Title: Analysis of Shared Heritability in Common Disorders of the Brain

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One Sentence Summary: Comprehensive heritability analysis of brain phenotypes demonstrates a clear role for common genetic variation across neurological and psychiatric disorders and behavioral-cognitive traits, with substantial overlaps in genetic risk.

Abstract: Disorders of the brain can exhibit considerable epidemiological comorbidity and share symptoms, provoking debate about their etiologic overlap. We quantified the genetic sharing of 25 brain disorders from genome-wide association studies of 215,683 patients and 657,164 controls, and their relationship to 17 phenotypes from 1,191,588 individuals. Psychiatric disorders share common variant risk, while neurological disorders appear more distinct from one another and from the psychiatric disorders. We also identify significant sharing between disorders and a number of brain phenotypes, including cognitive measures. Simulations were used to explore how power, diagnostic misclassification and phenotypic heterogeneity affect genetic correlations. These results highlight the importance of common genetic

variation as a risk factor for brain disorders and the value of heritability-based methods in understanding their etiology.

Main Text:

The classification of brain disorders has evolved over the past century, reflecting the medical and scientific communities' assessments of the presumed root causes of clinical phenomena such as behavioral change, loss of motor function, spontaneous movements or alterations of consciousness. Directly observable phenomena (such as the presence of emboli, protein tangles, or unusual electrical activity patterns) generally define and separate neurological disorders from psychiatric disorders(*1*). Understanding the genetic underpinnings and categorical distinctions between brain disorders may be helpful in informing the search for the biological pathways underlying their pathophysiology(*2, 3*).

In general, brain disorders (excepting those caused by trauma, infection, or cancer) show substantial heritability from twin and family studies(*4*). Epidemiological and twin studies have explored patterns of phenotypic overlaps(*5-7*), and comorbidity has been reported for many pairs of disorders, including bipolar disorder-migraine(*8*), stroke-major depressive disorder(MDD)(*9*), epilepsy-autism spectrum disorders (ASD), and epilepsy-attention deficit hyperactivity disorder (ADHD)(*10, 11*). Furthermore, there may also be direct etiological links, as e.g. mutations in the same ion channel genes confer pleiotropic risk for multiple distinct brain phenotypes(*12-14*). Genome-wide association studies (GWAS) have demonstrated that individual common risk variants can overlap across traditional diagnostic boundaries(*15, 16*), and that disorders like schizophrenia, MDD, and bipolar disorder can have genetic correlations(*17*).

GWAS have also demonstrated that common genetic variation contributes to the heritability of brain disorders. Generally, this occurs via the combination of many common variants, each with a small individual effect, with examples in Alzheimer's disease(*18*), bipolar disorder(*19*), migraine(*20*), Parkinson's disease(*21*), and schizophrenia(*22*). In addition to locus discovery, the degree of distinctiveness(*23*) across neurological and psychiatric phenotypes can be evaluated with the introduction of novel heritability-based methods(*24*) and sufficiently large sample sizes for robust heritability analysis. These analyses can shed light on the nature of these diagnostic boundaries and explore the extent of shared common variant genetic influences.

Study design

The Brainstorm consortium is a collaboration among GWAS meta-analysis consortia of 25 disorders (see Table 1), to perform a comprehensive heritability and correlation analysis of brain disorders. We included meta-analyses of any common brain disorders for which we could identify a GWAS meta-analysis consortium of sufficient size for heritability analysis. The total study sample consists of 215,683 cases of different brain disorders and 657,164 controls (Table 1), and

includes at least one representative of most ICD-10 blocks covering mental and behavioral disorders and diseases of the central nervous system. Also included are 1,191,588 samples for 13 "behavioral-cognitive" phenotypes (n=744,486) traditionally viewed as brain-related, and four "additional" phenotypes (n=447,102) selected to represent known, well-delineated etiological processes (immune disorders [Crohn's disease], vascular disease [coronary artery disease] and anthropomorphic measures [height and BMI]; Table 2).

GWAS summary statistics for the 42 disorders and phenotypes were centralized and underwent uniform quality control and processing(*25*)*(83)*. We used European-only meta-analyses for each disorder to avoid potential bias arising from ancestry differences, generating new meta-analyses for those datasets where the original sample sets had diverse ancestries. Clinically relevant subtypes from three disorders (epilepsy, migraine, and ischemic stroke) were also included; in these cases, the subtype datasets are parts of the top-level dataset (Table 1).

We have developed a heritability estimation method, linkage disequilibrium score regression (LDSC)(*24*), which was used to calculate heritability estimates and correlations, as well as to estimate their statistical significance from block jack-knife-based standard errors. More formally, we estimate the common variant heritability (h^2g) of each disorder, defined as the proportion of phenotypic variance in the population that could theoretically be explained by an optimal linear predictor formed using the additive effects of all common (minor allele frequency > 5%) autosomal SNPs. The genetic correlation for a pair of phenotypes is then defined as the correlation between their optimal genetic predictors. Heritability for binary disorders and phenotypes was transformed to the liability scale. We further performed a weighted-least squares regression analysis to evaluate whether differences relating to study makeup (such as sample size) were correlated with the magnitude of the correlation estimates. Finally, we performed a heritability partitioning analysis*(83)* using stratified LD score regression to examine whether the observed heritability for the disorders or phenotypes was enriched into any of the tissue-specific regulatory regions or functional category partitions of the genome, using ten top-level tissue-type and 53 functional partitions from Finucane et al.(*26*). Finally, simulated phenotype data was generated under different scenarios by permuting 120,267 genotyped individuals from the UK Biobank(*25*) to evaluate power and aid in interpreting the results(*83*).

Heritability estimates and their error sources

We observed a similar range of heritability estimates among the disorders and the behavioral-cognitive phenotypes (Fig. S1A-B and Table S1, S2), roughly in line with previously reported estimates from smaller datasets (Table S3). Three ischemic stroke subtypes (cardioembolic, large-vessel disease, and small-vessel disease) as well as the "agreeableness" personality measure from NEO Five-Factor Inventory(*27*) had insufficient evidence of additive heritability for robust analysis and thus were excluded from further analysis(*25*). The only

observed correlation between heritability estimates and factors relating to study makeup (Table S4; Fig. S1C-F) was a modest correlation between age of onset of the disorder and heritability, suggesting that early-onset brain disorders tend to be more heritable. Since some of our interpretation of the results depends on lack of observed correlation, we explored the behavior of observed correlation versus power (Fig. S2A), standard errors (Fig. S2B) and the individual results (Fig. S2C and D) to identify where we can be reasonably robust in claiming lack of correlation.

The common variant heritability estimates for the psychiatric and neurological disorders were generally somewhat lower than previously reported estimates from common variants (Table S5). A similar pattern was observed for the behavioral-cognitive traits, when comparing estimates reported here with those previously reported in smaller sample sizes(*28*) with the exception of 'openness', 'neuroticism', and 'never/ever smoked', suggesting that some attenuation in heritability is observed when moving to larger sample sizes. Measures related to cognitive ability, such as childhood cognitive performance (heritability estimate of 0.19, [SE 0.03]) and years of education (heritability estimate of 0.30 [SE 0.01]), yielded estimates that were more consistent with previous estimates of the heritability of intelligence(*29, 30*), suggesting that the cognitive measures may be less prone to phenotypic measurement error and/or have a higher heritability overall than the personality measures.

These heritability estimates should be interpreted somewhat cautiously, as they reflect the phenotype ascertained in each study, and will be deflated in the presence of diagnostic heterogeneity, ascertainment errors or unusual contributions of high-impact rare variants. To evaluate potential sources of these differences, we explored three approaches*(83)*: evaluating the differences in real data, simulation work (Table S5), and quantifying the magnitude of effect for potentially implied misclassification (Table S6).

In comparison to heritability estimates obtained using twin and family data, the more diverse selection and survival biases in the underlying data may attenuate the heritability estimates and correlations, as might increased within-disorder heterogeneity introduced by the larger meta-analyses. A related explanation for the lower estimates of heritability may be that increasing sample sizes have led to expanded inclusion criteria, meaning that less severely affected cases with a lower overall burden of risk factors (both genetic and environmental) might be included, which in turn would attenuate estimates of heritability. However, the successful identification of genome-wide significant loci suggests that these larger samples are nevertheless very useful for genetic studies, and the simulation results suggest that this has at most a limited effect on estimated genetic correlations (Fig S9). Even so, some of the pairs of phenotypes included here lack sufficient power for robust estimation of genetic correlations. Moreover, our analyses only examine the properties of common variant contributions and extending these analyses to include the effects of rare variants may further inform the extent of genetic overlap. For example, epilepsy and ASD show substantial overlap in genetic risk from de novo loss of functional mutations(*31*), in contrast to the limited common variant sharing observed in this study. This may suggest that the rare and common

variant contributions to genetic overlap may behave differently and that incorporating the two variant classes into a single analysis may provide further insight into brain disorder pathogenesis.

To address the possibility of methodological differences contributing to the differences in the estimates and although LDSC and REML have previously been shown to yield similar estimates from the same data(*24*), we performed our own comparison in Alzheimer's disease(*32*) (selected based on data availability). In Alzheimer's disease, the previously published heritability estimate (0.24 [SE 0.03]) is significantly different from the estimate in the current study (0.13 [SE 0.02]). These differences may reflect implicit heterogeneity in a much larger case collection used in the current study (effective sample size 10,494 vs. 46,669) and the potential reasons listed above, but they could also be due to methodological variability (most of the previous estimated listed in Table S3 are estimated with a different methodology). To evaluate this, we applied the same analytical process used in this paper to the summary statistics of the GERAD cohort (3,941 cases and 7,848 controls) from the Alzheimer's disease meta-analysis, where the previous heritability estimate was calculated. There, we obtained a heritability estimate of 0.25 [SE 0.04], which agrees closely with the published estimate of 0.24 [SE 0.03], suggesting that the different estimates may reflect differences between datasets rather than methodological variability.

Correlations among brain disorders

We observed widespread sharing across psychiatric disorders (Fig. 1 and S3) by expanding the number of brain disorder pairs studied beyond those previously reported(*17*), but similar sharing was not observed among neurological disorders. Among the psychiatric disorders, schizophrenia showed significant genetic correlation with most of the psychiatric disorders, while MDD was positively (though not necessarily significantly) correlated with every other disorder tested. Further, schizophrenia, bipolar disorder, anxiety disorders, MDD, and ADHD each showed a high degree of correlation to the four others (average genetic correlation [r_g]=0.40; Table S7A). Anorexia nervosa, obsessive-compulsive disorder (OCD), and schizophrenia also demonstrated significant sharing amongst themselves (Fig. 1). However, the common variant risk of both ASD and Tourette Syndrome (TS) appear to be distinct from other psychiatric disorders, although with significant correlation between TS, OCD, and MDD, as well as between ASD and schizophrenia. Similarly, post-traumatic stress disorder (PTSD) showed no significant correlation with any of the other psychiatric phenotypes (though some correlation to ADHD and MDD was observed). The modest power of the ASD, PTSD, and TS meta-analyses, however, limits the strength of this conclusion (Fig. S2C).

Neurological disorders showed a more limited extent of genetic correlation than the psychiatric disorders (Fig. 2 and S4, Table S7A), suggesting greater diagnostic specificity and/or more distinct etiologies. Parkinson's disease, Alzheimer's disease, generalized epilepsy, and multiple sclerosis showed little to no correlation with other brain disorders. The highest degree of

genetic correlation among the neurological disorders was observed with focal epilepsy (average r_g =0.46, excluding the other epilepsy datasets), though none were significant, reflecting the relatively modest power of the current focal epilepsy meta-analysis (Fig. S2C). However, the modest heritability and the broad pattern of sharing observed for focal epilepsy may be consistent with heterogeneity and potentially even diagnostic misclassification across a range of neurological conditions.

In the cross-category correlation analysis, the observed pattern is consistent with limited sharing across the included neurological and psychiatric disorders (Fig. 3; average r_g=0.03). The only significant cross-category correlations were with migraine, suggesting it may share some of its genetic architecture with psychiatric disorders; migraine-ADHD (r_g=0.26, p=8.81 x 10^{-8}), migraine-TS (r_g=0.19, p=1.80 x 10^{-5}), and migraine-MDD (r_g=0.32, p=1.42 x 10^{-22} for all migraine, r_g=0.23, p=5.23 x 10^{-5} for migraine without aura, r_g=0.28, p=1.00 x 10^{-4} for migraine with aura).

We observed several significant genetic correlations between the behavioral-cognitive or additional phenotypes and brain disorders (Fig. 4 and Table S7B). Results for cognitive traits were dichotomous among psychiatric phenotypes (Fig. S5A), with ADHD, anxiety disorders, MDD, and TS showing negative correlations to the cognitive measures and anorexia nervosa, ASD, bipolar disorder and OCD showing positive correlations. Schizophrenia showed more mixed results, with significantly negative correlation to intelligence but positive correlation to years of education. Among neurological phenotypes (Fig. S5B), the correlations were either negative or null, with Alzheimer's disease, epilepsy, ICH, ischemic stroke, early-onset stroke, and migraine showing significantly negative correlations. Correlations between college attainment and years of education with bipolar disorder(*24*), Alzheimer's disease, and schizophrenia have been previously reported(*33*)).

Among the personality and symptom measures, significant positive correlations were observed between neuroticism and anorexia nervosa, anxiety disorders, migraine, migraine without aura, MDD, OCD, schizophrenia, and TS (Fig. S6A and S6B; replicating previously reported correlations with MDD and schizophrenia(34)); between depressive symptoms and ADHD, anxiety disorder, bipolar disorder, MDD, and schizophrenia; and between subjective well-being and anxiety disorder, bipolar disorder, and MDD. For smoking-related measures, the only significant genetic correlations were between never/ever smoked and MDD (r_g=0.33, p=3.10 x 10^{-11}) as well as ADHD (r_g=0.37, p=3.15 x 10^{-6}).

Among the additional phenotypes, the two examples of disorders with well-defined etiologies had different results. Crohn's disease, representing immunological pathophysiology, showed no correlation with any of the study phenotypes, while the phenotype representing vascular pathophysiology (coronary artery disease) showed significant correlation to MDD (r_g=0.19, p=8.71 x 10^{-5}) as well as the two stroke-related phenotypes (r_g=0.69, p=2.47 x 10^{-6} to ischemic stroke and r_g=0.86, p=2.26 x 10^{-5} to early-onset stroke), suggesting shared genetic effects across

these phenotypes. Significant correlations were also observed for BMI, which was positively correlated with ADHD and MDD, and negatively correlated with anorexia nervosa (as previously reported with a different dataset(*24*)) and schizophrenia.

Our enrichment analysis (Fig. S7, Tables S8-12) demonstrated significant heritability enrichments between central nervous system (CNS) and generalized epilepsy, MDD, TS, college attainment, intelligence, neuroticism, never/ever smoked); depressive symptoms and adrenal/pancreatic cells and tissues, as well as between hematopoetic cells (category which includes immune system cells) and multiple sclerosis (Figs. S7A and S7B, Tables S8 and S9). We replicate the reported (CNS) enrichment for schizophrenia, bipolar disorder, and years of education (Tables S8, S9), and observe the reported enrichments for BMI (CNS), years of education (CNS), height (connective tissues and bone, cardiovascular system and other), and Crohn's disease (hematopoietic cells) from the same datasets (Fig. S7C, D)(*26*). We further note that the psychiatric disorders with large numbers of identified GWAS loci (bipolar disorder, MDD, and schizophrenia) and migraine, which was the only cross-correlated neurological disorder, show enrichment to conserved regions (Tables S10 and S12), while the other neurological disorders with similar numbers of loci (MS, Alzheimer's, and Parkinson's diseases) do not (Fig. S7A, B). Enrichment to conserved regions was also observed to neuroticism, intelligence and college attainment and to H3K9ac peaks for BMI (Tables S11 and S12).

Discussion

By integrating and analyzing the genome-wide association summary statistic data from consortia of 25 brain disorders, we find that psychiatric disorders broadly share a considerable portion of their common variant genetic risk, especially across schizophrenia, MDD, bipolar disorder, anxiety disorder, and ADHD, while neurological disorders are more genetically distinct. Across categories, psychiatric and neurologic disorders share relatively little common genetic risk, suggesting that multiple different and largely independently regulated etiological pathways may give rise to similar clinical manifestations (e.g., psychosis, which manifests in both schizophrenia(*35*) and Alzheimer's disease(*36*)). Except for migraine, which appears to share some genetic architecture with psychiatric disorders, the existing clinical delineation between neurology and psychiatry is corroborated at the level of common variant risk for the studied disorders.

We performed some exploratory analyses based on the observed results to address concerns about diagnostic overlap and misclassification, which are particularly relevant to psychiatric disorders due to their spectral nature. Given that the broad and continuous nature of psychiatric disorder spectra has long been clinically recognized(*37-39*) and that patients can, in small numbers, progress from one diagnosis to another(*40*), we evaluated to what extent this kind of diagnostic overlap could explain the observed correlations. Genetic correlation could arise if, for example,

patients progress through multiple diagnoses over their lifetime, or if some specific diagnostic boundaries between phenotype pairs are particularly porous to misclassification (Table S5). While it would *a priori* appear unlikely to observe large-scale misclassification of migraine as schizophrenia, for example, there may be more substantial misclassification between particular psychiatric disorders, consistent with the clinical controversies in classification. Previous work(*41*) suggests that substantial misclassification (on the order of 15-30%, depending on whether it is uni- or bi-directional) is required to introduce false levels of genetic correlation. We found that the observed levels of correlation are unlikely to appear in the absence of underlying genetic correlation (Table S6), as it is apparent that a very high degree of misclassification (up to 79%) would be required to produce the observed correlations in the absence of any true genetic correlation, and that reasonably expected misclassification would have limited impact on the observed r_g (Fig. S8). Therefore, these results suggest true sharing of a substantial fraction of the common variant genetic architecture among psychiatric disorders as well as between behavioral-cognitive measures and brain disorders. We also performed large-scale simulations to explore the effect of sample size, polygenicity and degree of correlation on power to detect significant correlations. First, we established that the observed heritability of the simulated misclassified traits in the UK Biobank data behaves as would be theoretically expected (Fig. S9A), and that the effects on observed correlation (Fig. S9B and S9C) are in line with the estimates from family data(*41*). Reasonably low levels of misclassification or changes to the exact level of heritability appear unlikely to induce significant correlations, as observed in the power analysis (Fig. S10), though a lower observed heritability caused by substantial misclassification (Fig. S9A) will decrease the power to estimate true genetic overlap.

The high degree of genetic correlation among the psychiatric disorders adds further evidence that current clinical diagnostics do not reflect specific genetic etiology for these disorders, and that genetic risk factors for psychiatric disorders do not respect clinical diagnostic boundaries. Rather, this suggests a more interconnected genetic etiology, in contrast to neurological disorders, and underscores the need to refine psychiatric diagnostics. This study may provide important 'scaffolding' to support a framework for investigating mental disorders, incorporating many levels of information to understand basic dimensions of brain function.

The observed positive genetic correlations are consistent with a few hypothetical scenarios. For example, it may reflect the existence of some portion of common genetic risk factors conferring risks for multiple psychiatric disorders and where other distinct additional factors, both genetic and non-genetic, contribute to the eventual clinical presentation. The presence of significant genetic correlation may also reflect the phenotypic overlap between any two disorders; for example, the sharing between schizophrenia and ADHD might reflect underlying difficulties in executive functioning, which are well-established in both disorders(*42*), and that the shared risk arises from a partial capture of its shared genetic component. Similarly, we might speculate that a shared mechanism underlying cognitive biases may extend from overvalued ideas to delusions (ranging from anorexia nervosa and OCD to schizophrenia), and that this heritable intermediate

trait confers pleiotropic risk to multiple outcomes. This kind of latent variable could give rise to the observed genetic correlation between disorders due to the shared portion of variation affecting that variable. While a combination of these is likely, more genome-wide significant loci are needed to evaluate these overlaps at the locus level.

Conversely, the low correlations observed across neurological disorders suggest that the current classification reflects relatively specific genetic etiologies, although the limited sample size for some of these disorders and lack of inclusion of disorders conceived as "circuit-based" in the literature, such as restless legs syndrome, sleep disorders and possibly essential tremor, constrains the full generalizability of this conclusion. Degenerative disorders (such as Alzheimer's and Parkinson's diseases) would not be expected *a priori* to share their polygenic risk profiles with a neuro-immunological disorder (like multiple sclerosis) or neurovascular disorder (like ischemic stroke). Similarly, we see limited evidence for the reported co-morbidity between migraine with aura and ischemic stroke(*43*) (r_g=0.29, p=0.099); however, the standard errors of this comparison are too high to draw strong conclusions. At the disorder subtype level, migraine with and without aura (r_g=0.48, p=1.79 x 10^{-5}) shows substantial genetic correlation, while focal and generalized epilepsy (r_g=0.16, p=0.388) show much less.

The few significant correlations across neurology and psychiatry, namely between migraine and ADHD, MDD, and TS, suggest modest shared etiological overlap across the neurology/psychiatry distinction. The co-morbidity of migraine with MDD, TS and ADHD has been previously reported in epidemiological studies(*44-47*), while in contrast, the previously reported co-morbidity between migraine and bipolar disorder seen in epidemiological studies (*48*) was not reflected in our estimate of genetic correlation (r_g=-0.03, p=0.406).

Several phenotypes show only very low-level correlations with any of the other disorders and phenotypes studied here, despite large sample size and robust evidence for heritability, suggesting their common variant genetic risk may largely be unique. Alzheimer's disease, Parkinson's disease, and multiple sclerosis show extremely limited sharing with the other phenotypes and with each other. Neuroinflammation has been implicated in the pathophysiology of each of these conditions(*49-51*), as it has for migraine(*52*) and many psychiatric conditions, including schizophrenia(*53*), but no considerable shared heritability was observed with either of those conditions nor with Crohn's disease, nor did we observe enrichment for immune-related tissues in the functional partitioning (Fig. S7) as for Crohn's disease. While this does not preclude the sharing of individual neuroinflammatory mechanisms in these disorders, the large-scale lack of shared common variant genetic influences supports the distinctiveness of disorder etiology. Further, we only observed significant enrichment of heritability for immunological cells and tissues in multiple sclerosis, showing that inflammation-specific regulatory marks in the genome do not show overall enrichment for common variant risk for either Alzheimer's or Parkinson's diseases (though this does not preclude the effects of specific, non-polygenic neuroinflammatory mechanisms(*54*)). Among psychiatric disorders, ASD and TS showed a similar absence of correlation with other disorders, although this could reflect small sample sizes.

Analysis of the Big Five personality measures suggest that the current sample sizes may be large enough for correlation testing; neuroticism, which has by far the largest sample size, shows several significant correlations. Most significant of these was to MDD (r_g=0.737, p=5.04 x 10^{-96}), providing evidence for the link between these phenotypes, as reported for polygenic risk scores(*55*) and twin studies(*56, 57*); as well as other psychiatric disorders (Fig. 4, Table S7B). The correlation between MDD and anxiety disorders, with a similar pattern of correlation and the dimensional measures of depressive symptoms, subjective well-being, and neuroticism suggests that they all tag a similar underlying etiology. The significant correlation between coronary artery disease and MDD supports the link between MDD and CAD(*58*), while the observed correlation between ADHD and smoking initiation (r_g=0.374, p=3.15 x 10^{-6}) is consistent with the epidemiological evidence of overlap(*59*) and findings from twin studies(*60*).

For the neurological disorders, five (Alzheimer's disease, intracerebral hemorrhage, ischemic and early-onset stroke, and migraine) showed significant negative genetic correlation to the cognitive measures, while a two (epilepsy and focal epilepsy) showed moderate negative genetic correlation (Fig. S5). For Alzheimer's disease, poor cognitive performance in early life has been linked to increased risk for developing the disorder(*61*), but to our knowledge no such connection has been reported for other phenotypes. Among the psychiatric disorders, ADHD, anxiety disorders and MDD show a significant negative correlation to cognitive and education attainment measures, while the remaining five of the eight psychiatric disorders (anorexia nervosa, ASD, bipolar disorder, OCD, and schizophrenia) showed significant positive genetic correlation with one or more cognitive measures. These results suggest the existence of a link between cognitive performance in early life and the genetic risk for both psychiatric and neurological brain disorders. The basis of the genetic correlations between education, cognition and brain disorders may have a variety of root causes including indexing performance differences on the basis of behavioral dysregulation (e.g., ADHD relating to attentional problems during cognitive tests) or may reflect ascertainment biases in certain disorders conditional on impaired cognition (e.g., individuals with lower cognitive reserve being more rapidly identified for Alzheimer's disease), but the results could also suggest a direct link between the underlying etiologies.

BMI shows significant positive genetic correlation to ADHD, consistent with a meta-analysis linking ADHD to obesity(*62*), and negative genetic correlation with anorexia nervosa, OCD, and schizophrenia. This is consistent with evidence for enrichment of BMI heritability in CNS tissues(*26*) that suggest neuronal involvement(*63*); this may also provide a partial genetic explanation for lower BMI in anorexia nervosa patients even after recovery(*64*). Given that no strong correlations were observed between BMI and any of the neurological phenotypes, it may be that BMI's brain-specific genetic architecture is more closely related to behavioral phenotypes. Ischemic stroke and BMI show surprisingly little genetic correlation in this analysis (r_g=0.07, p=0.26), suggesting that although BMI is a risk factor for stroke(*65*), there is little evidence for shared common genetic effects. These analyses also suggest that the reported reduced rates of cardiovascular disease in individuals with histories of anorexia nervosa(*66, 67*) are more likely

due to BMI-related secondary effects. The limited evidence of genetic correlation of anorexia nervosa with intracerebral hemorrhage, ischemic stroke, early-onset stroke and coronary artery disease suggest that any lower cardiovascular mortality is more likely due to direct BMI-related effects rather than genetic risk variants.

The genetic correlation results presented here indicate that the clinical boundaries for the studied psychiatric phenotypes do not reflect distinct underlying pathogenic processes. This suggests that genetically informed analyses may provide a basis for restructuring of psychiatric nosology, consistent with twin and family-based results. In contrast, neurological disorders show greater genetic specificity, and although it is important to emphasize that while some brain disorders are under-represented here, our results demonstrate the limited evidence for widespread common genetic risk sharing between psychiatric and neurological disorders. However, we provide strong evidence that both psychiatric and neurological disorders show robust correlations with cognitive and personality measures, suggesting new avenues for follow-up studies. Further study is needed to evaluate whether overlapping genetic contributions to psychiatric pathology may influence treatment choices. Ultimately, such developments give hope to reducing diagnostic heterogeneity and eventually improving the diagnostics and treatment of psychiatric disorders.

Materials and Methods

We collected GWAS meta-analysis summary statistics for 25 brain disorders and 17 other phenotypes from various consortia, and where necessary generated new, non-sex-stratified European-cohorts-only versions of the meta-analyses(*25*). All datasets underwent uniform quality control *(83).* For each trait, using the linkage disequilibrium score (LDSC) framework(*24*), the total additive common SNP heritability present in the summary statistics (h^2g) was estimated by regressing the association χ^2 statistic of a SNP against the total amount of common genetic variation tagged by that SNP, for all SNPs. Genetic correlations (r_g; i.e., the genome-wide average shared genetic risk) for pairs of phenotypes were estimated by regressing the product of Z-score for each phenotype and for each SNP, instead of the χ^2 statistic. Significance was assessed by Bonferroni multiple testing correction via estimating the number of independent brain disorder phenotypes via matrix decomposition *(83).* Functional and partitioning analyses for the GWAS datasets were also performed using LDSC. Power analyses and simulation work to aid in interpretation of the results were conducted using genotype data from the UK Biobank Resource *(83)*.

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Figure 1. *Genetic correlations across psychiatric phenotypes.*

Color of each box indicates the magnitude of the correlation, while size of the boxes indicates its significance (LDSC), with significant correlations filling each box completely. Asterisks indicate genetic correlations which are significantly different from zero 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.

Figure 2. *Genetic correlations across neurological phenotypes.*

Color of each box indicates the magnitude of the correlation, while size of the boxes indicates its significance (LDSC), with significant correlations filling each box completely. Asterisks indicate genetic correlations which are significantly different from zero after Bonferroni correction. Some phenotypes have substantial overlaps (see Table 1), e.g. all cases of generalized epilepsy are also cases of epilepsy. Asterisks indicate significant genetic correlation after multiple testing correction. ICH – intracerebral hemorrhage.

Figure 3. *Genetic correlations across neurological and psychiatric phenotypes.*

Color of each box indicates the magnitude of the correlation, while size of the boxes indicates its significance (LDSC), with significant correlations filling each box completely. Asterisks indicate genetic correlations which are significantly different from zero after Bonferroni correction. 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.

Figure 4. *Genetic correlations across brain disorders and behavioral-cognitive phenotypes.*

Color of each box indicates the magnitude of the correlation, while size of the boxes indicates its significance (LDSC), with significant correlations filling each box completely. Asterisks indicate genetic correlations which are significantly different from zero after Bonferroni correction. 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; BMI –body-mass index.

Table 1. *Brain disorder phenotypes used in the Brainstorm project.*

Psychiatric disorders				**Neurological disorders**			
Disorder	Source	Cases	Controls	Disorder	Source	Cases	Controls
ADHD	PGC-ADD2	12,645	84,435	Alzheimer's disease	IGAP	17,008	37,154
Anorexia nervosa	PGC-ED	3,495	11,105	Epilepsy	ILAE	7,779	20,439
Anxiety disorders	ANGST	5,761	11,765	Focal epilepsy	"	4,601	17,985
Autism spectrum disorder	PGC-AUT	6,197	7,377	Generalized epilepsy	"	2,525	16,244
Bipolar disorder	PGC-BIP2	20,352	31,358	Intracerebral hemorrhage	ISGC	1,545	1,481
Major depressive disorder	PGC-MDD2	16,823	25,632	Ischemic stroke	METASTROKE	10,307	19,326
OCD	PGC-OCDTS	2,936	7,279	Cardioembolic stroke	"	1,859	17,708
PTSD	PGC-PTSD	2,424	7,113	Early-onset stroke	"	3,274	11,012
Schizophrenia	PGC-SCZ2	33,640	43,456	Large-vessel disease	"	1,817	17,708
Tourette Syndrome	PGC-OCDTS	4,220	8,994	Small-vessel disease	"	1,349	17,708
				Migraine	IHGC	59,673	316,078
				Migraine with aura	"	6,332	142,817
				Migraine without aura	"	8,348	136,758
				Multiple sclerosis	IMSGC	5,545	12,153
				Parkinson's disease	IPDGC	5,333	12,019
Total psychiatric		*108,493*	*238,514*	*Total neurologic*		*107,190*	*418,650*

Indented phenotypes are part of a larger whole, e.g. the epilepsy study contains the samples from both focal epilepsy and generalized epilepsy; sample counts for such overlaps are shown in gray. ADHD – attention deficit hyperactivity disorder; OCD – obsessive-compulsive disorder. 'Anxiety disorders' refers to a meta-analysis of five subtypes (generalized anxiety disorder, panic disorder, social phobia, agoraphobia, and specific phobias). References are listed in Table S1 and data availability in Table S13.

Table 2. *Behavioral-cognitive and additional phenotypes used in the study.*

Phenotype	Source	Samples
Behavioral-cognitive phenotypes		
Cognitive		
Years of education (q)	SSGAC	293,723
College attainment (d)	"	120,917
Cognitive performance (q)	"	17,989
Intelligence (d)	CTG	78,308
Personality measures		
Subjective well-being	SSGAC	298,420
Depressive symptoms	"	161,460
Neuroticism (q)	"	170,911
Extraversion (q)	GPC	63,030
Agreeableness (q)	"	17,375
Conscientiousness (q)	"	17,375
Openness (q)	"	17,375
Smoking-related		
Never/ever smoked (d)	TAG	74,035
Cigarettes per day (q)	TAG	38,617
Additional phenotypes		
BMI (q)	GIANT	339,224
Height (q)	"	253,288
Coronary artery disease (d)	Cardiogram	86,995
Crohn's disease (d)	IIBDGC	20,883
Total		**1,124,048**

Indented phenotypes are part of a larger whole, e.g. samples in the college attainment analysis are a subset of those in the analysis for years of education; sample counts for such overlaps are shown in gray. (d) – dichotomous phenotype, (q) – quantitative phenotype. BMI – body-mass index. References and phenotype definitions are listed in Table S2, and data availability in Table S13.

Supplementary Materials

Print summary for aap8757, *Analysis of Shared Heritability in Common Disorders of the Brain,* by Anttila V. et al.

Introduction

Disorders of the brain can exhibit considerable epidemiological comorbidity and share symptoms, provoking debate about their etiologic overlap. However, detailed study of phenotypes with different ages of onset, severity and presentation presents a considerable challenge. Recently developed heritability methods allow us to accurately measure correlation of genome-wide common variant risk between two phenotypes from pools of different individuals, to understand how connected they, or at least their genetic risks, are on the genomic level. We quantified the degree of overlap for genetic risk factors of 25 common brain disorders, based on genome-wide association data for 215,683 patients and 657,164 controls, as well as 17 phenotypes from a total of 1,191,588 individuals.

Rationale

The classification of brain disorders has evolved over the last century, reflecting the medical and scientific communities' assessments of the presumed root causes of clinical phenomena such as behavioral change, loss of motor function, or alterations of consciousness. Directly observable phenomena (such as the presence of emboli, protein tangles, or unusual electrical activity patterns) generally define and separate neurological disorders from psychiatric disorders. Understanding the genetic underpinnings and categorical distinctions for brain disorders and related phenotypes may inform the search for their biological mechanisms.

Results

Common variant risk for psychiatric disorders was shown to correlate significantly, especially between ADHD, bipolar disorder, major depressive disorder (MDD) and schizophrenia. In contrast, neurological disorders appear more distinct from one another and from the psychiatric disorders, except for migraine, which was significantly correlated to ADHD, MDD and Tourette Syndrome. We demonstrate that the personality trait neuroticism in the general population is significantly correlated with almost every psychiatric disorder and migraine. We also identify significant sharing between disorders and early life cognitive measures in the general population (e.g. years of education and college attainment), demonstrating positive correlation with several psychiatric disorders (e.g. anorexia nervosa and bipolar disorder) and negative correlation with several neurological phenotypes (e.g. Alzheimer's disease and ischemic stroke), even though the latter are considered to result from specific processes that occur later in life. Extensive simulations were also performed to inform how power, diagnostic misclassification and phenotypic heterogeneity influence genetic correlations.

Conclusion

The high degree of genetic correlation among many of the psychiatric disorders adds further evidence that the current clinical boundaries among them do not reflect distinct underlying pathogenic processes, at least on the genetic level. This suggests a deeply interconnected nature, in contrast to neurological disorders, and underscores the need to refine psychiatric diagnostics. Genetically informed analyses may provide important 'scaffolding' to support such restructuring of psychiatric nosology, which likely requires incorporating many levels of information. In contrast, we find limited evidence for widespread common genetic risk sharing among neurological disorders or across neurological and psychiatric disorders. We show that both psychiatric and neurological disorders have robust correlations with cognitive and personality measures. Further study is needed to evaluate whether overlapping genetic contributions to psychiatric pathology may influence treatment choices. Ultimately, such developments give hope to reducing heterogeneity and eventually improving the diagnosis and treatment of psychiatric disorders.

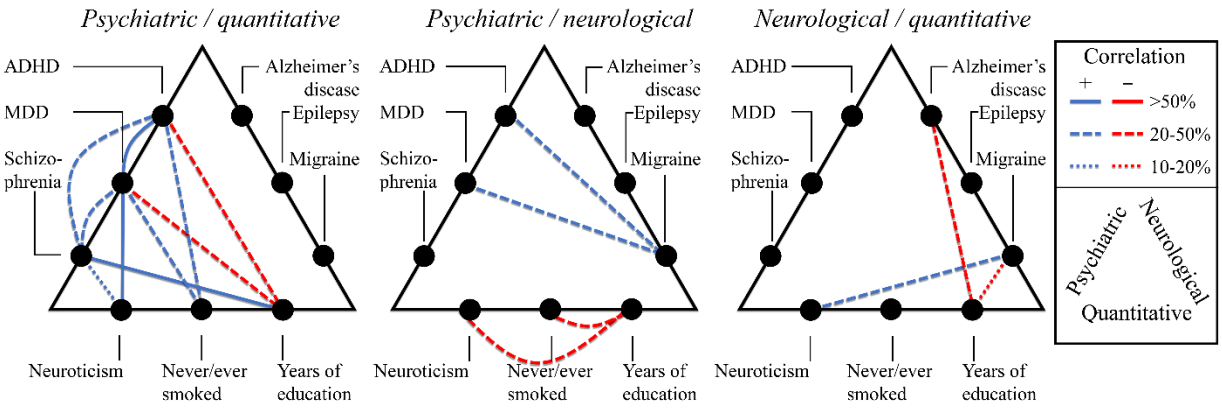
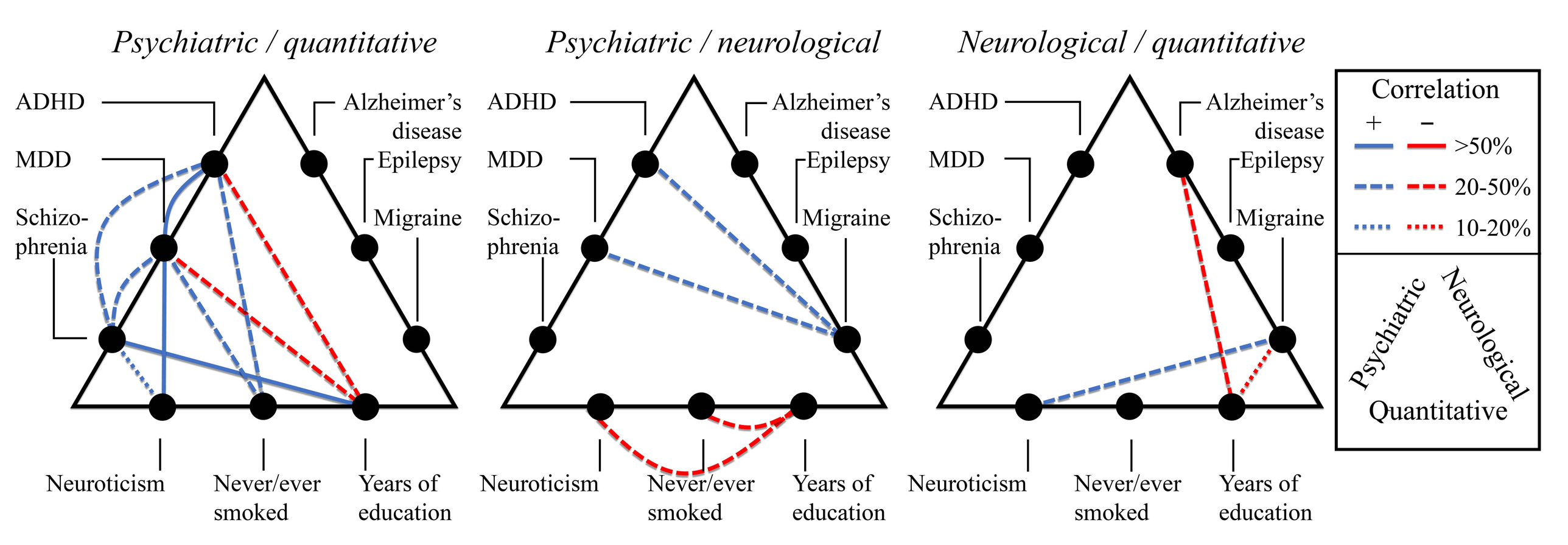


Figure Caption

Subsection of genetic risk correlations among brain disorders and quantitative phenotypes.

Heritability analysis of brain disorders points to pervasive sharing of genetic risk among psychiatric disorders, largely absent among neurological disorders, but present from both groups to neuro-cognitive quantitative phenotypes. Only significant correlations shown. Color and line solidity indicate direction and magnitude of correlation, respectively. ADHD – attention deficit hyperactivity disorder; MDD – major depressive disorder.


Psychiatric / quantitative
Psychiatric / neurological
Neurological / quantitative
ADHD
MDD
Schizo-
phrenia
Alzheimer's
disease
Epilepsy
Migraine
Neuroticism
Never/ever
smoked
Years of
education
Correlation
+
−
>50%
20-50%
10-20%
Psychiatric
Neurological
Quantitative

Supplementary Materials for

Analysis of Shared Heritability in Common Disorders of the Brain

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This PDF file includes:

Materials and Methods
Supplementary Text
Figs. S1-S10
Tables S1-6, S8-11

Other Supplementary Materials for this manuscript includes the following:

Tables S7, S12, S13 (separate 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(*84*), 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(*85*). 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(*86*) 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(*87*) (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(*88*). 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 (*89*)). 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)(*90, 91*). 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(*88*), using stratified LD score regression to identify enriched cell type groups, expanding on the work described in Finucane et al(*92*). 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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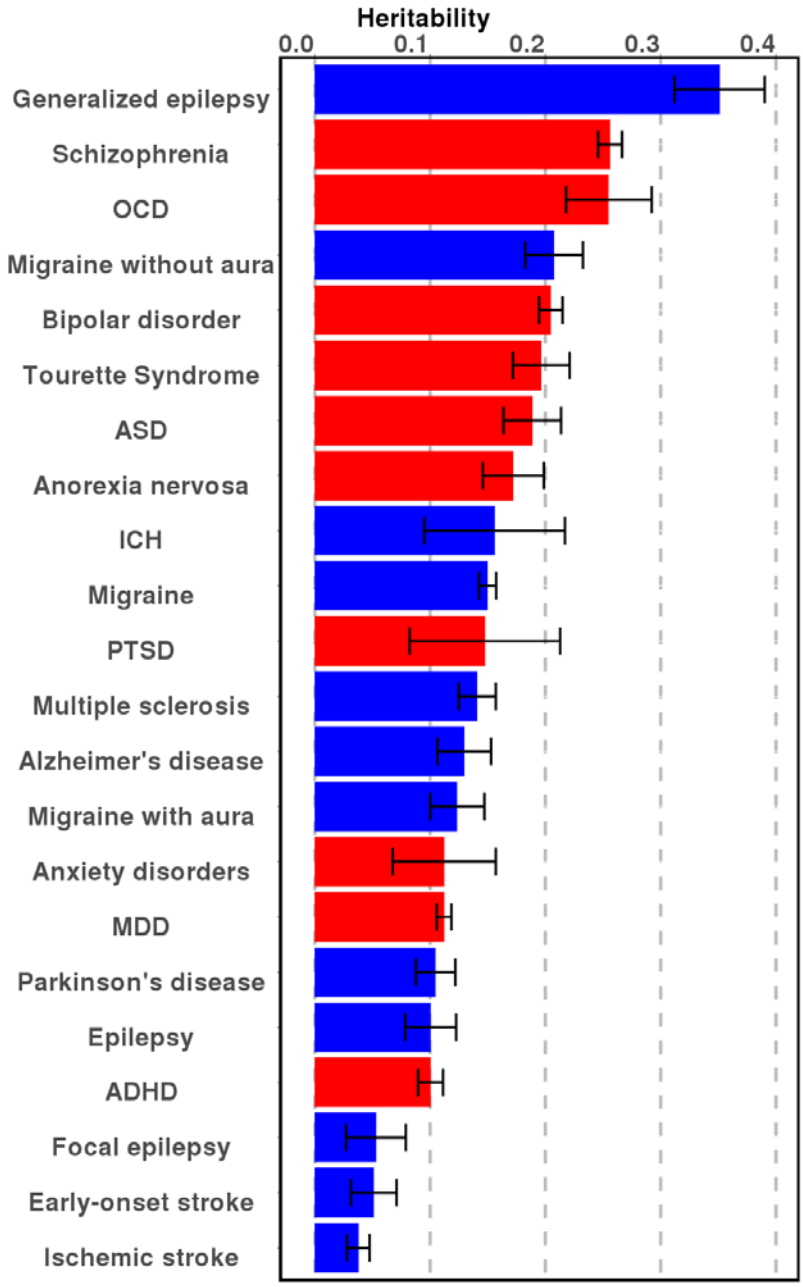


Fig. S1A. Heritability estimates for brain disorders

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.

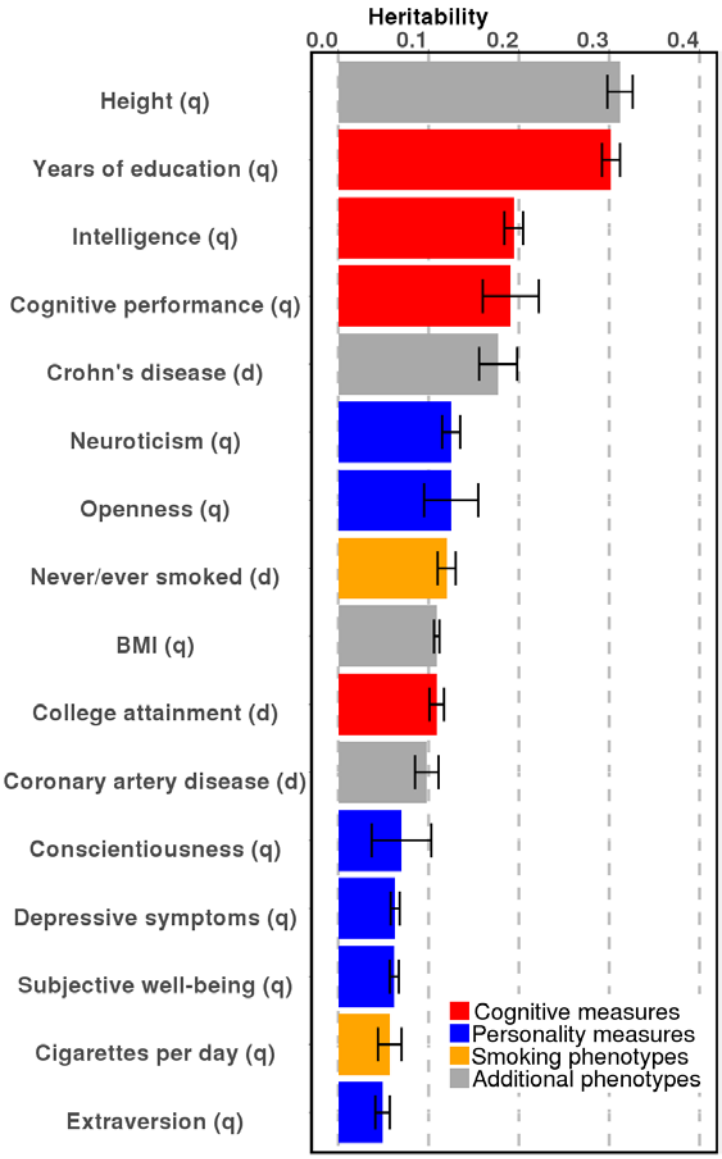


Fig. S1B. Heritability estimates for quantitative and additional phenotypes

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.

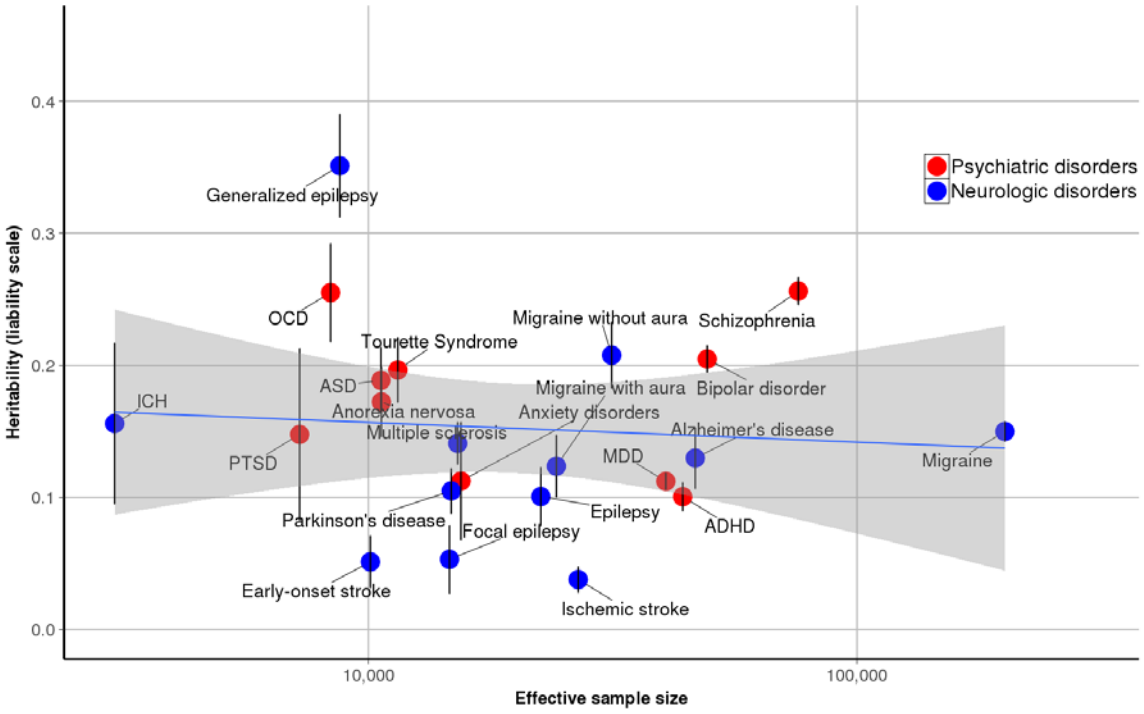


Fig. S1C. Heritability and effective sample size

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.

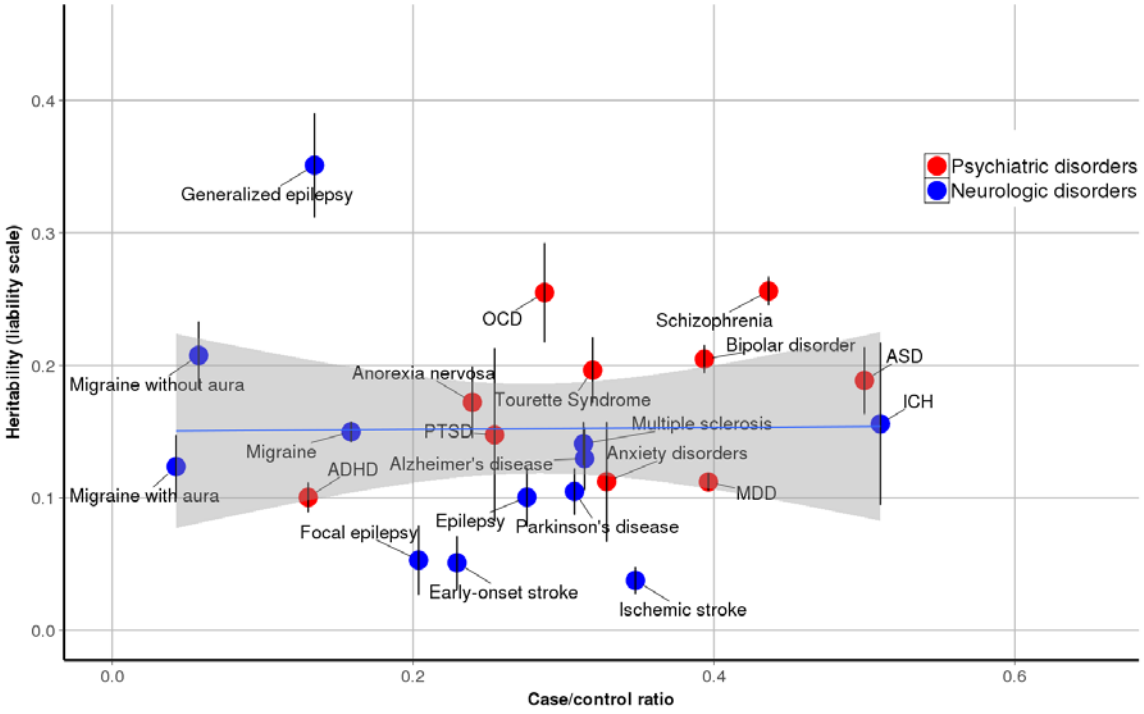


Fig. S1D. Heritability and case/control ratio

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.

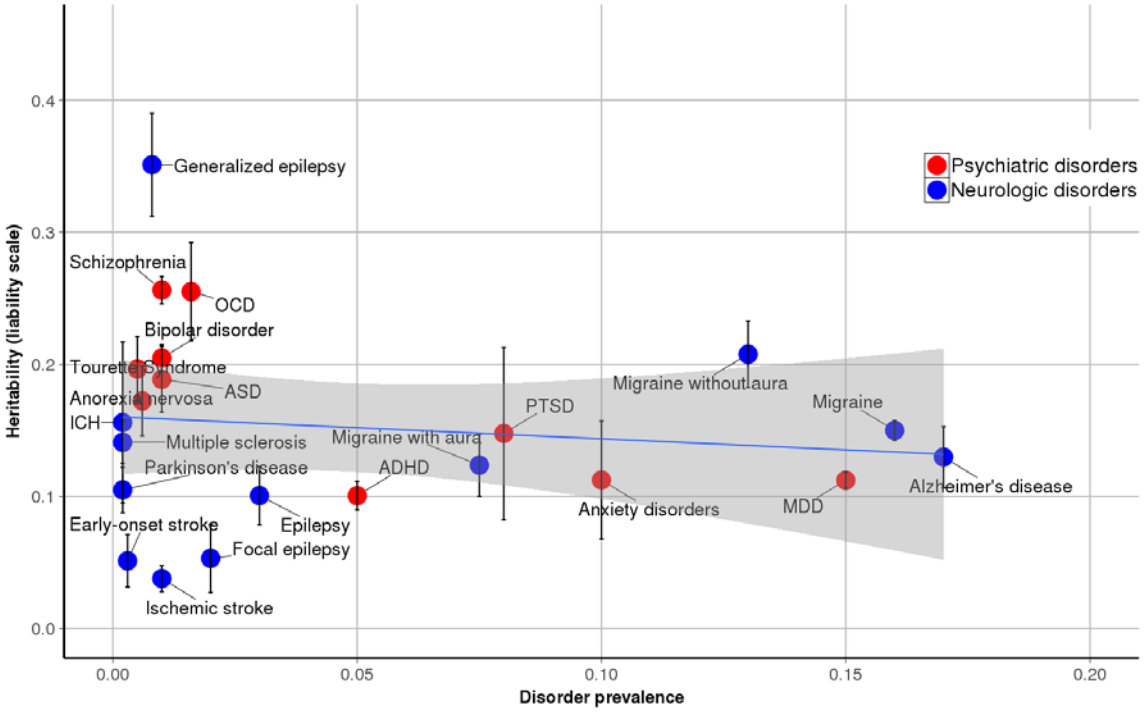


Fig. S1E. Heritability and disorder prevalence

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.

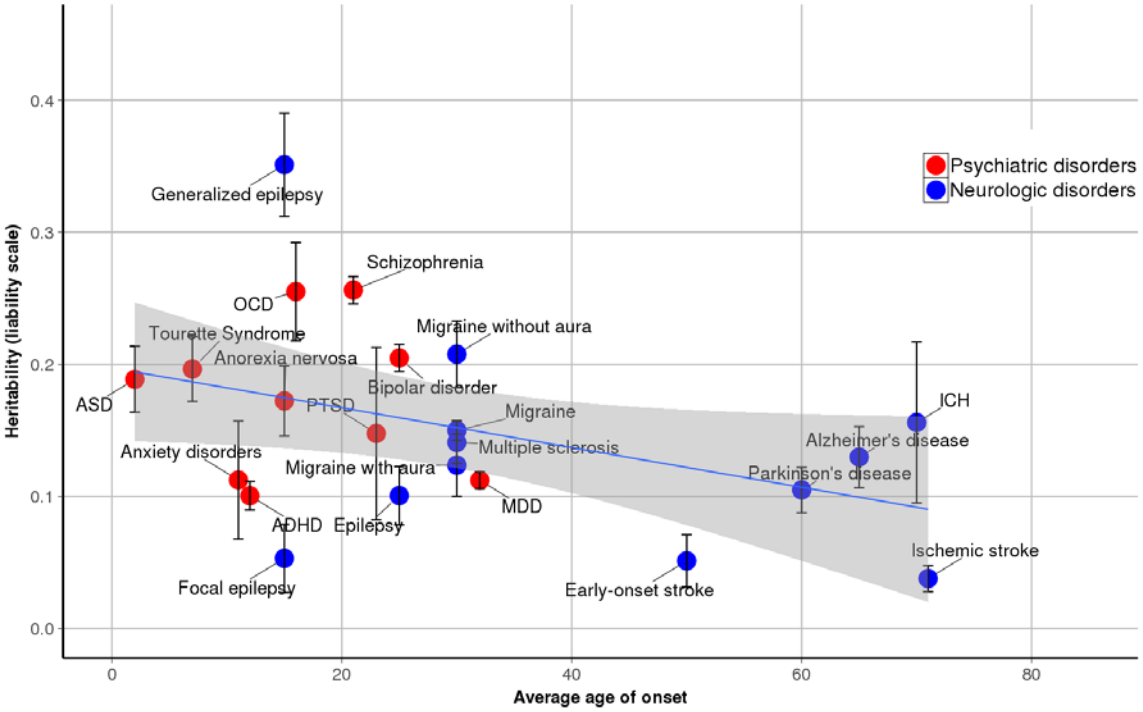
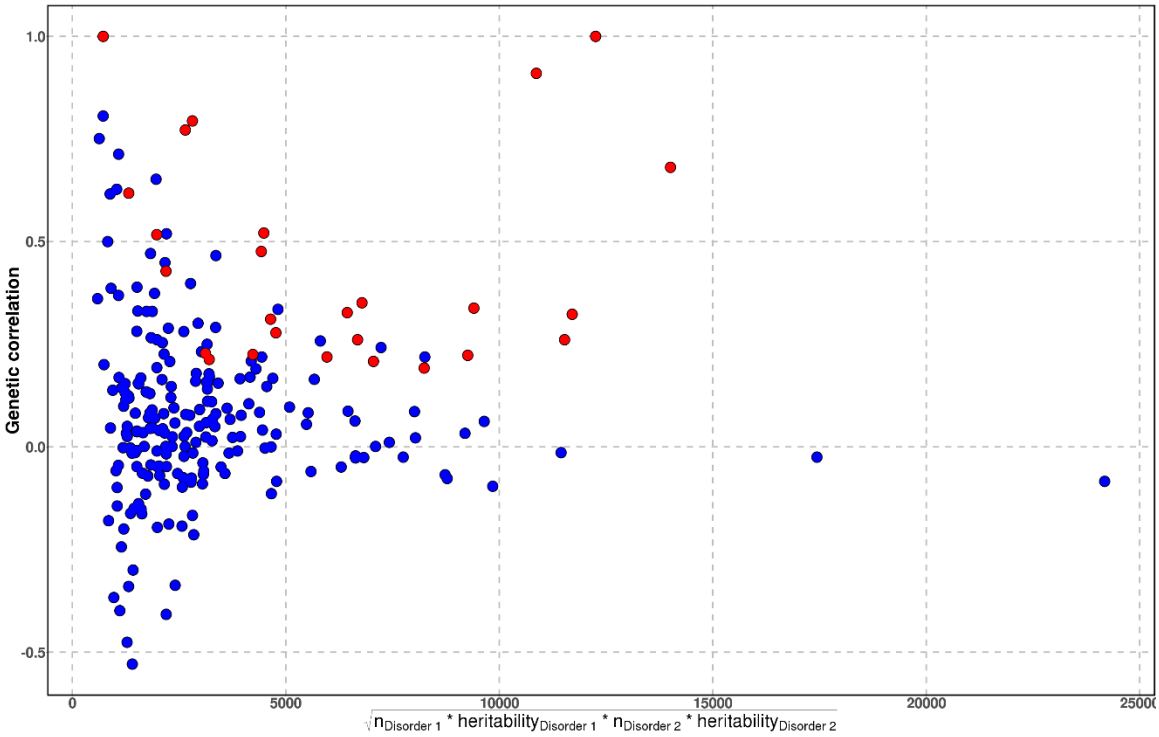


Fig. S1F. Heritability and average age of onset for the disorder.

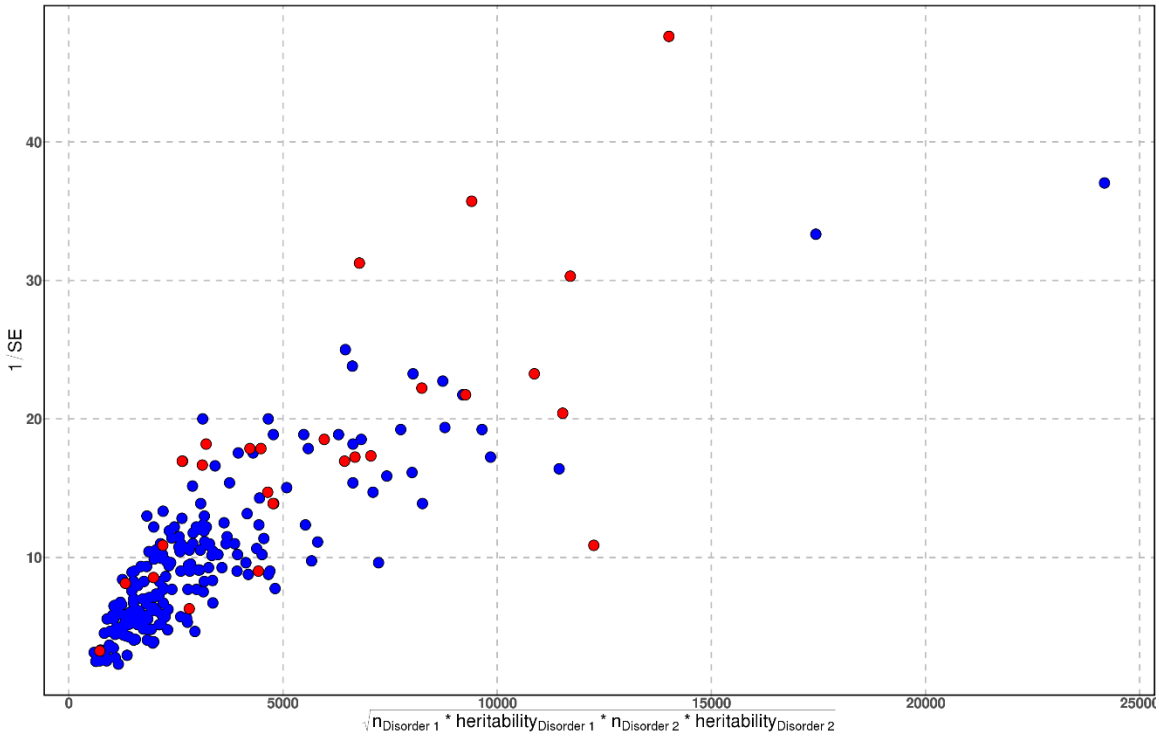
ADHD – attention deficit hyperactivity disorder; ASD – autism spectrum disorder; ICH – intracerebral hemorrhage; MDD – major depressive disorder; OCD – obsessive-compulsive disorder; PTSD – post-traumatic stress disorder. Shaded area shows 95% confidence interval. Error bars show one standard error.

Fig. S2A. Genetic correlations against power to detect heritability



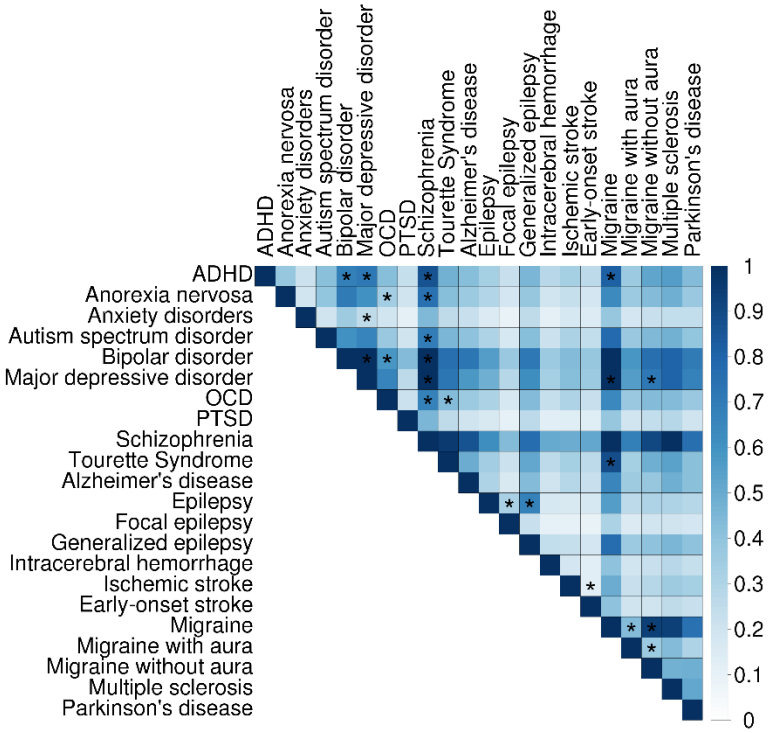
Red points show significant correlations among all disorder-disorder pairs. Two outlier values over 1 (see Table S7A) have been reduced to 1. The points close or equal to $r_g = 1$ are pairs of a top-level disorder with a subtype of the same disorder, where high correlation is expected, ie. all migraine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

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



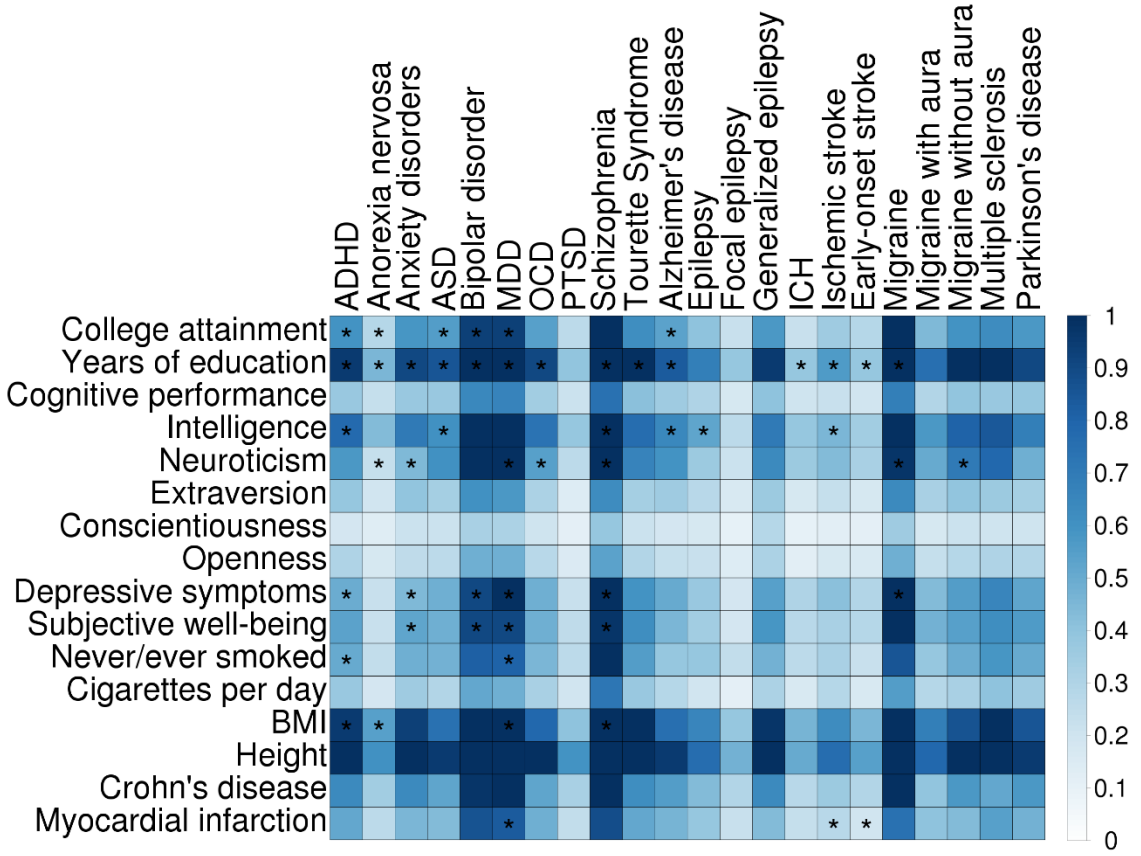
Red points show significant correlations among all disorder-disorder pairs. SE – standard error.

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.

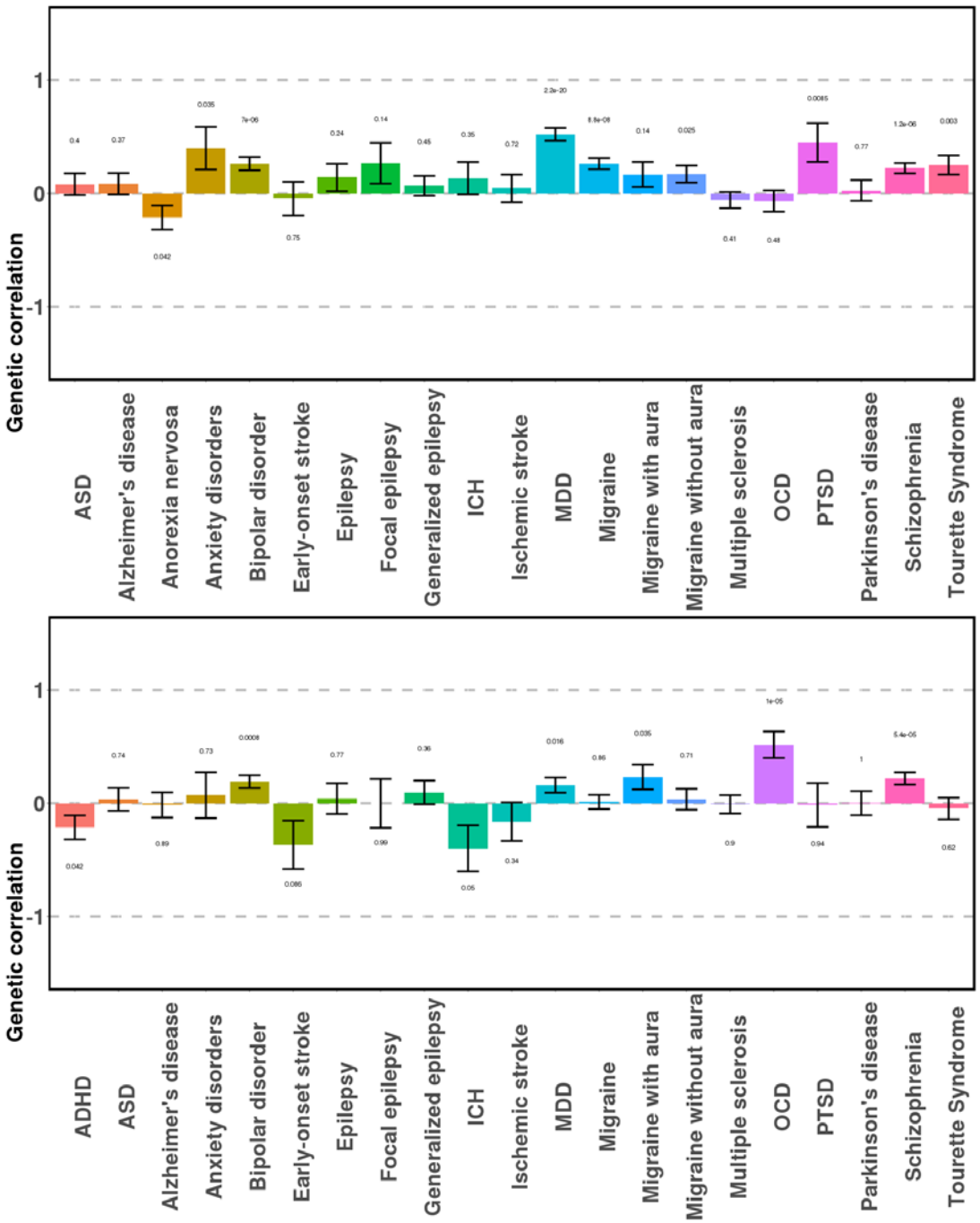


Fig. S3A and B. Genetic correlations for attention-deficit hyperactivity disorder (top) and anorexia nervosa (bottom).

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.

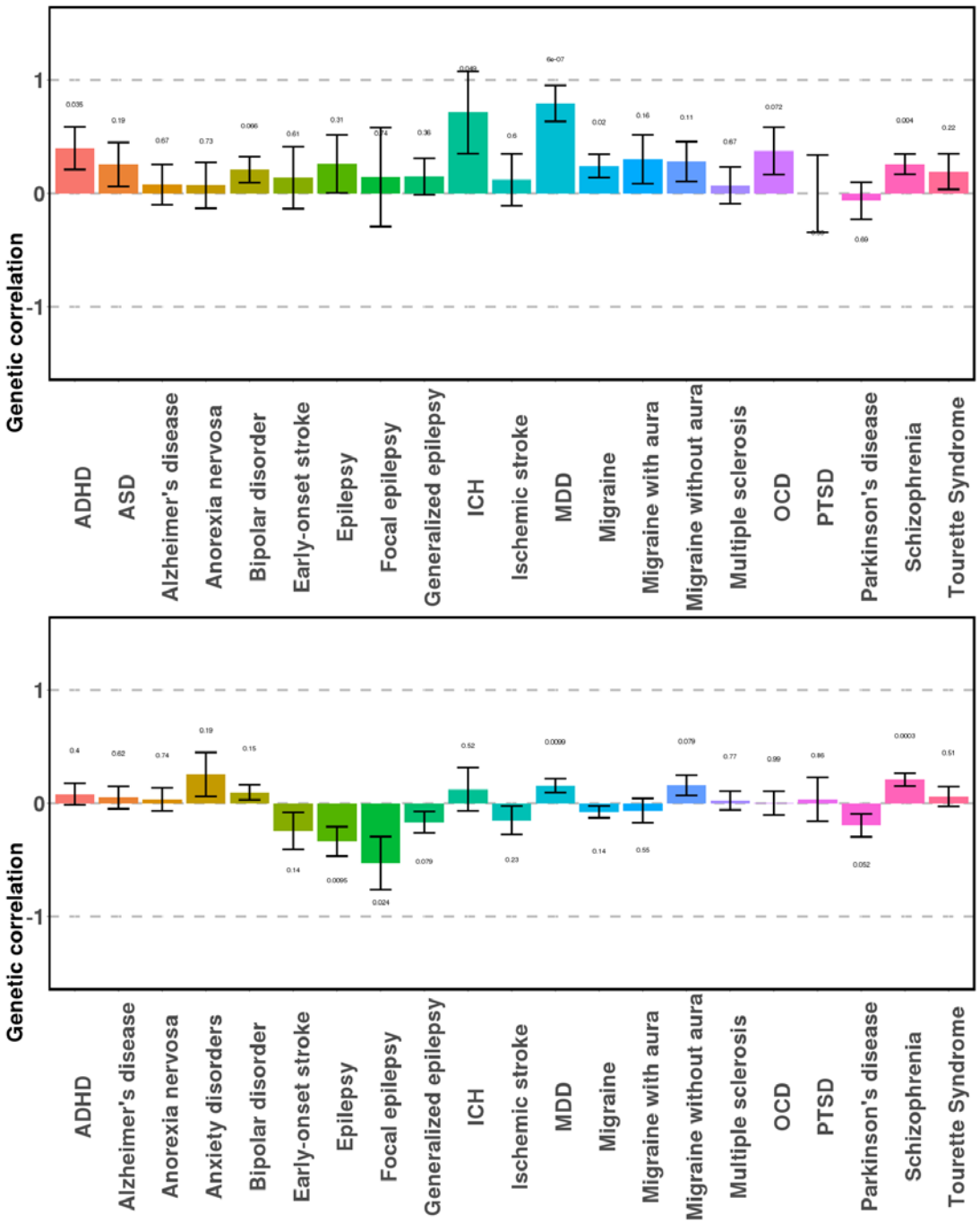


Fig. S3C and D. Genetic correlations for anxiety disorders (top) and autism spectrum disorder (bottom).

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.

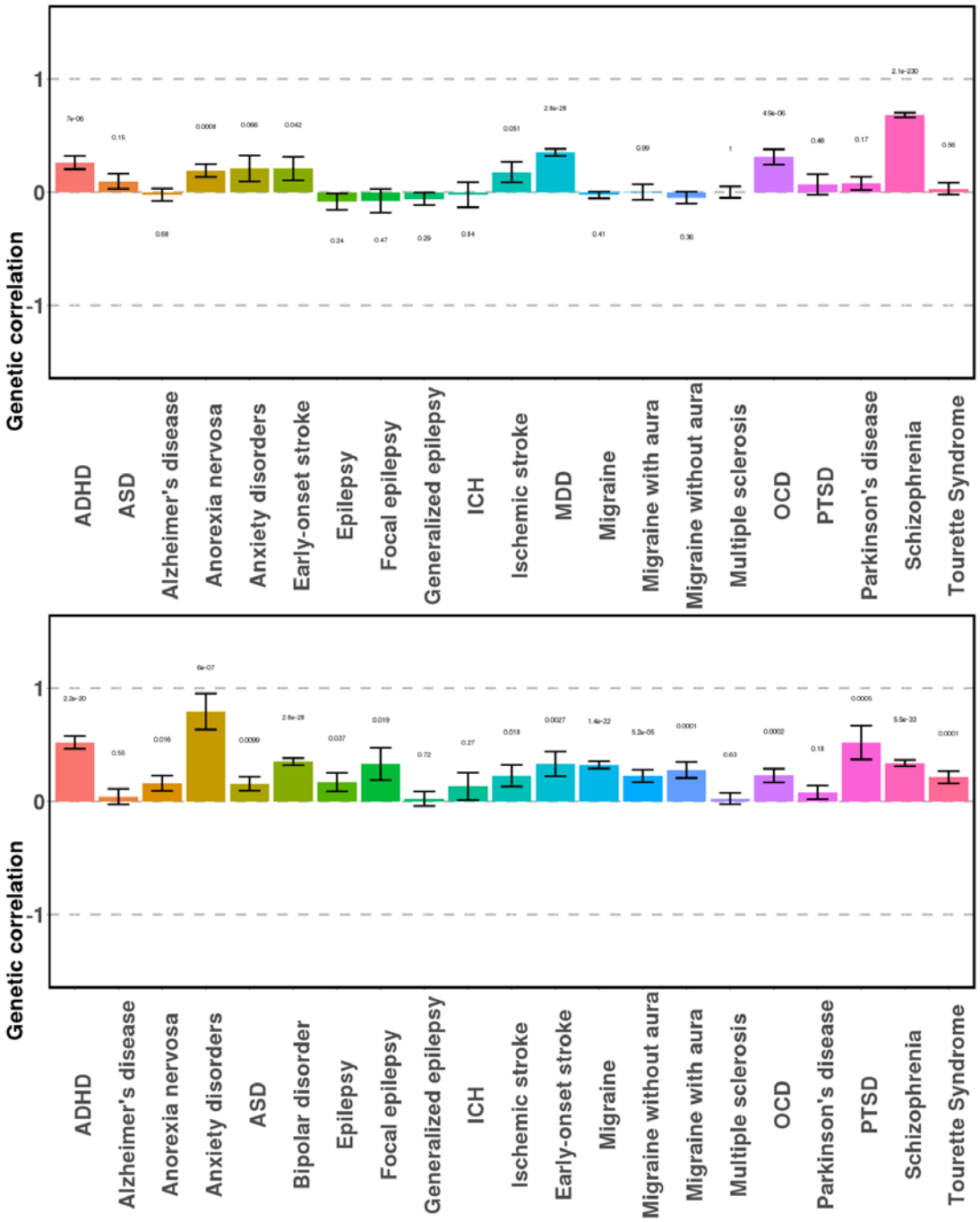


Fig. S3E and F. Genetic correlations for bipolar disorder (top) and major depressive disorder (bottom).

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.

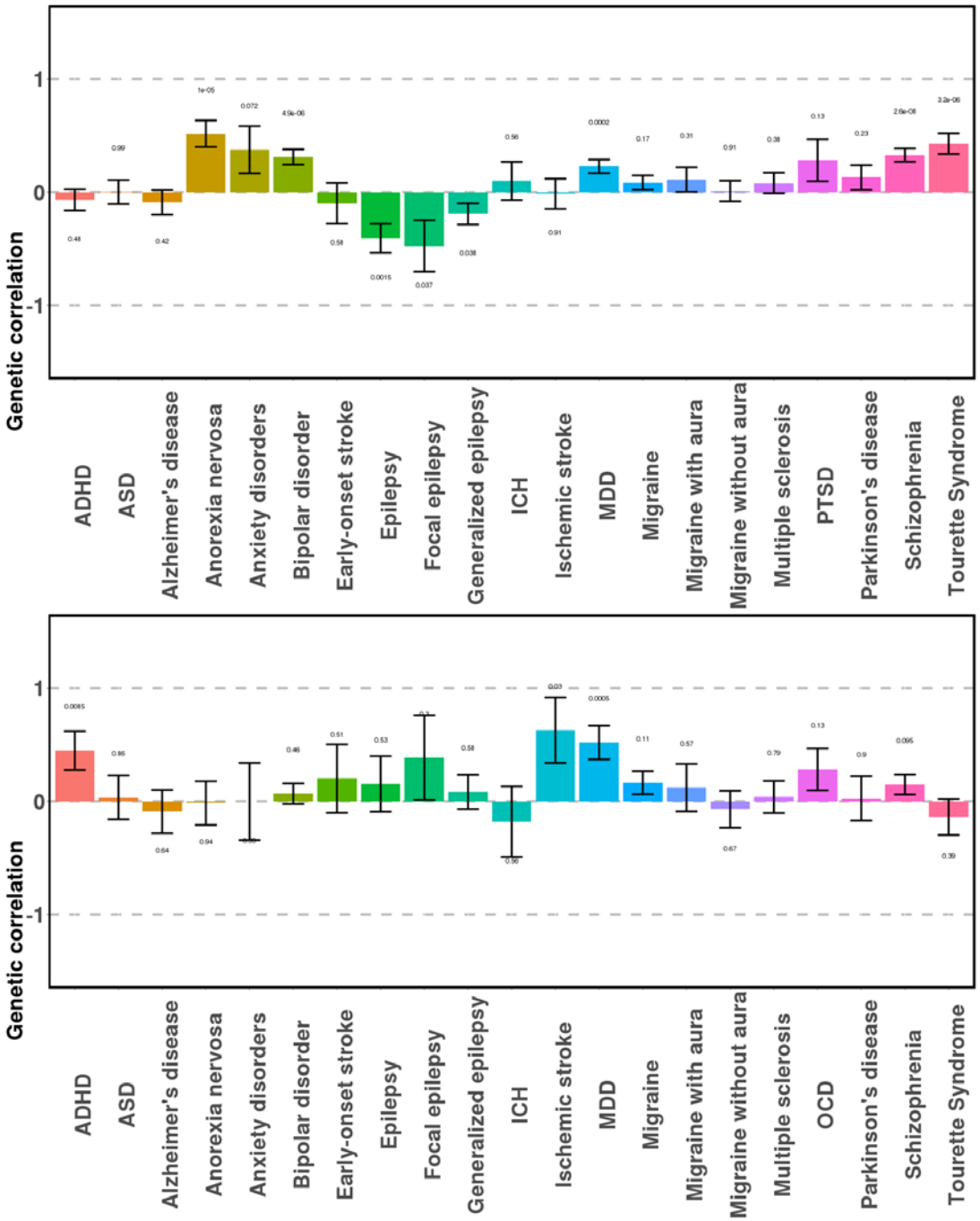


Fig. S3G and H. Genetic correlations for obsessive-compulsive disorder (top) and post-traumatic stress disorder (bottom).

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.

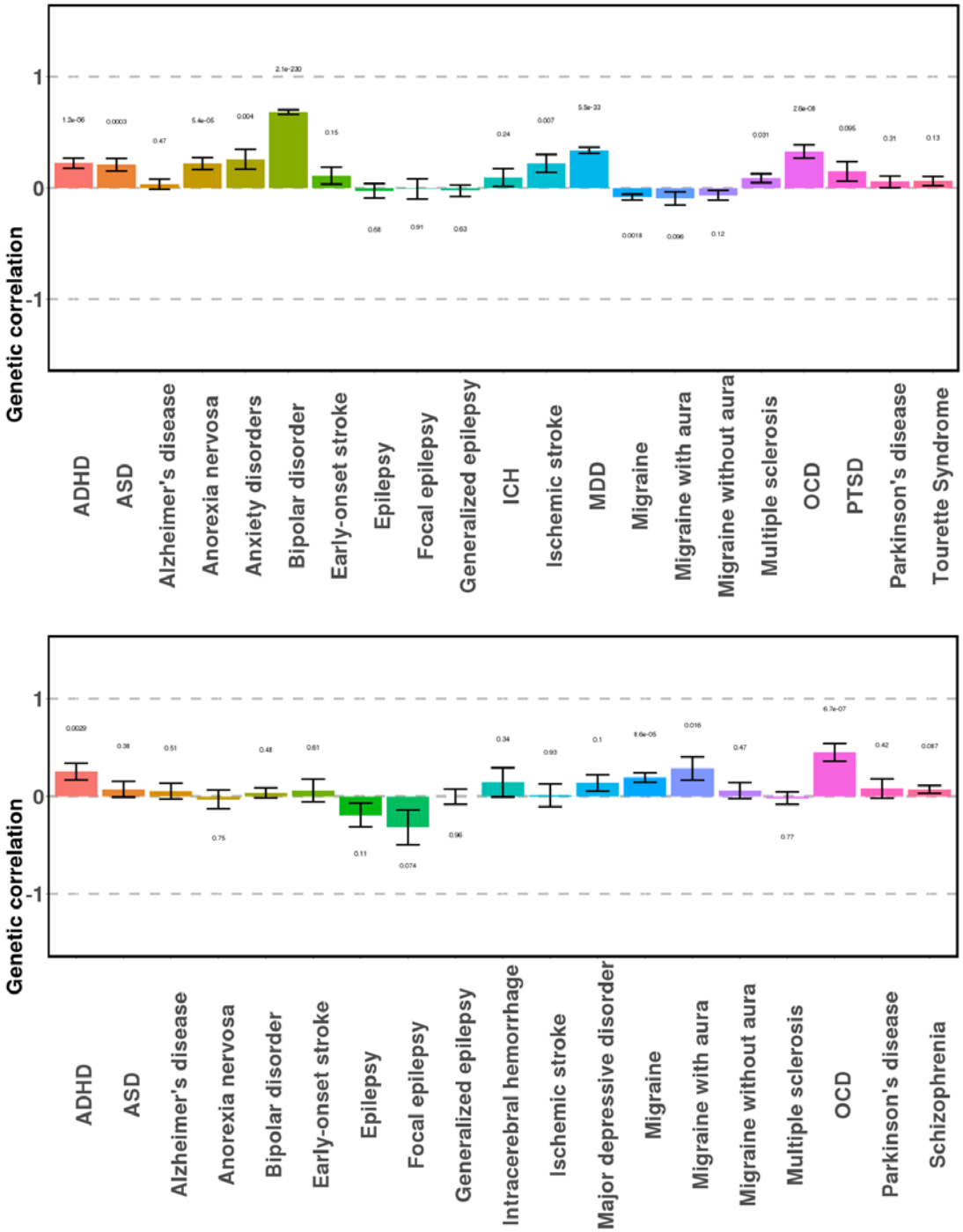


Fig. S3I and J. Genetic correlations for schizophrenia (top) and Tourette Syndrome (bottom).

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.

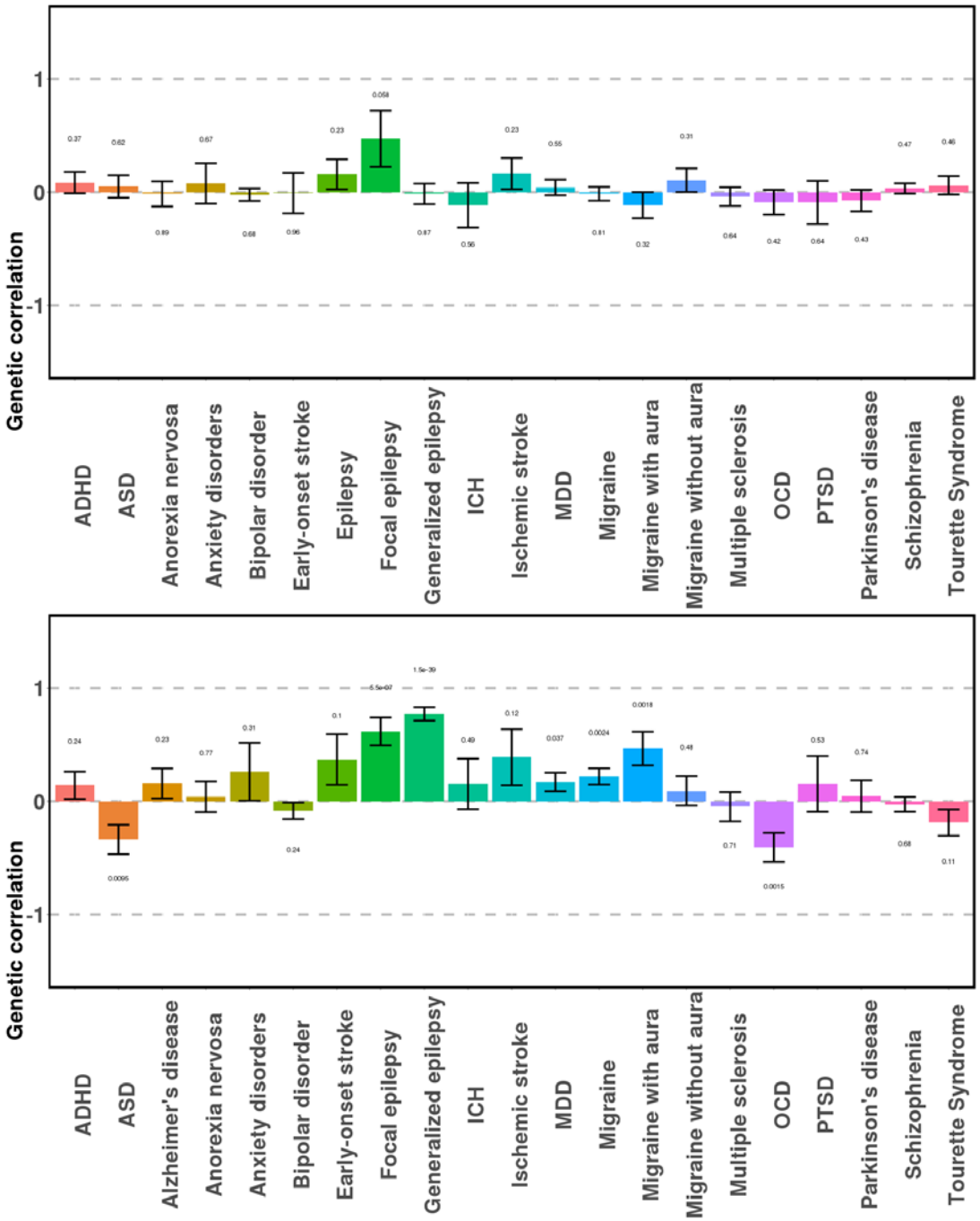


Fig. S4A and B. Genetic correlations for Alzheimer's disease (top) and epilepsy (bottom).

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.

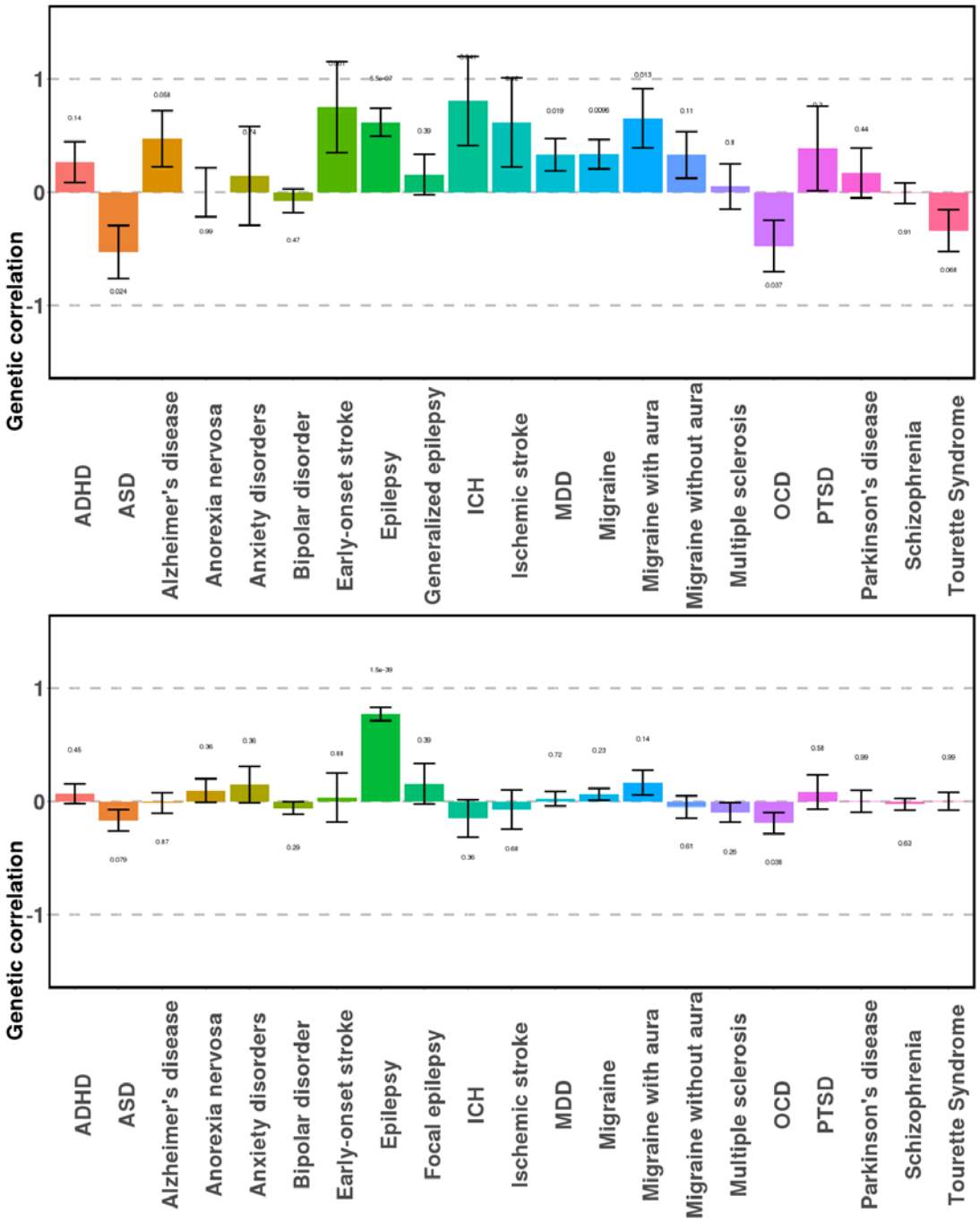


Fig. S4C and D. Genetic correlations for focal epilepsy (top) and generalized epilepsy (bottom).

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.

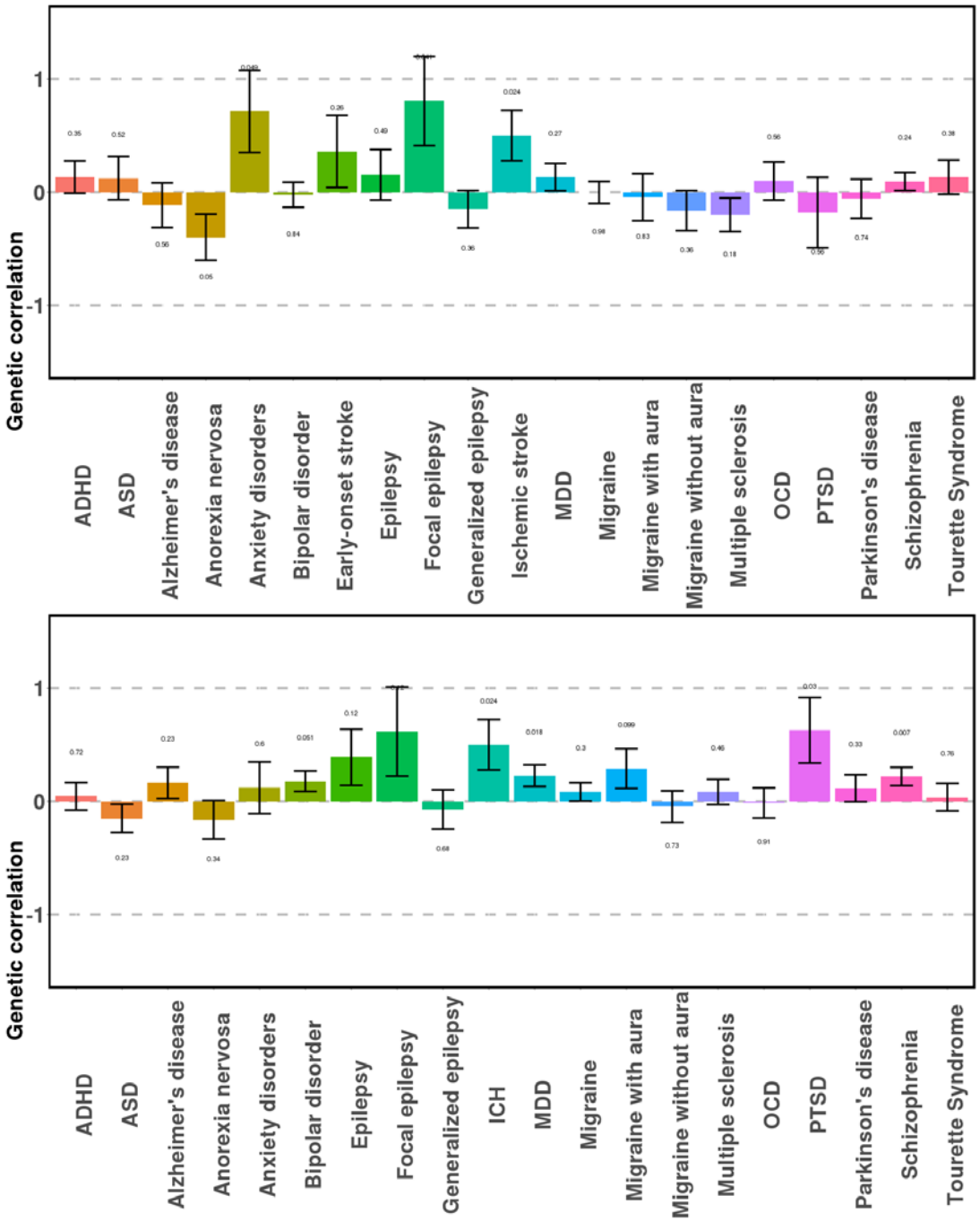


Fig. S4E and F. Genetic correlations for intracerebral hemorrhage (top) and ischemic stroke (bottom).

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.

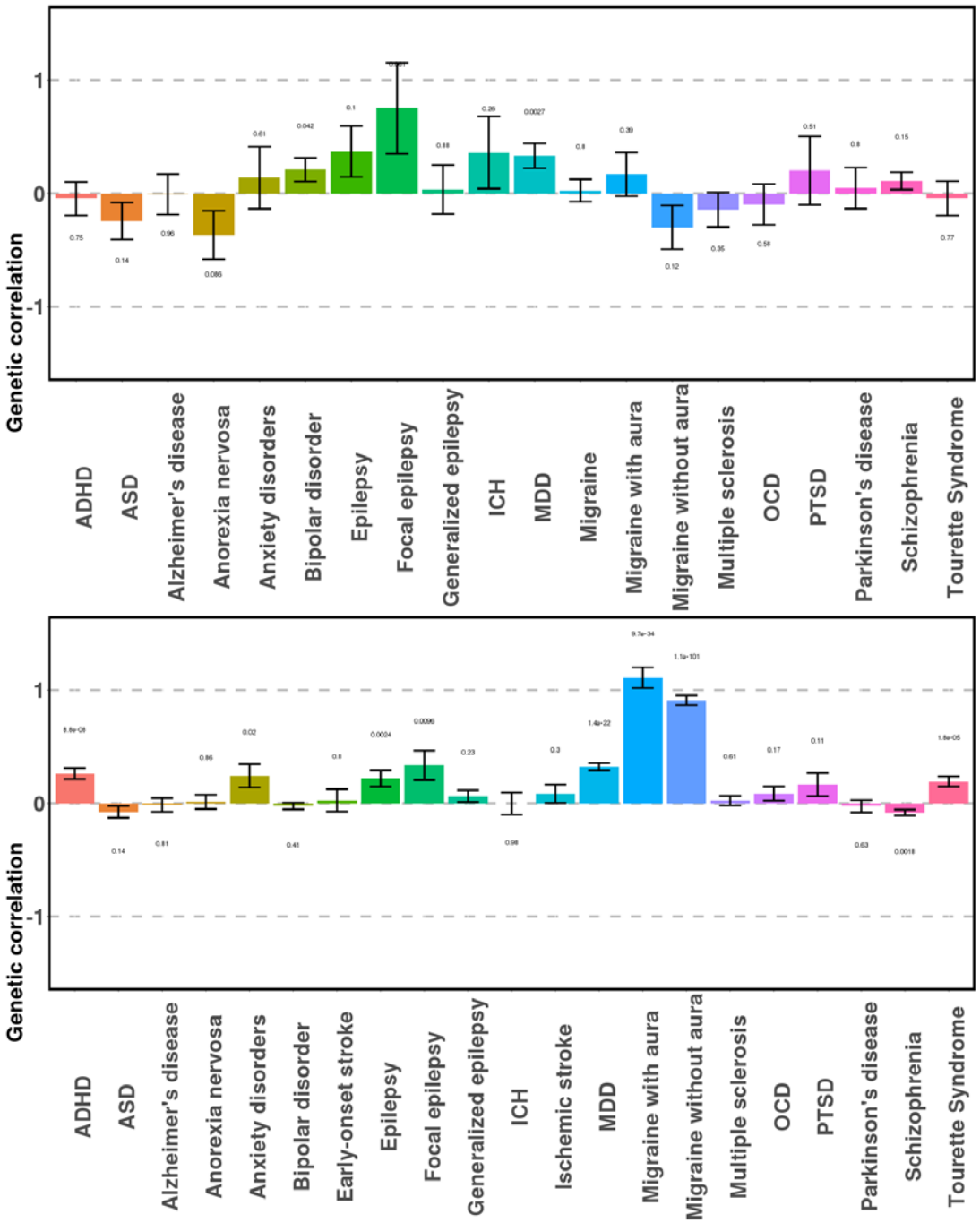


Fig. S4G and H. Genetic correlations for early-onset stroke (top) and migraine (bottom).

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.

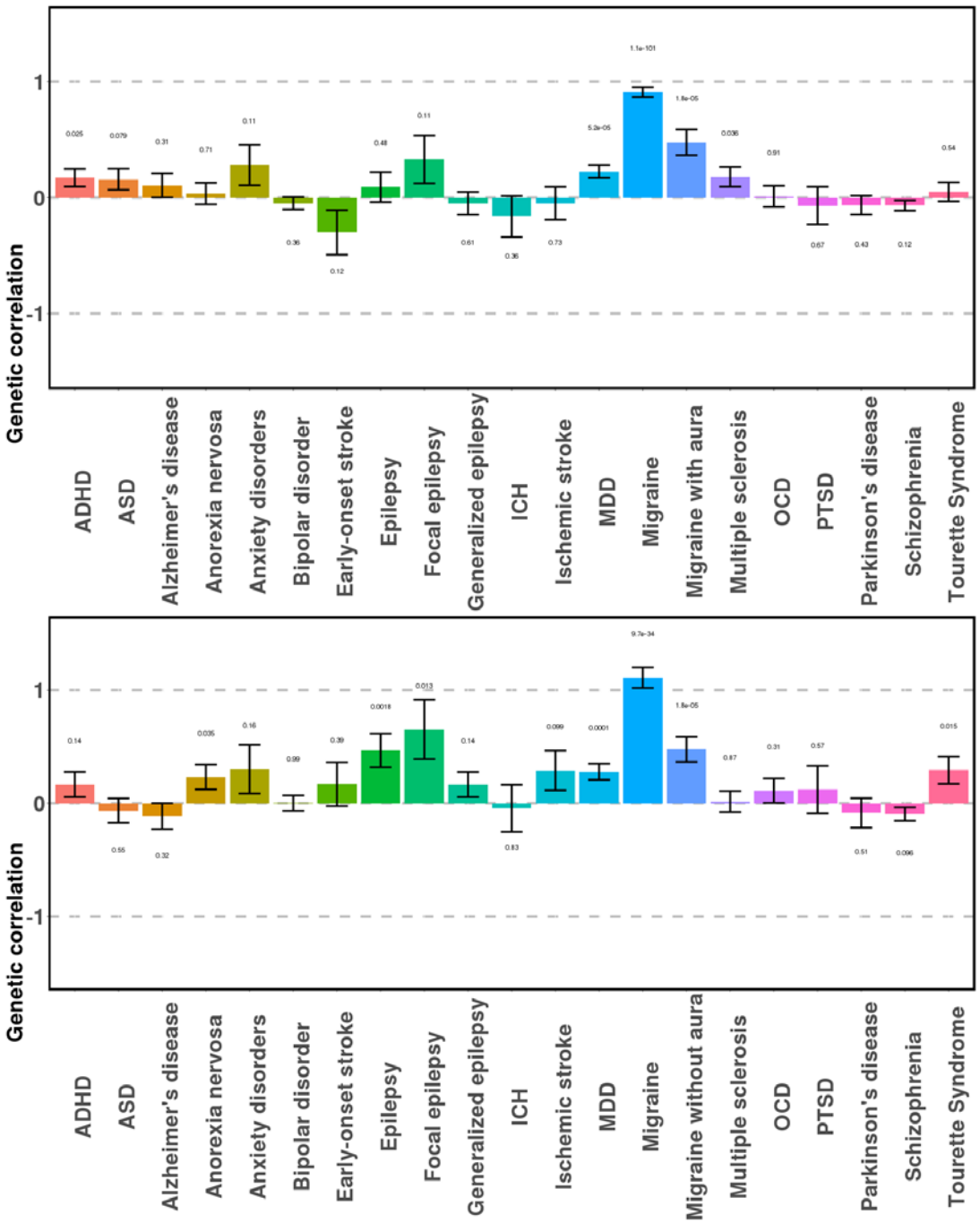


Fig. S4I and J. Genetic correlations for migraine without aura (top) and migraine with aura (bottom).

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.

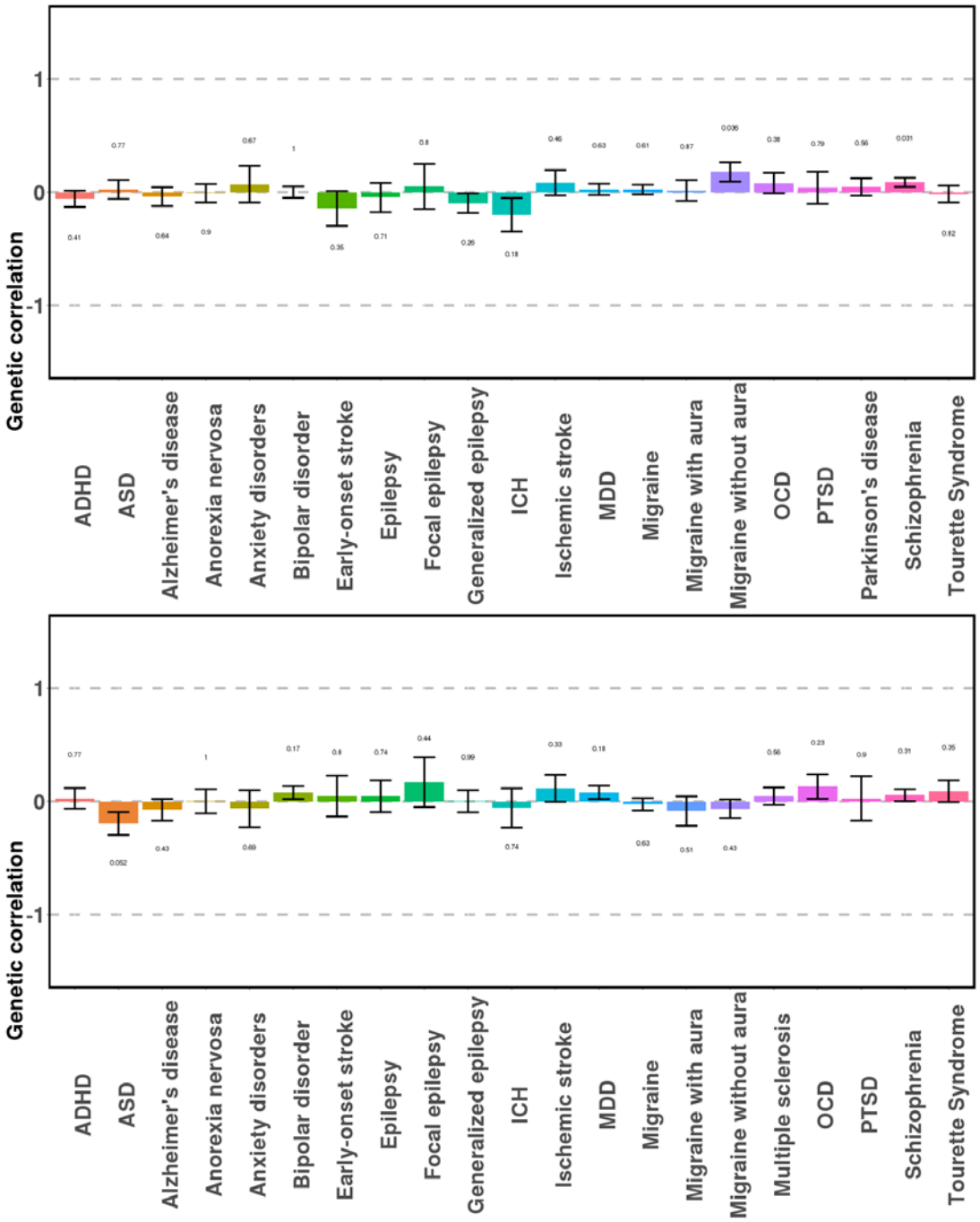


Fig. S4K and L. Genetic correlations for multiple sclerosis (top) and Parkinson's disease (bottom).

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.

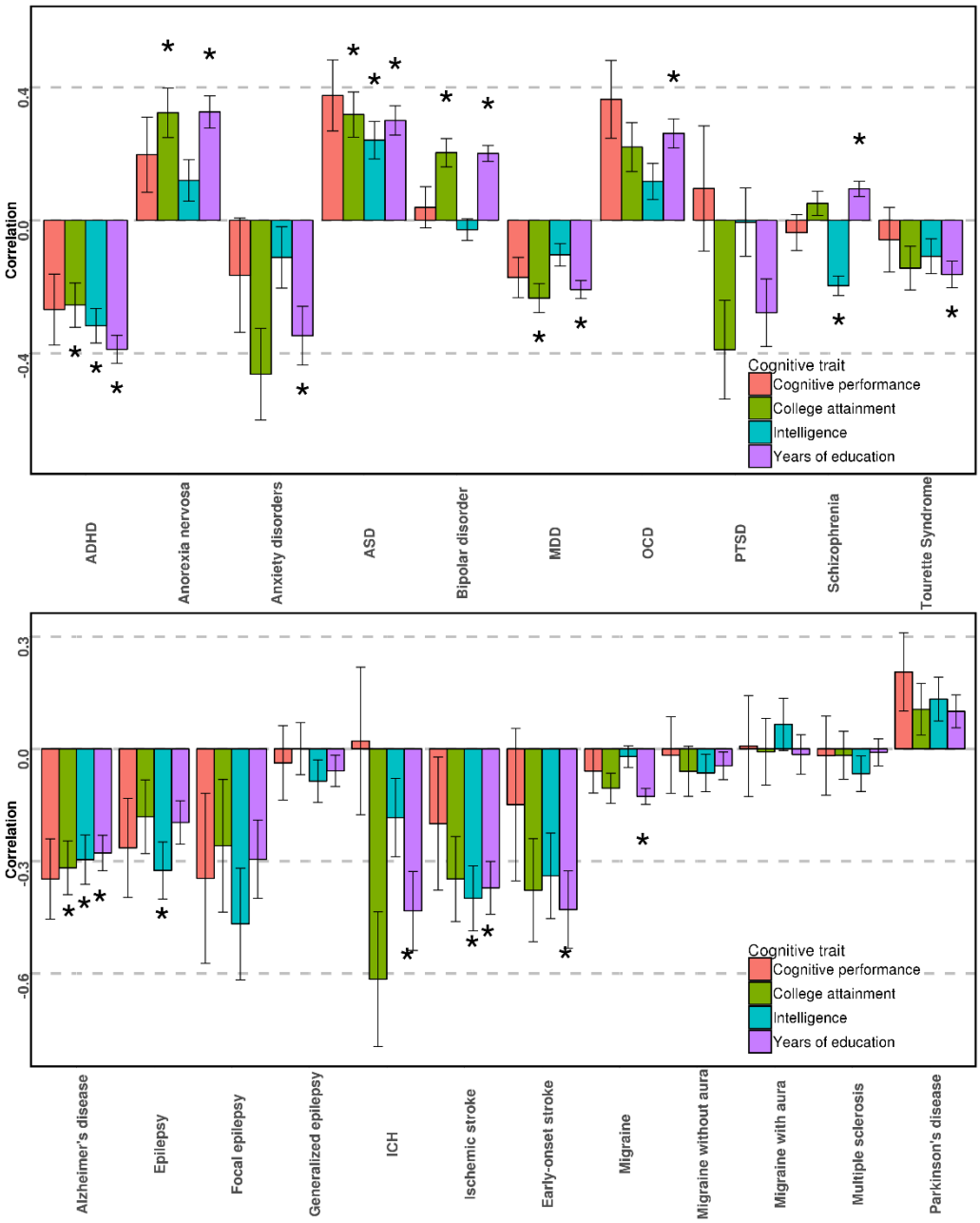


Fig. S5A and B. Genetic correlations for psychiatric and neurological disorders against cognitive measures.

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.

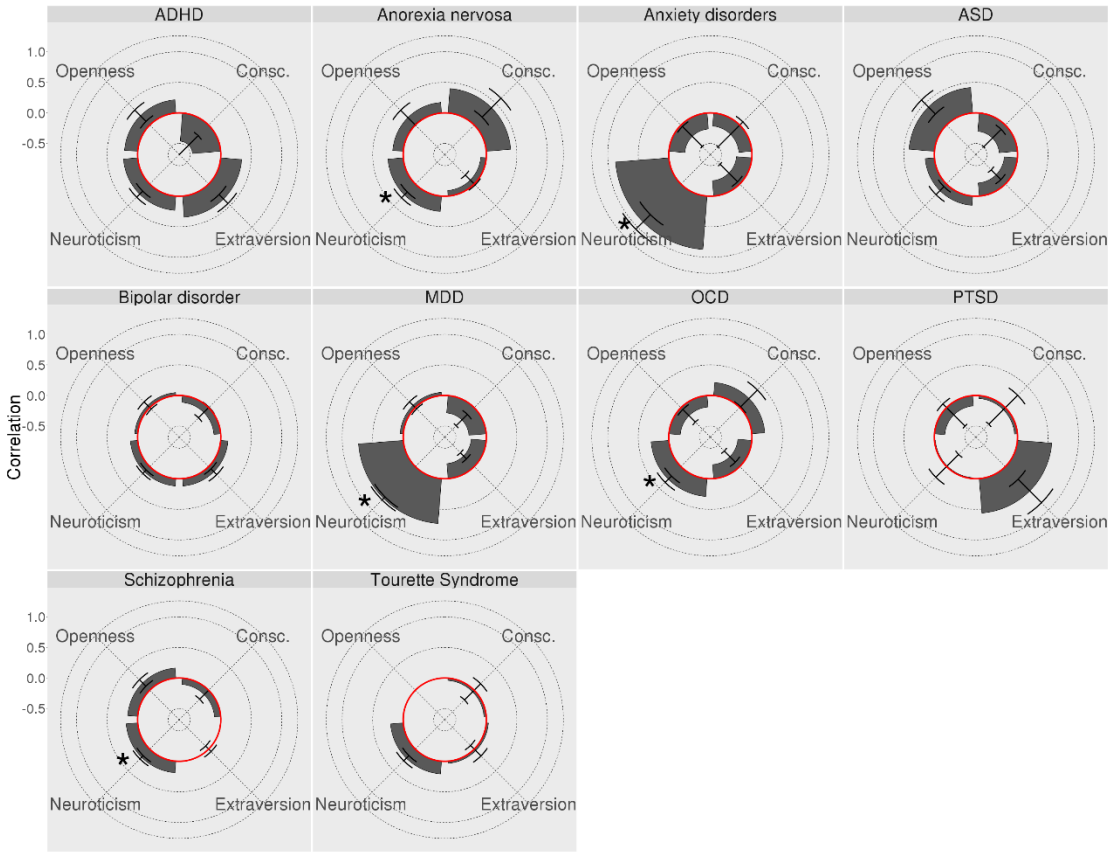


Fig. S6A. Genetic correlations for psychiatric disorders and four personality axes.
Grey sectors denote the extent of genetic correlation between each brain disorder and the four personality axes. Red line denotes zero correlation, with positive correlations on the outside and negative correlations on 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.

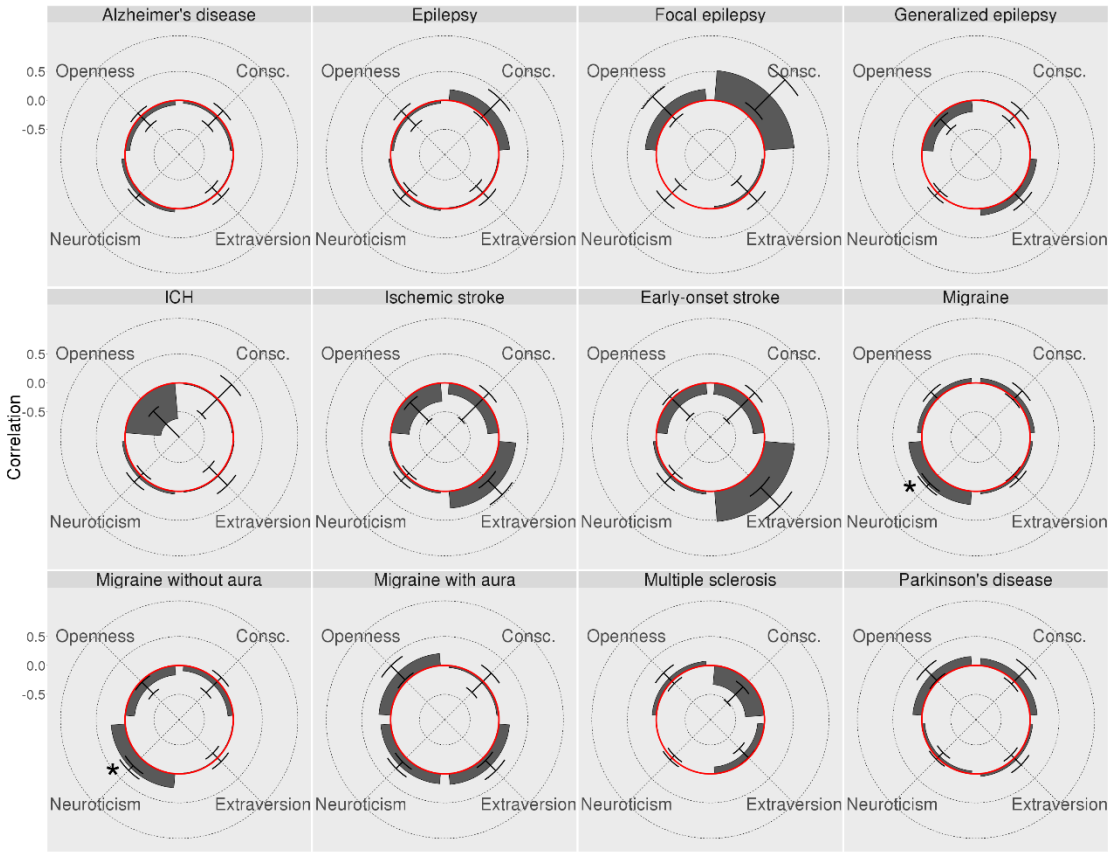


Fig. S6B. Genetic correlations for neurological disorders and four personality axes. Grey bars denote the extent of genetic correlation between each brain disorder and the four personality axes. Red line denotes zero correlation, with positive correlations on the outside and negative correlations on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

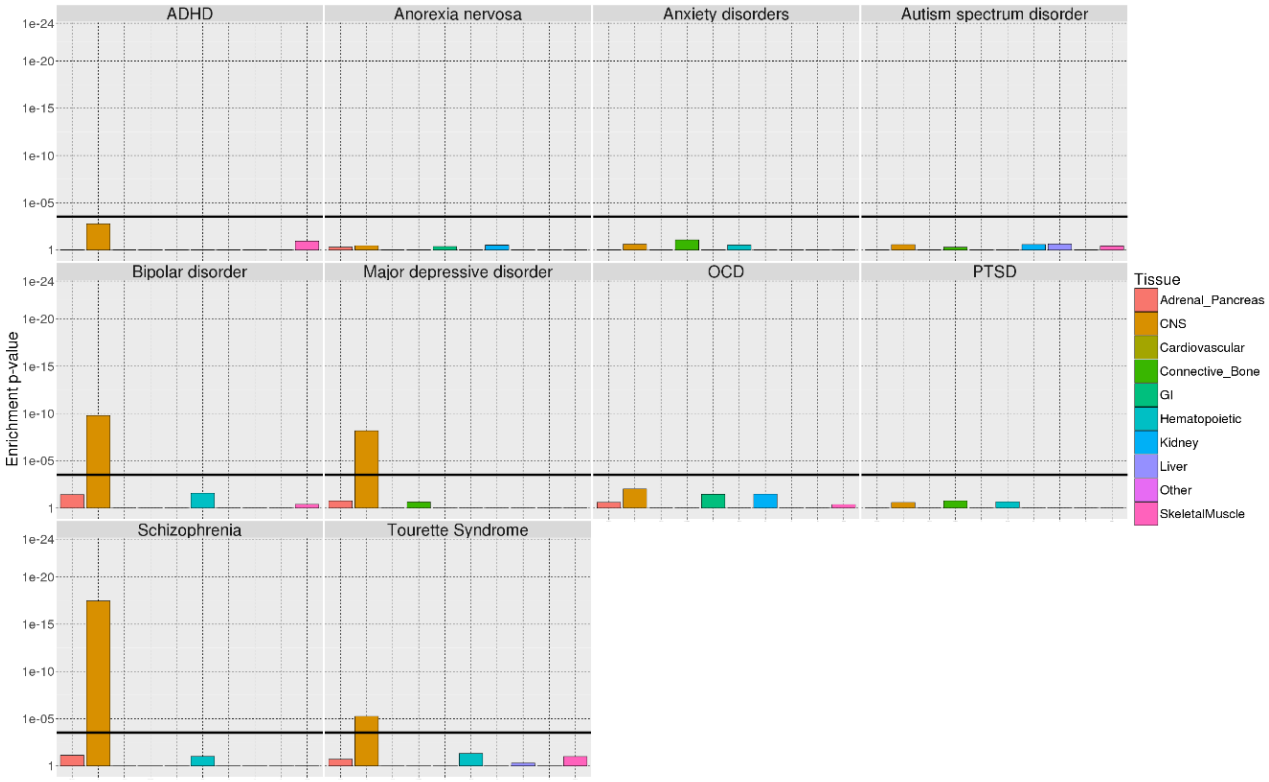


Fig. S7A. Tissue category heritability enrichment analysis in psychiatric phenotypes

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(*92*). Black line denotes significance threshold for Bonferroni multiple testing correction, $p=2.81 \times 10^{-4}$. Only positive enrichment reported.

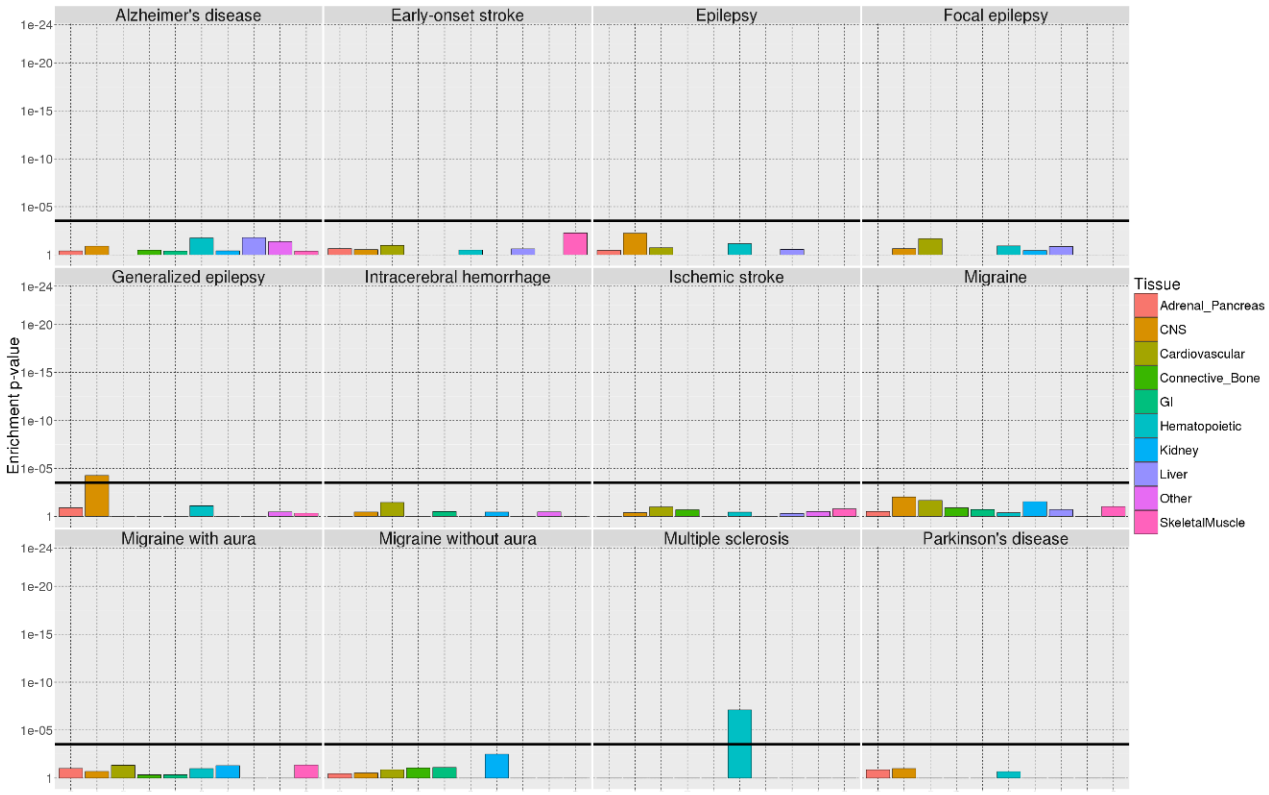


Fig. S7B. Tissue category heritability enrichment analysis in neurological phenotypes

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.

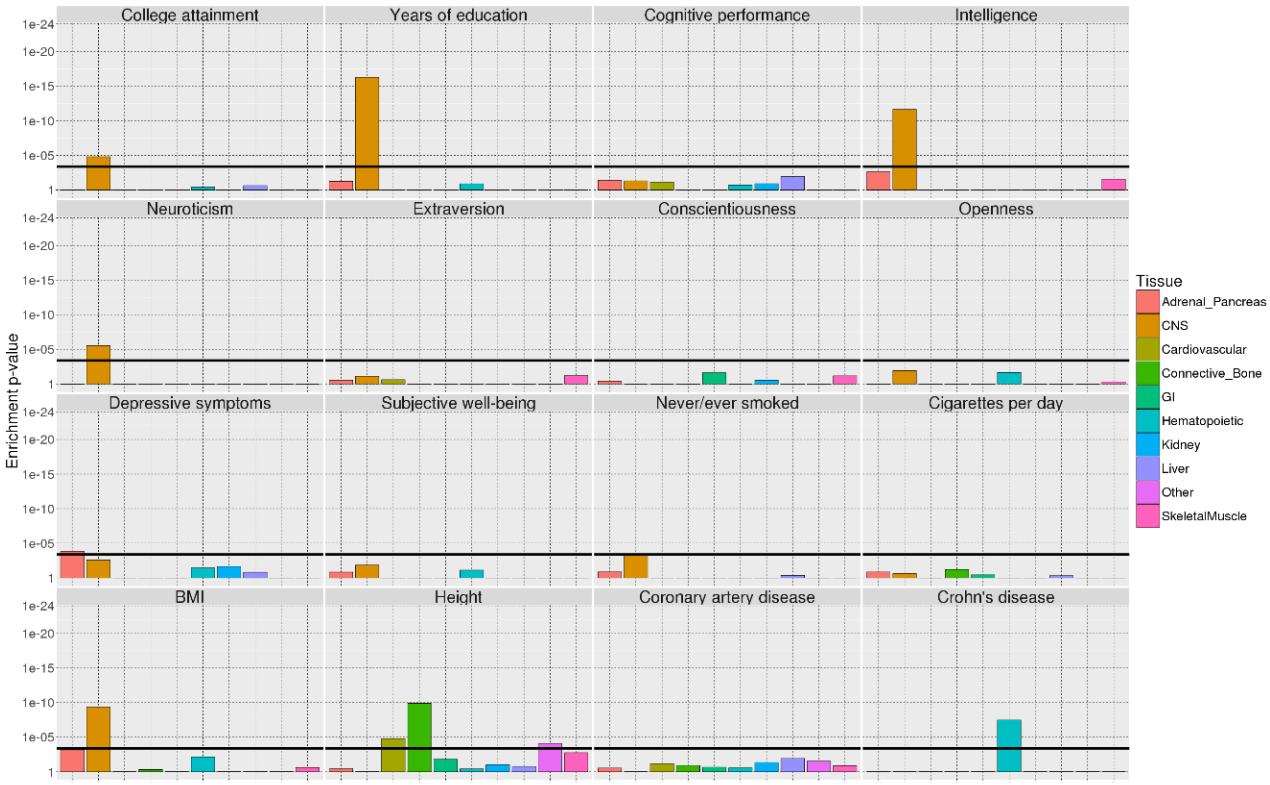


Fig. S7C. Tissue category heritability enrichment analysis in quantitative and additional phenotypes

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(*92*), and those for depressive symptoms in Okbay et al(*93*). The black line denotes significance threshold for Bonferroni multiple testing correction, $p=4.10 \times 10^{-4}$. Only positive enrichment reported.

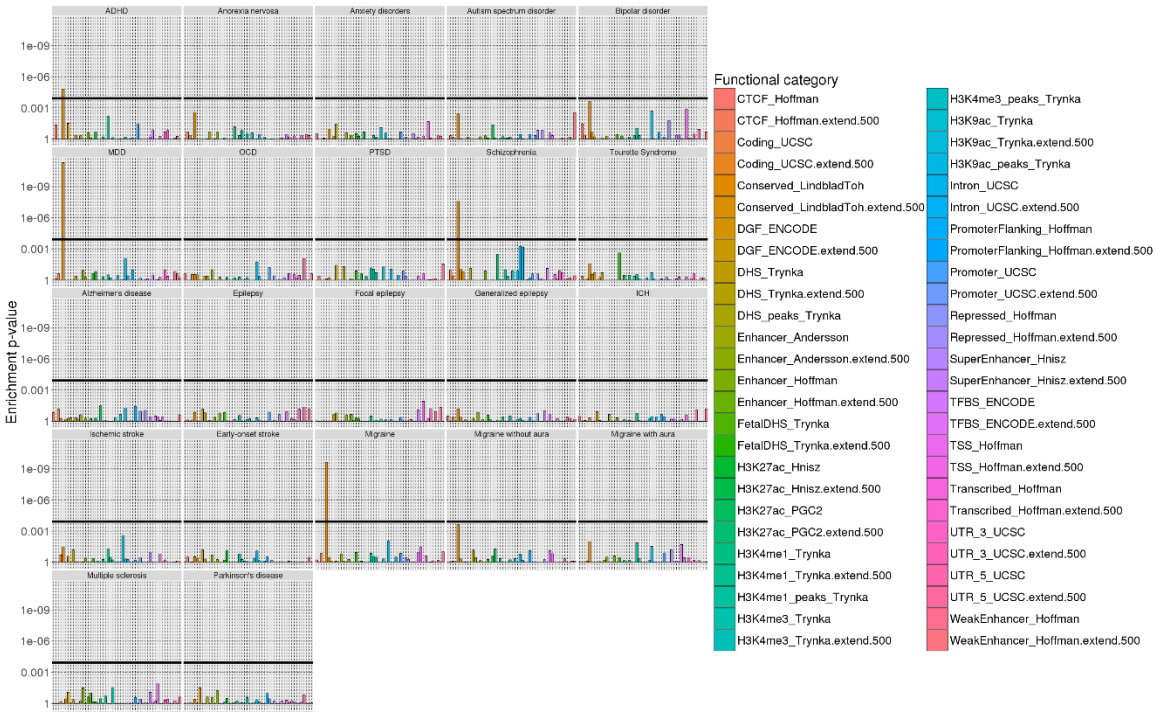


Fig. S7D. Partitioned heritability analysis across 53 functional categories in study disorders

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(*92*). The black line denotes significance threshold for Bonferroni multiple testing correction, $p=1.17 \times 10^{-4}$. Only positive enrichment reported.

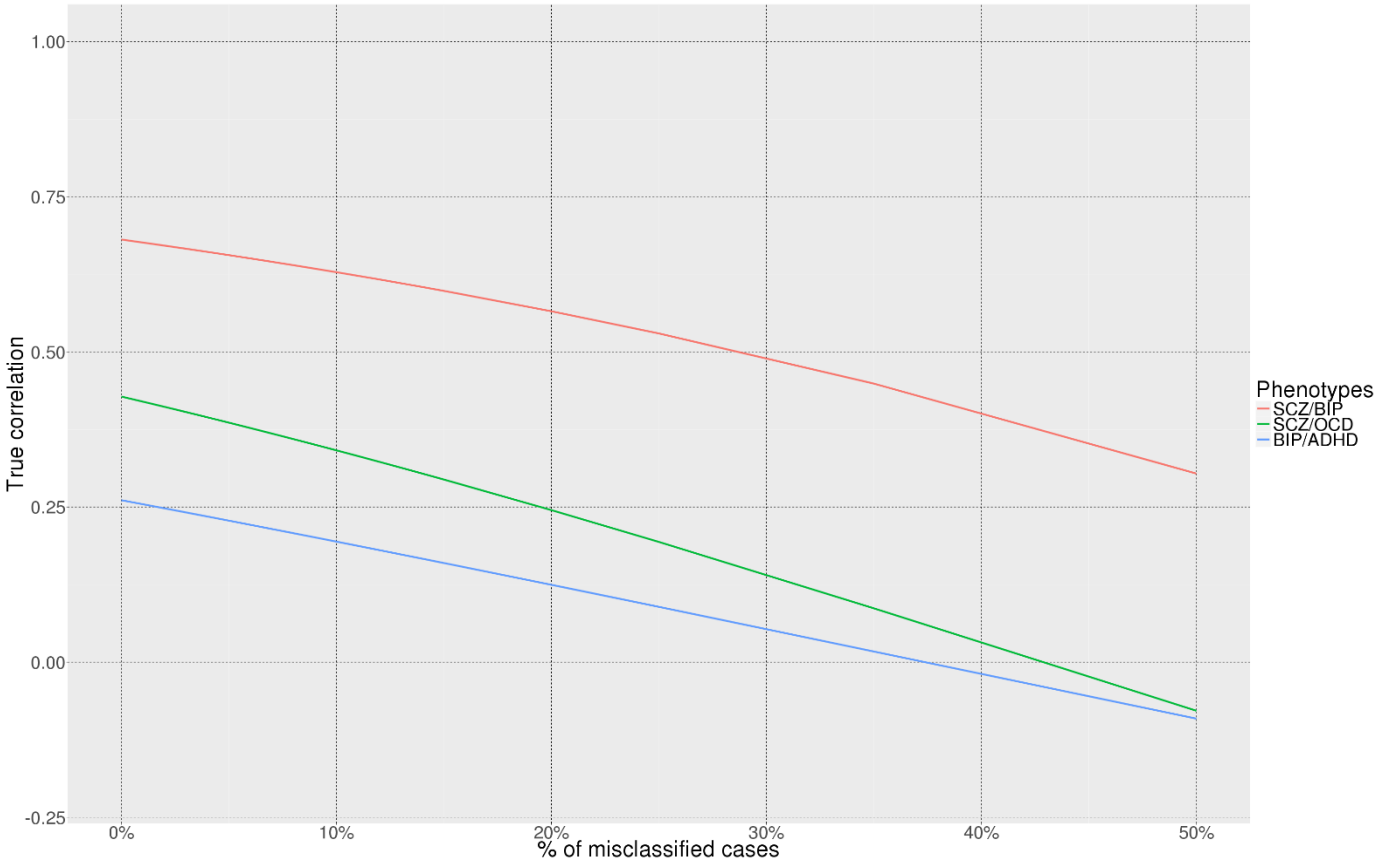


Fig. S8. Effect of case misclassification on true underlying genetic correlation given the observed results.

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.

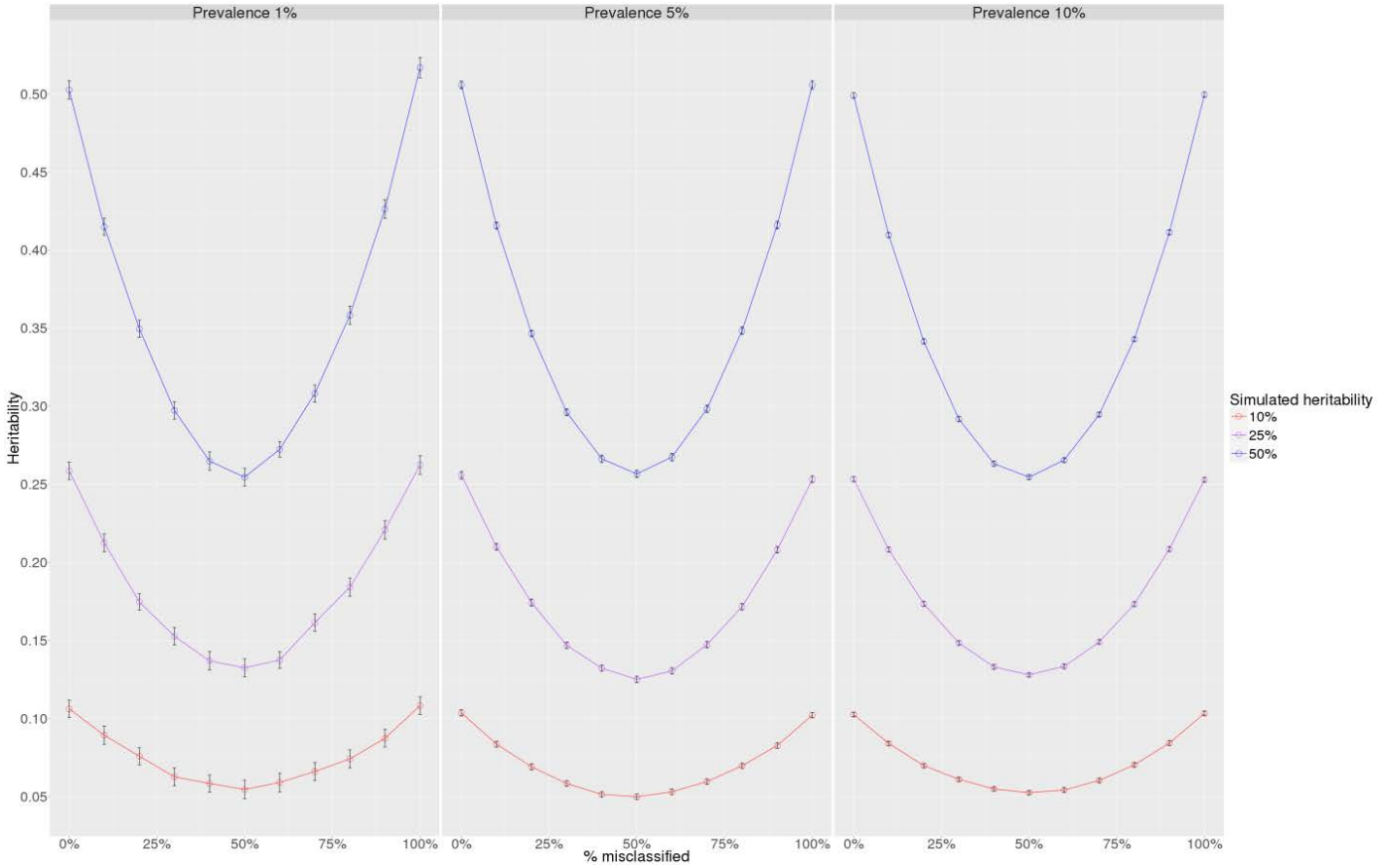


Fig. S9A. Effect of case misclassification on observed heritability

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

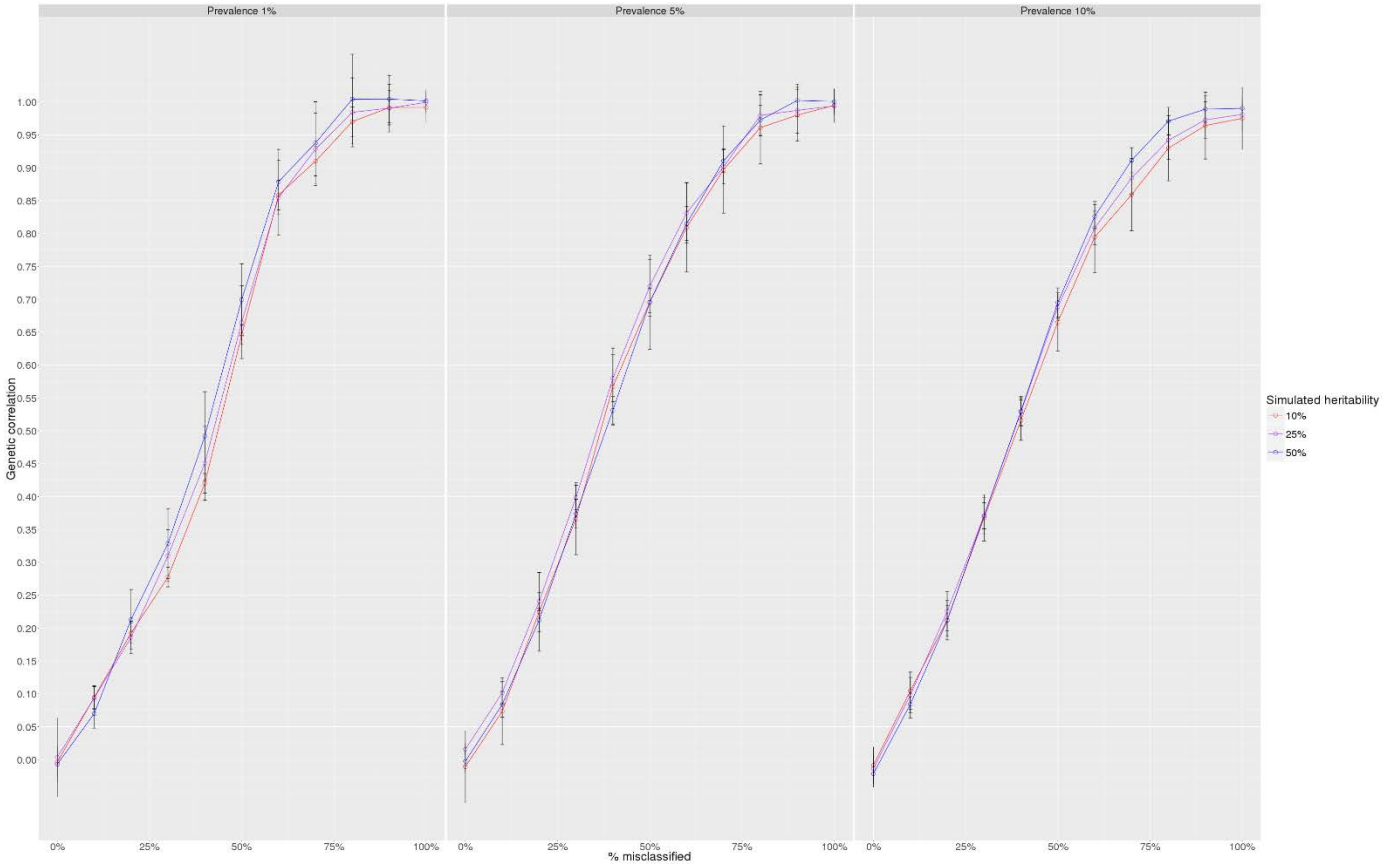


Fig. S9B. Effect of case misclassification on genetic correlation.

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

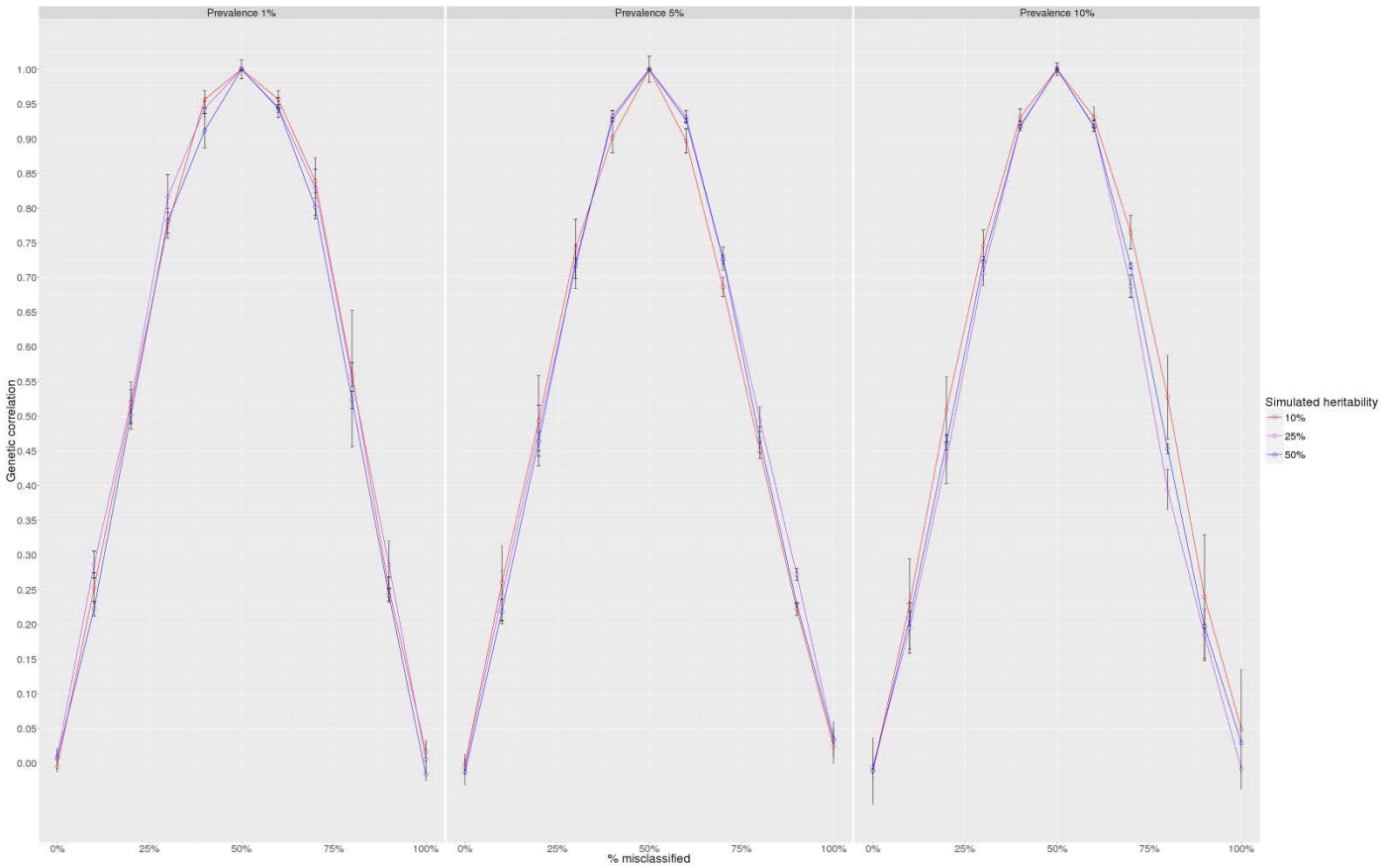


Fig. S9C. Effect of bidirectional case misclassification on genetic correlation

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

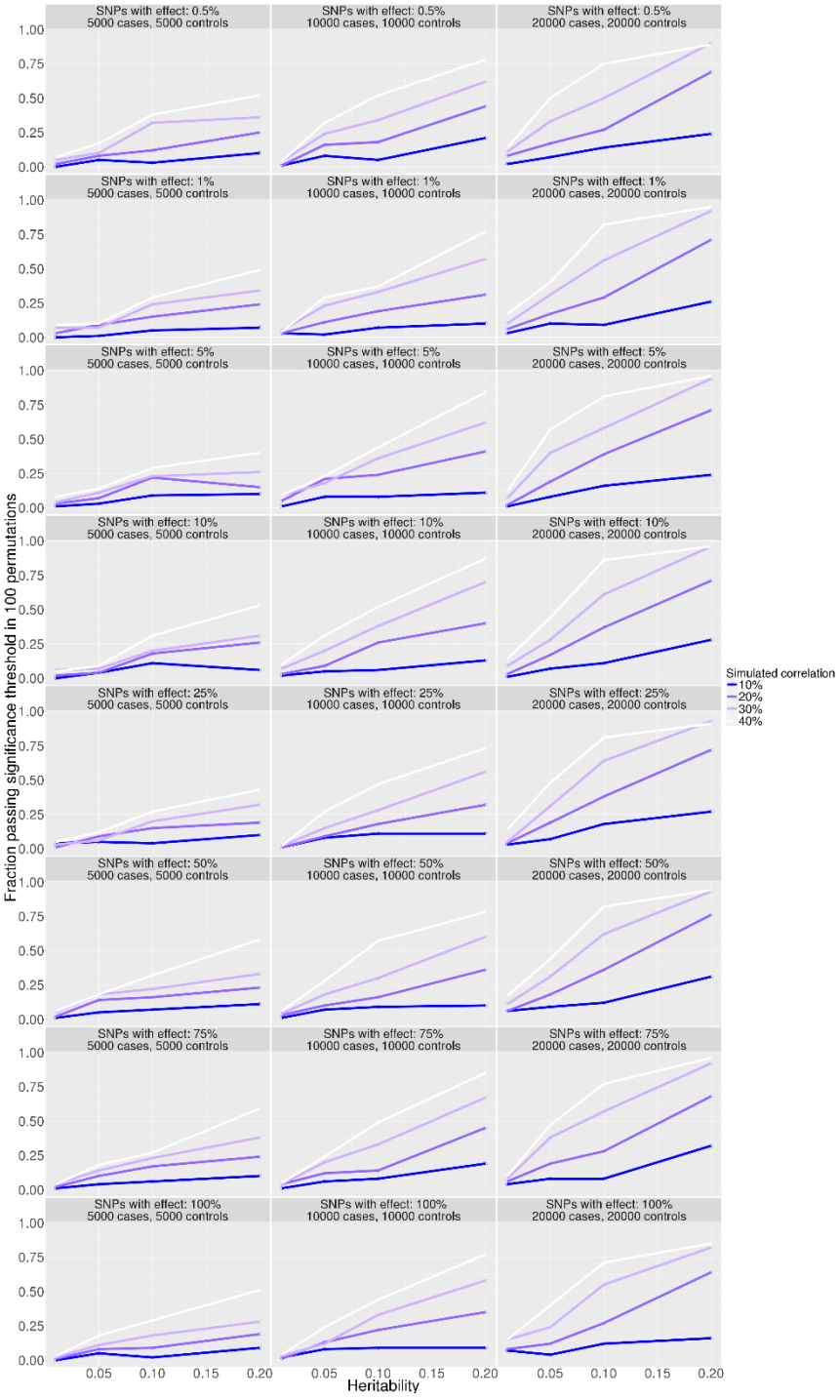


Fig. S10. Power analysis for detecting genetic correlations.

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(*94*), b(*95*), c(*96*), d(*97*), e(*98*), f(*99*), g(*100*), h(*101*), i(*102*), j(*103*), k(*104*), l(*105*), m(*106*), n(*107*), o(*108*), p(*109*), q(*110*), r(*111*), s(*112*), approximated from t(*113*), approximated from u(*114*), v(*115*), w(*116*), and x(*117*).

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	11,105	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	o
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	16,823	25,632	0.150	32	0.112 (0.006)	-	1.263	1.293	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	p
PTSD	2,424	7,113	0.080	23	0.148 (0.065)	-	1.107	1.102	1.014 (0.007)	d	q
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	r
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	s
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	t
Ischemic stroke	10,307	19,326	0.010	71	0.038 (0.010)	-	1.065	1.066	1.032 (0.006)	i	u
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	v
Migraine with aura	6,332	142,817	0.075	30	0.124 (0.024)	-	1.077	1.087	1.003 (0.007)	j	w
Migraine without aura	8,348	136,758	0.130	30	0.208 (0.025)	-	1.080	1.085	1.033 (0.007)	j	w
Multiple sclerosis	5,545	12,153	0.002	30	0.141 (0.016)	++	1.050	1.078	0.975 (0.008)	k	x
Parkinson's disease	5,333	12,019	0.002	60	0.105 (0.017)	+	1.026	1.044	0.965 (0.008)	l	x

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(*118*), b(*119*), c(*120*), d(*121*), e(*93*), f(*122*), g(*123*), h(*124*), i(*125*), j(*126*), k(*127*) and l(*128*).

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(*106*), b(*95*), c(*129*), d(*97*), e(*130*), f(*131*), g(*132*), h(*133*), and i(*134*). * - 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	0.112 (0.006)	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	0.534	-0.023	0.474
Effective sample size	1.039	0.002	0.320
Phenotype prevalence	0.341	-0.032	0.566
Age of onset	10.280	0.307	0.004*

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 (*135*), b(*136*), c(*137*). 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(*93*).

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

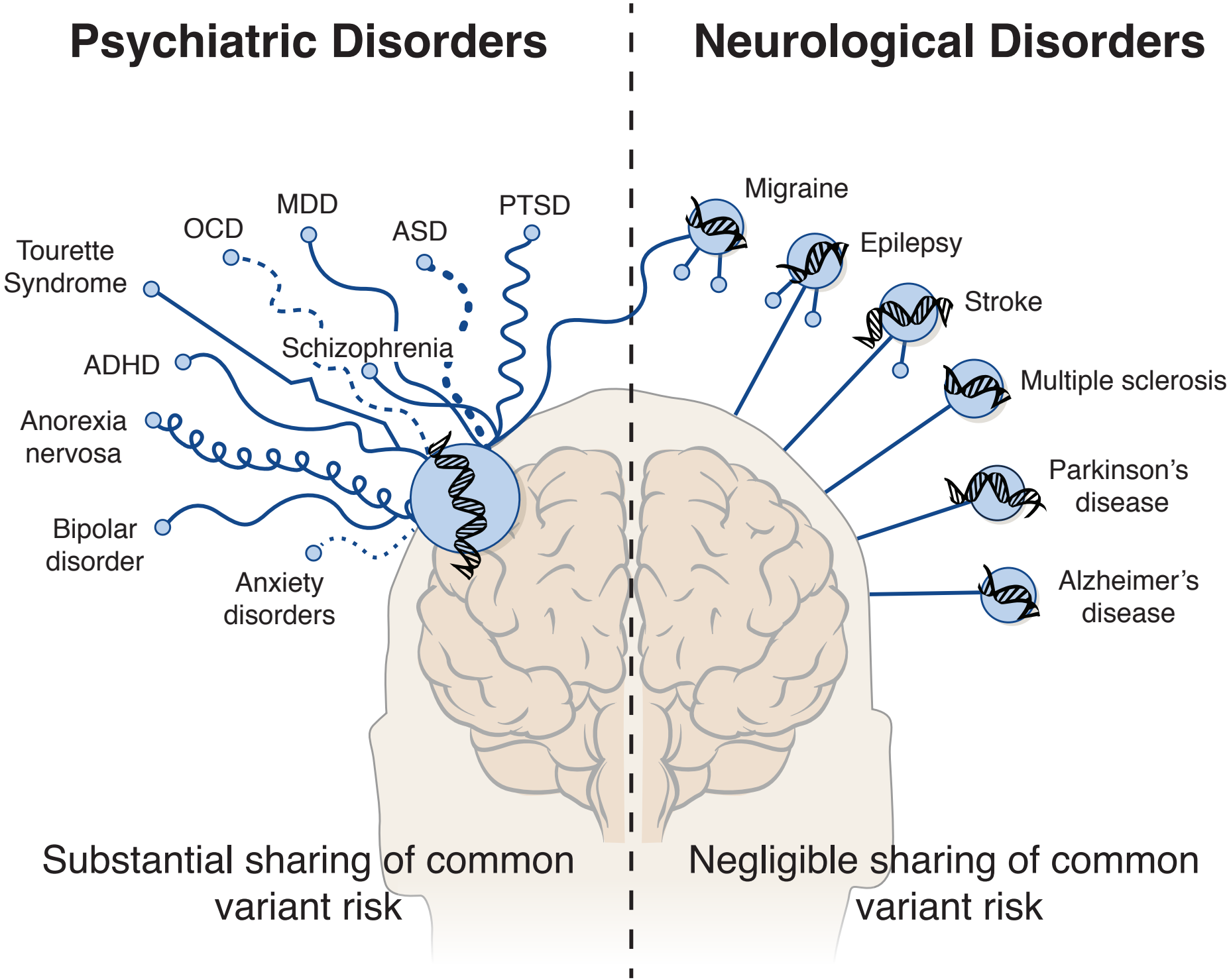
Table S11. Functional category enrichment analysis for behavioral-cognitive phenotypes and additional traits

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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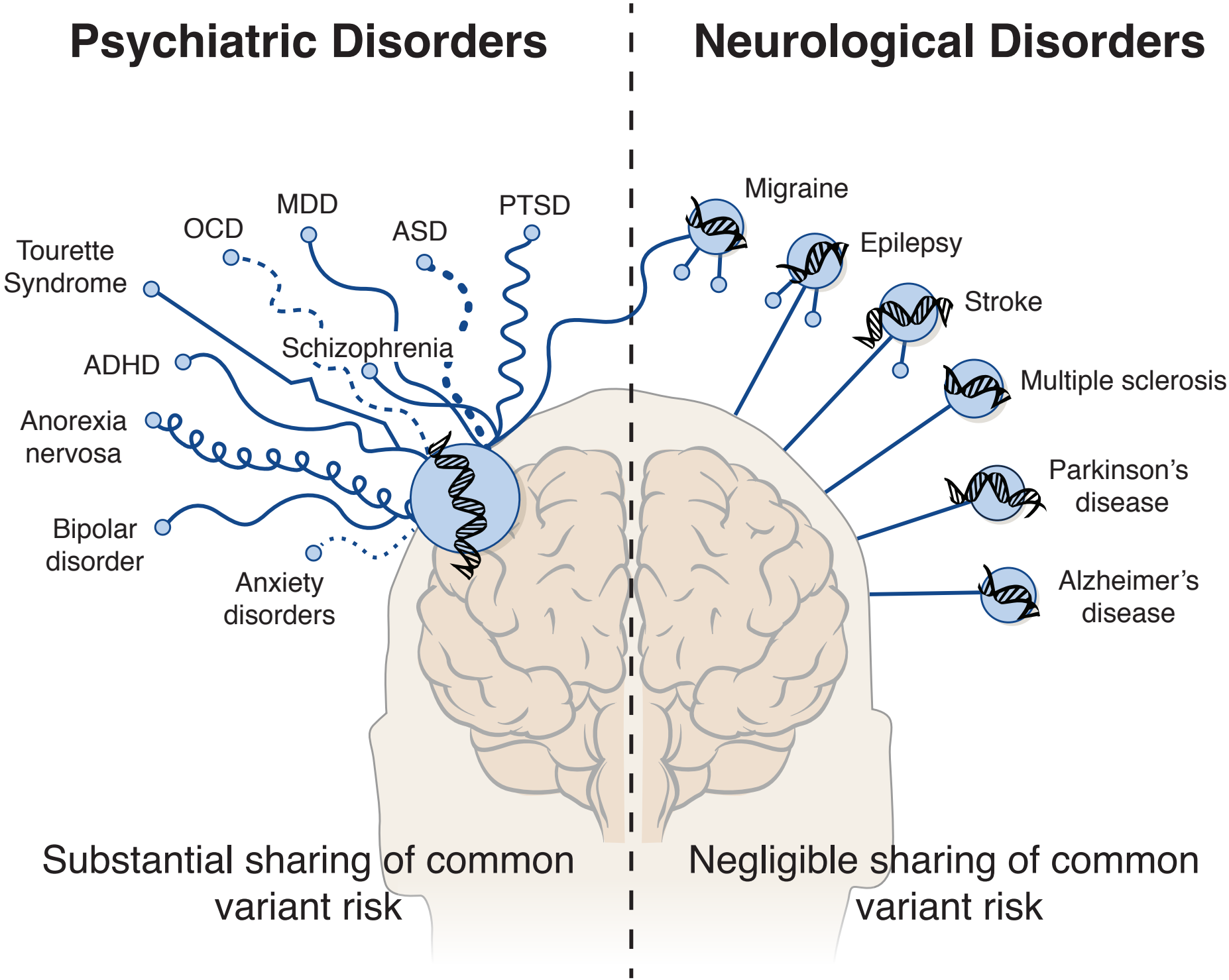

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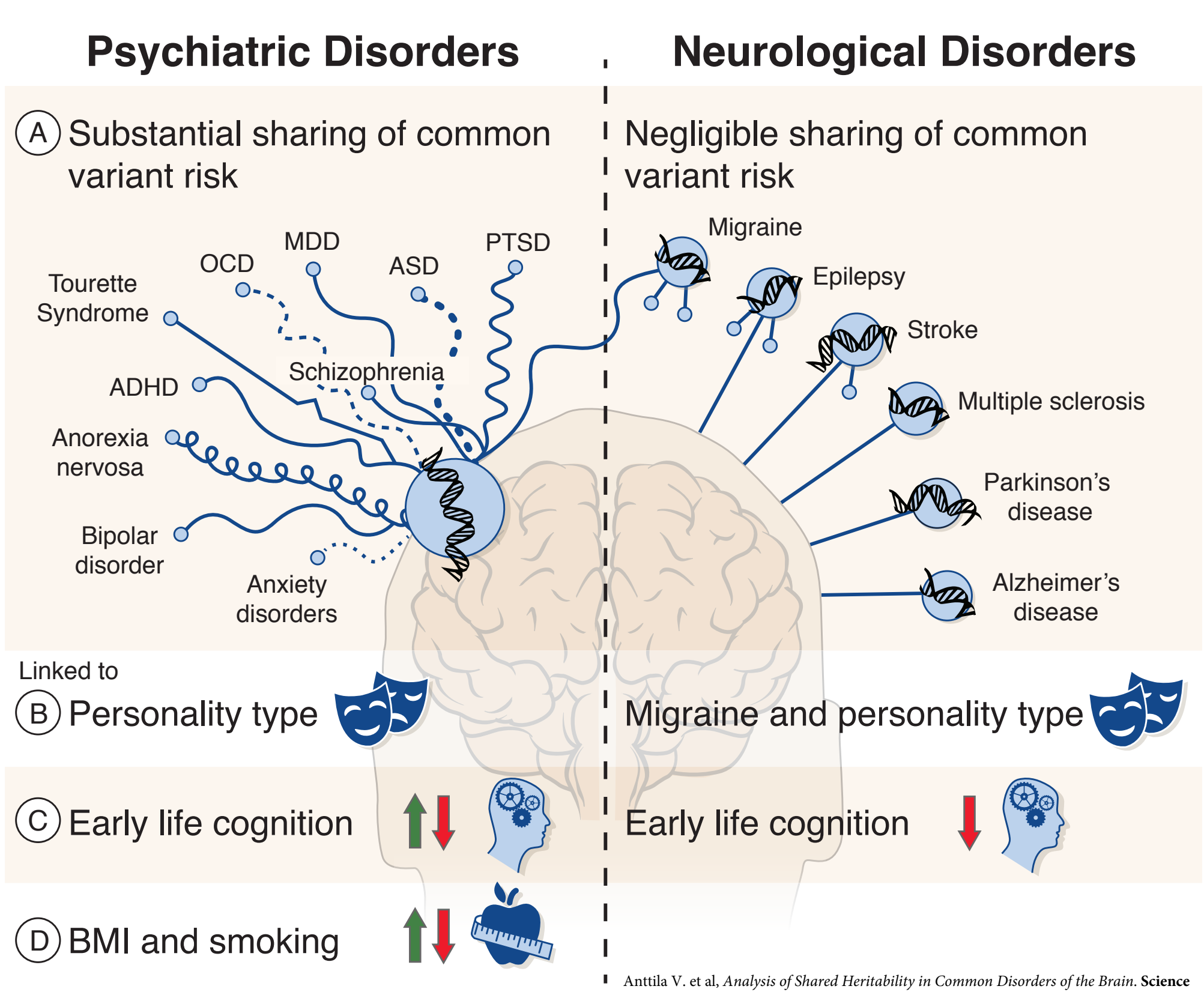

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Supplementary Table 7A: Disorder-disorder correlations.

Phenotype 1	Phenotype 2	Correlation	Correlation SE	P-value
ADHD	Alzheimer's disease	0.0845	-0.0945	0.3713
ADHD	Anorexia nervosa	-0.2135	-0.1048	0.0417
ADHD	Anxiety disorders	0.398	-0.1882	0.0345
ADHD	Autism spectrum disorder	0.0809	-0.0958	0.3986
ADHD	Bipolar disorder	0.2612	-0.0581	7.00E-06
ADHD	Epilepsy	0.1408	-0.121	0.2444
ADHD	Focal epilepsy	0.2655	-0.1801	0.1405
ADHD	Generalized epilepsy	0.0665	-0.0872	0.4455
ADHD	Intracerebral hemorrhage	0.134	-0.1433	0.3498
ADHD	Ischemic stroke	0.0438	-0.1214	0.7182
ADHD	Early-onset stroke	-0.0477	-0.1495	0.7498
ADHD	Major depressive disorder	0.5207	-0.0563	2.18E-20
ADHD	Migraine	0.2608	-0.0487	8.81E-08
ADHD	Migraine without aura	0.1703	-0.0759	0.0249
ADHD	Migraine with aura	0.1666	-0.1115	0.1352
ADHD	Multiple sclerosis	-0.0588	-0.0721	0.4148
ADHD	OCD	-0.0668	-0.0945	0.48
ADHD	Parkinson's disease	0.0262	-0.0906	0.7721
ADHD	PTSD	0.4488	-0.1706	8.50E-03
ADHD	Schizophrenia	0.2226	-0.0459	1.22E-06
ADHD	Tourette Syndrome	0.2504	-0.0843	0.003
Alzheimer's disease	Anorexia nervosa	-0.0151	-0.1113	0.8919
Alzheimer's disease	Anxiety disorders	0.077	-0.1783	0.6658
Alzheimer's disease	Autism spectrum disorder	0.0494	-0.0986	0.6162
Alzheimer's disease	Bipolar disorder	-0.0224	-0.0547	0.6821
Alzheimer's disease	Epilepsy	0.1577	-0.1325	0.2339
Alzheimer's disease	Focal epilepsy	0.4709	-0.2483	0.0579
Alzheimer's disease	Generalized epilepsy	-0.0154	-0.0911	0.8659
Alzheimer's disease	Intracerebral hemorrhage	-0.1145	-0.1968	0.5606
Alzheimer's disease	Ischemic stroke	0.1638	-0.1379	0.2348
Alzheimer's disease	Early-onset stroke	-0.0092	-0.1794	0.9592
Alzheimer's disease	Major depressive disorder	0.0414	-0.0696	0.5521
Alzheimer's disease	Migraine	-0.0144	-0.0606	0.8128
Alzheimer's disease	Migraine without aura	0.1054	-0.1042	0.3116
Alzheimer's disease	Migraine with aura	-0.1143	-0.1141	0.3165
Alzheimer's disease	Multiple sclerosis	-0.0394	-0.0832	0.6355
Alzheimer's disease	OCD	-0.0898	-0.1102	0.4152
Alzheimer's disease	Parkinson's disease	-0.0747	-0.0957	0.435
Alzheimer's disease	PTSD	-0.091	-0.1918	0.6352
Alzheimer's disease	Schizophrenia	0.0328	-0.0457	0.4722
Alzheimer's disease	Tourette Syndrome	0.0593	-0.0808	0.463
Anorexia nervosa	Anxiety disorders	0.0711	-0.203	0.7262
Anorexia nervosa	Autism spectrum disorder	0.0338	-0.1007	0.7371
Anorexia nervosa	Bipolar disorder	0.1904	-0.057	0.0008
Anorexia nervosa	Epilepsy	0.0405	-0.1357	0.7653
Anorexia nervosa	Focal epilepsy	-0.0019	-0.2159	0.993
Anorexia nervosa	Generalized epilepsy	0.0951	-0.1039	0.3602

Anorexia nervosa	Intracerebral hemorrhage	-0.399	-0.2034	0.0498
Anorexia nervosa	Ischemic stroke	-0.1623	-0.17	0.3396
Anorexia nervosa	Early-onset stroke	-0.3669	-0.2139	0.0862
Anorexia nervosa	Major depressive disorder	0.1599	-0.0663	0.0159
Anorexia nervosa	Migraine	0.0115	-0.0629	0.8555
Anorexia nervosa	Migraine without aura	0.0349	-0.0927	0.7068
Anorexia nervosa	Migraine with aura	0.2318	-0.1097	3.46E-02
Anorexia nervosa	Multiple sclerosis	-0.0098	-0.0818	0.9043
Anorexia nervosa	OCD	0.5168	-0.1172	1.04E-05
Anorexia nervosa	Parkinson's disease	0.0006	-0.1073	0.9952
Anorexia nervosa	PTSD	-0.0154	-0.1934	0.9365
Anorexia nervosa	Schizophrenia	0.2194	-0.0543	5.35E-05
Anorexia nervosa	Tourette Syndrome	-0.0468	-0.0955	0.6241
Anxiety disorders	Autism spectrum disorder	0.2539	-0.1945	0.1918
Anxiety disorders	Bipolar disorder	0.2091	-0.1139	0.0664
Anxiety disorders	Epilepsy	0.2606	-0.256	0.3086
Anxiety disorders	Focal epilepsy	0.1437	-0.4363	0.7419
Anxiety disorders	Generalized epilepsy	0.1473	-0.1602	0.3579
Anxiety disorders	Intracerebral hemorrhage	0.713	-0.3622	4.90E-02
Anxiety disorders	Ischemic stroke	0.1191	-0.2299	0.6044
Anxiety disorders	Early-onset stroke	0.1377	-0.2734	0.6146
Anxiety disorders	Major depressive disorder	0.7939	-0.159	5.97E-07
Anxiety disorders	Migraine	0.2417	-0.1042	0.0203
Anxiety disorders	Migraine without aura	0.2811	-0.1751	0.1084
Anxiety disorders	Migraine with aura	0.3014	-0.2155	0.1618
Anxiety disorders	Multiple sclerosis	0.0699	-0.1618	0.6659
Anxiety disorders	OCD	0.3745	-0.2084	0.0724
Anxiety disorders	Parkinson's disease	-0.0642	-0.1631	0.6939
Anxiety disorders	PTSD	-0.0028	-0.3413	0.9934
Anxiety disorders	Schizophrenia	0.2582	-0.0898	0.004
Anxiety disorders	Tourette Syndrome	0.1925	-0.1572	0.2207
Autism spectrum disorder	Bipolar disorder	0.0968	-0.0665	0.1455
Autism spectrum disorder	Epilepsy	-0.3372	-0.13	0.0095
Autism spectrum disorder	Focal epilepsy	-0.5292	-0.2346	0.0241
Autism spectrum disorder	Generalized epilepsy	-0.167	-0.095	0.0788
Autism spectrum disorder	Intracerebral hemorrhage	0.1239	-0.1904	0.5151
Autism spectrum disorder	Ischemic stroke	-0.1517	-0.1254	0.2265
Autism spectrum disorder	Early-onset stroke	-0.2436	-0.1631	0.1354
Autism spectrum disorder	Major depressive disorder	0.1552	-0.0602	0.0099
Autism spectrum disorder	Migraine	-0.077	-0.0516	0.1355
Autism spectrum disorder	Migraine without aura	0.1578	-0.0898	0.0788
Autism spectrum disorder	Migraine with aura	-0.0647	-0.108	0.549
Autism spectrum disorder	Multiple sclerosis	0.0243	-0.0839	0.7721
Autism spectrum disorder	OCD	0.001	-0.1064	0.9924
Autism spectrum disorder	Parkinson's disease	-0.1961	-0.1012	0.0525
Autism spectrum disorder	PTSD	0.0346	-0.1926	0.8575
Autism spectrum disorder	Schizophrenia	0.2082	-0.0577	0.0003
Autism spectrum disorder	Tourette Syndrome	0.0582	-0.0877	0.5067
Bipolar disorder	Epilepsy	-0.0839	-0.0719	0.2433
Bipolar disorder	Focal epilepsy	-0.0761	-0.1056	4.71E-01

Bipolar disorder	Generalized epilepsy	-0.0595	-0.0562	0.2896
Bipolar disorder	Intracerebral hemorrhage	-0.023	-0.1114	0.8363
Bipolar disorder	Ischemic stroke	0.178	-0.091	0.0506
Bipolar disorder	Early-onset stroke	0.2083	-0.1025	0.0423
Bipolar disorder	Major depressive disorder	0.3507	-0.0318	2.75E-28
Bipolar disorder	Migraine	-0.0251	-0.0302	0.4065
Bipolar disorder	Migraine without aura	-0.0486	-0.0532	3.61E-01
Bipolar disorder	Migraine with aura	0.001	-0.0676	0.9886
Bipolar disorder	Multiple sclerosis	0.0001	-0.0503	9.98E-01
Bipolar disorder	OCD	0.3108	-0.068	4.93E-06
Bipolar disorder	Parkinson's disease	0.0773	-0.0567	0.1724
Bipolar disorder	PTSD	0.0672	-0.0911	0.4608
Bipolar disorder	Schizophrenia	0.6808	-0.021	2.1E-230
Bipolar disorder	Tourette Syndrome	0.0309	-0.053	0.5597
Epilepsy	Focal epilepsy	0.6176	-0.1233	5.51E-07
Epilepsy	Generalized epilepsy	0.7719	-0.0587	1.53E-39
Epilepsy	Intracerebral hemorrhage	0.1541	-0.223	0.4896
Epilepsy	Ischemic stroke	0.3885	-0.2484	0.1178
Epilepsy	Early-onset stroke	0.3694	-0.225	0.1006
Epilepsy	Major depressive disorder	0.1706	-0.0816	0.0366
Epilepsy	Migraine	0.219	-0.0722	0.0024
Epilepsy	Migraine without aura	0.0912	-0.1296	0.4818
Epilepsy	Migraine with aura	0.4665	-0.1491	0.0018
Epilepsy	Multiple sclerosis	-0.048	-0.1297	0.7114
Epilepsy	OCD	-0.4081	-0.1283	0.0015
Epilepsy	Parkinson's disease	0.0459	-0.141	0.7448
Epilepsy	PTSD	0.1534	-0.2453	0.5318
Epilepsy	Schizophrenia	-0.0268	-0.0649	0.6798
Epilepsy	Tourette Syndrome	-0.1876	-0.1159	0.1054
Focal epilepsy	Generalized epilepsy	0.1549	-0.1796	0.3884
Focal epilepsy	Intracerebral hemorrhage	0.806	-0.3949	0.0412
Focal epilepsy	Ischemic stroke	0.6156	-0.3947	0.1189
Focal epilepsy	Early-onset stroke	0.7506	-0.401	0.0612
Focal epilepsy	Major depressive disorder	0.3305	-0.1413	0.0194
Focal epilepsy	Migraine	0.3351	-0.1294	0.0096
Focal epilepsy	Migraine without aura	0.3295	-0.2065	0.1106
Focal epilepsy	Migraine with aura	0.6517	-0.2624	0.013
Focal epilepsy	Multiple sclerosis	0.0504	-0.1993	0.8004
Focal epilepsy	OCD	-0.4762	-0.2284	0.0371
Focal epilepsy	Parkinson's disease	0.1685	-0.2197	0.443
Focal epilepsy	PTSD	0.3863	-0.3735	0.3009
Focal epilepsy	Schizophrenia	-0.0102	-0.0913	0.9114
Focal epilepsy	Tourette Syndrome	-0.3396	-0.1859	0.0678
Generalized epilepsy	Intracerebral hemorrhage	-0.1502	-0.165	0.3627
Generalized epilepsy	Ischemic stroke	-0.0715	-0.1733	0.68
Generalized epilepsy	Early-onset stroke	0.0333	-0.2171	0.878
Generalized epilepsy	Major depressive disorder	0.0231	-0.0645	0.7207
Generalized epilepsy	Migraine	0.0624	-0.0518	0.2284
Generalized epilepsy	Migraine without aura	-0.0494	-0.0981	0.6144
Generalized epilepsy	Migraine with aura	0.1661	-0.1115	0.1362

Generalized epilepsy	Multiple sclerosis	-0.0977	-0.0866	0.2593
Generalized epilepsy	OCD	-0.1928	-0.0931	0.0384
Generalized epilepsy	Parkinson's disease	0.0011	-0.0978	0.9909
Generalized epilepsy	PTSD	0.0827	-0.1507	0.5829
Generalized epilepsy	Schizophrenia	-0.0249	-0.0521	0.6328
Generalized epilepsy	Tourette Syndrome	0.0013	-0.0783	0.9872
Intracerebral hemorrhage	Ischemic stroke	0.4997	-0.2212	0.0239
Intracerebral hemorrhage	Early-onset stroke	0.3607	-0.319	0.2583
Intracerebral hemorrhage	Major depressive disorder	0.1333	-0.1209	2.70E-01
Intracerebral hemorrhage	Migraine	-0.003	-0.0979	0.9754
Intracerebral hemorrhage	Migraine without aura	-0.1632	-0.1773	0.3574
Intracerebral hemorrhage	Migraine with aura	-0.0445	-0.2078	0.8306
Intracerebral hemorrhage	Multiple sclerosis	-0.2004	-0.1483	0.1766
Intracerebral hemorrhage	OCD	0.0987	-0.1686	0.5582
Intracerebral hemorrhage	Parkinson's disease	-0.0577	-0.1725	0.7378
Intracerebral hemorrhage	PTSD	-0.1799	-0.3111	0.563
Intracerebral hemorrhage	Schizophrenia	0.0941	-0.0799	0.2386
Intracerebral hemorrhage	Tourette Syndrome	0.1324	-0.1516	0.3827
Ischemic stroke	Early-onset stroke	1.818	0.308	3.43E-09
Ischemic stroke	Major depressive disorder	0.2263	-0.0953	0.0176
Ischemic stroke	Migraine	0.0835	-0.0809	0.3024
Ischemic stroke	Migraine without aura	-0.0481	-0.1402	0.7317
Ischemic stroke	Migraine with aura	0.2892	-0.1751	0.0986
Ischemic stroke	Multiple sclerosis	0.0823	-0.1119	0.4622
Ischemic stroke	OCD	-0.0142	-0.1322	0.9145
Ischemic stroke	Parkinson's disease	0.1146	-0.1186	0.3338
Ischemic stroke	PTSD	0.6276	-0.2891	0.0299
Ischemic stroke	Schizophrenia	0.2192	-0.0814	7.00E-03
Ischemic stroke	Tourette Syndrome	0.0368	-0.1212	7.61E-01
Early-onset stroke	Major depressive disorder	0.3313	-0.1106	0.0027
Early-onset stroke	Migraine	0.0253	-0.0983	0.7968
Early-onset stroke	Migraine without aura	-0.3	-0.1922	0.1187
Early-onset stroke	Migraine with aura	0.1678	-0.1942	0.3875
Early-onset stroke	Multiple sclerosis	-0.1442	-0.1537	3.48E-01
Early-onset stroke	OCD	-0.0986	-0.1802	0.5842
Early-onset stroke	Parkinson's disease	0.0456	-0.1805	8.00E-01
Early-onset stroke	PTSD	0.2004	-0.3024	5.08E-01
Early-onset stroke	Schizophrenia	0.1106	-0.0771	0.1514
Early-onset stroke	Tourette Syndrome	-0.0448	-0.1532	0.7697
Major depressive disorder	Migraine	0.3232	-0.0331	1.42E-22
Major depressive disorder	Migraine without aura	0.2251	-0.0556	5.23E-05
Major depressive disorder	Migraine with aura	0.278	-0.0715	1.00E-04
Major depressive disorder	Multiple sclerosis	0.0241	-0.0504	6.32E-01
Major depressive disorder	OCD	0.2276	-0.0601	0.0002
Major depressive disorder	Parkinson's disease	0.0794	-0.0586	0.1752
Major depressive disorder	PTSD	0.5192	-0.1492	0.0005
Major depressive disorder	Schizophrenia	0.3377	-0.0282	5.45E-33
Major depressive disorder	Tourette Syndrome	0.2133	-0.055	0.0001
Migraine	Migraine without aura	0.9103	-0.0425	1.1E-101
Migraine	Migraine with aura	1.1103	-0.0917	9.74E-34

Migraine	Multiple sclerosis	0.022	-0.043	0.6091
Migraine	OCD	0.0857	-0.0618	0.1653
Migraine	Parkinson's disease	-0.0258	-0.0542	0.6337
Migraine	PTSD	0.1645	-0.1026	0.1088
Migraine	Schizophrenia	-0.0839	-0.0269	0.0018
Migraine	Tourette Syndrome	0.1916	-0.0447	1.8E-05
Migraine without aura	Migraine with aura	0.4763	-0.111	1.79E-05
Migraine without aura	Multiple sclerosis	0.1787	-0.0852	0.0358
Migraine without aura	OCD	0.0105	-0.0912	9.08E-01
Migraine without aura	Parkinson's disease	-0.0648	-0.0816	4.27E-01
Migraine without aura	PTSD	-0.0699	-0.1628	0.6675
Migraine without aura	Schizophrenia	-0.068	-0.0442	0.1236
Migraine without aura	Tourette Syndrome	0.0503	-0.0819	0.5396
Migraine with aura	Multiple sclerosis	0.0151	-0.0924	0.8699
Migraine with aura	OCD	0.1102	-0.1075	0.3055
Migraine with aura	Parkinson's disease	-0.086	-0.1304	0.5096
Migraine with aura	PTSD	0.1205	-0.2096	0.5654
Migraine with aura	Schizophrenia	-0.0958	-0.0576	0.0963
Migraine with aura	Tourette Syndrome	0.2914	-0.1197	0.0149
Multiple sclerosis	OCD	0.0807	-0.091	0.375
Multiple sclerosis	Parkinson's disease	0.0453	-0.0774	0.5583
Multiple sclerosis	PTSD	0.0385	-0.1427	0.7874
Multiple sclerosis	Schizophrenia	0.0867	-0.0401	0.0308
Multiple sclerosis	Tourette Syndrome	-0.0171	-0.0745	0.8184
OCD	Parkinson's disease	0.1301	-0.1074	0.2256
OCD	PTSD	0.2815	-0.1847	0.1275
OCD	Schizophrenia	0.3273	-0.0588	2.58E-08
OCD	Tourette Syndrome	0.4285	-0.092	3.18E-06
Parkinson's disease	PTSD	0.0253	-0.1949	0.8967
Parkinson's disease	Schizophrenia	0.0545	-0.0534	0.3073
Parkinson's disease	Tourette Syndrome	0.0904	-0.0965	0.3487
PTSD	Schizophrenia	0.1471	-0.088	0.0945
PTSD	Tourette Syndrome	-0.1382	-0.1599	0.3877
Schizophrenia	Tourette Syndrome	0.0627	-0.0416	0.1313

Significance threshold
$p < 3.35 \times 10\text{-}4$

Supplementary Table 12A: Tissue enrichment analysis results for brain disorc

Significant enrichments in bold

Psychiatric disorders

Phenotype	Tissue	Enrichment	SE	Coeff.	SE	Coeff. z-score
Schizophrenia	CNS	3.25	0.18	1.65E-07	1.92E-08	**8.62**
Bipolar disorder	CNS	3.81	0.32	1.43E-07	2.28E-08	**6.28**
Major depressive disorder	CNS	2.76	0.30	2.03E-08	3.58E-09	**5.68**
Tourette Syndrome	CNS	4.23	0.78	2.32E-07	5.29E-08	**4.39**
ADHD	CNS	2.03	0.74	2.02E-08	6.90E-09	2.93
OCD	CNS	3.93	1.08	1.51E-07	6.46E-08	2.34
Autism spectrum disorder	Liver	3.03	1.12	1.96E-07	8.48E-08	2.31
Bipolar disorder	Hematopoietic	1.99	0.22	4.52E-08	2.34E-08	1.93
Autism spectrum disorder	Other	2.20	0.56	1.33E-07	7.21E-08	1.84
OCD	Kidney	8.66	2.78	2.21E-07	1.20E-07	1.84
OCD	GI	3.07	1.10	1.35E-07	7.40E-08	1.82
Bipolar disorder	Adrenal_Pancreas	3.57	0.50	5.69E-08	3.20E-08	1.78
Tourette Syndrome	Hematopoietic	2.18	0.57	9.73E-08	5.81E-08	1.68
Schizophrenia	Adrenal_Pancreas	2.66	0.30	3.95E-08	2.74E-08	1.44
Anxiety disorders	Connective_Bone	12.32	6.99	7.43E-08	5.38E-08	1.38
Schizophrenia	Hematopoietic	1.53	0.16	2.81E-08	2.15E-08	1.31
Tourette Syndrome	SkeletalMuscle	3.06	1.09	1.00E-07	7.87E-08	1.28
ADHD	SkeletalMuscle	1.39	1.05	1.27E-08	1.04E-08	1.22
Autism spectrum disorder	Kidney	2.59	1.69	1.33E-07	1.37E-07	0.97
Major depressive disorder	Adrenal_Pancreas	2.69	0.50	5.91E-09	6.26E-09	0.94
Tourette Syndrome	Adrenal_Pancreas	2.83	1.25	7.17E-08	8.37E-08	0.86
Major depressive disorder	Connective_Bone	1.96	0.41	3.93E-09	5.27E-09	0.74
Anxiety disorders	CNS	8.03	4.33	2.78E-08	3.87E-08	0.72
Autism spectrum disorder	CNS	1.89	0.62	4.13E-08	6.08E-08	0.68
OCD	Adrenal_Pancreas	4.12	1.70	7.08E-08	1.05E-07	0.67
Anxiety disorders	Hematopoietic	5.44	3.15	2.70E-08	4.92E-08	0.55
Anorexia nervosa	Kidney	1.16	2.87	5.40E-08	1.03E-07	0.52
Autism spectrum disorder	SkeletalMuscle	1.86	0.86	4.54E-08	9.05E-08	0.50
Anorexia nervosa	CNS	0.99	1.00	2.10E-08	4.96E-08	0.42
Autism spectrum disorder	Adrenal_Pancreas	1.90	0.99	3.08E-08	9.76E-08	0.32
Bipolar disorder	SkeletalMuscle	2.96	0.42	6.97E-09	2.97E-08	0.23
Anorexia nervosa	GI	0.51	1.13	1.14E-08	5.64E-08	0.20
OCD	SkeletalMuscle	3.27	1.50	1.63E-08	8.92E-08	0.18
Autism spectrum disorder	Connective_Bone	1.36	0.72	2.82E-09	7.87E-08	0.04
Tourette Syndrome	Liver	1.60	1.26	2.49E-09	7.77E-08	0.03
Anorexia nervosa	Adrenal_Pancreas	1.19	1.87	1.50E-09	8.28E-08	0.02
Anorexia nervosa	SkeletalMuscle	0.90	1.50	-1.88E-09	6.85E-08	-0.03
Autism spectrum disorder	Hematopoietic	1.46	0.48	-3.43E-09	6.75E-08	-0.05
Major depressive disorder	Hematopoietic	1.07	0.24	-3.96E-10	4.25E-09	-0.09
Anorexia nervosa	Hematopoietic	-0.09	0.87	-5.42E-09	5.77E-08	-0.09
Anorexia nervosa	Other	0.88	0.98	-8.19E-09	5.51E-08	-0.15
OCD	Other	1.40	1.08	-1.32E-08	8.03E-08	-0.16

Anorexia nervosa	Connective_Bone	0.04	1.29	-1.08E-08	5.79E-08	-0.19
ADHD	Cardiovascular	0.42	1.10	-2.55E-09	1.19E-08	-0.21
OCD	Cardiovascular	2.89	1.56	-4.71E-08	9.27E-08	-0.51
OCD	Liver	2.74	1.74	-4.50E-08	8.65E-08	-0.52
ADHD	Hematopoietic	0.33	0.58	-4.79E-09	8.19E-09	-0.58
Schizophrenia	SkeletalMuscle	2.26	0.27	-1.58E-08	2.58E-08	-0.61
Anorexia nervosa	Liver	-0.19	1.69	-4.00E-08	6.18E-08	-0.65
ADHD	Other	0.17	0.71	-6.21E-09	9.15E-09	-0.68
Autism spectrum disorder	GI	1.43	0.69	-5.52E-08	7.86E-08	-0.70
Bipolar disorder	Connective_Bone	2.33	0.36	-1.87E-08	2.43E-08	-0.77
ADHD	Liver	0.19	1.22	-7.28E-09	9.42E-09	-0.77
Major depressive disorder	SkeletalMuscle	2.09	0.41	-4.02E-09	5.01E-09	-0.80
Anxiety disorders	Cardiovascular	6.90	4.65	-5.47E-08	6.53E-08	-0.84
OCD	Hematopoietic	0.21	0.93	-7.39E-08	8.44E-08	-0.87
Tourette Syndrome	Connective_Bone	1.09	0.99	-6.87E-08	7.07E-08	-0.97
Anxiety disorders	Other	3.90	3.00	-5.13E-08	5.12E-08	-1.00
ADHD	Connective_Bone	-0.02	0.96	-8.75E-09	8.65E-09	-1.01
Major depressive disorder	Kidney	2.15	0.68	-8.00E-09	7.35E-09	-1.09
Tourette Syndrome	GI	1.39	0.76	-7.42E-08	6.33E-08	-1.17
Tourette Syndrome	Other	1.18	0.72	-8.30E-08	7.00E-08	-1.19
Schizophrenia	Connective_Bone	1.80	0.25	-2.70E-08	2.27E-08	-1.19
OCD	Connective_Bone	1.19	1.29	-9.69E-08	7.66E-08	-1.27
Bipolar disorder	Liver	2.39	0.53	-3.80E-08	2.81E-08	-1.35
Tourette Syndrome	Cardiovascular	1.15	1.18	-1.21E-07	8.65E-08	-1.40
Autism spectrum disorder	Cardiovascular	1.35	0.92	-1.46E-07	1.02E-07	-1.43
ADHD	Kidney	-1.33	1.95	-2.25E-08	1.56E-08	-1.45
ADHD	Adrenal_Pancreas	-0.45	1.21	-1.56E-08	1.04E-08	-1.49
Anorexia nervosa	Cardiovascular	0.44	1.55	-1.03E-07	6.70E-08	-1.54
Tourette Syndrome	Kidney	-0.69	2.09	-1.76E-07	1.12E-07	-1.57
Schizophrenia	Liver	1.86	0.30	-4.14E-08	2.33E-08	-1.78
Major depressive disorder	Other	1.31	0.29	-8.82E-09	4.56E-09	-1.93
Anxiety disorders	SkeletalMuscle	4.23	4.48	-1.08E-07	5.52E-08	-1.96
Anxiety disorders	Adrenal_Pancreas	2.13	5.00	-1.33E-07	6.48E-08	-2.06
Anxiety disorders	Liver	2.73	4.89	-1.22E-07	5.82E-08	-2.09
Schizophrenia	Cardiovascular	2.13	0.28	-6.25E-08	2.88E-08	-2.17
Major depressive disorder	Liver	1.40	0.49	-1.20E-08	5.50E-09	-2.18
Bipolar disorder	Cardiovascular	2.37	0.43	-7.04E-08	3.05E-08	-2.31
Anxiety disorders	Kidney	1.76	7.29	-1.86E-07	7.96E-08	-2.34
Bipolar disorder	Kidney	2.04	0.79	-9.80E-08	4.00E-08	-2.45
ADHD	GI	-0.64	0.78	-1.93E-08	7.83E-09	-2.46
Bipolar disorder	Other	1.75	0.28	-6.08E-08	2.44E-08	-2.50
Bipolar disorder	GI	1.66	0.29	-6.83E-08	2.29E-08	-2.98
Major depressive disorder	Cardiovascular	1.81	0.48	-1.94E-08	6.09E-09	-3.19
Anxiety disorders	GI	-0.12	3.60	-1.83E-07	5.37E-08	-3.41
Schizophrenia	Other	1.31	0.17	-9.80E-08	2.37E-08	-4.13
Schizophrenia	Kidney	1.16	0.43	-1.40E-07	3.16E-08	-4.42
Schizophrenia	GI	1.15	0.20	-1.10E-07	2.45E-08	-4.51

Major depressive disorder	GI	0.74	0.31	-2.12E-08	4.33E-09	-4.89

lers, behavioral-cognitive phenotypes, and additional traits.

Neurological disorders

Phenotype	Tissue	Enrichment	SE	Coeff.	SE	Coeff. z-score
Multiple sclerosis	Hematopoietic	4.90	0.54	2.85E-07	5.44E-08	**5.24**
Generalized epilepsy	CNS	2.79	0.60	1.68E-07	4.34E-08	**3.87**
Migraine without aura	Kidney	8.80	2.14	2.96E-08	1.09E-08	2.72
Early-onset stroke	SkeletalMuscle	6.71	2.86	1.65E-07	6.49E-08	2.55
Epilepsy	CNS	2.47	1.01	6.62E-08	2.62E-08	2.53
Migraine	CNS	3.39	0.30	7.64E-09	3.25E-09	2.35
Alzheimer's disease	Liver	8.32	2.02	4.29E-08	2.01E-08	2.13
Alzheimer's disease	Hematopoietic	5.13	0.91	3.68E-08	1.76E-08	2.10
Migraine	Cardiovascular	4.30	0.51	9.58E-09	4.74E-09	2.02
Focal epilepsy	Cardiovascular	2.47	3.34	9.19E-08	4.55E-08	2.02
Migraine	Kidney	5.61	0.95	1.49E-08	7.83E-09	1.91
Intracerebral hemorrhage	Cardiovascular	9.75	7.68	6.35E-07	3.52E-07	1.81
Migraine with aura	SkeletalMuscle	6.80	1.67	1.24E-08	7.21E-09	1.72
Alzheimer's disease	Other	4.27	0.97	2.86E-08	1.67E-08	1.71
Migraine with aura	Cardiovascular	6.76	1.80	1.22E-08	7.24E-09	1.69
Migraine with aura	Kidney	10.13	2.99	1.69E-08	1.02E-08	1.65
Epilepsy	Hematopoietic	1.42	0.83	3.84E-08	2.62E-08	1.46
Migraine without aura	GI	4.00	0.91	8.59E-09	6.03E-09	1.42
Generalized epilepsy	Hematopoietic	1.52	0.53	6.48E-08	4.59E-08	1.41
Migraine without aura	Connective_Bone	4.70	1.09	8.79E-09	6.41E-09	1.37
Migraine	SkeletalMuscle	4.08	0.47	6.31E-09	4.78E-09	1.32
Migraine with aura	Adrenal_Pancreas	6.71	1.97	9.82E-09	7.56E-09	1.30
Parkinson's disease	CNS	3.85	0.79	9.66E-08	7.58E-08	1.28
Migraine with aura	Hematopoietic	2.68	0.84	7.38E-09	5.81E-09	1.27
Ischemic stroke	Cardiovascular	4.80	1.85	4.04E-08	3.21E-08	1.26
Early-onset stroke	Cardiovascular	4.61	2.92	9.05E-08	7.28E-08	1.24
Focal epilepsy	Hematopoietic	-0.36	2.07	3.45E-08	2.96E-08	1.16
Migraine	Connective_Bone	3.70	0.46	5.22E-09	4.60E-09	1.13
Generalized epilepsy	Adrenal_Pancreas	1.97	1.03	6.56E-08	5.80E-08	1.13
Alzheimer's disease	CNS	4.91	1.12	1.54E-08	1.37E-08	1.12
Migraine without aura	Cardiovascular	4.92	1.32	9.49E-09	8.50E-09	1.12
Parkinson's disease	Adrenal_Pancreas	4.91	1.49	9.06E-08	8.22E-08	1.10
Focal epilepsy	Liver	1.16	3.70	4.44E-08	4.15E-08	1.07
Ischemic stroke	SkeletalMuscle	4.04	1.62	2.79E-08	2.88E-08	0.97
Epilepsy	Cardiovascular	3.33	1.53	3.66E-08	4.10E-08	0.89
Migraine	GI	2.96	0.35	3.45E-09	4.00E-09	0.86
Migraine	Liver	3.78	0.56	4.32E-09	5.12E-09	0.84
Migraine with aura	CNS	4.24	1.15	4.05E-09	4.88E-09	0.83
Ischemic stroke	Connective_Bone	3.72	1.47	2.24E-08	2.73E-08	0.82
Parkinson's disease	Hematopoietic	2.63	0.89	4.23E-08	5.28E-08	0.80
Early-onset stroke	Adrenal_Pancreas	3.88	2.96	4.81E-08	6.63E-08	0.73
Focal epilepsy	CNS	-2.08	2.76	2.16E-08	2.98E-08	0.72

Early-onset stroke	Liver	3.05	3.05	4.44E-08	6.49E-08	0.68
Epilepsy	Liver	2.52	1.63	2.10E-08	3.60E-08	0.58
Migraine without aura	CNS	3.62	0.75	2.84E-09	5.19E-09	0.55
Early-onset stroke	CNS	1.94	1.92	2.27E-08	4.20E-08	0.54
Migraine	Adrenal_Pancreas	3.75	0.50	2.25E-09	4.43E-09	0.51
Intracerebral hemorrhage	GI	4.40	4.35	1.25E-07	2.55E-07	0.49
Early-onset stroke	Hematopoietic	0.52	1.57	2.58E-08	5.42E-08	0.48
Ischemic stroke	Other	2.86	1.15	1.21E-08	2.55E-08	0.47
Alzheimer's disease	Connective_Bone	5.02	1.41	8.91E-09	2.00E-08	0.44
Intracerebral hemorrhage	Other	3.57	3.77	9.92E-08	2.37E-07	0.42
Generalized epilepsy	Other	1.44	0.64	2.27E-08	5.46E-08	0.42
Migraine without aura	Adrenal_Pancreas	4.25	1.26	3.15E-09	7.91E-09	0.40
Intracerebral hemorrhage	CNS	3.65	3.78	8.30E-08	2.17E-07	0.38
Epilepsy	Adrenal_Pancreas	2.35	1.48	1.42E-08	3.76E-08	0.38
Intracerebral hemorrhage	Kidney	7.97	9.75	1.64E-07	4.38E-07	0.37
Focal epilepsy	Kidney	-1.64	5.06	1.95E-08	5.56E-08	0.35
Ischemic stroke	Hematopoietic	1.43	0.84	8.52E-09	2.47E-08	0.35
Alzheimer's disease	Kidney	8.69	3.00	7.52E-09	3.00E-08	0.25
Alzheimer's disease	Adrenal_Pancreas	5.50	1.70	5.06E-09	2.19E-08	0.23
Ischemic stroke	CNS	1.87	1.07	4.38E-09	1.99E-08	0.22
Alzheimer's disease	GI	4.11	1.06	3.59E-09	1.77E-08	0.20
Migraine	Hematopoietic	1.96	0.24	7.27E-10	3.65E-09	0.20
Alzheimer's disease	SkeletalMuscle	5.05	1.53	4.23E-09	2.19E-08	0.19
Migraine with aura	GI	3.59	1.18	8.23E-10	6.66E-09	0.12
Generalized epilepsy	SkeletalMuscle	1.39	0.88	5.46E-09	5.68E-08	0.10
Migraine with aura	Connective_Bone	4.37	1.46	5.42E-10	5.99E-09	0.09
Ischemic stroke	Liver	2.57	2.00	6.24E-10	3.06E-08	0.02
Early-onset stroke	Kidney	1.75	4.46	-2.37E-09	8.56E-08	-0.03
Early-onset stroke	Connective_Bone	1.67	2.37	-3.65E-09	5.70E-08	-0.06
Migraine with aura	Other	3.51	1.10	-5.64E-10	5.59E-09	-0.10
Migraine with aura	Liver	4.41	1.91	-1.19E-09	7.01E-09	-0.17
Generalized epilepsy	GI	1.12	0.67	-1.14E-08	5.35E-08	-0.21
Ischemic stroke	Adrenal_Pancreas	2.65	1.89	-1.04E-08	3.42E-08	-0.30
Parkinson's disease	Connective_Bone	3.12	1.88	-2.37E-08	7.62E-08	-0.31
Early-onset stroke	GI	0.73	2.30	-1.89E-08	5.68E-08	-0.33
Migraine	Other	2.70	0.29	-1.36E-09	3.99E-09	-0.34
Epilepsy	Kidney	1.83	2.25	-1.86E-08	5.09E-08	-0.37
Parkinson's disease	SkeletalMuscle	3.17	1.12	-3.55E-08	9.56E-08	-0.37
Parkinson's disease	Liver	3.55	1.41	-2.69E-08	6.93E-08	-0.39
Multiple sclerosis	SkeletalMuscle	4.10	0.77	-2.70E-08	5.85E-08	-0.46
Focal epilepsy	Adrenal_Pancreas	-3.19	3.94	-2.14E-08	4.61E-08	-0.47
Focal epilepsy	SkeletalMuscle	-3.35	4.05	-2.01E-08	4.28E-08	-0.47
Intracerebral hemorrhage	SkeletalMuscle	1.92	5.46	-1.52E-07	2.91E-07	-0.52
Migraine without aura	Liver	3.23	1.26	-3.71E-09	6.87E-09	-0.54
Migraine without aura	Other	2.84	0.79	-3.78E-09	6.78E-09	-0.56
Ischemic stroke	Kidney	1.55	2.88	-2.24E-08	3.87E-08	-0.58
Generalized epilepsy	Liver	0.61	1.01	-4.10E-08	6.53E-08	-0.63

Migraine without aura	Hematopoietic	2.36	0.63	-3.98E-09	6.21E-09	-0.64
Multiple sclerosis	Connective_Bone	3.73	0.71	-3.96E-08	6.08E-08	-0.65
Intracerebral hemorrhage	Connective_Bone	1.01	4.21	-1.51E-07	2.28E-07	-0.66
Parkinson's disease	Other	2.44	0.88	-3.87E-08	5.73E-08	-0.68
Early-onset stroke	Other	1.13	1.99	-3.53E-08	5.21E-08	-0.68
Generalized epilepsy	Connective_Bone	1.06	0.81	-3.46E-08	5.04E-08	-0.69
Migraine without aura	SkeletalMuscle	3.49	1.08	-5.11E-09	7.07E-09	-0.72
Focal epilepsy	Other	-2.66	2.67	-2.85E-08	3.72E-08	-0.77
Epilepsy	SkeletalMuscle	1.11	1.50	-2.77E-08	3.58E-08	-0.77
Ischemic stroke	GI	1.74	1.28	-2.03E-08	2.53E-08	-0.80
Multiple sclerosis	Adrenal_Pancreas	4.12	0.87	-5.48E-08	6.47E-08	-0.85
Intracerebral hemorrhage	Hematopoietic	1.40	2.75	-2.01E-07	2.27E-07	-0.88
Epilepsy	Connective_Bone	0.39	1.27	-3.02E-08	3.30E-08	-0.92
Parkinson's disease	GI	2.16	1.03	-5.20E-08	5.54E-08	-0.94
Multiple sclerosis	Kidney	5.86	1.39	-9.33E-08	8.70E-08	-1.07
Multiple sclerosis	CNS	2.75	0.50	-4.63E-08	4.17E-08	-1.11
Generalized epilepsy	Cardiovascular	0.71	0.99	-7.58E-08	6.50E-08	-1.17
Multiple sclerosis	Liver	4.33	0.93	-7.94E-08	6.01E-08	-1.32
Focal epilepsy	Connective_Bone	-5.31	3.73	-5.58E-08	3.46E-08	-1.61
Epilepsy	Other	0.24	0.95	-5.10E-08	2.98E-08	-1.71
Generalized epilepsy	Kidney	-0.84	1.57	-1.42E-07	8.14E-08	-1.75
Focal epilepsy	GI	-3.88	3.41	-6.58E-08	3.36E-08	-1.96
Alzheimer's disease	Cardiovascular	2.19	1.40	-4.47E-08	2.20E-08	-2.03
Intracerebral hemorrhage	Adrenal_Pancreas	-3.56	6.51	-6.66E-07	3.28E-07	-2.03
Multiple sclerosis	Cardiovascular	3.34	0.84	-1.38E-07	6.60E-08	-2.09
Parkinson's disease	Cardiovascular	1.74	1.55	-1.48E-07	6.90E-08	-2.15
Epilepsy	GI	-0.10	1.11	-7.08E-08	3.27E-08	-2.17
Intracerebral hemorrhage	Liver	-5.46	6.90	-7.03E-07	2.96E-07	-2.37
Parkinson's disease	Kidney	1.23	2.44	-2.18E-07	9.15E-08	-2.38
Multiple sclerosis	Other	2.24	0.51	-1.38E-07	5.35E-08	-2.57
Multiple sclerosis	GI	2.32	0.57	-1.96E-07	5.77E-08	-3.40

Behavioral-cognitive phenotypes and additional traits

Phenotype	Tissue	Enrichment	SE
Years of education	CNS	2.87	0.19
Intelligence	CNS	3.41	0.32
Height	Connective_Bone	5.32	0.38
BMI	CNS	2.67	0.18
Crohn's disease	Hematopoietic	4.19	0.43
Neuroticism	CNS	2.47	0.29
College attainment	CNS	3.31	0.45
Height	Cardiovascular	4.23	0.38
Height	Other	3.42	0.21
Depressive symptoms	Adrenal_Pancreas	5.15	0.94
Never/ever smoked	CNS	3.45	0.73
BMI	Adrenal_Pancreas	2.92	0.28
Height	SkeletalMuscle	4.06	0.33
Depressive symptoms	CNS	2.84	0.49
Intelligence	Adrenal_Pancreas	3.28	0.51
BMI	Hematopoietic	1.63	0.14
Coronary artery disease	Liver	4.57	1.00
Cognitive performance	Liver	3.85	1.81
Openness	CNS	4.84	1.82
Subjective well-being	CNS	3.33	0.52
Height	GI	3.04	0.23
Openness	Hematopoietic	3.49	1.46
Depressive symptoms	Kidney	5.42	1.30
Conscientiousness	GI	6.46	2.63
Coronary artery disease	Other	3.41	0.57
Intelligence	SkeletalMuscle	2.92	0.46
Depressive symptoms	Hematopoietic	1.70	0.38
Cognitive performance	Adrenal_Pancreas	3.44	1.76
Coronary artery disease	Kidney	5.90	1.62
Cognitive performance	CNS	2.42	1.00
Years of education	Adrenal_Pancreas	2.61	0.36
Cigarettes per day	Connective_Bone	2.95	1.50
Extraversion	SkeletalMuscle	4.26	1.39
Conscientiousness	SkeletalMuscle	7.72	3.08
Coronary artery disease	Cardiovascular	4.28	0.93
Cognitive performance	Cardiovascular	2.52	1.50
Subjective well-being	Hematopoietic	2.36	0.36
Extraversion	CNS	3.27	0.92
Height	Kidney	4.45	0.65
Coronary artery disease	Connective_Bone	3.89	0.78
Cognitive performance	Kidney	3.37	2.70
Years of education	Hematopoietic	1.45	0.15

Coronary artery disease	SkeletalMuscle	4.20	0.85
Never/ever smoked	Adrenal_Pancreas	3.60	1.12
Cigarettes per day	Adrenal_Pancreas	3.28	1.90
Subjective well-being	Adrenal_Pancreas	3.24	0.81
Depressive symptoms	Liver	3.26	0.91
Height	Liver	3.65	0.36
Cognitive performance	Hematopoietic	1.95	0.86
Coronary artery disease	GI	2.94	0.60
College attainment	Liver	3.01	0.75
BMI	SkeletalMuscle	2.26	0.25
Extraversion	Cardiovascular	3.82	1.42
Cigarettes per day	CNS	1.68	1.20
Coronary artery disease	Hematopoietic	2.18	0.44
Coronary artery disease	Adrenal_Pancreas	3.67	0.98
Extraversion	Adrenal_Pancreas	3.57	1.38
Conscientiousness	Kidney	9.92	5.61
Height	Adrenal_Pancreas	3.44	0.44
Cigarettes per day	GI	1.92	1.53
Height	Hematopoietic	2.20	0.21
College attainment	Hematopoietic	1.40	0.37
Conscientiousness	Adrenal_Pancreas	5.68	3.60
Never/ever smoked	Liver	2.52	1.14
BMI	Connective_Bone	1.89	0.24
Intelligence	Liver	2.00	0.50
Cigarettes per day	Liver	1.10	2.35
Openness	SkeletalMuscle	3.75	2.12
Cigarettes per day	Other	1.39	1.45
Extraversion	Connective_Bone	2.76	1.09
Conscientiousness	Liver	4.80	3.03
Neuroticism	Hematopoietic	1.18	0.30
College attainment	SkeletalMuscle	2.84	0.67
Cigarettes per day	Hematopoietic	1.18	1.00
College attainment	Connective_Bone	2.15	0.53
Never/ever smoked	SkeletalMuscle	2.48	1.01
Conscientiousness	Other	2.95	1.96
Crohn's disease	Kidney	5.13	1.26
Conscientiousness	CNS	3.15	2.04
Intelligence	Other	1.85	0.30
Extraversion	Other	2.38	0.95
Cognitive performance	Connective_Bone	0.99	1.23
Subjective well-being	Cardiovascular	2.47	0.73
Crohn's disease	SkeletalMuscle	3.71	0.69
Never/ever smoked	Connective_Bone	1.76	0.87
Conscientiousness	Cardiovascular	5.61	3.10
Neuroticism	Adrenal_Pancreas	1.71	0.44
Cigarettes per day	SkeletalMuscle	0.91	2.14
Openness	Kidney	3.45	4.23

Conscientiousness	Hematopoietic	2.02	1.56
Cognitive performance	SkeletalMuscle	0.72	1.47
College attainment	Adrenal_Pancreas	2.60	0.75
College attainment	Cardiovascular	3.05	0.72
Years of education	Liver	1.90	0.29
Crohn's disease	Liver	3.99	0.76
Years of education	SkeletalMuscle	2.08	0.25
Neuroticism	Liver	1.35	0.56
Subjective well-being	SkeletalMuscle	2.29	0.67
Subjective well-being	Liver	2.20	0.79
Extraversion	Hematopoietic	1.68	0.84
Subjective well-being	Other	1.99	0.42
Cognitive performance	GI	1.11	1.03
Openness	Liver	1.66	2.30
Cognitive performance	Other	0.98	1.00
Extraversion	GI	2.12	0.96
Never/ever smoked	Hematopoietic	1.16	0.53
Openness	Adrenal_Pancreas	2.19	2.33
Intelligence	Kidney	1.73	0.78
Conscientiousness	Connective_Bone	1.81	2.24
Subjective well-being	Kidney	2.04	1.32
Depressive symptoms	SkeletalMuscle	2.15	0.73
Crohn's disease	Connective_Bone	3.22	0.67
Subjective well-being	Connective_Bone	2.07	0.56
Intelligence	Hematopoietic	1.35	0.21
Never/ever smoked	Kidney	1.19	1.84
Extraversion	Kidney	0.72	2.39
Openness	Cardiovascular	2.75	2.23
Coronary artery disease	CNS	2.35	0.54
College attainment	Kidney	2.17	1.12
Crohn's disease	GI	2.92	0.53
Never/ever smoked	Other	1.66	0.67
Cigarettes per day	Kidney	-1.99	3.01
BMI	Liver	1.85	0.30
Openness	Connective_Bone	1.07	1.76
Never/ever smoked	Cardiovascular	2.53	1.01
College attainment	Other	1.74	0.45
Neuroticism	SkeletalMuscle	1.45	0.41
Neuroticism	Kidney	0.81	0.66
Intelligence	Cardiovascular	2.28	0.49
Cigarettes per day	Cardiovascular	-0.18	2.41
Years of education	Connective_Bone	1.64	0.22
Years of education	Cardiovascular	2.15	0.31
Crohn's disease	Other	2.29	0.48
Depressive symptoms	Connective_Bone	1.24	0.61
Extraversion	Liver	0.78	1.57
Depressive symptoms	Other	1.19	0.48

Never/ever smoked	GI	1.19	0.73
BMI	Kidney	2.01	0.45
Depressive symptoms	GI	1.36	0.51
Neuroticism	Other	1.20	0.32
College attainment	GI	1.53	0.45
Openness	GI	0.81	1.40
Intelligence	Connective_Bone	1.46	0.37
Neuroticism	Connective_Bone	0.85	0.37
Depressive symptoms	Cardiovascular	2.22	0.74
Crohn's disease	Cardiovascular	2.64	0.63
Crohn's disease	CNS	2.15	0.51
BMI	Other	1.43	0.16
Crohn's disease	Adrenal_Pancreas	2.85	0.72
BMI	Cardiovascular	1.80	0.27
Openness	Other	-0.60	1.48
Subjective well-being	GI	1.47	0.47
Neuroticism	GI	0.87	0.33
Years of education	Kidney	1.36	0.43
Height	CNS	2.41	0.22
Neuroticism	Cardiovascular	1.26	0.48
Years of education	Other	1.35	0.17
BMI	GI	1.33	0.19
Intelligence	GI	1.17	0.35
Years of education	GI	1.24	0.19

Coeff.	SE	Coeff. z-score
9.51E-08	1.15E-08	**8.29**
8.30E-08	1.23E-08	**6.73**
2.24E-07	3.55E-08	**6.32**
2.73E-08	4.46E-09	**6.13**
3.60E-07	6.66E-08	**5.41**
3.83E-08	8.45E-09	**4.53**
2.71E-08	6.52E-09	**4.16**
1.28E-07	3.08E-08	**4.15**
8.26E-08	2.19E-08	**3.78**
3.77E-08	1.04E-08	**3.62**
3.06E-08	9.13E-09	**3.35**
2.15E-08	6.69E-09	3.21
7.76E-08	2.65E-08	2.93
1.68E-08	6.05E-09	2.78
4.96E-08	1.96E-08	2.53
1.14E-08	4.62E-09	2.46
3.25E-08	1.43E-08	2.28
1.23E-07	5.42E-08	2.27
8.15E-08	3.61E-08	2.26
1.57E-08	7.13E-09	2.20
4.87E-08	2.24E-08	2.17
8.40E-08	4.18E-08	2.01
2.53E-08	1.26E-08	2.01
9.64E-08	4.89E-08	1.97
2.52E-08	1.32E-08	1.91
3.55E-08	1.97E-08	1.81
1.24E-08	6.93E-09	1.80
1.11E-07	6.34E-08	1.75
4.22E-08	2.48E-08	1.71
5.98E-08	3.58E-08	1.67
3.60E-08	2.25E-08	1.60
3.13E-08	2.02E-08	1.55
2.44E-08	1.59E-08	1.54
9.12E-08	6.07E-08	1.50
3.03E-08	2.03E-08	1.50
7.82E-08	5.44E-08	1.44
9.68E-09	6.75E-09	1.43
1.46E-08	1.04E-08	1.40
5.49E-08	4.14E-08	1.33
1.68E-08	1.41E-08	1.19
1.00E-07	8.48E-08	1.18
1.63E-08	1.40E-08	1.16

Key:
CNS
Connective_Bone
Hematopoietic
Cardiovascular
Other
Adrenal_Pancreas
SkeletalMuscle
Liver
GI
Kidney

For exact makeup of categories, see
H. K. Finucane et al., Partitioning heritability by function

1.86E-08	1.64E-08	1.13
1.50E-08	1.35E-08	1.11
2.87E-08	2.61E-08	1.10
1.01E-08	9.58E-09	1.06
8.96E-09	8.76E-09	1.02
2.38E-08	2.47E-08	0.96
3.85E-08	4.50E-08	0.86
1.04E-08	1.31E-08	0.80
6.78E-09	9.08E-09	0.75
4.44E-09	6.15E-09	0.72
1.32E-08	1.85E-08	0.71
1.23E-08	1.75E-08	0.71
7.71E-09	1.24E-08	0.62
9.94E-09	1.66E-08	0.60
1.03E-08	1.82E-08	0.57
4.98E-08	8.89E-08	0.56
1.24E-08	3.18E-08	0.39
8.11E-09	2.25E-08	0.36
7.25E-09	2.33E-08	0.31
2.50E-09	8.31E-09	0.30
1.88E-08	7.49E-08	0.25
2.02E-09	1.24E-08	0.16
3.25E-10	5.40E-09	0.06
1.03E-09	1.72E-08	0.06
1.40E-09	2.67E-08	0.05
6.73E-10	4.81E-08	0.01
-1.48E-10	2.20E-08	-0.01
-5.26E-10	1.36E-08	-0.04
-1.96E-09	4.62E-08	-0.04
-6.31E-10	9.35E-09	-0.07
-1.09E-09	9.04E-09	-0.12
-2.73E-09	2.15E-08	-0.13
-1.08E-09	8.28E-09	-0.13
-2.63E-09	1.45E-08	-0.18
-1.28E-08	5.32E-08	-0.24
-3.25E-08	1.26E-07	-0.26
-1.13E-08	3.91E-08	-0.29
-4.80E-09	1.62E-08	-0.30
-4.43E-09	1.36E-08	-0.33
-1.52E-08	4.59E-08	-0.33
-3.75E-09	1.05E-08	-0.36
-2.77E-08	7.71E-08	-0.36
-4.49E-09	1.21E-08	-0.37
-2.18E-08	5.71E-08	-0.38
-5.46E-09	1.38E-08	-0.40
-1.01E-08	2.48E-08	-0.41
-3.65E-08	8.73E-08	-0.42

-1.95E-08	4.67E-08	-0.42
-2.53E-08	5.74E-08	-0.44
-5.03E-09	1.08E-08	-0.47
-5.55E-09	1.11E-08	-0.50
-7.74E-09	1.49E-08	-0.52
-3.89E-08	6.97E-08	-0.56
-8.79E-09	1.53E-08	-0.57
-6.22E-09	1.08E-08	-0.58
-5.25E-09	8.98E-09	-0.58
-5.17E-09	8.45E-09	-0.61
-9.13E-09	1.41E-08	-0.65
-5.44E-09	8.21E-09	-0.66
-2.92E-08	4.33E-08	-0.68
-3.65E-08	5.27E-08	-0.69
-3.53E-08	4.80E-08	-0.74
-1.06E-08	1.36E-08	-0.78
-9.52E-09	1.18E-08	-0.81
-5.07E-08	5.76E-08	-0.88
-2.22E-08	2.41E-08	-0.92
-4.46E-08	4.76E-08	-0.94
-1.33E-08	1.36E-08	-0.97
-8.46E-09	8.59E-09	-0.98
-8.06E-08	8.19E-08	-0.98
-7.34E-09	7.45E-09	-0.99
-1.38E-08	1.31E-08	-1.05
-2.03E-08	1.90E-08	-1.07
-2.44E-08	2.26E-08	-1.08
-6.27E-08	5.69E-08	-1.10
-1.21E-08	1.08E-08	-1.12
-1.45E-08	1.26E-08	-1.15
-7.72E-08	6.65E-08	-1.16
-1.43E-08	1.23E-08	-1.16
-3.69E-08	3.11E-08	-1.19
-6.84E-09	5.57E-09	-1.23
-5.51E-08	4.39E-08	-1.26
-2.09E-08	1.55E-08	-1.34
-1.16E-08	8.44E-09	-1.37
-1.60E-08	1.16E-08	-1.38
-2.37E-08	1.69E-08	-1.40
-2.76E-08	1.94E-08	-1.42
-4.24E-08	2.86E-08	-1.49
-1.94E-08	1.29E-08	-1.50
-2.85E-08	1.90E-08	-1.50
-1.24E-07	8.14E-08	-1.52
-1.24E-08	7.60E-09	-1.64
-2.47E-08	1.49E-08	-1.66
-1.30E-08	7.34E-09	-1.77

-2.10E-08	1.16E-08	-1.81
-1.31E-08	6.99E-09	-1.87
-1.27E-08	6.68E-09	-1.91
-1.70E-08	8.82E-09	-1.93
-1.50E-08	7.54E-09	-2.00
-8.96E-08	4.38E-08	-2.04
-3.18E-08	1.47E-08	-2.17
-2.58E-08	1.12E-08	-2.30
-2.17E-08	9.38E-09	-2.31
-2.07E-07	8.91E-08	-2.33
-1.50E-07	6.09E-08	-2.45
-1.22E-08	4.77E-09	-2.56
-1.93E-07	7.38E-08	-2.62
-1.73E-08	6.44E-09	-2.68
-1.27E-07	4.50E-08	-2.81
-2.11E-08	7.31E-09	-2.89
-3.23E-08	9.97E-09	-3.24
-6.92E-08	2.02E-08	-3.43
-5.91E-08	1.71E-08	-3.46
-3.89E-08	1.10E-08	-3.53
-4.72E-08	1.32E-08	-3.58
-1.75E-08	4.70E-09	-3.73
-5.86E-08	1.56E-08	-3.76
-5.67E-08	1.26E-08	-4.49

al annotation using genome-wide association summary statistics. Nat Genet. 2015 Nov; 47(11): 1228–12

:35.

Supplementary Table 13: Data sources, responsible consortia, and data a

Data sources (valid as of 8/2/18)

Disorder or phenotype (reference)
Psychiatric disorders
ADHD
Anorexia nervosa(68)
Anxiety disorder(69)
Autism spectrum disorders(70)
Bipolar disorder
Major depressive disorder
OCD – PGC
PTSD – PGC
Schizophrenia(22)
Tourette Syndrome
Neurological disorders
Alzheimer's disease(18)
Epilepsy and subtypes, focal and generalized(71)
Intracerebral hemorrhage(72)
Ischemic stroke and subtypes (cardioembolic, early onset, small vessel and large vessel)(73)
Migraine and subtypes, migraine with and without aura
Multiple sclerosis(74)
Parkinson's disease(21)
Behavioral-cognitive phenotypes
College attainment, years of education(75)
Childhood cognitive performance(76)
Extraversion, agreeableness, conscientiousness and openness (27)
IQ(77)
Neuroticism, depressive symptoms and subjective well-being(78)
Never/ever smoked, cigarettes per day(79)
Additional phenotypes
BMI(63)
Height(80)
Crohn’s disease(81)
Coronary artery disease(82)
Genotype data used for simulations and power analyses
UK Biobank

vailability

Consortium or dataset identifier	Availability
PGC-ADD2	Freely available
PGC-ED	Freely available
ANGST	Freely available
PGC-AUT	Freely available
PGC-BIP2	By application, later freely available
PGC-MDD2	By application, later freely available
PGC-TSOCD	Freely available
PGC-PTSD	Freely available
PGC-SCZ2	Freely available
PGC-TSOCD	By application
IGAP	Freely available
ILAE	Freely available
ISGC	Freely available (PMC3980413)
METASTROKE dataset of the ISGC	Freely available (PMC3490334)
IHGC	By application
IMSGC	By application
IPDGC	By application
SSGAC	Freely available
SSGAC	Freely available
GPC	Freely available
CTG	Freely available
SSGAC	Freely available
TAG	Freely available
GIANT	Freely available
GIANT	Freely available
IIBDGC	Freely available
CARDIoGRAM	Freely available
UK Biobank	Available through application

Address

http://www.med.unc.edu/pgc/results-and-downloads
http://www.med.unc.edu/pgc/results-and-downloads
http://www.med.unc.edu/pgc/results-and-downloads
http://www.med.unc.edu/pgc/results-and-downloads
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http://www.med.unc.edu/pgc/results-and-downloads
http://www.med.unc.edu/pgc/pgc-workgroups

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http://web.pasteur-lille.fr/en/recherche/u744/igap/igap_download.php
http://www.epigad.org/gwas_ilae2014/
http://cerebrovascularportal.org/informational/downloads
http://cerebrovascularportal.org/informational/downloads
http://www.headachegenetics.org/content/datasets-and-cohorts
http://imsgenetics.org/?page_id=83
www.pdgene.org

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http://www.thessgac.org/data
http://www.thessgac.org/data
http://www.tweelingenregister.org/GPC/
http://ctg.cncr.nl/software/summary_statistics
http://www.thessgac.org/data
http://www.med.unc.edu/pgc/results-and-downloads

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https://www.broadinstitute.org/collaboration/giant
https://www.broadinstitute.org/collaboration/giant
http://www.ibdgenetics.org/downloads.html
http://www.cardiogramplusc4d.org/data-downloads/

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amsportal.ukbiobank.ac.uk

ADHD
Anorexia nervosa
Anxiety disorders
ASD
Bipolar disorder
MDD
OCD
PTSD
Schizophrenia
Tourette Syndrome

Genetic correlation
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
-1

P-value significance
0.8
0.6
0.4
0.2
0.05
0.001
* <3.35 x 10^{-4}

Alzheimer's disease
Epilepsy
Focal epilepsy
Generalized epilepsy
ICH
Ischemic stroke
Early-onset stroke
Migraine
Migraine with aura
Migraine without aura
Multiple sclerosis
Parkinson's disease

Genetic correlation
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
-1

P-value significance
0.8
0.6
0.4
0.2
0.05
0.001
* <3.35 x 10^{-4}

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ADHD
Anorexia nervosa
Anxiety disorders
ASD
Bipolar disorder
MDD
OCD
PTSD
Schizophrenia
Tourette Syndrome

Genetic correlation
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
-1

P-value significance
0.8
0.6
0.4
0.2
0.05
0.001
* <3.35 x 10^{-4}

ADHD
Anorexia nervosa
Anxiety disorders
ASD
Bipolar disorder
MDD
OCD
PTSD
Schizophrenia
Tourette Syndrome
Alzheimer's disease
Epilepsy
Focal epilepsy
Generalized epilepsy
ICH
Ischemic stroke
Early-onset stroke
Migraine
Migraine with aura
Migraine without aura
Multiple sclerosis

College attainment
Years of education
Cognitive performance
Intelligence

Neuroticism
Extraversion
Conscientiousness
Openness
Depressive symptoms
Subjective well-being

Never/ever smoked
Cigarettes per day

BMI
Height
Crohn's disease
Myocardial infarction

Genetic correlation
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
-1

P-value significance
0.8
0.6
0.4
0.2
0.05
0.001
* <2.30 x 10^{-4}