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The multivariate genetic architecture of psychiatric and insulin resistance multimorbidity

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ABSTRACT

Psychiatric disorders frequently co-occur with insulin resistance (IR)-related conditions, including obesity, type 2 diabetes mellitus (T2DM), and metabolic syndrome (MetS). While genetic correlations have been reported, the genetics underlying this multimorbidity remains underexplored. Here, we investigate the joint genetic architecture of psychiatric-IR multimorbidity and explore links with the brain, tissue-specific gene expression, potential underlying biological mechanisms, and repurposable drugs. Genomic structural equation modeling (SEM) was applied to genome-wide association studies (GWAS) from five psychiatric disorders (attention-deficit/hyperactivity disorder (ADHD), anorexia nervosa (AN), major depressive disorder (MDD), obsessive-compulsive disorder (OCD), schizophrenia) and three IR-related conditions (MetS, obesity, T2DM) (N = 9725–933,970) previously showing pairwise genetic correlations. Factor analyses identified a latent genetic factor (Psych-IR factor) capturing shared genetics across psychiatric disorders (excluding schizophrenia) and IR-related conditions. Positive loadings were observed for ADHD, MDD, and IR-related conditions and negative loadings for AN and OCD. This factor showed genetic correlations with temporal, occipital, and total brain surface areas. A multivariate GWAS of the Psych-IR factor identified 150 associated loci and 366 genes (128 novel). Gene-set associations included insulin binding and Notch-signaling pathways, while gene-property analyses implicated the cerebellum, brain cortex, and pituitary gland, notably during prenatal development. Transcriptome-wide SEM (T-SEM) assessed tissue-specific gene expression associations and identified 499 genes (191 novel), including immune-related genes within the major histocompatibility complex (MHC) region. Drug repurposing analysis suggested six therapeutic candidates, including memantine and rosiglitazone. Enrichment of prioritized genes highlighted the chr16p11.2 region, BDNF-signaling, and lipid metabolism pathways. These findings

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advance understanding of the genetic and biological mechanisms underpinning psychiatric-IR multimorbidity, informing future research on precision medicine initiatives.

1. Introduction

The co-occurrence of psychiatric disorders and somatic insulin resistance (IR)-related conditions, such as obesity, type 2 diabetes mellitus (T2DM) and metabolic syndrome (MetS), is often observed (Perry et al., 2021; Wimberley et al., 2022). Obesity not only increases the risk of T2DM and MetS, but also of a broad range of psychiatric disorders (Leutner et al., 2023). Moreover, large-scale population data indicate bidirectional associations between T2DM and various psychiatric disorders, including neurodevelopmental, mood, and psychotic disorders (Wimberley et al., 2022). Such multimorbidity complicates clinical management (Kraus et al., 2023; Skou et al., 2022) and is linked to more severe outcomes; for instance, T2DM has been associated to more severe depression, while depression is linked to higher rates of complications and mortality in T2DM (Fanelli and Serretti, 2022; Possidente et al., 2023).

IR generally refers to a reduced response to insulin stimulation on peripheral tissues, resulting in elevated blood glucose levels (DeFronzo et al., 2015; Gluvic et al., 2017). However, it is increasingly evident that insulin signaling also has significant effects on the brain (Agrawal et al., 2021), where it is implicated in synaptic plasticity, neuroprotection, and neuronal survival (Pomytkin et al., 2018). Preclinical evidence further supports a role of insulin signaling in neuropsychiatric processes. A recent meta-analysis of 215 preclinical studies demonstrated that insulin dysregulation alters glutamatergic, dopaminergic, GABAergic, and serotonergic pathways, including reductions in N-methyl-D-aspartate (NMDA) receptor subunits, *PSD-95* expression, and dopamine transporter activity, findings that overlap with biological mechanisms implicated in psychiatric disorders (de Bartolomeis et al., 2023). Accumulating evidence links IR-related conditions with cognitive deficits across multiple domains (Fanelli et al., 2022; Ottomana et al., 2023). Central IR disrupts dopaminergic signaling in mesolimbic regions including the ventral tegmental area and nucleus accumbens, with downstream effects on motivation and reward processing (Gruber et al., 2023; Lyra E Silva et al., 2019). IR is also associated with prefrontal cortical atrophy and impaired performance in working memory and executive tasks, including set-shifting and cognitive flexibility (Sullivan et al., 2023). Structural correlates of IR have also been described in Alzheimer's disease, and bipolar disorder, particularly in the parietal-occipital junction, medial temporal regions, hippocampus, and ventromedial prefrontal cortex (Mansur et al., 2021; Morris et al., 2014; Mullins et al., 2017).

While many studies attribute metabolic disturbances in psychiatric patients to unhealthy lifestyles, sedentary habits, or the chronic use of psychotropic medications (e.g., Grajales et al., 2019), evidence suggests that these associations are not merely by-products of such factors. Glycemic and metabolic imbalances have been detected even in drug-naïve psychiatric patients at disorder onset, implying potential shared pathogenic mechanisms (Garrido-Torres et al., 2021). Genetic studies reinforce the hypothesis of a shared biological basis for this multimorbidity, showing significant genetic correlations between several psychiatric disorders — including attention-deficit/hyperactivity disorder (ADHD), anorexia nervosa (AN), obsessive-compulsive disorder (OCD), major depressive disorder (MDD), and schizophrenia (SCZ) — and IR-related conditions such as MetS, obesity, and T2DM (Fanelli, Franke, et al., 2022). Additionally, a family-based study indicated that relatives of individuals with a psychiatric disorder have an increased risk of T2DM (Wimberley et al., 2024). These findings suggest that shared underlying mechanisms are important for the multimorbidity between psychiatric disorders and IR-related conditions.

While bivariate genetic analyses have been instrumental for identifying shared genetic etiologies between pairs of psychiatric and IR-related conditions, the joint genetic architecture and biological substrates underlying the multimorbidity across these two groups of conditions has not been explored. To address this gap, we employed genomic structural equation modeling (genomic SEM) — a multivariate approach that enables analyzing the shared genetic architecture of multiple complex traits simultaneously (Grotzinger et al., 2019)— to explore the genetic factor structure best explaining the shared genetics between five psychiatric disorders and three IR-related conditions (MetS, obesity, and T2DM) that have previously shown significant pairwise genetic correlations (i.e., positive genetic correlations with ADHD and MDD; negative with AN, OCD, and SCZ) (Fanelli, Franke, et al., 2022). These psychiatric disorders were therefore selected on empirical genomic grounds rather than on clinical similarity. Specifically, ADHD, AN, MDD, OCD, and SCZ were included because previous analyses showed significant genetic correlations with one or more IR-related phenotypes, making them suitable candidates for multivariate modeling of psychiatric-IR multimorbidity. Using the genomic SEM framework, we also examined the genetic relationships between any identified latent factor representing psychiatric-IR multimorbidity and brain morphometry (Grasby et al., 2020; Hibar et al., 2017; Satizabal et al., 2019), and estimated the effects of single-nucleotide polymorphisms (SNPs), genes, and gene sets on such latent factors. Given that many loci identified through genome-wide association study (GWAS) likely exert their effects via modulation of gene expression (e.g., as expression quantitative trait loci [eQTLs] (Westra et al., 2013)), transcriptome-wide association studies (TWASs) can help to quantify the contribution of gene expression to complex traits (Gusev et al., 2016). Here, we employed transcriptome-wide structural equation modeling (T-SEM)—which extends TWASs by modeling tissue-specific gene expression within a multivariate network of genetically overlapping traits (Grotzinger et al., 2022)—to investigate the association between brain-specific transcriptomic patterns and any identified multimorbidity factor, also aiming to uncover genes whose tissue-specific gene expression might overlap with brain molecular signatures of repurposable drugs.

2. Experimental procedures

2.1. Input univariate genome-wide association study summary statistics

As input for genomic factor analyses and further genomic SEM/T-SEM analyses, we used univariate GWAS summary statistics from European ancestry cohorts for five psychiatric disorders (i.e., ADHD, AN, MDD, OCD, and SCZ) and three somatic IR-related conditions (i.e., MetS, obesity, and T2DM) (Table 1). Details regarding sample ascertainment, phenotype description, and analytical procedures for the univariate GWASs are available in the original publications listed in Table 1. SNP-based heritability for each phenotype was estimated using Linkage Disequilibrium Score Regression (LDSC; (Bulik-Sullivan et al., 2015)) and is reported on the liability scale (Table 1).

2.2. Genomic structural equation modeling

2.2.1. Genomic factor analyses

In order to model the genomic factor structure underlying the psychiatric and somatic IR-related conditions investigated here, we conducted a series of factor analyses based on the genetic covariance matrices derived from LDSC analyses within genomic SEM (Grotzinger et al., 2019). Standard genomic SEM procedures and default filtering parameters were used (see further description in **Supplementary**

information). We then first conducted exploratory factor analyses (EFA) on the output of the LDSC analyses performed on the odd chromosomes using the *factanal* function of R with promax rotation, which allows factors to be correlated. We tested solutions for up to three latent factors, while retaining factors that explained at least 20% of the variance. Based on the results of the EFA, we performed confirmatory factor analyses (CFA) for the one-factor and two-factor models using the genetic covariance matrix from the LDSC with even chromosomes, where factors were assigned to traits when their standardized loading exceeded 0.20 in the corresponding EFA. The model uses Diagonally Weighted Least Square and was specified so that the variance of each latent factor is fixed to 1 (i.e., unit variance identification). Model fit was assessed using standard measures in SEM, as described in Grotzinger et al. (2019) and in **Supplementary information**. Finally, the CFA model with best fit in even chromosomes was also assessed for all autosomes.

2.2.2. Genetic correlations with brain morphometry

Brain morphometry phenotypes were selected because they represented the largest available ENIGMA-derived cortical and subcortical GWAS summary statistics, providing broad coverage of genetically informed brain structure while maximizing statistical power and comparability across regions. We used genomic SEM to model the genetic covariances and correlations between any identified latent factor (s) encompassing both psychiatric and IR-related conditions and the GWAS summary statistics of 1) the bilateral averages of cortical thickness and surface area (SA) (adjusted for mean thickness and total SA, respectively) of 34 brain regions and the total brain (N = 33,992; Grasby et al., 2020); and 2) eight subcortical volumes (Hibar et al., 2017; Satizabal et al., 2019), namely nucleus accumbens (N = 32,562), amygdala (N = 34,431), brainstem (N = 28,809), caudate nucleus (N = 37,741), globus pallidus (N = 34,413), putamen (N = 37,571), thalamus (N = 34,464), and hippocampus (N = 33,536). The GWAS of cortical regions were adjusted for either mean thickness or total SA, accordingly, and the subcortical GWAS were adjusted for total intracranial or brain volume. We refer the reader to the original publications (cortical thickness and SA (Grasby et al., 2020); subcortical volumes (Hibar et al., 2017; Satizabal et al., 2019)) for further details about how these brain-related univariate GWASs were performed. Bonferroni correction was applied to account for multiple comparisons, thus adjusting the significance threshold (α_{Bonf} = 0.05/78 brain phenotypes = 6.41 × 10^{-4}).

We further computed heterogeneity statistics (Q_{trait}) for the associations of such latent factor(s) with the brain morphological traits, as described in (Grotzinger et al., 2019). For each brain phenotype, the Q_{trait} heterogeneity index evaluates to which extent that trait operates through the latent factor, compared to operating through the individual disorders/conditions that compose the latent factor. A significant Q_{trait} ($P < 6.41 \times 10^{-4}$) indicates that the pattern of associations between the brain trait and the individual disorders/conditions is not well accounted for by the factor.

2.2.3. Multivariate GWAS and follow-up of identified latent factor(s) representing psychiatric-IR multimorbidity

We used genomic SEM (Grotzinger et al., 2019) to conduct a multivariate GWAS on any identified latent factor(s) representing psychiatric-IR multimorbidity (see **Supplementary information** for further details). Similarly to the Q_{trait} statistics described above, we performed SNP-level tests of heterogeneity (Q_{SNP}) to evaluate whether each SNP had consistent pleiotropic effects on the factor components (i.e., input disorders/conditions) that effectively only operate via the shared liability or whether there was evidence of heterogeneity, indicating that the SNP effect is not fully mediated by the factor (Grotzinger et al., 2019).

We further analyzed the results of the multivariate GWAS using Functional Mapping and Annotation of Genome-Wide Association Studies (FUMA v1.5.6; (Watanabe et al., 2017)), which included associated loci identification as well as gene-based, gene-set, and gene-property analyses implement with Multi-marker Analysis of Genomic Annotation (MAGMA v1.08; (De Leeuw et al., 2015)). Detailed description can be found in **Supplementary information**. We also ran the FUMA analyses on the eight GWAS summary statistics of the individual phenotypes that served as input for genomic SEM, in order to compare the significant loci and genes identified for the multivariate GWAS. Genomic loci and genes associated with the latent factor that did not overlap with those associated with the individual phenotypes were considered as novel/unique to the multimorbidity factor.

2.3. Transcriptome-wide structural equation modeling

T-SEM was used to investigate the effects of tissue-specific gene expression on the genetic multimorbidity factor representing the shared genetics of psychiatric disorders and IR-related conditions (Grotzinger et al., 2022). See **Supplementary information** for detailed T-SEM procedures. In summary, as a first step, univariate, summary-based TWASs were performed using FUSION (Gusev et al., 2016) to test the association between each of the eight individual input phenotypes (Table 1) and predicted tissue-specific gene expression related to 15 brain and pituitary gland tissues from the Genotype-Tissue Expression (GTEx) v8 and PsychENCODE consortia (Gandal et al., 2018; The GTEx Consortium et al., 2020). For each gene, the tissue-specific gene expression estimates produced by univariate TWASs were then used to expand both the genetic and sampling covariance matrices estimated in genomic SEM. As a second step, T-SEM was employed. We applied a Bonferroni correction to adjust for multiple testing across 16,542 unique genes, resulting in a significance threshold of $\alpha_{Bonf} = 3.02 \times 10^{-6}$. Furthermore, to identify genes with potentially trait-specific effects, we

Table 1
Contributing univariate genome-wide association study datasets.

Univariate GWAS	Cases	Controls	Total sample	Population prevalence	SNP-based heritability (SE)	GWAS Reference
ADHD	38,691	186,843	225,534	0.087	0.213 (0.010)	(Demontis et al., 2023)
AN	16,992	55,525	72,517	0.009	0.165 (0.011)	(Watson et al., 2019)
MDD	170,756	329,443	500,199	0.21	0.290 (0.045)	(Howard et al., 2019)
OCD	2688	7037	9725	0.02	0.094 (0.004)	(IOCDF-GC/OCGAS, 2018)
SCZ	53,386	77,258	130,644	0.01	0.223 (0.008)	(Trubetskoy et al., 2022)
MetS	59,677	231,430	291,107	0.25	0.201 (0.011)	(Lind, 2019)
Obesity[a]	9805	235,085	244,890	0.39	0.267 (0.025)	(Watanabe et al., 2019)
T2DM	80,154	853,816	933,970	0.1	0.174 (0.008)	(Mahajan et al., 2022)

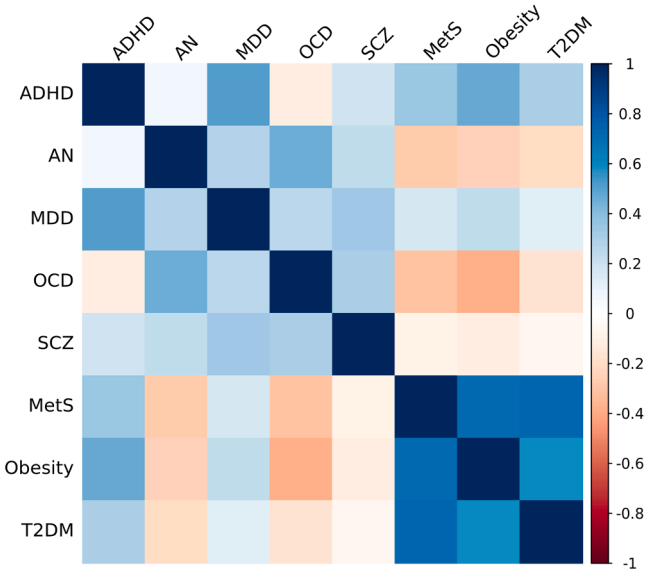
Note. Population prevalences were used for the liability scale conversion and were retrieved from their original publications and/or (Grotzinger et al., 2019) for the psychiatric traits, from (O'Neill and O'Driscoll, 2015) for MetS, from (World Health Organization, 2018) for obesity, and from (Kumar et al., 2024) for T2DM.
Abbreviations: ADHD, attention-deficit/hyperactivity disorder; AN, anorexia nervosa; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; SCZ, schizophrenia; MetS, metabolic syndrome; T2DM, type 2 diabetes mellitus; SE, standard error; GWAS, genome-wide association study; SNP, single-nucleotide polymorphism.
[a]GWAS ATLAS ID: 3687, UK Biobank phenotype field 41204 (41204_E66), which refers to the trait 'Diagnoses - secondary ICD-10: E66 Overweight and obesity'.

also computed gene heterogeneity statistics (Q_{Gene}) as a χ^2 difference test between a common pathways model (where gene expression predicts the multimorbidity latent factor) and an independent pathways model (where the gene expression only predicts specific psychiatric or IR-conditions defining the factor) (Grotzinger et al., 2022). To ensure robustness, we excluded from the list of significantly associated genes those with significant Q_{Gene} values, through using the same Bonferroni corrected threshold.

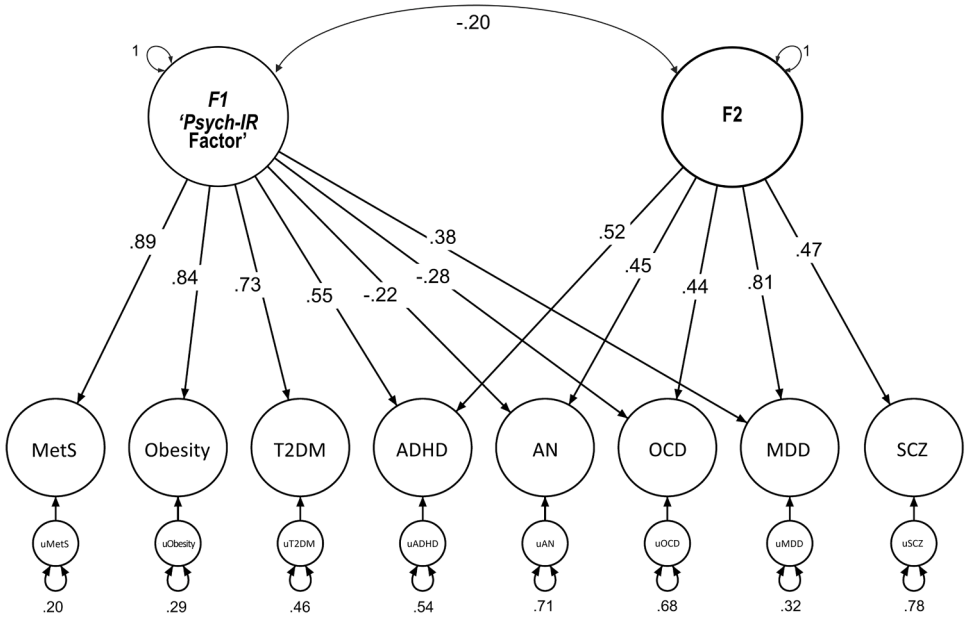
If not otherwise specified, the MHC region was excluded from follow-up analyses due to its highly complex linkage disequilibrium (LD) structure, which may confound genetic association signals and inflate the number of false-positive findings. However, to provide a comprehensive assessment of its potential impact on the results, we also conducted parallel T-SEM analyses including the MHC region, and findings from both T-SEM analyses are presented to ensure transparency and completeness in reporting.

2.4. Drug repurposing analysis

To identify potential therapeutic candidates for the psychiatric-IR multimorbidity, we used PharmOmics, a tissue-specific, cross-species transcriptomic database of drug-induced gene expression signatures



(a)



(b)

Fig. 1. Multivariate genetic architecture of five psychiatric disorders and three somatic IR-related conditions. a. Heatmap of pairwise genetic correlations based on all autosomes estimated using LDSC regression within genomic SEM; b. Path diagram for the final confirmatory factor model with standardized parameter estimates. Circles represent the genetic components of each disorder, condition, or common genetic factor. One-headed arrows represent regression relationships from the independent variables pointing towards the dependent variables. Two-headed arrow between variables represent a covariance relationship. Two-headed arrows connecting the variable to itself represent residual variance. ADHD, attention-deficit/hyperactivity disorder; AN, anorexia nervosa; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; SCZ, schizophrenia; MetS, metabolic syndrome; T2DM, type 2 diabetes mellitus.

(https://mergeomics.research.idre.ucla.edu/runpharmomics.php#; Chen et al., 2022). Input gene lists were derived from significant tissue-specific gene expression associations identified by T-SEM. Upregulated and downregulated genes (based on T-SEM Z scores) were submitted separately to PharmOmics to assess their overlap with drug-induced gene signatures. A full description of the analytical pipeline and database composition is available in **Supplementary information**.

We selected drug repurposing candidates based on: 1) Food and Drug Administration approval (https://www.accessdata.fda.gov/; accessed September 2024) for conditions other than psychiatric disorders; 2) predicted blood-brain barrier permeability; 3) availability of nervous tissue-derived gene signatures in PharmOmics; 4) cross-species concordance of directionality (based on Jaccard scores and P-values); and 5) significant P-values and negative Jaccard scores, indicating an opposing gene regulation pattern that could potentially reverse disease-related molecular changes.

2.5. Enrichment analyses of prioritized genes

In order to compose a list of prioritized genes, we merged the list of significantly associated genes identified through 1) the MAGMA gene-based analysis of the multivariate GWAS and 2) the tissue-specific expression analyses in T-SEM. We used FUMA v1.5.6 (Watanabe et al., 2017) to conduct enrichment analyses to test for overrepresentation of the prioritized genes in a wide range of pre-defined gene sets (**Supplementary information**).

3. Results

3.1. Genetic factor structure underlying psychiatric and somatic IR-related conditions

We formally modeled the genetic covariance structure of the five psychiatric (ADHD, AN, MDD, OCD, and SCZ) and three somatic IR-related (MetS, obesity, and T2DM) phenotypes that are genetically correlated (Fanelli, et al., 2022a; and Fig. 1a). Descriptives of the input data can be found in Table 1. Exploratory factor analyses suggested the two-factor solution as the best model (variance explained: $R^2(F1) = 32.1\%$, $R^2(F2) = 20\%$, $R^2(Total) = 52.1\%$), since the one-factor solution explained only 31.4% of the variance, while the third factor in a three-factor model explained only 15.2% of the variance (**Supplementary Table S1**). Confirmatory factor analyses, both in the even chromosomes and in the full set of autosomes, confirmed that a two-correlated-factors model fits the data well (for all autosomes: $\chi^2 = 78.559$, $df = 15$, $P\chi^2 = 1.28 \times 10^{-10}$, $AIC = 120.559$, $CFI = 0.978$, $SRMR = 0.053$; **Supplementary Table S2;** see also **Supplementary Table S3**) and revealed a small negative genetic correlation between the two factors ($r_g = -0.204$; $SE = 0.043$; $P = 2.02 \times 10^{-6}$; Fig. 1b). The first factor consists of all psychiatric disorders, except SCZ, and all somatic IR-related conditions investigated. This factor is hereafter referred to as the psychiatric and IR-related (Psych-IR) multimorbidity factor. The second factor consists of all five psychiatric disorders investigated, but none of the somatic ones.

Given our aim of unraveling the genetic architecture underlying the psychiatric and IR-related multimorbidity, subsequent results are focused on the Psych-IR multimorbidity factor, which was taken forward to investigate its relationship with brain morphometry, to conduct a multivariate GWAS, exploring it at multiple levels, as well as to conduct T-SEM and drug repurposing analysis.

3.2. Genetic overlap between the Psych-IR multimorbidity factor and brain morphometry

We examined patterns of genomic correlations between the Psych-IR multimorbidity factor and brain morphometry (**Supplementary Figure S1**). We observed significant negative genetic correlations between the Psych-IR multimorbidity factor and total SA ($r_g = -0.151$; $SE = 0.033$; $P = 4.89 \times 10^{-6}$) and inferior temporal SA ($r_g = -0.183$; $SE = 0.045$; $P = 4.60 \times 10^{-5}$), while the factor had a positive genetic correlation with lateral occipital SA ($r_g = 0.113$; $SE = 0.032$; $P = 5.01 \times 10^{-4}$) (Fig. 2). Follow-up Q_{trait} index analyses revealed no significant sign of heterogeneity involving the three significant genetically correlated brain traits, indicating that the implication of these brain structures are indeed via the common pathway of the Psych-IR multimorbidity factor (rather than independent pathways of individual psychiatric disorders and somatic IR-related conditions). **Supplementary Table S4** provides genetic correlation estimates and Q_{trait} results for all brain traits analyzed.

3.3. Multivariate GWAS of the Psych-IR multimorbidity factor

Through a multivariate GWAS of the Psych-IR multimorbidity factor ($N_{eff} = 622{,}007.6$), we identified 11,672 genome-wide significant SNPs, which were distributed across 168 independent risk loci (**Supplementary Table S5**). There were 9324 significant Q_{SNPs} (of which, 2539 were genome-wide significant SNPs for the Psych-IR factor), indicating that the effects of these SNPs are not fully mediated by the latent genomic factor. Since we are interested in understanding the shared genetic basis of this multimorbidity, significant Q_{SNPs} were removed from downstream analyses (in order to reduce heterogeneity), along with those in LD ($r^2 > 0.1$, 250 kb) with them. The final Psych-IR factor multivariate GWAS summary statistics contains 8834 genome-wide significant SNPs, distributed across 150 independent loci (**Figure 3; Supplementary Figure S2**). Out of the 150 independent genomic loci, 46 did not overlap with the genomic loci associated in the input univariate GWAS of the psychiatric and somatic IR-related conditions that compose the latent factor (**Supplementary Table S6**).

3.4. Genes, gene sets, and gene-property associations with the Psych-IR multimorbidity factor

Gene-based analysis identified 366 genome-wide associated genes (Fig. 3). Of these, 128 (35%) are considered novel, in the sense that they were not significantly associated with the individual phenotypes that compose the factor (**Supplementary Table S7**). Gene-set analyses revealed six gene sets associated with the Psych-IR multimorbidity factor after Bonferroni correction for multiple testing, including one representing insulin binding (GOMF_INSULIN_BINDING; MsigDB M26667) and one implicating NOTCH signaling (REACTOME_SIGNALING_BY_NOTCH; MsigDB M10189), in addition to four gene sets of general Gene Ontology (GO) Biological Processes (Table 2).

MAGMA gene-property tissue expression analyses were performed to identify tissue specificity of the gene-based associations of the Psych-IR multimorbidity factor and showed associations with the brain and pituitary general tissue types (**Supplementary Figure S3a**). A more fine-grained examination of the tissue types in question revealed that the Psych-IR factor was associated with highly expressed genes in specific brain tissues, namely the cerebellum, cerebellar hemisphere, cortex, and frontal cortex Brodmann Area (BA) 9, as well as the pituitary gland (**Supplementary Figure S3b**). The tissue expression analyses across 11 different general developmental stages of the brain implicated early, early-mid, and late-mid-prenatal stages (**Supplementary Figure S3c**), while no associations were found across the brain samples representing 29 different ages of the brain (BrainSpan; Kang et al., 2011).

3.5. Multivariate TWAS

After excluding 31 unique genes (spanning 73 gene-tissue pairs; **Supplementary Table S9**) with significant Q_{Gene} statistics, T-SEM identified 462 unique genes whose expression in brain tissues was associated with the Psych-IR multimorbidity factor (a heatmap of the

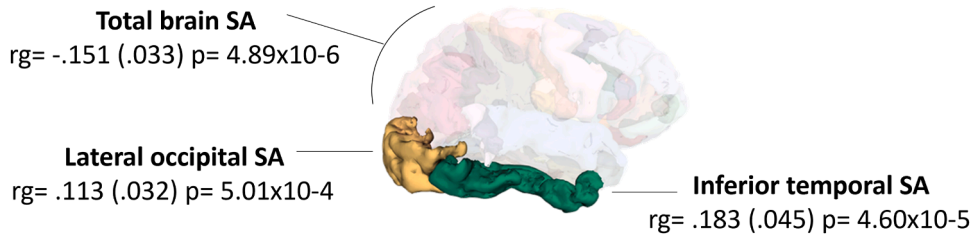


Fig. 2. Genetic correlations (r_g) between the Psych-IR multimorbidity factor and brain morphometric traits. Areas highlighted indicate the significant genetic correlations with total brain surface area (SA), lateral occipital SA, and inferior temporal SA. Visualization was performed using the ENIGMA-Vis tool (Shatokhina et al., 2021).

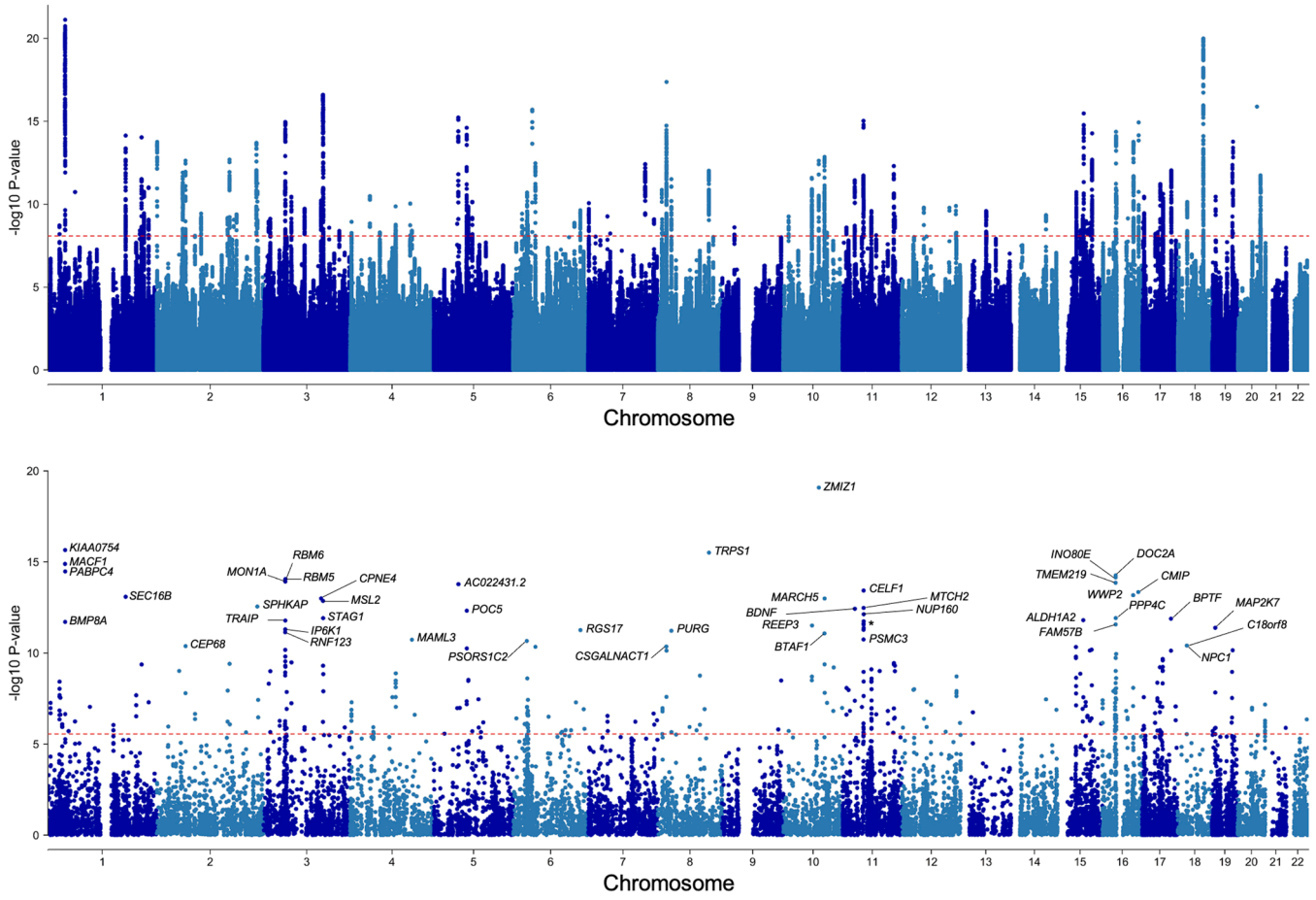


Fig. 3. SNP-based (top) and gene-based (bottom) Manhattan plots of the Psych-IR multimorbidity factor multivariate GWAS. Dotted red line represents the genome-wide significance threshold of 5×10^{-8} for the SNP-based plot and of 2.78×10^{-6} (i.e., $\alpha_{Bonf} = 0.05/17{,}977$ protein coding genes) for the gene-based plot. Gene names are shown for the top 50 out of the 366 genome-wide significant genes. The * on chromosome 11 represents the FNBP4, SPI1, NDUFS3, AGBL2, SLC39A13 genes, in descending order. For a full list of significant genomic loci and associated genes, see **Supplementary Tables S6** and **S7**.

Table 2
Gene sets significantly associated with the Psych-IR multimorbidity factor.

Significant gene sets	N_{genes}	P	P_{Bonf}
GOBP_POSITIVE_REGULATION_OF_RNA_METABOLIC_PROCESS	1657	1.38×10^{-7}	0.0023
GOBP_NEGATIVE_REGULATION_OF_BIOSYNTHETIC_PROCESS	1390	1.89×10^{-7}	0.0032
GOBP_POSITIVE_REGULATION_OF_MACROMOLECULE_BIOSYNTHETIC_PROCESS	1723	5.48×10^{-7}	0.0093
REACTOME_SIGNALING_BY_NOTCH	183	7.60×10^{-7}	0.0129
GOBP_NEGATIVE_REGULATION_OF_NUCLEOBASE_CONTAINING_COMPOUND_METABOLIC_PROCESS	1316	9.03×10^{-7}	0.0153
GOMF_INSULIN_BINDING	5	1.58×10^{-6}	0.0268

Abbreviations: N_{genes}, number of genes included in the gene set; P, MAGMA gene-set association P-value; P_{Bonf}, P-value after Bonferroni multiple testing correction for all the MsigDB gene sets tested.

most significant genes in each tissue and across tissues is depicted in **Supplementary Figure S4** and **S5,** respectively; **Supplementary Table S10**). Among these, 188 genes were not significant in any univariate TWAS of the input phenotypes and are therefore considered novel (**Supplementary Table S11**). Among the top significantly up-regulated genes, *MST1R, MTCH2, RNF123, RP11–69E11.4, SNF8*, and *BMP8A* were recurrent across several tissues (**Supplementary Table S11** and **Figure S5;** see also the Miami plot of the analysis including the MHC region in Fig. 4). Among the top significantly down-regulated genes, *RBM6, INO80E, RPAP1, C18orf8, VPS11*, and *MAPK3* were recurrent across tissues (**Supplementary Table S11**). Of note, seven genes — *ANKDD1B, C17orf58, CRHR1, JMY, MAPT, PAM*, and *POC5* — demonstrated significant associations with the multimorbidity factor but showed discordant expression effects across different brain tissues (**Supplementary Table S12**).

In the T-SEM analysis including the MHC region, 37 additional unique genes were significant (**Figure 4; Supplementary Figures S6-S7**), including three novel genes (i.e., *HSD17B8, RPS18*, and *UQCC2*) that were not significant in any of the univariate TWASs (**Supplementary Table S13**). Among this region, the expression of the *HLA-DRB5* gene was the most frequently associated (significant across 14 tissues) with the multimorbidity factor, followed by *MICB* (12 tissues), and *CYP21A2* (11 tissues) (**Supplementary Table S14**). Among the up-regulated MHC genes, the most significant were *HCG27* and *AGER* in the anterior cingulate cortex and *CYP21A2* in the putamen. Among the down-regulated MHC genes, the most significant were *NOTCH4* in the hippocampus and cerebellum, *C4A* in the cortex, and *HLA-DRB1* in the nucleus accumbens. (**Supplementary Table S15**). These top three down-regulated genes were also the most significant ones among the whole set of MHC-related genes.

3.6. Potential repurposable drugs

PharmOmics identified six candidate compounds with transcriptomic signatures inversely matching the gene expression profiles associated with the Psych-IR multimorbidity factor (**Supplementary Table S16**). In humans (*Homo sapiens*), bevacizumab — an anti-angiogenic monoclonal antibody having a role in cancer treatment — emerged as a potential candidate and demonstrated significant gene expression overlap in nervous tissues. In mice (*Mus musculus*), the analysis highlighted memantine, rosiglitazone, levodopa, cyclophosphamide, and ceftriaxone as leading candidates for repurposing. Memantine and rosiglitazone, known for their neuroprotective and anti-diabetic properties, respectively, showed robust overlap with the multimorbidity factor gene signatures. Additionally, levodopa, a precursor of dopamine and a commonly used drug in Parkinson's disease, along with cyclophosphamide and ceftriaxone, both of which are involved in immune modulation and neuroprotection, also demonstrated significant overlap.

3.7. Enrichment analyses of the Psych-IR prioritized genes

A total of 534 protein-coding genes were used as input for the combined gene set enrichment analyses, comprising 215 significantly associated genes derived from the MAGMA gene-based analysis of the Psych-IR multivariate GWAS, 179 genes derived from the T-SEM analyses, and 140 genes that were overlapping between these two approaches. There were 518 genes with unique Entrez IDs, which were compared against a total of 18,605 unique Entrez background protein-coding genes. After false discovery rate (FDR) correction for multiple testing within category/subcategory, we observed significant enrichments in 110 pre-computed sets from the Molecular Signatures Database (MsigDB v2023; Liberzon et al., 2011) (encompassing 104 unique gene sets) and in 201 sets of reported genes from the GWAS-Catalog

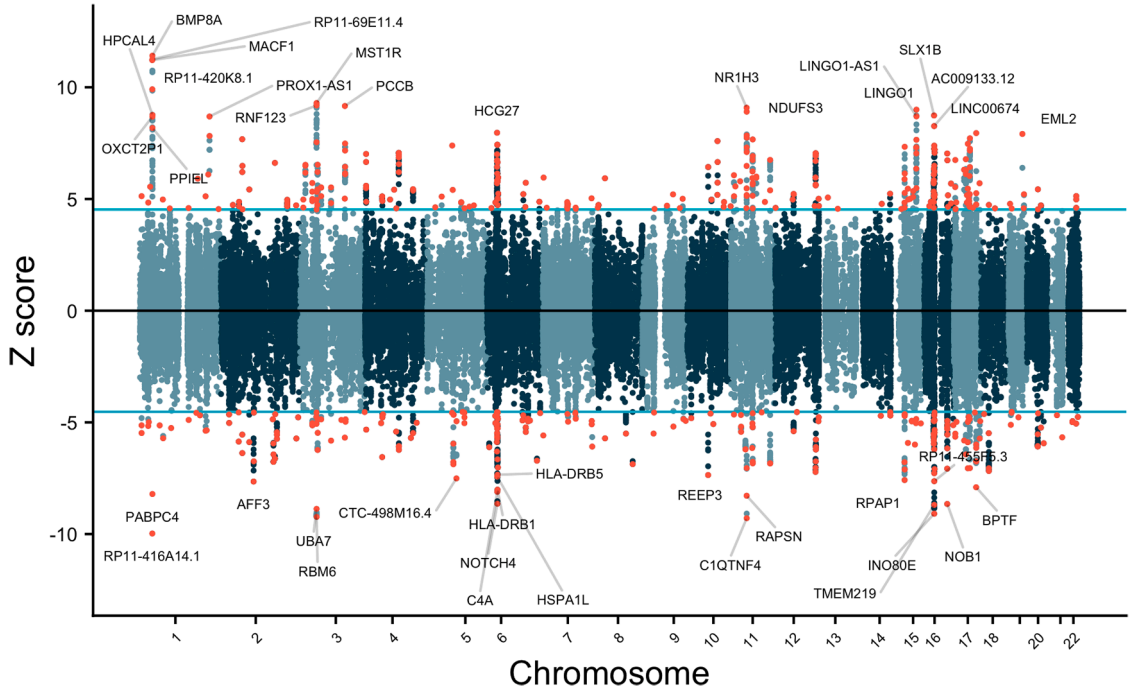


Fig. 4. Miami plot of Z statistics for the estimated gene expression effects on the Psych-IR multimorbidity factor. Z statistics are signed such that orange dots on the upper and lower half of the plot reflect genes whose up-regulated and down-regulated expression, respectively, is significantly associated with the multimorbidity factor. The light blue horizontal lines reflect the Bonferroni-corrected significance threshold. Genes exceeding this threshold are shown as orange dots. For genes significant in multiple tissues, only the most significant instance is highlighted in orange. Up to 40 unique Bonferroni-significant genes are labeled across tissues. Genes with significant Q_{Gene} statistics are not included.

(**Supplementary Table S8**). More specifically, these include significant enrichments in 14 (MsigDB c1) positional gene sets. The most significant enrichment was in position chr16p11, which also had the highest proportion of overlapping genes with the gene set (i.e., 39 overlapping genes out of 97 in the gene set). There were also four significantly enriched (MsigDB c2) curated gene sets, two of which are also related with the chr16p11 region: the WP_16P112_PROXIMAL_DELETION_SYNDROME and the WP_16P112_DISTAL_DELETION_SYNDROME gene sets (both also significant in the analyses within the MsigDB c2:All Canonical Pathways (CP) and the MsigDB c2:CP/WikiPathways subcategories). Additional enrichments were found for three gene sets within the MsigDB c2:CP/WikiPathways subcategory, one of them related to the brain-derived neurotrophic factor (BDNF) signaling pathway and two related to familial hyperlipidemia; one MsigDB c5:GO:molecular functions gene set; three MsigDB c8 cell type signatures gene sets; and 79 MsigDB c3:Transcription Factor targets gene sets. No significant enrichment was observed among other categories of pre-defined gene sets.

4. Discussion

This study leveraged state-of-the-art multivariate genomic and transcriptomic methods to uncover the shared genetic architecture underlying the frequent co-occurrence of psychiatric disorders and somatic IR-related conditions. We identified a latent Psych-IR multimorbidity factor reflecting common genetic liability across ADHD, AN, MDD, OCD, MetS, obesity, and T2DM. The multivariate GWAS of this factor revealed 150 loci and 366 genes, many of which were considered novel. Gene-set analysis implicated insulin binding and Notch signaling pathways. Genetic correlations associated the Psych-IR factor with brain morphometry, implicating structures involved in multisensory integration, while tissue specificity analyses pointed to the cerebellum, cortex, and pituitary gland. Transcriptomic analyses excluding the MHC region identified 462 genes whose expression in brain and pituitary tissues was associated with the factor, including 188 undetected by univariate TWASs; parallel analyses including the MHC region identified 37 additional genes. Top up-regulated genes suggest roles for immune modulation, mitochondrial function, and energy balance, while down-regulated genes highlight disruptions in chromatin remodeling and signal transduction. Enrichment analyses of prioritized genes identified additional pathways related to neurodevelopment and lipid metabolism, including BDNF signaling and 16p11.2 deletion syndromes. Drug repurposing identified compounds – such as memantine and rosiglitazone – whose transcriptomic signatures oppose those associated with the Psych-IR factor, suggesting candidate targets for translational research.

4.1. Genetic architecture of psychiatric-IR multimorbidity

The identification of a common Psych-IR multimorbidity genetic factor extends prior studies that primarily explored pairwise correlations between these related conditions (Fanelli, Franke, et al., 2022; Fanelli et al., 2025; Hübel et al., 2019). Our multivariate approach uncovered shared genetic variants and mechanisms across them, though with opposite loadings for some conditions on the Psych-IR factor. ADHD and MDD loaded positively, while AN and OCD showed negative loadings, consistent with prior pairwise genetic correlations (Fanelli, Franke, et al., 2022). AN's negative loading reflects its clinical profile of weight loss, contrasting with IR-related conditions (American Psychiatric Association, 2013; Walsh et al., 2023). Although epidemiological data showed increased co-occurrence of OCD and T2DM (Wimberley et al., 2022), recent familial studies report lower parental T2DM prevalence in OCD, consistent with the negative genetic loading and suggesting potential environmental/lifestyle influences (Wimberley et al., 2024). Despite SCZ's clinical overlap with metabolic dysregulation, particularly during antipsychotic treatment, SCZ displayed weak genetic loading and was not retained in the Psych-IR factor. This finding should not be interpreted as evidence against a biological relationship between SCZ and metabolic dysfunction. Rather, SCZ appears to represent a distinct and more heterogeneous case within psychiatric-IR multimorbidity. Global genetic correlations show inverse associations between SCZ and MetS/body mass index (BMI), but not with T2DM and related glycemic traits (Fanelli, Franke, et al., 2022). In contrast, local genetic correlation analyses revealed both protective and risk-conveying regions between SCZ and IR-related conditions, indicating that opposite genetic effects may coexist across the genome (Fanelli et al., 2025). Such regional heterogeneity may attenuate genome-wide genetic correlations and reduce loading on a common latent factor. This interpretation is consistent with Su et al. (2022), who reported positive familial aggregation between SCZ and T2DM but negative SCZ polygenic loading for T2DM, suggesting that environmental, lifestyle, or treatment-related factors may partly explain their clinical comorbidity.

4.2. Gene-level findings and biological pathways

A key contribution of this study is the identification of genetic loci associated with psychiatric-IR multimorbidity, including genes undetected by univariate GWASs, while supporting some established candidate biological pathways. Among the top genes identified by the Psych-IR multivariate GWAS, *ZMIZ1* – involved in transcriptional regulation and neurodevelopment – showed the strongest association and had been previously implicated by the T2DM GWAS (Mahajan et al., 2022). *DOC2A*, located at chr16p11, is involved in Ca^{2+}-dependent neurotransmitter release and is predominantly brain-expressed. Other top genes include *MACF1* (cytoskeletal regulation), *TRPS1* (transcription regulation), *PABPC4* (mRNA stability), and tumor suppressors *RBM5* and *RBM6*. Among the novel genes, the top three (*KCTD13, GDPD3*, and *MAPK3*) are all within the chr16p11.2 region (discussed in detail below). These are followed by *MST1*, whose receptor (*MST1R*) was the most up-regulated gene in T-SEM and mediated immune-inflammatory pathways (Huang et al., 2020). Other highly up-regulated T-SEM genes across several tissues include *MTCH2* (adipocyte differentiation, mitochondrial function); *RNF123/KPC1* and *SNF8* (cellular homeostasis, immune regulation) (Kravtsova-Ivantsiv et al., 2015; Kumthip et al., 2017) *BMP8A* (steroidogenesis and energy balance). Among the top down-regulated and recurrent genes across tissues, *RBM6* and *INO80E* are involved in DNA repair and chromatin remodeling, *VPS11* in vesicular trafficking, and *MAPK3* in signal transduction and cell differentiation. Among the novel genes, *STX4, EHD4*, and *USP46* participate in neurotransmission, vesicle trafficking, and insulin signaling – bridging neural and metabolic processes – while *ZNF268* and *MCM9* regulate transcription and genomic stability. Collectively, the novel genes highlight molecular mechanisms at the intersection of central nervous system function and peripheral metabolism.

While the interpretation of MHC findings requires caution due to high LD and gene density, results support immune system involvement. Frequently associated immune-related genes include *HLA-DRB5*, linked to SCZ, MDD, Parkinson's disease, and diabetes; *MICB*, a marker of cellular stress-induced immune dysregulation; and *CYP21A2*, involved in glucocorticoid and mineralocorticoid biosynthesis. Glucocorticoids influence neuroplasticity and *BDNF* expression, essential for synaptic integrity and cognitive function (Tsimpolis et al., 2024). The MHC implication aligns with prior local genetic correlation evidence linking psychiatric and IR-related conditions (Fanelli et al., 2025).

Gene-set analyses of the Psych-IR multivariate GWAS implicated

insulin binding and Notch signaling pathways, supporting a central role for metabolic dysregulation in psychiatric-IR multimorbidity. The insulin binding gene set comprises five genes, three of which — *IDE, IGF1R*, and *INSR* — showed genome-wide significance in the gene-based results. IDE encodes the insulin-degrading enzyme, implicated in T2DM, cognition, and neurodegeneration; *INSR* encodes the insulin receptor; and *IGF1R* encodes the insulin-like growth factor 1 receptor, which is involved in neurogenesis, synaptic plasticity, and neuroprotective processes. While insulin signaling has been previously linked to psychiatric disorders (Fanelli, Franke, et al., 2022; Fanelli et al., 2025), our findings reinforce the potential to explore this pathway further as a gateway for managing the co-occurrence of psychiatric disorders and somatic IR-related conditions. The Notch signaling pathway also showed significant enrichment, aligning with its relevance to both metabolic and brain-related phenotypes. It is involved in metabolic regulation, e.g., active Notch signaling correlates with IR and may influence glucose metabolism through its effects on hepatic function (Valenti et al., 2013), and in learning, memory, and social behavior (Salazar et al., 2020); it has also been implicated in neurodevelopment, neuronal connectivity and neurogenesis (R. Zhang et al., 2018).

Subsequent enrichment analyses of our prioritized genes (i.e., combined list of significantly associated genes from the multivariate GWAS and T-SEM analyses) revealed additional gene sets implicated in psychiatric-IR multimorbidity. Noteworthy are the ones related to proximal and distal chromosome 16p11.2 deletion syndromes, BDNF signaling, and familial hyperlipidemia (types 3 and 4). Both 16p11.2 deletion syndromes (OMIM#611913 and OMIM#613444) are rare genetic conditions marked by developmental delay, speech impairments, and a high prevalence of psychiatric disorders. Up to 74% of affected individuals exhibit obesity and hyperphagia (Vos et al., 2024; Zufferey et al., 2012), underscoring their relevance to both metabolic and psychiatric domains. The enrichment of the BDNF signaling pathway highlights its integrative role across neural and metabolic processes. During development, BDNF supports neuronal survival, differentiation, and synaptic plasticity and has established links to psychiatric disorders (Zou et al., 2024). Additionally, BDNF interacts with insulin pathways and modulates metabolic function (Bathina and Das, 2015); low BDNF levels have been associated with glucose and lipid dysregulation (Krabbe et al., 2007; Xia et al., 2022), while exercise, which increases BDNF levels, improves both insulin sensitivity and cognition (Dadkhah et al., 2023). Gene sets related to familial hyperlipidemia types 3 and 4 also showed significance. Type 3 involves impaired clearance of intermediate-density lipoproteins due to mutations in the *APOE* gene, of which the protein plays a role in lipid transport and metabolism (Javvaji et al., 2024). *APOE* was among our genome-wide significant genes and harbors the most common genetic risk factor for Alzheimer's disease (Jackson et al., 2024). Familial hyperlipidemia type 4 is characterized by elevated triglycerides and very-low density lipoproteins in the blood (Goyal et al., 2024). Dyslipidemia, a common feature in both psychiatric disorders (e.g., MDD, SCZ) and somatic IR-related conditions (e.g., MetS), contributes to chronic inflammation, oxidative stress, and endothelial dysfunction, exacerbating IR (Higashi, 2023; Zorkina et al., 2024). Together, these findings suggest that disrupted lipid metabolism may be a key mechanism in the shared pathophysiology of psychiatric and IR-related conditions.

4.3. Brain morphology and developmental tissue specificity

In terms of brain morphometry implication, the Psych-IR multimorbidity factor showed negative genetic correlations with total SA and inferior temporal SA – a region involved in higher-order visual processing and memory retrieval (Conway, 2018; Mruczek and Sheinberg, 2007). The inferior temporal cortex has been previously linked to obesity and IR (W. Chen et al., 2023). The Psych-IR factor was also positively correlated with the lateral occipital cortex, implicated in shape and multisensory visual perception (Zhang et al., 2004), where altered glucose metabolism has been linked to cognitive deficits and IR-related hypoperfusion (Cui et al., 2017; Wijtenburg et al., 2019). These findings align with prior evidence linking IR to reduced cortical – but not subcortical – gray matter volume in individuals with MetS (Lu et al., 2021). Another link to the brain is found in the tissue expression analyses of the Psych-IR factor gene associations, which showed specificity to brain tissues, particularly the cerebellum and frontal cortex (BA9), and the pituitary gland. While traditionally linked to motor control, the cerebellum is increasingly recognized for its role in cognitive and emotional regulation (Adamaszek et al., 2017; Koziol et al., 2014; Schmahmann, 2019; Stoodley, 2012), with IR linked to reduced gray matter volume, altered functional connectivity, and decreased glucose metabolism in this region (Chen et al., 2022; Chen et al., 2014; Zhang et al., 2024a). The frontal cortex, specifically BA9, is central to executive functioning processes that are frequently impaired in psychiatric disorders, including decision-making and working memory (Friedman and Robbins, 2022; Miller and Cohen, 2001) and relies on insulin signaling for synaptic plasticity and neuronal health (Arnold et al., 2018; Fanelli et al., 2022; Kleinridders et al., 2014). Additionally, the implication of the pituitary gland points to a possible involvement of the hypothalamic-pituitary-adrenal (HPA) axis, which regulates stress response and metabolic function. Dysregulation of the HPA axis is well-established in both psychiatric disorders and metabolic diseases, and may represent a shared pathway contributing to their co-occurrence (Joseph and Golden, 2017; Stetler and Miller, 2011). Moreover, the gene expression specificity to prenatal brain tissues suggests that the genetic factors underlying the Psych-IR factor act during early neurodevelopment. This finding is consistent with Developmental Origins of Health and Disease models, which propose that perinatal stressors and metabolic perturbations may program long-term vulnerability to metabolic disturbances, brain structural abnormalities, cognitive impairment, and psychiatric outcomes (Garcia-Rizo and Bitanihirwe, 2025). In psychosis, this framework has recently been proposed as a model linking perinatal stressful events with adult metabolic manifestations, clinical heterogeneity, and increased morbidity (Garcia-Rizo and Bitanihirwe, 2025). This interpretation is also consistent with epidemiological evidence showing that maternal IR-related conditions, including T2DM, gestational diabetes, and obesity, are associated with increased risk of psychiatric disorders in offspring, including neurodevelopmental, mood, psychotic, and eating-disorder phenotypes (Kong, Chen, et al., 2020, 2020). Although our analyses cannot directly test prenatal exposure mechanisms, the convergence between prenatal brain tissue specificity and epidemiological evidence of maternal metabolic influences suggests that part of the shared genetic architecture between psychiatric and IR-related conditions may originate during early brain development rather than reflecting only adult lifestyle, medication exposure, or illness chronicity.

4.4. Clinical translation and drug repurposing

From a clinical standpoint, our results support the need for integrated psychiatric and metabolic care while also identifying candidate compounds for future pharmacological investigation. PharmOmics identified six compounds with transcriptomic signatures opposing those associated with the Psych-IR multimorbidity factor, including memantine, rosiglitazone, levodopa, cyclophosphamide, bevacizumab, and ceftriaxone. These findings should be considered hypothesis-generating, as transcriptomic signature reversal does not necessarily translate into clinical efficacy and does not account for pharmacokinetic properties, tissue specificity, dose-response relationships, safety, or psychiatric tolerability.

Among these candidates, memantine and rosiglitazone currently appear most suitable for further translational prioritization. Memantine has a neuropsychiatric rationale through NMDA-receptor modulation, with meta-analytic evidence from double-blind randomized controlled trials suggesting a small but significant effect on depressive symptoms

across major psychiatric disorders, particularly mood disorders, and acceptable tolerability (Hsu et al., 2022). Evidence from SCZ trials further supports psychiatric feasibility, with reported effects on negative symptoms and cognition, although this evidence should be interpreted as indirect for the Psych-IR factor because SCZ was not retained in the final latent factor (Zheng et al., 2018). Rosiglitazone has a more direct metabolic rationale as a peroxisome proliferator-activated receptor gamma (PPAR-γ) agonist with insulin-sensitizing actions and mechanistic links to adiponectin signaling, neuroinflammation, BDNF-related pathways, and adult neurogenesis (Guo et al., 2017; Lim et al., 2021). Preclinical evidence indicates antidepressant- and anxiolytic-like effects of rosiglitazone through a PPAR-γ–adiponectin axis, while clinical evidence remains limited to small studies suggesting improvement in depressive symptoms in individuals with IR (Guo et al., 2017; Rasgon et al., 2010; Toba-Oluboka et al., 2022). Its prioritization is also consistent with broader evidence suggesting antidepressant effects of PPAR-γ agonists, particularly pioglitazone, although historical concerns regarding cardiovascular safety, weight gain, and fluid retention warrant careful evaluation before psychiatric translation (Moulton et al., 2018; Nissen and Wolski, 2007).

In contrast, bevacizumab, cyclophosphamide, levodopa, and ceftriaxone require more cautious interpretation. Cyclophosphamide has mechanistic relevance to immune-mediated metabolic and neuropsychiatric phenotypes because immunosuppressive regimens including cyclophosphamide have been used in severe autoimmune IR syndromes and autoimmune encephalitis, conditions that may include prominent psychiatric manifestations (Dinoto et al., 2022; Yang et al., 2017). However, its cytotoxic and immunosuppressive profile makes psychiatric repurposing unlikely outside narrowly defined immune-mediated subgroups. Bevacizumab, an anti-vascular endothelial growth factor (VEGF) monoclonal antibody, has a plausible but indirect mechanistic link to brain-metabolic biology through VEGF/hypoxia-regulated vascular and glucose-transport pathways (Heijmen et al., 2014; Kuang et al., 2017; Zhang et al., 2024b). Nevertheless, this rationale remains speculative for psychiatric-IR multimorbidity, and anti-angiogenic safety concerns substantially limit its translational suitability. Levodopa should also be interpreted cautiously given its dopaminergic mechanism and potential to worsen psychotic symptoms in susceptible individuals (Connolly and Lang, 2014). Ceftriaxone, a third generation cephalosporin antibiotic, should likewise be interpreted cautiously, as prolonged antibiotic exposure may alter gut microbiome composition and decrease short-chain fatty acid production, potentially affecting metabolic regulation (Holota et al., 2019; Miao et al., 2021). Future research should prioritize candidates with convergent transcriptomic, mechanistic, and safety support and assess them in biomarker-informed experimental studies and randomized-controlled trials enriched for individuals with psychiatric-metabolic multimorbidity.

4.5. Strengths and limitations

The strengths of this study lie in the use of large-scale GWAS datasets, advanced multivariate genomic methods, and integration of transcriptomic data, enabling detection of shared genetic factors undetectable by univariate GWAS/TWAS analyses, offering novel insights into the genetic and biological bases of psychiatric-IR multimorbidity. However, some limitations remain. The functions and pathway roles of many identified genes are still poorly understood and European-ancestry GWASs limit generalizability. In addition, T-SEM approaches assume uniform gene-expression effects across traits, potentially oversimplifying complex biology (Grotzinger et al., 2022); we employed the Q_{Gene} statistic to mitigate the risk of false-positives that could arise from such assumptions (Grotzinger et al., 2022). Nonetheless, gene regulation is dynamic and context-dependent, influenced by epigenetics and environment (Pascual-Ahuir et al., 2020), factors not captured here. Our drug repurposing findings remain hypothesis-generating, constrained by limited availability of human brain transcriptomic data, cross-species differences, potential off-target effects, and uncertainty regarding clinical tolerability. Several identified compounds, including bevacizumab and cyclophosphamide, have toxicity profiles that may limit psychiatric applications, whereas levodopa may exacerbate psychotic symptoms in susceptible individuals (Connolly and Lang, 2014). Therefore, transcriptomic prioritization should not be interpreted as evidence of clinical suitability without pharmacological and clinical validation. Finally, this study was not preregistered, although all analyses followed established genomic SEM and T-SEM procedures.

5. Conclusions

In conclusion, this study identified a common genetic Psych-IR multimorbidity factor capturing psychiatric and IR-related conditions. Its genetic architecture implicates pathways regulating brain function and metabolic processes, particularly during neurodevelopment. These findings refine our understanding of the genetic basis and biological mechanisms of psychiatric-IR multimorbidity. Integrating genomic and transcriptomic analyses identified candidate therapeutic targets, providing a basis for biologically informed intervention development. Our findings may inform future translational studies and guide targeted treatment strategies for individuals with psychiatric-metabolic multimorbidity.

Author contributions

NRM, GF, and JB conceptualized the study. NRM and GF curated the code and scripts, generated the figures, carried out the analyses, interpreted the results, and wrote the original draft of the manuscript, under JB's supervision. IE contributed to formal analysis. MK, ES, AF, IHR, GP, KAA, JH, TW, MA, CB, WJJ, AS, CF, BF, and JB contributed to the interpretation of the results and revised the original manuscript draft. JB, GP, and BF were responsible for project coordination and funding acquisition. All authors contributed to and have approved the final manuscript.

Ethical statement

We used publicly available summary statistics of genome-wide association studies conducted by external consortia; thus, no specific authorization was required from the local Ethics Committee. No individual genotypic data were used or collected.

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Declaration of competing interest

GF reports institutional travel support from industry-funded research activities with Epitech and participation in clinical trials sponsored by Janssen-Cilag and Bioprojet Pharma; related payments were institutional, not personal. IHR was an employee, and GP is the director and chief scientific officer of Drug Target ID, Ltd., but their activities at this company do not constitute competing interests with regard to this paper. AS has served as a consultant or speaker for Abbott, Abbvie, Angelini, AstraZeneca, Clinical Data, Boehringer, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Innovapharma, Italfarmaco, Janssen, Lundbeck, Naurex, Pfizer, Polifarma, Sanofi, and Servier and Taliaz. During the past three years, JH and BF have received lecture honoraria as part of continuing medical education programs sponsored by Medice, all outside the submitted work. All the other authors declare no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2026.112906.

Data availability

Multivariate GWAS and TWAS summary statistics of the Psych-IR multimorbidity factor are available upon reasonable request to the authors.

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