Analysis of shared heritability in common disorders of the brain

Verneri Anttila, Brenda Sullivan, Hilary Finucane, Walter Walters, Jose Bras, Laramie Duncan, Valentina Price, Guido Falcone, Padhraig Gormley, Rainer Malik, et al.

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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.

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
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 hyperactivity 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 interconnected 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 pathophysiology (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...
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 ($h^2_g$) 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 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 (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, $P = 8.81 \times 10^{-8}$), migraine and TS ($r_g$ = 0.19, $P = 1.80 \times 10^{-5}$), 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 previously 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 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, 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 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, 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 ($h^2_g$) was estimated by regressing the association $\chi^2$ 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 $\chi^2$ statistic, for each phenotype and for each SNP. Significance was assessed by Bonferroni multiple testing correction via estimating the number of independent brain disorder phenotypes 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

Refer to Web version on PubMed Central for supplementary material.

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The Brainstorm Consortium

Verneri Anttila1,2,3,*, Brendan Bulik-Sullivan1,3, Hilary K. Finucane2,3,4,5, Raymond K. Walters1,2,3, Jose Bras6,7, Laramie Duncan1,2,3,8, Valentina Escott-Price9,10, Guido J. Falcone11,12,13, Padhraig Gormley1,2,3,11, Rainer Malik14, Nikolaos A. Patsopoulos3,15, Stephan Ripke1,2,3,16, Zhi Wei17, Dongmei Yu2,11, Phil H. Lee2,11, Patrick Turley1,3, Benjamin Grenier-Boley18,19,20, Vincent Chouraki18,19,20,21, Yoichiro Kamatani22,23, Claudine Berr24,25,26, Luc Letenneur27,28, Didier Hannequin29,30, Philippe Amouyel18,19,20,21, Anne Boland31, Jean-François Deleuze31, Emmanuelle Duron32,33, Badri N. Vardarajan34, Christiane Reitz35, Alison M. Goate36, Matthew J. Huentelman37, M. Ilyas Kamboh38, Eric B. Larson39,40, Ekaterina Rogaeva41, Peter St George-Hyslop41,42, Hakon Hakonarson43,44,45, Walter A. Kukull46, Lindsay A. Farrer47, Lisa L. Barnes48,49,50, Thomas G. Beach51, F. Yesim Demirci38, Elizabeth Head52, Christine M. Hulette53, Gregory A. Jicha54, John S.K. Kawe55, Jeffrey A. Kaye56, James B. Leverenz57, Allan I. Levey58,
Jordan W. Smoller1,2,11, Patrick Sullivan641,648, Jonathan Rosand3,11,12,13, Aiden Corvin2,649,* †, Benjamin M. Neale1,2,3,* †

1Analytic Translational Genetics Unit, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA. 2Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Cambridge, Massachusetts, USA. 3Program in Medical and Population Genetics, Broad Institute of MIT and Harvard, Cambridge, Massachusetts, USA. 4Department of Mathematics, Massachusetts Institute of Technology, Cambridge, Massachusetts, USA. 5Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA. 6UK Dementia Research Institute, University College London, London, UK. 7Department of Molecular Neuroscience, Institute of Neurology, University College London, London, UK. 8Department of Psychiatry and Behavioral Science, Stanford University, Stanford, California, USA. 9Cardiff University, Medical Research Council Center for Neuropsychiatric Genetics & Genomics, Institute of Psychology, Medicine & Clinical Neuroscience, Cardiff, UK. 10Dementia Research Institute, Cardiff University, Cardiff, UK. 11Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA, USA. 12Department of Neurology, Massachusetts General Hospital, Boston, MA, USA. 13Harvard Medical School, Boston, MA, USA. 14Institute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich, Munich, Germany. 15Department of Neurology, Brigham & Women’s Hospital, Harvard Medical School, Boston, MA, USA. 16Charité Universitätsmedizin Berlin, Berlin, Germany. 17Department of Computer Science, New Jersey Institute of Technology, New Jersey, USA. 18INSERM U1167 LabEx DISTALZ, Lille, France. 19Institut Pasteur de Lille, U1167, Lille, France. 20Université de Lille, U1167, RID-AGE, Risk Factors and Molecular Determinants of Aging-Related Diseases, Lille, France. 21Centre Hosp. Univ Lille, Lille, France. 22Laboratory for Statistical Analysis, RIKEN Center for Integrative Medical Sciences, Yokohama, Japan. 23Center for Genomic Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan. 24INSERM U1061 - Neuropsychiatry: Epidemiological and Clinical Research, Montpellier, France. 25University of Montpellier, Montpellier, France. 26Memory Research and Resources Center, Department of Neurology, Montpellier University Hospital Gui de Chauliac, Montpellier, France. 27INSERM, UMR 1219, Bordeaux, France. 28University of Bordeaux, Bordeaux, France. 29Rouen University Hospital, Rouen, France. 30Inserm U1245, Rouen, France. 31Centre National de Recherche en Génomique Humaine (CNRGH), Institut de biologie François Jacob, CEA, Evry, France. 32Department of Gerontology, Hôpital Broca, AH-HP, Paris, France. 33Hôpital Paul Brousse Université Paris Sud XI, Le Kremlin-Bicêtre, Paris, France. 34Gertrude H. Sergievsky Center and Dept of Neurology, Columbia University, New York, NY, USA. 35Columbia University, New York, NY, USA. 36Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY, USA. 37Translational Genomics Research Institute, Neurogenomics Division, Phoenix, AZ, USA. 38University of Pittsburgh, Pittsburgh, PA, USA. 39Kaiser Permanente Washington Health Research Institute, Seattle, WA, USA. 40Department of Medicine, University of Washington, WA, USA. 41Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto, Toronto, Canada. 42Cambridge Institute for Medical Research, University of Cambridge, Cambridge, UK. 43Center for Applied Genomics of The Children’s Hospital of Philadelphia, Philadelphia, PA, USA. 44Division of Science. Author manuscript; available in PMC 2018 August 17.
Human Genetics, Children’s Hospital of Philadelphia, Philadelphia, PA, USA. 45Department of Pediatrics, The Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA. 46National Alzheimer Coordinating Center (NACC), Department of Epidemiology, University of Washington, Seattle, WA, USA. 47Department of Medicine, Boston University School of Medicine, Boston, MA, USA. 48Rush Alzheimers Disease Center, Chicago, IL, USA. 49Department of Neurological Sciences, Rush Medical College, Chicago, IL, USA. 50Department of Behavioral Sciences, Rush Medical College, Chicago, IL, USA. 51Banner Sun Health Research Institute, Sun City, AZ, USA. 52Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY, USA. 53Department of Pathology, Duke University School of Medicine, Durham, NC, USA. 54College of Medicine, University of Kentucky, Lexington, KY, USA. 55Department of Biology, Brigham Young University, Provo, UT, USA. 56Layton Aging & Alzheimer’s Disease Center, Oregon Health & Science University, Portland, OR, USA. 57Lou Ruvo Center for Brain Health, Neurological Institute, Cleveland Clinic, Cleveland, OH, USA. 58Department of Neurology, School of Medicine, Emory University, Atlanta, GA, USA. 59Department of Pathology, University of Michigan Medical School, Ann Arbor, MI, USA. 60University of New Mexico Health Sciences Center, Albuquerque, NM, USA. 61Institute for Memory Impairments and Neurological Disorders, University of California, Irvine, CA, USA. 62Department of Neurology, Oregon Health and Science University, Portland, OR, USA. 63Department of Neurology and Parkinson’s Disease Research and Clinical Care Center (PADRECC), Portland Veterans Affairs Medical Center, Portland, OR, USA. 64Indiana Alzheimer Disease Center, Indiana University School of Medicine, Indianapolis, IN, USA. 65Keck School of Medicine of the University of Southern California, Los Angeles, CA, USA. 66Byrd Alzheimer’s Institute, University of South Florida, Tampa, FL, USA. 67Department of Pathology, University of Utah, Salt Lake City, UT, USA. 68Department of Pathology, University of Washington, Seattle, WA, USA. 69Boston University School of Medicine, Boston, MA, USA. 70Department of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA. 71School of Biotechnology, Dublin City University, Glasnevin, Dublin, Ireland. 72Functional Genomics Center Zurich, ETH/IZH-Zurich, Zurich, Switzerland. 73Department of Medical Genetics, Cambridge Institute for Medical Research, Cambridge, UK. 74UK Dementia Research Institute, Cambridge, UK. 75School of Medicine, Cardiff University, Cardiff, UK. 761st and 3rd Departments of Neurology, Aristotle University of Thessaloniki, Thessaloniki, Greece. 77Greek Association of Alzheimer’s Disease and Related Disorders, Thessaloniki, Greece. 78Maurice Wohl Clinical Neuroscience Institute, Institute of Psychiatry, Psychology and Neuroscience, King’s College London, London, UK. 79Dementia Research Centre, UCL Institute of Neurology, London, UK. 80Sorbonne University, GRC n° 21, Alzheimer Precision Medicine (APM), AP-HP, Pitié-Salpêtrière Hospital, Paris, France. 81Institute of Memory and Alzheimer’s Disease (IM2A), Department of Neurology, Pitié-Salpêtrière Hospital, AP-HP, Paris, France. 82Brain & Spine Institute (ICM), INSERM U 1127, CNRS UMR 7225, Paris, France. 83AXA Research Fund & Sorbonne University Chair, Paris, France. 84MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Cardiff, UK. 85Institute of Psychological Medicine and Clinical Neurosciences, School of Medicine, Cardiff University, Cardiff, UK. 86Institute of Prion Diseases and MRC Prion Unit, University College London, London, UK. 87Centre for Public Health, Queens University Belfast, Belfast, UK. 88Human
Department of Genomics, School of Life Sciences, University of Nottingham, Nottingham UK.

90 Institute of Human Genetics, School of Medicine, University of Bonn & University Hospital Bonn, Bonn, Germany. 91Department of Neurodegeneration, UCL Institute of Neurology, London, UK. 92QIMR Berghofer Medical Research Institute, Brisbane, Australia. 93Institute of Psychiatry Psychology and Neuroscience, Kings College London, UK. 94Institute of Medical Genetics and Pathology, University Hospital Basel, Basel, Switzerland. 95Human Genomics Research Group, Department of Biomedicine, University of Basel, Basel, Switzerland. 96Department of Psychiatry and Psychotherapy, Friedrich-Alexander-Universität Erlangen-Nürnberg University Hospital, Erlangen, Germany.

97Department of Psychiatry and Global Brain Health Institute, Trinity College, Dublin, Ireland. 98Division of Psychiatry, Molecular Psychiatry Laboratory, University College London, London, UK. 99Maurice Wohl Clinical Neuroscience Institute, Department of Basic and Clinical Neuroscience, King’s College London, London, UK. 100King’s College Hospital, London, UK. 101Cardiovascular Health Research Unit, Department of Medicine, University of Washington, Seattle, WA, USA. 102Fundació ACE, Institut Català de Neurociències Aplicades, Barcelona, Spain and Universitat Internacional de Catalunya, Barcelona, Spain. 103Facultat de Medicina i Ciències de la Salut, Universitat Internacional de Catalunya (UIC), Barcelona, Spain. 104Glenn Biggs Institute for Alzheimer’s and Neurodegenerative Diseases, University of Texas Health Sciences Center, San Antonio, Texas, USA. 105Neurology and Neurogenetics Core, Framingham Heart Study, Framingham, MA, USA. 106School of Medicine, Boston University, Boston, MA, USA. 107School of Public Health, Boston University, Boston, MA, USA. 108Framingham Heart Study, Framingham, MA, USA. 109Department of Biostatistics, University of Washington, Seattle, WA, USA. 110Department of Epidemiology, Erasmus Medical Centre, Rotterdam, the Netherlands. 111Center for Translational & Computational Neuroimmunology, Columbia University Medical Center, New York, NY, USA. 112Neurogenetics Program, Departments of Neurology and Human Genetics, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, USA. 113Center For Autism Research and Treatment, Semel Institute, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, USA. 114Institute for Precision Health, University of California, Los Angeles, Los Angeles, CA, USA. 115Department of Psychiatry, Saarland University Hospital, Homburg, Germany. 116Institute for Social Medicine, Occupational Health and Public Health (ISAP), University of Leipzig, Leipzig, Germany. 117Institute for Translational Genomics and Population Sciences, Departments of Pediatrics and Medicine, LABioMed at Harbor-UCLA Medical Center, Torrance, CA, USA. 118Department of Neurology II, Kepler University Clinic, Johannes Kepler University, Linz, Austria. 119Massachusetts General Hospital, Boston, MA, USA. 120Washington University School of Medicine, St. Louis, MO, USA. 121Communication and Research Unit for Musculoskeletal Disorders (FORMI), Oslo University Hospital, Oslo, Norway. 122Department of Neurology, Oslo University Hospital, Oslo, Norway. 123Institute for Molecular Medicine Finland (FIMM), HiLIFE, University of Helsinki, Helsinki, Finland. 124Estonian Genome Center, Institute of Genomics, University of Tartu, Tartu, Estonia. 125llumina Inc., San Diego, CA, USA. 12623andMe Inc., Mountain View, CA, USA. 127Institute of Public Health, Charité – Universitätsmedizin Berlin, Berlin, Germany. 128Department of Biological Psychology,
Vrije Universiteit Amsterdam, Amsterdam, The Netherlands. 129Department of Neurology, Leiden University Medical Center, Leiden, The Netherlands. 130Institute for Stroke and Dementia Research, Klinikum der Universitaet Muenchen, Munich, Germany. 131Department of Neurology and Epileptology, Hertie Institute for Clinical Brain Research, University of Tuebingen, Tuebingen, Germany. 132Department of Neuroscience, Karolinska Institutet, Stockholm, Sweden. 133Institute of Human Genetics, University of Ulm, Ulm, Germany. 134Department of Radiology and Nuclear Medicine, Erasmus Medical Centre, Rotterdam, the Netherlands. 135Department of Clinical Chemistry, Fimlab Laboratories and Finnish Cardiovascular Research Center-Tampere, Faculty of Medicine and Life Sciences, University of Tampere, Tampere, Finland. 136Department of Ophthalmology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland. 137Department of Public Health, University of Helsinki, Helsinki, Finland. 138Brigham and Women’s Hospital, Boston, MA. 139Department of Neurology, University Hospital Essen, Germany. 140Landspitali National University Hospital, Reykjavik, Iceland. 141Avera Institute for Human Genetics, Sioux Falls, SD, USA. 142Department of Psychiatry, VU University Medical Center, Amsterdam, The Netherlands. 143Department of Neurology, Helsinki University Central Hospital, Helsinki, Finland. 144Institute for Molecular Bioscience, University of Queensland, Brisbane, Australia. 145Department of Medicine, Harvard Medical School, Boston, MA, USA. 146Boston VA Research Institute, Boston, MA, USA. 147Brigham Women’s Hospital Division of Aging, Harvard Medical School, Boston, MA, USA. 148Department of Physiology, Anatomy and Genetics, University of Oxford, Oxford, UK. 149Max Planck Institute of Psychiatry, Munich, Germany. 150Munich Cluster for Systems Neurology (SyNergy), Munich, Germany. 151Institute of Translational Medicine, University of Liverpool, Liverpool, UK. 152Institute of Clinical Molecular Biology, Kiel University and University Hospital Schleswig-Holstein, Kiel, Germany. 153Clinic of Internal Medicine I, University Hospital Schleswig-Holstein, Kiel, Germany. 154National Institute for Health and Welfare, Helsinki, Finland. 155Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, MA, USA. 156Kiel Pain and Headache Center, Kiel, Germany. 157Pediatric Neurology Research Group, Vall d’Hebron Research Institute, Autonomous University of Barcelona, Barcelona, Spain. 158Headache Unit, Neurology Department, Hospital Vall d’Hebron, Barcelona, Spain. 159Headache Research Group, VHIR, Autonomous University of Barcelona, Barcelona, Spain. 160Danish Headache Center, Rigshospitalet Glostrup and University of Copenhagen, Copenhagen, Denmark. 161Institute of Biological Psychiatry, Roskilde, Denmark. 162Department of Clinical Sciences, University of Copenhagen, Copenhagen, Denmark. 163Lundbeck Foundation Initiative for Integrative Psychiatric Research, iPSYCH, Aarhus, Denmark. 164Institute of Human Genetics, University Medical Center Hamburg-Eppendorf, Hamburg, Germany. 165Karolinska Institutet, Stockholm, Sweden. 166Department of Human Genetics, Leiden University Medical Center, Leiden, The Netherlands. 167Division of Clinical Neuroscience, Oslo University Hospital and University of Oslo, Oslo, Norway. 168Netherlands Twin Register, Vrije Universiteit, Amsterdam, the Netherlands. 169Division of Preventive Medicine, Brigham and Women’s Hospital, Boston, MA, USA. 170Statistical and Genomic Epidemiology Laboratory, Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Queensland, Australia. 171Department of Clinical and Experimental Epilepsy, UCL Institute of Neurology, London, UK. 172Centre for Genomic
Sciences, University of Hong Kong, Hong Kong. 173Epilepsy Research Centre, University of Melbourne, Heidelberg, Australia. 174Quantinuum Research LLC, San Diego, CA, USA. 175Cooper Medical School of Rowan University, Camden, NJ, USA. 176Thomas Jefferson University Hospital, Philadelphia, PA, USA. 177Children’s Hospital of Philadelphia, Philadelphia, PA, USA. 178Epilepsy Society, Chalfont-St-Peter, Bucks, UK. 179Centre de Recherche du Centre Hospitalier de l’Université de Montréal and Department of Neurosciences, Université de Montréal, Montréal, Canada. 180Neurogenetics Group, VIB-CMN, Antwerp, Belgium. 181University of Antwerp, Antwerp, Belgium. 182Department of Neurology, Antwerp University Hospital, Antwerp, Belgium. 183Department of Neurology, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium. 184Division of Neurology, Children’s Hospital of Philadelphia, Philadelphia, PA, USA. 185Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA. 186Department of Biomedical Sciences, Cooper Medical School of Rowan University, Camden, NJ, USA. 187Department of Psychiatry, Center for Neurobiology and Behavior, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA. 188NYU School of Medicine, New York, NY, USA. 189Amplexa Genetics A/S, Odense, Denmark. 190Institute of Mental Health, University of Nottingham, Nottingham, UK. 191Human Genetics, School of Life Sciences, University of Nottingham, Nottingham UK. 192Epilepsy Center/Neurocenter, Kuopio University Hospital, Kuopio, Finland. 193Institute of Clinical Medicine, School of Medicine, Faculty of Health Sciences, University of Eastern Finland, Kuopio, Finland. 194Department of Epileptology, University Bonn Medical Center, Bonn, Germany. 195Institute of Experimental Epileptology and Cognition Research, University Bonn Medical Center, Bonn, Germany. 196Department of Clinical and Experimental Epilepsy, NIHR University College London Hospitals Biomedical Research Centre, UCL Institute of Neurology, London. 197Department of Genetics, University Medical Center Utrecht, the Netherlands. 198Epilepsy Foundation in the Netherlands (SEIN), Heemstede, the Netherlands. 199Departments of Pediatrics and Neurology, Ohio State University, Columbus, OH, USA. 200Nationwide Children’s Hospital, Columbus, OH, USA. 201Department of Neurology, University of California, San Francisco, CA, USA. 202Department of Molecular and Cellular Therapeutics, Royal College of Surgeons in Ireland, Dublin, Ireland. 203Center for Molecular Medicine, University Medical Center Utrecht, Utrecht, the Netherlands. 204Danish Epilepsy Centre, Filadelfia, Dianalund, Denmark. 205Institute for Regional Health Services, University of Southern Denmark, Odense, Denmark. 206Trinity College Dublin, Dublin, Ireland. 207United Christian Hospital, Hong Kong. 208Hong Kong Sanatorium and Hospital, Hong Kong. 209Epilepsy Research Centre, University of Melbourne, Austin Health, Heidelberg, Australia. 210Department of Neurology, University of Cincinnati, Cincinnati, OH, USA. 211UC Gardner Neuroscience Institute, Cincinnati, OH, USA. 212Department of Neurology, Duke University School of Medicine, Durham, NC, USA. 213Cologne Center for Genomics (CCG), University of Cologne, Cologne, Germany. 214Department of Neurology, Beth Israel Deaconess Medical Center, Boston, MA, USA. 215Department of Neurology, Inselspital, Bern University Hospital, University of Bern, Switzerland. 216Department of Neurology, University of Munich Hospital, Grosshadern, University of Munich, Germany. 217Department of Medicine, The University of Melbourne, Austin Health, Melbourne, Victoria, Australia. 218Department of Paediatrics, Royal Children's Hospital, The University of Melbourne, Melbourne, Victoria, Australia. 219Florey...
Institute of Neuroscience and Mental Health, Melbourne, Victoria, Australia. 220Institute of Neuropathology, Bonn University Medical School, Bonn, Germany. 221UCL Institute of Neurology, London, UK. 222Chalfont Centre for Epilepsy, Bucks, UK. 223University Hospital of Wales, Cardiff, UK. 224Department of Neurology, Thomas Jefferson University, Philadelphia, PA, USA. 225Pediatric Neurology and Muscular Diseases Unit-Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health University of Genoa, "G. Gaslini" Institute, Genova, Italy. 226Department of Epileptology, University Hospital Bonn, Bonn, Germany. 227Section of Epileptology, Department of Neurology, University Hospital RWTH Aachen, Aachen, Germany. 228Institute of Applied Health Research, University of Birmingham, UK. 229Department of Neurology, Admiraal De Ruyter Hospital, Goes, The Netherlands. 230Laboratory of Neurogenetics, G. Gaslini Institute, Genova, Italy. 231Institute for Genomic Medicine, Columbia University Medical Center, New York, NY, USA. 232University of Liverpool, Liverpool, UK. 233Walton Centre NHS Foundation Trust, Liverpool, UK. 234Department of Neurology and Epileptology, University Hospital Tuebingen, Tuebingen, Germany. 235Department of Neurology, University of Ulm, Ulm, Germany. 236CWZ Hospital, Nijmegen, Netherlands. 237Department of Neurology, Medical University of Vienna, Austria. 238Hertie-Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany. 239German Center for Neurodegenerative Diseases (DZNE), Tübingen, Germany. 240Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, MD, USA. 241INSERM U1220, IRSD, Toulouse, France. 242Université Paul Sabatier, Toulouse, France. 243Centre for Genetic Epidemiology, Institute for Clinical Epidemiology and Applied Biometry, University of Tübingen, Germany. 244Department of Molecular Neuroscience, Institute of Neurology, University College London, London, UK. 245Division of Life Science, Hong Kong University of Science and Technology, Hong Kong Special Administrative Region, China. 246Department of Genetics, Center for Molecular Medicine, University Medical Center Utrecht, Utrecht, The Netherlands. 247Big Data Institute, Li Ka Shing Centre for Health Information and Discovery, University of Oxford, Oxford, UK. 248University of Lincoln, Lincoln, UK. 249Faculty of Health and Medicine, University of Newcastle, Callaghan, Australia. 250University of Newcastle, Callaghan, Australia. 251Hunter Medical Research Institute, Newcastle, Australia. 252Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA, USA. 253Division of Neurocritical Care and Emergency Neurology, Massachusetts General Hospital, Boston, MA, USA. 254Department of Cerebrovascular Diseases, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy. 255PhD Program in Neuroscience, University Milano-Bicocca, Monza, Italy. 256Austin Health, Heidelberg, Australia. 257University of Virginia Center for Public Health Genomics, University of Virginia, Charlottesville, VA, USA. 258Dept of Medicine, University of Maryland School of Medicine, Baltimore, MD, USA. 259Geriatrics Research and Education Clinical Center, Baltimore Veterans Administration Medical Center, Baltimore, MD, USA. 260Centre for Prevention of Stroke and Dementia, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK. 261Institute of Cardiovascular Research, Royal Holloway University of London, London, UK. 262Ashford & St Peters NHS Foundation Trust, Surrey, UK. 263University of Edinburgh, Edinburgh, UK. 264Instituto Nacional de Saúde Doutor Ricardo Jorge, Lisboa, Portugal. 265Biosystems and Integrative Sciences Institute - BioISI, University of Lisboa, Lisboa, Portugal. 266Department of
Clinical Neurosciences, University of Cambridge, Cambridge, UK.  
267Department of Neurology, Jagiellonian University Medical College, Kraków, Poland.  
268The Warren Alpert Medical School of Brown University, Providence, RI, USA.  
269Department of Neurology, College of Medicine-Jacksonville, University of Florida, Jacksonville, FL, USA.  
270University of Split School of Medicine, Split, Croatia.  
271University of North Carolina at Chapel Hill, Chapel Hill, NC, USA.  
272Icahn School of Medicine at Mount Sinai, New York, NY, USA.  
273Wellcome Centre for Human Genetics, Nuffield Department of Medicine, University of Oxford, Oxford, UK.  
274Oxford Centre for Diabetes, Endocrinology and Metabolism, Nuffield Department of Medicine, University of Oxford, Oxford, UK.  
275Department of Human Genetics, Wellcome Sanger Institute, Hinxton, Cambridgeshire, UK.  
276MRC Social, Genetic and Developmental Psychiatry Centre, King's College London, London, UK.  
277Genes and Disease Programme, Centre for Genomic Regulation (CRG), Barcelona, Spain.  
278Department of Adult Psychiatry, Poznan University of Medical Sciences, Poland.  
279Clinicum, Department of Public Health, University of Helsinki, Finland.  
280Department of Adolescent Psychiatry, Helsinki University Central Hospital, Helsinki, Finland.  
281Harvard Medical School/McLean Hospital, Belmont, MA, USA.  
282Norwegian Institute of Public Health, Oslo, Norway.  
283University of Oslo, Oslo, Norway.  
284Department of Medicine, Surgery and Dentistry "Scuola Medica Salernitana", University of Salerno, Italy.  
285Eating Disorders Unit, Department of Child and Adolescent Psychiatry, Medical University of Vienna, Vienna, Austria.  
286Center for Integrative Genomics, University of Lausanne, Lausanne, Switzerland.  
287Kartini Clinic, Portland, OR, USA.  
288Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA.  
289MRC Integrative Epidemiology Unit and Bristol Medical School, University of Bristol, Bristol, UK.  
290Zorg op Orde BV, Leidschendam, The Netherlands.  
291Division of Psychological & Social Medicine and Developmental Neurosciences, Faculty of Medicine, Technischen Universität Dresden, Dresden, Germany.  
292Department of Child & Adolescent Psychiatry & Psychosomatic Medicine of University Clinics, RWTH Aachen, Aachen, Germany.  
293Altrecht Eating Disorders Rintveld, Altrecht Mental Health Institute, Zeist, The Netherlands.  
294Faculty of Social Sciences, University of Utrecht, Utrecht, the Netherlands.  
295Medical Genetics Unit, Department SDB, University of Padova, Padova, Italy.  
296UOC Genetica ed Epidemiologia Clinica Az. Ospedaliera, Padova, Italy.  
297Department of Human Genetics, CHU Sart-Tilman, University of Liège, Liège, Belgium.  
298Department of Rheumatology, CHU Sart-Tilman, University of Liège, Liège, Belgium.  
299Department of Cancer Epidemiology and Prevention, Cancer Center and M. Sklodowska-Curie Institute of Oncology, Warsaw, Poland.  
300Department of Psychiatry, University of Medical Sciences, Poznan, Poland.  
301Department of Psychiatry, University of Perugia, Perugia, Italy.  
302Department of Mental and Physical Health and Preventive Medicine, University of Campania “Luigi Vanvitelli”, Naples, Italy.  
303Eating Disorders Unit, 1st Psychiatric Department, National and Kapodistrian University of Athens, Athens, Greece.  
304Aglaia Kyriakou Childrens Hospital, Athens, Greece.  
305Eating Disorders Unit, Department of Psychiatry, First Faculty of Medicine, Charles University, Prague, Czech Republic.  
306General University Hospital, Prague, Czech Republic.  
307Medical University of Vienna, Austria.  
308School of Psychology, Flinders University, Adelaide, Australia.  
309Division of Medical Genetics, University Hospital Basel, Basel, Switzerland.  
310Genomics Research Group, Department of Biomedicine, University of Basel, Basel,
Switzerland. 311 Vall d’Hebron Research Institute, Barcelona, Spain. 312 Institut de Recerca Sant Joan de Déu, Barcelona, Spain. 313 Institut de Biomedicina de la Universitat de Barcelona (IBUB), Barcelona, Spain. 314 Department of Genetics, Microbiology & Statistics, Faculty of Biology, University of Barcelona, Barcelona, Spain. 315 Centre for Genomic Regulation (CRG), Barcelona, Spain. 316 Departments of Psychology and Human & Molecular Genetics, College Behavioral and Emotional Health Institute, Virginia Commonwealth University, Richmond, Virginia. 317 Broad Institute of MIT and Harvard, Cambridge, USA. 318 NORMENT, Div. of Mental Health and Addiction, University of Oslo, Oslo, Norway. 319 Oslo University Hospital, Oslo, Norway. 320 Department of Psychology, University of Oslo, Norway. 321 K. G. Jebsen Centre for Research on Neuropsychiatric Disorders, University of Bergen, Bergen, Norway. 322 Department of Biological and Medical Psychology, University of Bergen, Bergen, Norway. 323 NORMENT, K.G. Jebsen Center for Psychosis Research, Department of Clinical Science, University of Bergen, Norway. 324 Department of Medical Genetics, Haukeland University Hospital, Bergen, Norway. 325 Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA. 326 Seaver Autism Center for Research and Treatment, Icahn School of Medicine at Mount Sinai, New York, NY, USA. 327 Department of Genetics and Genomic Sciences, and Institute for Genomics and Multiscale Biology, Icahn School of Medicine at Mount Sinai, New York, NY, USA. 328 The Mindich Child Health & Development Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA. 329 Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA. 330 McLaughlin Centre and Department of Molecular Genetics, University of Toronto, Toronto, Canada. 331 The Centre for Applied Genomics, Hospital for Sick Children, Toronto, Canada. 332 Biopsychosocial Corporation, Vienna, Austria. 333 Department of Psychiatry and Psychotherapy, Medical University of Vienna, Vienna, Austria. 334 Zentren für Seelische Gesundheit, BBRZ-Med, Vienna, Austria. 335 Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden. 336 Rheumatology Unit, Department of Medicine, Karolinska Institutet and Karolinska University Hospital, Solna, Sweden. 337 Weill Cornell Medical College, New York, New York, USA. 338 School of Medicine, University of North Dakota, Grand Forks, ND, USA. 339 Neuropsychiatric Research Institute, Fargo, ND, USA. 340 Department of Psychiatry & Biobehavioral Sciences, Semel Institute for Neuroscience & Human Behavior, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, CA, USA. 341 BioRealm, Walnut, California, USA. 342 Oregon Research Institute, Eugene, OR, USA. 343 Department of Psychiatry, University of California San Diego, La Jolla, CA, USA. 344 Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Instituto de Salud Carlos III, Madrid, Spain. 345 Department of Psychiatry, Hospital Universitari Vall d’Hebron, Barcelona, Spain. 346 Psychiatric Genetics Unit, Group of Psychiatry, Mental Health and Addiction, Vall d’Hebron Research Institute (VHIR), Universitat Autònoma de Barcelona, Barcelona, Spain. 347 Department of Psychiatry and Legal Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain. 348 Biomedical Network Research Centre on Mental Health (CIBERSAM), Instituto de Salud Carlos III, Madrid, Spain. 349 Universitat Autònoma de Barcelona, Barcelona, Spain. 350 Programa Corporatiu “Neurodevelopment Disorders along Life Span”, Institut Català de la Salut, Barcelona, Spain. 351 Clinica Galatea y PAIMM, Mental Health Program for Impaired Physicians, Barcelona, Spain. 352 Child and Adolescent Mental Health Unit, Hospital
Universitario Mútua de Terrassa, Barcelona, Spain. 
K.G. Jebsen Centre for Neuropsychiatric Disorders, Department of Biomedicine, University of Bergen, Norway. 
Division of Psychiatry, Haukeland University Hospital, Bergen, Norway. 
K.G. Jebsen Centre for Neuropsychiatric Disorders, Department of Clinical Science, University of Bergen, Norway. 
Institute of Medical Informatics and Statistics, Kiel University, Kiel, Germany. 
Child and Adolescent Psychiatry/Psychotherapy, University Medical Center, Goettingen, Germany. 
Institute of Psychiatry, Psychology and Neuroscience, King’s College London, London, UK. 
Clinic for Child and Adolescent Psychiatry and Psychotherapy, University of Duisburg-Essen, Essen, Germany. 
Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany. 
Department of Human Genetics, Radboud University Medical Center, Nijmegen, The Netherlands. 
Department of Psychiatry, Rudboud University Medical Center, Nijmegen, The Netherlands. 
Donders Institute for Brain, Cognition and Behaviour, Radboud University, Nijmegen, The Netherlands. 
Department of Cognitive Neuroscience, Donders Institute for Brain, Cognition and Behavior, Radboud University Medical Centre, Nijmegen, The Netherlands. 
Karakter Child and Adolescent Psychiatry University Center, Nijmegen, The Netherlands. 
Department of Psychiatry & Human Genetics, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, The Netherlands. 
Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, University Hospital Frankfurt, Frankfurt am Main, Germany. 
Laboratory of Psychiatric Neurobiology, Institute of Molecular Medicine, I.M. Sechenov First Moscow State Medical University, Moscow, Russia. 
Department of Translational Psychiatry, School for Mental Health and Neuroscience (MHeNS), Maastricht University, Maastricht, The Netherlands. 
Division of Molecular Psychiatry, Center of Mental Health, University of Wuerzburg, Wuerzburg, Germany. 
Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University Hospital Frankfurt, Goethe University, Frankfurt am Main, Germany. 
Center of Mental Health, Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University Hospital of Wuerzburg, Wuerzburg, Germany. 
School of Psychology, Cardiff University, UK. 
Central Institute of Mental Health, Department of Genetic Epidemiology in Psychiatry, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany. 
National Centre for Register-based Research, Aarhus University, Aarhus, Denmark. 
Hospital of Telemark, Kragerø, Norway. 
Department of Biomedicine and Human Genetics, Aarhus University, Aarhus, Denmark. 
Center for Integrative Sequencing (iSEQ), Aarhus University, Aarhus, Denmark. 
Aarhus Genome Center, Aarhus, Denmark. 
Department of Psychology, Emory University, Atlanta, GA, USA. 
Department of Medical Informatics and Clinical Epidemiology, Oregon Health & Science University, Portland, OR, USA. 
Department of Psychological and Brain Sciences, University of Iowa, Iowa City, IA, USA. 
Departamento de Genética, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil. 
ADHD Outpatient Clinic, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil. 
Neurosciences and Mental Health Program, Research Institute, Hospital for Sick Children, Toronto, Canada. 
University of Toronto, Toronto, Canada. 
Hospital for Sick Children, Toronto, Canada. 
Department of Psychiatry, University of California, Los Angeles, Los Angeles, CA, USA. 
Semel Institute for Neuroscience & Human Science. Author manuscript; available in PMC 2018 August 17.
Behavior, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, CA, USA. 391ADHD Outpatient Clinic, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil. 392Department of Psychiatry, Faculdade de Medicina, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil. 393Department of Psychiatry, University of California, San Francisco, San Francisco, CA, USA. 394Institute for Human Genetics, University of California, San Francisco, San Francisco, CA, USA. 395Weill Institute for Neurosciences, University of California, San Francisco, San Francisco, CA, USA. 396Department of Pharmacy and Biotechnology, University of Bologna, Bologna, Italy. 397Department of Psychiatry, University of British Columbia, Vancouver, Canada. 398Institute of Mental Health, University of British Columbia, Vancouver, Canada. 399Stella Maris Clinical Research Institute for Child and Adolescent Neuropsychiatry, Pisa, Italy.

400Sorbonne Université, INSERM, CNRS, Neuroscience Paris Seine, Institut de Biologie Paris Seine, Paris, France. 401NIHR Biomedical Research Centre in Mental Health Maudsley Hospital, London, UK. 402Department of Human Genetics, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, CA, USA. 403LifeOmic, Indianapolis, IN, USA. 404Department of Psychiatry and Behavioral Sciences, Duke University, Durham, NC, USA. 405University Clinic of Pediatrics, Faculty of Medicine, University of Coimbra, Coimbra, Portugal. 406Child Developmental Center, Hospital Pediátrico, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal. 407Mindich Child Health and Development Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA. 408Dept of Clinical Genetics, Our Lady's Children's Hospital, Crumlin, Dublin, Ireland. 409School of Medicine and Medical Science, University College Dublin, Dublin, Ireland. 410Division of Molecular Genome Analysis and Division of Cancer Genome Research, German Cancer Research Center (DKFZ), Heidelberg, Germany. 411Inserm U955, Psychiatrie Translationnelle, Créteil, France. 412Faculté de Médecine, Université Paris Est, Créteil, France. 413Fondation FondaMental, Créteil, France. 414Children's Hospital Los Angeles, Los Angeles, CA, USA. 415Yale Center for Genome Analysis, Yale University, New Haven, CT, USA. 416Department of Genetics, Yale University School of Medicine, New Haven, CT, USA. 417Division of Child and Adolescent Psychiatry, Department of Psychiatry and Human Behavior, Brown University, Providence, RI, USA. 418Institute of Neuroscience, Newcastle University, Newcastle, UK. 419Newcastle Upon Tyne Hospitals NHS Foundation Trust, Newcastle, UK. 420Northumberland, Tyne & Wear NHS Foundation Trust, Northumberland, UK. 421Genomics Medicine Ireland, Dublin, Ireland. 422Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden. 423Department of Psychiatry, Hospital for Sick Children and University of Toronto, Toronto, Canada. 424Program in Genetics and Genome Biology, Hospital for Sick Children, Toronto, Canada. 425Department of Psychiatry, Carver College of Medicine, University of Iowa, Iowa City, IA, USA. 426Division of Medical Genetics, Department of Medicine, University of Washington, Seattle, WA, USA. 427Department of Psychiatry, University of Illinois at Chicago, Chicago, IL, USA. 428Tufts University School of Medicine, Portland, ME, USA. 429Center for Psychiatric Research, Maine Medical Center Research Institute, Portland, ME, USA. 430Department of Psychiatry, Tufts University School of Medicine, Boston, MA, USA. 431Child and Adolescent Psychiatry Department, Robert Debre Hospital, APHP, Paris, France. 432Human Genetics and Cognitive Functions, Institut Pasteur, Paris, France. 433Centre d'Etudes et de Recherches en Psychopathologie et
Psychologie de la Santé (CERPPS), Université Toulouse Jean Jaurès, Toulouse, France. 434 CERESA, Toulouse, France. 435 Institut Universitaire de France, Paris, France. 436 Academic Centre on Rare Diseases University College Dublin (ACoRD/UCD), Dublin, Ireland. 437 McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA. 438 Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Munich, Germany. 439 Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Göttingen, Germany. 440 Department of Psychiatry and Behavioral Sciences, Johns Hopkins University, Baltimore, MD, USA. 441 Human Genetics Branch, National Institute of Mental Health, National Institutes of Health, US Department of Health and Human Services, Bethesda, MD, USA. 442 Molecular and Behavioral Neuroscience Institute, University of Michigan, Ann Arbor, MI, USA. 443 Department of Psychiatry, University of Michigan, Ann Arbor, MI, USA. 444 SRH University Heidelberg, Academy for Psychotherapy, Heidelberg, Germany. 445 Division of Neuroscience, School of Medicine, University of Dundee, Dundee, UK. 446 Advanced Interventions Service, NHS Tayside, Dundee, UK. 447 NORMENT, K.G. Jebsen Centre for Psychosis Research, Institute of Clinical Medicine, University of Oslo, Oslo, Norway. 448 Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway. 449 Cognitive Genetics and Cognitive Therapy Group, Neuroimaging, Cognition and Genomics (NICOG) Centre, School of Psychology and Discipline of Biochemistry, National University of Ireland Galway, Galway, Ireland. 450 Division of Psychiatry, University of Edinburgh, Edinburgh, UK. 451 Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden. 452 Center for Molecular Medicine, Karolinska University Hospital, Stockholm, Sweden. 453 Université Paris Est, Faculté de Médecine, Créteil, France. 454 Neuroscience Research Australia, Sydney, Australia. 455 School of Medical Sciences, University of New South Wales, Sydney, Australia. 456 Unidad de Salud Mental, Hospital Regional Universitario de Malaga, Malaga, Spain. 457 Instituto de Investigación Biomédica de Málaga (IBIMA), Malaga, Spain. 458 Department of Biomedicine, University of Basel, Basel, Switzerland. 459 Institute of Medical Genetics and Pathology, University Hospital Basel, Basel, Switzerland. 460 Institute of Neuroscience and Medicine (INM-1), Research Centre Jülich, Jülich, Germany. 461 Institute of Human Genetics, University of Bonn, Bonn, Germany. 462 Department of Psychiatry and Psychotherapy, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany. 463 School of Psychiatry, University of New South Wales, Sydney, Australia. 464 Black Dog Institute, Sydney, Australia. 465 University of Chicago, Chicago, IL, USA. 466 Washington University, St. Louis, MO, USA. 467 Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA. 468 Department of Psychiatry, Dalhousie University, Halifax, Canada. 469 National Institute of Mental Health, Klecan, Czech Republic. 470 Montreal Neurological Institute, McGill University, Montréal, Canada. 471 Department of Neurology and Neurosurgery, McGill University, Montréal, Canada. 472 Department of Psychiatry, McGill University, Montréal, Canada. 473 University College London, London, UK. 474 Center for Neurobehavioral Genetics, Semel Institute for Neuroscience & Human Behavior, University of California at Los Angeles, Los Angeles, CA, USA. 475 UMC Utrecht, Utrecht, The Netherlands. 476 SUNY Downstate Medical Center, Brooklyn, NY, USA. 477 Hospital for Psychiatry and Psychotherapy, Cologne, Germany. 478 Laboratory of Psychiatric Genetics, Department of Psychiatry, Poznan University of Medical Sciences, Science. Author manuscript; available in PMC 2018 August 17.
Poznan, Poland. 479Douglas Mental Health University Institute, McGill University, Montreal, Canada. 480Department of Translational Research in Psychiatry, Max-Planck Institute for Psychiatry, Munich, Germany. 481National Centre for Mental Health, MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Cardiff, UK. 482Department Complex Trait Genetics, Center for Neurogenomics and Cognitive Research, VU University, Amsterdam, The Netherlands. 483Department Clinical Genetics, VU University Medical Center, Amsterdam Neuroscience, Amsterdam, The Netherlands. 484Department of Neurology, Klinikum rechts der Isar, Technical University of Munich, Munich, Germany. 485Institute of Human Genetics, University of Bonn, Bonn, Germany. 486Department of Psychiatry (UPK), University of Basel, Basel, Switzerland. 487Discipline of Psychiatry, University of Adelaide, Adelaide, Australia. 488Queensland Brain Institute, University of Queensland, Brisbane, Australia. 489Bela Menso Brain and Behaviour Centre, James Cook University, Varsity Lakes, Australia. 490Bond University, Faculty of Society and Design, Robina, Australia. 491Division of Psychiatry, Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK. 492Centre for Genomic and Experimental Medicine, University of Edinburgh, Edinburgh, UK. 493Interfaculty Institute for Genetics and Functional Genomics, University Medicine Greifswald, Greifswald, Germany. 494Department of Biochemistry and Molecular Biology II, Institute of Neurosciences, Center for Biomedical Research, University of Granada, Granada, Spain. 495Bioinformatics Research Centre, Aarhus University, Aarhus, Denmark. 496Child Health Research Centre, University of Queensland, Brisbane, Australia. 497Child and Youth Mental Health Service, Children’s Health Queensland Health and Hospital Service, Brisbane, Australia. 498Brain and Mind Centre, University of Sydney, Sydney, Australia. 499School of Psychology and Counselling, Faculty of Health, Institute of Health and Biomedical Innovation, Queensland University of Technology, Queensland, Australia. 500University of Queensland, Brisbane, Australia. 501Department of Psychiatry, Harvard Medical School, Boston, MA, USA. 502Amsterdam Public Health Research Institute, VU Medical Center, Amsterdam, the Netherlands. 503Department of Research and Innovation, GGZ Ingeest, Specialised Mental Health Care, Amsterdam, the Netherlands. 504Janssen Research & Development LLC, Titusville, NJ, USA. 505Institute of Clinical Chemistry and Laboratory Medicine, University Medicine Greifswald, Greifswald, Germany. 506German Centre for Cardiovascular Research (DZHK e.V.), Partner Site Greifswald, Greifswald, Germany. 507Research School of Behavioural and Cognitive Neurosciences, Department of Psychiatry, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands. 508Department of Psychiatry GGZ INGEEST, Amsterdam, the Netherlands. 509Department of Cell Biology, SUNY Downstate Medical Center, Brooklyn, NY, USA. 510Mathison Centre for Mental Health Research & Education, Hotchkiss Brain Institute, Cumming School of Medicine, University of Calgary, Calgary, Canada. 511Departments of Psychiatry and Medical Genetics, Cumming School of Medicine, University of Calgary, Calgary, Canada. 512Krembil Research Institute, University Health Network, Toronto, Canada. 513Grupo de Genética Molecular, Instituto de Biología, Facultad de Ciencias Exactas y Naturales, Universidad de Antioquia, Medellín, Colombia. 514Johns Hopkins University School of Medicine, Baltimore, MD, USA. 515Department of Psychiatry, Sao Paulo Medical School, University of Sao Paulo, Sao Paulo, Brazil. 516Depto. Farmacogenética, Instituto Nacional de Psiquiatría Ramon de la Fuente Muñiz, Mexico City, Mexico. 517University of
Groningen, Groningen, the Netherlands. 518Department of Psychiatry, University of Groningen and University Medical Center, Groningen, the Netherlands. 519Department of Specialized Trainings, GGZ Drenthe Mental Health Care Services, Assen, the Netherlands. 520Ospedale San Raffaele, Milano, Italy. 521Bio4Dreams Srl, Milan, Italy. 522University of California, San Francisco, CA, USA. 523Yale University School of Medicine, New Haven, CT, USA. 524Department of Psychiatry, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands. 525Netherlands Institute for Neuroscience, Royal Netherlands Academy of Arts and Sciences, Amsterdam, the Netherlands. 526Department of Child and Adolescent Psychiatry, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands. 527Centre National Maladie 'Syndrome Rare Gilles de la Tourette', Groupe Hospitalier Pitié-Salpêtrière, Paris, France. 528Assistance Publique-Hôpitaux de Paris, Département de Neurologie, Groupe Hospitalier Pitié-Salpêtrière, Paris, France. 529Sorbonne Universités, UPMC Université Paris 06, UMR S 1127, CNRS UMR 7225, ICM, Paris, France. 530Bioinformatics Interdepartmental Program, University of California, Los Angeles, Los Angeles, CA, USA. 531De Basculè, Amsterdam, The Netherlands. 532Department of Child and Adolescent Psychiatry, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands. 533Carver College of Medicine, University of Iowa, Iowa City, IA, USA. 534MRC Unit on Risk & Resilience in Mental Disorders, Department of Psychiatry, University of Cape Town, Cape Town, South Africa. 535Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, USA. 536Department of Psychiatry and Human Behavior, University of California, Irvine, Irvine, CA, USA. 537Department of Neurology, University of Florida, Gainesville, FL, USA. 538Sección de Neuropediatría, Instituto de Biomedicina de Sevilla, Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Seville, Spain. 539Yulius Academy, Yulius Mental Health Organization, Barendrecht, The Netherlands. 540Department of Psychology, University of Denver, Denver, CO, USA. 541Faculdade de Medicina FMUSP, Universidade de São Paulo, São Paulo, Brazil. 542Unidad de Trastornos del Movimiento, Servicio de Neurología y Neurofisiología Clínica, Instituto de Biomedicina de Sevilla, Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Seville, Spain. 543Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Madrid, Spain. 544National Institute of Genomic Medicine (INMEGEN), Ciudad de México, Mexico. 545Clinical Research, Grupo Médico Carracci, Mexico City, Mexico. 546Departments of Neurology and Neurosurgery, University of Florida, Gainesville, FL, USA. 547Fixel Center for Neurological Diseases, University of Florida, Gainesville, FL, USA. 548McKnight Brain Institute, University of Florida, Gainesville, FL, USA. 549Department of Psychiatry, Yale School of Medicine, New Haven, CT, USA. 550Department of Biological Sciences, Purdue University, West Lafayette, Indiana, USA. 551Division of Adolescent and Child Psychiatry, Department of Psychiatry, Lausanne University Hospital, Lausanne, Switzerland. 552Child and Adolescent Mental Health Centre, Mental Health Services Capital Region Copenhagen, University of Copenhagen, Copenhagen, Denmark. 553Moscow Institute of Physics and Technology, Dolgoprudny, Institutsky 9, Moscow, Russia. 554Department of Psychiatry, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, CA, USA. 555Frederick W. Thompson Anxiety Disorders Centre, Sunnybrook Health Sciences Centre, Toronto, Canada. 556Department of Psychiatry, University of Toronto, Toronto, Canada. 557Division of...
Neuropsychiatry, University College London, London, UK. 558Department of Child and Adolescent Psychiatry, Faculty of Medicine, Technischen Universität Dresden, Dresden, Germany. 559Child and Adolescent Psychiatry Unit (UPIA), Department of Psychiatry, Federal University of São Paulo, Brazil. 560Yale Child Study Center, Yale University School of Medicine, New Haven, CT, USA. 561University Health Network, University of Toronto, Toronto, Canada. 562Youthdale Treatment Centers, Toronto, Canada. 563Groote Schuur Hospital, Cape Town, South Africa. 564Department of Molecular Biology and Genetics, Democritus University of Thrace, Alexandroupolis, Greece. 565Laboratory of Pharmaceutical Biotechnology, Ghent University, Ghent, Belgium. 566Pfizer, Inc., New York, NY, USA. 567Department of Child Psychiatry, Medical University of Warsaw, Warsaw, Poland. 568Sorbonne Université, Faculty of Médecine, Paris, France. 569Reference center for Gilles de la Tourette syndrome, Pitie-Salpetriere Hospital, Paris, France. 570Department of Physiology, Saint Antoine Hospital, Paris, France. 571Butler Hospital, Providence, RI, USA. 572Alpert Medical School of Brown University, Providence, RI, USA. 573Department of Psychiatry and Psychotherapy, University Medicine Greifswald, Greifswald, Germany. 574Institute of Human Genetics, University Hospital Essen, University Duisburg-Essen, Essen, Germany. 575INSEERM, U 1127, CNR S UMR 7225, Sorbonne Universités, UPMC Univ Paris 06 UMR S 1127, Paris, France. 576IGBMC, CNRS UMR 7104/INSERM U964/Université de Strasbourg, Illkirch, France. 577Vanderbilt University Medical Center, Nashville, TN, USA. 578Escuela de Ciencias de la Salud, Universidad Pontificia Bolivariana, Medellín, Colombia. 579Laboratorio de Genética Molecular, SIU, Universidad de Antioquia, Medellín, Colombia. 580School of Nursing, Louisiana State University Health Sciences Center, New Orleans, LA, USA. 581Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, The Netherlands. 582School of Biomedical Sciences and Pharmacy, The University of Newcastle, Callaghan, Australia. 583Priority Research Centre for Brain and Mental Health Research, Hunter Medical Research Institute, Newcastle, Australia. 584Schizophrenia Research Institute, Sydney, Australia. 585Institute of Mental Health, Singapore, Singapore. 586Assistance Publique - Hôpitaux de Paris, GH Pitié-Salpêtrière, Paris, France. 587Sorbonne Université, CNRS UMR 7222 Institut des Systèmes Intelligents et Robotiques, Paris, France. 588Departments of Medicine and Psychiatry, School of Medicine University of Cantabria-IDIVAL, University Hospital Marqués de Valdecilla, Santander, Spain. 589Minerva Neurosciences Inc., Waltham, MA, USA. 590Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel. 591VA Boston Healthcare System, Boston, MA, USA. 592APC Microbiome Ireland, University College Cork, Cork, Ireland. 593Department of Psychiatry, University College Cork, Cork, Ireland. 594Neuroimaging, Cognition and Genomics (NICOG) Centre, School of Psychology, National University of Ireland Galway, Galway, Ireland. 595Center for Psychiatric Genetics, NorthShore University HealthSystem Research Institute, Evanston, IL, USA. 596Department of Psychiatry and Behavioral Neuroscience, University of Chicago, Chicago, IL, USA. 597Arkin, Amsterdam, the Netherlands. 598Department for Congenital Disorders, Statens Serum Institut, Copenhagen, Denmark. 599Department of Medical Genetics, Medical University, Sofia, Bulgaria. 600Department of Molecular Bases of Human Genetics, Institute of Molecular Genetics, Russian Academy of Sciences, Moscow, Russia. 601Latvian Biomedical Research and Study Centre, Riga, Latvia. 602Vilnius University, Vilnius, Lithuania. 603Institute of Mental Health, Lee Kong Chian School of Medicine, Nanyang Technological University,
Singapore, Singapore. 604Department of Human Genetics, Institute of Molecular Genetics, Russian Academy of Sciences, Moscow, Russia. 605Hunter New England Local Health District, Newcastle, Australia. 606Department of Psychiatry, Institute of Helsinki, Helsinki, Finland. 607Department of Psychiatry, Psychosomastics and Psychotherapy, Center of Mental Health, University Hospital Wuerzburg, Wuerzburg, Germany. 608Department of Biomedicine, Aarhus University, Aarhus, Denmark. 609Department of Clinical Neuroscience, Centre for Psychiatry Research, Karolinska Institutet, Stockholm, Sweden. 610Centre for Neuroimaging and Cognitive Genomics (NICOG), National University of Ireland, Galway, Galway, Ireland. 611NCBES Galway Neuroscience Centre, National University of Ireland, Galway, Galway, Ireland. 612Department of Psychiatry, Royal College of Surgeons in Ireland, Dublin, Ireland. 613Philipps-Universität Marburg and Marburg University Hospital UKGM, Marburg, Germany. 614Department of Psychiatry and Psychotherapy, Jena University Hospital, Jena, Germany. 615Maastricht University Medical Centre, Maastricht, the Netherlands. 616Department of Psychiatry, King’s College London, London, UK. 617Melbourne Neuropsychiatry Centre, Department of Psychiatry, University of Melbourne & Melbourne Health, Victoria, Australia. 618Centre for Neural Engineering, Department of Electrical and Electronic Engineering, University of Melbourne, Victoria, Australia. 619Oxford Health NHS Foundation Trust, Oxford, UK. 620Department of Psychiatry, University of Oxford, Oxford, UK. 621Department of Psychiatry and Behavioral Sciences, NorthShore University HealthSystem Research Institute, Evanston, IL, USA. 622Faculty of Science, Medicine and Health, University of Wollongong, Wollongong, Australia. 623Yong Loo Lin School of Medicine, National University of Singapore, Singapore. 624Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore. 625School of Biomedical Sciences, Chinese University of Hong Kong, Shatin, Hong Kong. 626KIZ-CUHK Joint Laboratory of Bioresources and Molecular Research of Common Diseases, Kunming Institute of Zoology, Chinese Academy of Sciences, Kunming, China. 627Chinese University of Hong Kong, Hong Kong. 628Sheba Medical Center, Ramat Gan, Israel. 629Departments of Psychiatry and Genetics, Washington University School of Medicine, St. Louis, MO, USA. 630UCL Genetics Institute, University College London, London, UK. 631Centre for Psychiatry, Barts and the London School of Medicine and Dentistry, London, UK. 632School of Medicine & Public Health, University of Newcastle, Callaghan, Australia. 633Priority Research Centre for Health Behaviour, University of Newcastle, Callaghan, Australia. 634Research Unit, Sørlandet Hospital, Kristiansand, Norway. 635Department of Statistics and Applied Probability, University of California, Santa Barbara, CA, USA. 636Computational Research Division, Lawrence Berkeley National Laboratory, University of California at Berkeley, Berkeley, CA, USA. 637NSW Health Pathology, Newcastle, Australia. 638Virginia Institute for Psychiatric and Behavioral Genetics, Department of Psychiatry, Virginia Commonwealth University, Richmond, VA, USA. 639Institute of Psychiatry, Psychology & Neuroscience, Social Genetics & Developmental Psychiatry Center, MRC, Kings College London, London, UK. 640NIHR Maudsley Biomedical Research Centre, South London & Maudsley NHS Trust & King’s College London, London, UK. 641Departments of Psychiatry and Nutrition, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA. 642Departments of Psychiatry and of Neuroscience and Physiology, SUNY Upstate Medical University, Syracuse, NY, USA.
Psychiatry, Virginia Commonwealth University, Richmond, VA, USA.  
Division Biomedical Genetics, University Medical Center Utrecht, Utrecht, the Netherlands.  
Department of Psychiatry and UF Genetics Institute, University of Florida, Gainesville, FL, USA.  
Division of Cognitive and Behavioral Neurology, Brigham and Women’s Hospital, Boston, MA, USA.  
Department of Neurology, Yale School of Medicine, New Haven, CT, USA.  
Department of Genetics and Psychiatry, University of North Carolina School of Medicine, Chapel Hill, North Carolina, USA.  
Neuropsychiatric Genetics Research Group, Department of Psychiatry, Trinity College Dublin, Dublin, Ireland.

Corresponding author. verneri.anttila@gmail.com (V.A.); acorvin@tcd.ie (A.C.); bneale@broadinstitute.org (B.M.N.)

†These authors contributed equally to this work.

REFERENCES AND NOTES


25. See materials and methods and other supplementary materials.


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.

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<th>Psychiatric disorders</th>
<th>Source</th>
<th>Cases</th>
<th>Controls</th>
<th>Neurological disorders</th>
<th>Source</th>
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<td>Focal epilepsy</td>
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<td>4601*</td>
<td>17,985*</td>
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<td>20,352</td>
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<td>Cardioembolic stroke</td>
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<td>1859*</td>
<td>17,708*</td>
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<td>Early onset stroke</td>
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<td>33,640</td>
<td>43,456</td>
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</tr>
<tr>
<td>Migraine</td>
<td>IMSGC</td>
<td>59,673</td>
<td>316,078</td>
<td>Migraine</td>
<td>&quot;</td>
<td>6332*</td>
<td>142,817*</td>
</tr>
<tr>
<td>Migraine with aura</td>
<td>&quot;</td>
<td>8348*</td>
<td>136,758</td>
<td>Migraine without aura</td>
<td>&quot;</td>
<td>5545</td>
<td>12,153</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>IMSGC</td>
<td>5333</td>
<td>12,019</td>
<td>Parkinson’s disease</td>
<td>IPDGC</td>
<td>107,190</td>
<td>418,650</td>
</tr>
</tbody>
</table>

* 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.

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

* Sample counts represent overlap with preceding dataset.