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Analysis of shared heritability in common disorders of the brain

The Brainstorm Consortium

Abstract

Disorders of the brain can exhibit considerable epidemiological comorbidity and often share symptoms, provoking debate about their etiologic overlap. We quantified the genetic sharing of 25 brain disorders from genome-wide association studies of 265,218 patients and 784,643 control participants and assessed their relationship to 17 phenotypes from 1,191,588 individuals. Psychiatric disorders share common variant risk, whereas neurological disorders appear more distinct from one another and from the psychiatric disorders. We also identified significant sharing between disorders and a number of brain phenotypes, including cognitive measures. Further, we conducted simulations to explore how statistical 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.

Abstract

INTRODUCTION: Brain disorders may exhibit shared symptoms and substantial epidemiological comorbidity, inciting debate about their etiologic overlap. However, detailed study of phenotypes with different ages of onset, severity, and presentation poses 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 and assess how connected they, or at least their genetic risks, are on the genomic level. We used genome-wide association data for 265,218 patients and 784,643 control participants, as well as 17 phenotypes from a total of 1,191,588 individuals, to quantify the degree of overlap for genetic risk factors of 25 common brain disorders.

RATIONALE: Over the past century, the classification of brain disorders has evolved to reflect the medical and scientific communities' assessments of the presumed root causes of clinical

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Data and materials availability: Data sources for the GWAS summary statistics used in the study and their availability, as well as the study-specific acknowledgments, are provided in the supplementary materials (table S13 and supplementary text, respectively).

SUPPLEMENTARY MATERIALS

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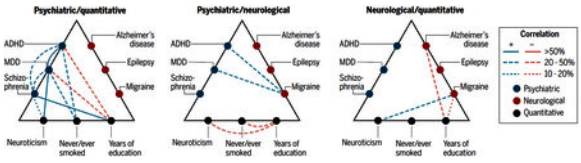
phenomena such as behavioral change, loss of motor function, or alterations of consciousness. Directly observable phenomena (such as the presence of emboli, protein tangles, or unusual electrical activity patterns) generally define and separate neurological disorders from psychiatric disorders. Understanding 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 among attention deficit hyper-activity disorder (ADHD), bipolar disorder, major depressive disorder (MDD), and schizophrenia. By 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, in the general population, the personality trait neuroticism is significantly correlated with almost every psychiatric disorder and migraine. We also identify significant genetic sharing between disorders and early life cognitive measures (e.g., years of education and college attainment) in the general population, 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 statistical 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 their current clinical boundaries do not reflect distinct underlying pathogenic processes, at least on the genetic level. This suggests a deeply intercon nected nature for psychiatric disorders, 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. By 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 may pave the way toward reduced heterogeneity and improved diagnosis and treatment of psychiatric disorders.



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. These correlations are largely absent among neurological disorders but are present for both groups in relation to neurocognitive quantitative phenotypes. Only significant correlations shown. Line color and solidity indicate direction and magnitude of correlation, respectively.

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 patho-physiology (2, 3).

Studies of twins and families have indicated that, in general, brain disorders (excepting those caused by trauma, infection, or cancer) show substantial heritability (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 and migraine (8), stroke and major depressive disorder (MDD) (9), epilepsy and autism spectrum disorder (ASD), and epilepsy and attention deficit hyperactivity disorder (ADHD) (10, 11). Furthermore, direct etiological links may also exist—e.g., mutations in the same ion channel genes confer pleiotropic risk for multiple distinct brain phenotypes (12–14). Genome-wide association studies (GWASs) have demonstrated that individual common risk variants can overlap across traditional diagnostic boundaries (15, 16) and that disorders such as schizophrenia, MDD, and bipolar disorder can have genetic correlations (17).

GWASs have also demonstrated that common genetic variation contributes to the heritability of brain disorders. Generally, this occurs via the combination of many common variants—examples include Alzheimer's disease (18), bipolar disorder (19), migraine (20), Parkinson's disease (21), and schizophrenia (22)—each with a small individual effect. 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, a collaboration among GWAS meta-analysis consortia for 25 disorders (Table 1), was assembled 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 265,218 cases of different brain disorders and 784,643 controls (Table 1) and includes at least one representative of most ICD-10 (10th revision of the International Statistical Classification of Diseases and Related Health Problems) blocks covering mental and behavioral disorders and diseases of the central nervous system (CNS). Also included are 1,191,588 samples for 13 behavioral-cognitive phenotypes (n = 744,486 individuals) traditionally viewed as brain-related, as well as 4 additional phenotypes (n = 447,102 individuals) selected to represent known, well-delineated etiological processes {immune disorders (Crohn's disease), vascular disease

(coronary artery disease), and anthropomorphic measures [height and body mass index (BMI)]} (Table 2).

GWAS summary statistics for the 42 disorders and phenotypes were centralized and underwent uniform quality control and processing (25). To avoid potential bias arising from ancestry differences, we used European-only meta-analyses for each disorder and generated 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 data-sets are parts of the top-level dataset (Table 1).

We have developed a heritability estimation method, linkage disequilibrium score (LDSC) regression (24), which was used to calculate heritability estimates and correlations, as well as to estimate their statistical significance from block jackknife–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 single-nucleotide polymorphisms (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 (25) by means of stratified LD score regression to examine whether the observed heritability for the disorders or pheno-types was enriched into any of the tissue-specific regulatory regions or functional category partitions of the genome, using 10 top-level tissue-type and 53 functional partitions from Finucane *et al*. (26). Simulated phenotype data was then generated under different scenarios by permuting 120,267 genotyped individuals from the UK Biobank (25) to evaluate statistical power and aid in interpreting the results (25).

Heritability estimates and their error sources

We observed a similar range of heritability estimates among the disorders and the behavioral-cognitive phenotypes (fig. S1, A and B, and table S1 and 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 the NEO Five-Factor Inventory (27) had insufficient evidence of additive heritability for robust analysis and thus were excluded from further examination (25). The only observed correlation between heritability estimates and factors relating to study makeup (table S4 and fig. S1, C to F) was a modest correlation between age of disorder onset and heritability, suggesting that early onset brain disorders tend to be more heritable. Because 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. S2, C 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). When comparing estimates reported here with those previously reported in studies with smaller sample sizes (28), a similar pattern was observed for the behavioral-cognitive traits, with the exception of “openness,” “neuroticism,” and “never/ever smoked” (defined as those who have never smoked versus those who have smoked at some point) 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 herita bility 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 (25): evaluating the differences in real data, simulation work (table S5), and quantifying the magnitude of effect for potentially implied misclassification (table S6).

In comparison with 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 may 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 examine only the properties of common variant contributions; 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-function 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 GREML have previously been shown to yield similar estimates from the same data (24), we performed our own comparison in Alzheimer’s disease data (32) (selected on the basis of 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 versus 46,669) and the potential reasons listed above, but they could also be due to methodological variability (most of the previous approximations 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 (Genetic and Environmental Risk in Alzheimer's Disease) cohort (3941 cases and 7848 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 approximations may reflect differences between datasets rather than methodological variability.

Correlations among brain disorders

We observed widespread sharing across psychiatric disorders (Fig. 1 and fig. 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, whereas 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 among themselves (Fig. 1), as did Tourette syndrome (TS), OCD, and MDD, as well as ASD and schizophrenia. 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), and both ASD and TS appear to potentially be more distinct from the other psychiatric disorders. 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 that of the psychiatric disorders (Fig. 2, fig. S4, and table S7A), suggesting greater diagnostic specificity and/or more distinct etiologies. Parkinson's disease, Alzheimer's disease, generalized epilepsy, and multiple sclerosis (MS) showed little to no correlation with other brain disorders. The highest degree of genetic correlation among the neurological disorders was observed for focal epilepsy (average r_g = 0.46, excluding the other epilepsy datasets), though none of the correlations 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 that this disorder may share some of its genetic architecture with psychiatric disorders: migraine and ADHD (r_g = 0.26, P = 8.81×10^{-8}), migraine and TS (r_g = 0.19, P = 1.80×10^{-5}), and

migraine and MDD (r_g = 0.32, P = 1.42 × 10^{-22} for all migraine; r_g = 0.23, P = 5.23 × 10^{-5} for migraine without aura; r_g = 0.28, P = 1.00 × 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 a significantly negative correlation to intelligence but a positive correlation to years of education. Among neurological phenotypes (fig. S5B), the correlations were either negative or null, with Alzheimer's disease, epilepsy, intracerebral hemorrhage (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. S6, A and B; 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 × 10^{-11}) as well as ADHD (r_g = 0.37, P = 3.15 × 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, whereas the phenotype representing vascular pathophysiology (coronary artery disease) showed significant correlation to MDD (r_g = 0.19, P = 8.71 × 10^{-5}) as well as the two stroke-related phenotypes (r_g = 0.69, P = 2.47 × 10^{-6} g to ischemic stroke and r_g = 0.86, P = 2.26 × 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 previous ly reported with a different dataset (24)] and schizophrenia.

Our enrichment analysis (fig. S7 and tables S8 to S12) demonstrated significant heritability enrichments between the CNS and generalized epilepsy, MDD, TS, college attainment, intelligence, neuroticism, and the never/ever smoked trait; between depressive symptoms and adrenal/pancreatic cells and tissues; as well as between hematopoietic cells (including immune system cells) and MS (fig. S7, A and B, and tables S8 and S9). We replicated the reported (CNS) enrichment for schizophrenia, bipolar disorder, and years of education (tables S8 and S9) and observed 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. S7, C and D) (26). 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), whereas the other neurological disorders with similar numbers of loci (MS, Alzheimer's disease, and Parkinson's disease) do not (fig. S7, A and B). Enrichment to conserved regions was also observed for 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 consor tia 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, whereas 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.

On the basis of the observed results, we performed some exploratory analyses to address concerns about diagnostic overlap and misclassification, which are particularly relevant to psychiatric disorders, owing 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). Although, for instance, migraine and schizophrenia are unlikely to be mistaken for one another, 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 to 30%, depending on whether it is uni- or bidirectional) 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. S9, B and C) 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 finding suggests a more interconnected genetic etiology, in contrast to that of 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, this observation 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 nongenetic, 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 over-valued 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, owing to the shared portion of variation affecting that variable. Though 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 the lack of inclusion of disorders conceived as "circuit-based" (e.g., restless legs syndrome, sleep disorders, and possibly essential tremor) constrain the full generalizability of this conclusion. On the basis of our observations, degenerative disorders (such as Alzheimer's and Parkinson's diseases) would therefore not be expected to share their polygenic risk profiles with a neuroimmunological disorder (such as MS) or neurovascular disorder (such as ischemic stroke). Similarly, we see limited evidence for the reported comorbidity 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 ($r_g = 0.48$, $P = 1.79 \times 10^{-5}$) show substantial genetic correlation, whereas 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 comorbidity of migraine with MDD, TS, and ADHD has been previously reported in epidemiological studies (44–47), whereas the previously reported comorbidity 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 that we studied, despite large sample size and robust evidence for heritability, which suggests that their common variant genetic risk may largely be unique. Alzheimer's disease, Parkinson's disease, and MS 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 observed for Crohn's disease. Although 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 observed significant enrichment of heritability for immunological cells and tissues in MS only, 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, not particularly polygenic neuroinflammatory mechanisms (54)]. Among psychiatric disorders, ASD and TS showed a similar absence of correlation with other disorders, although this may 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 ($r_g = 0.737$, $P = 5.04 \times 10^{-96}$), 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 and 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), and the observed correlation between ADHD and smoking initiation ($r_g = 0.374$, $P = 3.15 \times 10^{-6}$) is consistent with the epidemio-logical 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, whereas 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, whereas 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, BMI's brain-specific genetic architecture may be 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 suggests that any lower cardiovascular mortality is more likely due to direct BMI-related effects rather than to 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 underrepresented 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, indicating avenues for follow-up studies. Further analysis is needed to evaluate whether overlapping genetic contributions to psychiatric pathology may influence treatment choices. Ultimately, such developments are promising steps toward reducing diagnostic heterogeneity and eventually improving the diagnostics and treatment of psychiatric disorders.

Materials and methods summary

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 cohort– only versions of the meta-analyses (25). All datasets underwent uniform quality control (25). For each trait, by using the 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-scores, rather than the χ^2 statistic, for each phenotype and for each SNP. Significance was assessed by Bonferroni multiple testing correction via estimating the number of independent brain disorder pheno-types via matrix decomposition (25). Functional and partitioning analyses for the GWAS data-sets were also performed using LDSC regression. Power analyses and simulation work to aid in interpretation of the results were conducted using genotype data from the UK Biobank resource (25).

Supplementary Material

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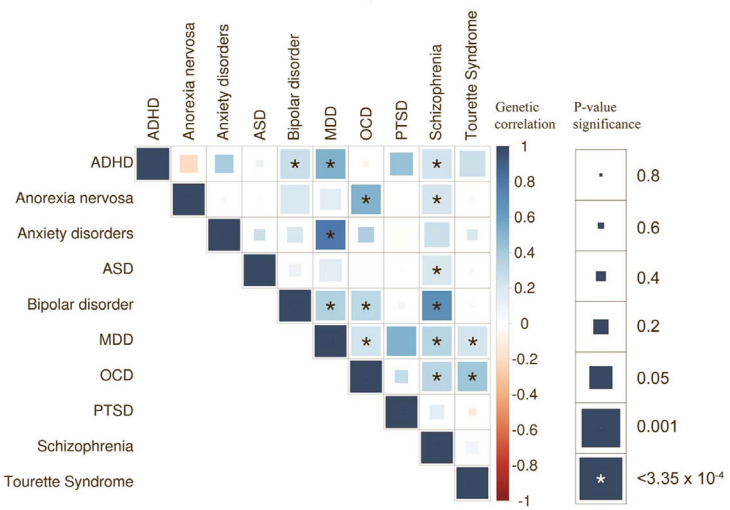

Fig. 1. Genetic correlations across psychiatric phenotypes.

The color of each box indicates the magnitude of the correlation, and the size of the box indicates its significance (LDSC), with significant correlations filling each square completely. Asterisks indicate genetic correlations that are significantly different from zero after Bonferroni correction.

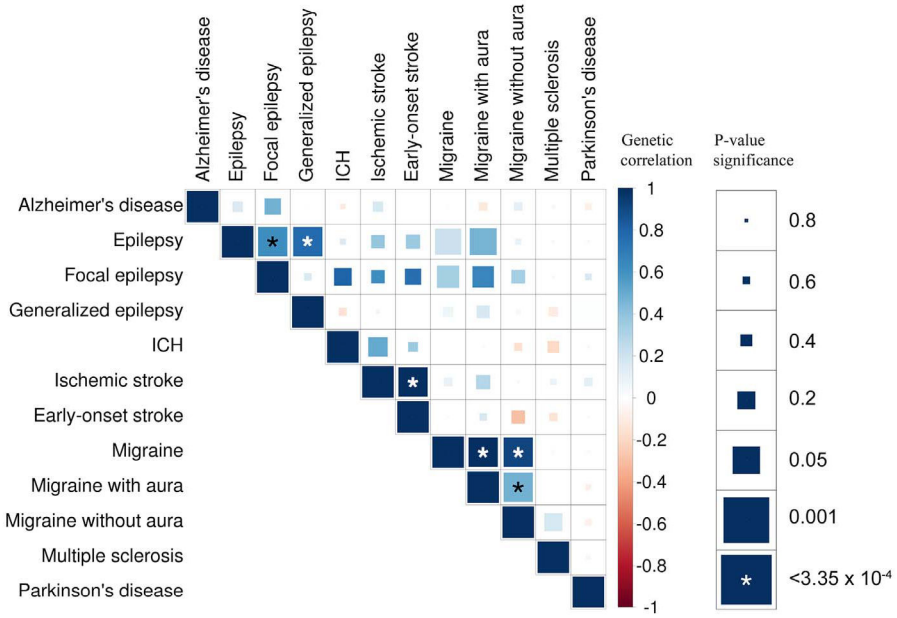

Fig. 2. Genetic correlations across neurological phenotypes.

The color of each box indicates the magnitude of the correlation, and the size of the box indicates its significance (LDSC), with significant correlations filling each square completely. Asterisks indicate genetic correlations that are significantly different from zero after Bonferroni correction. Some phenotypes have substantial overlaps (Table 1)—for instance, all cases of generalized epilepsy are also cases of epilepsy. Asterisks indicate significant genetic correlation after multiple testing correction.

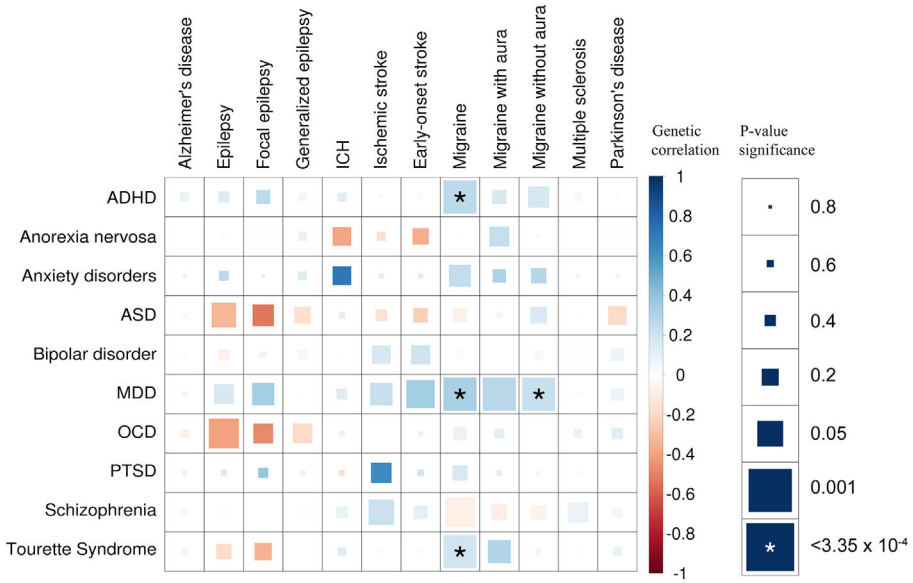

Fig. 3. Genetic correlations across neurological and psychiatric phenotypes.

The color of each box indicates the magnitude of the correlation, and the size of the box indicates its significance (LDSC), with significant correlations filling each square completely. Asterisks indicate genetic correlations that are significantly different from zero after Bonferroni correction.

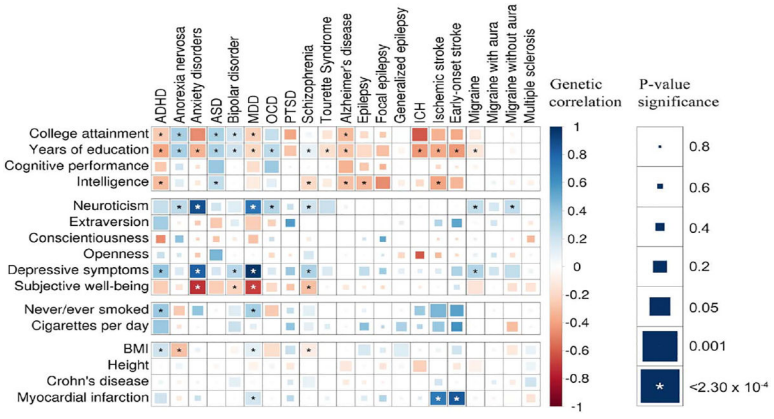

Fig. 4. Genetic correlations across brain disorders and behavioral-cognitive phenotypes.
The color of each box indicates the magnitude of the correlation, and the size of the box indicates its significance (LDSC), with significant correlations filling each square completely. Asterisks indicate genetic correlations that are significantly different from zero after Bonferroni correction.

Table 1.

Brain disorder phenotypes used in the Brainstorm project.

Indented phenotypes are part of a larger whole (e.g., the epilepsy study contains the samples from both focal epilepsy and generalized epilepsy). “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 PGC-ADD2, Psychiatric Genomics Consortium (PGC) Attention Deficit Disorder Working Group; PGC-ED, PGC Eating Disorder Working Group; ANGST, Anxiety Neuro Genetics STudy; PGC-AUT, PGC Autism Spectrum Disorder Working Group; PGC-BIP2, PGC Bipolar Disorder Working Group; PGC-MDD2, PGC Major Depressive Disorder Working Group; PGC-OCDTS, PGC Obsessive Compulsive Disorder and Tourette Syndrome Working Group; PGC-PTSD, PGC Posttraumatic Stress Disorder Working Group; PGC-SCZ2, PGC Schizophrenia Working Group; IGAP, International Genomics of Alzheimer’s Project; ILAE, International League Against Epilepsy Consortium on Complex Epilepsies; ISGC, International Stroke Genetics Consortium; METASTROKE, a consortium of the ISGC; IHGC, International; Headache Genetics Consortium; IMSGC, International Multiple Sclerosis Genetics Consortium; IPDGC, International Parkinson’s Disease Genomics Consortium. W indicates same as above.

Psychiatric disorders				Neurological disorders			
Disorder	**Source**	**Cases**	**Controls**	**Disorder**	**Source**	**Cases**	**Controls**
Attention deficit hyperactivity disorder	PGC-ADD2	12,645	84,435	Alzheimer’s disease	IGAP	17,008	37,154
Anorexia nervosa	PGC-ED	3495	10,982	Epilepsy	ILAE	7779	20,439
Anxiety disorders	ANGST	5761	11,765	Focal epilepsy	“	4601*	17,985*
Autism spectrum disorder	PGC-AUT	6197	7377	Generalized epilepsy	“	2525*	16,244*
Bipolar disorder	PGC-BIP2	20,352	31,358	Intracerebral hemorrhage	ISGC	1545	1481
Major depressive disorder	PGC-MDD2	66,358	153,234	Ischemic stroke	METASTROKE	10,307	19,326
Obsessive-compulsive disorder	PGC-OCDTS	2936	7279	Cardioembolic stroke	“	1859*	17,708*
Posttraumatic stress disorder	PGC-PTSD	2424	7113	Early onset stroke	“	3274*	11,012*
Schizophrenia	PGC-SCZ2	33,640	43,456	Large-vessel disease	“	1817*	17,708*
Tourette syndrome	PGC-OCDTS	4220	8994	Small-vessel disease	“	1349*	17,708*
				Migraine	IHGC	59,673	316,078
				Migraine with aura	“	6332*	142,817*
				Migraine without aura	“	8348*	136,758*
				Multiple sclerosis	IMSGC	5545	12,153
				Parkinson’s disease	IPDGC	5333	12,019
Total psychiatric		158,028	365,993	Total neurologic		107,190	418,650

* Sample count for a phenotype that is part of a larger group.

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

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). (d), dichotomous phenotype; (q), quantitative phenotype. References and phenotype definitions are listed in table S2, and data availability in table S13. SSGAC, Social Science Genetic Association Consortium; CTG, Complex Trait Genetics Lab; GPC, Genetics of Personality Consortium; TAG, Tobacco and Genetics Consortium; GIANT, Genetic Investigation of ANthropometric Traits consortium; Cardiogram, CARDIoGRAMplusC4D Consortium; IIBDGC, International Inflammatory Bowel Disease Genetics Consortium.

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	IIBDGC	20,883
Total		1,124,048

* Sample counts represent overloap with oreceding dataset.