

Analysis of shared heritability in common disorders of the brain

Brainstorm Consortium

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

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57

58
59 **One Sentence Summary: Comprehensive heritability analysis of brain phenotypes demonstrates a**
60 **clear role for common genetic variation across neurological and psychiatric disorders and**
61 **behavioral-cognitive traits, with substantial overlaps in genetic risk.**

62 **Abstract:** Disorders of the brain exhibit considerable epidemiological comorbidity and frequently share
63 symptoms, provoking debate about the extent of their etiologic overlap. We quantified the genetic sharing
64 of 24 brain disorders and 16 phenotypes based on summary statistics from genome-wide association studies.
65 Psychiatric disorders show substantial sharing of common variant risk, while neurological disorders appear
66 more distinct from one another. We observe limited evidence of sharing between neurological and
67 psychiatric disorders, but do identify sharing between several quantitative measures and brain disorders.
68 We also performed extensive simulations to explore power and the impact of diagnostic misclassification
69 and phenotypic heterogeneity. These results highlight the importance of common genetic variation as a
70 source of risk for brain phenotypes and the value of heritability-based methods in understanding their
71 etiology.

72 **Main Text:**

73 The classification of brain disorders has evolved over the past century, reflecting the
74 medical and scientific communities' best assessments of the presumed root causes of clinical
75 phenomena such as behavioral change, loss of motor function, spontaneous movements or
76 alterations of consciousness. A division between neurology and psychiatry developed, with the
77 more directly observable phenomena (such as the presence of emboli, protein tangles, or unusual
78 electrical activity patterns) generally defining the neurological disorders(1). Applying modern
79 methods to understand the genetic underpinnings and categorical distinctions between brain
80 disorders may be helpful in informing next steps in the search for the biological pathways that
81 underlie their pathophysiology(2, 3).

82 In general, brain disorders (here excepting those caused by trauma, infection or cancer)
83 show substantial heritability from twin and family studies (4). Epidemiological and twin studies
84 have explored patterns of phenotypic overlaps(5-7), and substantial comorbidity has been reported
85 for many pairs of disorders, including bipolar disorder-migraine(8), stroke-major depressive
86 disorder(MDD)(9), epilepsy-autism spectrum disorders (ASD) and epilepsy-attention deficit
87 hyperactivity disorder (ADHD)(10). Furthermore, neurological and psychiatric research has
88 shown that mutations in the same ion channel genes confer pleiotropic risk for multiple distinct
89 brain phenotypes(11-13). Recently, genome-wide association studies (GWAS) have demonstrated
90 that individual common risk variants show overlap across traditional diagnostic boundaries (14,

91 15), and that disorders like schizophrenia, MDD and bipolar disorder can have strong genetic
92 correlations(16).

93 GWAS have also demonstrated that common genetic variation substantially contributes to
94 the heritability of brain disorders. In most cases, this occurs via many common variants with small
95 risk effects, as has been the case with Alzheimer’s disease(17), bipolar disorder(18), migraine(19),
96 Parkinson’s disease(20), and schizophrenia(21). In addition to locus discovery, larger sample sizes
97 enable analyses of shared genetic influences, to improve our understanding of the degree of
98 distinctiveness of brain disorders(22). Using recently developed heritability-based methods(23)
99 we can now extend our evaluation of the nature of these diagnostic boundaries and explore the
100 extent of shared common variant genetic influences across a wide set of neurological and
101 psychiatric phenotypes.

102

103 *Study design*

104 We formed the Brainstorm consortium, a collaboration among GWAS meta-analysis
105 consortia of 24 disorders (see Data sources), to perform the first comprehensive heritability and
106 correlation analysis of brain disorders. The study sample consists of 212,367 brain disorder cases
107 and 647,979 controls (Table 1), including every common brain disorder for which we could
108 identify a meta-analysis consortium and reflecting the respective current diagnostic gold standards.
109 This includes at least the most common representative in each ICD-10 block in F20-59 (mental
110 and behavioral disorders) and G20-G47 (diseases of the central nervous system). Also included
111 are 1,113,280 samples for 12 “behavioral-cognitive” phenotypes (n=666,178) chosen for being
112 traditionally viewed as brain-related, and four “additional” phenotypes (n=447,102), selected to
113 represent known, well-delineated etiological processes (e.g. immune disorders [Crohn’s disease]
114 and vascular disease [coronary artery disease]; Table 2).

115 GWAS summary statistics for the 40 disorders and phenotypes were centralized and
116 underwent uniform quality control and processing(24). We generated European-only meta-
117 analyses for each disorder to avoid potential biases arising from ancestry differences, as many of
118 the brain disorder datasets included sample sets from diverse ancestries. We have recently
119 developed a novel heritability estimation method, linkage disequilibrium score regression
120 (LDSC)(23), which was used to calculate heritability estimates and correlations, as well as to
121 estimate their statistical significance from block jack-knife-based standard errors. Heritability for
122 binary disorders and phenotypes was transformed to liability-scale. We further performed a
123 weighted-least squares regression analysis to evaluate whether differences relating to study
124 makeup (such as sample size) were correlated with the magnitude of the correlation estimates. We
125 also performed a heritability partitioning analysis using stratified LD score regression to examine
126 whether the observed heritability was enriched in any tissue-specific regulatory partitions of the
127 genome, using the ten top-level tissue-type and 53 functional partitions from Finucane et al. (25).

128 Finally, simulated phenotype data was generated under several different scenarios by permuting
129 the 120,267 genotyped individuals from the UK Biobank (24) to both evaluate power and aid in
130 interpreting the results (see Supplementary Text).

131

132 *Heritability and correlations among brain disorders*

133 We observed a similar range of heritability estimates among the disorders and the
134 behavioral-cognitive phenotypes (Fig. S1A-B and Table S1, S2), roughly in line with previously
135 reported estimates in smaller datasets (see Table S3 and Supplementary Text). Three ischemic
136 stroke subtypes (cardioembolic, large-vessel disease and small-vessel disease) as well as the
137 “agreeableness” personality measure from NEO Five-Factor Inventory(26) had insufficient
138 evidence for additive heritability for robust analysis and were excluded from further analysis(24).
139 We did not observe a correlation between heritability estimates and factors relating to study
140 makeup (Table S4; Fig S1C-F).

141 In expanding on the number of pairwise comparisons in brain disorders, we observed
142 widespread sharing across psychiatric disorders (Fig. 1 and S3) beyond those previously reported
143 (16), but not among neurological disorders. Among the psychiatric disorders, schizophrenia in
144 particular showed significant genetic correlation with most of the psychiatric disorders. Further,
145 schizophrenia, bipolar disorder, anxiety disorders, MDD and ADHD each showed a high degree
146 of correlation to the four others (average $r_g=0.40$; Table S5). Anorexia nervosa, OCD and
147 schizophrenia also demonstrated significant sharing amongst themselves. Tourette’s syndrome
148 (TS) was only significantly correlated with OCD and migraine and not with any of the other
149 disorders. From this analysis, the common variant risk of both ASD and TS appear to be somewhat
150 distinct from other psychiatric disorders, although with some evidence of correlation between TS
151 and OCD and between ASD and schizophrenia. The modest power of the ASD and TS meta-
152 analyses, however, limits the strength of this conclusion.

153 Neurological disorders revealed greater specificity, and a more limited extent of genetic
154 correlation than the psychiatric disorders (Fig. 2 and S4, Table S5). Parkinson’s disease,
155 Alzheimer’s disease, generalized epilepsy and multiple sclerosis showed little to no correlation
156 with any other brain disorders. Focal epilepsy showed the highest degree of genetic correlation
157 among the neurological disorders (average $r_g =0.46$, excluding other epilepsy datasets), though
158 none were significant, reflecting the relatively modest power of the current focal epilepsy meta-
159 analysis. However, the modest heritability and the broad pattern of sharing observed for focal
160 epilepsy may be consistent with considerable heterogeneity and potentially even diagnostic
161 misclassification across a range of neurological conditions.

162 In the cross-category correlation analysis, the overall pattern is consistent with limited
163 sharing across the included neurological and psychiatric disorders (Fig. 3; average $r_g=0.03$). The
164 only significant cross-category correlations were with migraine, suggesting it may share some of

165 its genetic architecture with psychiatric disorders; migraine-ADHD ($r_g=0.26$, $p=8.81 \times 10^{-8}$),
166 migraine-TS ($r_g=0.19$, $p=1.80 \times 10^{-5}$), and migraine-MDD ($r_g=0.32$, $p=1.42 \times 10^{-22}$ for all
167 migraine, $r_g=0.23$, $p=5.23 \times 10^{-5}$ for migraine without aura, $r_g=0.28$, $p=1.00 \times 10^{-4}$ for migraine
168 with aura).

169 We observed several significant genetic correlations between the behavioral-cognitive or
170 additional phenotypes and brain disorders (Fig. 4 and S5, Table S6). Years of education showed a
171 significant correlation to each psychiatric disorder (negative for ADHD, anxiety disorders, MDD
172 and TS; positive for the others), while five neurological phenotypes (Alzheimer's disease and the
173 four "vascular" phenotypes, intracerebral hemorrhage, all and early-onset stroke and migraine)
174 showed a significant negative correlation (Fig. S6; correlations with bipolar disorder(23),
175 Alzheimer's disease and schizophrenia have been previously reported(27)). Among the personality
176 measures, significant positive correlations were observed for neuroticism (anxiety disorders,
177 migraine, migraine without aura and OCD; Fig. S7), depressive symptoms (ADHD, anxiety
178 disorder, bipolar disorder, MDD, and schizophrenia) and subjective well-being (anxiety disorder,
179 bipolar disorder, MDD, as well as replicating the previously reported correlation between
180 neuroticism with both MDD and schizophrenia(28)). For smoking-related measures, the only
181 significant genetic correlations were to never/ever smoked (MDD: $r_g=0.33$, $p=3.10 \times 10^{-11}$ and
182 ADHD: $r_g=0.37$, $p=3.15 \times 10^{-6}$).

183 Among the additional phenotypes, the two diseases chosen as examples of disorders with
184 well-defined etiologies had different results: Crohn's disease, representing immunological
185 pathophysiology, showed no correlation with any of the study phenotypes, while the phenotype
186 representing vascular pathophysiology (coronary artery disease) showed significant correlation to
187 MDD ($r_g=0.19$, $p=8.71 \times 10^{-5}$) as well as the two stroke-related phenotypes ($r_g=0.69$, $p=2.47 \times 10^{-6}$
188 to ischemic stroke and $r_g=0.86$, $p=2.26 \times 10^{-5}$ for early-onset stroke), suggesting shared genetic
189 effects across these phenotype. Significant correlations were also observed for BMI, which was
190 positively correlated with ADHD and MDD, and negative correlated with anorexia nervosa (as
191 previously reported with a different dataset(23)) and schizophrenia.

192 Functional enrichment analysis (Table S7 and S8) replicated the previously reported central
193 nervous system (CNS) enrichment for schizophrenia and bipolar disorder (here in a larger dataset
194 compared to the original report (25), but with considerable sample overlap). We also demonstrated
195 novel significant heritability enrichments to CNS (for generalized epilepsy, MDD, TS, college
196 attainment, neuroticism, never/ever smoked) and to immune system cells and tissues (multiple
197 sclerosis).

198

199 *Discussion*

200 By integrating and analyzing the current genome-wide association summary statistic data
201 from consortia of 24 brain disorders, we find that psychiatric disorders broadly share a

202 considerable portion of their common variant genetic risk, especially across schizophrenia, MDD,
203 bipolar disorder, anxiety disorder and ADHD, while neurological disorders are more genetically
204 distinct. Across categories, psychiatric and neurologic disorders share relatively little of their
205 common genetic risk, suggesting that multiple different and largely independently regulated
206 etiological pathways may give rise to similar clinical manifestations (e.g., psychosis, which
207 manifests in both schizophrenia(29) and Alzheimer’s disease(30)). Except for migraine, which
208 appears to share genetic architecture with psychiatric disorders, the existing clinical delineation
209 between neurology and psychiatry is recapitulated at the level of common variant risk for the
210 studied disorders.

211 Given that the broad and continuous nature of psychiatric disorder spectra in particular has
212 been clinically recognized for a long time(31-33), we evaluated whether diagnostic
213 misclassification (given that genetic correlations are always a function of the underlying
214 ascertained phenotypes) could cause the observed correlations. For example, substantial numbers
215 of cases progressing through multiple diagnoses over lifetime or some the diagnostic boundaries
216 between some phenotype pairs being particularly porous to misclassification, congruent with the
217 clinical controversies in classification, could give rise to the appearance of correlation. Previous
218 work(34) suggests that even substantial misclassification is likely insufficient to introduce high
219 levels of genetic correlation. We expanded on this work by performing a series of simulations
220 across a variety of scenarios. These simulations demonstrate that reasonable levels of
221 misclassification or changes in the exact level of heritability appear unlikely to induce substantial
222 changes in the estimated genetic correlation (Fig. S8, S9, Table S9 and Supplementary Text),
223 though the lower resulting heritability (Fig. S8A) would decrease the power to estimate the genetic
224 overlap (Fig S10). Further, such evidence of genetic overlap is unlikely to appear in the absence
225 of underlying genetic correlation (Table S10), as it is apparent that very high (up to 79%) degree
226 of misclassification would be required to produce the observed correlations in the absence of any
227 true genetic correlation. Therefore, the observed correlations suggest true sharing of a substantial
228 fraction of the common variant genetic architecture among psychiatric disorders as well as between
229 behavioral-cognitive measures and brain disorders.

230 The high degree of genetic correlation among the psychiatric disorders adds further
231 evidence that current clinical diagnostics do not reflect the underlying genetic etiology of these
232 disorders, and that genetic risk factors for psychiatric disorders do not respect clinical diagnostic
233 boundaries. This suggests an interconnected nature for their genetic etiology, in contrast to
234 neurological disorders, and underscores the need to refine psychiatric diagnostics. This study may
235 provide important ‘scaffolding’ to support a new research framework for investigating mental
236 disorders, incorporating many levels of information to understand basic dimensions of brain
237 function, such as through the National Institute of Mental Health’s RDoC initiative.

238 The observed positive genetic correlations are consistent with a few different scenarios.
239 For example, r_g may reflect the existence of some portion of common genetic risk factors
240 conferring equal risks to multiple disorders where other distinct additional factors contribute to the

241 eventual clinical presentation. The presence of significant genetic correlation may also reflect the
242 phenotypic overlap between any two disorders; for example, the sharing between schizophrenia
243 and ADHD might reflect underlying difficulties in executive functioning, which are well-
244 established in both disorders(35). Similarly, the sharing between anorexia nervosa, OCD and
245 schizophrenia may reflect a shared mechanism underlying cognitive biases that extend from
246 overvalued ideas to delusions. Another scenario is that a heritable intermediate trait confers risk to
247 multiple outcomes, thereby giving rise to the genetic correlation, as the genetic influences on this
248 trait will be shared for both outcomes (e.g., obesity as a risk factor for both type 2 diabetes and
249 coronary artery disease), or even that the majority common genetic effects are shared between a
250 pair of traits, but each individual effect may confer different degrees of risk and lead to different
251 aggregate genetic risk profiles. While a combination of these is likely, it will become increasingly
252 feasible to evaluate these overlaps at the locus level in the future as more genome-wide significant
253 loci are identified.

254 The low correlations observed across neurological disorders suggest that the current
255 classification reflects relatively specific genetic etiologies, although the limited sample size for
256 some of these disorders and lack of inclusion of disorders conceived as “circuit-based” in the
257 literature, such as restless legs syndrome, sleep disorders and possibly essential tremor, constrains
258 the generalizability of this conclusion. Generally, this analysis recapitulates the current
259 understanding of the relatively distinct primary etiology underlying these disorders; degenerative
260 disorders (such as Alzheimer’s and Parkinson’s diseases) would not be expected *a priori* to share
261 their polygenic risk profiles with a neuro-immunological disorder (like multiple sclerosis) or
262 neurovascular disorder (like ischemic stroke). Similarly, we see limited evidence for the reported
263 co-morbidity between migraine with aura and ischemic stroke(36) ($r_g=0.29$, $p=0.099$); however,
264 the standard errors of this comparison are too high to draw strong conclusions. At the disorder
265 subtype level, migraine with and without aura ($r_g=0.48$, $p=1.79 \times 10^{-5}$) show substantial genetic
266 correlation, while focal and generalized epilepsy ($r_g=0.16$, $p=0.388$) show much less.

267 The few significant correlations across neurology and psychiatry, namely between
268 migraine and ADHD, MDD and TS, suggest modest shared etiological overlap across the
269 neurology/psychiatry distinction. The co-morbidity of migraine with MDD and ADHD has been
270 previously reported in epidemiological studies (37-39), while in contrast, the previously reported
271 co-morbidity between migraine and bipolar disorder seen in epidemiological studies (40) was not
272 reflected in our estimate of genetic correlation ($r_g=-0.03$, $p=0.406$).

273 Several phenotypes show only very low-level correlations with any of the other studied
274 disorders and phenotypes, despite large sample size and robust evidence for heritability, suggesting
275 their common variant genetic risk may largely be unique. Alzheimer’s disease, Parkinson’s
276 disease, and multiple sclerosis show extremely limited sharing with the other phenotypes and with
277 each other. Neuroinflammation has been implicated in the pathophysiology of each of these
278 conditions(41-43), as it has for migraine(44) and schizophrenia(45), but no considerable shared
279 heritability was observed with either of those conditions nor with Crohn’s disease. While this

280 observation does not preclude shared neuroinflammatory mechanisms in these disorders, it does
281 suggest that on a large scale, common variant genetic influences on these inflammatory
282 mechanisms are not shared between the disorders. Further, we only observed significant
283 enrichment of heritability to immunological cells and tissues in multiple sclerosis, showing that
284 inflammation-specific regulatory marks in the genome do not show overall enrichment for
285 common variant risk for either Alzheimer's or Parkinson's diseases (though this does not preclude
286 the effects of specific, non-polygenic neuroinflammatory mechanisms(46)). Among psychiatric
287 disorders, ASD and TS showed a similar absence of correlation with other disorders, although this
288 could reflect small sample sizes.

289 Analysis of the Big Five personality measures suggests that the current sample sizes for
290 personality data are now starting to be sufficiently large for correlation testing; neuroticism, which
291 has by far the largest sample size, shows a number of significant correlations. Most significant of
292 these was to MDD ($r_g=0.737$, $p=5.04 \times 10^{-96}$), providing further evidence for the link between
293 these phenotypes, reported previously with polygenic risk scores(47) and twin studies(48, 49);
294 others included schizophrenia, anxiety disorders, migraine, migraine without aura, and OCD
295 (Table S6). Further, the observation of strong correlation between MDD and anxiety disorders
296 together with their remarkably strong and similar patterns of correlation between each of these
297 disorders and the dimensional measures of depressive symptoms, subjective well-being, and
298 neuroticism suggests that they all tag a fundamentally similar underlying etiology. The novel
299 significant correlation between coronary artery disease and MDD supports the long-standing
300 epidemiological observation of a link between MDD and CAD(50), while the observed correlation
301 between ADHD and smoking initiation ($r_g=0.374$, $p=3.15 \times 10^{-6}$) is consistent with the
302 epidemiological evidence of overlap(51) and findings from twin studies(52), supporting the
303 existing hypothesis that impulsivity inherent in ADHD may drive smoking initiation and
304 potentially dependence (though other explanations, such as reward system dysfunction would fit
305 as well).

306 For the neurological disorders, five (Alzheimer's disease, intracerebral hemorrhage,
307 ischemic and early-onset stroke, and migraine) showed significant negative genetic correlation to
308 the cognitive measures, while a further two (epilepsy and focal epilepsy) showed moderate
309 negative genetic correlation (Fig. S6). For Alzheimer's disease, poor cognitive performance in
310 early life has been linked with increased risk for developing the disorder in later life(53), but to
311 our knowledge no such connection has been reported for the other phenotypes. ADHD, anxiety
312 disorders and MDD show a significant negative correlation to cognitive and education attainment
313 measures, while the remaining five of the eight psychiatric disorders (anorexia nervosa, ASD,
314 bipolar disorder, OCD, and schizophrenia) showed significant positive genetic correlation with
315 one or more cognitive measures. These results strongly suggest the existence of a link between
316 cognitive performance already in early life and the genetic risk for both psychiatric and
317 neurological brain disorders. The basis of the genetic correlations between education, cognition
318 and brain disorders may have a variety of root causes including, indexing performance differences

319 based on behavioral dysregulation (e.g., ADHD relating to attentional problems during cognitive
320 tests) or may reflect ascertainment biases in certain disorders conditional on impaired cognition
321 (e.g., individuals with lower cognitive reserve being more rapidly identified for Alzheimer's
322 disease).

323 BMI shows significant positive genetic correlation to ADHD, consistent with a meta-
324 analysis linking ADHD to obesity(54), and negative genetic correlation with anorexia nervosa,
325 OCD and schizophrenia. These results connect well with the evidence for enrichment of BMI
326 heritability in CNS tissues(25) and that many reported signals suggest neuronal involvement(55);
327 this may also provide a partial genetic explanation for lower BMI in anorexia nervosa patients
328 even after recovery(56). Given that no strong correlations were observed between BMI and any of
329 the neurological phenotypes, it is possible to hypothesize that BMI's brain-specific genetic
330 architecture is more closely related to behavioral phenotypes. Ischemic stroke and BMI show
331 surprisingly little genetic correlation in this analysis ($r_g=0.07$, $p=0.26$), suggesting that although
332 BMI is a strong risk factor for stroke(57), there is little evidence for shared common genetic effects.
333 These analyses also suggest that the reported reduced rates of cardiovascular disease in individuals
334 with histories of anorexia nervosa (58, 59) are due to BMI-related effects; with the limited evidence
335 of genetic correlation of anorexia nervosa with intracerebral hemorrhage, ischemic stroke, early-
336 onset stroke and coronary artery disease, these results suggest that any lower cardiovascular
337 mortality is more likely due to direct BMI-related effects rather than shared common genetic risk
338 variants.

339 Broadly it is apparent that the current clinical boundaries for the studied psychiatric
340 phenotypes do not appear to reflect distinct underlying pathogenic processes based on the genetic
341 evidence, while in contrast, the studied neurological disorders show much greater genetic
342 specificity. Although it is important to emphasize that while some disorders are under-represented
343 here (e.g. personality disorders in psychiatry and circuit-based disorders such as restless leg
344 syndrome in neurology), these results clearly demonstrate the limited evidence for widespread
345 common genetic risk sharing between psychiatric and neurological disorders, while on the other
346 hand providing strong evidence for links between them and behavioral-cognitive measures. We
347 highlight the need for some degree of restructuring of psychiatric nosology and that genetically
348 informed analyses may provide a good basis for such activities, consistent with the historical
349 knowledge from twin- and family-based results. Further elucidation of individual disorders and
350 their genetic overlap, especially as distinct loci map onto a subset of disorders and etiological
351 processes, may form the basis for either defining new clinical phenotypes or support a move to a
352 more continuous view of psychiatric phenotypes. Ultimately, such developments give hope for
353 reducing diagnostic heterogeneity and eventually improving the diagnosis and treatment of
354 psychiatric disorders.

355

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517 available either directly from, or via application submitted in, the web addresses listed below. Data on coronary artery
518 disease has been contributed by CARDIoGRAMplusC4D investigators and have been downloaded from
519 www.CARDIOGRAMPLUSC4D.ORG. matSpD is available at neurogenetics.qimrberghofer.edu.au/matSpD/. This
520 research has been conducted using the UK Biobank Resource (application #18597).

521
522

523 **Data sources**

524 **Disorder or phenotype – Consortium or dataset identifier – web address:**

525 *Psychiatric disorders*

526 ADHD – PGC-ADD2 - <http://www.med.unc.edu/pgc/results-and-downloads>
527 Anorexia nervosa – PGC-ED - <http://www.med.unc.edu/pgc/results-and-downloads>
528 Anxiety disorder – ANGST - <http://www.med.unc.edu/pgc/results-and-downloads>
529 Autism spectrum disorders(16) – PGC-AUT - <http://www.med.unc.edu/pgc/results-and-downloads>
530 Bipolar disorder – PGC-BIP2 - <http://www.med.unc.edu/pgc/results-and-downloads> (soon)
531 Major depressive disorder – PGC-MDD2 - <http://www.med.unc.edu/pgc/results-and-downloads> (soon)
532 OCD – IOCDFGC - <https://iocdf.org/>
533 Schizophrenia(21) – PGC-SCZ2 - <http://www.med.unc.edu/pgc/results-and-downloads>
534 Tourette Syndrome – TSAIGC – <http://www.med.unc.edu/pgc/results-and-downloads>

535

536 *Neurological disorders*

537 Alzheimer's disease(17) – IGAP - <http://www.pasteur-lille.fr/en/recherche/u744/igap>
538 Epilepsy and subtypes, focal and generalized(60) – ILAE – http://www.epigad.org/page/show/gwas_index
539 Intracerebral hemorrhage(61) – ISGC - <http://www.strokegenetics.com/>
540 Ischemic stroke and subtypes (cardioembolic, early-onset, small-vessel and large-vessel)(62) – METASTROKE
541 dataset of the ISGC – <http://www.strokegenetics.com/>
542 Migraine and subtypes, migraine with and without aura – IHGC – www.headachegenetics.org
543 Multiple sclerosis(63) – IMSGC - http://eaglep.case.edu/imsgc_web
544 Parkinson's disease(20) – IPDGC – www.pdgene.org

545

546 *Behavioral-cognitive phenotypes*

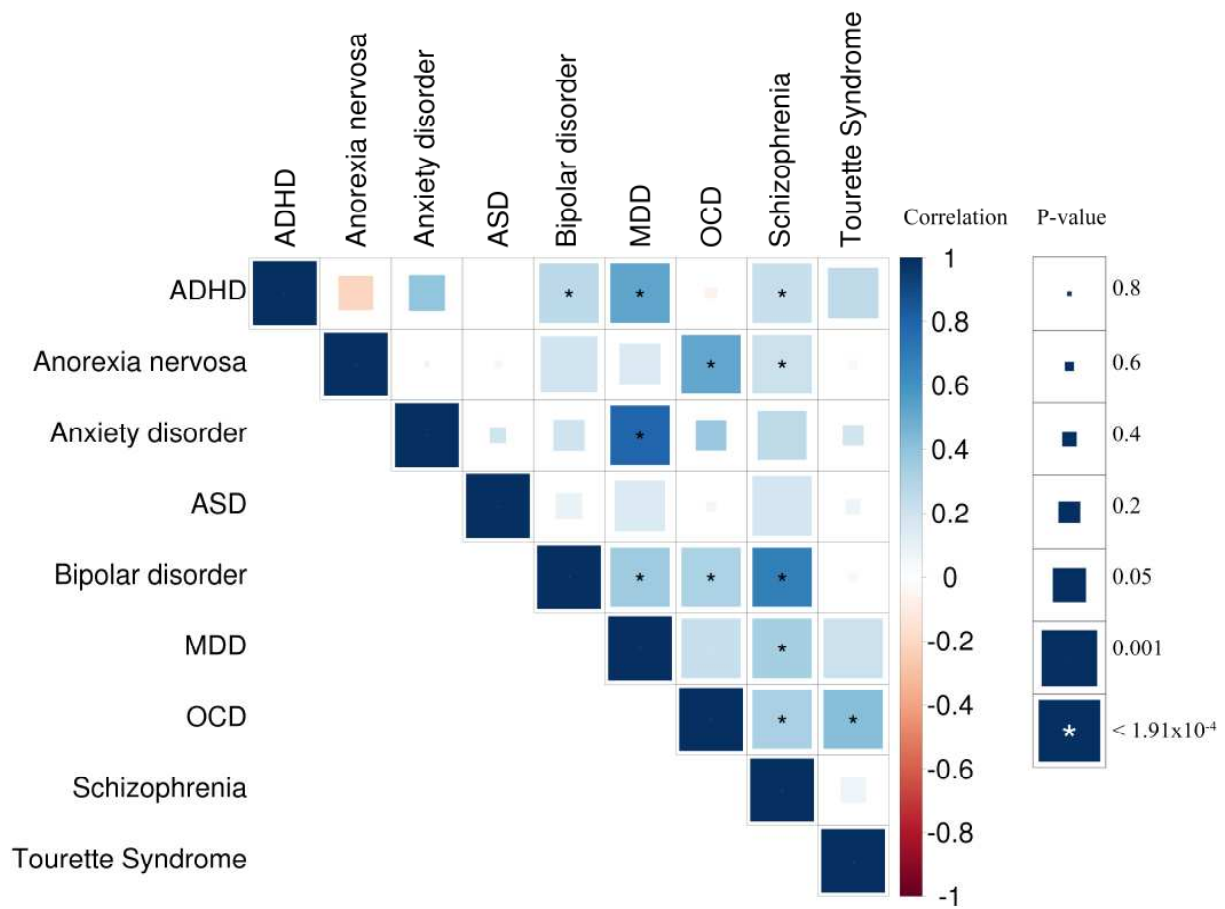
547 College attainment, years of education(64) – SSGAC – <http://www.thessgac.org/data>
548 Childhood cognitive performance(65) – SSGAC – <http://www.thessgac.org/data>
549 Extraversion, agreeableness, conscientiousness and openness (26) – GPC – <http://www.tweelingenregister.org/GPC/>
550 Neuroticism, depressive symptoms and subjective well-being (66) – SSGAC - <http://www.thessgac.org/data>
551 Never/ever smoked, cigarettes per day(67) - TAG - <http://www.med.unc.edu/pgc/results-and-downloads>

552

553 *Additional phenotypes*

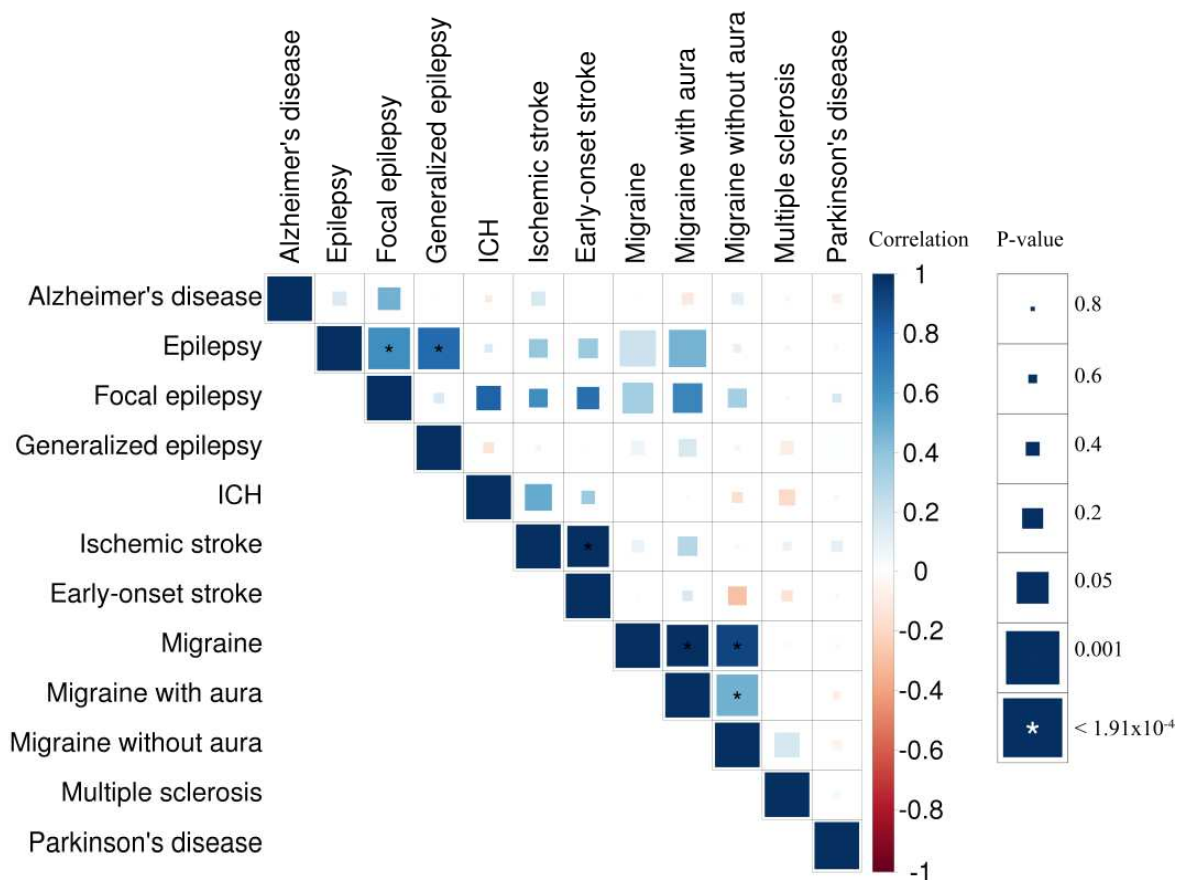
554 BMI(55) – GIANT – <https://www.broadinstitute.org/collaboration/giant>
555 Height(68) – GIANT – <https://www.broadinstitute.org/collaboration/giant>
556
557 Crohn's disease(69) – IIBDGC - <http://www.ibdgenetics.org/downloads.html>
558 Coronary artery disease(70) – Cardiogram – <http://www.cardiogramplusc4d.org/downloads/>

559 **Figure 1.** Genetic correlation matrix across psychiatric phenotypes.

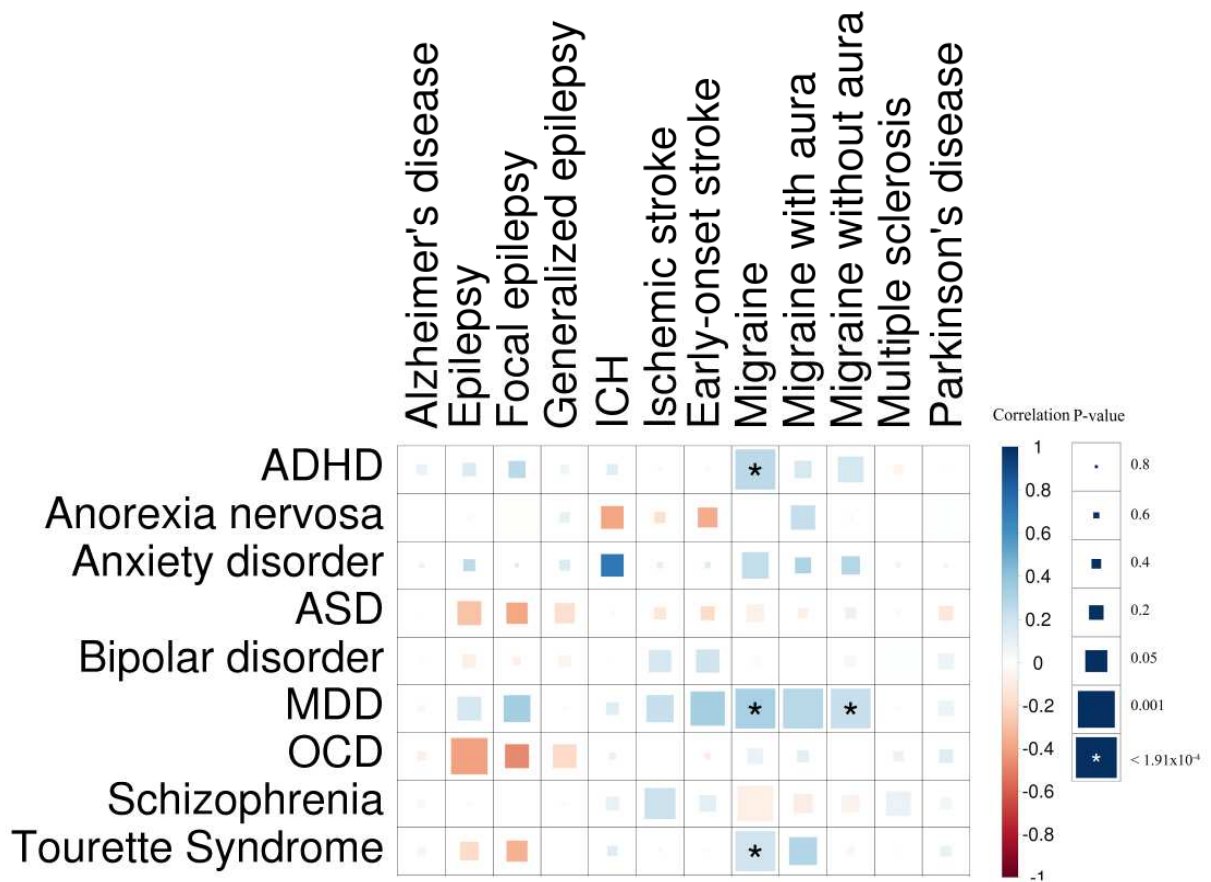


560
 561 *Color of each box indicates the magnitude of the correlation, while size of the boxes indicates its significance, with*
 562 *significant correlations filling each box completely. Asterisks indicate genetic correlations which are significant*
 563 *after Bonferroni correction. ADHD – attention deficit hyperactivity disorder; ASD – autism spectrum disorder;*
 564 *MDD – major depressive disorder; OCD – obsessive-compulsive disorder.*

565 **Figure 2.** Genetic correlation matrix across neurological phenotypes.



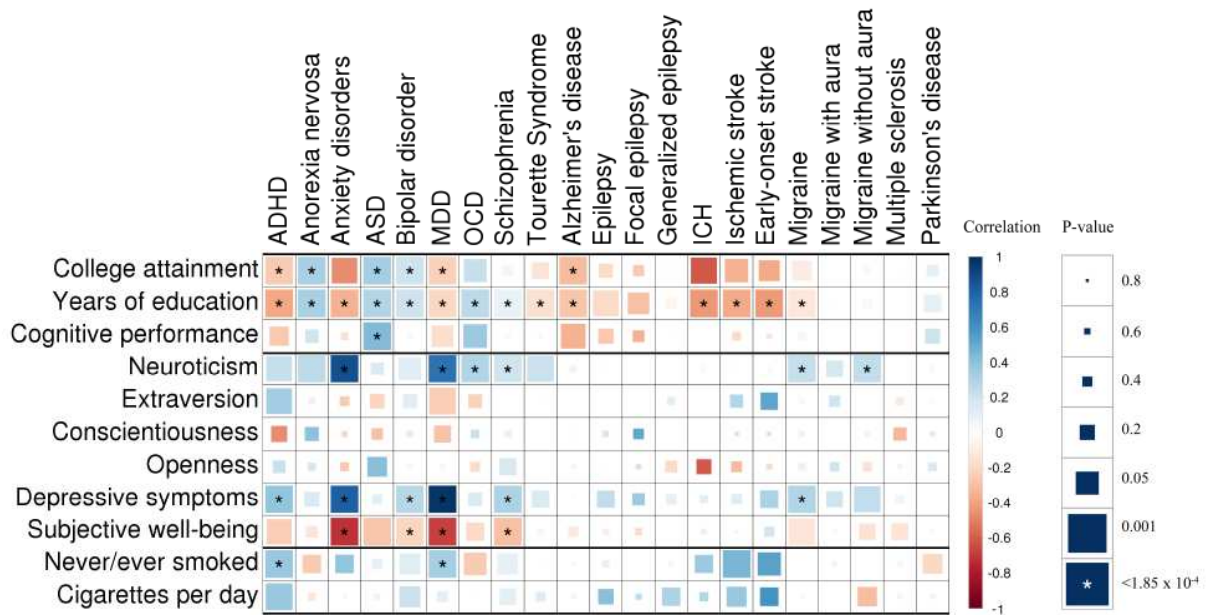
573 **Figure 3.** Genetic correlation matrix across neurological and psychiatric phenotypes.



574

575 *Color of each box indicates the magnitude of the correlation, while size of the boxes indicates its significance, with*
 576 *significant correlations filling each box completely. Asterisks indicate genetic correlations which are significant*
 577 *after Bonferroni correction. ADHD – attention deficit hyperactivity disorder; ASD – autism spectrum disorder; ICH*
 578 *– intracerebral hemorrhage; MDD – major depressive disorder; OCD – obsessive-compulsive disorder.*

579 **Figure 4.** Genetic correlation matrix across brain disorders and behavioral-cognitive phenotypes.



580

581 Color of each box indicates the magnitude of the correlation, while size of the boxes indicates its significance, with
 582 significant correlations filling each box completely. Asterisks indicate genetic correlations which are significant
 583 after Bonferroni correction. ADHD – attention deficit hyperactivity disorder; ASD – autism spectrum disorder; ICH
 584 – intracerebral hemorrhage; MDD – major depressive disorder; OCD – obsessive-compulsive disorder; BMI –
 585 body-mass index.

586 **Table 1.** Brain disorder phenotypes used in the Brainstorm project. Indented phenotypes are part of a larger whole,
587 e.g. the epilepsy study consists of the joint analysis of focal epilepsy and generalized epilepsy. Numbers in gray denote
588 a sample set which is non-unique, e.g. cardioembolic stroke samples are a subset of ischemic stroke samples. ADHD
589 – attention deficit hyperactivity disorder; OCD – obsessive-compulsive disorder. ‘Anxiety disorders’ refers to a meta-
590 analysis of five subtypes (generalized anxiety disorder, panic disorder, social phobia, agoraphobia and specific
591 phobias). Source details are listed under Data Sources and the references in Table S1.

592

Psychiatric disorders				Neurological disorders			
Disorder	Source	Cases	Controls	Disorder	Source	Cases	Controls
ADHD	PGC-ADD2	12,645	84,435	Alzheimer's disease	IGAP	17,008	37,154
Anorexia nervosa	PGC-ED	3,495	11,105	Epilepsy	ILAE	7,779	20,439
Anxiety disorders	ANGST	5,761	11,765	Focal epilepsy	"	4,601	17,985
Autism spectrum disorder	PGC-AUT	5,305	5,305	Generalized epilepsy	"	2,525	16,244
Bipolar disorder	PGC-BIP2	20,352	31,358	Intracerebral hemorrhage	ISGC	1,545	1,481
Major depressive disorder	PGC-MDD2	16,823	25,632	Ischemic stroke	METASTROKE	10,307	19,326
OCD	PGC-OCCTS	2,936	7,279	Cardioembolic stroke	"	1,859	17,708
Schizophrenia	PGC-SCZ2	33,640	43,456	Early-onset stroke	"	3,274	11,012
Tourette Syndrome	PGC-OCCTS	4,220	8,994	Large-vessel disease	"	1,817	17,708
				Small-vessel disease	"	1,349	17,708
				Migraine	IHGC	59,673	316,078
				Migraine with aura	"	6,332	142,817
				Migraine without aura	"	8,348	136,758
				Multiple sclerosis	IMSGC	5,545	12,153
				Parkinson's disease	IPDGC	5,333	12,019
<i>Total psychiatric</i>		<i>105,177</i>	<i>229,329</i>	<i>Total neurologic</i>		<i>107,190</i>	<i>418,650</i>

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595 **Table 2.** Behavioral-cognitive and additional phenotypes used in the study. Numbers in gray denote overlapping study
 596 sets, e.g. samples in the college attainment analysis are a subset of those in the analysis for years of education. (d) –
 597 dichotomous phenotype, (q) – quantitative phenotype. BMI – body-mass index. Source details are listed under Data
 598 Sources, while references are listed in Table S2.

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

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602	Supplementary Materials
603	Materials and methods
604	Supplementary Text
605	Comparison with previous heritability estimates
606	Effect of misclassification
607	Correlation by misclassification alone
608	Study-specific acknowledgements
609	Consortium memberships
610	Figures S1-10
611	Tables S1-9