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Analysis of Shared Heritability in Common Disorders of the Brain

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

61 **Abstract:** Disorders of the brain exhibit considerable epidemiological comorbidity and frequently share
62 symptoms, provoking debate about the extent of their etiologic overlap. We quantified the genetic sharing
63 of 25 brain disorders based on summary statistics from genome-wide association studies of 215,683
64 patients and 657,164 controls, and their relationship to 17 phenotypes from 1,191,588 individuals.
65 Psychiatric disorders show substantial sharing of common variant risk, while neurological disorders
66 appear more distinct from one another. We observe limited evidence of sharing between neurological and
67 psychiatric disorders, but do identify robust sharing between disorders and several cognitive measures, as
68 well as disorders and personality types. We also performed extensive simulations to explore how power,
69 diagnostic misclassification and phenotypic heterogeneity affect genetic correlations. These results
70 highlight the importance of common genetic variation as a source of risk for brain disorders and the value
71 of heritability-based methods in understanding their etiology.

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

81 In general, brain disorders (here excepting those caused by trauma, infection or cancer)
82 show substantial heritability from twin and family studies (4). Epidemiological and twin studies
83 have explored patterns of phenotypic overlaps(5-7), and substantial comorbidity has been
84 reported for many pairs of disorders, including bipolar disorder-migraine(8), stroke-major
85 depressive disorder(MDD)(9), epilepsy-autism spectrum disorders (ASD) and epilepsy-attention
86 deficit hyperactivity disorder (ADHD)(10, 11). Furthermore, neurological and psychiatric
87 research has shown that mutations in the same ion channel genes confer pleiotropic risk for
88 multiple distinct brain phenotypes(12-14). Recently, genome-wide association studies (GWAS)
89 have demonstrated that individual common risk variants show overlap across traditional
90 diagnostic boundaries (15, 16), and that disorders like schizophrenia, MDD and bipolar disorder
91 can have strong genetic correlations(17).

92 GWAS have also demonstrated that common genetic variation substantially contributes
93 to the heritability of brain disorders. In most cases, this occurs via many common variants, each
94 of small effect, with examples in Alzheimer’s disease(18), bipolar disorder(19), migraine(20),
95 Parkinson’s disease(21), and schizophrenia(22). In addition to locus discovery, the degree of
96 distinctiveness (23) across a wide set of neurological and psychiatric phenotypes can now be
97 evaluated with the introduction of novel heritability-based methods(24) and sufficiently large
98 sample sizes. These analyses can shed light on the nature of these diagnostic boundaries and
99 explore the extent of shared common variant genetic influences.

100

101 *Study design*

102 We formed the Brainstorm consortium, a collaboration among GWAS meta-analysis
103 consortia of 25 disorders (see Data sources), to perform the first comprehensive heritability and
104 correlation analysis of brain disorders. We included all common brain disorders for which we
105 could identify a GWAS meta-analysis consortium of sufficient size for heritability analysis that
106 was willing to participate. The total study sample consists of 215,683 cases of different brain
107 disorders and 657,164 controls (Table 1), and provides coverage of a majority of ICD-10 blocks
108 covering mental and behavioral disorders and diseases of the central nervous system. Also
109 included are 1,191,588 samples for 13 “behavioral-cognitive” phenotypes (n=744,486) chosen
110 for being traditionally viewed as brain-related, and four “additional” phenotypes (n=447,102)
111 selected to represent known, well-delineated etiological processes (e.g. immune disorders
112 [Crohn’s disease] and vascular disease [coronary artery disease]; Table 2) or anthropomorphic
113 measures (height and BMI).

114 GWAS summary statistics for the 42 disorders and phenotypes were centralized and
115 underwent uniform quality control and processing(25). Where necessary, we generated
116 European-only meta-analyses for each disorder to avoid potential biases arising from ancestry
117 differences, as many of the brain disorder datasets included sample sets from diverse ancestries.
118 Clinically relevant subtypes from three disorders (epilepsy, migraine and ischemic stroke) were
119 also included; in these cases, the analyzed datasets are subsets of the top-level dataset, as shown
120 in Table 1.

121 We have recently developed a novel heritability estimation method, linkage
122 disequilibrium score regression (LDSC)(24), which was used to calculate heritability estimates
123 and correlations, as well as to estimate their statistical significance from block jack-knife-based
124 standard errors. Heritability for binary disorders and phenotypes was transformed to the liability-
125 scale. We further performed a weighted-least squares regression analysis to evaluate whether
126 differences relating to study makeup (such as sample size) were correlated with the magnitude of
127 the correlation estimates. We also performed a heritability partitioning analysis using stratified
128 LD score regression to examine whether the observed heritability was enriched in any tissue-

129 specific regulatory partitions of the genome, using the ten top-level tissue-type and 53 functional
130 partitions from Finucane et al. (26). Finally, simulated phenotype data was generated under
131 several different scenarios by permuting the 120,267 genotyped individuals from the UK
132 Biobank (25) to both evaluate power and aid in interpreting the results (see Supplementary Text).

133

134 *Heritability and correlations among brain disorders*

135 We observed a similar range of heritability estimates among the disorders and the
136 behavioral-cognitive phenotypes (Fig. S1A-B and Table S1, S2), roughly in line with previously
137 reported estimates obtained from smaller datasets (see Table S3 and Supplementary Text). Three
138 ischemic stroke subtypes (cardioembolic, large-vessel disease and small-vessel disease) as well
139 as the “agreeableness” personality measure from NEO Five-Factor Inventory(27) had insufficient
140 evidence of additive heritability for robust analysis and thus were excluded from further
141 analysis(25). We did not observe a correlation between heritability estimates and factors relating
142 to study makeup (Table S4; Fig. S1C-F). Since some of the results interpretation depends on lack
143 of observed correlation, we explored the behavior of observed correlation vs power (Fig. S2A),
144 standard errors (Fig. S2B) and the individual results (Fig. S2C and D) to identify where we can
145 be reasonably robust in claiming lack of correlation with current datasets.

146 In expanding on the number of pairwise comparisons in brain disorders, we observed
147 widespread sharing across psychiatric disorders (Fig. 1 and S3) beyond those previously reported
148 (17), but not among neurological disorders. Among the psychiatric disorders, schizophrenia
149 showed significant genetic correlation with most of the psychiatric disorders, while MDD was
150 positively (though not necessarily significantly) correlated with every other disorder tested.
151 Further, schizophrenia, bipolar disorder, anxiety disorders, MDD and ADHD each showed a high
152 degree of correlation to the four others (average $r_g=0.40$; Table S5). Anorexia nervosa,
153 obsessive-compulsive disorder (OCD) and schizophrenia also demonstrated significant sharing
154 amongst themselves. On the other hand, the common variant risk of both ASD and Tourette
155 Syndrome (TS) appear to be somewhat distinct from other psychiatric disorders, although with
156 significant correlation between TS, OCD and MDD, as well as between ASD and schizophrenia.
157 Post-traumatic stress disorder (PTSD) alone showed no significant correlation with any of the
158 other psychiatric phenotypes (though some correlation to ADHD and MDD was observed, Fig.
159 1). The modest power of the ASD, PTSD and TS meta-analyses, however, limits the strength of
160 this conclusion (Fig. S2C).

161 Neurological disorders revealed greater specificity, and a more limited extent of genetic
162 correlation than the psychiatric disorders (Fig. 2 and S4, Table S5). Parkinson’s disease,
163 Alzheimer’s disease, generalized epilepsy and multiple sclerosis showed little to no correlation
164 with any other brain disorders. Focal epilepsy showed the highest degree of genetic correlation
165 among the neurological disorders (average $r_g =0.46$, excluding other epilepsy datasets), though

166 none were significant, reflecting the relatively modest power of the current focal epilepsy meta-
167 analysis (Fig. S2C). However, the modest heritability and the broad pattern of sharing observed
168 for focal epilepsy may be consistent with considerable heterogeneity and potentially even
169 diagnostic misclassification across a range of neurological conditions.

170 In the cross-category correlation analysis, the overall pattern is consistent with limited
171 sharing across the included neurological and psychiatric disorders (Fig. 3; average $r_g=0.03$). The
172 only significant cross-category correlations were with migraine, suggesting it may share some of
173 its genetic architecture with psychiatric disorders; migraine-ADHD ($r_g=0.26$, $p=8.81 \times 10^{-8}$),
174 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
175 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
176 with aura).

177 We observed several significant genetic correlations between the behavioral-cognitive or
178 additional phenotypes and brain disorders (Fig. 4, Table S6). Results for cognitive traits were
179 dichotomous among psychiatric phenotypes (Fig. S5A), with ADHD, anxiety disorders, MDD
180 and Tourette Syndrome showing negative correlations to the cognitive measures, while anorexia
181 nervosa, ASD, bipolar disorder and OCD showed positive correlations. Schizophrenia showed
182 more mixed results, with significantly negative correlation to intelligence but positive correlation
183 to years of education. Among neurological phenotypes (Fig. S5B), the correlations were all
184 either negative or null, with Alzheimer's disease, epilepsy, ICH, ischemic stroke, early-onset
185 stroke and migraine showing significantly negative correlations. Correlations with bipolar
186 disorder(24), Alzheimer's disease and schizophrenia have been previously reported(28)).

187 Among the personality measures, significant positive correlations were observed for
188 neuroticism (anorexia nervosa, anxiety disorders, migraine, migraine without aura, MDD, OCD,
189 schizophrenia and Tourette Syndrome; Fig. S6A), depressive symptoms (ADHD, anxiety
190 disorder, bipolar disorder, MDD, and schizophrenia) and subjective well-being (anxiety disorder,
191 bipolar disorder, MDD, as well as replicating the previously reported correlation between
192 neuroticism with both MDD and schizophrenia(29)). For smoking-related measures, the only
193 significant genetic correlations were to never/ever smoked (MDD: $r_g=0.33$, $p=3.10 \times 10^{-11}$ and
194 ADHD: $r_g=0.37$, $p=3.15 \times 10^{-6}$).

195 Among the additional phenotypes, the two diseases chosen as examples of disorders with
196 well-defined etiologies had different results: Crohn's disease, representing immunological
197 pathophysiology, showed no correlation with any of the study phenotypes, while the phenotype
198 representing vascular pathophysiology (coronary artery disease) showed significant correlation
199 to MDD ($r_g=0.19$, $p=8.71 \times 10^{-5}$) as well as the two stroke-related phenotypes ($r_g=0.69$, $p=2.47 \times$
200 10^{-6} to ischemic stroke and $r_g=0.86$, $p=2.26 \times 10^{-5}$ for early-onset stroke), suggesting shared
201 genetic effects across these phenotype. Significant correlations were also observed for BMI,
202 which was positively correlated with ADHD and MDD, and negatively correlated with anorexia
203 nervosa (as previously reported with a different dataset(24)) and schizophrenia.

204 Our enrichment analysis (Fig. S7, Table S7 and S8) demonstrated novel significant
205 heritability enrichments between central nervous system (CNS) and generalized epilepsy, MDD,
206 TS, college attainment, intelligence, neuroticism, never/ever smoked); depressive symptoms and
207 adrenal/pancreatic cells and tissues, as well as between immune system cells and multiple
208 sclerosis. We also note with interest that the psychiatric disorders with large numbers of
209 identified GWAS loci (bipolar disorder, MDD and schizophrenia) and the only cross-correlated
210 neurological disorder with the same (migraine) all show enrichment to conserved regions, while
211 the other neurological disorders with similar numbers of loci (MS and Alzheimer's and
212 Parkinson's diseases) do not (Fig. S7A, B). Significant enrichment to conserved regions was also
213 observed to neuroticism, intelligence and college attainment and to H3K9ac peaks for BMI. We
214 also replicate the previously reported (CNS) enrichment for schizophrenia, bipolar disorder and
215 years of education (here in a larger dataset compared to the original report, but with considerable
216 sample overlap), and observe the previously reported enrichments for BMI (CNS), years of
217 education (CNS), height (connective tissues and bone, cardiovascular system and other) and
218 Crohn's disease (hematopoietic cells) from the same datasets (Fig. S7C, D) (26).

219

220 *Discussion*

221 By integrating and analyzing the current genome-wide association summary statistic data
222 from consortia of 25 brain disorders, we find that psychiatric disorders broadly share a
223 considerable portion of their common variant genetic risk, especially across schizophrenia,
224 MDD, bipolar disorder, anxiety disorder and ADHD, while neurological disorders are more
225 genetically distinct. Across categories, psychiatric and neurologic disorders share relatively little
226 of their common genetic risk, suggesting that multiple different and largely independently
227 regulated etiological pathways may give rise to similar clinical manifestations (e.g., psychosis,
228 which manifests in both schizophrenia(30) and Alzheimer's disease(31)). Except for migraine,
229 which appears to share some genetic architecture with psychiatric disorders, the existing clinical
230 delineation between neurology and psychiatry is recapitulated at the level of common variant
231 risk for the studied disorders.

232 Given that the broad and continuous nature of psychiatric disorder spectra in particular
233 has been clinically recognized for a long time(32-34) and that patients can, in small numbers,
234 progress from one diagnosis to another(35), we evaluated to what extent diagnostic
235 misclassification could explain the observed correlations. Genetic correlation could arise if, for
236 example, substantial numbers of patients progress through multiple diagnoses over their lifetime,
237 or if some specific diagnostic boundaries between phenotype pairs are particularly porous to
238 misclassification; while it would be unlikely to observe large-scale misclassification of migraine
239 as schizophrenia, for example, there may be more substantial misclassification between other
240 pairs, consistent with the clinical controversies in classification. Previous work(36) suggests that
241 substantial misclassification (on the order of 15-30%, depending on whether it is uni- or

242 bidirectional) is required to introduce high levels of genetic correlation. We sought to confirm
243 and expand upon these estimates by performing large-scale simulations and calculating the
244 resulting correlations across a variety of scenarios (Fig. S8, S9, Table S9 and Supplementary
245 Text). First, we established that the observed heritability of the simulated misclassified traits
246 behaves as expected (Fig. S8A), and that the effects on observed correlation (Fig. S8B and S8C)
247 are in line with the estimates from family data(36). We further explored the effect of
248 misclassification on observed r_g given the correlation observed in real data. Reasonably low
249 levels of misclassification or changes to the exact level of heritability appear unlikely to induce
250 substantial changes in the estimated genetic correlation, though a lower observed heritability
251 caused by substantial misclassification (Fig. S8A) will decrease the power to estimate the genetic
252 overlap, as observed in the power analysis (Fig. S10). Further, such evidence of genetic overlap
253 is unlikely to appear in the absence of underlying genetic correlation (Table S10), as it is
254 apparent that a very high degree of misclassification (up to 79%) would be required to produce
255 the observed correlations in the absence of any true genetic correlation. Therefore, the observed
256 correlations suggest true sharing of a substantial fraction of the common variant genetic
257 architecture among psychiatric disorders as well as between behavioral-cognitive measures and
258 brain disorders.

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

267 The observed positive genetic correlations are consistent with a few different scenarios.
268 For example, r_g may reflect the existence of some portion of common genetic risk factors
269 conferring equal risks to multiple disorders where other distinct additional factors contribute to
270 the eventual clinical presentation. The presence of significant genetic correlation may also reflect
271 the phenotypic overlap between any two disorders; for example, the sharing between
272 schizophrenia and ADHD might reflect underlying difficulties in executive functioning, which
273 are well-established in both disorders(37). Similarly, the sharing between anorexia nervosa, OCD
274 and schizophrenia may reflect a shared mechanism underlying cognitive biases that extend from
275 overvalued ideas to delusions. Another scenario is that a heritable intermediate trait confers risk
276 to multiple outcomes, thereby giving rise to the genetic correlation, as the genetic influences on
277 this trait will be shared for both outcomes (e.g., obesity as a risk factor for both type 2 diabetes
278 and coronary artery disease), or that even the majority of common genetic effects are shared
279 between a pair of traits, but each individual effect may confer different degrees of risk and lead
280 to different aggregate genetic risk profiles. While a combination of these is likely, it will become

281 increasingly feasible to evaluate these overlaps at the locus level as more genome-wide
282 significant loci are identified in the future.

283 The low correlations observed across neurological disorders suggest that the current
284 classification reflects relatively specific genetic etiologies, although the limited sample size for
285 some of these disorders and lack of inclusion of disorders conceived as “circuit-based” in the
286 literature, such as restless legs syndrome, sleep disorders and possibly essential tremor,
287 constrains the generalizability of this conclusion. Generally, this analysis recapitulates the
288 current understanding of the relatively distinct primary etiology underlying these disorders;
289 degenerative disorders (such as Alzheimer’s and Parkinson’s diseases) would not be expected *a*
290 *priori* to share their polygenic risk profiles with a neuro-immunological disorder (like multiple
291 sclerosis) or neurovascular disorder (like ischemic stroke). Similarly, we see limited evidence for
292 the reported co-morbidity between migraine with aura and ischemic stroke(38) ($r_g=0.29$,
293 $p=0.099$); however, the standard errors of this comparison are too high to draw strong
294 conclusions. At the disorder subtype level, migraine with and without aura ($r_g=0.48$, $p=1.79 \times 10^{-5}$)
295 shows substantial genetic correlation, while focal and generalized epilepsy ($r_g=0.16$, $p=0.388$)
296 show much less.

297 The few significant correlations across neurology and psychiatry, namely between
298 migraine and ADHD, MDD and TS, suggest modest shared etiological overlap across the
299 neurology/psychiatry distinction. The co-morbidity of migraine with MDD, Tourette Syndrome
300 and ADHD has been previously reported in epidemiological studies (39-42), while in contrast,
301 the previously reported co-morbidity between migraine and bipolar disorder seen in
302 epidemiological studies (43) was not reflected in our estimate of genetic correlation ($r_g=-0.03$,
303 $p=0.406$).

304 Several phenotypes show only very low-level correlations with any of the other disorders
305 and phenotypes studied here, despite large sample size and robust evidence for heritability,
306 suggesting their common variant genetic risk may largely be unique. Alzheimer’s disease,
307 Parkinson’s disease, and multiple sclerosis show extremely limited sharing with the other
308 phenotypes and with each other. Neuroinflammation has been implicated in the pathophysiology
309 of each of these conditions(44-46), as it has for migraine(47) and many psychiatric conditions,
310 including schizophrenia(48), but no considerable shared heritability was observed with either of
311 those conditions nor with Crohn’s disease, nor did we observe enrichment for immune-related
312 tissues in the functional partitioning (Fig. S7) as we did for Crohn’s disease. While this
313 observation does not preclude shared neuroinflammatory mechanisms in these disorders, it does
314 suggest that on a large scale, common variant genetic influences on these inflammatory
315 mechanisms are not shared between these disorders. Further, we only observed significant
316 enrichment of heritability for immunological cells and tissues in multiple sclerosis, showing that
317 inflammation-specific regulatory marks in the genome do not show overall enrichment for
318 common variant risk for either Alzheimer’s or Parkinson’s diseases (though this does not
319 preclude the effects of specific, non-polygenic neuroinflammatory mechanisms(49)). Among

320 psychiatric disorders, ASD and TS showed a similar absence of correlation with other disorders,
321 although this could reflect small sample sizes.

322 Analysis of the Big Five personality measures suggest that the current sample sizes for
323 personality data are beginning to be sufficiently large for correlation testing; neuroticism, which
324 has by far the largest sample size, shows several significant correlations. Most significant of
325 these was to MDD ($r_g=0.737$, $p=5.04 \times 10^{-96}$), providing further evidence for the link between
326 these phenotypes, reported previously with polygenic risk scores(50) and twin studies(51, 52);
327 others included schizophrenia, anxiety disorders, migraine, migraine without aura, and OCD
328 (Table S6). Further, the observation of strong correlation between MDD and anxiety disorders
329 together with their remarkably strong and similar patterns of correlation between each of these
330 disorders and the dimensional measures of depressive symptoms, subjective well-being, and
331 neuroticism suggests that they all tag a fundamentally similar underlying etiology. The novel
332 significant correlation between coronary artery disease and MDD supports the long-standing
333 epidemiological observation of a link between MDD and CAD(53), while the observed
334 correlation between ADHD and smoking initiation ($r_g=0.374$, $p=3.15 \times 10^{-6}$) is consistent with
335 the epidemiological evidence of overlap(54) and findings from twin studies(55), supporting the
336 existing hypothesis that impulsivity inherent in ADHD may drive smoking initiation and
337 potentially dependence (though other explanations, such as reward system dysfunction would fit
338 as well).

339 For the neurological disorders, five (Alzheimer's disease, intracerebral hemorrhage,
340 ischemic and early-onset stroke, and migraine) showed significant negative genetic correlation to
341 the cognitive measures, while a further two (epilepsy and focal epilepsy) showed moderate
342 negative genetic correlation (Fig. S5). For Alzheimer's disease, poor cognitive performance in
343 early life has been linked to increased risk for developing the disorder in later life(56), but to our
344 knowledge no such connection has been reported for the other phenotypes. ADHD, anxiety
345 disorders and MDD show a significant negative correlation to cognitive and education attainment
346 measures, while the remaining five of the eight psychiatric disorders (anorexia nervosa, ASD,
347 bipolar disorder, OCD, and schizophrenia) showed significant positive genetic correlation with
348 one or more cognitive measures. These results strongly suggest the existence of a link between
349 cognitive performance already in early life and the genetic risk for both psychiatric and
350 neurological brain disorders. The basis of the genetic correlations between education, cognition
351 and brain disorders may have a variety of root causes including indexing performance
352 differences based on behavioral dysregulation (e.g., ADHD relating to attentional problems
353 during cognitive tests) or may reflect ascertainment biases in certain disorders conditional on
354 impaired cognition (e.g., individuals with lower cognitive reserve being more rapidly identified
355 for Alzheimer's disease).

356 BMI shows significant positive genetic correlation to ADHD, consistent with a meta-
357 analysis linking ADHD to obesity(57), and negative genetic correlation with anorexia nervosa,
358 OCD and schizophrenia. These results are consistent with the evidence for enrichment of BMI

359 heritability in CNS tissues(26) and that many reported signals suggest neuronal involvement(58);
360 this may also provide a partial genetic explanation for lower BMI in anorexia nervosa patients
361 even after recovery(59). Given that no strong correlations were observed between BMI and any
362 of the neurological phenotypes, it is possible to hypothesize that BMI's brain-specific genetic
363 architecture is more closely related to behavioral phenotypes. Ischemic stroke and BMI show
364 surprisingly little genetic correlation in this analysis ($r_g=0.07$, $p=0.26$), suggesting that although
365 BMI is a strong risk factor for stroke(60), there is little evidence for shared common genetic
366 effects. These analyses also suggest that the reported reduced rates of cardiovascular disease in
367 individuals with histories of anorexia nervosa (61, 62) are due to BMI-related effects; with the
368 limited evidence of genetic correlation of anorexia nervosa with intracerebral hemorrhage,
369 ischemic stroke, early-onset stroke and coronary artery disease, these results suggest that any
370 lower cardiovascular mortality is more likely due to direct BMI-related effects rather than
371 shared common genetic risk variants.

372 It is broadly apparent from the results presented here that the current clinical boundaries
373 for the studied psychiatric phenotypes do not reflect distinct underlying pathogenic processes
374 based on the genetic evidence, while in contrast, the studied neurological disorders show much
375 greater genetic specificity. Although it is important to emphasize that while some disorders are
376 under-represented here (e.g. personality disorders in psychiatry and circuit-based disorders [such
377 as restless leg syndrome] in neurology), these results clearly demonstrate the limited evidence for
378 widespread common genetic risk sharing between psychiatric and neurological disorders, while
379 providing strong evidence for links between them and behavioral-cognitive measures. We
380 highlight the need for some degree of restructuring of psychiatric nosology and that genetically
381 informed analyses may provide a good basis for such activities, consistent with the historical
382 knowledge from twin and family-based results. Further elucidation of individual disorders and
383 their genetic overlap, especially as distinct loci map onto a subset of disorders and etiological
384 processes, may form the basis for either defining new clinical phenotypes or support a move to a
385 more continuous view of psychiatric phenotypes. Further study is needed to evaluate whether
386 overlapping genetic contributions to psychiatric pathology may influence optimal treatment
387 choices. Ultimately, such developments give hope to reducing diagnostic heterogeneity and
388 eventually improving the diagnostics and treatment of psychiatric disorders.

389

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394 **References:**

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562

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

571
572

573 **Data sources**

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

575 *Psychiatric disorders*

576 ADHD – PGC-ADD2 - <http://www.med.unc.edu/pgc/results-and-downloads>
577 Anorexia nervosa(63) – PGC-ED - <http://www.med.unc.edu/pgc/results-and-downloads>
578 Anxiety disorder(64) – ANGST - <http://www.med.unc.edu/pgc/results-and-downloads>
579 Autism spectrum disorders(65) – PGC-AUT - <http://www.med.unc.edu/pgc/results-and-downloads>
580 Bipolar disorder – PGC-BIP2 - <http://www.med.unc.edu/pgc/results-and-downloads> (soon)
581 Major depressive disorder – PGC-MDD2 - <http://www.med.unc.edu/pgc/results-and-downloads> (soon)
582 OCD – PGC-OCDS - <http://www.med.unc.edu/pgc/results-and-downloads>
583 PTSD – PGC-PTSD - <http://www.med.unc.edu/pgc/results-and-downloads>
584 Schizophrenia(22) – PGC-SCZ2 – <http://www.med.unc.edu/pgc/results-and-downloads>
585 Tourette Syndrome – TSAIGC – <http://www.med.unc.edu/pgc/results-and-downloads>

586 587 *Neurological disorders*

588 Alzheimer's disease(18) – IGAP - <http://www.pasteur-lille.fr/en/recherche/u744/igap>
589 Epilepsy and subtypes, focal and generalized(66) – ILAE – http://www.epigad.org/page/show/gwas_index
590 Intracerebral hemorrhage(67) – ISGC - <http://www.strokegenetics.com/>
591 Ischemic stroke and subtypes (cardioembolic, early-onset, small-vessel and large-vessel)(68) – METASTROKE
592 dataset of the ISGC – <http://www.strokegenetics.com/>
593 Migraine and subtypes, migraine with and without aura – IHGC – www.headachegenetics.org
594 Multiple sclerosis(69) – IMSGC - http://eaglep.case.edu/ims_gc_web
595 Parkinson's disease(21) – IPDGC – www.pdgene.org

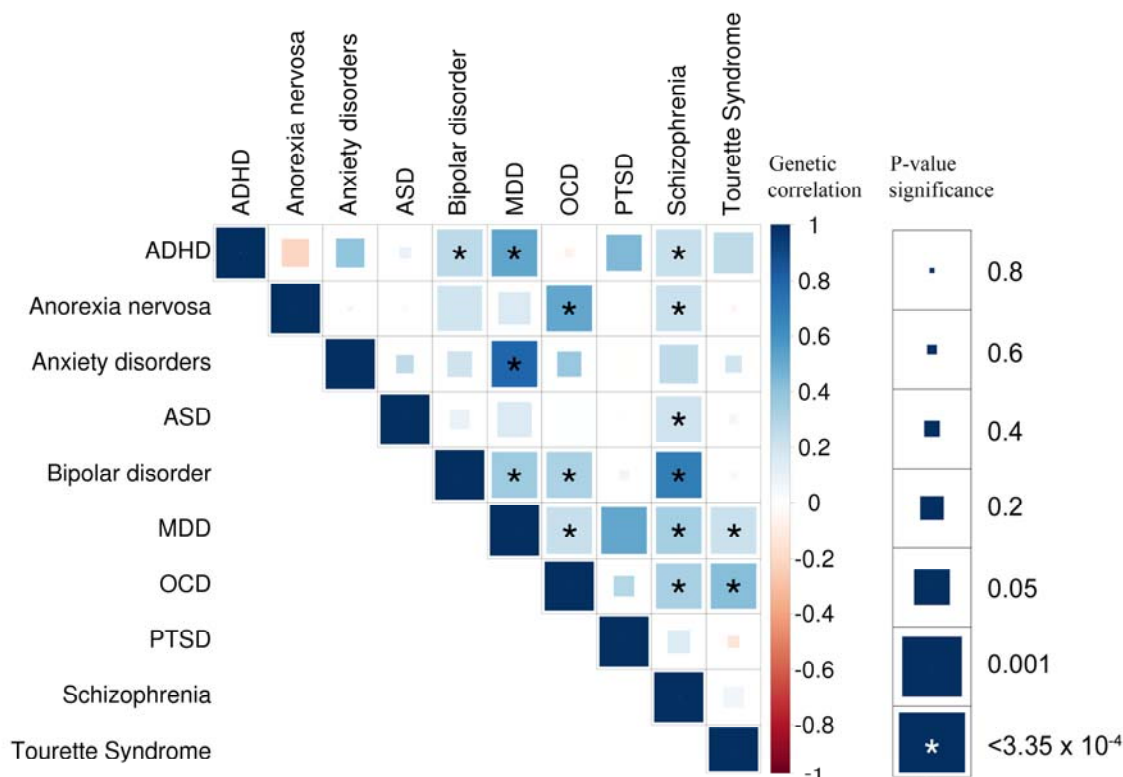
596 597 *Behavioral-cognitive phenotypes*

598 College attainment, years of education(70) – SSGAC – <http://www.thessgac.org/data>
599 Childhood cognitive performance(71) – SSGAC – <http://www.thessgac.org/data>
600 Extraversion, agreeableness, conscientiousness and openness (27) – GPC – <http://www.tweelingenregister.org/GPC/>
601 IQ(72) – CTG - http://ctg.cncr.nl/software/summary_statistics
602 Neuroticism, depressive symptoms and subjective well-being (73) – SSGAC - <http://www.thessgac.org/data>
603 Never/ever smoked, cigarettes per day(74) - TAG - <http://www.med.unc.edu/pgc/results-and-downloads>

604 605 *Additional phenotypes*

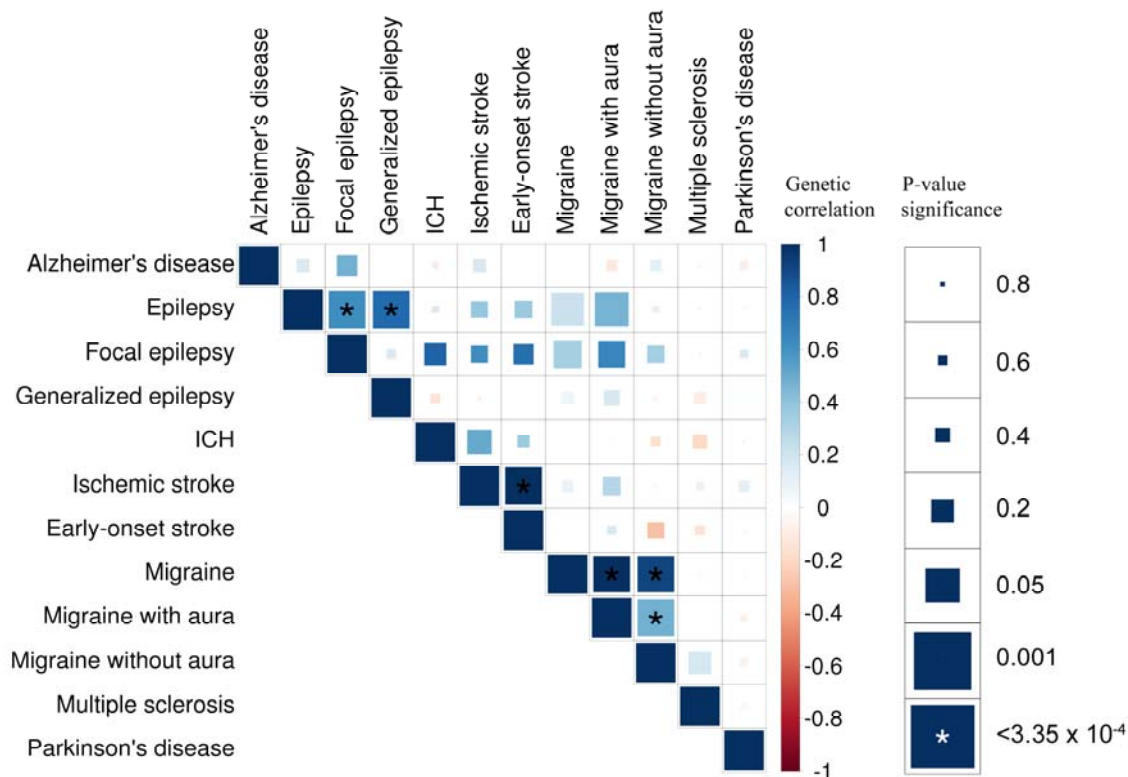
606 BMI(58) – GIANT – <https://www.broadinstitute.org/collaboration/giant>
607 Height(75) – GIANT – <https://www.broadinstitute.org/collaboration/giant>
608 Crohn's disease(76) – IBDGC - <http://www.ibdgenetics.org/downloads.html>
609 Coronary artery disease(77) – Cardiogram – <http://www.cardiogramplusc4d.org/downloads/>

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



611
 612 *Color of each box indicates the magnitude of the correlation, while size of the boxes indicates its significance, with*
 613 *significant correlations filling each box completely. Asterisks indicate genetic correlations which are significant*
 614 *after Bonferroni correction. ADHD – attention deficit hyperactivity disorder; ASD – autism spectrum disorder;*
 615 *MDD – major depressive disorder; OCD – obsessive-compulsive disorder; PTSD – post-traumatic stress disorder.*

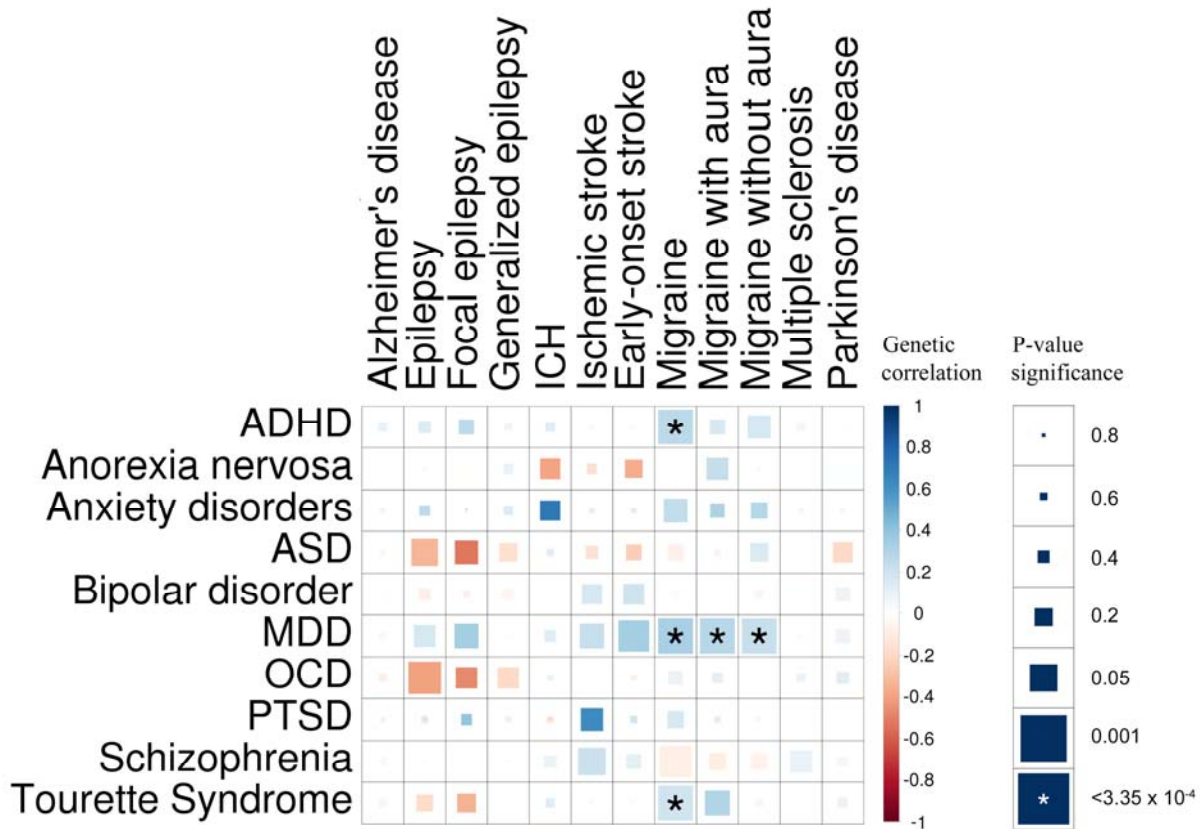
616 **Figure 2.** Genetic correlation matrix across neurological phenotypes.



617
 618 *Color of each box indicates the magnitude of the correlation, while size of the boxes indicates its significance, with*
 619 *significant correlations filling each box completely. Asterisks indicate genetic correlations which are significant*
 620 *after Bonferroni correction. Some phenotypes have substantial overlaps (see Table 1), e.g. all cases of generalized*
 621 *epilepsy are also cases of epilepsy. Asterisks indicate significant genetic correlation after multiple testing*
 622 *correction. ICH – intracerebral hemorrhage.*

623

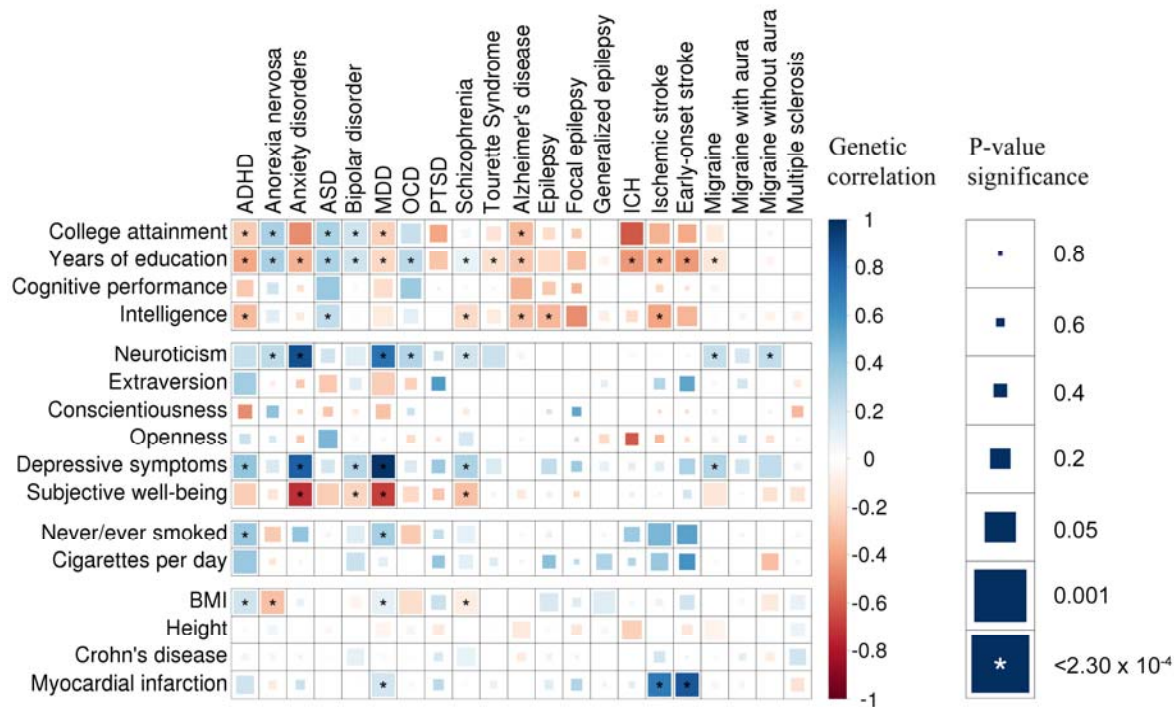
624 **Figure 3.** Genetic correlation matrix across neurological and psychiatric phenotypes.



625

626 *Color of each box indicates the magnitude of the correlation, while size of the boxes indicates its significance, with*
 627 *significant correlations filling each box completely. Asterisks indicate genetic correlations which are significant*
 628 *after Bonferroni correction. ADHD – attention deficit hyperactivity disorder; ASD – autism spectrum disorder; ICH*
 629 *– intracerebral hemorrhage; MDD – major depressive disorder; OCD – obsessive-compulsive disorder; PTSD –*
 630 *post-traumatic stress disorder.*

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



632
 633 *Color of each box indicates the magnitude of the correlation, while size of the boxes indicates its significance, with*
 634 *significant correlations filling each box completely. Asterisks indicate genetic correlations which are significant*
 635 *after Bonferroni correction. ADHD – attention deficit hyperactivity disorder; ASD – autism spectrum disorder; ICH*
 636 *– intracerebral hemorrhage; MDD – major depressive disorder; OCD – obsessive-compulsive disorder; PTSD –*
 637 *post-traumatic stress disorder; BMI –body-mass index.*

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

644

Psychiatric disorders

Neurological disorders

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

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646

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

Phenotype	Source	Samples
Behavioral-cognitive phenotypes		
<i>Cognitive</i>		
Years of education (q)	SSGAC	293,723
College attainment (d)	"	120,917
Cognitive performance (q)	"	17,989
Intelligence (d)	CTG	78,308
<i>Personality measures</i>		
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
<i>Smoking-related</i>		
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

651

652

653 **Supplementary Materials**

654 Materials and methods

655 Supplementary Text

656 Comparison with previous heritability estimates

657 Effect of phenotypic misclassification

658 Study-specific acknowledgements

659 Consortium memberships

660 Figures S1-10

661 Tables S1-10