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Supplementary Materials for

Analysis of shared heritability in common disorders of the brain

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Tables S7, S12, and S13 (Excel files)

Materials and Methods

Data processing

We obtained GWAS meta-analysis summary statistics for 25 brain disorders and 17 phenotypes. Wherever non-European cohorts formed a part of those meta-analyses, we generated non-sex-stratified European-cohorts-only version of the meta-analysis of each disorder together with the primary analysts for each disorder to avoid bias stemming from ancestry differences. Prior to heritability analysis, each dataset underwent additional filtering: markers were excluded for not being present among the HapMap Project Phase 3 SNPs(*83*), having an allele mismatch to 1000 Genomes alleles, ambiguous strand information, INFO score <0.9 (where available), MAF<1%, and if considerable missingness in the meta-analysis was observed (where available; defined as effective per-SNP sample size less than two thirds of the 90th percentile of total sample size). To remove a potential source of bias, the major histocompatibility complex region (all SNPs on chromosome 6 between 25 and 35 Mb) was removed from all datasets, as was the region surrounding the APOE locus (all SNPs on chromosome 19 between 44 and 47 Mb) from the Alzheimer's disease summary data.

Simulations

To evaluate the robustness of these results under various scenarios, we performed various simulations using data from the UK Biobank(*84*). Details about the UK Biobank project are available at http://www.ukbiobank.ac.uk. Data for the current analyses were obtained under an approved data request (application number #18597).

We used data from the interim release of 152,376 samples, originally genotyped on the UK BiLEVE Axiom array and the UK Biobank Axiom array. We filtered individuals for Caucasian ancestry and recommended removals to arrive at a final dataset of 120,267 individuals. Simulated datasets were generated to evaluate the behavior of correlation estimates 1) under different degrees of misclassification; 2) under different heritability estimates for the two traits and 3) under different liability thresholds (232 simulation conditions, 100 replicates per condition, for a total of 2.95 billion simulated individuals).

In each simulation replicate, two sets of simulated quantitative phenotypes with heritability ranging from 5-50% and prevalence ranging from 1-10% (relevant to the study phenotypes) were generated by assigning 5% of total SNPs to have simulated effect sizes drawn from $N\left(0, \sqrt{\frac{h^2}{0.05\,M}}\right)$, where h^2 is the heritability and M is the total number of markers in the genome, standardized for minor allele frequency (p) by $\sqrt{2 * p * (1-p)}$. Individual phenotypes were simulated by calculating the sum of mean centered betas multiplied by the individual's risk alleles with the –score option in PLINK v1.90b3.38(*85*) and adding noise term e, drawn from $N(0, \sqrt{1-h^2})$, to achieve phenotypes which sum to $N(0, h^2)$. Dichotomous phenotypes were generated by assigning top 1%, 5% and 10% of each heritability simulation to be cases, and misclassification scenarios by mixing the simulated betas with those from a second, independently simulated phenotype in proportions ranging between 0-100%. Association statistics were created using an additive test in PLINK v1.90b3.38, and LDSC was used to calculate correlation estimates.

Simulation results were summarized to evaluate three specific scenarios considered relevant to the challenges (particularly for the psychiatric disorders, due to their spectrum-like behavior) in brain disorder co-morbidity:

1. *Effect of misclassification on phenotype heritability*. Given that we generally observe slightly lower heritability estimates in this study than reported in the literature with previous studies (which generally have used smaller, possibly less heterogeneous datasets), we generated 100 replicates each of simulated phenotypes at several prevalence and heritability values, and with varying degrees of misclassification of cases from a second, independent phenotype (Fig. S9A). These results demonstrate that while large-scale misclassification will impact the estimated heritability, very large misclassification proportions are required to by themselves give rise to large-scale changes in the observed heritability to the degree shown in Table S3.

2. *Effect of co-morbidity on genetic correlation*. Given the overlapping epidemiology of some phenotypes and the potential to observe false positive correlations due to non-trivial case misclassification, we created a range of phenotypes with varying mixing portions of correctly diagnosed cases (λ) and incorrectly diagnosed cases (1-λ) from an independent second phenotype and evaluated the genetic correlation between the hybrid phenotype and the second phenotype. This simulates the real-world scenario where e.g. (1-λ) proportion of bipolar cases would in fact be misclassified cases of schizophrenia free of bipolar disorder (Fig. S9B). We also derived a formula (see "Effect of co-morbidity and phenotypic misclassification on correlation estimates" below) to estimate the degree of misclassification required to produce the observed correlations in the absence of true genetic correlation (Table S6).

3. *Effect of bidirectional comorbidity on genetic correlation*. We expanded the simulation from the previous scenario given misclassification in both directions, i.e. where a proportion (1-λ) of bipolar disorder cases are misclassified schizophrenia cases and the same proportion of schizophrenia cases are misclassified bipolar disorder cases (Fig. S9C).

Power calculations

Using the same methodology as described for the simulations, we created 100 replicated pairs of datasets, each with varying sample sizes (10,000, 20,000 and 40,000 individuals with a 50/50 case/control split, randomly selected from the UK Biobank data; see section above), heritabilities (1%, 5%, 10% and 20%) and polygenicity (simulating 0.5%-100% of markers contributing to the heritability). In the second set of similarly created replicates, phenotypes were additionally created to be 10%, 20%, 30%, or 40% correlated to their pair in the first set. LDSC was used to calculate the correlation between the pair (Figure S10).

Heritability analysis

For a given trait, the total additive common SNP heritability in a set of GWAS summary statistics (h^2g) is estimated by regressing the association χ^2 statistic of a SNP against the total amount of common genetic variation tagged by that SNP (i.e., the sum of r^2 between that SNP and all surrounding SNPs within a 1 Mb window, termed the LD score). The LD scores themselves, for each SNP with MAF 5-50% in the Hapmap3 data, were obtained from previously published data(*24*) (https://github.com/bulik/ldsc) but

edited by removing the at the time erroneously included HLA region markers [chr6, 20-36 Mb]. Genetic correlations, r_g, (i.e., the genome-wide average shared genetic risk) for a pair of phenotypes was similarly estimated by regressing the product of Z-score for each phenotype for each SNP, instead of the χ^2 statistic. The LD score referenced above is estimated from a common reference panel (for this work, the European subset of the 1000 Genomes Project reference). In this framework, including LD in the regression allows us to distinguish and account for LD-independent error sources (such as sample sharing and population stratification) from LD-dependent sources, like polygenic signal). It is essential to use an approach which is not biased by sample overlaps when analyzing summary statistics, given the large amount of control sharing between the GWAS meta-analyses in the study. P-values and effect directions for each phenotype were used to create a set of directional χ^2 statistics, which were then regressed against the SNP LD scores (as the χ^2 statistic is dependent on the amount of variation tagged by the SNP).

A univariate regression of these statistics against the LD statistic of each SNP was used to estimate the heritability for each phenotype using LDSC v1.0.0(*24*). When converting the results to liability scale, we assumed that all controls were unselected for all brain disorders as well as coronary artery disease and Crohn's disease from the additional phenotypes (u = 1 for the formula presented in (*86*)). Phenotypes with a univariate heritability Z-score < 2 were excluded from further analysis (cardioembolic, large-, and small-vessel stroke and agreeableness personality measure), leaving 21 brain disorder phenotypes and 16 traits of interest. In the genetic correlation analysis, the product of χ^2 statistics from the two phenotypes was similarly regressed.

Significance was assessed by Bonferroni multiple testing correction by estimating the number of independent brain disorder phenotypes by matrix decomposition of the genetic correlation results using matSpD (see Links)(*87, 88*). The number of independent disorder phenotypes was estimated to be 17.7943 (from 22 initial disorders, after exclusions), yielding a Bonferroni-corrected threshold of $p < 3.35 \times 10^{-4}$ for disorder-disorder pairs; 12.1925 independent phenotypes (from 16 initial phenotypes, after exclusions) for a threshold of $p < 7.33 \times 10^{-4}$ for phenotype-phenotype pairs and a total of 216.96 disorder-phenotype pairs for a threshold of $p < 2.30 \times 10^{-4}$.

Functional enrichment and partitioning analysis

Partitioning analysis was conducted using LDSC v1.0.0(*24*), using stratified LD score regression to identify enriched cell type groups, expanding on the work described in Finucane et al(*26*). First, we obtained genome annotations for each of ten cell type groups, created by taking a union of regions with any of four histone modifications (H3K4me1, H3K4me3, H3K27ac, H3K9ac) in any cell type belonging to the cell type group. We then added each of these ten annotations to the full baseline model one at a time and performed LD score regression for each of the resulting ten models. For each of these ten analyses, we computed a Z-score for the regression coefficient corresponding to the cell type group, and we used this to test the hypothesis that the cell type group contributes positively to SNP heritability after controlling for the 53 categories in the full baseline model. Significance threshold was estimated from the number of independent phenotypes across 10 tissue categories and 53 functional categories (latter evaluated as 24 independent categories due to overlapping category structure) for Bonferroni thresholds

of $p < 2.81 \times 10^{-4}$ and 1.17×10^{-4}, respectively. For the behavioral-cognitive traits and additional traits, the corresponding thresholds were $p < 4.10 \times 10^{-4}$ and $p < 1.71 \times 10^{-4}$.

Correlation between heritability and dataset-specific factors

A weighted-least squares analysis was conducted among the brain disorder phenotypes in R, version 3.2, to determine what, if any, phenotype and dataset descriptive factors correlate with univariate heritability estimates. Weights were estimated using the squares of the standard errors of the univariate heritability estimates from the LD score regression analysis.

Supplementary text

Effect of co-morbidity and phenotypic misclassification on correlation estimates

We derived a formula to quantify the effect of case misclassification on the estimated genetic correlation between two traits, given the degree of misclassification, the observed heritability and the true genetic correlation. We assume both traits have similar sample and population prevalence.

Let λ be the fraction of correctly classified cases of phenotype 1, with the remainder being cases of phenotype 2 misclassified as cases of phenotype 1, β_1 and β_2 be true effects for phenotypes 1 and 2 on an arbitrary SNP. Therefore, the effect of the SNP on the misspecified phenotype 1 is α:

$$\alpha \equiv \lambda\beta_1 + (1-\lambda)\beta_2$$

Before considering the impact on the estimated genetic correlation, we note that this change in SNP effects means the heritability of the observed (potentially misclassified) phenotype may differ from the heritability of the true phenotype 1. Noting that the observed heritability for each phenotype is proportional to the variance of their effect sizes, we first calculate

$$\begin{aligned}\mathrm{Var}(\alpha) &= \mathrm{Var}\,(\lambda\beta_1 + (1-\lambda)\beta_2) \\ &= \lambda^2\,\mathrm{Var}\,(\beta_1) + 2\lambda(1-\lambda)\mathrm{Cov}(\beta_1,\beta_2) + (1-\lambda)^2\,\mathrm{Var}(\beta_2) \\ &= \lambda^2\,\mathrm{Var}\,(\beta_1) + 2\lambda(1-\lambda)r_g\sqrt{\mathrm{Var}(\beta_1)\,\mathrm{Var}(\beta_2)} + (1-\lambda)^2\,\mathrm{Var}(\beta_2)\end{aligned}$$

Then assuming standardized regression coefficients (e.g. following the LD score regression model), this can be written in terms of observed (obs) and true heritabilities for the two phenotypes and the number of genome-wide variants M as

$$\frac{h^2_{1,obs}}{M} = \lambda^2\frac{h_1^2}{M} + 2\lambda\,(1-\lambda)\,r_g\sqrt{\frac{h_1^2}{M}}\sqrt{\frac{h_2^2}{M}} + (1-\lambda)^2\,\frac{h_2^2}{M}$$

$$h^2_{1,obs} = \lambda^2 h_1^2 + 2\lambda\,(1-\lambda)\,r_g\sqrt{h_1^2 h_2^2} + (1-\lambda)^2 h_2^2$$

This allows solving for $\sqrt{h_1^2}$ using a quadratic equation,

$$0 = \lambda^2 h_1^2 + 2\lambda\,(1-\lambda)\, r_g \sqrt{h_1^2 h_2^2} + \,(1-\lambda)^2 h_2^2 - \, h_{1,obs}^2$$

$$\sqrt{h_1^2}_1 = \frac{-2\lambda(1-\lambda)\, r_g \sqrt{h_2^2} \,\pm\, \sqrt{4\lambda^2\,(1-\lambda)^2 r_g^2\, h_2^2 - 4\lambda^2\,\left[(1-\lambda)^2\, h_2^2 - \, h_{1,obs}^2\right]}}{2\lambda^2}$$

$$= \frac{-2\lambda(1-\lambda)\, r_g\, \sqrt{h_2^2} \,\pm\, 2\lambda \sqrt{(1-\lambda)^2\left(r_g^2 - 1\right) h_2^2 + \, h_{1,obs}^2}}{2\lambda^2}$$

$$= \frac{-(1-\lambda)\, r_g \sqrt{h_2^2} \,\pm \sqrt{(1-\lambda)^2\left(r_g^2 - 1\right) h_2^2 + \, h_{1,obs}^2}}{\lambda}$$

Note that the sign of the first term in the numerator will be opposite of the sign of r_g. Therefore if we select the sign of the phenotype so that $r_g > 0$, then we must add the second term to ensure $\sqrt{h_1^2} > 0$. This gives us

$$\sqrt{h_1^2} = \frac{-(1-\lambda)\, r_g \sqrt{h_2^2} + \sqrt{(1-\lambda)^2\left(r_g^2 - 1\right) h_2^2 + \, h_{1,obs}^2}}{\lambda}$$

Note that this will not be bounded above by one when λ is small. This is not surprising since a small λ implies that most of the cases reported for phenotype 1 are in fact cases for phenotype 2, making particular combinations of h_2^2, $h_{1,obs}^2$ and r_g infeasible for certain values of λ. From the above, the determinant of the quadratic form must be positive, thus

$$h_{1,obs}^2 \geq (1-\lambda)^2\left(1 - \, r_g^2\right) h_2^2$$

Similarly, the determinant of the quadratic formula, solving for h_2^2, implies

$$h_1^2 \leq \frac{h_{1,obs}^2}{\lambda^2\left(1 - \, r_g^2\right)}$$

This is the case unless no misclassification is present ($\lambda = 0$) or the phenotypes are functionally equivalent ($r_g^2 = 1$).

We can now return to the original question regarding the relationship between r_g and $r_{g,obs}$ in the presence of phenotype misclassification. We derive for the SNP effects of α and β_2:

$$r_{g,obs} \equiv \mathrm{Corr}(\alpha, \beta_2)$$
$$= \frac{\mathrm{Cov}\,(\alpha, \beta_2)}{\sqrt{\mathrm{Var}(\alpha)\mathrm{Var}(\beta_2)}}$$
$$= \frac{\mathrm{Cov}\,[\lambda\beta_1 + (1-\lambda)\beta_2, \beta_2]}{\sqrt{\mathrm{Var}(\alpha)\mathrm{Var}(\beta_2)}}$$

$$= \frac{\lambda \operatorname{Cov}(\beta_1, \beta_2) + (1-\lambda)\operatorname{Var}(\beta_2)}{\sqrt{\operatorname{Var}(\alpha)\operatorname{Var}(\beta_2)}}$$
$$= \frac{\lambda\, r_g \sqrt{\operatorname{Var}(\beta_1)\operatorname{Var}(\beta_2)} + (1-\lambda)\operatorname{Var}(\beta_2)}{\sqrt{\operatorname{Var}(\alpha)\operatorname{Var}(\beta_2)}}$$
$$= \lambda\, r_g \frac{\sqrt{\operatorname{Var}(\beta_1)}}{\sqrt{\operatorname{Var}(\alpha)}} + (1-\lambda)\frac{\sqrt{\operatorname{Var}(\beta_2)}}{\sqrt{\operatorname{Var}(\alpha)}}$$

Again assuming standardized regression coefficients, the variances can be written in terms of heritability as

$$r_{g,obs} = \frac{\lambda\, r_g \sqrt{h_1^2} + (1-\lambda)\sqrt{h_2^2}}{\sqrt{h_{1,obs}^2}}$$

Rearranging and substituting the expression for $\sqrt{h_1^2}$ from above, assuming $r_g > 0$, gives

$$r_g = \frac{r_{g,obs}\sqrt{h_{1,obs}^2} - (1-\lambda)\sqrt{h_2^2}}{\lambda\sqrt{h_1^2}}$$

$$= \frac{r_{g,obs}\sqrt{h_{1,obs}^2} - (1-\lambda)\sqrt{h_2^2}}{\lambda} \frac{\lambda}{-(1-\lambda)\, r_g\sqrt{h_2^2} + \sqrt{(1-\lambda)^2\left(r_g^2-1\right)h_2^2 + h_{1,obs}^2}}$$
$$= \frac{r_{g,obs}\sqrt{h_{1,obs}^2} - (1-\lambda)\sqrt{h_2^2}}{\sqrt{(1-\lambda)^2\left(r_g^2-1\right)h_2^2 + h_{1,obs}^2} - (1-\lambda)\, r_g\sqrt{h_2^2}}$$

Note that in the case with no misclassification, i.e. $\lambda = 1$,

$$r_g = \frac{r_{g,obs}\sqrt{h_{1,obs}^2}}{\sqrt{h_{1,obs}^2}} = r_{g,obs}$$

To examine the effects of co-morbidity has on the estimates, Table S5 shows numerical solutions for the estimated true correlation of some selected disorder pairs based on literature estimates of co-morbidity, assuming unidirectional misclassification and that $h_{1,obs}^2$ is equal to true h_1^2 (ie. that both disorders are roughly as heritable). For this table, we substituted the lambda values (see table for reference) and used the formula above to estimate what the true r_g would be, based on the observed r_g in this study. Figure S8 shows how the true genetic correlation estimates for those pairs behave across a range of λ values, given the observed r_g in this study, under the same assumptions as Table S5.

We further estimate what degree of unidirectional misclassification would be required to produce the significant r_g values we observe in the paper, in the absence of any true correlation. Given $r_g = 0$,

$$r_{g,obs} = \frac{(1-\lambda)\sqrt{h_2^2}}{h_{1,obs}^2}$$

$$\lambda = 1 - r_{g,obs}\frac{h_{1,obs}^2}{\sqrt{h_2^2}}$$

Table S6 lists the implied values of misclassification (1-λ) required to produce the observed significant r_g values between brain disorders in the study, if no true correlation between the phenotypes exists.

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IPDGC (Parkinson’s disease)

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Peng Szatkiewicz, Chrysecolla Taico, Stephanie Zerwas, Sara E. Trace, Oliver S. P. Davis, Sietske G. Helder, Roland Burghardt, Martina de Zwaan, Karin Egberts, Stefan Ehrlich, Beate Herpertz-Dahlmann, Wolfgang Herzog, Hartmut Imgart, André Scherag, Susann Scherag, Stephan Zipfel, Nicolas Ramoz, Unna N. Danner, Carolien de Kove, Judith Hendriks, Bobby P.C. Koeleman, Roel A. Ophoff, Annemarie A. van Elburg, Maurizio Clementi, Daniela Degortes, Monica Forzan, Elena Tenconi, Elisa Docampo, Susana Jimenez-Murcia, Jolanta Lissowska, Neonilia Szeszenia-Dabrowska, Joanna Hauser, Leila Karhunen, Ingrid Meulenbelt, P. Eline Slagboom, Steve Crawford, Alfonso Tortorella, Mario Maj, George Dedoussis, Fragiskos Gonidakis, Konstantinos Tziouvas, Artemis Tsitsika, Hana Papežová, Lenka Slachtova, Debora Martaskova, James L. Kennedy, Robert D. Levitan, Zeynep Yilmaz, Julia Huemer, Gudrun Wagner, Paul Lichtenstein, Gerome Breen, Sarah Cohen-Woods, Sven Cichon, Ina Giegling, Stefan Herms, Dan Rujescu, Stefan Schreiber, H-Erich Wichmann, Christian Dina, Giovanni Gambaro, Nicole Soranzo, Antonio Julià, Sara Marsal, Raquel Rabionet, Danielle M. Dick, Aarno Palotie, Samuli Ripatti, Ole A. Andreassen, Thomas Espeseth, Astri Lundervold, Ivar Reinvang, Vidar M. Steen, Stephanie Le Hellard, Morten Mattingsdal, Ioanna Ntalla, Vladimir Bencko, Lenka Foretova, Marie Navratilova, Dalila Pinto, Stephen W. Scherer, Harald Aschauer, Laura Carlberg, Alexandra Schosser, Lars Alfredsson, Bo Ding, Leonid Padyukov, Gursharan Kalsi, Marion Roberts, Darren W. Logan, Xavier Estivill, Anke Hinney, Patrick F. Sullivan, David A. Collier, Eleftheria Zeggini and Cynthia M. Bulik

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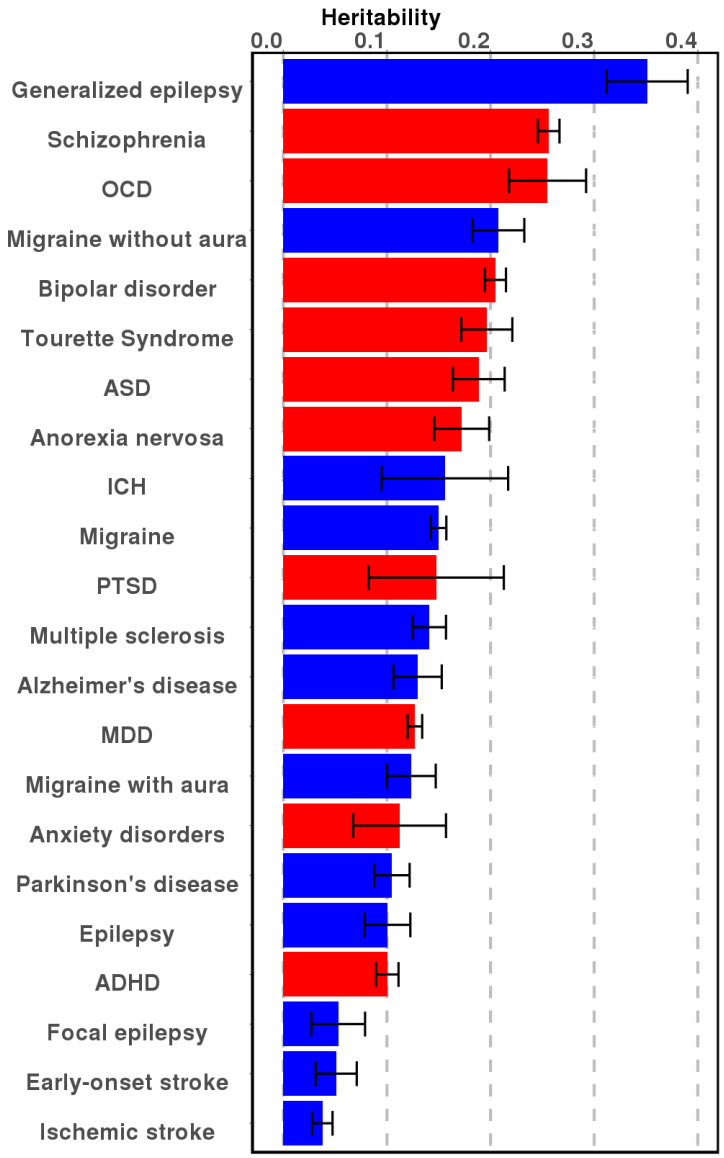


Fig. S1A. Heritability estimates for brain disorders

Red bars denote psychiatric disorders, while blue bars denote neurological disorders. ADHD – attention deficit hyperactivity disorder; ASD – autism spectrum disorder; ICH – intracerebral hemorrhage; MDD – major depressive disorder; OCD – obsessive-compulsive disorder; PTSD – post-traumatic stress disorder. Error bars show one standard error.

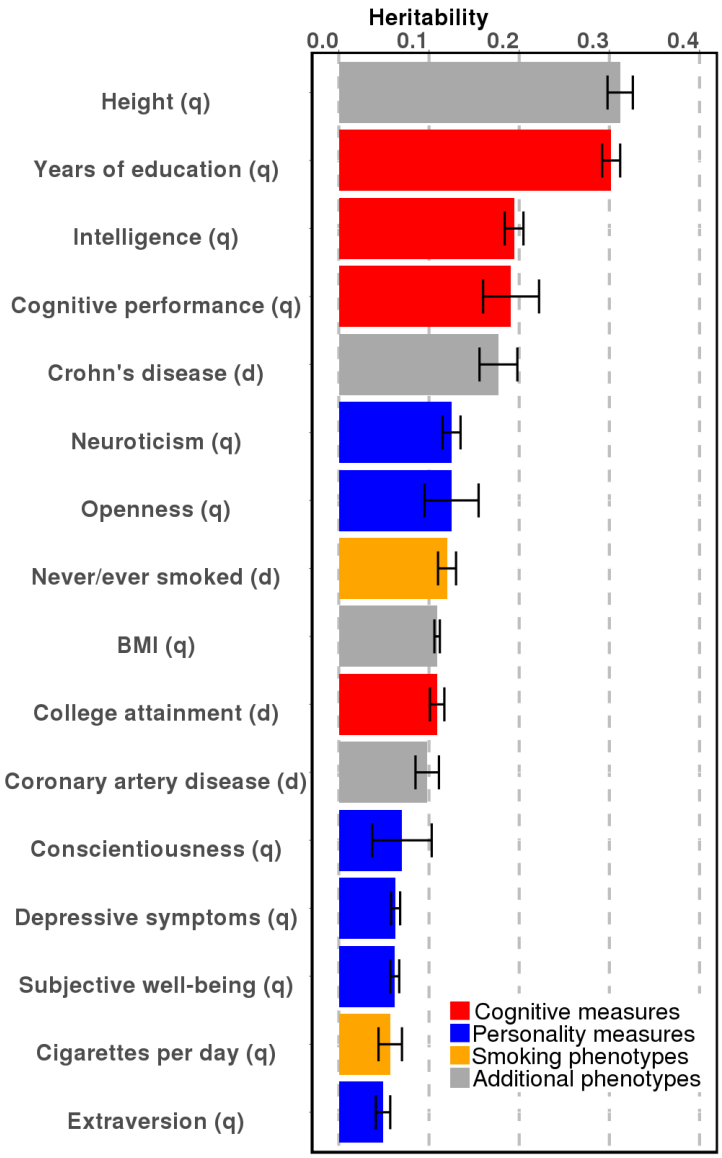


Fig. S1B. Heritability estimates for quantitative and additional phenotypes

BMI – body-mass index. Heritabilities are reported on the observed scale for quantitative phenotypes (q) and liability scale for dichotomous phenotypes (d). Error bars show one standard error.

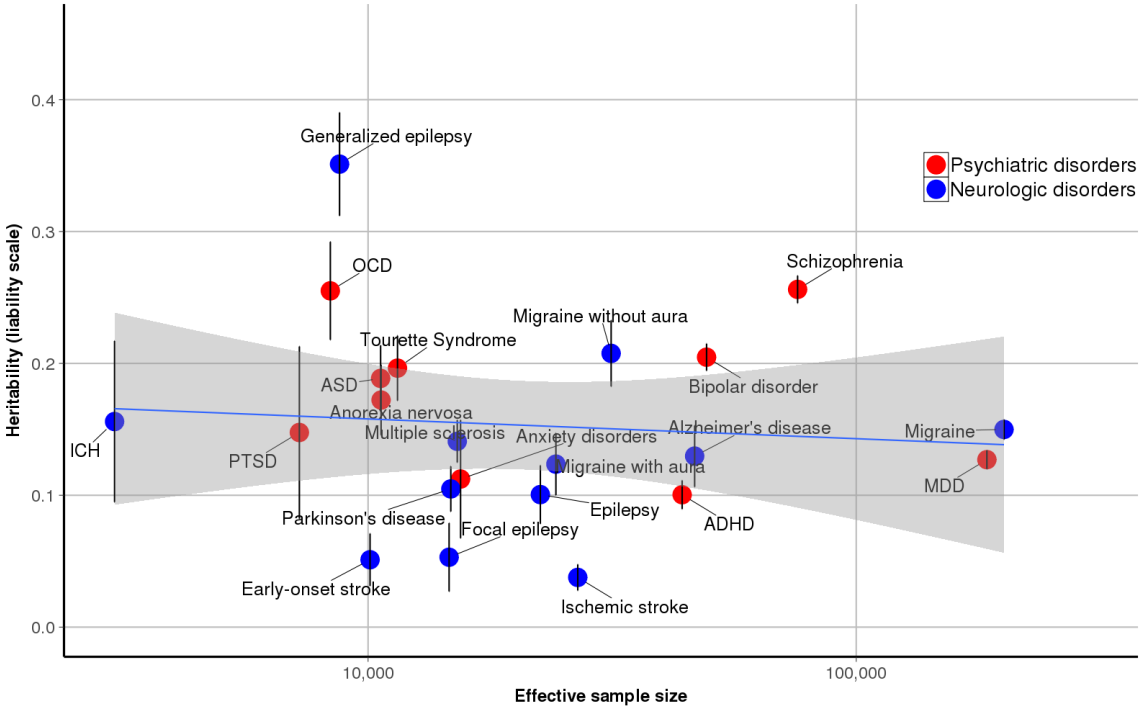


Fig. S1C. Heritability and effective sample size

ADHD – attention deficit hyperactivity disorder; ASD – autism spectrum disorder; ICH – intracerebral hemorrhage; MDD – major depressive disorder; OCD – obsessive-compulsive disorder; PTSD – post-traumatic stress disorder. Shaded area shows 95% confidence interval. Error bars show one standard error.

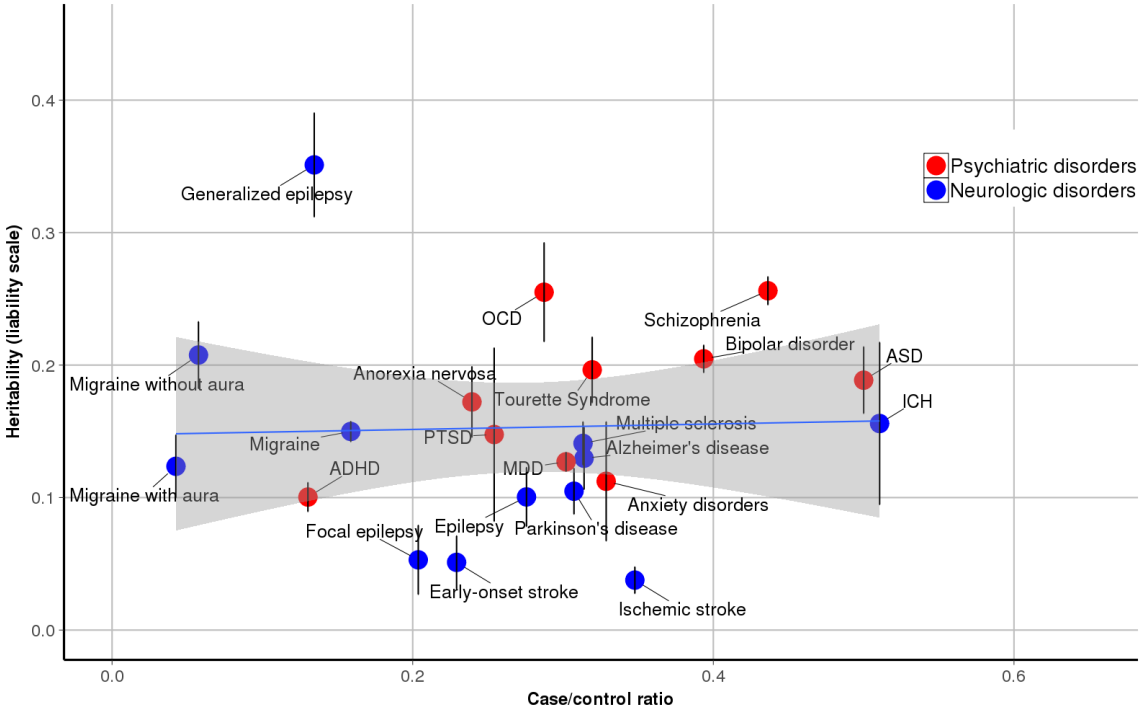


Fig. S1D. Heritability and case/control ratio

ADHD – attention deficit hyperactivity disorder; ASD – autism spectrum disorder; ICH – intracerebral hemorrhage; MDD – major depressive disorder; OCD – obsessive-compulsive disorder; PTSD – post-traumatic stress disorder. Shaded area shows 95% confidence interval. Error bars show one standard error.

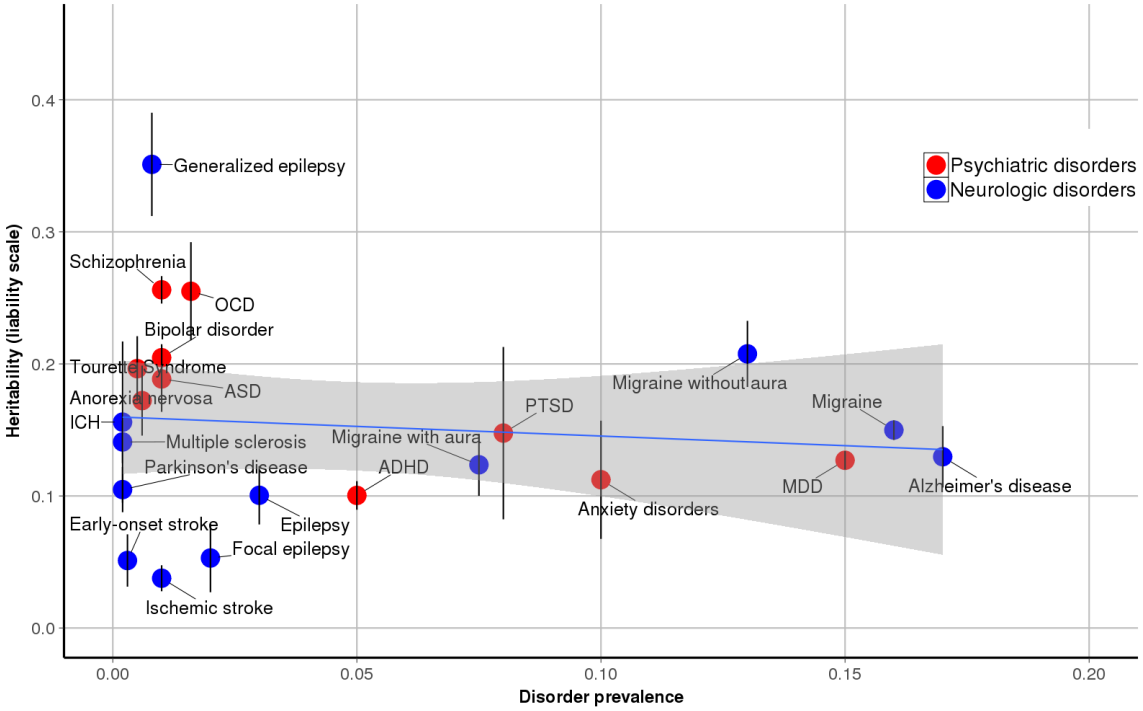


Fig. S1E. Heritability and disorder prevalence

ADHD – attention deficit hyperactivity disorder; ASD – autism spectrum disorder; ICH – intracerebral hemorrhage; MDD – major depressive disorder; OCD – obsessive-compulsive disorder; PTSD – post-traumatic stress disorder. Shaded area shows 95% confidence interval. Error bars show one standard error.

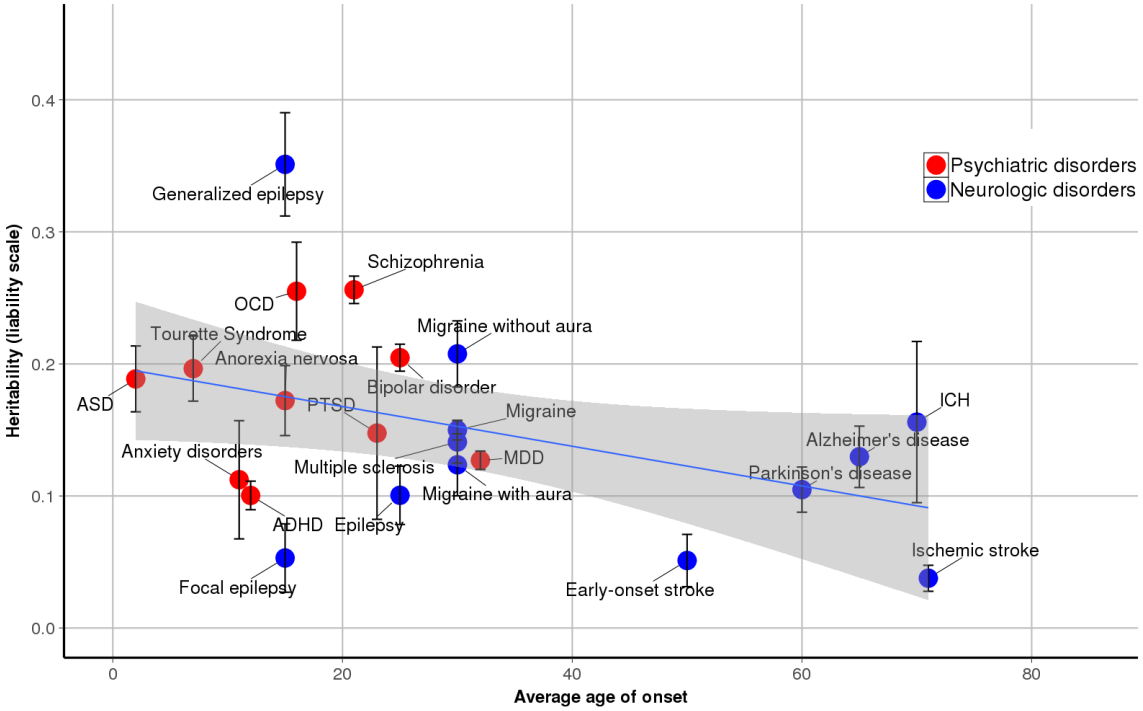
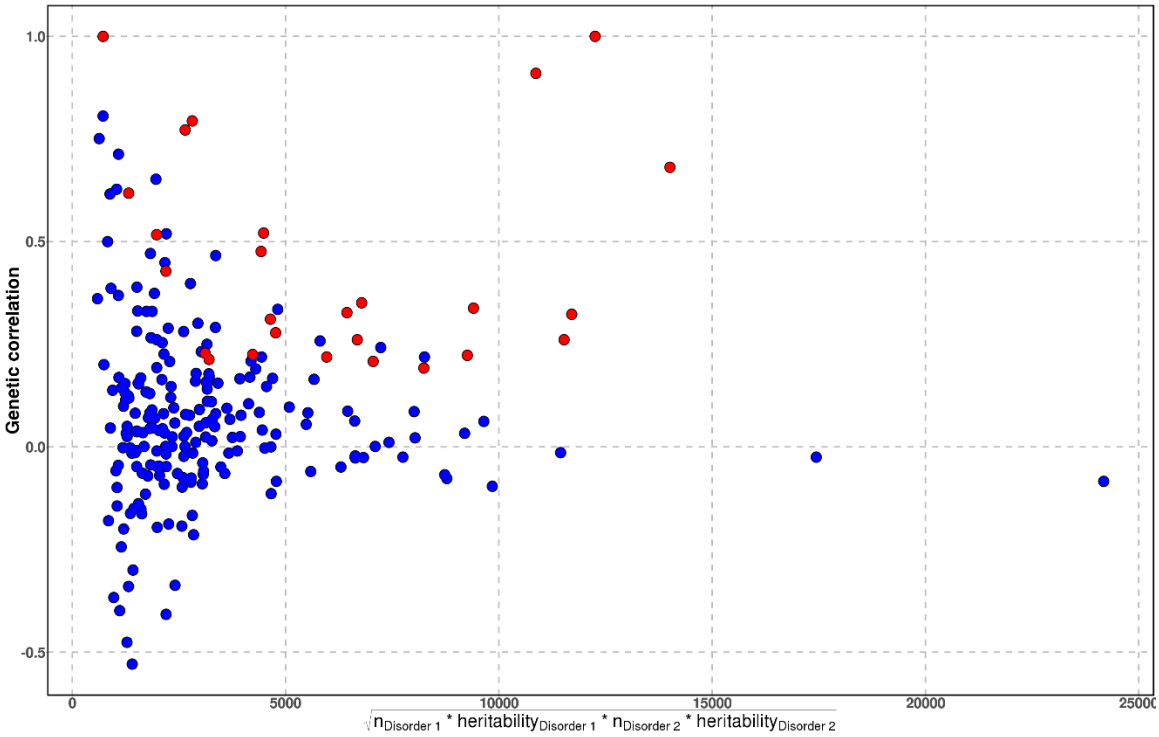


Fig. S1F. Heritability and average age of onset for the disorder.

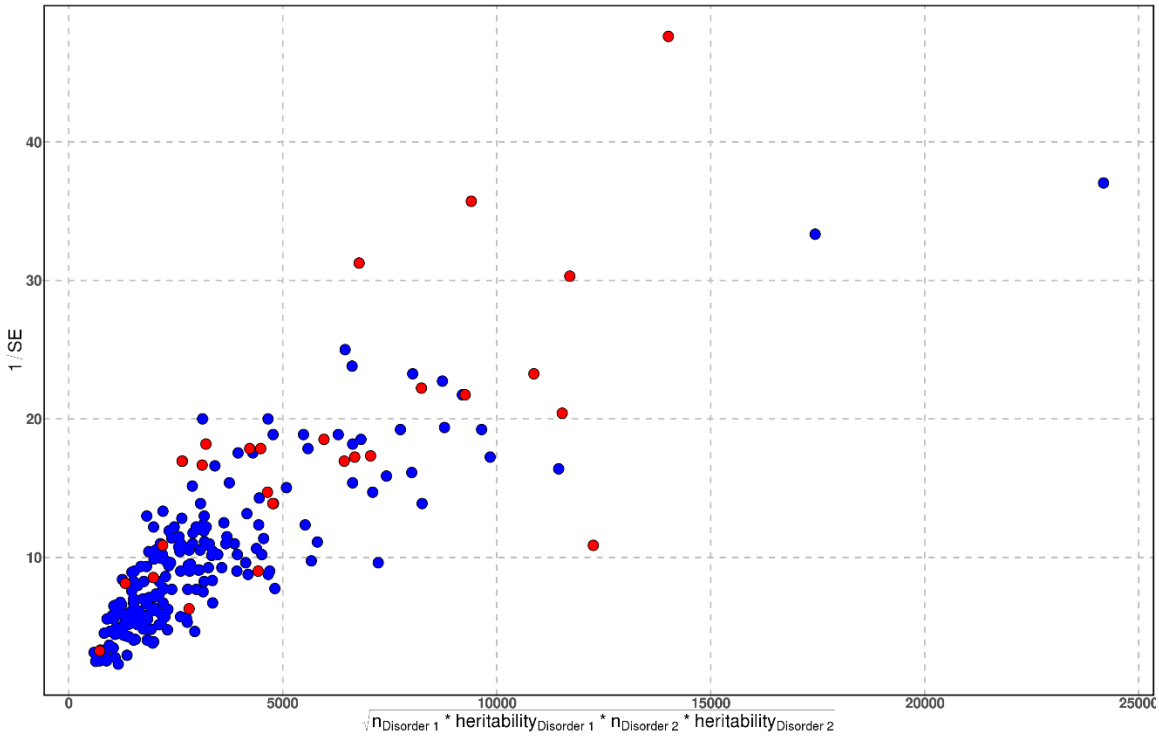
ADHD – attention deficit hyperactivity disorder; ASD – autism spectrum disorder; ICH – intracerebral hemorrhage; MDD – major depressive disorder; OCD – obsessive-compulsive disorder; PTSD – post-traumatic stress disorder. Shaded area shows 95% confidence interval. Error bars show one standard error.

Fig. S2A. Genetic correlations against power to detect heritability



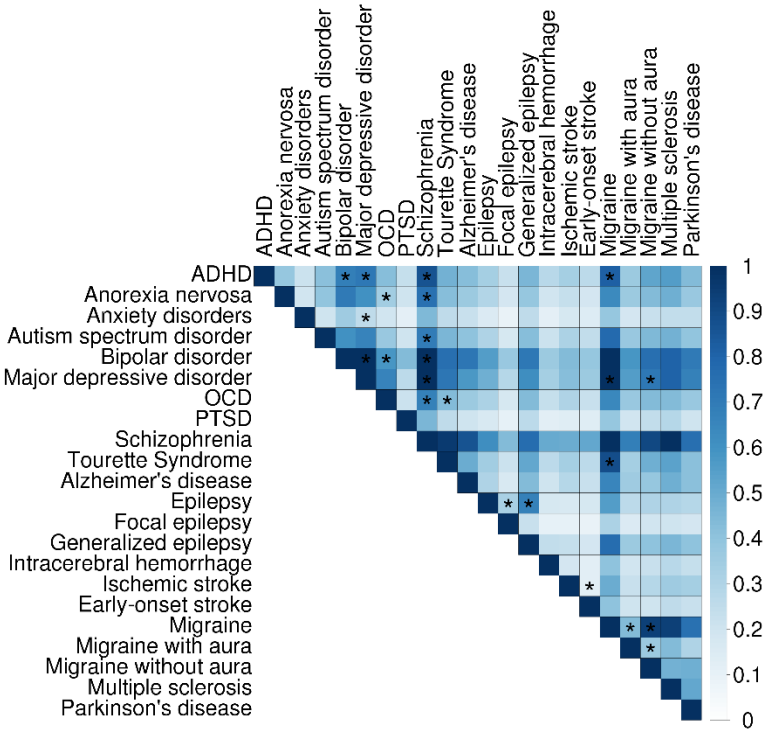
Red points show significant correlations among all disorder-disorder pairs. Two outlier values over 1 (see Table S7A) have been reduced to 1. The points close or equal to $r_g = 1$ are pairs of a top-level disorder with a subtype of the same disorder, where high correlation is expected, ie. all migraine and migraine with aura.

Fig. S2B. Inverses of standard errors against power to detect heritability



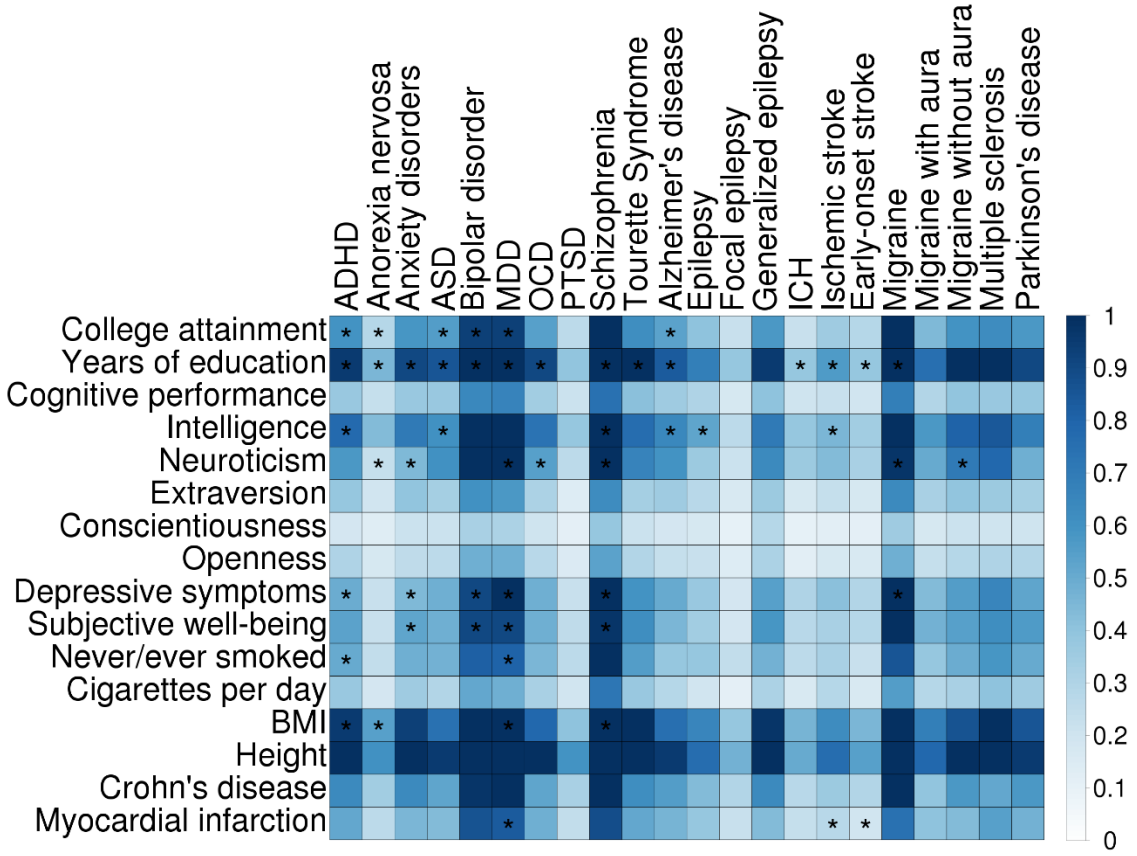
Red points show significant correlations among all disorder-disorder pairs. SE – standard error.

Fig. S2C. Matrix of standard errors for the genetic correlations for disorder-disorder pairs.



Plotted values indicate 1/standard error * 1/25 (1/25 chosen for scaling convenience); darker shades indicate tests with more power. Six outlier values over 1 (see Table S7A) have been reduced to 1. Asterisks highlight results which are significant after Bonferroni correction. ADHD - attention deficit hyperactivity disorder; OCD – obsessive-compulsive disorder; PTSD – post-traumatic stress disorder.

Fig. S2D. Matrix of standard errors for the genetic correlations for disorder-phenotype pairs.



Plotted values indicate 1/standard error * 1/25 (1/25 chosen for scaling convenience); darker shades indicate tests with more power. 39 outlier values over 1 (see Table S7B) have been reduced to 1. Asterisks highlight results which are significant after Bonferroni correction. ADHD - attention deficit hyperactivity disorder; ASD – autism spectrum disorder; BMI – body-mass index; ICH – intracerebral hemorrhage; MDD – major depressive disorder; OCD – obsessive-compulsive disorder; PTSD – post-traumatic stress disorder.

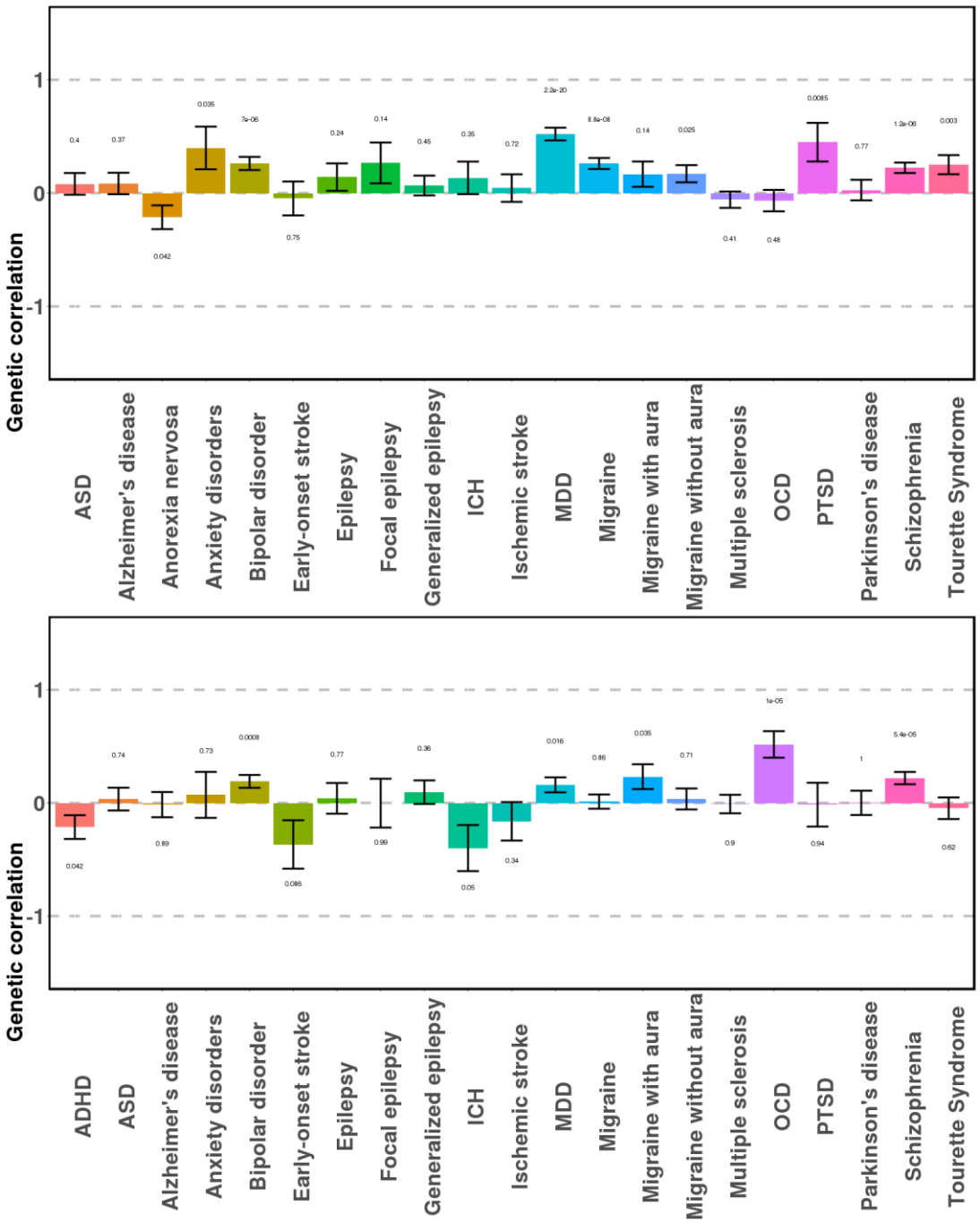


Fig. S3A and B. Genetic correlations for attention-deficit hyperactivity disorder (top) and anorexia nervosa (bottom).

ADHD - attention deficit hyperactivity disorder; ASD – autism spectrum disorder; ICH – intracerebral hemorrhage; MDD – major depressive disorder; OCD – obsessive-compulsive disorder; PTSD – post-traumatic stress disorder. P-values for correlation are shown at the end of each bar. Error bars show one standard error.

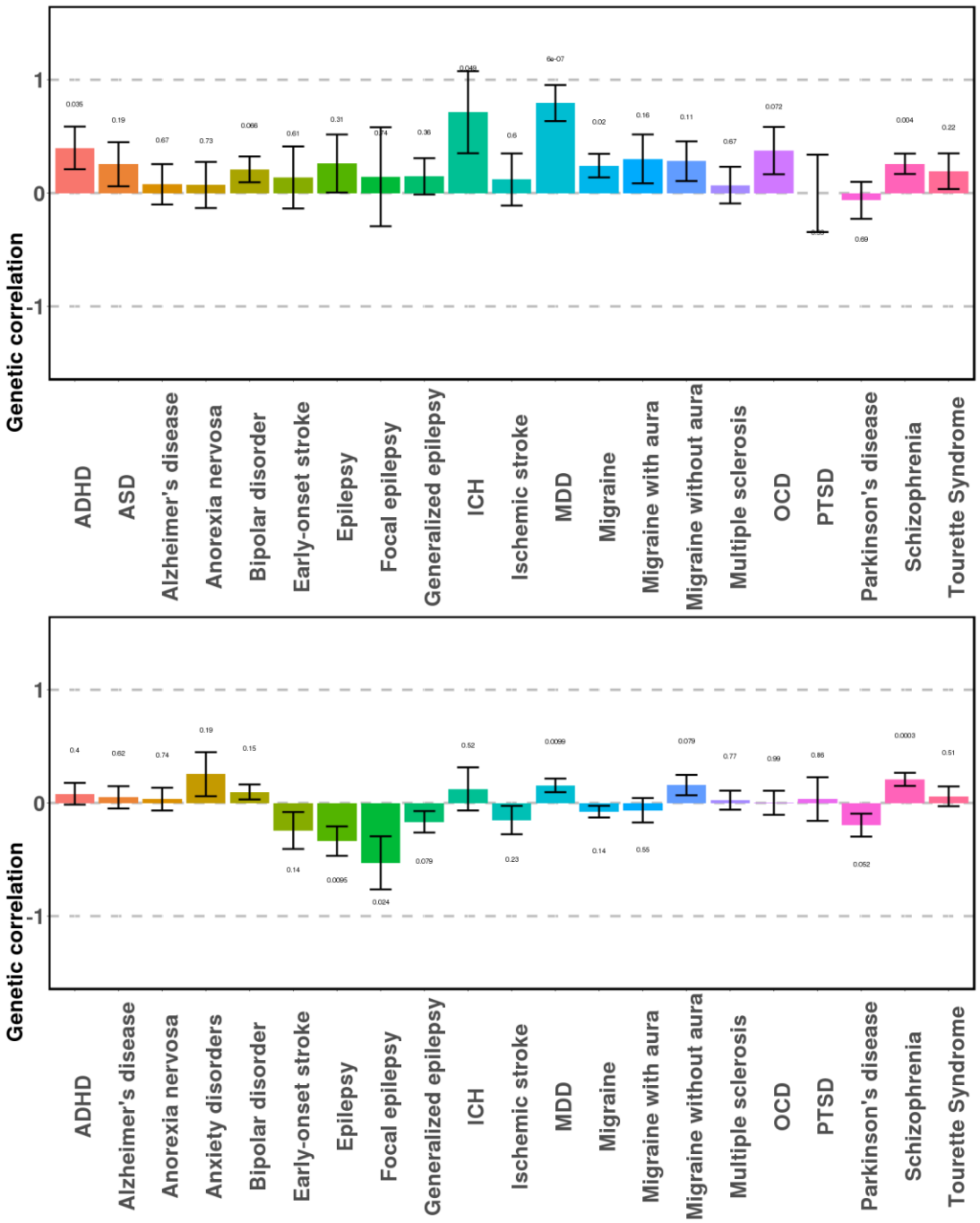


Fig. S3C and D. Genetic correlations for anxiety disorders (top) and autism spectrum disorder (bottom).

ADHD - attention deficit hyperactivity disorder; ASD – autism spectrum disorder; ICH – intracerebral hemorrhage; MDD – major depressive disorder; OCD – obsessive-compulsive disorder; PTSD – post-traumatic stress disorder. P-values for correlation are shown at the end of each bar. Error bars show one standard error.

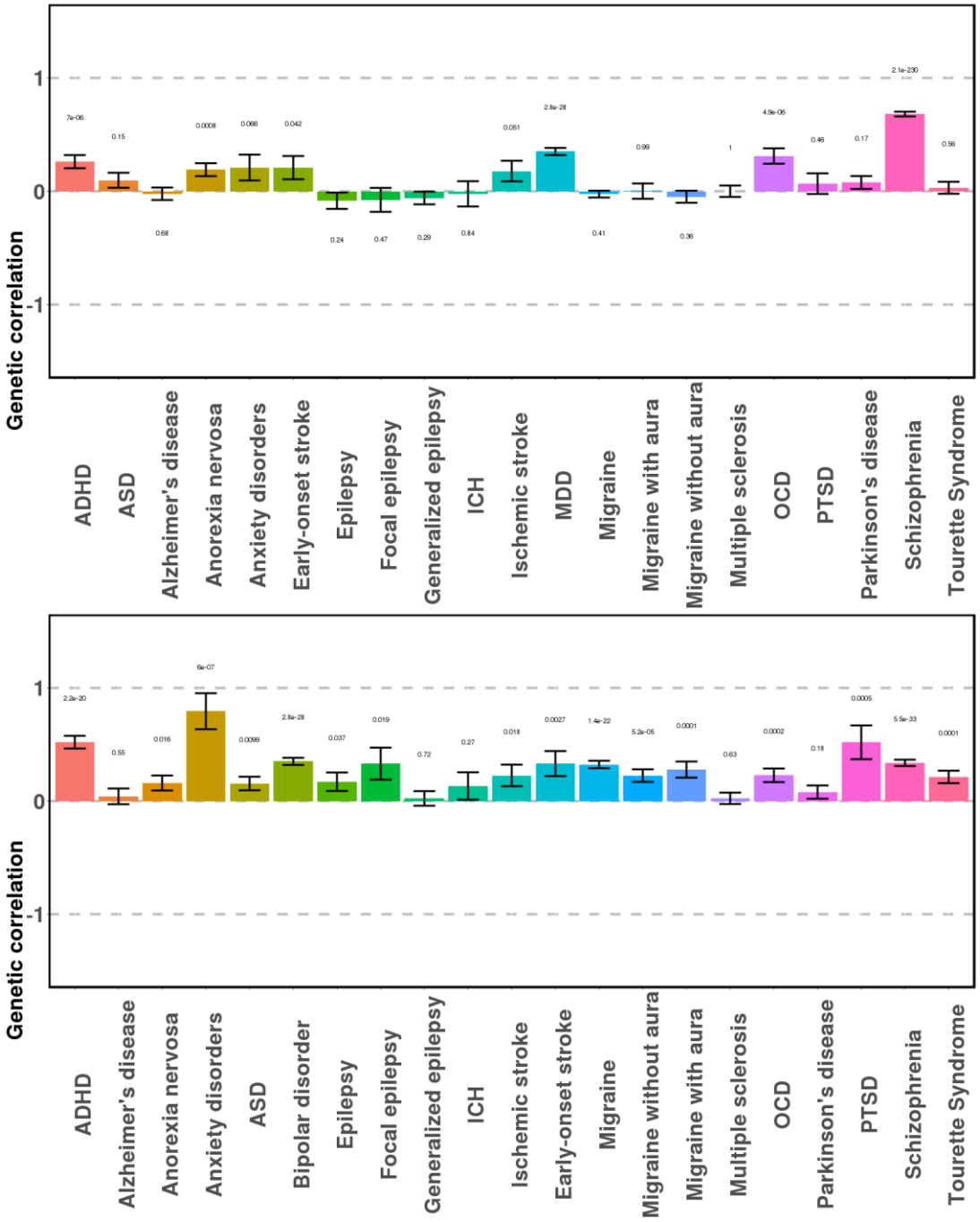


Fig. S3E and F. Genetic correlations for bipolar disorder (top) and major depressive disorder (bottom).

ADHD - attention deficit hyperactivity disorder; ASD – autism spectrum disorder; ICH – intracerebral hemorrhage; MDD – major depressive disorder; OCD – obsessive-compulsive disorder; PTSD – post-traumatic stress disorder. P-values for correlation are shown at the end of each bar. Error bars show one standard error.

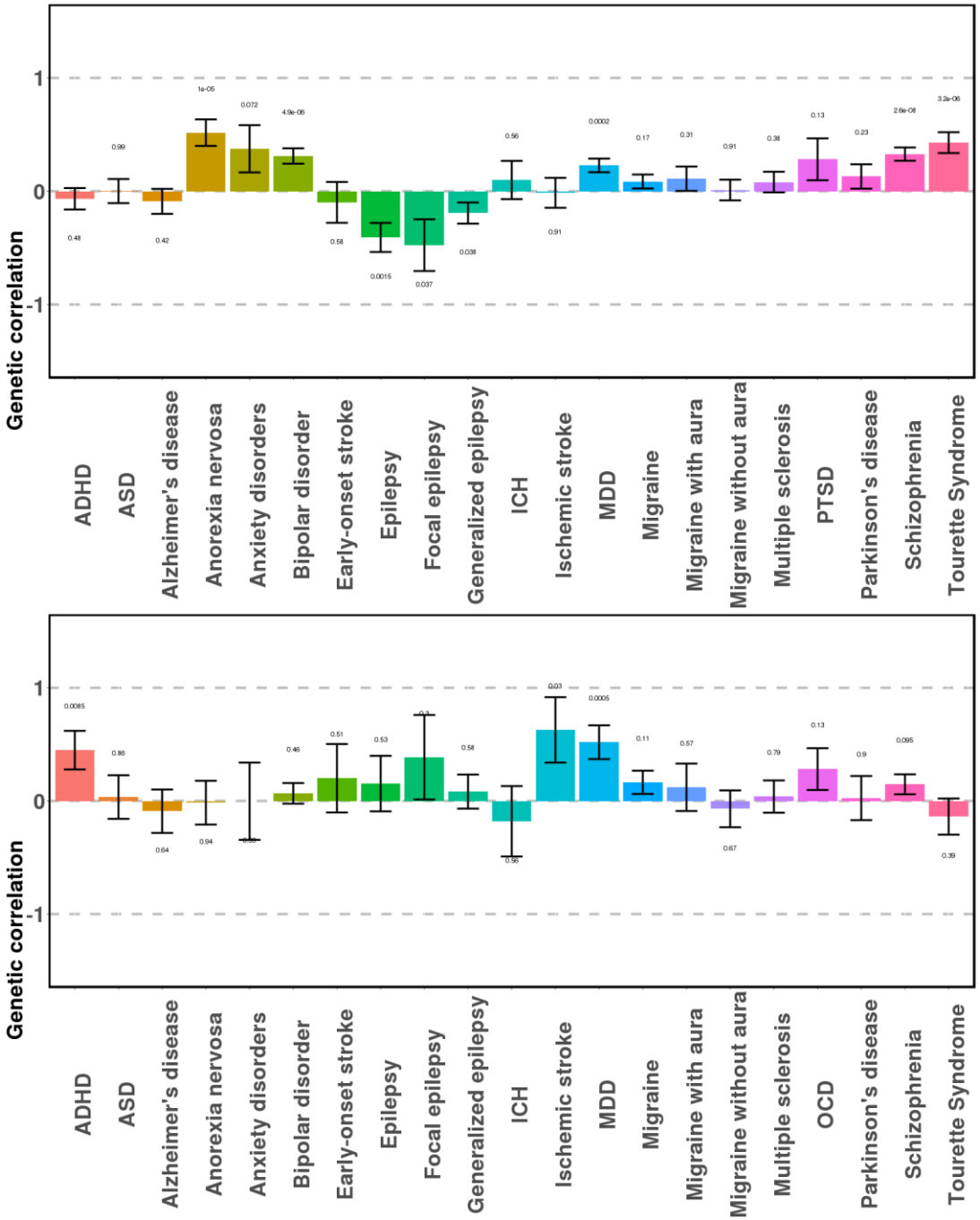


Fig. S3G and H. Genetic correlations for obsessive-compulsive disorder (top) and post-traumatic stress disorder (bottom).

ADHD - attention deficit hyperactivity disorder; ASD – autism spectrum disorder; ICH – intracerebral hemorrhage; MDD – major depressive disorder; OCD – obsessive-compulsive disorder; PTSD – post-traumatic stress disorder. P-values for correlation are shown at the end of each bar. Error bars show one standard error.

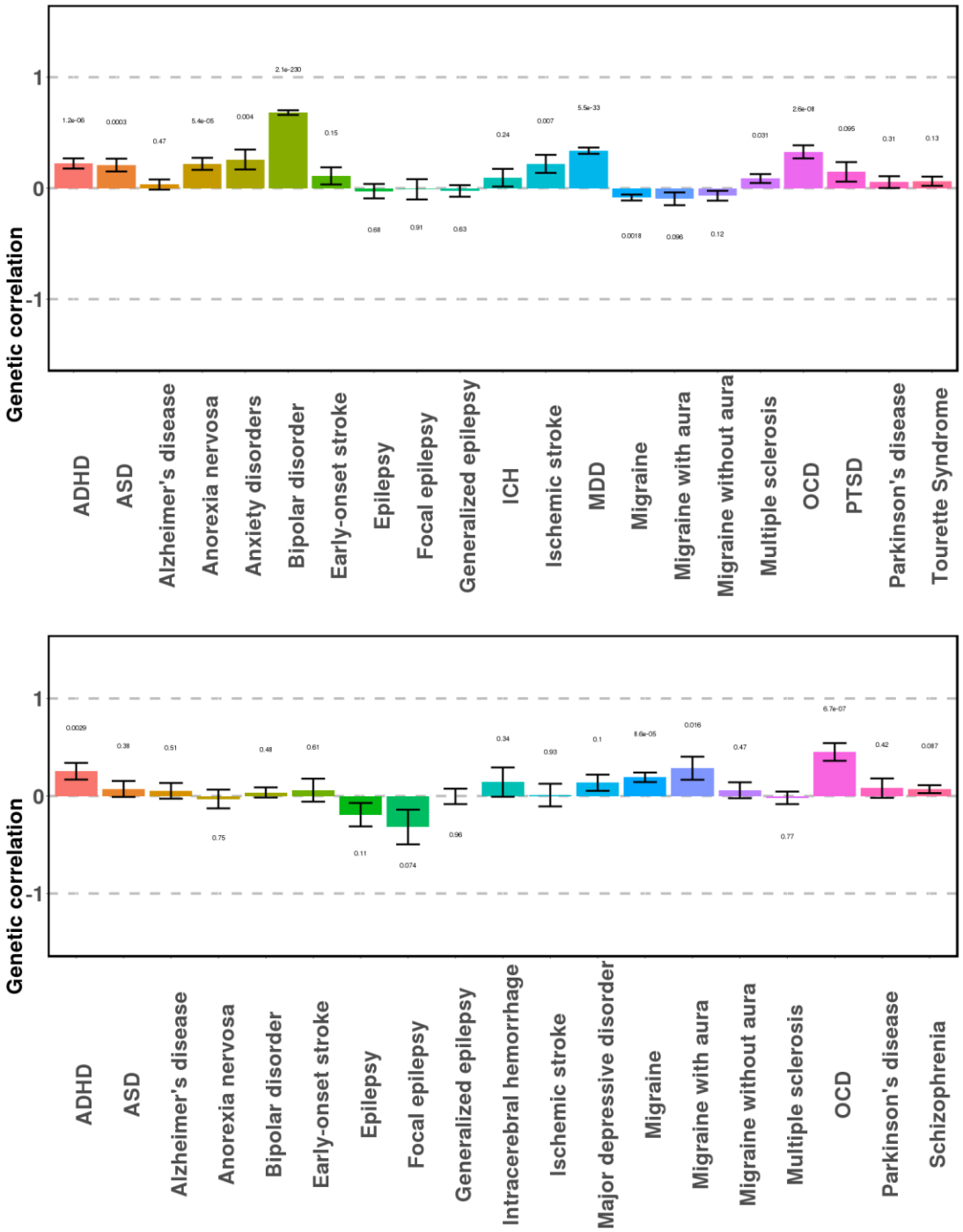


Fig. S3I and J. Genetic correlations for schizophrenia (top) and Tourette Syndrome (bottom).

ADHD - attention deficit hyperactivity disorder; ASD – autism spectrum disorder; ICH – intracerebral hemorrhage; MDD – major depressive disorder; OCD – obsessive-compulsive disorder; PTSD – post-traumatic stress disorder. P-values for correlation are shown at the end of each bar. Error bars show one standard error.

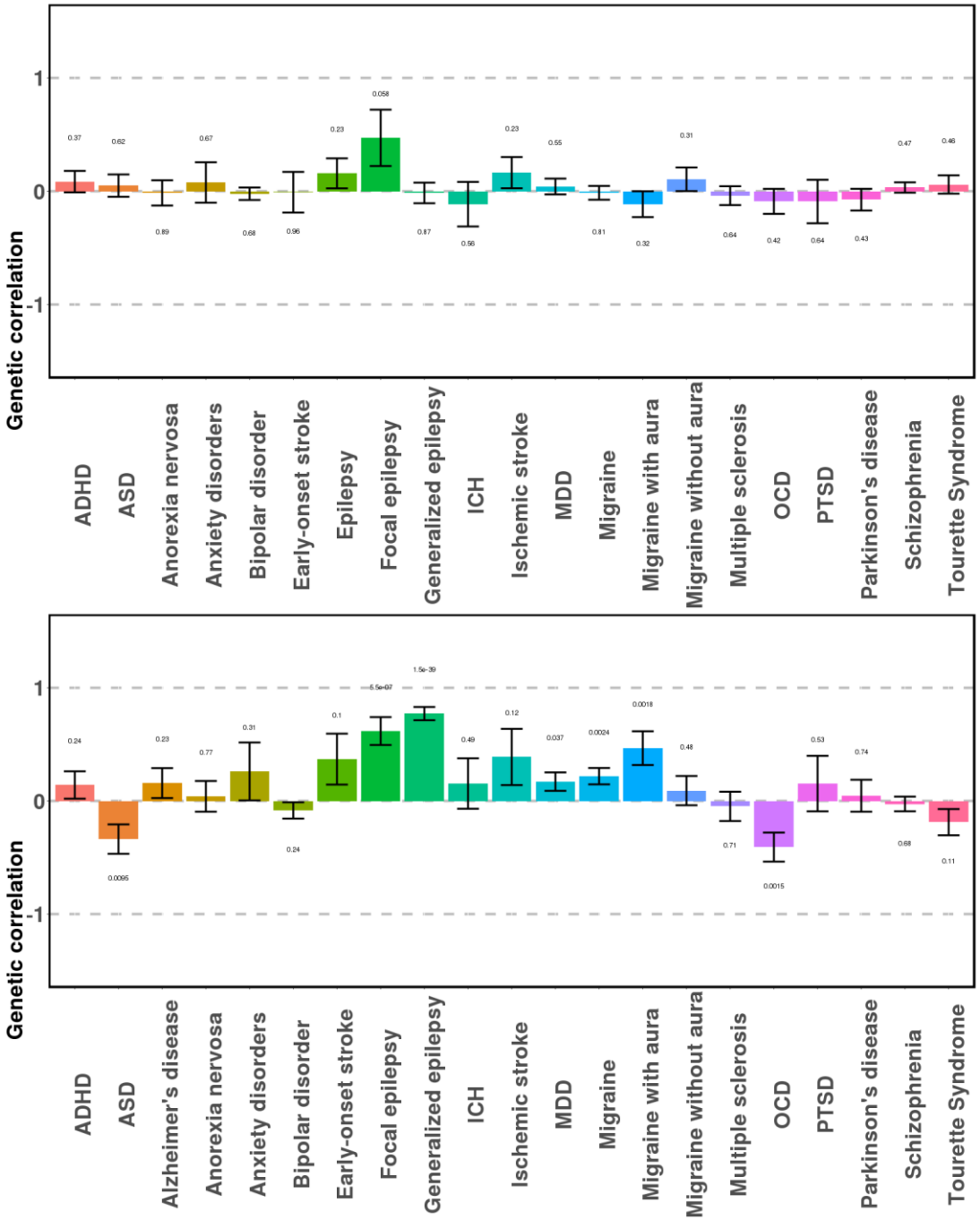


Fig. S4A and B. Genetic correlations for Alzheimer's disease (top) and epilepsy (bottom).

ADHD - attention deficit hyperactivity disorder; ASD – autism spectrum disorder; ICH – intracerebral hemorrhage; MDD – major depressive disorder; OCD – obsessive-compulsive disorder; PTSD – post-traumatic stress disorder. P-values for correlation are shown at the end of each bar. Error bars show one standard error.

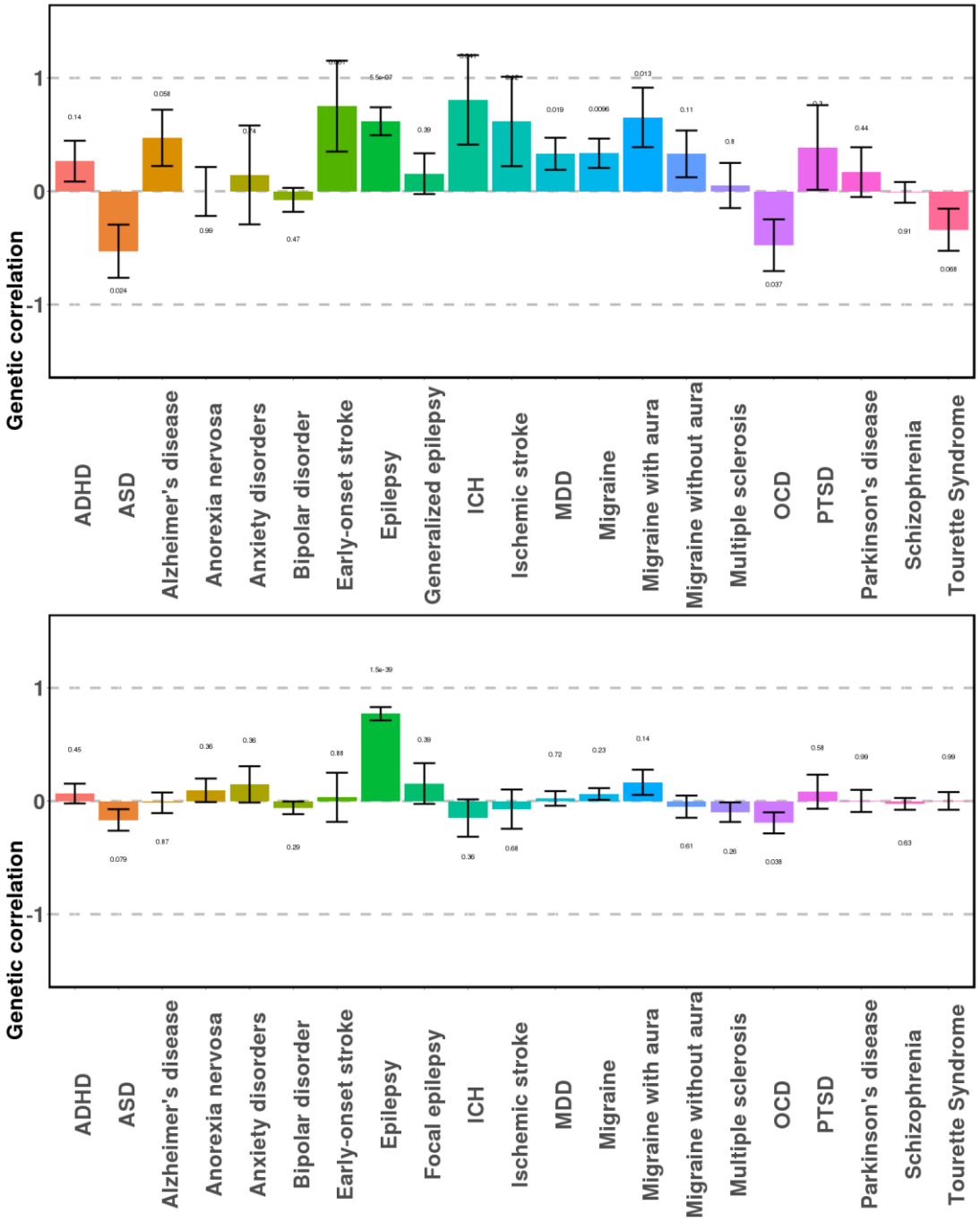


Fig. S4C and D. Genetic correlations for focal epilepsy (top) and generalized epilepsy (bottom).

ADHD - attention deficit hyperactivity disorder; ASD – autism spectrum disorder; ICH – intracerebral hemorrhage; MDD – major depressive disorder; OCD – obsessive-compulsive disorder; PTSD – post-traumatic stress disorder. P-values for correlation are shown at the end of each bar. Error bars show one standard error.

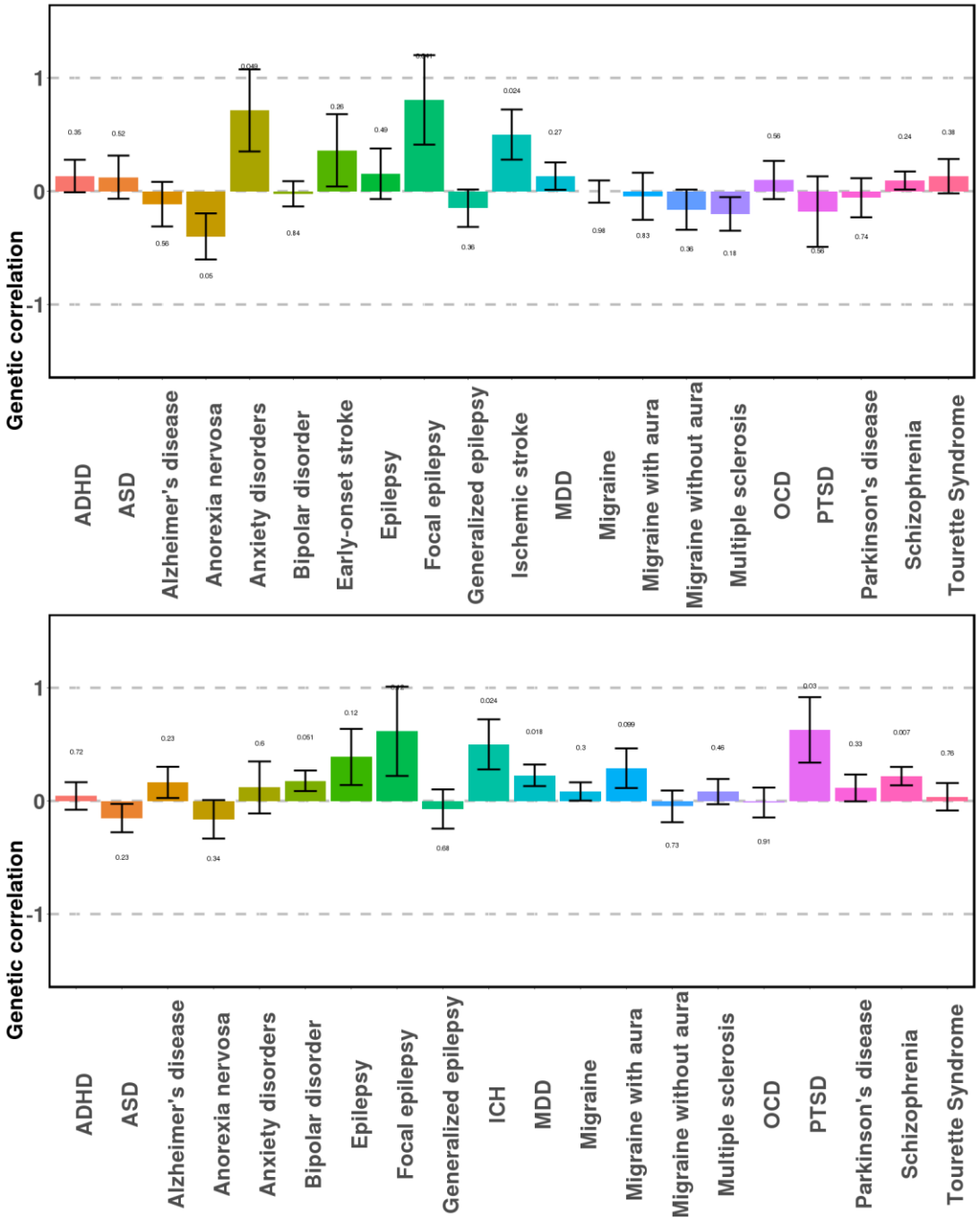


Fig. S4E and F. Genetic correlations for intracerebral hemorrhage (top) and ischemic stroke (bottom).

ADHD - attention deficit hyperactivity disorder; ASD – autism spectrum disorder; ICH – intracerebral hemorrhage; MDD – major depressive disorder; OCD – obsessive-compulsive disorder; PTSD – post-traumatic stress disorder. P-values for correlation are shown at the end of each bar. Error bars show one standard error.

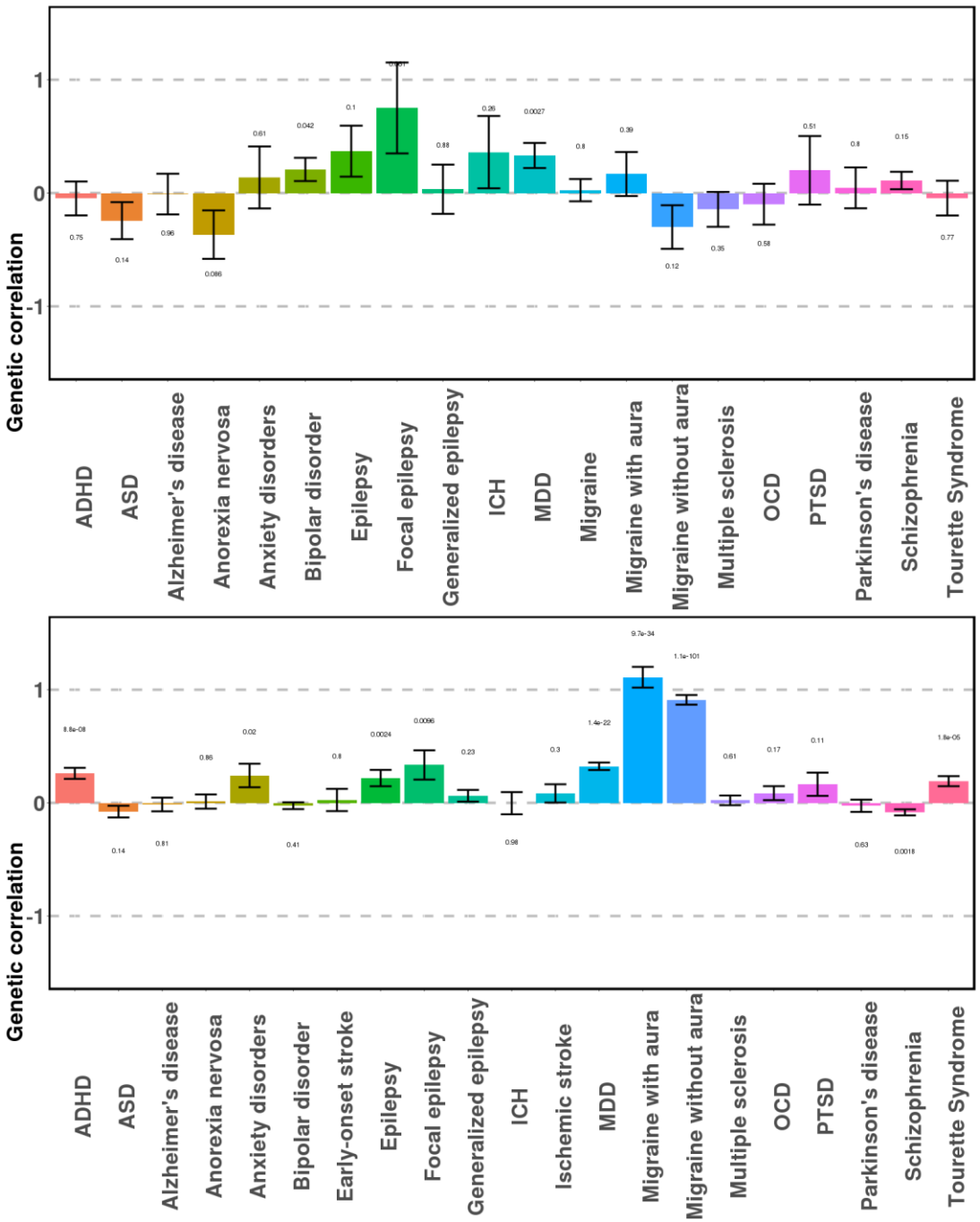


Fig. S4G and H. Genetic correlations for early-onset stroke (top) and migraine (bottom).

ADHD - attention deficit hyperactivity disorder; ASD – autism spectrum disorder; ICH – intracerebral hemorrhage; MDD – major depressive disorder; OCD – obsessive-compulsive disorder; PTSD – post-traumatic stress disorder. P-values for correlation are shown at the end of each bar. Error bars show one standard error.

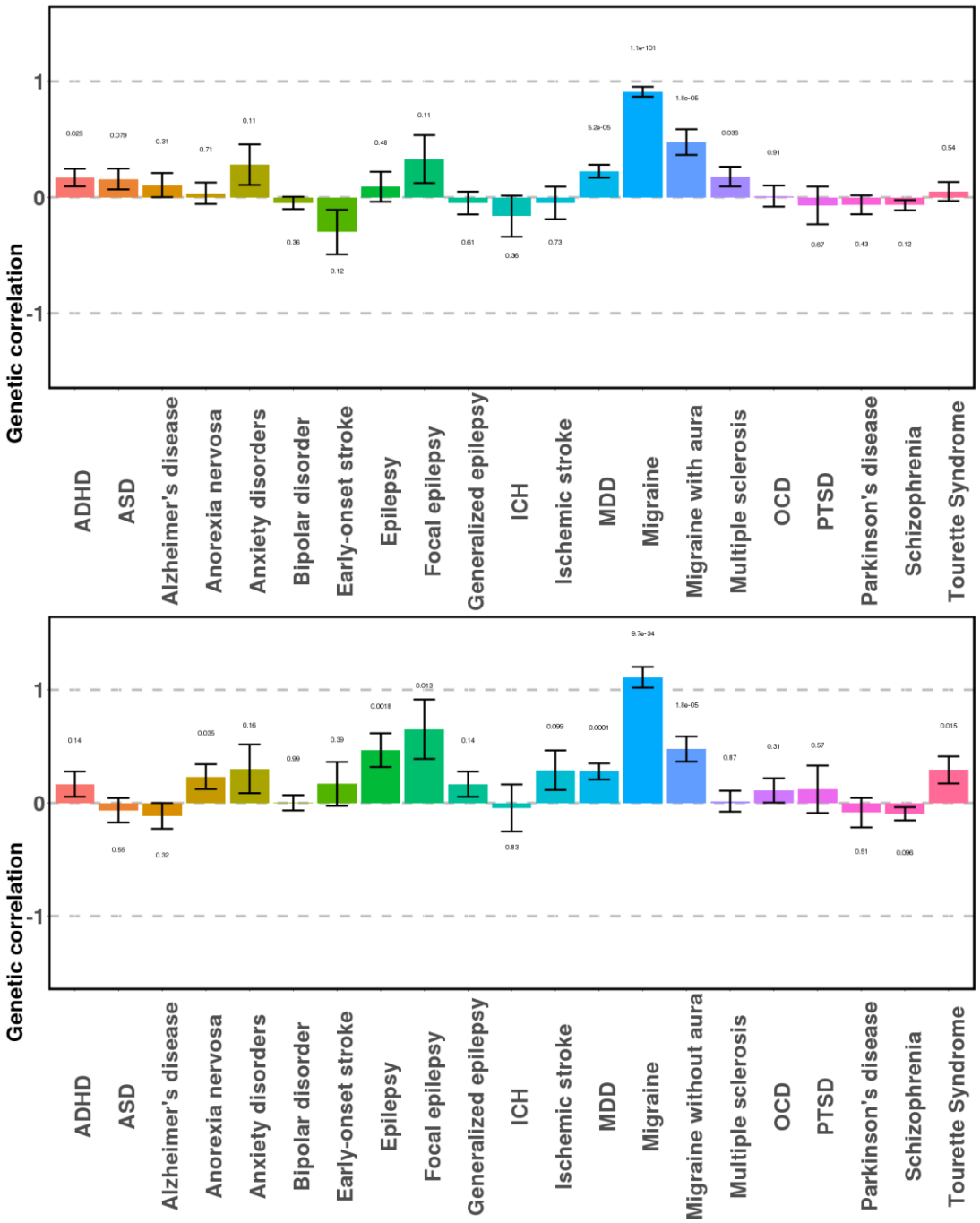


Fig. S4I and J. Genetic correlations for migraine without aura (top) and migraine with aura (bottom).

ADHD - attention deficit hyperactivity disorder; ASD – autism spectrum disorder; ICH – intracerebral hemorrhage; MDD – major depressive disorder; OCD – obsessive-compulsive disorder; PTSD – post-traumatic stress disorder. P-values for correlation are shown at the end of each bar. Error bars show one standard error.

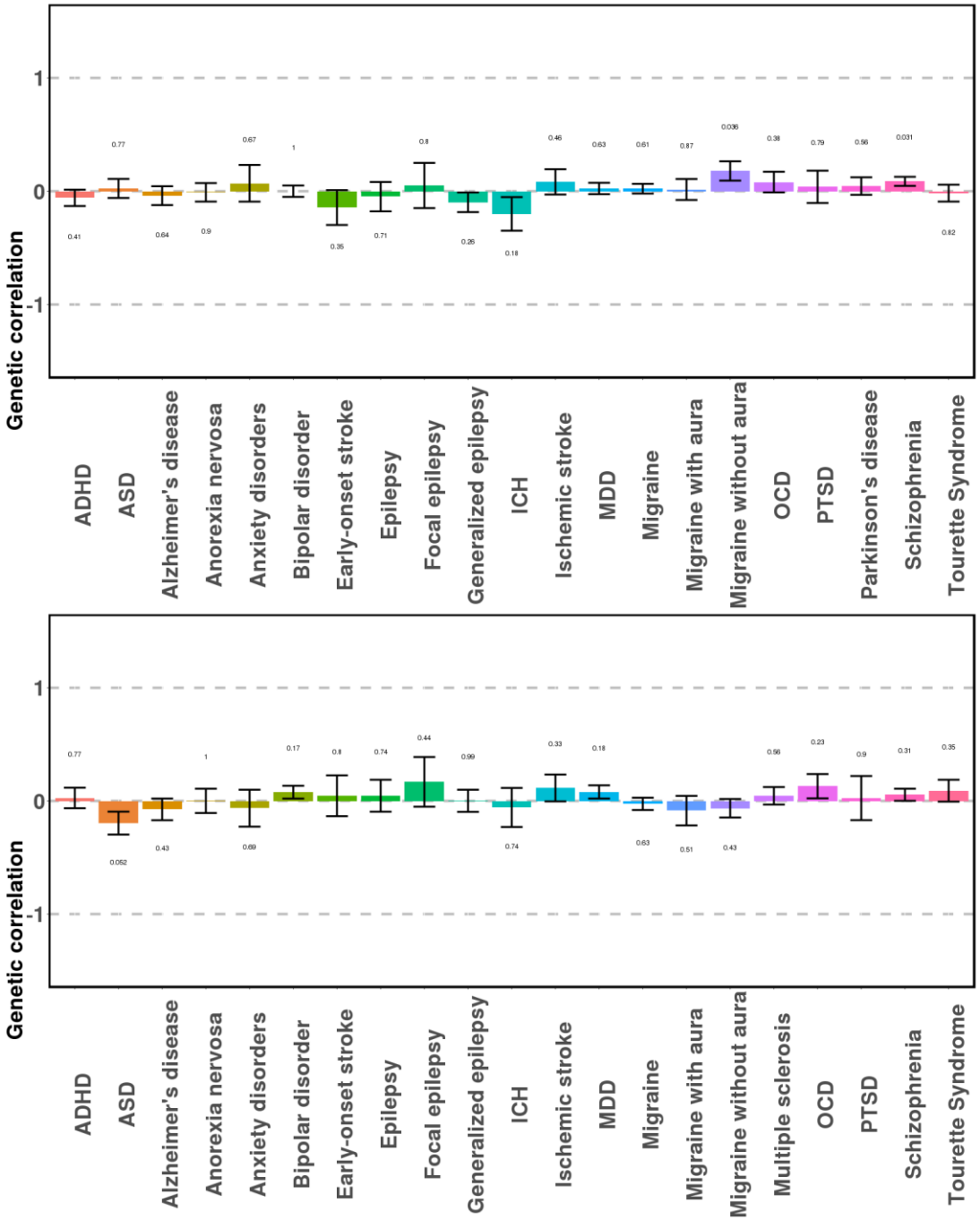


Fig. S4K and L. Genetic correlations for multiple sclerosis (top) and Parkinson's disease (bottom).

ADHD - attention deficit hyperactivity disorder; ASD – autism spectrum disorder; ICH – intracerebral hemorrhage; MDD – major depressive disorder; OCD – obsessive-compulsive disorder; PTSD – post-traumatic stress disorder. P-values for correlation are shown at the end of each bar. Error bars show one standard error.

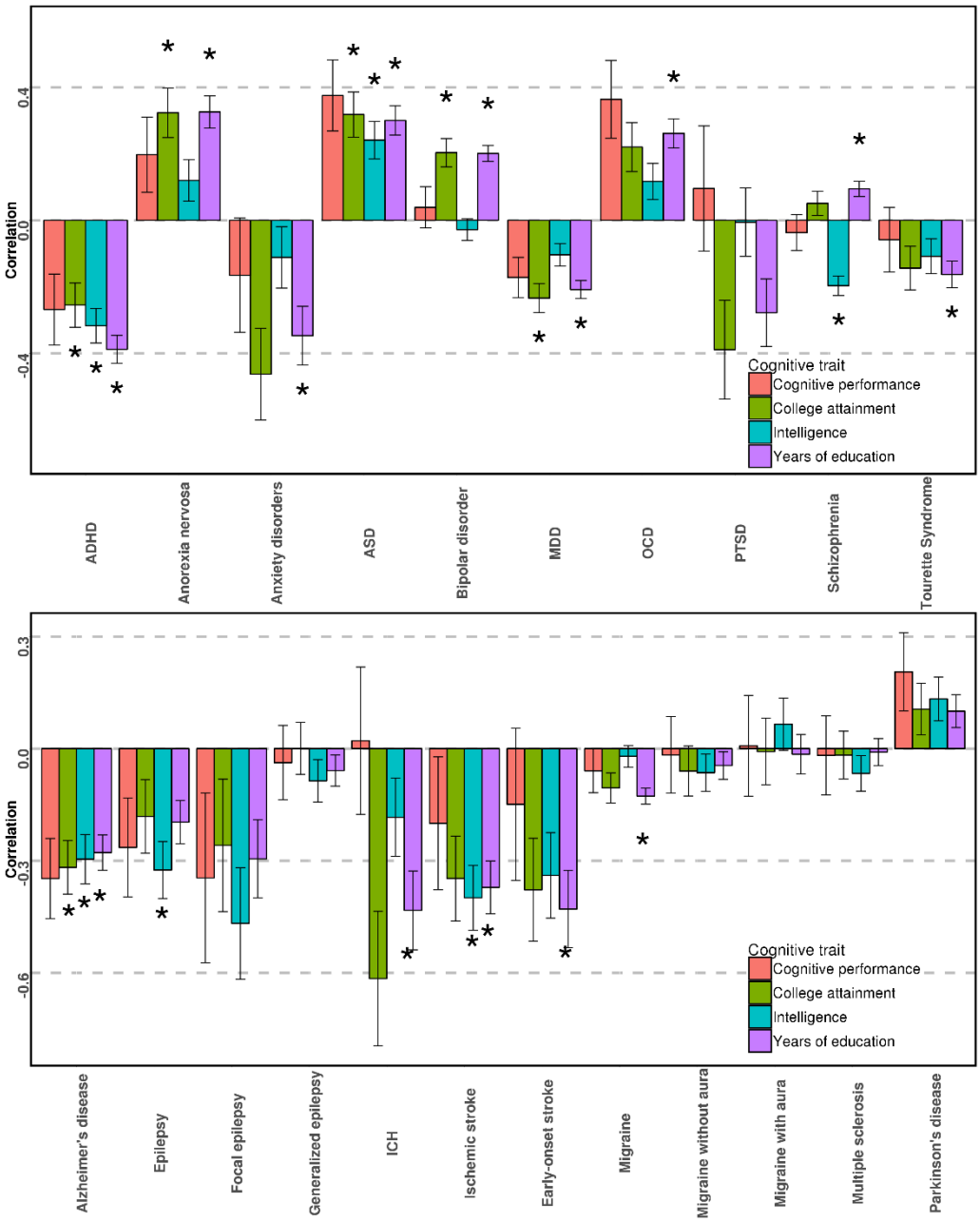


Fig. S5A and B. Genetic correlations for psychiatric and neurological disorders against cognitive measures.

Asterisks highlight results which are significant after Bonferroni correction. ADHD - attention deficit hyperactivity disorder; ASD – autism spectrum disorder; MDD – major depressive disorder; OCD – obsessive-compulsive disorder; PTSD – post-traumatic stress disorder; ICH – intracerebral hemorrhage. Dotted line divides the psychiatric phenotypes from the neurological phenotypes. Error bars show one standard error.

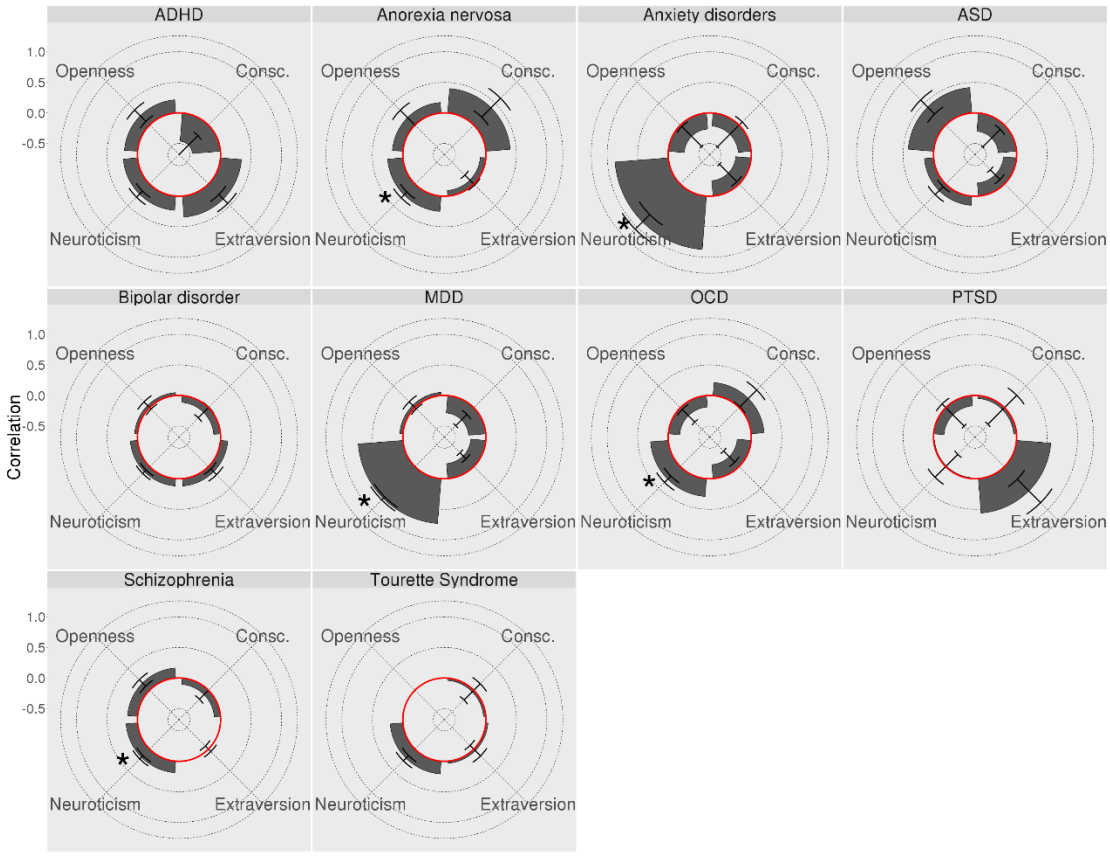


Fig. S6A. Genetic correlations for psychiatric disorders and four personality axes. Grey sectors denote the extent of genetic correlation between each brain disorder and the four personality axes. Red line denotes zero correlation, with positive correlations on the outside and negative correlations on the inside. Error bars show one standard error. Asterisks highlight results which are significant after Bonferroni correction. Consc. – Conscientiousness; ADHD - attention deficit hyperactivity disorder; ASD – autism spectrum disorder; MDD – major depressive disorder; OCD – obsessive-compulsive disorder; PTSD – post-traumatic stress disorder.

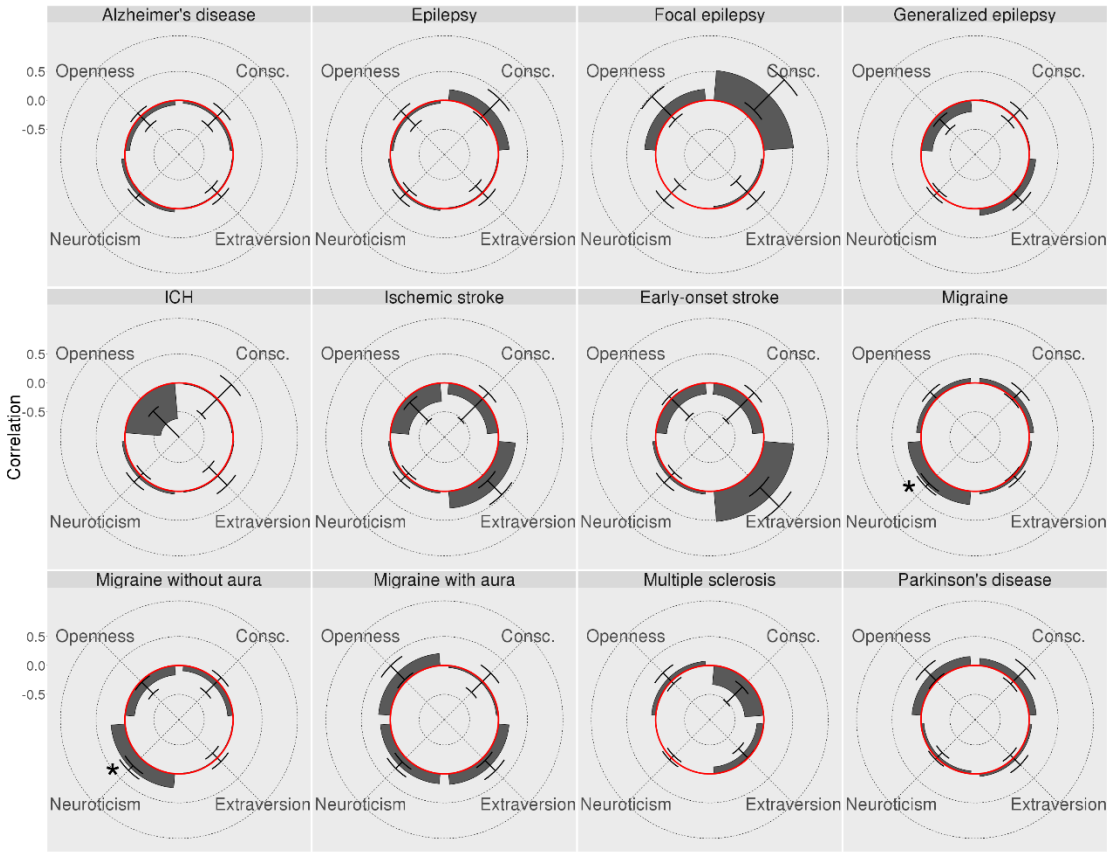


Fig. S6B. Genetic correlations for neurological disorders and four personality axes. Grey bars denote the extent of genetic correlation between each brain disorder and the four personality axes. Red line denotes zero correlation, with positive correlations on the outside and negative correlations on the inside. Error bars show one standard error. Asterisks highlight results which are significant after Bonferroni correction. Consc. – Conscientiousness; ICH – intracerebral hemorrhage.

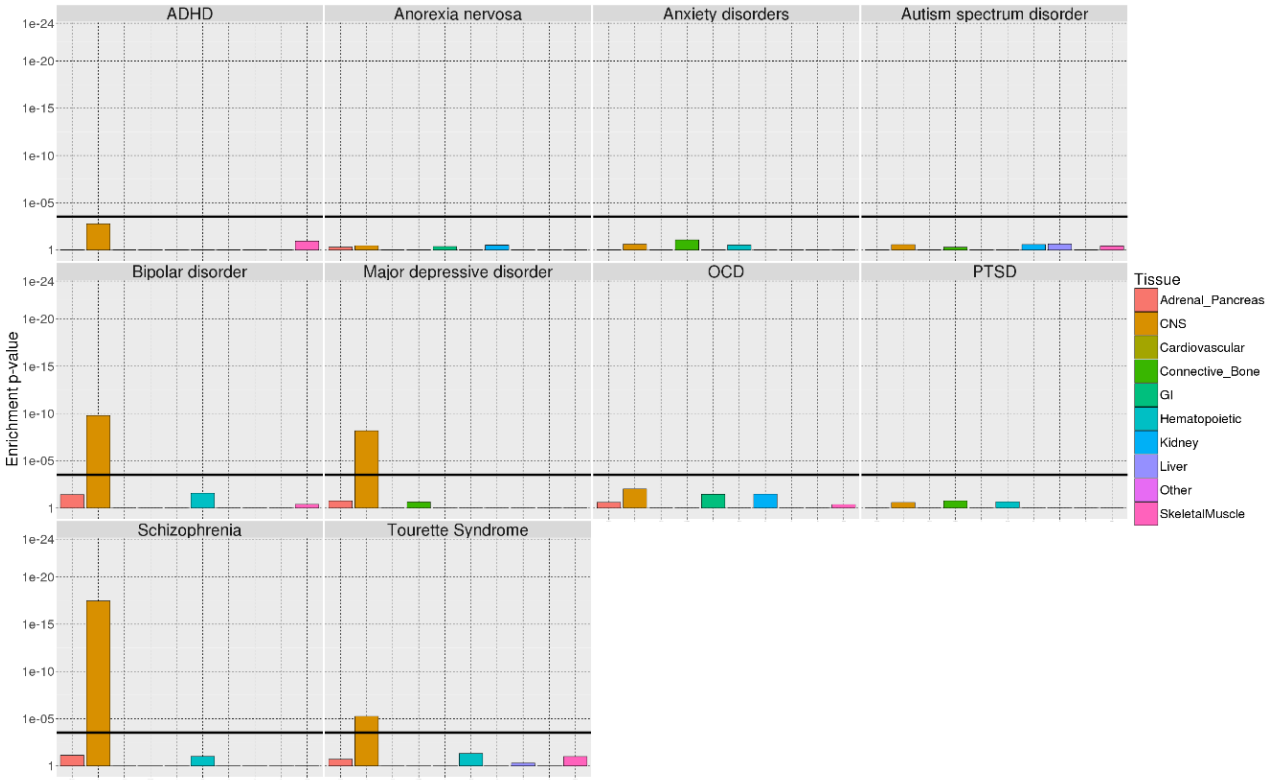


Fig. S7A. Tissue category heritability enrichment analysis in psychiatric phenotypes

ADHD – attention deficit hyperactivity disorder; CNS – central nervous system; GI – gastro-intestinal system; OCD – obsessive-compulsive disorder; PTSD – post-traumatic stress disorder. Results for largely overlapping dataset in schizophrenia has been previously reported in Finucane et al(*26*). Black line denotes significance threshold for Bonferroni multiple testing correction, $p=2.81 \times 10^{-4}$. Only positive enrichment reported.

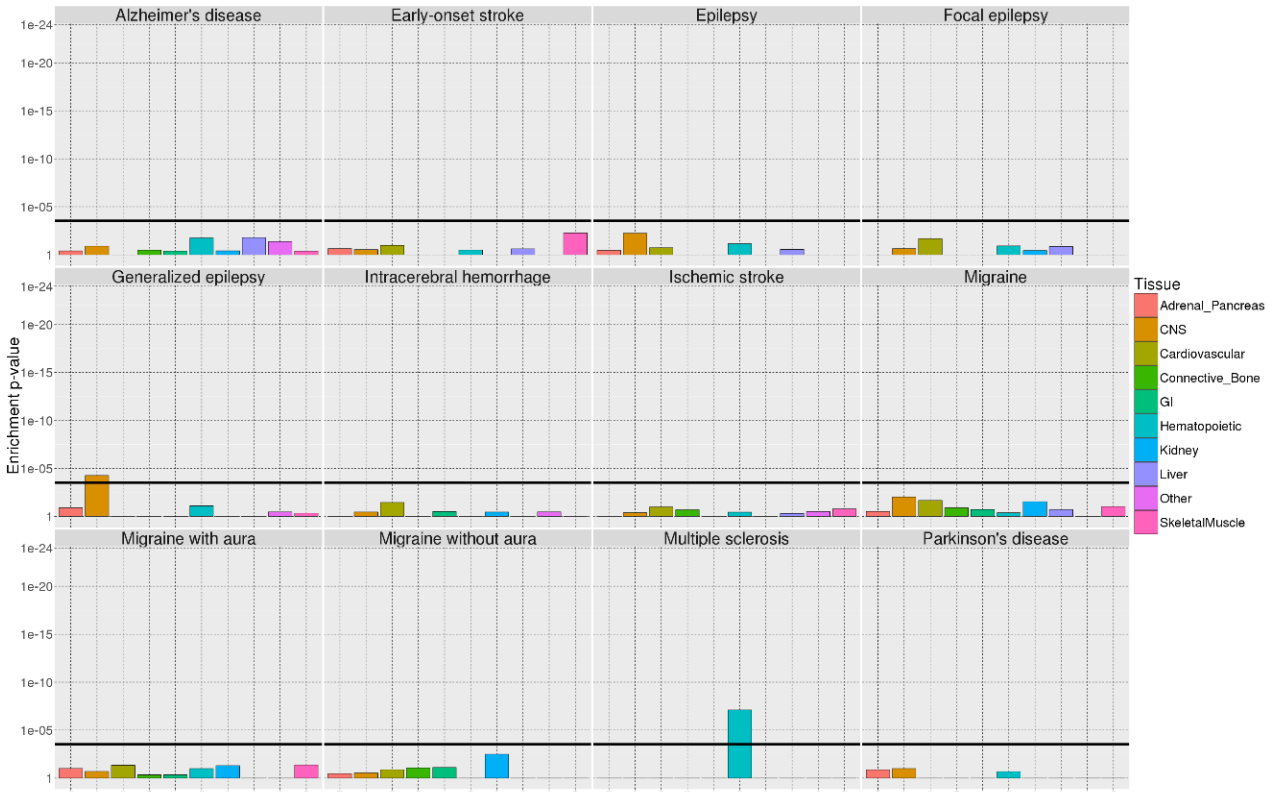


Fig. S7B. Tissue category heritability enrichment analysis in neurological phenotypes

CNS – central nervous system; GI – gastro-intestinal system. Black line denotes significance threshold for Bonferroni multiple testing correction, $p=2.81 \times 10^{-4}$. Only positive enrichment reported.

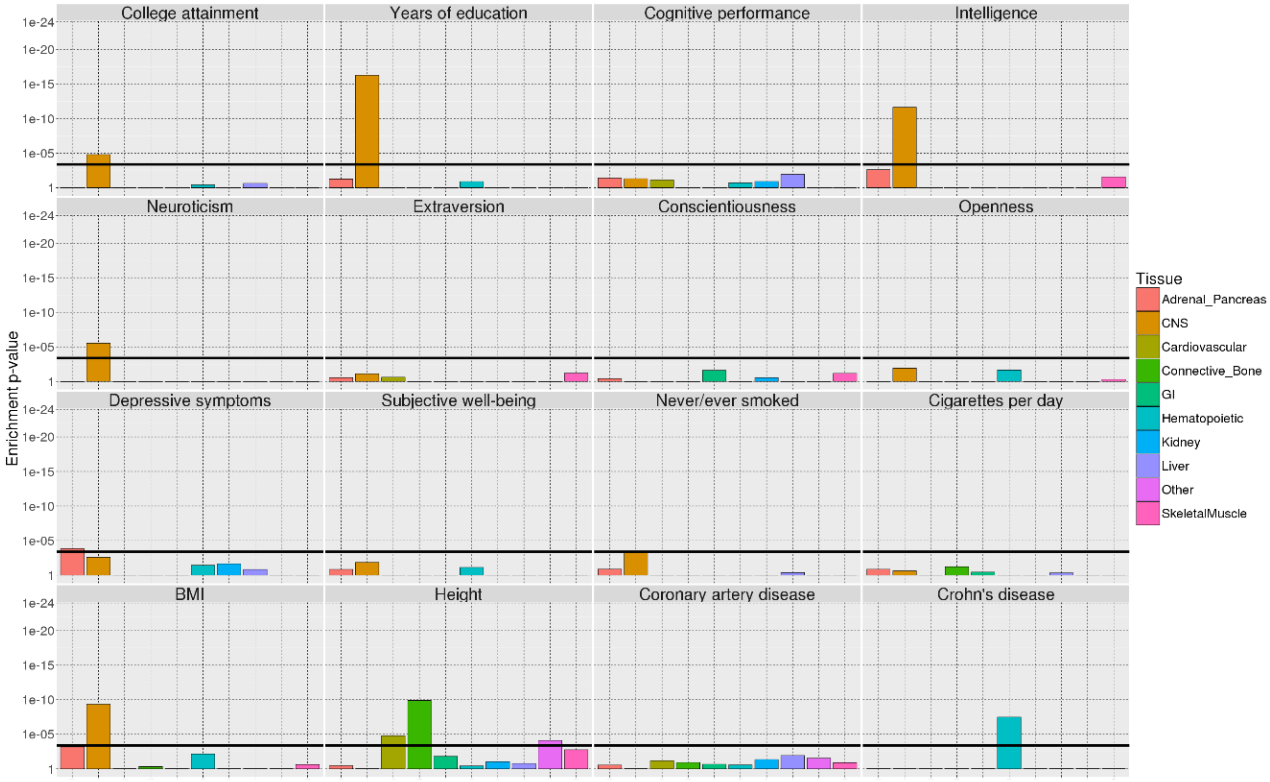


Fig. S7C. Tissue category heritability enrichment analysis in quantitative and additional phenotypes

BMI – body-mass index. CNS – central nervous system; GI – gastro-intestinal system. Results for identical datasets in BMI, Crohn's disease and height have been previously reported in Finucane et al(*26*), and those for depressive symptoms in Okbay et al(*78*). The black line denotes significance threshold for Bonferroni multiple testing correction, $p=4.10 \times 10^{-4}$. Only positive enrichment reported.

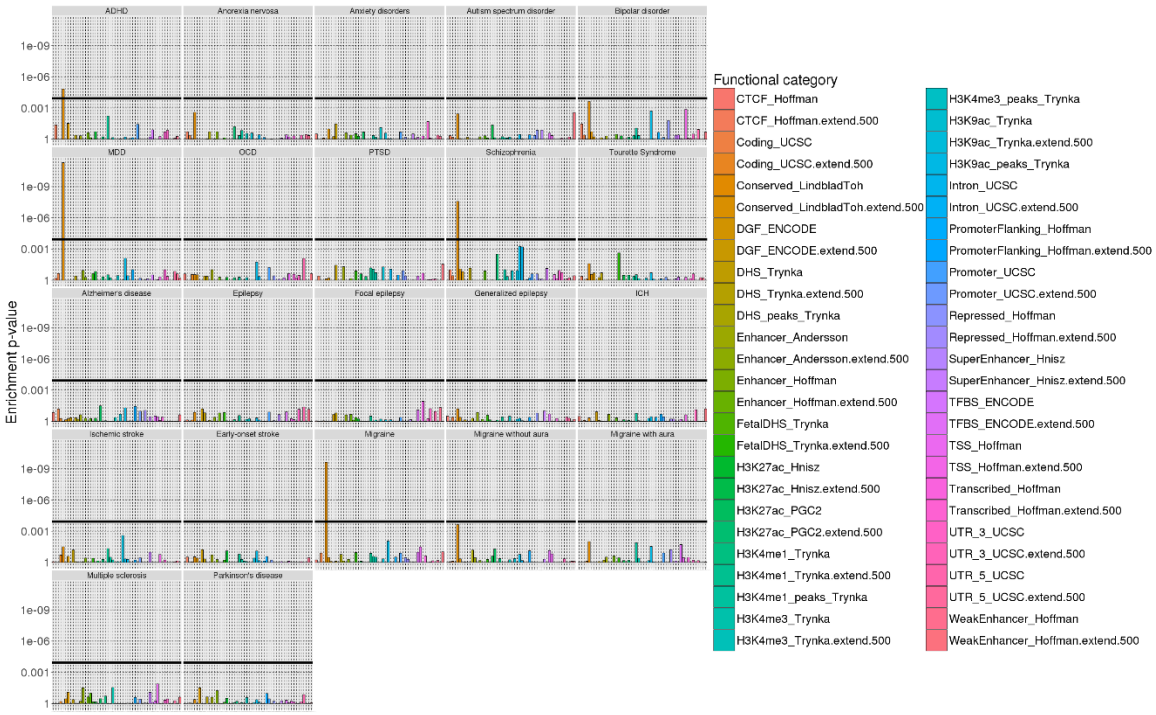


Fig. S7D. Partitioned heritability analysis across 53 functional categories in study disorders

ADHD - attention deficit hyperactivity disorder; ICH – intracerebral hemorrhage; MDD – major depressive disorder; OCD – obsessive-compulsive disorder; PTSD – post-traumatic stress disorder. Results for a largely overlapping dataset in schizophrenia have been previously reported in Finucane et al(*26*). The black line denotes significance threshold for Bonferroni multiple testing correction, $p=1.17 \times 10^{-4}$. Only positive enrichment reported.

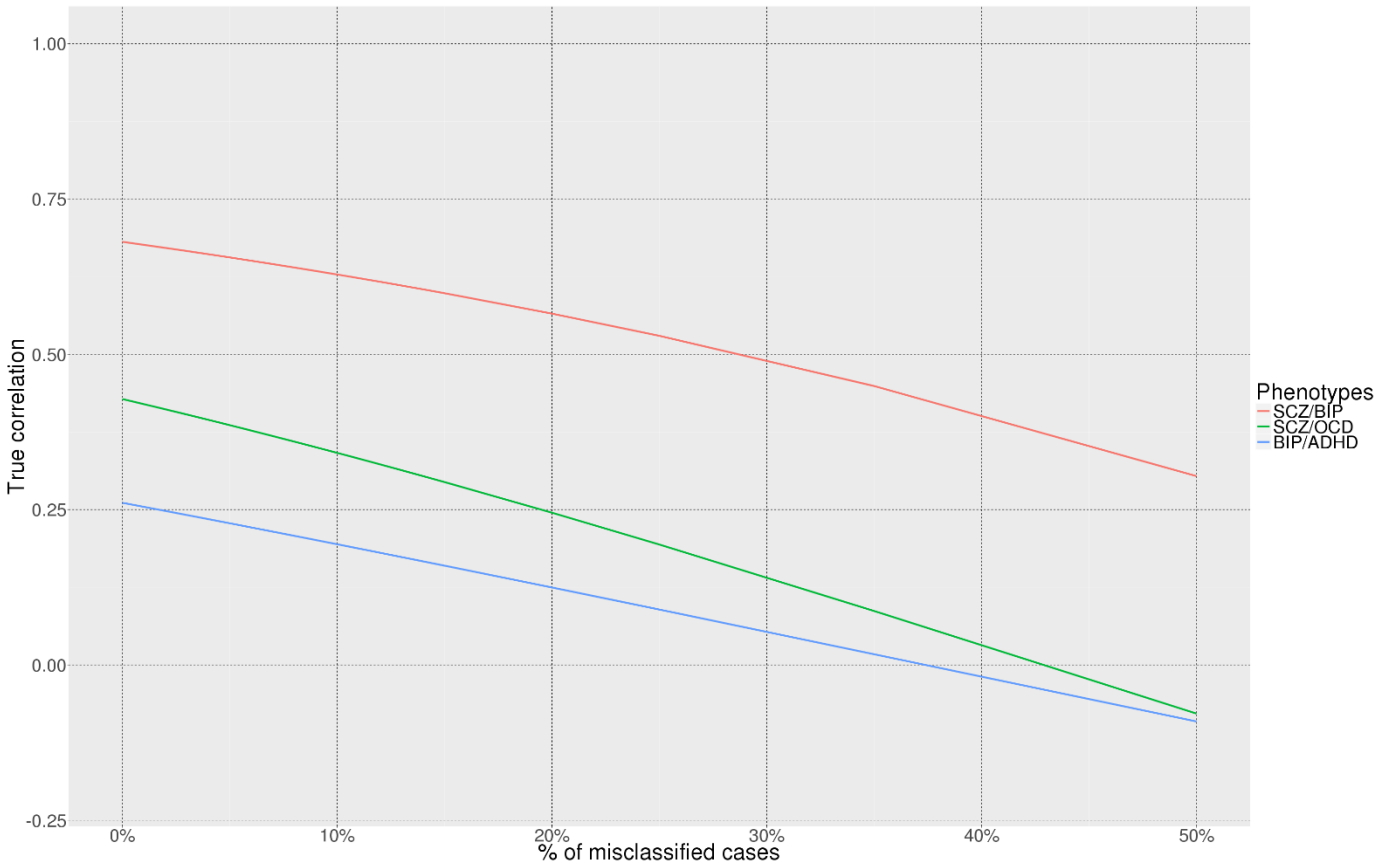


Fig. S8. Effect of case misclassification on true underlying genetic correlation given the observed results.

ADHD - attention deficit hyperactivity disorder; BIP – bipolar disorder; OCD – obsessive-compulsive disorder; SCZ – schizophrenia. Genetic correlations as a function of misclassification based on derivation described in the section "Effect of co-morbidity and phenotypic misclassification on correlation estimates", for the same phenotype pairs as reported in Table S5.

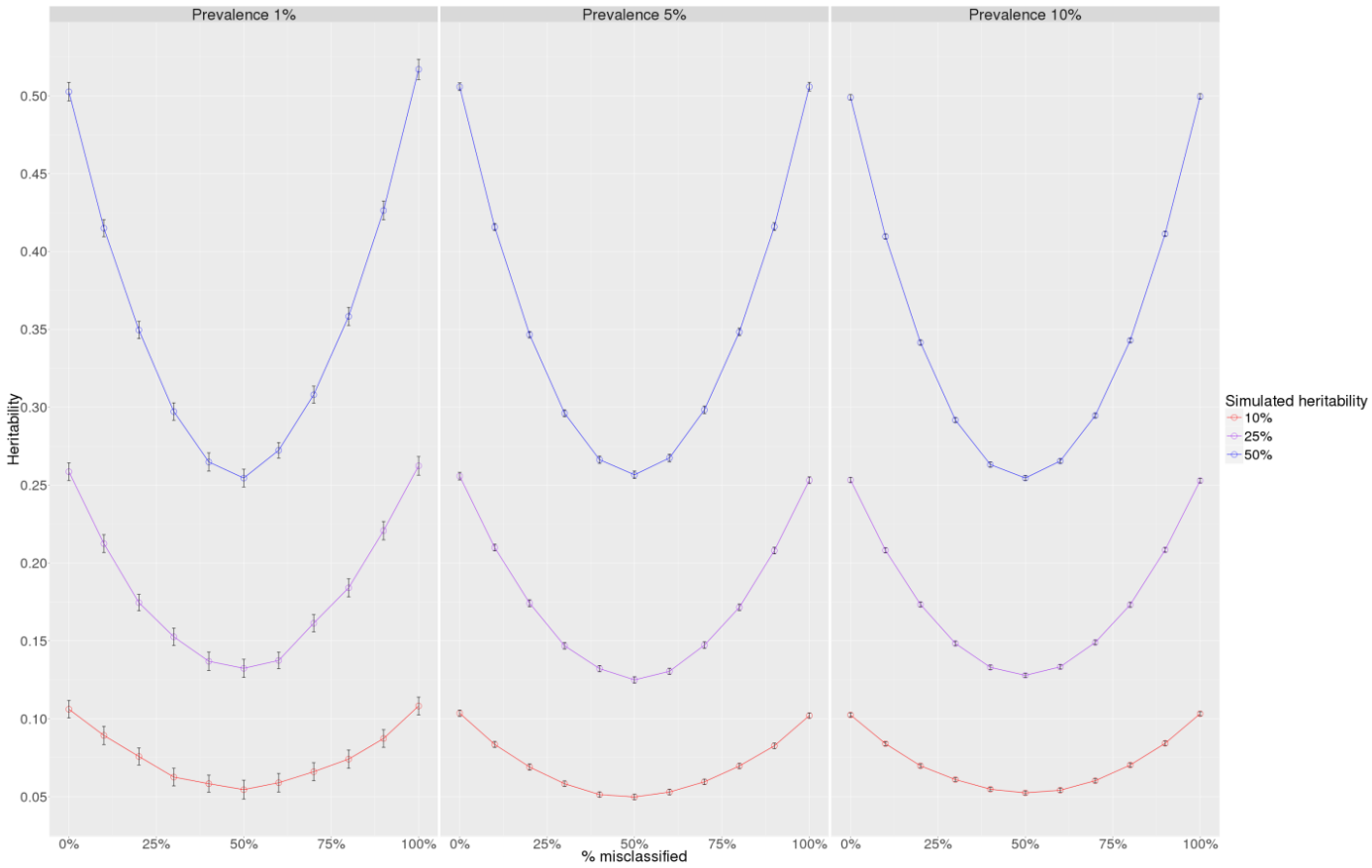


Fig. S9A. Effect of case misclassification on observed heritability

See Supplementary Text "Effect of co-morbidity and phenotypic misclassification on correlation estimates" for details. Error bars show one standard error.

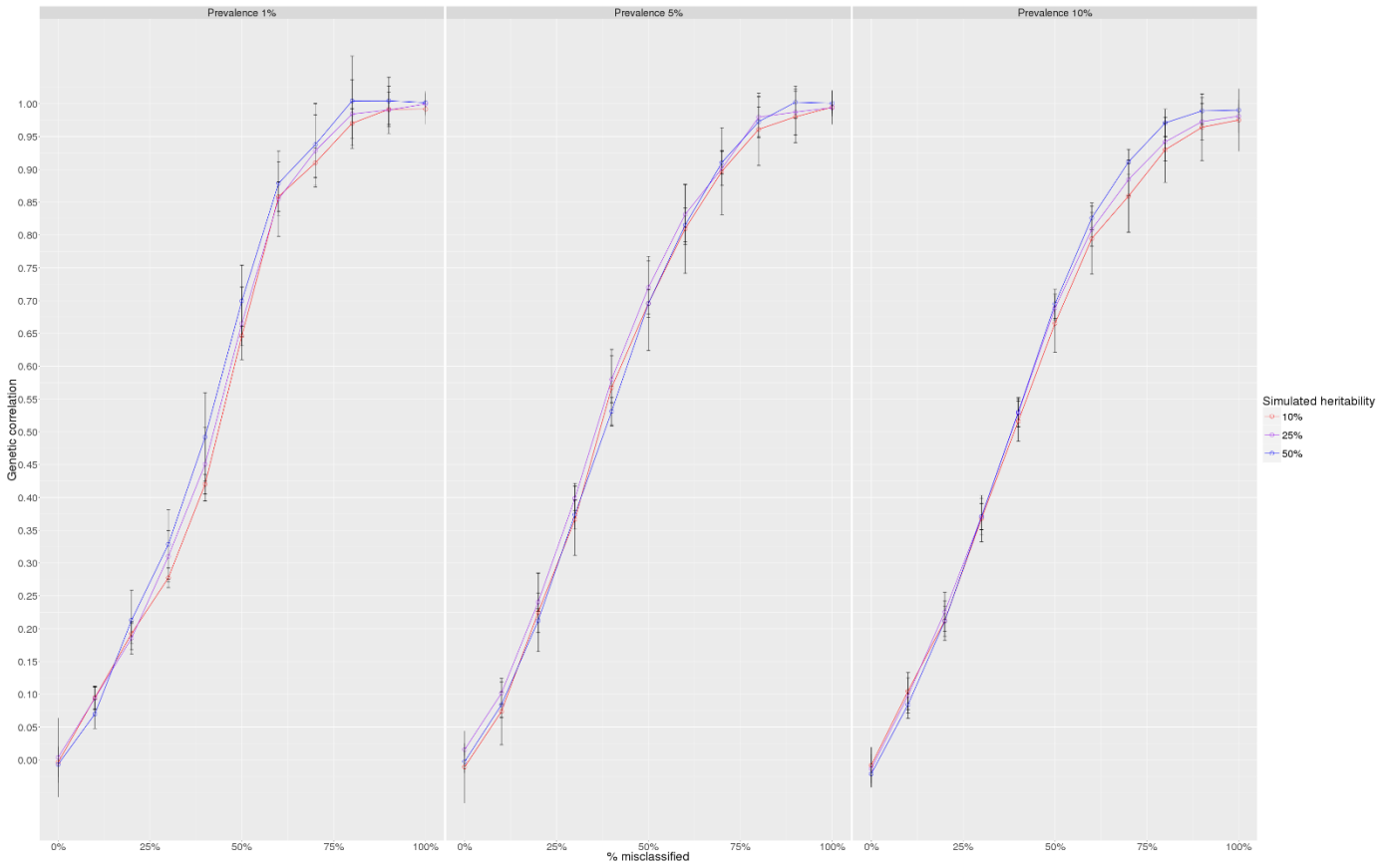


Fig. S9B. Effect of case misclassification on genetic correlation.

See Supplementary Text "Effect of co-morbidity and phenotypic misclassification on correlation estimates" for details. Error bars show one standard error.

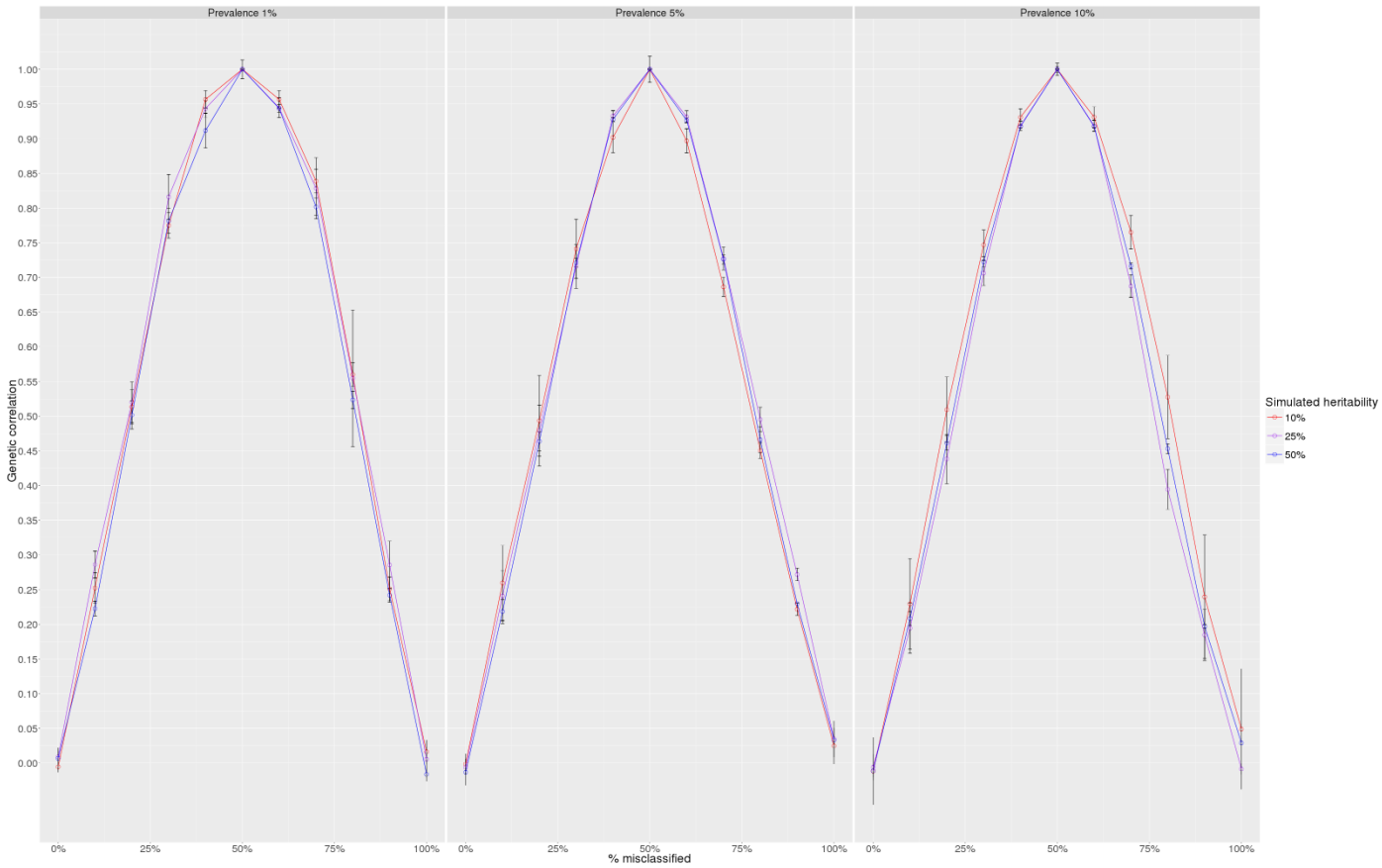


Fig. S9C. Effect of bidirectional case misclassification on genetic correlation

See Supplementary Text "Effect of co-morbidity and phenotypic misclassification on correlation estimates" for details. Error bars show one standard error.

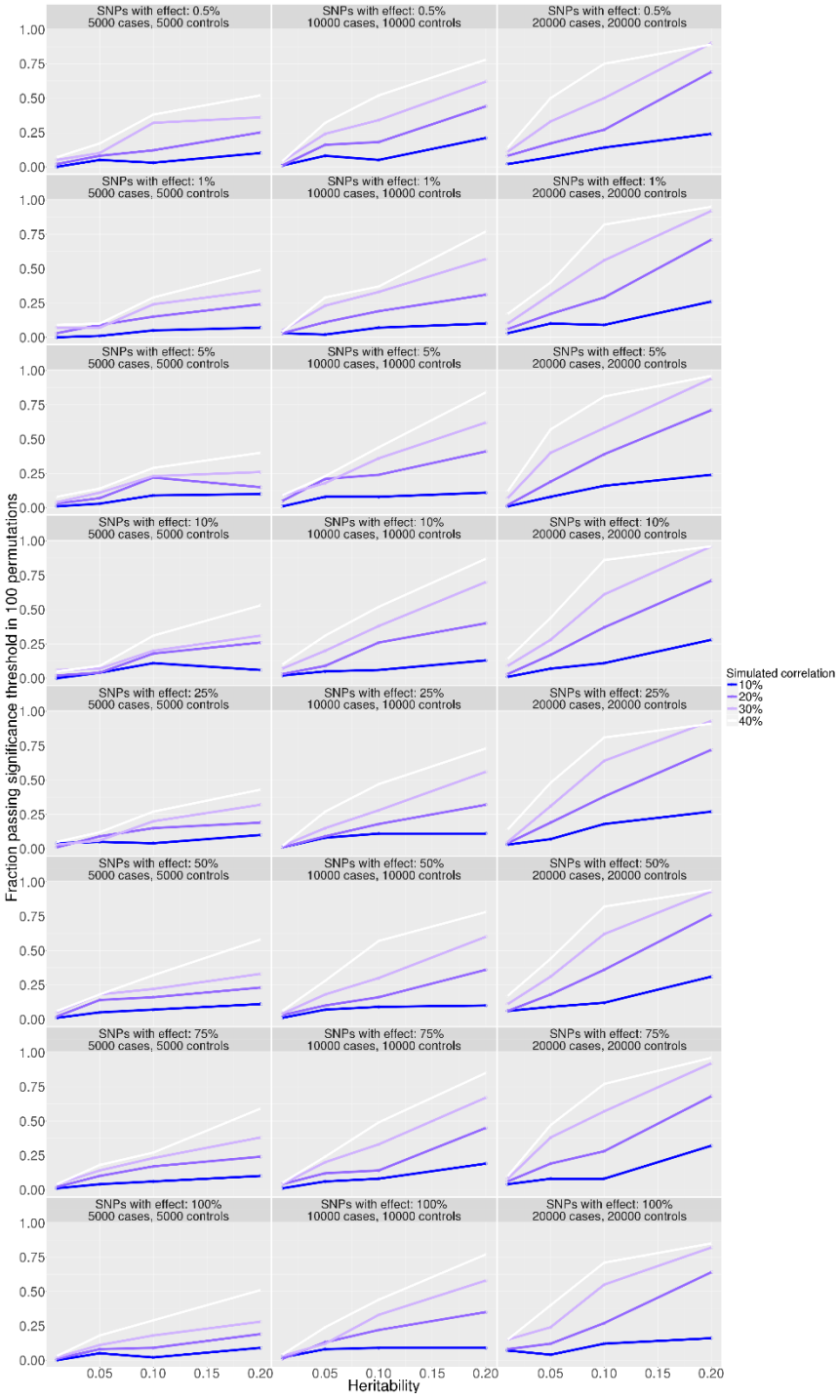


Fig. S10. Power analysis for detecting genetic correlations.

Shown at each combination of parameters is the fraction of simulations out of 100 replicates which detect the simulated correlation between the pair of phenotypes and are within the 95% confidence interval from the true correlation.

Table S1. Dataset features for the brain disorder phenotypes.

ADHD – attention deficit hyperactivity disorder; OCD – obsessive-compulsive disorder; PTSD – post-traumatic stress disorder; Pop. prev. – population prevalence; AOE – average age of onset; GC – genomic control; Publ. – publication for genotype data; MUP – manuscript under preparation; Preval. ref. – publication for prevalence estimate; PC – personal communication. All age of onset estimates based on personal communication and constitute rough estimates. Anxiety disorders refers to a meta-analysis of five subtypes (generalized anxiety disorder, panic disorder, social phobia, agoraphobia and specific phobias; see reference). Numbers in gray denote a dataset which is non-unique, e.g. all cardioembolic stroke cases and controls are also part of ischemic stroke cases and controls, respectively. For genomic control, - : no GC; + : study-level GC; ++ : meta-analysis GC. Note: genomic control will impact the univariate estimate of heritability, but the genetic correlation estimation is robust to genomic control. References are: a(*68*), b(*69*), c(*70*), d(*89*), e(*22*), f(*18*), g(*71*), h(*72*), i(*73*), j(*90*), k(*74*), l(*91*), m(*17*), n(*92*), o(*93*), p(*94*), q(*95*), r(*96*), s(*97*), approximated from t(*98*), approximated from u(*99*), v(*100*), and w(*101*).

Phenotype	Cases	Controls	Pop. prev.	AOE	Heritability (SE)	GC	Mean χ^2	Lambda	Intercept (SE)	Publ.	Preval. ref.
Psychiatric disorders											
ADHD	12,645	84,435	0.050	12	0.100 (0.011)	-	1.102	1.107	1.014 (0.007)	MUP	m
Anorexia nervosa	3,495	10,982	0.006	15	0.172 (0.027)	+	1.077	1.086	1.012 (0.008)	a	n
Anxiety disorders	5,761	11,765	0.100	11	0.112 (0.045)	-	1.035	1.030	1.003 (0.008)	b	b
Autism spectrum disorder	6,197	7,377	0.010	2	0.189 (0.025)	-	1.081	1.071	0.987 (0.009)	c	m
Bipolar disorder	20,352	31,358	0.010	25	0.205 (0.010)	-	1.324	1.387	1.021 (0.010)	MUP	m
Major depressive disorder	66,358	153,234	0.150	32	0.127 (0.007)	-	1.299	1.263	1.005 (0.010)	MUP	m
OCD	2,936	7,279	0.016	16	0.255 (0.037)	-	1.059	1.065	1.000 (0.007)	MUP	o
PTSD	2,424	7,113	0.080	23	0.148 (0.065)	-	1.107	1.102	1.014 (0.007)	d	p
Schizophrenia	33,640	43,456	0.010	21	0.256 (0.010)	-	1.588	1.768	1.059 (0.012)	e	m
Tourette's syndrome	4,220	8,994	0.005	7	0.196 (0.025)	-	1.096	1.103	1.010 (0.007)	MUP	q
Neurological disorders											
Alzheimer's disease	17,008	37,154	0.170	65	0.130 (0.023)	-	1.093	1.104	1.038 (0.007)	f	PC
Epilepsy	7,779	20,439	0.030	25	0.101 (0.022)	+	1.047	1.057	0.993 (0.010)	g	r
Focal epilepsy	4,601	17,985	0.020	15	0.053 (0.026)	+	1.023	1.013	0.988 (0.009)	g	PC
Generalized epilepsy	2,525	16,244	0.008	15	0.351 (0.039)	+	1.065	1.081	0.960 (0.009)	g	PC
Intracerebral hemorrhage	1,545	1,481	0.002	70	0.156 (0.060)	-	1.038	1.037	1.012 (0.007)	h	s
Ischemic stroke	10,307	19,326	0.010	71	0.038 (0.010)	-	1.065	1.066	1.032 (0.006)	i	t
Cardioembolic stroke	1,859	17,708	-	-	-	-	1.061	1.047	1.049 (0.006)	i	-
Early-onset stroke	3,274	11,012	0.003	50	0.051 (0.020)	-	1.029	1.033	1.009 (0.007)	i	PC
Large-vessel disease	1,817	17,708	-	-	-	-	1.061	1.053	1.052 (0.006)	i	-
Small-vessel disease	1,349	17,708	-	-	-	-	1.048	1.047	1.052 (0.006)	i	-
Migraine	59,673	316,078	0.160	30	0.150 (0.007)	-	1.293	1.375	1.036 (0.010)	j	u
Migraine with aura	6,332	142,817	0.075	30	0.124 (0.024)	-	1.077	1.087	1.003 (0.007)	j	v
Migraine without aura	8,348	136,758	0.130	30	0.208 (0.025)	-	1.080	1.085	1.033 (0.007)	j	v
Multiple sclerosis	5,545	12,153	0.002	30	0.141 (0.016)	++	1.050	1.078	0.975 (0.008)	k	w
Parkinson's disease	5,333	12,019	0.002	60	0.105 (0.017)	+	1.026	1.044	0.965 (0.008)	l	w

Table S2. Dataset features for the behavioral-cognitive and additional phenotypes

Numbers in gray denote a sample set which is non-unique, e.g. all samples in the BMI analysis are also part of the height analysis. SE – standard error; Ref. – reference; ISCE - International Standard Classification of Education (1997); NEO-FFI - Neuroticism-Extraversion-Openness Five-Factor Inventory; BMI – body-mass index; CAD – coronary artery disease; MI – myocardial infarction; (d) – dichotomous phenotype; (q) – quantitative phenotype. References are: a(*33*), b(*75*), c(*76*), d(*77*), e(*78*), f(*102*), g(*27*), h(*79*), i(*63*), j(*80*), k(*81*) and l(*82*).

Phenotype	n	Heritability (SE)	Mean χ^2	Lambda	Intercept (SE)	Ref.	Definition
Cognitive measures							
Years of education (q)	293,723	0.302 (0.010)	1.645	1.475	0.938 (0.009)	a	Years of schooling, measured with the ISCE scale
College attainment (d)	120,917	0.109 (0.008)	1.223	1.194	1.021 (0.009)	b	College completion (ISCE scale value >=5)
Cognitive performance (q)	17,989	0.191 (0.031)	1.075	1.065	1.001 (0.009)	c	General cognitive ability in childhood (ages 6-18)
Intelligence (q)	78,308	0.194 (0.010)	1.299	1.260	1.015 (0.008)	d	Intelligence measures (fluid intelligence scores in adults or general cognitive ability in children)
Personality measures							
Subjective well-being (q)	298,420	0.062 (0.005)	1.152	1.130	1.001 (0.007)	e	Self-assessed psychological well-being, based on positive affect or life satisfaction questionnaires
Depressive symptoms (q)	161,460	0.063 (0.005)	1.153	1.133	1.000 (0.007)	e	Score for depressive symptoms, based on positive affect or life satisfaction questionnaires
Neuroticism (q)	170,911	0.125 (0.010)	1.307	1.237	0.994 (0.010)	e	Personality score for neuroticism symptoms, based on positive affect or life satisfaction questionnaires
Extraversion (q)	63,030	0.049 (0.008)	1.073	1.065	1.008 (0.007)	f	Extraversion personality trait, as measured by several different questionnaires
Agreeableness (q)	17,375	-	1.010	0.999	1.001 (0.010)	g	NEO-FFI questionnaire for personality scores
Conscientiousness (q)	17,375	0.070 (0.033)	1.029	1.020	1.001 (0.009)	g	NEO-FFI questionnaire for personality scores
Openness (q)	17,375	0.125 (0.030)	1.037	1.041	0.988 (0.009)	g	NEO-FFI questionnaire for personality scores
Smoking-related measures							
Never/ever smoked (d)	74,035	0.120 (0.010)	1.103	1.090	0.996 (0.006)	h	Lifetime cigarette consumption >= 100
Cigarettes per day (q)	38,617	0.057 (0.013)	1.049	1.053	1.007 (0.006)	h	Average or maximum number of cigarettes per day
Additional phenotypes							
BMI (q)	339,224	0.109 (0.003)	1.158	1.038	0.672 (0.008)	i	BMI, as measured
Height (q)	253,288	0.312 (0.014)	2.949	2.001	1.325 (0.019)	j	Height, as measured
Coronary artery disease (d)	86,995	0.098 (0.013)	1.145	1.105	1.027 (0.009)	k	Presence of CAD, MI, or both
Crohn's disease (d)	20,883	0.177 (0.021)	1.242	1.143	1.028 (0.012)	l	Presence of Crohn's disease

Table S3. Comparison of heritability estimates in this study with previously reported estimates based on SNP data.

ADHD – attention deficit hyperactivity disorder; ESS – effective sample size; OCD – obsessive-compulsive disorder; SE – standard error. References previous reports are: a(*17*), b(*68*), c(*103*), d(*89*), e(*32*), f(*104*), g(*105*), h(*106*), and i(*107*). * - Previously reported heritability for anxiety disorders is an LDSC analysis of the same dataset; difference between the estimates is due to the current study estimating heritability under unscreened controls.

	Previously reported		*Current study*		
Phenotype	Heritability (SE)	ESS	Heritability (SE)	ESS	Reference
Psychiatric disorders					
ADHD	0.28 (0.023)	12,374	0.100 (0.011)	43,992	a
Anorexia nervosa	-	-	0.172 (0.027)	10,633	-
Anxiety disorders*	0.10 (0.037)	15,469	0.112 (0.045)	15,469	b
Autism spectrum disorder	0.17 (0.025)	6,729	0.189 (0.025)	10,610	a
Bipolar disorder	0.25 (0.012)	15,391	0.205 (0.010)	49,367	a
Major depressive disorder	0.21 (0.021)	18,416	0.127 (0.007)	40,627	a
OCD	0.37 (0.070)	3,394	0.255 (0.037)	8,369	c
PTSD*	0.15(0.060)	7,232	0.148 (0.065)	7,232	d
Schizophrenia	0.23 (0.008)	20,811	0.256 (0.010)	75,846	a
Tourette's syndrome	0.58 (0.090)	2,146	0.196 (0.025)	11,489	c
Neurological disorders			0.130 (0.023)		
Alzheimer's disease	0.24 (0.030)	7,095	0.101 (0.022)	46,669	e
Epilepsy	0.32 (0.046)	4,041	0.053 (0.026)	22,538	f
Focal epilepsy	0.23 (0.102)	3,229	0.351 (0.039)	14,655	f
Generalized epilepsy	0.36 (0.117)	1,134	0.156 (0.060)	8,741	f
Intracerebral hemorrhage	0.29 (0.110)	1,663	0.038 (0.010)	3,025	g
Ischemic stroke	0.38 (0.052)	8,025	-	26,888	h
Cardioembolic stroke	0.33 (0.074)	2,592	0.051 (0.020)	6,730	h
Early-onset stroke	-	-	-	10,095	h
Large-vessel disease	0.40 (0.076)	2,698	-	6,592	-
Small-vessel disease	0.16 (0.077)	1,993	0.150 (0.007)	5,014	h
Migraine	-	-	0.124 (0.024)	200,785	-
Migraine with aura	-	-	0.208 (0.025)	24,253	-
Migraine without aura	-	-	0.141 (0.016)	31,471	-
Multiple sclerosis	0.30 (0.030)	3,523	0.105 (0.017)	15,231	e
Parkinson's disease	0.27 (0.053)	20,798	0.105 (0.017)	14,776	i

Table S4. Heritability estimates and selected study variables in weighted-least squares analysis.

P-values are uncorrected for multiple testing. Age of onset refers to the average age of onset of the disorder. Asterisk indicates results which are significant after Bonferroni correction for four tests.

Study feature	F-statistic	Adjusted R^2	P-value
Case/control ratio	1.758	0.035	0.200
Effective sample size	0.145	-0.042	0.707
Phenotype prevalence	0.075	-0.046	0.788
Age of onset	10.990	0.322	0.003*

Table S5. Implied true correlations between selected phenotypes, given co-morbidity estimates from literature.

ADHD – attention deficit hyperactivity disorder; OCD – obsessive-compulsive disorder. References used for λ values (proportion of cases correctly called cases) are a (*40*), b(*35*), c(*108*). From reference a, λ was calculated by summing over all relevant disorder progression paths. See Supplementary text ("Effect of co-morbidity and phenotypic misclassification on correlation estimates") for further details.

Phenotype 1	Phenotype 2	True r_g	Observed r_g	λ	$h_{1,obs}$	h_2	Reference
Schizophrenia	Bipolar disorder	0.654	0.681	0.946	0.506	0.453	a
Schizophrenia	OCD	0.120	0.428	0.683	0.506	0.505	b
Bipolar disorder	ADHD	0.043	0.261	0.686	0.453	0.316	c
Bipolar disorder	Schizophrenia	0.514	0.681	0.808	0.453	0.506	a

Table S6. Proportions of unidirectional misclassification.

Listed are the proportions of unidirectional misclassification which would be required to reach the observed genetic correlation under the assumption of no true genetic correlation for the significantly correlated disorder-disorder pairs in this study, in order of decreasing significance. ADHD – attention deficit hyperactivity disorder; ASD – autism spectrum disorder; MDD – major depressive disorder; OCD – obsessive-compulsive disorder. Type-subtype pairs (e.g. epilepsy and focal epilepsy) have been excluded.

Phenotype 1	Phenotype 2	Observed r_g	Misclassification %
Bipolar disorder	Schizophrenia	0.681	54.5%
MDD	Schizophrenia	0.338	14.8%
Bipolar disorder	MDD	0.351	64.2%
MDD	Migraine	0.323	24.8%
ADHD	MDD	0.521	46.5%
OCD	Schizophrenia	0.327	32.6%
ADHD	Migraine	0.261	17.9%
Anxiety disorders	MDD	0.794	79.4%
ADHD	Schizophrenia	0.223	8.7%
OCD	Tourette Syndrome	0.428	55.7%
Bipolar disorder	OCD	0.311	25.0%
ADHD	Bipolar disorder	0.261	12.7%
Anorexia nervosa	OCD	0.517	34.9%
Migraine	Tourette Syndrome	0.192	14.3%
MDD	Migraine without aura	0.225	12.2%
Anorexia nervosa	Schizophrenia	0.219	14.7%
MDD	Migraine with aura	0.278	29.4%
MDD	Tourette Syndrome	0.213	12.2%
MDD	OCD	0.228	10.0%
ASD	Schizophrenia	0.208	15.5%

Table S7 (separate file). Disorder-disorder (A), disorder-phenotype (B) and phenotype-phenotype (C) correlation results.

Table S8. Tissue enrichment analysis for brain disorders.

Results shown for phenotype-tissue pairs where P-value for enrichment coefficient p-value below the Bonferroni threshold ($p < 2.81 \times 10^{-4}$; data for all pairs in Table S12A). CNS – central nervous system; Coeff. – coefficient; SE – standard error. Results for schizophrenia in a largely overlapping dataset have been previously reported in Finucane et al (38).

Phenotype	Tissue	Enrichment	SE	Coeff.	SE	Coeff. p-value
Schizophrenia	CNS	3.25	0.18	1.65E-07	1.92E-08	3.35E-18
Bipolar disorder	CNS	3.81	0.32	1.43E-07	2.28E-08	1.69E-10
Major depressive disorder	CNS	2.76	0.30	2.03E-08	3.58E-09	6.73E-09
Multiple sclerosis	Hematopoietic	4.90	0.54	2.85E-07	5.44E-08	8.03E-08
Tourette Syndrome	CNS	4.23	0.78	2.32E-07	5.29E-08	5.67E-06
Generalized epilepsy	CNS	2.79	0.60	1.68E-07	4.34E-08	5.44E-05

Table S9. Tissue enrichment analysis for behavioral-cognitive phenotypes and additional traits

Results shown for phenotype-tissue pairs where P-value for enrichment coefficient p-value below the Bonferroni threshold ($p < 4.10 \times 10^{-4}$; data for all pairs in Table S12A). BMI – body-mass index; CNS – central nervous system; Coeff. – coefficient; SE – standard error. Results for the same dataset in height, BMI and Crohn's disease have been previously reported in Finucane et al (38), and depressive symptoms in Okbay et al(*78*).

Phenotype	Tissue	Enrichment	SE	Coeff.	SE	Coeff. p-value
Years of education	CNS	2.87	0.19	9.51E-08	1.15E-08	5.66E-17
Intelligence	CNS	3.38	0.31	8.34E-08	1.20E-08	2.26E-12
Height	Connective_Bone	5.32	0.38	2.24E-07	3.55E-08	1.31E-10
BMI	CNS	2.67	0.18	2.73E-08	4.46E-09	4.39E-10
Crohn's disease	Hematopoietic	4.19	0.43	3.60E-07	6.66E-08	3.15E-08
Neuroticism	CNS	2.47	0.29	3.83E-08	8.45E-09	2.95E-06
College attainment	CNS	3.31	0.45	2.71E-08	6.52E-09	1.59E-05
Height	Cardiovascular	4.23	0.38	1.28E-07	3.08E-08	1.66E-05
Height	Other	3.42	0.21	8.26E-08	2.19E-08	7.84E-05
Depressive symptoms	Adrenal_Pancreas	5.15	0.94	3.77E-08	1.04E-08	1.47E-04
Never/ever smoked	CNS	3.45	0.73	3.06E-08	9.13E-09	4.04E-04

Table S10. Functional category enrichment analysis for brain disorders

Results shown for phenotype-tissue pairs where P-value for enrichment coefficient p-value below the Bonferroni threshold ($p < 1.17 \times 10^{-4}$; data for all pairs in Table S12B). ADHD – attention deficit hyperactivity disorder; Coeff. – coefficient; SE – standard error. Results for schizophrenia in a largely overlapping dataset have been previously reported in Finucane et al (38).

Phenotype	Category	Enrichment	SE	Coeff.	SE	Coeff. p-value
Major depressive disorder	Conserved_LindbladToh	19.14	2.50	1.74E-07	2.52E-08	2.42E-12
Migraine	Conserved_LindbladToh	16.88	2.08	1.09E-07	1.72E-08	1.15E-10
Schizophrenia	Conserved_LindbladToh	11.03	1.55	6.73E-07	1.21E-07	1.27E-08
ADHD	Conserved_LindbladToh	27.15	6.24	2.00E-07	4.61E-08	7.46E-06
Migraine without aura	Conserved_LindbladToh	20.64	4.99	9.63E-08	2.61E-08	1.12E-04
Bipolar disorder	Conserved_LindbladToh	9.95	1.98	3.80E-07	1.03E-07	1.17E-04

Table S11. Functional category enrichment analysis for behavioral-cognitive phenotypes and additional traits

Results shown for phenotype-tissue pairs where P-value for enrichment coefficient p-value below the Bonferroni threshold ($p < 1.71 \times 10^{-4}$; data for all pairs in Table S12B). BMI – body-mass index; Coeff. – coefficient; SE – standard error. Results for the same dataset in height and BMI have been previously reported in Finucane et al (38).

Phenotype	Category	Enrichment	SE	Coeff.	SE	Coeff. p-value
BMI	Conserved_LindbladToh	16.68	1.69	2.76E-07	3.34E-08	7.28E-17
Years of education	Conserved_LindbladToh	14.96	1.68	6.56E-07	8.80E-08	4.67E-14
Height	Conserved_LindbladToh	11.07	1.59	5.15E-07	9.79E-08	7.20E-08
BMI	H3K9ac_peaks_Trynka	7.00	0.97	1.18E-07	2.41E-08	4.79E-07
Neuroticism	Conserved_LindbladToh	11.96	2.95	2.26E-07	5.10E-08	4.50E-06
Intelligence	Conserved_LindbladToh	13.50	2.56	3.51E-07	8.24E-08	9.77E-06
College attainment	Conserved_LindbladToh	16.32	3.31	1.61E-07	3.92E-08	1.98E-05

Table S12 (separate file). Tissue (A) and functional category (B) enrichment analysis results for brain disorders, behavioral-cognitive phenotypes, and additional traits.

Table S13 (separate file). Data sources, responsible consortia, and data availability.

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25. See materials and methods and other supplementary materials.

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