of polygenic risk and association with brain structure in major psychiatric disorders

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Psychiatric disorders are complex, polygenic conditions characterized by patterned structural brain alterations. Whether these changes reflect transcriptional dysregulation driven by genetic risk remains unclear. We introduce a novel imaging-transcriptomics framework that integrates transcriptome-wide association studies (TWAS) with brain transcriptomic atlases to predict macroscale structural brain abnormalities across seven disorders: attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), anorexia nervosa (AN), bipolar disorder (BD), major depressive disorder (MDD), obsessive-compulsive disorder (OCD), and schizophrenia (SCZ). We generated disorder-related Gene Expression-based Disorder Associated Risk (GEDAR) maps and assessed their spatial correlation with observed brain alterations thereby establishing a structured approach to map polygenic transcriptional risk onto macroscale brain phenotypes. We found significant transcriptomic-anatomical correlations in MDD (cortical and subcortical), SCZ (subcortical), and ADHD (subcortical), indicating that regional transcriptional vulnerability might contribute to varying extents to the anatomical expression of genetic risk in these disorders. Pathway enrichment analysis on genetically predicted differentially expressed genes for those disorders where we found spatial correlations between GEDAR maps and observed structural changes revealed immune-related processes as dominant in MDD and SCZ, and neurodevelopmental pathways in ADHD. Importantly, spatial transcriptomic-anatomical alignment did not scale with between-disorder differences in heritability, pointing instead toward additional influences like developmental timing or environmental interactions. These findings underscore the potential and limitations of imaging transcriptomics as a framework for bridging the gap between genetic architecture and systems-level brain changes in psychiatric disorders.

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INTRODUCTION

Psychiatric disorders are complex brain conditions with multifactorial aetiologies, arising from the interplay between genetic, environmental, and neurodevelopmental factors [1]. Traditional research approaches have often examined either genetic susceptibility or neuroanatomical alterations in isolation. However, growing evidence suggests that integrating these levels of analysis could yield deeper insights into the biological mechanisms underlying psychiatric conditions [2–5].

Genome-wide association studies (GWAS) have advanced our understanding of the genetic architecture of mental illness by identifying hundreds of risk loci across disorders. The Psychiatric Genomics Consortium (PGC), established in 2007, has been instrumental in these efforts. Aggregating data from over 400,000 individuals across 36 countries [6], these studies have unravelled the highly polygenic nature of psychiatric disorders by showing that many common variants of small effect contribute to overall liability. At the same time, neuroimaging techniques have emerged as powerful tools to investigate brain structure and function in mental illness, informing new system-level models of pathology grounded on brain biology. Large-scale efforts such as the ENIGMA (Enhancing NeuroImaging Genetics through Meta-Analysis) consortium have enabled harmonized analyses of magnetic resonance imaging (MRI) data across thousands of participants, revealing reproducible patterns of structural brain alterations in various psychiatric conditions [7, 8]. These patterns include both disorder-specific and transdiagnostic differences, which are not randomly distributed across the brain but instead suggest regional variation in vulnerability—potentially shaped by intrinsic biological properties [9, 10].

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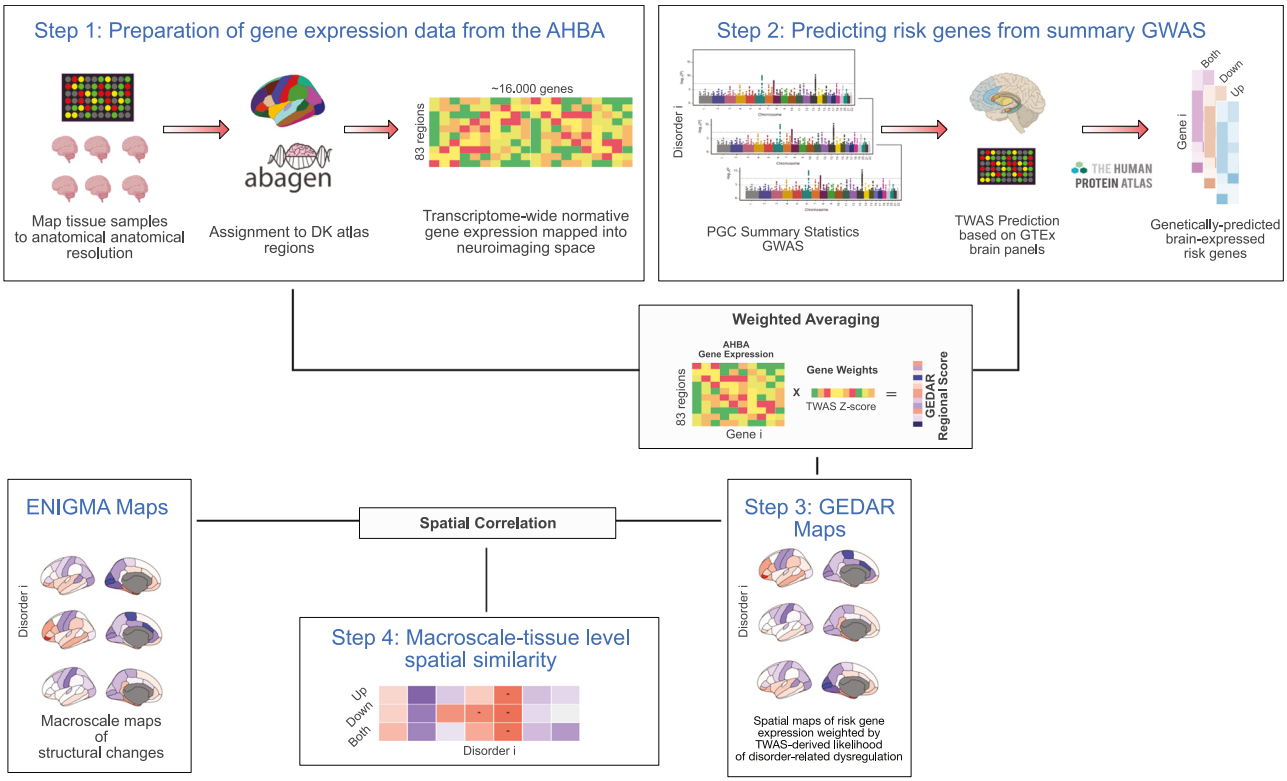

Fig. 1 Step-by-step multimodal integration workflow combining genetic, transcriptomic, and neuroimaging data. Step 1: transcriptomic data from the Allen Human Brain Atlas (AHBA) are mapped onto cortical regions defined by the Desikan-Killiany (DK) atlas using the *abagen* toolbox, generating region-specific gene expression profiles. Step 2: transcriptome-wide association studies (TWAS) are performed using the *S-MultiXcan* method, leveraging genome-wide association study (GWAS) summary statistics from the Psychiatric Genomics Consortium (PGC) and predictive models trained on expression data from 11 brain regions in the Genotype-Tissue expression (GTEx) database. Genes are filtered to retain only those expressed in brain tissue, according to the Human Protein Atlas. Regional gene expression profiles from the AHBA are weighted by TWAS derived gene weights from either up- or down-regulated genes or both. The resulting genetically predicted gene-expression differences are spatially mapped onto cortical regions (Step 3) using the Gene Expression-based Disorder-Associated Risk (GEDAR) approach, generating disorder-related cortical expression maps. Finally, these GEDAR-derived expression maps are compared with structural neuroimaging data from the ENIGMA consortium, linking molecular genetic risk factors to observed macroscale structural brain alterations in psychiatric disorders (Step 4).

Neuroimaging phenotypes have been increasingly conceptualized as intermediate markers on the path from genes to behaviour [11]. Imaging genetics, a discipline that integrates genomic and neuroimaging data, has uncovered biological pathways linking genetic risk to brain phenotypes [12]. A central assumption of this field is that dysregulated molecular processes —e.g., altered gene expression or protein function—translate into macroscale changes in brain structure and function. These changes, in turn, underlie the behavioural and clinical features of psychiatric disorders [13]. Yet, whether the patterned imaging phenotypes documented in patient groups can be predicted directly from the spatial distribution of genetically-encoded risk gene expression profiles remain an open empirical question.

A potentially informative way to address this question would be to ask whether regional brain changes observed in large-scale neuroimaging studies, such as those from ENIGMA, can be spatially predicted using knowledge about the genetically influenced gene expression and the constitutive molecular architecture of the human brain. The availability of the Allen Human Brain Atlas (AHBA) [14] – the most comprehensive resource of spatial gene expression in the human brain – now offers this possibility [2]. Imaging transcriptomics is an emergent line of research which investigates whether patterns of brain changes align spatially with regional gene expression, thereby linking molecular and systems-level pathology. Exploratory studies have shown that genes whose spatial expression correlates with brain alterations in disorders such as schizophrenia [3, 15], major depressive disorder [16], and autism [15] are often enriched for known disorder-related genetic risk, suggesting that regional brain vulnerability may be rooted in the local molecular landscape [17]. However, the field is still missing a structured framework to integrate GWAS summary statistics, transcriptomic prediction, and neuroimaging phenotypes to probe the genetic risk–mRNA transcription–brain anatomy–disorder axis continuum. Studying several disorders in parallel offers a unique opportunity to achieve the later goal given the wide variation in genetic and environmental contributions across conditions. For example, schizophrenia and attention-deficit/hyperactivity disorder (ADHD) exhibit high heritability (~75–80%), while disorders such as major depressive disorder (MDD) show more moderate estimates (~35–45%), implying a larger role for environmental factors [18]. This variability implies that that the degree to which brain changes can be predicted from genetically regulated gene expression dysregulation could scale with a disorder's heritability, but this remains largely untested.

In this study, we sought to address this gap by introducing and testing a cross-disciplinary framework combining bioinformatics, statistical genetics, and neuroimaging methods to investigate whether regional patterns of brain structural change can be predicted from polygenic risk-informed gene expression signatures (Fig. 1). We first applied S-MultiXcan [19] to GWAS summary statistics to perform transcriptome-wide association studies (TWAS), identifying genes whose expression levels are genetically predicted to be dysregulated in relation to seven major psychiatric disorders:

Table 1. Summary of the sample sizes in the Genome Wide Association Studies (GWAS) from the Psychiatric Genomic Consortium (PGC) used in our analysis (sample size and publication reference).

Disorder	Sample size (HC)	Sample size (Patients)	Reference
ADHD	186,843	38,691	Demontis et al. [68]
ASD	27,969	18,381	Grove et al. [69]
AN	55,525	16,992	Watson et al. [70]
BD	371,539	41,917	Mullins et al. [71]
MDD	902, 757	88,316	Meng et al. [72]
OCD	7037	2688	IOCD and OCGAS [73]
SCZ	35,362	22,778	Lam et al. [74]

ADHD, autism spectrum disorder (ASD), anorexia nervosa (AN), bipolar disorder (BD), MDD, obsessive–compulsive disorder (OCD), and schizophrenia (SCZ). The resulting TWAS-derived estimates of genetically inferred disorder-related gene expression were then integrated with spatial transcriptomic data from AHBA to generate Gene Expression–based Disorder-Associated Risk (GEDAR) maps. These maps characterize how patterns of genetically predicted transcriptional dysregulation linked to each disorder's polygenic architecture are distributed across cortical and subcortical regions of the adult human brain. We then compared GEDAR maps with regional cortical thickness and subcortical volume differences from ENIGMA case–control meta-analyses to assess the spatial correspondence between genetically inferred transcriptional vulnerability and observed brain structural alterations. Finally, we examined whether the strength of these transcriptomic–anatomical associations varied systematically with heritability estimates from twin studies and conducted pathway enrichment analyses to identify the biological processes associated with disorders showing significant GEDAR–ENIGMA alignment.

METHODS

In Fig. 1, we provide an overview of the integrative workflow and datasets used in this study. The analytical pipeline combines genetic, transcriptomic, and neuroimaging resources in a stepwise manner to map the spatial correspondence between genetically predicted gene-expression patterns and brain structural alterations across major psychiatric disorders. Below, we describe each component of the workflow in detail, including the genomic datasets, transcriptomic prediction procedures, spatial mapping and correlation analyses, and downstream pathway enrichment steps.

Psychiatric GWAS datasets

We obtained publicly available GWAS summary statistics from the PGC for seven psychiatric disorders: ADHD, ASD, AN, BD, MDD, OCD, and SCZ. Details on sample size, ancestry composition, and imputation procedures are available in the corresponding PGC publications listed in Table 1.

TWAS and gene expression prediction

At first, we developed a spatial model of brain structural variation by mapping polygenic risk to genes using H-MAGMA [20], integrating gene expression data, and correlating dysregulation scores with psychiatric disorder-related cortical and subcortical abnormalities from ENIGMA (for more information see Supplementary Material). This resulted in a list of prioritised genes based on predicted cumulative risk of dysregulation, with no information of change whether genes are down-regulated or up-regulated. Direction of regulation might be an important factor in explaining regional variation in brain structural changes, since upregulated genes could be protective and down-regulated pathological (or vice-versa) leading potential downstream effects on brain structure to be cancelled out. Since direction was a feature we wanted to account for, we turned to TWAS [21] performed using the S-MultiXcan framework to estimate genetically predicted gene expression levels from GWAS summary statistics [19]. S-MultiXcan models trained on the 11 brain tissue panels from the Genotype-Tissue Expression (GTEx) dataset v8 [22] were used to generate gene-level Z-scores representing up- or down-regulation across tissues. S-MultiXcan takes S-PrediXcan Z-scores (or betas) for each gene across multiple tissues and applies a multivariate regression that accounts for cross-tissue correlation, resulting in expression association statistics that reflect the joint association signal across tissues. This was the ideal approach for our study, due to incomplete correspondence between GTEx tissues and regions of the parcellations used in the study (i.e., Desikan-Killiany for cortical regions and aseg for subcortical regions). This strategy also ensured uniform application of gene expression predictions across the entire cortical and subcortical atlas.

Gene expression and GEDAR calculation

Regional microarray expression data were obtained from 6 post-mortem brains (17% female, ages 24.0–57.0, mean 42.50 ± 13.38) provided by the AHBA[14]. Regional data were processed with the *abagen* toolbox (version 0.1.3; https://github.com/rmarkello/abagen) [23] using the Desikan-Killiany (DK) atlas for cortical regions and the aseg atlas for subcortical regions [24, 25]. The obtained regional expression matrix comprised 83 rows, corresponding to brain regions (cortical and subcortical), and 15,633 columns, corresponding to the retained genes after filtering out genes with below background expression signal. To increase specificity to genes expressed in the brain, the resulting genes were filtered by the genes identified in the Human Protein Atlas (HPA) [26] as expressed (i.e., genes that have an expression above cut-off of 1 normalised transcript per million (nTPM).

The Gene Expression-based Disorder Associated Risk (GEDAR) score for region j was calculated using the following formula:

$$GEDAR_j = \sum_i w_i \cdot Ge_{i,j}$$

Where w_i indicates the weight for gene i as expressed by the predicted TWAS Z-score, and $Ge_{i,j}$ the gene expression for region j and gene i as expressed by the AHBA. We first analysed the effect of genetic-risk informed TWAS associated signals by using the sign of the Z-score as proxy for the gene directionality (i.e., adding the weighted effect of positive Z-scores and removing the effects of negative Z-scores). Furthermore, to evaluate the effects of gene directionality, we applied two additional weighting schemes where we consider separately *up-* and *down-regulated* TWAS association signals. Importantly, the definition of *up-* and *down-regulation* is based solely from TWAS Z-score. In the up-regulated scheme, we included only genes with positive TWAS Z-scores, while the down-regulated scheme included genes with negative Z-scores only. The AHBA data provided the spatial distribution of expression across regions but did not determine regulation direction. Likewise, GTEx tissue models were used for transcriptome prediction, not for classification of up- or down-regulation. We then calculated the GEDAR brain maps for all disorders and weighting schemes using three arbitrary thresholds (top 1, 5, and 10%) of the TWAS-predicted differentially regulated genes, ranked according to FDR-corrected TWAS p-value. Lower thresholds also commonly used in the calculation of polygenic risk scores (e.g., 0.1 and 0.5%) [27] were not used in this study as we noticed that they would result mostly in the selection of only a few single genes, which would be equivalent to a single candidate and not a polygenic gene approach. GEDAR scores were calculated independently for each region of the DK atlas and aseg atlas for subcortical regions to match the regions of the ENIGMA parcellation, thus obtaining a cortical and a subcortical GEDAR brain map for each investigated disorder. We additionally investigate the specificity of the resulting significant genes by exploring the similarity across disorders of TWAS-predicted genes in terms of Jaccard's similarity index.

Table 2. Summary of ENIGMA's cortical thickness and subcortical volume data used for the study.

Feature	Disorder	Sample size (HC)	Sample size (Patients)	Age (yrs)	Sex (F)	Reference
Thickness	ADHD	1934	2246	19.22 ± 11.31	25.9%	Hoogman et al. [75]
	ASD	1651	1571	15.62 ± 8.52	19%	Van Rooij et al. [76]
	AN	963	685	21	100%	Walton et al. [77]
	BD	4056	2447	-	-	Hibar et al. [78]
	MDD	7957	2148	-	-	Schmaal et al. [79]
	OCD	1436	1498	-	-	Boedhoe et al. [80]
	SCZ	5098	4474	HC: 32.8 Patients: 32.3	HC: 47% Patients: 44%	Van Erp et al. [81]
Subcortical volumes	ADHD	1529	1713	18.6 ± 11.81	34%	Hoogman et al [43]
	ASD	1651	1571	15.62 ± 8.52	19%	Van Rooij et al. [76]
	AN	963	685	21	100%	Walton et al. [77]
	BD	2594	1710	-	56%	Hibar et al. [82]
	MDD	7199	1728	-	-	Schmaal et al. [83]
	OCD	1472	1495	-	-	Boedhoe et al. [84]
	SCZ	2540	2028	31 HC 34 Patients	48% HC 31% Patients	Van Erp et al. [85]

We provide summary data on the sample sizes, mean age and proportion of female participants, discriminating between groups where data was available.
ADHD attention deficit and hyperactivity disorder, *ASD* autism spectrum disorder, *AN* anorexia nervosa, *BD* bipolar disorder, *MDD* major depressive disorder, *OCD* obsessive-compulsive disorder and *SCZ* Schizophrenia.
Fields where data were not reported in the original publication are indicated as "-" in the table.

ENIGMA structural brain changes reference maps

We used disorder-specific structural brain maps from the ENIGMA consortium, based on large-scale case–control meta-analyses of MRI data. Briefly, cortical thickness and subcortical volumes (caudate, putamen, pallidum, nucleus accumbens, thalamus, hippocampus, amygdala and lateral ventricles) were extracted using FreeSurfer (http://surfer.nmr.mgh.harvard.edu) from high-resolution T1-weighted MRI brain scans. FreeSurfer segments and parcellates the cortical surface to provide precise measurements across predefined regions of interest (ROIs) based on the DK atlas. For each disorder, we extracted regional meta-analytical Cohen's *d* effect sizes for cortical thickness and subcortical volumes. These ENIGMA-derived maps served as the neuroimaging reference phenotype for testing GEDAR–brain alignment. Although both cortical thickness and surface area are standardly inspected as outcome metrics by ENIGMA studies, we decided to focus on thickness only as this metric has been shown to present higher regional heritability (thickness: 0.20 – 0.76 vs surface area: 0.03 – 0.75), which means its variation is under stronger genetic control. This would therefore offer larger statistical power to test our hypotheses while keeping the need for multiple testing correction at the necessary minimum [28]. Details on the samples used in each ENIGMA study and respective sources are summarized in Table 2.

Spatial correlation analysis

We calculated Spearman rank correlations between regional GEDAR scores and ENIGMA Cohen's *d* values for each disorder, separating between cortical and subcortical regions. To account for spatial autocorrelation in cortical data, we applied a spherical spin permutation method (n = 1000 rotations) using the *neuromaps* toolbox (https://github.com/netneurolab/neuromaps) [29] - Vasa method [30]. Subcortical correlations were tested using standard permutation due to lack of surface geometry. Results were considered significant at $p_{spin} < 0.05$. This approach provides family-wise error–controlled p_{spin} values and is widely used in imaging–transcriptomic analyses to minimize false positives arising from spatial dependence. Because each spin test already accounts for spatial structure, additional multiple-comparison correction across disorders, thresholds, and directionality schemes was not applied to avoid excessive type II error. Instead, effect sizes (Spearman's ρ) and corresponding p_{spin} values for all analyses are reported in Supplementary Tables, and false discovery rate (FDR) correction was applied across thresholds within each disorder.

Meta-analytical estimates of differentially expressed genes in post-mortem brain samples

We performed an additional analysis comparing GEDAR brain maps calculated from differentially expressed genes in post-mortem brain samples reported in the literature by Sadeghi et al. [31]. We used the same procedure as previously described for projecting the genes on all regions using the reported effect sizes as weights. The analysis was performed to assess whether genes predicted from TWAS on brain specific tissue models would yield different results from differentially expressed genes identified experimentally from a well-powered meta-analysis of transcriptomic studies in post-mortem brain samples. This additional analysis could not be performed on all disorders investigated here but only on a subset (ASD, BD, MDD and SCZ) as data for the other disorders were not included in the original meta-analytical work from Sadeghi et al. [31]. For the correlation analysis, we used the same procedure described above.

Heritability in twin-studies

We compiled data on heritability estimates from twin studies for the seven psychiatric disorders included in this study to contextualize the extent of genetic influence across conditions. A summary of these data and respective sources are presented in Table 3. We decided to rely on heritability estimates from twin studies instead of SNP-estimated heritability to avoid circularity as we used GWAS summary statistics to run our TWAS analyses. Moreover, SNP-based estimates are influenced by sample size variability across GWAS datasets and capture only common variant effects, potentially introducing bias and confounding the interpretation of cross-disorder comparisons due to differences in power and the extent of "missing heritability." These twin-based heritability values thus provide a more robust reference framework for interpreting the observed variation in the correspondence between genetically predicted transcriptomic risk (GEDAR) and regional brain structural alterations. Specifically, we explored whether disorders with higher heritability show stronger spatial alignment between gene

expression-based risk maps and neuroimaging phenotypes. To do so, we computed Spearman correlation coefficients between heritability estimates and GEDAR–ENIGMA correlation values across the seven psychiatric disorders. For each disorder, we used the midpoint of the reported heritability range from twin studies as a summary measure. This analysis was performed separately for each combination of gene regulation scheme (negative, positive, both), inclusion threshold (top 1, 5, and 10% of genes), and brain compartment (cortical or subcortical). Spearman correlations and associated *p*-values were computed using the *scipy.stats.spearmanr* function in Python.

Pathway enrichment analysis

To explore the biological significance of genes included in each GEDAR map estimation (i.e., TWAS identified genes) for which we found significant association with observed structural changes (by disorder, direction, and threshold), we conducted gene ontology (GO) and pathway enrichment analysis using the ToppGene Suite (https://toppgene.cchmc.org/). We focused on Gene Ontology (GO) Biological Processes (GO:BP), Molecular Function (GO:MF) and Cellular Component (GO:CC). Functional enrichment analysis was performed using the g:Profiler g:GOSt online tool (version e112_eg59_p19_87fff33f, accessed on January 31, 2025), an online tool for functional profiling of gene lists [32]. To account for multiple testing, we applied the g:SCS (Set Counts and Sizes) threshold as implemented by the g:GOSt tool (Reimand et al., 2007). Pathways with a false discovery rate (FDR)–corrected $p < 0.05$ were considered as significantly enriched.

Table 3. Twin-based heritability estimates for seven psychiatric disorders.

Disorder	Twin-based Heritability Estimate (h^2)	Reference
ASD	70–90%	Tick et al., [86]
SCZ	75–80%	Hilker et al., [87]
ADHD	70–80%	Faraone & Larsson, [88]
BD	60–85%	McGuffin et al., [89]
AN	50–60%	Yilmaz et al., [90]
OCD	45–60%	van Grootheest et al., [91]
MDD	35–45%	Sullivan et al., [92]

Heritability estimates (h^2) represent the proportion of variance in liability explained by genetic factors, as determined by twin studies. Estimates are presented alongside references to the original source studies.
ADHD attention deficit and hyperactivity disorder, *ASD* autism spectrum disorder, *AN* anorexia nervosa, *BD* bipolar disorder, *MDD* major depressive disorder, *OCD* obsessive-compulsive disorder and *SCZ* Schizophrenia.

RESULTS

TWAS prediction

The TWAS analysis conducted using S-MultiXcan across the 11 GTex brain tissue panels, identified a similar number of differentially expressed genes per disorder, ranging from 2759–2768: ADHD (N = 2759), ASD (N = 2767), AN (N = 2763), BD (N = 2767), MDD (N = 2764), OCD (N = 2764), and SCZ (N = 2768). Volcano plots depicting expression change in either direction are shown for each disorder in Fig. 2. All disorders displayed a characteristic U-shaped pattern, reflecting balanced distributions of up-regulated (positive Z-score) and down-regulated (negative Z-score) genes. Although the overall distribution of gene expression changes was broadly similar across disorders, some showed more pronounced clustering. In particular, AN exhibited *SPINK8* as the most significantly down-regulated gene ($Z = -5.24$, $p < 0.001$), while OCD was characterized by *BRD2* down-regulation ($Z = -0.50$, $p < 0.001$). MDD showed *NEGR1* as the most significantly up-regulated gene ($Z = 5.60$, $p < 0.001$). For SCZ, two distinct gene clusters were observed: an up-regulated cluster (*NOTCH4*, $Z = 5.00$, $p < 0.001$), and a larger down-regulated cluster involving *BRD2* ($Z = -4.13$), *AGER* ($Z = -5.63$), *HLA-DMB* ($Z = -7.66$), *HLA-DMA* ($Z = -7.96$), and *CCHCR1* ($Z = -6.85$), all $p < 0.001$. These TWAS-derived gene-level expression signatures served as the foundation for generating GEDAR maps, allowing us to test whether genetically predicted transcriptional alterations project onto macroscale brain structural differences.

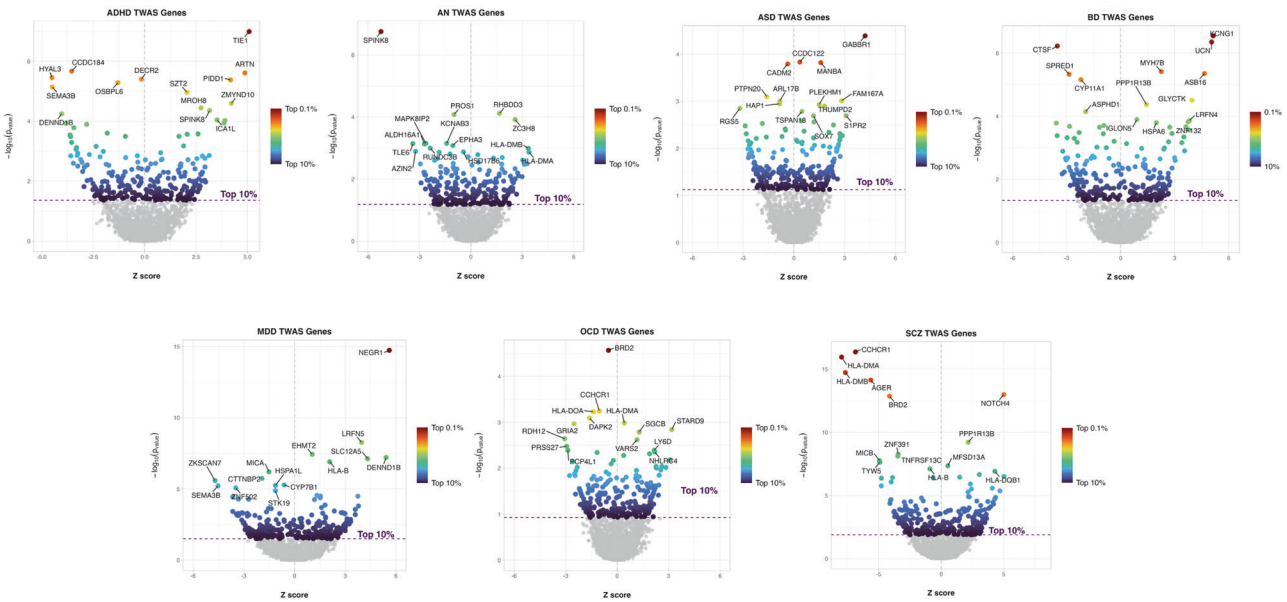

Fig. 2 Predicted TWAS differentially regulated genes. Volcano plots depicting differentially regulated genes as predicted by the application of S-MultiXcan to PGC available GWAS summary data from each disorder. The x axis displays TWAS predicted effect sizes (z-scores) and the y axis -log10 (p-values). Colour bar highlights variation in -log10(p-values) within the range of the top 10% most significant genes. Labelled genes represent the top 1%. Attention Deficit and Hyperactivity Disorder (ADHD), Anorexia Nervosa (AN), Autism Spectrum Disorder (ASD), bipolar disorder (BD), Major Depressive Disorders (MDD), Obsessive-Compulsive Disorder (OCD) and Schizophrenia (SCZ).

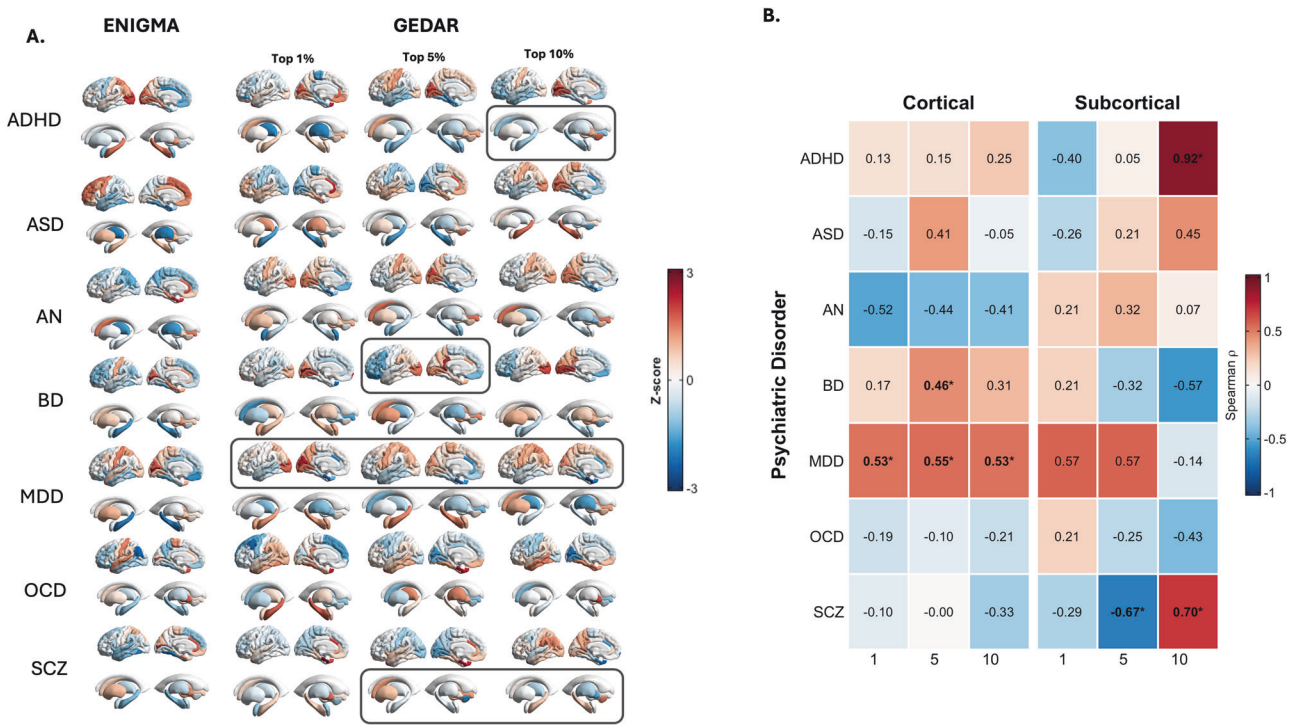

Fig. 3 Correlation between ENIGMA and GEDAR brain maps (calculated from both up- and down-regulated TWAS genes). A shows regional distributions of Z-scores of Cohen's d effect sizes capturing changes in cortical thickness and subcortical volumes between patients and healthy-controls as provided by the respective ENIGMA meta-analysis (left panel); we also display our estimated GEDAR maps estimated from both up- and down-regulated TWAS genes by applying three different thresholds (top 10, 5 and 1%) to select the most differentially expressed genes. **B** depicts spearman correlations between ENIGMA maps of structural differences and GEDAR maps calculated at the three different thresholds separately for cortical and subcortical regions. Significance was calculated by generating 1000 random spin permutations to account for spatial autocorrelation. The * highlights significant correlations at $p_{spin} < 0.05$. Attention Deficit Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD), Anorexia Nervosa (AN), Bipolar Disorder (BD), Major Depressive Disorder (MDD), Obsessive Compulsive Disorder (OCD), Schizophrenia (SCZ).

Correlations between GEDAR maps and brain structural changes

Regional distributions of the GEDAR scores (Z-scores) are presented in Figs. 3, 4 and 5 as calculated from both up-and down-regulated genes, only up-regulated and only down-regulated genes respectively, at different thresholds. In each GEDAR, the top 10% of genes fully contained the genes in the lower thresholds (i.e., 5 and 1%). We display alongside maps of the regional distribution of ENIGMA effect sizes quantifying structural changes in patients compared to healthy controls for visual comparison. The resulting spatial distributions exhibited moderate-to-high correlations across disorders (Supplementary Fig. 2). To determine whether this between-disorder similarity could be explained by overlap in the gene sets used for GEDAR estimation, we assessed cross-disorder gene overlap. Genes contributing to GEDAR scores (up-, down-regulated, and combined) showed minimal overlap between disorders (maximum Jaccard index = 0.15; maximum number of overlapping genes = 20; Supplementary Figs. 3–4).

Combined Up- and down-regulated genes. In cortical regions, significant correlations were found for BD at the top 5% threshold ($\rho = 0.456$, $p_{spin} = 0.01$), and for MDD at all thresholds (top 10%: $\rho = 0.529$, $p_{spin} = 0.005$; top 5%: $\rho = 0.546$, $p_{spin} = 0.003$; top 1%: $\rho = 0.531$, $p_{spin} = 0.003$). In subcortical regions, significant correlations emerged for ADHD at the top 10% threshold ($\rho = 0.919$, $p_{spin} = 0.002$), and for SCZ at both the top 10% ($\rho = 0.703$, $p_{spin} = 0.04$) and 5% thresholds ($\rho = -0.667$, $p_{spin} = 0.04$). None of the remaining correlations reached significance (Fig. 3, Supplementary Table S1). As a sensitivity analysis, we applied FDR correction for multiple comparisons across thresholds, independently for each disorder. After correction, all results in cortical regions survived multiple comparisons correction, while in subcortical regions only the significant results for ADHD at the top 10% threshold survived correction (Supplementary Fig. 5, Supplementary Table S1).

Up-Regulated genes only. In cortical regions, we found significant correlations for MDD at the top 1% threshold ($\rho = 0.396$, $p_{spin} = 0.031$), while in subcortical regions only correlations for ADHD at the top 1% threshold reached significance ($\rho = -0.775$, $p_{spin} = 0.029$). None of the remaining correlations reached significance (Fig. 4, Supplementary Table S2). None of the results survived correction in our sensitivity analysis correcting for multiple comparisons across thresholds (Supplementary Fig. 6, Supplementary Table S2).

Down-Regulated genes only. In cortical regions, we found significant correlations for ADHD at the top 10% ($\rho = -0.300$, $p_{spin} = 0.049$) and 5% ($\rho = -0.401$, $p_{spin} = 0.009$) thresholds, and for MDD at the top 10% threshold ($\rho = -0.424$, $p_{spin} = 0.017$). In subcortical regions, SCZ showed significant negative correlations at both the top 10% ($\rho = -0.703$, $p_{spin} = 0.039$) and 5% thresholds ($\rho = -0.721$, $p_{spin} = 0.04$). None of the remaining correlations reached significance (Fig. 5, Supplementary Table S3). In our sensitivity analysis, only the correlation with ADHD at the top 5% threshold survived FDR correction for multiple comparisons (Supplementary Fig. 7, Supplementary Table S3).

GEDAR maps based on empirical differentially expressed genes in post-mortem brain samples of patients with psychiatric disorders

Correlation analyses using gene sets derived from meta-analytical investigations of differentially expressed genes determined in

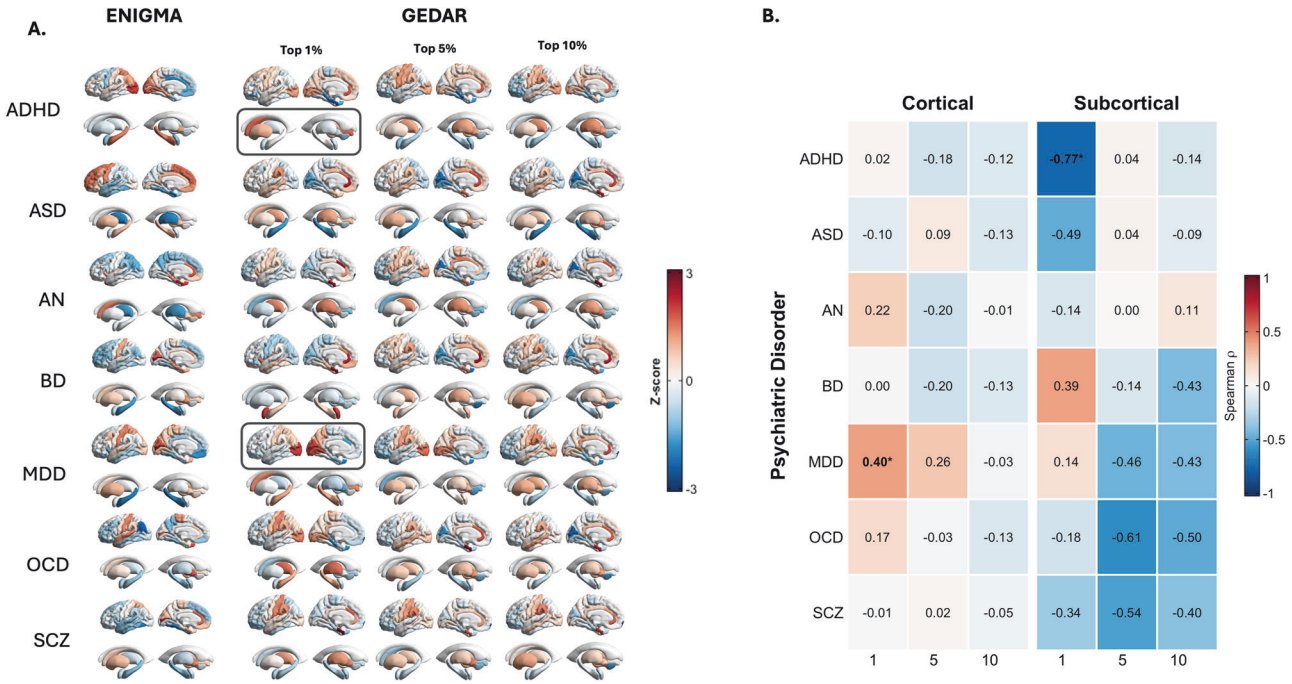

Fig. 4 Correlation between ENIGMA and GEDAR brain maps (calculated from up-regulated TWAS genes). A shows regional distributions of Z-scores of Cohen's d effect sizes capturing changes in cortical thickness and subcortical volumes between patients and healthy-controls as provided by the respective ENIGMA meta-analysis (left panel); we also display our estimated GEDAR maps estimated from up-regulated TWAS genes by applying three different thresholds (top 10, 5 and 1%) to select the most differentially expressed genes. **B** depicts spearman correlations between ENIGMA maps of structural differences and GEDAR maps calculated at the three different thresholds separately for cortical and subcortical regions. Significance was calculated by generating 1000 random spin permutations to account for spatial autocorrelation. The * highlights significant correlations at $p_{spin} < 0.05$. Attention Deficit Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD), Anorexia Nervosa (AN), Bipolar Disorder (BD), Major Depressive Disorder (MDD), Obsessive Compulsive Disorder (OCD), Schizophrenia (SCZ).

post-mortem brain samples yielded significant associations only for MDD. Significant correlations were found across all thresholds in both cortical (10%: $\rho = -0.550$, $p_{spin} = 0.002$; 5%: $\rho = -0.546$, $p_{spin} = 0.002$; 1%: $\rho = -0.579$, $p_{spin} < 0.001$) and subcortical regions (10, 5, and 1% thresholds all $\rho = -0.750$, $p_{spin} \approx 0.026$–0.029) suggesting that spatial patterns of gene expression alterations mirror regional brain structural changes in the disorder. No significant associations were found for ASD, BD, or SCZ (Fig. 6).

Association between between-disorders heritability and GEDAR–ENIGMA spatial correlation

We computed Spearman correlations between heritability and GEDAR–ENIGMA spatial alignment across disorders for each combination of scheme (upregulated, downregulated, both), threshold (top 1, 5 and 10%), and brain compartment (cortical and subcortical). Correlation coefficients ranged from −0.929 to 0.607. Significant negative correlations ($p < 0.05$) were observed only for GEDARs calculated from up-regulated gene sets in cortical regions at the top 1% threshold, and in the combined gene sets in in the subcortical compartment at the top 1% threshold (Fig. 7, Supplementary Table S4). All correlations survived additional FDR multiple-correction across thresholds (Supplementary Table S4).

Pathway enrichment analysis

Up-Regulated pathways. For MDD, at the top 10% threshold, we found significant enrichment for two pathways involving protein sequestering activity ($p_{adj} = 2.975 \times 10^{-2}$) and the MHC protein complex ($p_{adj} = 9.378 \times 10^{-3}$) (Supplementary Table S5).

Down-Regulated pathways. In ADHD, at the top 10% threshold, we found significant enrichment for three pathways: regulation of nervous system development ($p_{adj} = 1.585 \times 10^{-2}$), regulation of neurogenesis ($p_{adj} = 1.651 \times 10^{-2}$), and regulation of multicellular organismal development ($p_{adj} = 4.499 \times 10^{-2}$). At the top 5% threshold, only enrichment for the catenin complex emerged as significant ($p_{adj} = 2.011 \times 10^{-2}$)—highlighting β-catenin's role in cell adhesion (via cadherin–actin linkage) and Wnt signaling-mediated transcriptional regulation. For MDD, at the top 10% threshold, we found significant enrichment for 35 pathways. Several of these pathways were related to the MHC complex (e.g., protein complex binding $p_{adj} = 8.406 \times 10^{-5}$, class II components $p_{adj} = 4.166 \times 10^{-2}$), immune response (e.g., $p_{adj} = 6.290 \times 10^{-3}$), antigen processing (e.g., $p_{adj} = 6.025 \times 10^{-4}$), and broader cellular components (e.g., cell surface $p_{adj} = 1.192 \times 10^{-4}$, membrane side $p_{adj} = 1.006 \times 10^{-3}$, extracellular matrix $p_{adj} = 3.754 \times 10^{-2}$). For SCZ, at both the top 5 and 10% thresholds, we found significant enrichment for 53 pathways, including those involved in immune activity (MHC complex $p_{adj} = 7.425 \times 10^{-3}$, antigen binding $p_{adj} = 1.029 \times 10^{-2}$, adaptive immune response $p_{adj} = 2.938 \times 10^{-3}$), cognition (via MAPK/ERK-mediated synaptic plasticity $p_{adj} = 3.070 \times 10^{-2}$), and leukocyte regulation (involving JAK-STAT and NF-κB pathways $p_{adj} = 1.799 \times 10^{-2}$) (Supplementary Table S5).

DISCUSSION

This study introduces a novel and generalizable framework for mapping polygenic transcriptional risk onto macroscale brain phenotypes in psychiatric disorders, namely Gene Expression-based Disorder Associated Risk (GEDAR). Inspired by the logic of polygenic risk scores (PRS), which quantify individual genetic liability by aggregating small effects across many variants, our approach extends this concept into the spatial domain. Unlike

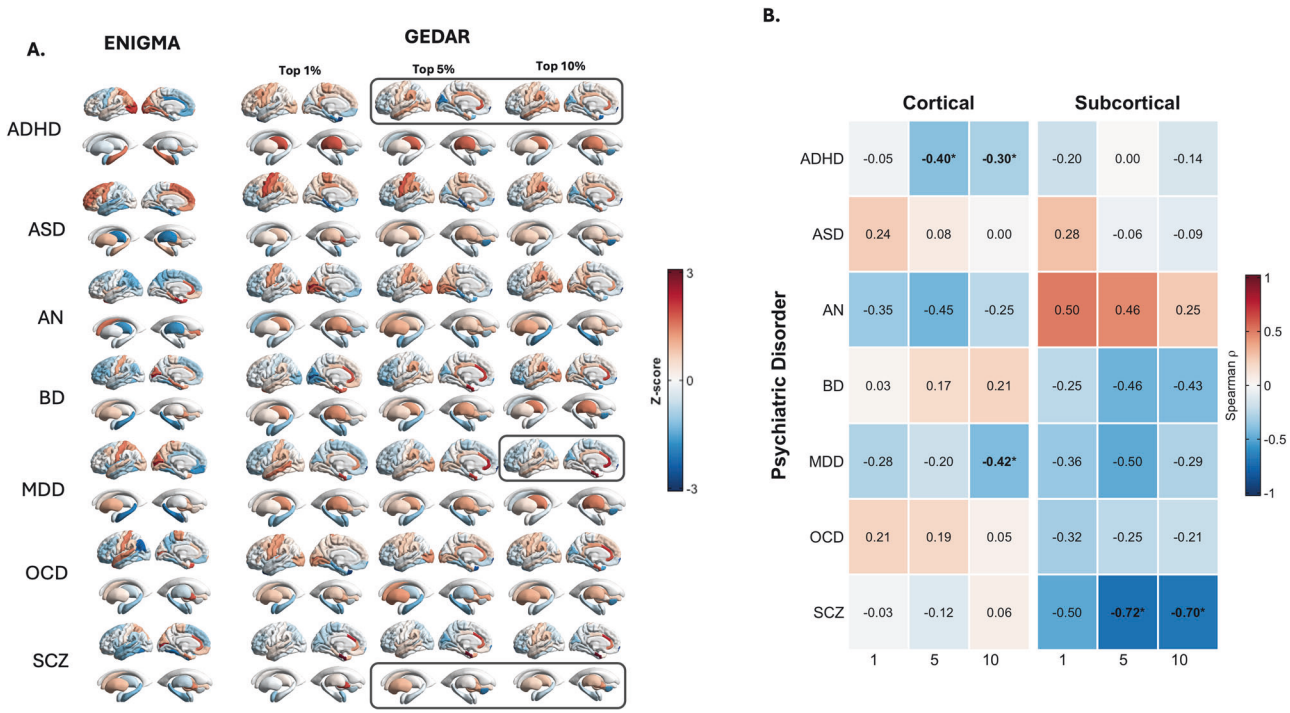

Fig. 5 Correlation between ENIGMA and GEDAR brain maps (calculated from down-regulated TWAS genes). A shows regional distributions of Z-scores of Cohen's d effect sizes capturing changes in cortical thickness and subcortical volumes between patients and healthy-controls as provided by the respective ENIGMA meta-analysis (left panel); we also display our estimated GEDAR maps estimated from down-regulated TWAS genes by applying three different thresholds (top 10, 5 and 1%) to select the most differentially expressed genes. **B** depicts spearman correlations between ENIGMA maps of structural differences and GEDAR maps calculated at the three different thresholds separately for cortical and subcortical regions. Significance was calculated by generating 1000 random spin permutations to account for spatial autocorrelation. The * highlights significant correlations at $p_{spin} < 0.05$. Abbreviations: Attention Deficit Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD), Anorexia Nervosa (AN), Bipolar Disorder (BD), Major Depressive Disorder (MDD), Obsessive Compulsive Disorder (OCD), Schizophrenia (SCZ).

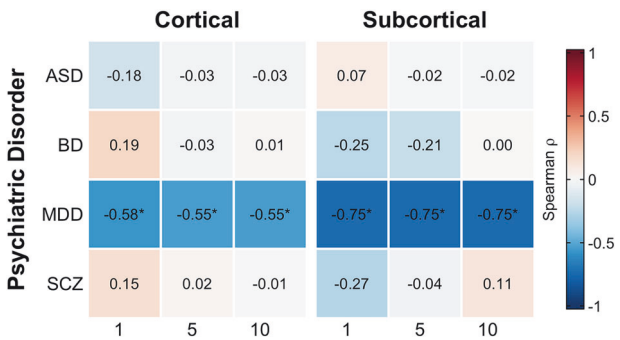

Fig. 6 Correlation between ENIGMA and GEDAR brain maps (calculated from empirically determined differentially expressed genes). Spearman correlations between ENIGMA maps of structural changes and GEDAR maps calculated from differentially expressed genes in post-mortem brain samples at the three different thresholds separately for cortical and subcortical regions. Significance was calculated by generating 1000 random spin permutations to account for spatial autocorrelation. The * highlights significant correlations at $p_{spin} < 0.05$. Attention Deficit Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD), Anorexia Nervosa (AN), Bipolar Disorder (BD), Major Depressive Disorder (MDD), Obsessive Compulsive Disorder (OCD), Schizophrenia (SCZ).

PRS, which provide individual-level indices of genetic risk, the GEDAR framework integrates genetically predicted gene expression profiles from TWAS with spatial transcriptomic data from the AHBA to generate spatial maps of regional vulnerability, quantifying how genetically inferred gene dysregulation distributes across the normative transcriptomic architecture of the adult human brain. These maps were then compared with structural neuroimaging meta-analyses from the ENIGMA consortium to test whether regional brain alterations observed across major psychiatric disorders mirror the spatial organization of genetically predicted transcriptional dysregulation - and to what extent this correspondence varies across conditions with differing heritability and developmental profiles.

We found that predicted transcriptomic dysregulation captured by GEDAR scores significantly correlated with regional brain structural differences within a subset of disorders. These effects were strongest in MDD, where robust associations were observed across cortical and subcortical regions and across multiple thresholds of gene inclusion. Notably, both TWAS-predicted and empirically-derived differentially expressed genes from post-mortem brain samples yielded significant correlations in MDD, reinforcing the idea that transcriptomic signatures - whether genetically inferred or empirically derived - are spatially aligned with the disorder's neuroanatomical profile. These findings suggest that MDD-related structural changes, which often involve limbic and prefrontal cortices, may partly reflect regionally patterned gene expression regulation. Pathway analyses indicated that many of the biological processes enriched in MDD were immune-related, including components of the major histocompatibility complex (MHC). This pattern aligns with previous evidence linking immune dysregulation and cortical thinning, as well as other structural brain alterations observed in MDD [33–36]. The enrichment of immune and inflammatory pathways underscores not only the regional impact of transcriptomic dysregulation on brain anatomy but also the broader contribution of immune signalling to MDD pathophysiology [34, 37, 38]. These insights may help guide therapeutic innovation, particularly ongoing

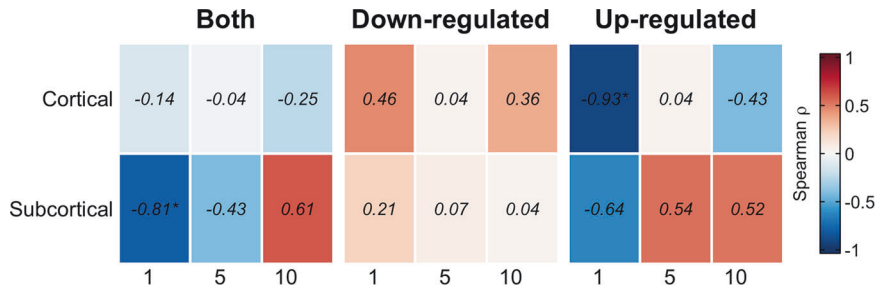

Fig. 7 Correlations between heritability and GEDAR–ENIGMA correlation across disorders. The heatmaps depict Spearman correlations coefficients calculated between the middle point of heritability intervals and the estimated GEDAR-ENIGMA correlation. Both refers to GEDARs calculated from up- and down-regulated genes combined, while down- and up-regulated subplots refer to GEDARs calculate with either up- or down-regulated genes only. The * highlights significant correlations at a $p < 0.05$.

efforts to target immune-related mechanisms [39] to mitigate the structural and functional consequences of the disorder. More generally, the findings highlight the value of integrating genetic and transcriptomic data with neuroimaging to reveal biologically grounded mechanisms underlying psychiatric conditions

In contrast, other disorders such as schizophrenia (SCZ) and attention-deficit/hyperactivity disorder (ADHD) exhibited significant associations primarily in subcortical regions. For SCZ, these were predominantly driven by down-regulated genes and involved key immune-related transcripts, including several MHC-related genes, highlighting the role of neuroimmune interactions in subcortical vulnerability [40–42]. In ADHD, gene expression changes aligned with known striatal alterations and were enriched for pathways involved in neurodevelopment and cell adhesion, such as the catenin complex and Wnt signalling [43–46]. The catenin complex, in particular, is crucial for establishing and maintaining neuronal connectivity during brain development, as it mediates cell–cell adhesion through interactions with cadherins at synaptic junctions. β-catenin, a key component of this complex, also acts as an intracellular signalling molecule downstream of Wnt, influencing gene expression patterns important for neuronal proliferation, differentiation, and synaptic plasticity [47, 48]. These associations highlight how transcriptomic perturbations may contribute to regional specificity in structural brain differences observed in ADHD, reinforcing the idea that subcortical circuits, especially within the striatum, may be uniquely sensitive to genetically regulated developmental processes in early-onset psychiatric disorders [49, 50]. These insights further support existing neurodevelopmental frameworks and pinpoint the catenin complex as a biologically plausible target for future mechanistic studies and therapeutic interventions in ADHD and related neurodevelopmental conditions.

We note, however, that methodological choices regarding thresholds for gene inclusion in GEDAR score calculations appeared influential in specific cases. For example, in schizophrenia, GEDAR scores derived from combined sets of up- and down-regulated genes at a less stringent threshold (top 5%) resulted in a shift in the correlation direction from positive to negative compared to the stricter threshold (top 1%). When analyses were conducted separately for up- and down-regulated genes, negative associations generally emerged, suggesting potential opposing transcriptional effects. While we included combined up- and down-regulated gene sets to maximize sensitivity to spatial associations, these observations indicate that interpreting combined transcriptional signatures warrants caution. Specifically, TWAS Z-scores represent associations with a given trait due to genetic factors, rather than direct observation of gene regulation in cases, and combining genes with opposing expression directions inherently assumes shared directionality of biological effects, potentially obscuring true regional expression patterns [27]. Moreover, differences in the sign of the associations across up- and down-regulated genes may themselves provide clues about the polarity of underlying processes - for example, whether particular gene sets are preferentially associated with increases or decreases in cortical thickness or subcortical volume, potentially reflecting protective versus pathological influences on brain structure. Although TWAS-based approaches alone (without fine-mapping) cannot determine causality or establish whether predicted up- or down-regulation is beneficial or detrimental to anatomical structure, variations in GEDAR results across thresholds and directionality schemes should not necessarily be viewed as inconsistencies. For example, when correlations differ between analyses restricted to up- versus down-regulated genes, or between more and less stringent significance thresholds, these shifts may indicate that distinct biological processes or gene classes contribute differently to the spatial association. In this sense, the threshold- and direction-dependent variability in GEDAR outcomes can itself provide useful information about the heterogeneity of gene–brain relationships rather than reflecting methodological noise.

Interestingly, bipolar disorder (BD) showed more modest correspondence between GEDAR and neuroimaging phenotypes, with significant effects emerging only at specific thresholds. For other disorders, including autism spectrum disorder (ASD), anorexia nervosa (AN), and obsessive-compulsive disorder (OCD), associations were limited or absent. This variability most likely reflect the extent to which observed brain changes are mediated by factors not captured by genetically predicted expression - such as post-transcriptional regulation [17], alternative splicing [51–53], epigenetic modifications [54], environmental exposures [55] or developmental timing [56]. To clarify whether the limited predictive power in some disorders was due to the use of TWAS-predicted genes rather than actual transcriptional abnormalities, we also tested GEDAR maps constructed from empirically identified differentially expressed genes. These analyses again yielded significant associations only for MDD, suggesting that in other disorders, the spatial distribution of gene expression—regardless of whether inferred or observed - may not align with the anatomical profile of structural alterations. This points to a fundamental challenge: while gene expression is undoubtedly relevant to brain structure and function, its contribution may be more salient in some disorders than others or may operate through intermediate biological mechanisms not readily captured by bulk transcriptomic data.

The differential strength of transcriptomic–anatomical associations across psychiatric disorders is intriguing in itself and might provide important biological insights. While disorders like MDD demonstrated robust associations, the limited or absent correlations observed in ASD, AN, and OCD, which predominantly fall into neurodevelopmental categories[74], may reflect critical differences in developmental timing rather than methodological shortcomings. Specifically, the transcriptomic signatures most relevant to neurodevelopmental disorders likely occur during prenatal or early-life periods [57, 58], long before structural

alterations become evident on adult MRI scans. Because TWAS predominantly capture genetically regulated, relatively stable patterns of gene expression based primarily on adult reference data, these approaches align closely with conditions like MDD, characterized by ongoing pathological processes in adulthood. Conversely, for disorders such as ASD or AN, early developmental mechanisms may be paramount and thus not adequately captured by adult-derived transcriptomic maps. Framing our results in this context provides a meaningful interpretation and underscores the need for future research incorporating developmentally informed gene expression datasets and longitudinal imaging–transcriptomic designs to better capture the critical windows during which gene expression influences neuroanatomical development. However, another relevant consideration is the potential confounding effect of psychotropic medication use in ENIGMA cohorts, particularly in disorders such as schizophrenia, bipolar disorder, and major depression. While our transcriptomic predictions are genetically driven, it remains possible that medication exposure could shape regional structural phenotypes in ways that amplify - or obscure - GEDAR alignment. This may partly explain the absence of significant correlations in less medicated cohorts such as ASD or AN. Future analyses stratifying patients by medication status or illness duration (e.g., first-episode vs chronic) could help clarify this issue.

Although we observed some tendency for disorders with higher heritability, such as SCZ and ADHD, to show stronger GEDAR–neuroimaging correspondence, this relationship was not uniform. MDD, which has moderate heritability, yielded some of the most consistent associations, while BD and ASD—with higher heritability—showed weaker to no effects. Further reinforcing this interpretation, we could not find a possible positive association between heritability and the strength of spatial association between GEDAR and ENIGMA maps of structural changes. Where this reached significance, the association was in fact negative, which contradicts our initial predictions. These findings suggest that heritability alone does not determine how well gene expression predicts brain changes; rather, the molecular architecture, developmental profile, and pathophysiological mechanisms specific to each disorder likely modulate this relationship [55, 59], highlighting that further research is needed to clarify the precise neurobiological mechanisms underlying changes in brain structure documented in patients with psychiatric disorders through the use of neuroimaging techniques. Future studies could revisit this question using independent GWAS datasets to test the relationship between GEDAR–ENIGMA coupling and SNP-based heritability estimates in a non-circular manner, provided that differences in sample size and power are adequately controlled.

Several limitations should be acknowledged. First, GEDAR maps are based on predicted transcriptomic alterations and may not fully capture the complexity of gene regulation in the human brain [60]. Second, while the AHBA offers unparalleled spatial resolution, it is derived from a small number of neurotypical adult donors, limiting its generalizability across populations and developmental stages [2, 14]. Third, the reliance on summary-level imaging and genetic data limits our ability to assess individual-level variation when psychiatric disorders and associated structural brain changes are now understood to be highly heterogenous at a regional level [61–63]. Related to this, we note that the transcriptomic reference (AHBA) and neuroimaging data (ENIGMA) are derived from different participant groups. GEDAR therefore assumes that normative spatial gradients of gene expression in the AHBA generalize to the populations studied in ENIGMA. Prior work suggests these gradients are robust and align with multiple independent neuroimaging phenotypes [15, 64], but the approach cannot capture disorder-specific or inter-individual variation in gene expression. Our results should thus be interpreted as mapping genetically predicted dysregulation onto the architecture of the healthy adult brain, with future work needed to integrate patient-derived transcriptomic data directly matched to neuroimaging

Fourth, it is also important to note that our TWAS approach involved averaging across all S-PrediXcan tissue panels, rather than tailoring gene expression prediction to specific brain regions. While using distinct tissue panels for each brain region could potentially offer more anatomical specificity, this strategy is currently constrained by the lack of direct correspondence between the GTEx panels and the Desikan–Killiany atlas. Some GTEx tissues map cleanly to multiple brain regions, while others map ambiguously or not at all. To address this, we prioritized anatomical coverage over regional specificity, trading a degree of transcriptomic granularity for the ability to analyse all available ENIGMA regions uniformly. Future work could explore hybrid approaches that combine region-specific predictions where feasible or integrate emerging resources that offer finer-grained transcriptomic spatial mapping. Fifth, our analyses used adult-derived transcriptomic reference models (GTEx v8 and AHBA), which may not capture developmentally critical transcriptional patterns relevant to early-onset disorders. The release of neurodevelopmentally informed eQTL resources (e.g., the human and non-human developmental GTEx [65]) will allow future studies to more accurately model the spatiotemporal dynamics of gene expression during prenatal and early postnatal development, a critical period for disorders such as ASD, ADHD, and AN. Lastly, while our enrichment analyses highlighted immune-related processes in MDD and SCZ and neurodevelopmental pathways in ADHD, it is important to emphasize that these results are based on statistical over-representation tests of TWAS-derived gene sets. As such, they suggest biologically plausible candidate mechanisms but do not constitute direct tests of pathway function. Future work incorporating experimental transcriptomic datasets, single-cell resolution analyses, or targeted pathway perturbation studies will be required to validate these associations.

Overall, this study provides preliminary evidence supporting the notion that genetically driven transcriptomic dysregulation is spatially aligned, to varying degrees, with regional brain structural changes in some psychiatric disorders, particularly MDD. Our findings highlight the potential of this integrative framework to advance our understanding of the molecular basis of disease-related brain changes while underscoring the need for refined, multi-omic, and cell-type-specific methods to capture the full spectrum of gene expression dynamics [66, 67]. As our understanding of the molecular and cellular complexity of the human brain expands, future research should aim to incorporate additional biological layers and multi-omics data, such as single-cell transcriptomics, alternative splicing and epigenetics to build a more comprehensive understanding of how genetically encoded molecular changes might map on the full cascade from genome to brain to behaviour and shape the neuroanatomy of psychiatric disorders. In the meantime, we provide an exploratory integrative tool for hypothesis generation about transcriptional–anatomical coupling, complementary to but conceptually distinct from PRS, with future methodological work needed to further formalize its statistical properties.

DATA AVAILABILITY

All GWAS summary statistics used in this study were obtained from the publicly available resources of the Psychiatric Genomics Consortium (https://www.med.unc.edu/pgc). Neuroimaging data were derived from meta-analytic results published by the ENIGMA consortium (http://enigma.ini.usc.edu). Gene expression data were sourced from the Allen Human Brain Atlas (https://human.brain-map.org/). GTEx panels used for the TWAS analyses and methods originating this dataset are available at https://www.gtexportal.org/home/. Meta-analytical estimates of gene differential regulation in post-mortem brain samples and heritability estimates data are available from the corresponding sources cited within the main text and supplementary materials.

CODE AVAILABILITY

Code and reproducible workflows for GEDAR computation, spatial statistics (including spin permutations), enrichment analyses, and figure generation are available at https://github.com/alegiac95/METAXCAN_TWAS_ANALYSIS. A versioned snapshot will be archived with a DOI upon acceptance to ensure long-term accessibility.

REFERENCES

1. Arias D, Saxena S, Verguet S. Quantifying the global burden of mental disorders and their economic value. eClinicalMedicine. 2022;54:101675.
2. Martins D, Giacomel A, Williams SCR, Turkheimer F, Dipasquale O, Veronese M. Imaging transcriptomics: convergent cellular, transcriptomic, and molecular neuroimaging signatures in the healthy adult human brain. Cell Rep. 2021;37:110173.
3. Knight SR, Abbasova L, Zeighami Y, Hansen JY, Martins D, Zelaya F, et al. Transcriptional and neurochemical signatures of cerebral blood flow alterations in individuals with schizophrenia or at clinical high risk for psychosis. Biol Psychiatry. 2025;98:144–55.
4. Hansen JY, Markello RD, Vogel JW, Seidlitz J, Bzdok D, Misic B. Mapping gene transcription and neurocognition across human neocortex. Nat Hum Behav. 2021;5:1240–50.
5. Hansen JY, Shafiei G, Markello RD, Smart K, Cox SML, Nørgaard M, et al. Mapping neurotransmitter systems to the structural and functional organization of the human neocortex. Nat Neurosci. 2022;25:1569–81.
6. Sullivan PF. The psychiatric GWAS consortium: big science comes to psychiatry. Neuron. 2010;68:182–6.
7. Thompson PM, Stein JL, Medland SE, Hibar DP, Vasquez AA, Renteria ME, et al. The ENIGMA consortium: large-scale collaborative analyses of neuroimaging and genetic data. Brain Imaging Behav. 2014;8:153–82.
8. Thompson PM, Jahanshad N, Ching CRK, Salminen LE, Thomopoulos SI, Bright J, 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. 2020;10:100.
9. Opel N, Goltermann J, Hermesdorf M, Berger K, Baune BT, Dannlowski U. Cross-Disorder analysis of brain structural abnormalities in six major psychiatric disorders: a secondary analysis of mega- and meta-analytical findings from the ENIGMA consortium. Biol Psychiatry. 2020;88:678–86.
10. Bourque VR, Poulain C, Proulx C, Moreau CA, Joober R, Forgeot d'Arc B, et al. Genetic and phenotypic similarity across major psychiatric disorders: a systematic review and quantitative assessment. Transl Psychiatry. 2024;14:1–10.
11. Rasetti R, Weinberger DR. Intermediate phenotypes in psychiatric disorders. Curr Opin Genet Dev. 2011;21:340–8.
12. Glahn DC, Paus T, Thompson PM. Imaging genomics: mapping the influence of genetics on brain structure and function. Hum Brain Mapp. 2007;28:461–3.
13. Bogdan R, Salmeron BJ, Carey CE, Agrawal A, Calhoun VD, Garavan H, et al. Imaging genetics and genomics in psychiatry: a critical review of progress and potential. Biol Psychiatry. 2017;82:165–75.
14. Shen EH, Overly CC, Jones AR. The allen human brain atlas: comprehensive gene expression mapping of the human brain. Trends Neurosci. 2012;35:711–4.
15. Dear R, Wagstyl K, Seidlitz J, Markello RD, Arnatkevičiūtė A, Anderson KM, et al. Cortical gene expression architecture links healthy neurodevelopment to the imaging, transcriptomics and genetics of autism and schizophrenia. Nat Neurosci. 2024;27:1075–86.
16. Liu W, Su JP, Zeng LL, Shen H, Hu DW. Gene expression and brain imaging association study reveals gene signatures in major depressive disorder. Brain Commun. 2024;6:fcae258.
17. Arnatkeviciute A, Fulcher BD, Bellgrove MA, Fornito A. Imaging transcriptomics of brain disorders. Biol Psychiatry Glob Open Sci. 2022;2:319–31.
18. Brainstorm Consortium The, Anttila V, Bulik-Sullivan B, Finucane HK, Walters RK, Bras J, et al. Analysis of shared heritability in common disorders of the brain. Science. 2018;360:eaap8757.
19. Barbeira AN, Pividori M, Zheng J, Wheeler HE, Nicolae DL, Im HK. Integrating predicted transcriptome from multiple tissues improves association detection. PLOS Genet. 2019;15:e1007889.
20. Sey NYA, Pratt BM, Won H. Annotating genetic variants to target genes using H-MAGMA. Nat Protoc. 2023;18:22–35.
21. Mai J, Lu M, Gao Q, Zeng J, Xiao J. Transcriptome-wide association studies: recent advances in methods, applications and available databases. Commun Biol. 2023;6:1–10.
22. GTEx Consortium The. The GTEx Consortium atlas of genetic regulatory effects across human tissues. Science. 2020;369:1318–30.
23. Markello RD, Arnatkeviciute A, Poline JB, Fulcher BD, Fornito A, Misic B. Standardizing workflows in imaging transcriptomics with the abagen toolbox. eLife. 2021;10:e72129.
24. Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. NeuroImage. 2006;31:968–80.
25. Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, et al. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron. 2002;33:341–55.
26. Thul PJ, Lindskog C. The human protein atlas: a spatial map of the human proteome. Protein Sci. 2018;27:233–44.
27. Choi SW, Mak TSH, O'Reilly PF. Tutorial: a guide to performing polygenic risk score analyses. Nat Protoc. 2020;15:2759–72.
28. Panizzon MS, Fennema-Notestine C, Eyler LT, Jernigan TL, Prom-Wormley E, Neale M, et al. Distinct genetic influences on cortical surface area and cortical thickness. Cereb Cortex. 2009;19:2728–35.
29. Markello RD, Hansen JY, Liu ZQ, Bazinet V, Shafiei G, Suárez LE, et al. neuromaps: structural and functional interpretation of brain maps. Nat Methods. 2022;19:1472–9.
30. Váša F, Seidlitz J, Romero-Garcia R, Whitaker KJ, Rosenthal G, Vértes PE, et al. Adolescent tuning of association cortex in human structural brain networks. Cereb Cortex. 2018;28:281–94.
31. Sadeghi I, Gispert JD, Palumbo E, Muñoz-Aguirre M, Wucher V, D'Argenio V, et al. Brain transcriptomic profiling reveals common alterations across neurodegenerative and psychiatric disorders. Computational Struct Biotechnol J. 2022;20:4549–61.
32. Kolberg L, Raudvere U, Kuzmin I, Adler P, Vilo J, Peterson H. G:Profiler—Interoperable web service for functional enrichment analysis and gene identifier mapping (2023 Update). Nucleic Acids Res. 2023;51:W207–12.
33. Li J, Seidlitz J, Suckling J, Fan F, Ji GJ, Meng Y, et al. Cortical structural differences in major depressive disorder correlate with cell type-specific transcriptional signatures. Nat Commun. 2021;12:1647.
34. Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. Biol Psychiatry. 2009;65:732–41.
35. Wohleb ES, Franklin T, Iwata M, Duman RS. Integrating neuroimmune systems in the neurobiology of depression. Nat Rev Neurosci. 2016;17:497–511.
36. Lima-Ojeda JM, Rupprecht R, Baghai TC. Neurobiology of depression: a neurodevelopmental approach. World J Biol Psychiatry. 2018;19:349–59.
37. Goldsmith DR, Bekhbat M, Mehta ND, Felger JC. Inflammation-Related functional and structural dysconnectivity as a pathway to psychopathology. Biol Psychiatry. 2023;93:405–18.
38. Strike PC, Wardle J, Steptoe A. Mild acute inflammatory stimulation induces transient negative mood. J Psychosom Res. 2004;57:189–94.
39. Simon MS, Arteaga-Henríquez G, Algendy AF, Siepmann T, Illigens BM. Anti-Inflammatory treatment efficacy in major depressive disorder: a systematic review of meta-analyses. NDT. 2023;19:1–25.
40. Mokhtari R, Lachman HM. The major histocompatibility complex (MHC) in schizophrenia: a review. J Clin Cell Immunol. 2016;7:479.
41. Caseras X, Simmonds E, Pardiñas AF, Anney R, Legge SE, Walters JTR, et al. Common risk alleles for schizophrenia within the major histocompatibility complex predict white matter microstructure. Transl Psychiatry. 2024;14:194.
42. Cheng W, van der Meer D, Parker N, Hindley G, O'Connell KS, Wang Y, et al. Shared genetic architecture between schizophrenia and subcortical brain volumes implicates early neurodevelopmental processes and brain development in childhood. Mol Psychiatry. 2022;27:5167–76.
43. Hoogman M, Bralten J, Hibar DP, Mennes M, Zwiers MP, Schweren L, et al. Subcortical brain volume differences of participants with ADHD across the lifespan: an ENIGMA collaboration. lancet Psychiatry. 2017;4:310–9.
44. Poelmans G, Pauls DL, Buitelaar JK, Franke B. Integrated genome-wide association study findings: identification of a neurodevelopmental network for attention deficit hyperactivity disorder. AJP. 2011;168:365–77.
45. Hawi Z, Cummins TDR, Tong J, Johnson B, Lau R, Samarrai W, et al. The molecular genetic architecture of attention deficit hyperactivity disorder. Mol Psychiatry. 2015;20:289–97.
46. Adegbola A, Lutz R, Nikkola E, Strom SP, Picker J, Wynshaw-Boris A. Disruption of *CTNND2*, encoding delta-catenin, causes a penetrant attention deficit disorder and myopia. Hum Genet Genomics Adv. 2020;1:100007.
47. Uchida N, Honjo Y, Johnson KR, Wheelock MJ, Takeichi M. The catenin/cadherin adhesion system is localized in synaptic junctions bordering transmitter release zones. J Cell Biol. 1996;135:767–79.
48. Bamji SX, Shimazu K, Kimes N, Huelsken J, Birchmeier W, Lu B, et al. Role of β-Catenin in synaptic vesicle localization and presynaptic assembly. Neuron. 2003;40:719–31.
49. Okada N, Fukunaga M, Miura K, Nemoto K, Matsumoto J, Hashimoto N, et al. Subcortical volumetric alterations in four major psychiatric disorders: a mega-analysis study of 5604 subjects and a volumetric data-driven approach for classification. Mol Psychiatry. 2023;28:5206–16.
50. Ohi K, Shimada T, Kataoka Y, Yasuyama T, Kawasaki Y, Shioiri T, et al. Genetic correlations between subcortical brain volumes and psychiatric disorders. Br J Psychiatry. 2020;216:280–3.

51. Barbosa-Morais NL, Irimia M, Pan Q, Xiong HY, Gueroussov S, Lee LJ, et al. The evolutionary landscape of alternative splicing in vertebrate species. Science. 2012;338:1587–93.
52. Weyn-Vanhentenryck SM, Feng H, Ustianenko D, Duffié R, Yan Q, Jacko M, et al. Precise temporal regulation of alternative splicing during neural development. Nat Commun. 2018;9:2189.
53. Aya F, Valcárcel J. Shaping human brain development and vulnerability through alternative splicing. Cell Genomics. 2024;4:100584.
54. Nestler EJ, Peña CJ, Kundakovic M, Mitchell A, Akbarian S. Epigenetic basis of mental illness. Neuroscientist. 2016;22:447–63.
55. Caspi A, Moffitt TE. Gene–environment interactions in psychiatry: joining forces with neuroscience. Nat Rev Neurosci. 2006;7:583–90.
56. Paus T, Keshavan M, Giedd JN. Why do many psychiatric disorders emerge during adolescence? Nat Rev Neurosci. 2008;9:947–57.
57. Qi X, Wu C, Du Y, Cheng S, Wen Y, Ma M, et al. Comparing GWAS and brain structure-specific gene expression profiles identifies psychiatric disorder-related brain structures at different developmental stages. Neurosci Bull. 2020;36:1046–50.
58. Miller JA, Ding SL, Sunkin SM, Smith KA, Ng L, Szafer A, et al. Transcriptional landscape of the prenatal human brain. Nature. 2014;508:199–206.
59. Mufford MS, Stein DJ, Dalvie S, Groenewold NA, Thompson PM, Jahanshad N. Neuroimaging genomics in psychiatry—a translational approach. Genome Med. 2017;9:102.
60. Vialle RA, de Paiva Lopes K, Bennett DA, Crary JF, Raj T. Integrating whole-genome sequencing with multi-omic data reveals the impact of structural variants on gene regulation in the human brain. Nat Neurosci. 2022;25:504–14.
61. Feczko E, Miranda-Dominguez O, Marr M, Graham AM, Nigg JT, Fair DA. The heterogeneity problem: approaches to identify psychiatric subtypes. Trends Cognit Sci. 2019;23:584–601.
62. Segal A, Parkes L, Aquino K, Kia SM, Wolfers T, Franke B, et al. Regional, circuit and network heterogeneity of brain abnormalities in psychiatric disorders. Nat Neurosci. 2023;26:1613–29.
63. Marquand AF, Rezek I, Buitelaar J, Beckmann CF. Understanding heterogeneity in clinical cohorts using normative models: beyond case-control studies. Biol Psychiatry. 2016;80:552–61.
64. Wagstyl K, Adler S, Seidlitz J, Vandekar S, Mallard TT, Dear R, et al. Transcriptional cartography integrates multiscale biology of the human cortex. Jbabdi S, de Lange FP, editors elife. 2024;12:RP86933.
65. Coorens THH, Guillaumet-Adkins A, Kovner R, Linn RL, Roberts VHJ, Sule A, et al. The human and non-human primate developmental GTEx projects. Nature. 2025;637:557–64.
66. Villa C, Yoon JH. Multi-Omics for the understanding of brain diseases. Life. 2021;11:1202.
67. Bhattacharya A, Li Y, Love MI. MOSTWAS: multi-omic strategies for transcriptome-wide association studies. PLOS Genet. 2021;17:e1009398.
68. Demontis D, Walters GB, Athanasiadis G, Walters R, Therrien K, Nielsen TT, et al. Genome-Wide analyses of ADHD Identify 27 risk loci, refine the genetic architecture and implicate several cognitive domains. Nat Genet. 2023;55:198–208.
69. Grove J, Ripke S, Als TD, Mattheisen M, Walters RK, Won H, et al. Identification of common genetic risk variants for autism spectrum disorder. Nat Genet. 2019;51:431–44.
70. Watson HJ, Yilmaz Z, Thornton LM, Hübel C, Coleman JRI, Gaspar HA, et al. Genome-Wide association study identifies eight risk loci and implicates metabo-psychiatric origins for anorexia nervosa. Nat Genet. 2019;51:1207–14.
71. Mullins N, Forstner AJ, O'Connell KS, Coombes B, Coleman JRI, Qiao Z, et al. Genome-Wide association study of more than 40,000 bipolar disorder cases provides new insights into the underlying biology. Nat Genet. 2021;53:817–29.
72. Meng X, Navoly G, Giannakopoulou O, Levey DF, Koller D, Pathak GA, et al. Multi-Ancestry genome-wide association study of major depression aids locus discovery, fine mapping, gene prioritization and causal inference. Nat Genet. 2024;56:222–33.
73. International Obsessive Compulsive Disorder Foundation Genetics Collaborative (IOCDF-GC) and OCD Collaborative Genetics Association Studies (OCGAS). Revealing the complex genetic architecture of obsessive-compulsive disorder using meta-analysis. Mol Psychiatry. 2018;23:1181–8.
74. Lam M, Chen CY, Li Z, Martin AR, Bryois J, Ma X, et al. Comparative genetic architectures of schizophrenia in east asian and european populations. Nat Genet. 2019;51:1670–8.
75. Hoogman M, Muetzel R, Guimaraes JP, Shumskaya E, Mennes M, Zwiers MP, et al. Brain imaging of the Cortex in ADHD: a coordinated analysis of large-scale clinical and population-based samples. Am J psychiatry. 2019;176:531–42.
76. van Rooij D, Anagnostou E, Arango C, Auzias G, Behrmann M, Busatto GF, et al. Cortical and subcortical brain morphometry differences between patients with autism spectrum disorder and healthy individuals across the lifespan: results from the ENIGMA ASD working group. AJP. 2018;175:359–69.
77. Walton E, Bernardoni F, Batury VL, Bahnsen K, Larivière S, Abbate-Daga G, et al. Brain structure in acutely underweight and partially weight-restored individuals with anorexia nervosa: a coordinated analysis by the ENIGMA eating disorders working group. Biol Psychiatry. 2022;92:730–8.
78. Hibar DP, Westlye LT, Doan NT, Jahanshad N, Cheung JW, Ching CRK, et al. Cortical abnormalities in bipolar disorder: an MRI analysis of 6503 individuals from the ENIGMA bipolar disorder working group. Mol Psychiatry. 2018;23:932–42.
79. Schmaal L, Hibar DP, Sämann PG, Hall GB, Baune BT, Jahanshad N, et al. Cortical abnormalities in adults and adolescents with major depression based on brain scans from 20 cohorts worldwide in the ENIGMA major depressive disorder working group. Mol Psychiatry. 2017;22:900–9.
80. Boedhoe PSW, Schmaal L, Abe Y, Alonso P, Ameis SH, Anticevic A, et al. Cortical abnormalities associated with pediatric and adult obsessive-compulsive disorder: findings from the ENIGMA obsessive-compulsive disorder working group. AJP. 2018;175:453–62.
81. van Erp TGM, Walton E, Hibar DP, Schmaal L, Jiang W, Glahn DC, et al. Cortical brain abnormalities in 4474 individuals with schizophrenia and 5098 control subjects via the enhancing neuro imaging genetics through meta analysis (ENIGMA) consortium. Biol Psychiatry. 2018;84:644–54.
82. Hibar DP, Westlye LT, van Erp TGM, Rasmussen J, Leonardo CD, Faskowitz J, et al. Subcortical volumetric abnormalities in bipolar disorder. Mol Psychiatry. 2016;21:1710–6.
83. Schmaal L, Veltman DJ, van Erp TGM, Sämann PG, Frodl T, Jahanshad N, et al. Subcortical brain alterations in major depressive disorder: findings from the ENIGMA major depressive disorder working group. Mol Psychiatry. 2016;21:806–12.
84. Boedhoe PSW, Schmaal L, Abe Y, Ameis SH, Arnold PD, Batistuzzo MC, et al. Distinct subcortical volume alterations in pediatric and adult ocd: a worldwide meta- and mega-analysis. AJP. 2017;174:60–9.
85. van Erp TGM, Hibar DP, Rasmussen JM, Glahn DC, Pearlson GD, Andreassen OA, et al. Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium. Mol Psychiatry. 2016;21:547–53.
86. Tick B, Bolton P, Happé F, Rutter M, Rijsdijk F. Heritability of autism spectrum disorders: a meta-analysis of twin studies. J Child Psychol Psychiatry. 2016;57:585–95.
87. Hilker R, Helenius D, Fagerlund B, Skytthe A, Christensen K, Werge TM, et al. Heritability of schizophrenia and schizophrenia spectrum based on the nationwide danish twin register. Biol Psychiatry. 2018;83:492–8.
88. Faraone SV, Larsson H. Genetics of attention deficit hyperactivity disorder. Mol Psychiatry. 2019;24:562–75.
89. McGuffin P, Rijsdijk F, Andrew M, Sham P, Katz R, Cardno A. The heritability of bipolar affective disorder and the genetic relationship to unipolar depression. Arch Gen Psychiatry. 2003;60:497–502.
90. Zerwas S, Bulik CM. Genetics and epigenetics of eating disorders. Psychiatr Ann. 2011;41:532–8.
91. Van Grootheest DS, Cath DC, Beekman AT, Boomsma DI. Twin studies on obsessive–compulsive disorder: a review. Twin Res Hum Genet. 2005;8:450–8.
92. Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: review and meta-analysis. AJP. 2000;157:1552–62.

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AUTHOR CONTRIBUTIONS

AG - data curation, formal analysis, writing (original draft), writing (review and editing). TP – conceptualisation, writing (review and editing). RD – conceptualisation, writing (review and editing). GN - data curation, formal analysis, writing (review and editing). FT - writing (review and editing), funding acquisition. SCRW - writing (review and editing), funding acquisition. MV - writing (review and editing). DM – conceptualisation, writing (original draft), writing (review and editing), supervision (shared). DD – conceptualisation, writing (original draft), writing (review and editing), supervision (shared).

COMPETING INTERESTS

the authors declare no competing interests.

ETHICS

This study used exclusively secondary analyses of publicly available anonymized data and did not involve the collection of new human participant data. As such, ethical approval and informed consent were handled by the original studies that generated the datasets. All procedures in the original studies were conducted in accordance with institutional and international research ethics guidelines.

ADDITIONAL INFORMATION

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