Supplementary text: Genetic structure of major depression symptoms in clinical and population cohorts

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Genotyping and QC

Psychiatric Genomics Consortium (PGC). The analysis used data from 24 cohorts from the PGC MDD datasets that had symptom data on cases. Data was drawn from the following cohorts:

- BiDirect (bidi1)
- BOMA (boma)
- CoFams (cof3)
- PsyCoLaus (col3)
- GenRED (gens, grnd)
- GenPod/Newmeds (gep3)
- GSK (gsk2)
- Jannsen (janpy)
- MPIP/MARS (mmi2, mmo4)
- NESDA/NTR (nes1)
- QIMR (qi3c, qi6c, qio2)
- RADIANT (rad3, rage, rai2, rau2, rde4)
- Rotterdam (rot4)
- SHIP (shp0)
- STAR*D (stm2)
- TwinGene (twg2)

The genotypes were processed through Ricopili (Lam et al., 2020) with the following QC: SNP missingness < 0.05; sample missingness < 0.02; autosomal heterozygosity deviation (|Fhet|<0.2); and SNP Hardy-Weinberg equilibrium ($P>10^{-6}$ in controls, $P>10^{-10}$ in cases). QC'd genotypes were then imputed to the 1000 Genomes Reference Panel (The 1000 Genomes Project Consortium, 2015). Information on cohort genotyping and additional processing steps is available in (Wray et al., 2018).

Australian Genetics of Depression Study (AGDS). Genotyping was conducted using the Illumina Infinium Global Screening Array platform and QC'd for unknown or ambiguous map position and strand alignment, missingness >5%, HWE < 1×10^{-6}, MAF<1%. Genotypes were imputed to HRCr1.1. Individuals were excluded with missing rate > 3%, inconsistent sex, or if deemed ancestry outliers from the European population (6 standard deviations from the first two genetic principal components from 1000 Genomes). Imputed genotype dosages were used for the analyses. GWAS was carried out in SAIGE (Zhou et al., 2018) using a generalized linear mixed model with genotyping batch and 10 PCs as covariates. Variants with MAF<1% and imputation accuracy score <0.7 were excluded.

Avon Longitudinal Study of Parents and Children (ALSPAC). ALSPAC children were genotyped using the Illumina HumanHap550 quad chip genotyping platforms. Individuals were excluded on the basis of gender mismatches; minimal or excessive heterozygosity; disproportionate levels of individual missingness (>3%) and insufficient sample replication (IBD < 0.8). Population stratification was assessed by multidimensional scaling analysis, removing samples that clustered outside the CEU HapMap2 population. SNPs with a minor allele frequency of < 1%, a call rate of < 95% or evidence for violations of Hardy-Weinberg equilibrium (P < 5E-7) were removed. Cryptic relatedness was measured as proportion of identity by descent (IBD > 0.1). Related subjects that passed all other quality control thresholds were retained during subsequent phasing and imputation. 9,115 subjects and 500,527 SNPs passed these quality control filters. Imputation of the target data was performed using Impute V2.2.2 against 1000 genomes reference panel (Phase 1, Version 3) (all polymorphic SNPs excluding singletons), using all 2186 reference haplotypes (including non-Europeans). This resulted in 28,699,419 SNPs, with 8,282,911 SNPs with a MAF >0.01 and info score of >0.8. Analysis were conducted using SNPTEST v2.5.2, adjusting for sex and the first 10 principal components of ancestry.

Generation Scotland (GS:SFHS). GWAS data was obtained using the Illumina OmniExpress array, and imputed using the Haplotype Research Consortium (HRC) dataset. Further details of methods here https://pubmed.ncbi.nlm.nih.gov/28270201/. GWAS was conducted in regenie with 4 PCs removing SNPs with MAC < 100, genotype missingness > 10%, INFO < 0.1, and HWE p > 1e-15.

Estonian Biobank (EstBB). The samples from the Estonian Biobank have been genotyped at the Genotyping Core Facility of the Institute of Genomics, University of Tartu using the Global Screening Array (GSAv1.0, GSAv2.0, and GSAv2.0_EST) from Illumina. Altogether 155,772 samples have been genotyped and PLINK format files exported using GenomeStudio v2.0.4. Individuals were excluded from the analysis if their call-rate was <95% or if the sex defined based on heterozygosity of the X chromosome did not match the sex in the phenotype data. Variants were excluded if the call-rate was < 95% and HWE p-value <1e-4 (autosomal variants only). Variant positions were updated to genome build 37 and all alleles were switched to the TOP strand using tools and reference files provided at https://www.well.ox.ac.uk/~wrayner/strand/. After QC the dataset contained 154,201 samples for imputation. Before imputation variants with MAF<1% and indels were removed. Prephasing was done using the Eagle v2.3 software. The number of conditioning haplotypes Eagle2 uses when phasing each sample was set to: --Kpbwt=20000. Imputation was done using Beagle v.28Sep18.793 with effective population size ne=20,000. An Estonian population specific imputation reference of 2,297 WGS samples was used. The analysis was performed using the SAIGE software, including related individuals and adjusting for the first 10 principal components (PCs) of the genotype matrix, as well as for birth year, birth year squared and sex.

UK Biobank (UKB). Imputed genotypes were analysed from the version 3 release (Bycroft et al., 2018). Imputed genotypes were QC'd to INFO >= 0.1, MAC >= 100, HWE P > 1e-10, max alleles = 2, and duplicate markers removed. Association analysis was performed as a logistic regression in Plink2 (Chang et al., 2015) with genotyping array and 20 PCs as covariates.

Ethics statements

Ethical approval was obtained from the ALSPAC Ethics and Law Committee and the local research ethics committees (project number B3118). Consent for biological samples has been collected in accordance with the Human Tissue Act (2004). GWAS data was generated by Sample Logistics and Genotyping Facilities at Wellcome Sanger Institute and LabCorp (Laboratory Corporation of America) using support from 23andMe.

All participants in AGDS provided informed consent that they had read and understood the study information sheets and to confirm that they would be willing to provide a saliva sample for genotyping and downstream generic analyses. All study protocols were approved by the QIMR Berghofer Medical Research Institute Human Research Ethics Committee - approval numbers P2118, P1309 and P2304.

The activities of the EstBB are regulated by the Human Genes Research Act, which was adopted in 2000 specifically for the operations of the EstBB. Individual-level data analysis in the EstBB was carried out under ethical approvals [1.1-12/2860 & 1.1-12/624] from the Estonian Committee on Bioethics and Human Research (Estonian Ministry of Social Affairs), using data according to the release application [3-10/GI-28207] from the Estonian Biobank.

Ethical approval for the GS:SFHS data collection was obtained from the Tayside Committee on Medical Research Ethics A (ref 05/S1401/89). Generation Scotland is currently approved as a Research Tissue Bank by the East of Scotland Research Ethics Service (ref 20/ES/0021).

UK Biobank received ethical approval from the Research Ethics Committee (reference 11/NW/0382).

Confirmatory factor analysis model schematics

Supplementary Figure S1. Schematic drawings of the CFA models

Schematics to illustrate factor structures of the models that were tested. See main text Table 1 for symptom abbreviations and Supplementary Tables S4,6 for factor structures and coefficients.

Figure S1a: Model A: Common factor

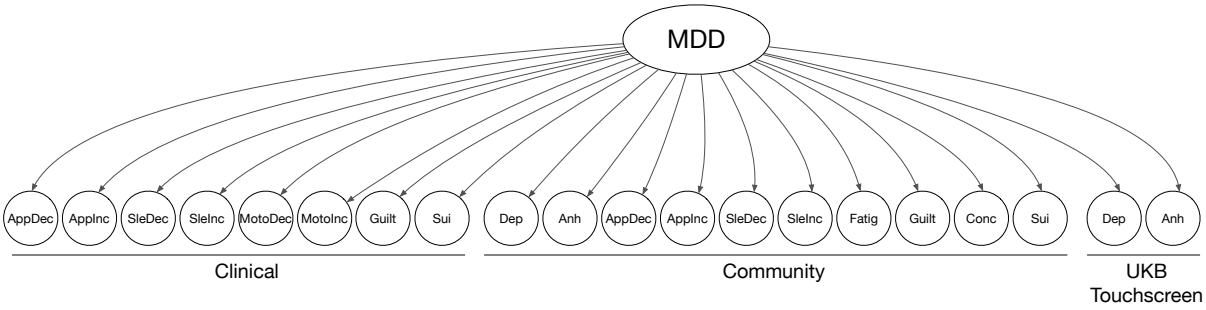


Figure S1b: Model B: Clinical and community factors

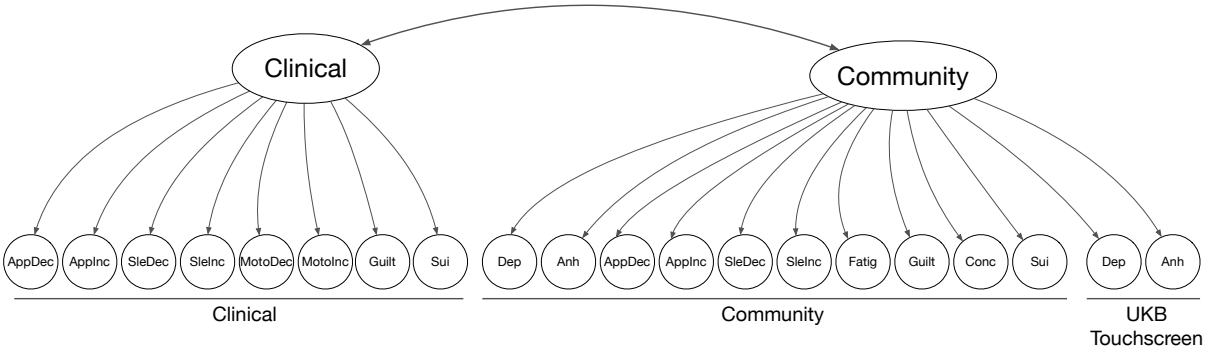


Figure S1c: Model C: Gating measurement factor

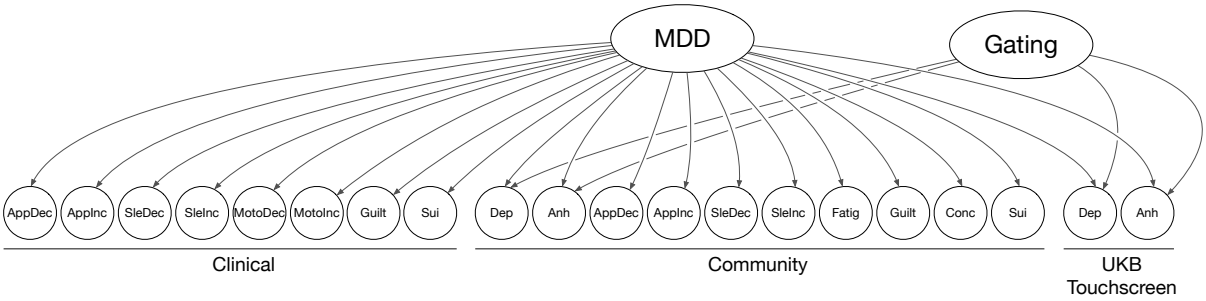


Figure S1d: Model D: Clinical-Community-Gating factors

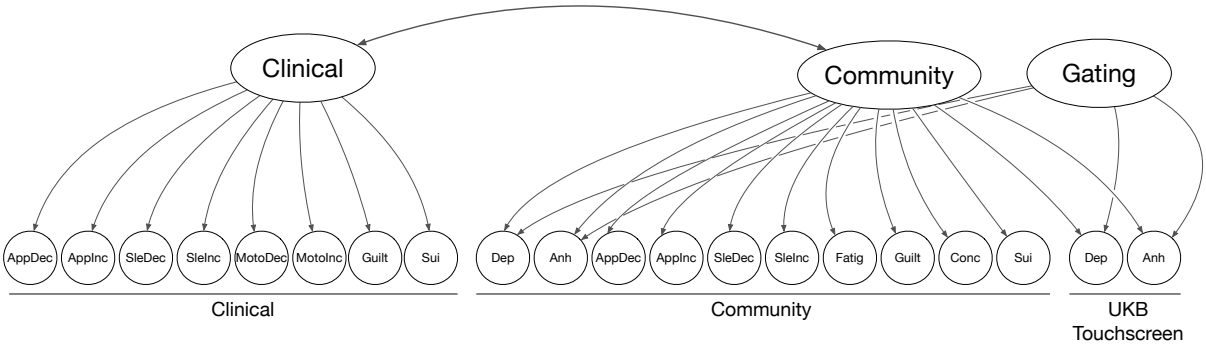


Figure S1e: Model E: Psychological-Somatic

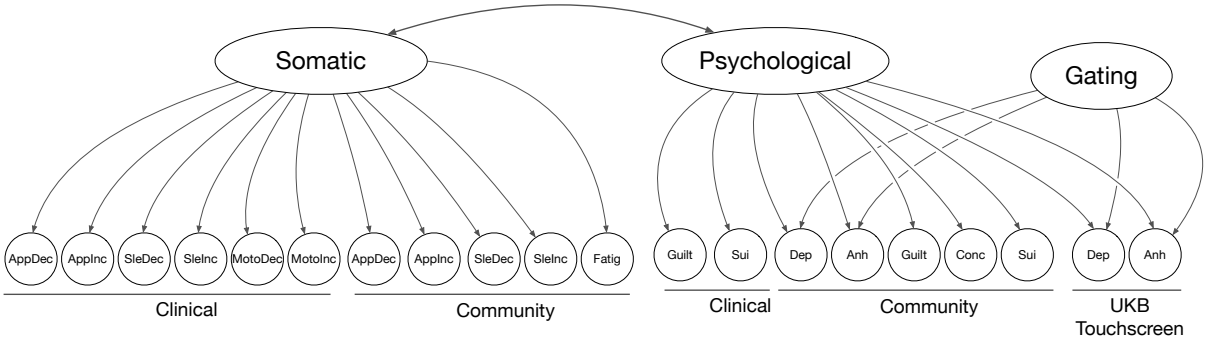


Figure S1f: Model F: Psychological- Neurovegetative

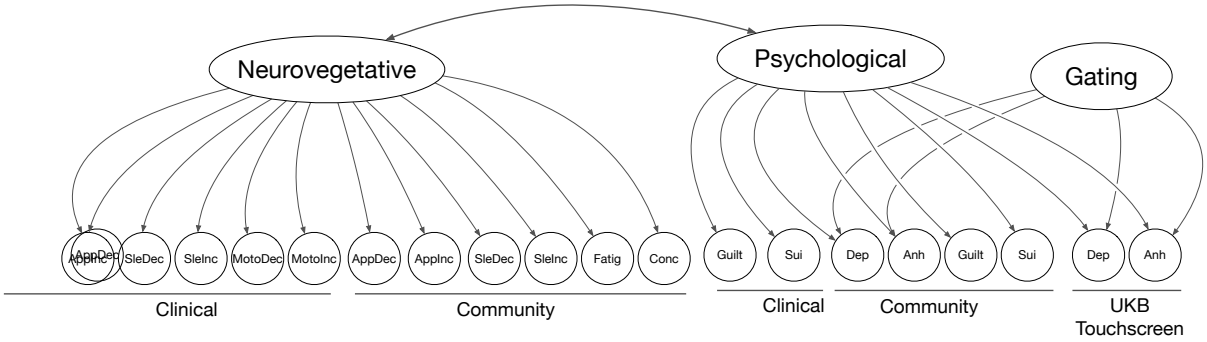


Figure S1g: Model G: Affective-Neurovegetative

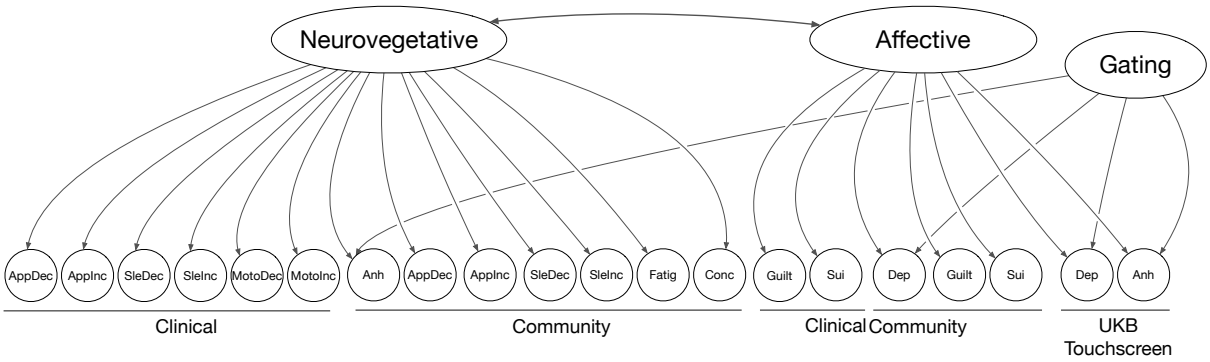


Figure S1h: Model H: Cognitive-Mood-Neurovegetative

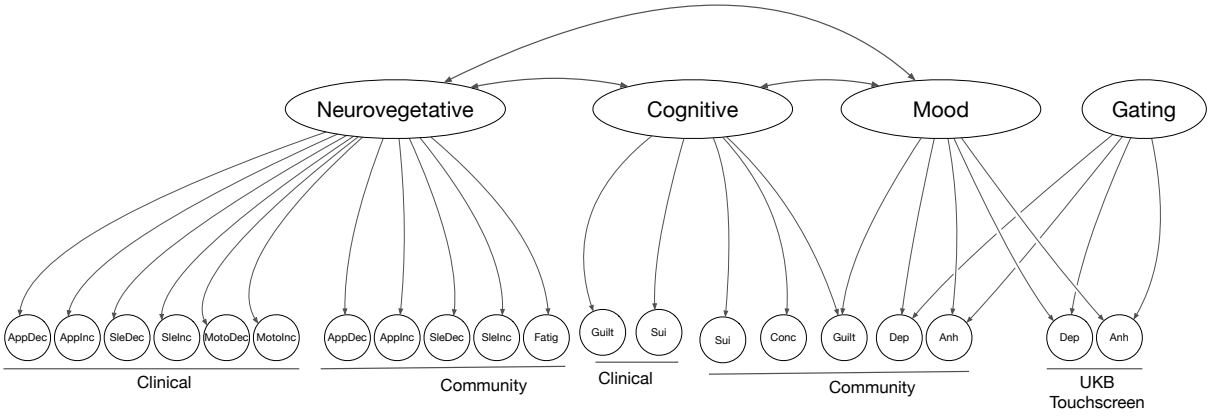


Figure S1i: Model I: Appetite-Vegetative-Cognitive/Mood

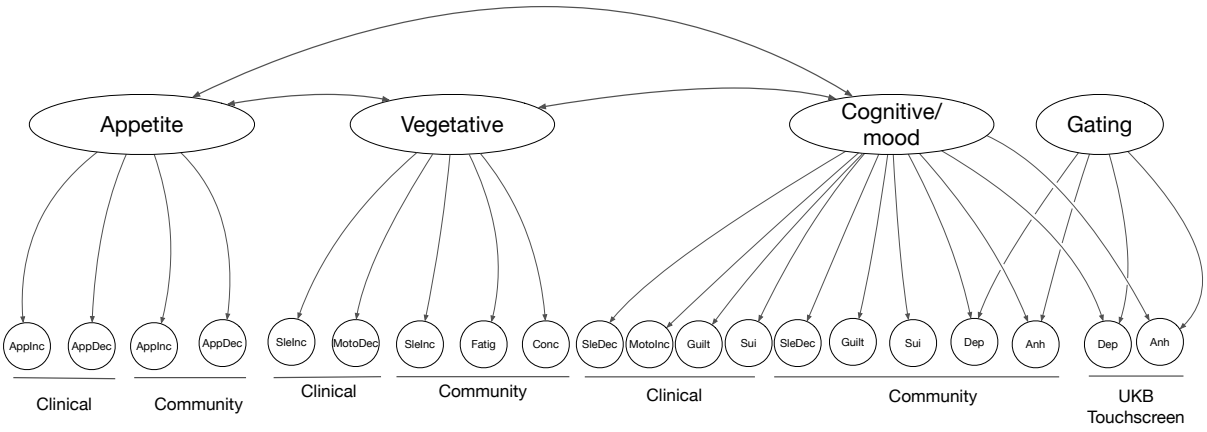
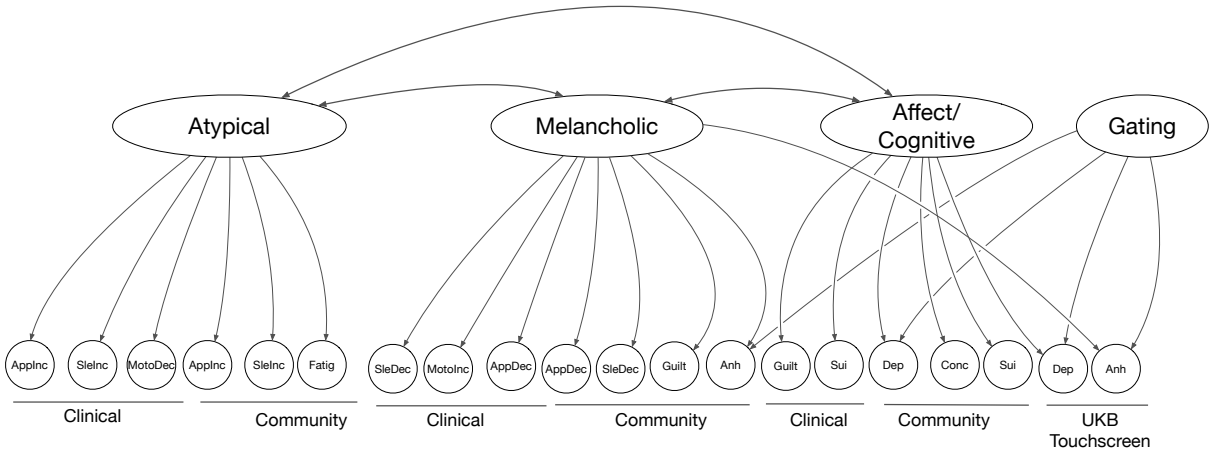
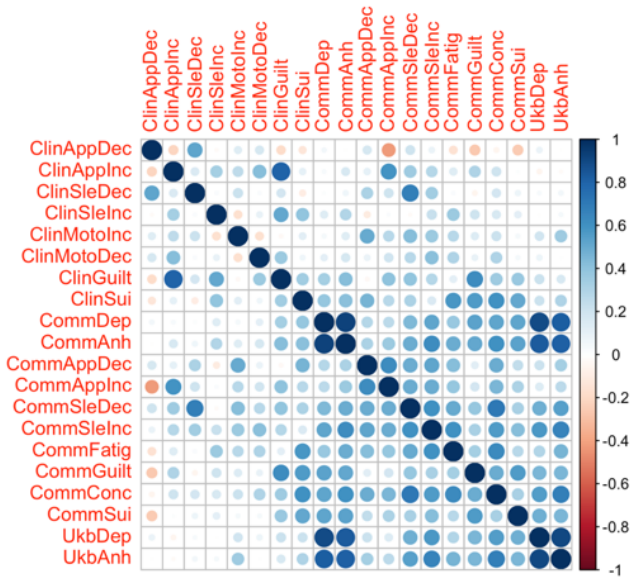


Figure S1j: Model J: Atypical-Melancholic-Affect/Cognitive



Symptom genetic correlations

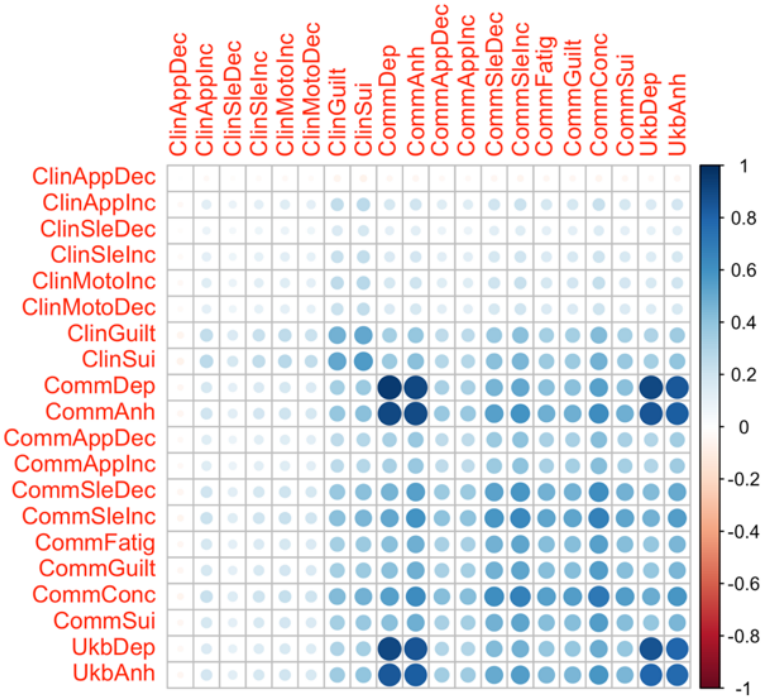
Supplementary Figure S2. Genetic correlations between symptoms



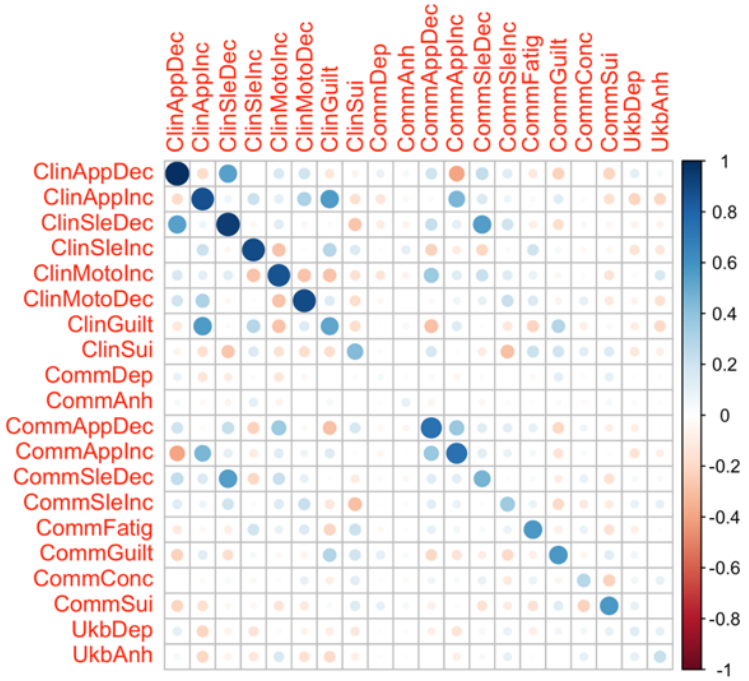
Supplementary Figure S3. Model implied and residual proportions of genetic correlations

Variance and covariances scaled by total genetic variance of each symptom.

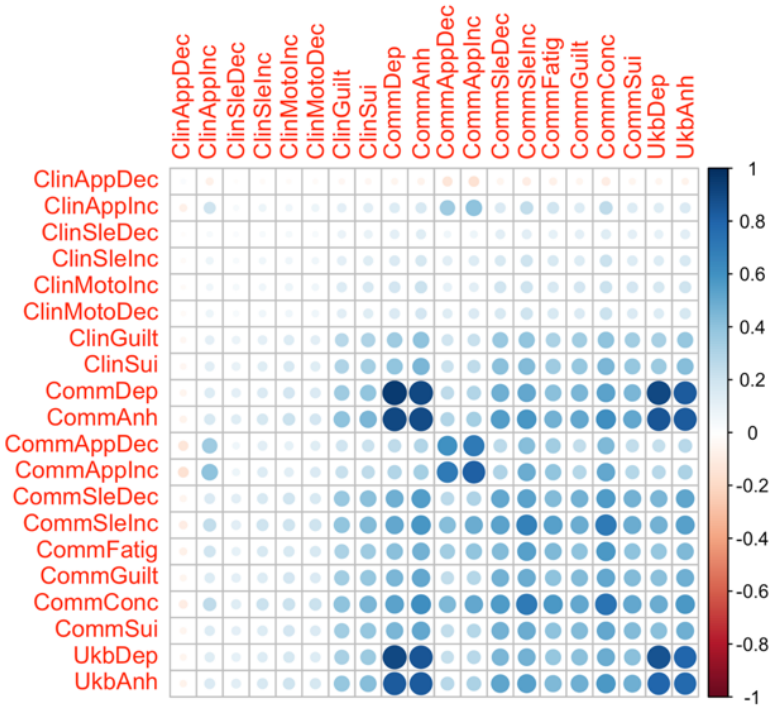
Supplementary Figure S3a. Model implied proportions of genetic correlations for Clinical-Community-Gating factors (Model D)



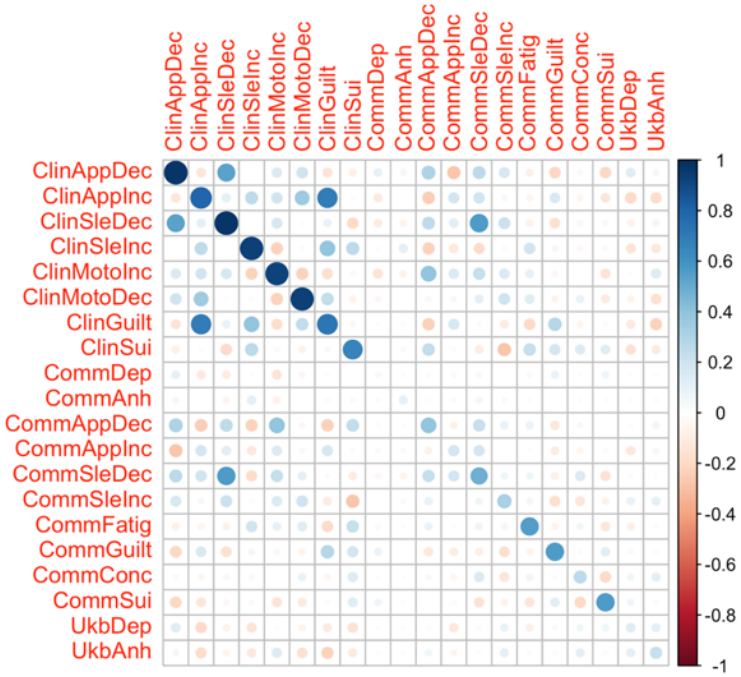
Supplementary Figure S3b. Model residual proportions of genetic correlations for Clinical-Community-Gating factors (Model D)



Supplementary Figure S3c. Model implied proportions of genetic correlations for Appetite-Vegetative-Cognitive/Mood factors (Model I)



Supplementary Figure S3d. Model residual proportions of genetic correlations for Appetite-Vegetative-Cognitive/Mood factors (Model I)



External phenotype summary statistics

For the genetic multiple regression analysis, we used the following summary statistics:

- Alcohol dependence (Walters et al., 2018)
- Anxiety (Grotzinger et al., 2022)
- Bipolar disorder (Mullins et al., 2021)
- Body mass index (Pulit et al., 2019)

- Educational attainment (Okbay et al., 2022)
- Major depression (Als et al., 2022)
- Major depressive disorder (Wray et al., 2018)
- Neuroticism (Nagel et al., 2018)
- Pain (multisite chronic pain) (Johnston et al., 2019)
- Post-traumatic stress disorder (Nievergelt et al., 2019)
- Sleep (long sleep duration) (Dashti et al., 2018)
- Smoking (cigarettes per day) (Liu et al., 2019)

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