Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs

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Summary paragraph

Most psychiatric disorders are moderately to highly heritable. The degree to which genetic variation is unique to individual disorders versus shared across disorders is unclear. We use genome-wide genotype data from the Psychiatric Genomics Consortium (PGC) of cases and controls for schizophrenia (SCZ), bipolar disorder (BPD), major depressive disorder (MDD), autism spectrum disorders (ASD), and attention deficit hyperactivity disorder (ADHD). We apply univariate and bivariate methods for estimation of genetic variation within and covariation between disorders. SNPs explained 17-29% of the variance in liability. The genetic correlation calculated from common SNPs is high for SCZ/BPD (0.68±SE 0.04), moderate for SCZ/MDD (0.43±0.06), BPD/MDD (0.47±0.06), ADHD/MDD (0.32±0.07), low between SCZ/ASD (0.16±0.06), and non-significant for other pairs of disorders as well as with the negative control of Crohn's Disease. This empirical evidence for a shared genetic etiology between psychiatric disorders can inform nosology and encourages investigation of common pathophysiologies for the related disorders.

Text

Current classification of psychiatric disorders reflects clinical syndromes with largely unknown etiology and is based on historical descriptions provided by prominent clinicians over the last 125 years. Family (including twin and adoption) studies provide consistent evidence that genetic factors are involved in these syndromes[1]. In principle, family studies allow quantification of shared genetic etiology, through estimation of heritability (the proportion of variance in liability attributable to additive genetic factors) of disorders and the genetic correlation between them. However, difficulties in ascertaining samples of sufficient size mean that estimates of genetic correlations are few. Nonetheless, family studies suggest correlated familial-genetic liabilities to BPD and SCZ[2,3], BPD and MDD[2,3] and ASD and ADHD[4-6] (**Supplementary Table 1**). Phenotypic and genetic overlap has also been suggested for ASD and SCZ[7-11], ASD and BPD[9], BPD and ADHD[12] and MDD and ADHD[13]. Some of these relationships have been supported by recent evidence of shared molecular risk factors[14-16], but the extent of these relationships remains unclear given the small proportion of risk associated with these individually identified variants.

The genomics era provides new opportunities to explore the shared genetic etiology of disorders. Genome-wide association studies (GWAS) assess common genetic polymorphisms (e.g., SNPs) at several hundred thousand positions in the genome. The experimental paradigm of GWAS is identification of individual variants associated with case-control status[17]. However, these data can be used to estimate the total variance in liability explained by SNPs ("SNP-heritability", *SNP-h*^{2}) through estimation of genetic similarities (relationships) between cases and controls using SNP genotypes[18,19]. The pair-wise genetic relationships that contribute to the estimate are very small, but the large number of pairwise relationships in a case-control sample generates estimates with reasonable precision. The

SNP-h^2 is an estimate of the total variance in liability to disease explained by the SNPs together. Genetic variation is estimated when case-case pairs and control-control pairs are, on average, more similar genome-wide than case-control pairs. The *SNP-h*^{2} is a lower bound for the total narrow sense heritability, as the former cannot include contributions from causal variants not tagged by the measured SNPs, mostly less common and rare causal variants. A bivariate extension[20] of these genome-wide methods estimates the genetic correlation (*SNP-r*$_g$) explained by SNPs between case-control samples collected independently for two disorders (see **online Methods**). The correlation is positive when the cases of one disorder show higher genetic similarity to the cases of the other disorder than to their controls. A negative correlation is possible if the cases of one disorder are less similar genome-wide to the cases of the other disorder than they are to controls. A genetic correlation of zero is estimated if the genome-wide relationship between cases of one disorder is the same with cases as with controls of the other disorder. As a correlation, a high SNP-*r*$_g$ is achieved when the covariance term between the traits is similar in magnitude to the variance terms. Therefore, we also report the SNP-coheritability between pairs of disorders, which is the covariance between disorders on the liability scale and allows comparison of the shared liability attributable to SNPs on the same scale as the *SNP-h*^{2}. Here, we apply the univariate and bivariate methods to the five disorders of the PGC**:** SCZ[21], BPD[22], MDD[23], ASD[24,25] and ADHD[26] analysed in the PGC cross-disorder group association study[25], together with additional ADHD data sets[27-30] (**Table 1**).

RESULTS

SNP-heritabilities for the five disorders

In our linear mixed model we estimate the variance in case-control status explained by SNPs[18] (heritability on the observed scale, CC in **Table 1**). Cases in case-control samples are highly ascertained compared to in the population, and since the different disorder cohorts

have different proportions of cases, the CC estimates are difficult to interpret and compare. For this reason, we report *SNP-h*^{2} on the liability scale, in which a linear transformation[18] is applied based on a user-specified estimate of the disorder risk of the study-base population (disorder risk, *K*). For each disorder we consider three values of *K* (**Table 1**) and we convert the *SNP-h*^{2} to a predicted risk to 1st-degree relatives (*SNP*-λ_{1st}) given *K*. We benchmark the *SNP*-λ_{1st} risk to risk to 1st-degree relatives (λ_{1st}) consistent with estimates of heritabilities reported from family studies given *K*. Our estimates of *SNP*-λ_{1st} are robust, and of *SNP-h*^{2} are reasonably robust, to the likely range of *K* and show that an important part of the heritabilities or familial risk estimated from family studies are associated with common SNPs. Twice the standard error of estimates approximates the magnitude of parameter that is possible to detect as significantly different from zero given the available sample sizes[31].

SNP-coheritabilities and SNP-correlations (*SNP-r$_g$*) between all pairwise combinations of disorders

The relationships between disorders are expressed as SNP-coheritabilities (**Fig. 1**). The *SNP-r$_g$* is high for SCZ/BPD 0.68 (s.e. 0.04), moderate for SCZ/MDD 0.43 (0.06), BPD/MDD 0.47 (0.06), ADHD/MDD 0.32 (0.07), low between SCZ/ASD 0.16 (0.06), and non-significant for other pairs of disorders (**Supplementary Table 1**). The SNP-*r$_g$* correlation is expected to be equal to the *r$_g$* from family studies only if the genetic correlation is the same across the allelic frequency spectrum and if the linkage disequilibrium between genotyped and causal variants is similar for both disorders. The sample size for ASD is the smallest but still can detect correlations of > |0.18| to be different from zero in bivariate analyses with all other disorders.

Our results provide empirical evidence that SCZ, BPD and MDD have a shared genetic etiology. Since some SCZ and BPD cohorts were collected in the same clinical environments,

we investigated possible impact of non-independent collection of SCZ/BPD samples sets but found no significant change in the estimates (**Supplementary Table 2**). The correlation between SCZ and ASD is significant but small (0.16 s.e. 0.06, p = 0.0071). In general, our analyses suggest that while common genetic variants contribute to both childhood-onset disorders (ASD, ADHD) and disorders usually diagnosed after childhood (SCZ, BPD, MDD), the sharing of common variants between them is modest.

The pattern of our results (i.e., which pairs of disorders demonstrate genetic overlap) is consistent with the polygenic profile score[32] results from the PGC cross-disorder analyses[25]. The profile score method uses SNP associations from one disorder to construct a linear predictor in another disorder. The profile scores explained small but significant proportions of the variance[25], expressed as Nagelkerke's R^2 (maximum of 2.5% between SCZ and BPD). To achieve a high R^2 requires accurate estimation of effect sizes of individual SNPs and depends on the size of the discovery sample. In contrast, our approach uses SNPs to estimate genome-wide similarities between pairs of individuals, resulting in unbiased estimates of the relationships between disorders, with larger sample sizes generating smaller standard errors of the estimates. Our estimates are on the liability scale, allowing direct comparison to genetic parameters estimated in family studies, whereas a genetic interpretation of Nagelkerke's R^2 is less straightforward[33].

Genomic partitioning of SNP-heritabilities and SNP-coheritabilities

The heritabilities explained by SNPs can be partitioned according to SNP annotation by estimation of genetic similarity matrices from multiple, non-overlapping SNP sets. For the five disorders, and the five disorder pairs showing a significant SNP correlation, we partitioned the *SNP-h^2* and SNP-coheritabilities explained by functional annotation, allocating SNPs to one of three sets: i) in genes preferentially expressed in the central nervous system (CNS+)[34,35], ii) in other genes and iii) not in genes, with genes defined with

50kb boundaries from their start/stop positions. The SNPs in the CNS+ gene set represented 0.20 of the total set, both in number and megabases. However, the proportion of the variance explained by SNPs attributable to this SNP set is significantly greater than 0.20 for SCZ (0.30, p = 7.6 e-08) and BPD (0.32,p = 5.4e-06) and for the SCZ/BPD coheritability (0.37, p = 8.5e-08, **Fig. 2, Supplementary Table 3**). For other disorders or pairs of disorders, the estimates explained by CNS+ SNPs do not differ from chance expectation (**Supplementary Table 3**), although their large standard errors suggest we cannot address this question with precision. For the SCZ/BPD data we also partitioned the heritabilities explained by SNPs by minor allele frequency (MAF) (**Supplementary Table 4**) and by chromosome (**Supplementary Figure 1**). The high standard errors on estimates limits interpretation; but the results are consistent with a polygenic architecture of many common variants of small effect dispersed throughout the genome. The MAF partitioning suggests that an important part of the variance explained by SNPs is attributable to common causal variants (this was investigated in detail for SCZ[35]), but the low contribution to the total variance explained from SNPs with MAF < 0.1 reflects, at least in part, under-representation of SNPs with low MAF in the analysis (minimum MAF = 0.01) relative to those present in the genome.

Within disorder heterogeneity

In order to benchmark the estimates of genetic sharing across disorders, we estimated sharing between data sub-sets of the same disorder. We split the data for each disorder into 2 or 3 independent sets and estimated the *SNP-h^2* from each subset, and the SNP-coheritability between each pair of subsets within a disorder (**Fig. 3a**, **Supplementary Table 5**). The estimates of SNP-h^2 from the data sub-sets are typically higher than the SNP- h^2 from the combined sample; we note that published estimates from individual cohorts of BPD[18], MDD[36] and ASD[37] were also higher. Since both traits in these data sub-set bivariate analyses are from the same disorder, the SNP-coheritability is also an estimate of the SNP-

h^2 for the disorder, but these are generally lower than the estimates of SNP-heritability from individual data sub-sets. These results generate SNP-correlations that are less than one, and sometimes significantly so (**Supplementary Table 5**). The SCZ/BPD SNP correlation (0.68 s.e. 0.04) is of comparable magnitude as the SNP-correlations between BPD data sets (0.63 s.e. 0.11, 0.88 s.e. 0.09 and 0.55 s.e. 0.10 ; **Fig 3a,b** for SNP coheritabilities), adding further weight to the conclusion that SCZ and BPD may be part of the same etiological spectrum.

The estimates of heritability from both univariate (**Fig. 3a** red/pink bars) and bivariate analyses (**Fig. 3a** blue bars) are more heterogeneous for BPD, MDD and ADHD than for SCZ and ASD. Several reasons could explain why SNP-heritabilities from univariate analyses of a single data set could generate higher estimates than from bivariate analyses of independent data sets[35], including loss of real signal or dilution of artefacts. Loss of real signal may occur because individual cohorts are more homogeneous, both phenotypically (e.g., use of the same assessment protocols), and genetically (e.g. because linkage disequilibrium (LD) between causal variants and analyzed SNPs might be higher within than between cohorts). On the other hand, artefacts could generate consistent differences in case vs control genotypes within case-control data sets. In the derivation of our methodology[18], we emphasised that any factors making SNP genotypes of cases more similar to other cases, and controls more similar to controls, will produce SNP-heritability. The fitting as covariates of principal components derived from the SNP data corrects both for population stratification and for genotyping artefacts, but residual population stratification[38] could remain, although this bias should be small[38,39]. Partitioning SNP-heritability by chromosome in analyses where each chromosome is fitted individually compared to analyses where all chromosomes are fitted jointly is an empirical strategy to assess residual stratification[35,40] and we find no such evidence here (**Supplementary Figure 1**). Stringent QC helps (as applied here) to remove artefacts, but artefactual differences between cases and controls may remain, particularly

for data sets in which cases and controls have been genotyped independently[41]. As more data sets accumulate, the contributions from artefacts are diluted since the random directional effects of artefacts (including population stratification) are not consistent across data sets. For this reason, significant SNP-coheritabilities are unlikely to reflect artefacts and provide a lower bound on SNP-heritability.

Pseudo-controls

One strategy adopted in GWAS to guard against artefacts of population stratification is to genotype trio samples (cases and their parents) and then analyse the data as a case-control sample with controls generated as genomic complements of the cases (i.e. "pseudo-controls"). The ADHD subset 1 and most of the ASD sample are comprised of case-pseudo control samples and, consistent with limiting the impact of artefacts from population stratification or genotyping, it is noted that the lowest SNP-heritability of the 5 psychiatric disorders is for ASD and that the estimate of SNP-heritability is lower for ADHD subset 1 than for ADHD subset 2. However, under a polygenic model, assortative mating[42] or preferential ascertainment of multiplex families could diminish the expected mean difference in liability between pseudo-controls and cases[37], which would result in an underestimation of SNP-heritability from case/pseudo-control compared to case/control analyses and also non-zero estimates of SNP-heritability from pseudo-control/control analyses as shown in analysis of ASD data[37].

Negative control – SNP-coheritabilities with Crohn's Disease

As a negative control analysis, we conducted bivariate analyses between each of the PGC data sets with Crohn's Disease (CD) from the International IBD Genetics Consortium (IIBDGC)[43]. While onset of MDD is not uncommon after diagnosis with CD[44], and while gastrointestinal pathology is commonly comorbid with ASD[45], there is no strong evidence of

a familial relationship between psychiatric disorders and CD. Despite a substantial SNP-h^2 for CD (0.19 s.e. 0.01), none of the SNP-coheritabilities with the psychiatric disorders differed significantly from zero (**Fig. 3c**, **Supplementary Table 6**, **Supplementary Note**). Lastly, the genomic partitioning by annotation of variance in CD explained by SNPs showed, as expected, no excess of variance attributable to SNPs in the CNS+ gene set (**Fig. 2**). Our results provide no evidence for common genetic pleiotropy between CD and ASD consistent with a non-genetic e.g. microbial[47] explanation for the comorbid gastrointestinal symptoms in ASD.

Potential impact of misclassification of disorders

Misclassification between disorders could inflate estimates of genetic correlation/ coheritability[48]. Indeed, some level of misclassification between psychiatric disorders is expected. For example, longitudinal studies[4950] of first admissions with psychosis based on research interviews showed that with long term follow-up ~15% of subjects initially diagnosed with bipolar disorder were re-diagnosed with schizophrenia while ~4% of schizophrenia diagnoses were re-classified as bipolar disorder. Cases selected for GWAS contributing to PGC to date are more likely to have achieved a stable diagnosis compared to first admission cases. However, assuming these levels of misclassification, the genetic correlation between BPD and SCZ of "true" diagnoses is still high, estimated[48] to be 0.55. Likewise, since a modest proportion of cases diagnosed with MDD followed over time ultimately meet criteria for BPD[51] our estimated genetic correlation between these two disorders may be modestly inflated by misclassification. On the other hand, if moderate to high genetic correlations between the major adult disorders are true, then overlapping symptoms and misdiagnosis between disorders might be expected. The SNP-r_g between SCZ and MDD also is unlikely to reflect misdiagnosis since misclassification between these disorders is rare[51]. Excluding the five of the 18 PGC-SCZ cohorts containing schizoaffective

disorder cases[21] (**Supplementary Table 7)** or MDD cohorts ascertained from community rather than clinical settings (**Supplementary Table 8**) had little impact on the SNP-rg estimates **.**

DISCUSSION

Our results show direct, empirical, quantified, molecular evidence for an important genetic contribution to the five major psychiatric disorders. The *SNP-h^2* estimates for each disorder: SCZ 0.21 (s.e. 0.02), BPD 0.25 (s.e. 0.01), MDD 0.21 (s.e. 0.01), ASD 0.14 (s.e. 0.02), ADHD 0.32 (s.e. 0.02) are considerably less than the heritabilities estimated from family studies (see **Table 1**). Yet they show that common SNPs make an important contribution to the overall variance, implying that additional individual common SNP associations can be discovered as sample size increases[52]. SNP- h^2 are a lower bound of narrow sense heritability because they exclude contributions from some causal variants (mostly rare variants) not associated with common SNPs. Although the SNP-heritability estimate is similar for MDD as for other disorders, much larger sample sizes will be needed because the high disorder risk implies lower power for the same sample size[53]. The SNP- h^2 are all lower than those reported for height (0.45 s.e. 0.03)[40] but the estimates are in the same ball-park to those reported for other complex traits and diseases using the same QC pipeline, such as BMI (0.17 s.e. 0.03)[40], Alzheimer's Disease (0.24 s.e.0.03), multiple sclerosis (0.30 s.e.0.03) and endometriosis (0.26 s.e.0.04)[41].

Our results show molecular evidence for the sharing of genetic risk factors across key psychiatric disorders. Traditionally, quantification of the genetic relationship between disorders has been thwarted by the need for cohorts of families or twins assessed for multiple disorders. Problems of achieving genetically informative samples of sufficient size and without associated ascertainment biases for the rarer psychiatric disorders have meant that few studies have produced meaningful estimates of genetic correlations. Importantly,

our estimates of heritability and genetic correlation are made using very distant genetic relationships between individuals, both within and between disorders, so that shared environmental factors are unlikely to contaminate our estimates. Likewise, our estimates are unlikely to be confounded by non-additive genetic effects, since the coefficients of non-additive genetic variance between very distant relatives are negligible[54].

The estimates of SNP-genetic correlation (SNP-r_g) between disorders reflect genome-wide pleiotropy of variants tagged by common SNPs and whether these are the same as correlations across the allelic frequency spectrum may differ between disorder pairs. For example, a high SNP-r_g but a low genetic correlation estimated from family studies (r_g) could reflect that the same common variants contribute to the genetic susceptibility of both disorders, while the diagnostic-specific variants are less common variants. For this reason, the comparison of SNP-r_g with r_g estimated from family studies is not straightforward. Nonetheless we benchmark our estimates in this way, calculating the increased risk of disorder B in first-degree relatives of probands with disorder A ($\lambda_{A,B}$) from the SNP-r_g to allow comparison with literature values (**Supplementary Table 1**). A meta-analysis[55] reported the increased risk of BPD in first-degree relatives of SCZ probands compared to first-degree relatives of control probands ($\lambda_{SCZ,BP}$) to be 2.1, which implies a maximum genetic correlation between them of 0.3 (assuming that the disorder risks for SCZ and BPD are both 1%, and their heritabilities are 81% and 75%, **Table 1**). However, a large-scale Swedish family and adoption study[56] estimated the genetic correlation between SCZ and BPD to be +0.60, similar to that found here. Profiling scoring analyses using genome-wide SNPs[32] was the first to demonstrate clearly a genetic relationship based on molecular data, but quantification as a genetic correlation was not reported. The evidence of shared genetic risk factors for SCZ and BPD was strengthened by our analyses of the CNS+ gene set where we saw a clear enrichment in variants shared by these two disorders.

Our finding of a substantial SNP-r_g of +0.43 between SCZ and MDD is intriguing and contrary to conventional wisdom about the independence of familial risk for these disorders. However, since MDD is common, even a high genetic correlation implies only modest incremental risk. Assuming that the disorder risks and heritabilities for SCZ and MDD in Table 1, then a the genetic correlation between them of 0.43 predicts an increased risk of MDD in first-degree relatives of SCZ probands compared to first-degree relatives of control probands ($\lambda_{\square\square\square\square\square\square\square\square\square\square}$ of 1.6. In fact, meta-analysis of five studies interview-based research studies of families are broadly consistent with our results ($\lambda_{\square\square\square\square\square\square\square}$ = 1.5, 95% CI 1.2-1.8, **Supplementary Table 9**), suggesting that familial coaggregation of MDD and SCZ reflects genetic effects rather than a consequence of living in a family environment that includes a severely ill family member. If replicated by future work, our empirical molecular genetic evidence of a partly shared genetic etiology for SCZ and MDD has important nosological and research implications, placing MDD as part of a broad psychiatric genetic spectrum. A shared genetic etiology between BPD and MDD has been shown in family studies[2,3] but the SNP-r_g of 0.47 is lower than the estimate of 0.65 from a twin study[57].

Our results show a small but significant SNP-r_g between SCZ and ASD. A lower genetic correlation between SCZ and ASD than between SCZ and BPD is consistent with the Swedish national epidemiological studies which reported higher odds ratios in siblings between SCZ and BPD[56] than between SCZ and ASD[9]. These results imply a modest overlap of common genetic etiologic processes in these two disorders consistent with emerging evidence from discovery of copy number variants where both shared variants (e.g 15q13.3, 1q2.1 and 17q12 deletions[58,59]) and same gene but different variants (deletions associated with schizophrenia and duplications associated with autism, and vice versa[10]) have been reported. The small ASD sample size thwarted attempts of further explorative partitioning of the SNP coheritability between SCZ and ASD.

The lack of overlap between ADHD and ASD is surprising and not consistent with family and data linkage studies, which indicate that the two disorders share genetic risk factors[5,6,60,61]. Some rare copy number variants are seen in both disorders[16]. As noted above, the use of pseudo-controls for many of the ASD and ADHD cohorts may impact on all results for these disorders. Ideally we would investigate the impact of pseudo-controls given the hierarchical diagnostic system (autism, but not autism spectrum is an exclusion criterion for most ADHD data sets) on estimates of the SNP-coheritability, but the small ASD sample size prohibits such analyses. We also found no overlap between ADHD and bipolar disorder despite meta-analytic support for an increased risk for ADHD in relatives of BPD I (a subtype of BPD with more extreme manic symptoms than the other major BPD subtype) patients and an increased risk for BPD I in relatives of ADHD patients [12]. This could mean that the familial link between the two disorders is mediated by environmental risk factors or that the shared genetic factors are not part of the common allelic spectrum. Alternatively, the etiologic link between ADHD and BPD might be limited to BPD I or early onset BPD[12] which therefore is difficult for us to detect. Our finding of genetic overlap between ADHD and MDD is consistent with evidence from studies showing increased rates of ADHD in families of depressed probands and increased rates of depression in families of ADHD probands [12,13].

Our results should be interpreted in the context of four potentially important methodological limitations. First, any artefacts, that make SNP genotypes more similar between cases than between cases vs. controls could inflate estimates of SNP-heritability[18], but to a much lesser extent SNP–coheritability. Second, the sample sizes varied considerably across the five disorders. Although the *SNP-h^2* are expected to be unbiased, estimates from smaller samples are accompanied by larger standard errors, blurring their interpretation. Third, while applying similar diagnostic criteria, the clinical methods of ascertainment and the specific study protocols, including which specific interview instruments were employed, varied across sites. We cannot now determine the degree to which our results might have

been influenced by the between-site differences in the kinds of patients seen or in their assessments. Fourth, by combining samples from geographical regions, contributions from less common associated variants specific to populations are diluted compared to what could be achieved if the same sample size had been ascertained from a single homogeneous population.

In summary, we report SNP-heritabilities that are significantly greater than zero for all five disorders studied. We have used the largest psychiatric GWAS data sets currently available and our results provide important pointers for future studies. Our results demonstrate that the dearth of significant associations from psychiatric GWAS to date, particularly for MDD, ASD and ADHD, reflects lack of power to detect common associated variants of small effect rather than absence of such variants. Hence as sample sizes increase the success afforded to other complex genetic diseases[52] in progressing understanding of their etiology is achievable for psychiatric disorders, as already being shown for SCZ[62]. We also provide evidence for a substantial sharing of the genetic risk variants "tagged" by these SNPs for SCZ/BPD, BPD/MDD, SCZ/MDD, ADHD/MDD and, to a lesser extent, SCZ/ASD. Our results will likely contribute to efforts now underway to base psychiatric nosology on a firmer empirical footing. Furthermore, they will encourage investigations into shared pathophysiologies across disorders including potential clarification of common therapeutic mechanisms.

Note: Supplementary information is available on the Nature Genetics website.

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COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

Figure 1. Evidence for genome-wide pleiotropy between psychiatric disorders. a. Proportion of variance in liability (SNP-heritability), and proportion of covariance in liability between disorder (SNP-coheritability) for 5 major psychiatric disorders. 95% error bars are estimate ± 1.96 standard error.

Figure 2 Genomic partitioning of SNP-heritability/SNP-coheritability by annotation. Proportion of SNPs attributable to genes in CNS+ set (red bar), proportion of SNP-heritability explained by SNPs attributed to SNPs in CNS+ set (dark green bar), proportion of SNP-coheritability attributed to SNPs in CNS+ set (light green bar), proportion of SNP-heritability for Crohn's Disease attributed to SNPs in CNS+ set (orange bar). 95% error bars are estimate ± 1.96 standard error. *** $p < 10^{-5}$ from test that proportion of heritability explained by SNPs = proportion of SNPs.

Figure 3 SNP-heritabilities and coheritabilities. a) For each disorder the SNP-heritabilities are estimated from univariate analyses of the full data set (dark green bars) or from subsets (red/pink bars). They are also estimated from bivariate analyses in which different subsets of the same disorder comprise the two traits (blue bars). Test of heterogeneity of estimates, p-value for Cochrane's Q, SCZ: 0.3, BPD: 1×10^{-6}, MDD: 4×10^{-3}, ADHD: 9×10^{-6}, ASD: 0.99 Higgins' I2, SCZ: 21%, BPD: 86%, MDD: 71% ADHD: 91% ASD:0 b) For comparison the coheritabilities using the full data sets from Figure 1. c) As a negative control, estimates of coheritabilities with Crohn's Disease (CD), a disease not expected to be genetically related to psychiatric disorders. 95% error bars are estimate ± 1.96 standard error.

Table 1. Univariate analyses: sample description, SNP-heritabilities and recurrence risk to first-degree relatives

	SCZ	BPD	MDD	ASD	ADHD
SNPs(imputed)	915354	995971	962093	982100	917066
Cases	9087	6704	9041	3303	4163
Controls	12171	9031	9381	3428[a]	12040[a]
N cohorts	17	11	9	8	8
Primary Reference	[21]	[22]	[23]	[24,25]	[26-30]
CC (s.e.)	0.41 (0.015)	0.44 (0.021)	0.18 (0.017)	0.31 (0.046)	0.25 (0.020)
Disorder risk for the study-base population (disorder risk, *K*) used in Figures and Supplementary Tables					
K	0.01	0.01	0.15	0.01	0.05
SNP-h^2 (s.e.)	0.23 (0.008)	0.25 (0.012)	0.21 (0.021)	0.17 (0.023)	0.28 (0.023)
$\lambda_{1st\text{-}SNP}$ (s.e)	2.10 (0.05)	2.23 (0.08)	1.27 (0.03)	1.75 (0.14)	1.71 (0.07)
λ_{1st}	8.8	9.6	1.5	8.7	3.5
Lower bound for disorder risk (*K*)					
K	0.004	0.007	0.1	0.001	0.03
SNP-h^2 (s.e.)	0.19 (0.007)	0.23 (0.010)	0.19 (0.020)	0.11 (0.017)	0.24 (0.020)
$\lambda_{1st\text{-}SNP}$ (s.e)	2.14 (0.06)	2.25 (0.08)	1.31 (0.03)	1.79 (0.15)	1.77 (0.07)
λ_{1st}	14.4	11.7	1.7	29.4	4.5
Upper bound for disorder risk (*K*)					
K	0.012	0.015	0.2	0.015	0.08
SNP-h^2 (s.e.)	0.24 (0.009)	0.27 (0.013)	0.23 (0.023)	0.19 (0.028)	0.32 (0.026)
$\lambda_{1st\text{-}SNP}$ (s.e)	2.10 (0.05)	2.20 (0.07)	1.24 (0.02)	1.74 (0.13)	1.65 (0.06)
λ_{1st}	8.0	7.7	1.4	7.0	2.8
Heritability estimated from twin/family studies[63]					
h^2	0.81	0.75	0.37	0.80	0.75

SCZ: schizophrenia, BPD: bipolar disorder, MDD: major depressive disorder, ASD: autism spectrum disorders, ADHD: attention deficit hyperactivity disorder. CC=SNP-heritability estimated on case-control scale. SNP-h^2 SNP-heritability on liability scale given assumed *K*. All estimates of SNP-h^2 are highly significantly different from zero. $\lambda_{1st\text{-}SNP}$ recurrence risk to first degree relatives calculated from SNP-h^2 liability and *K*. λ_{1st} recurrence risk to first degree relatives calculated from h^2 from twin/family studies and *K* . a) some cohorts include cases and pseudo-controls where pseudo-controls are the genomic complements of the cases derived from genotyping of proband-parent trios.

Methods

Data & quality control (QC)

A summary of the data available for analysis is listed in **Table 1** and comprise data used in the PGC-Cross Disorder Group analysis[25] together with newly available ADHD samples[27-30]. Data upload to the PGC central server follows strict guidelines to ensure local ethics committee approval for all contributed data (https://pgc.unc.edu/). Data from all study cohorts were processed through the stringent PGC pipeline[25]. Imputation of autosomal SNPs used the CEU+TSI Hapmap Phase 3 data as the reference panel[21]. For each analysis (univariate or bivariate), we retained only SNPs that had minor allele frequency > 0.01 and imputation R^2 > 0.6 in all contributing cohort sub-samples (imputation cohorts). Different QC strategies were investigated in detail for the raw and PGC imputed genotyped data of the International Schizophrenia Consortium, a subset of the PGC SCZ sample[35]. The CD samples from the International IBD Genetics Consortium (IIBDGC)[43] were processed through the same QC and imputation pipeline as the PGC data, generating a data set of 5054 cases and 11496 controls from 6 imputation cohorts.

In each analysis, individuals were excluded to ensure that all cases and controls were completely unrelated in the classical sense, so that no pairs of individuals had a genome-wide similarity relationship greater than 0.05 (equivalent to about second-cousins). This procedure removed ancestry outliers (over and above those already removed in the PGC QC pipeline, **Supplementary Figures 2-5**) and ensured that overlapping control sets were allocated randomly between disorders in the bivariate analyses. Exact numbers of cases and controls used in each analysis are listed in **Supplementary Tables 1-8**.

Linear mixed model for estimation of SNP-heritability and SNP-coheritability

We use the methods presented in Lee *et al*.[18,35] Briefly, we estimate the variance in case-control status explained by all SNPs using a linear mixed model,

$$\mathbf{y} = \mathbf{X}\boldsymbol{\beta} + \mathbf{g} + \mathbf{e} \quad (1)$$

where **y** is a vector of case (=1) or control (=0) status (the "observed scale"), **β** is a vector for fixed effects of the overall mean (intercept), sex, sample cohort and 20 ancestry principal components, **g** is the vector of random additive genetic effects based on aggregate SNP information, and **e** is a vector of random error effects. **X** is an incidence matrix for the fixed effects relating these effects to individuals. The variance structure of phenotypic observations is V(**y**) = $\mathbf{V} = \mathbf{A}\sigma_g^2 + \mathbf{I}\sigma_e^2$, where σ_g^2 is additive genetic variance tagged by the SNPs, σ_e^2 is error variance, **A** is the realized similarity relationship matrix estimated from SNP data[19] and **I** is an identity matrix. All variances are estimated on the observed case-control scale and are transformed to the liability scale, which requires specification of the disorder risk, *K*, to estimate SNP-h^2. Risk to first-degree relatives is calculated from *K* and SNP-h^2 based on the liability threshold model[64].

The bivariate analyses use a bivariate extension of equation (1)[20]. The two traits are measured on different individuals, but the equations are related through the genome-wide similarities estimated from SNPs. Genetic and residual variances for the traits are estimated as well as the genetic covariance σ_{g12}. The genetic correlation coefficient (r_g) is $\sigma_{g12}/(\sigma_{g1}\sigma_{g2})$ and is approximately the same on the observed case-control scale as on the liability scale[20] so does not depend on specifications of *K*. The covariance, σ_{g12}, can be transformed to the liability scale accounting for assumed disorder risks and proportions of cases and controls in the samples of each disorder[20] and it equals the coheritability[54], $r_g h_1 h_2$. We used the approximated chi-square test statistic (estimate/s.e.)^2 to test if estimates were significantly different from zero. We checked that this simple approximation agreed well with the more formal and computer-intensive likelihood ratio test for several examples.

Heterogeneity of SNP-heritabilities was tested using Cochran's[65] Q and Higgins'[66] I^2, acknowledging potential non-independence of the 6 estimates (3 subsets plus 3 subset pairs).

Disorder risk for the study-base population (disorder risk, K)

The estimates of SNP-h^2 and SNP-coheritability from the linear model are on the case-control scale and so depend partly on the proportion of cases and controls in the sample. The transformation to the liability scale allows benchmarking of SNP-h^2 to estimates of heritability from family studies, and the transformation accounts for the proportion of cases in the sample and depends on the assumed disorder risk (*K*). The appropriate choice of *K* depends on the definitions of both the phenotype (including ascertainment strategy) and the population, which may differ between cohorts. We consider lower and upper bounds for *K* in Table 1 to cover the range of possible values. *SNP-*r_g estimates are independent of scale and hence are not dependent on the choice of *K*.

Genome partitioning linear mixed model

We partitioned the variance explained by the SNPs in several ways. For example, for the univariate linear model $\mathbf{y} = \mathbf{X} + \sum_{t=1}^{n} g_t + \mathbf{e}$ with V(**y**) = $\mathbf{V} = \sum_{t=1}^{n} \mathbf{A}_t \sigma^2_{g_{tc}} + \mathbf{I} \sigma^2_e$

where *n* is the number of subsets from any non-overlapping partitioning of SNPs; *n* = 22 for the joint analysis by chromosome, *n* = 5 for the analysis by MAF bin and *n* = 3 for the analysis of SNP by gene annotation in which SNPs were classed as "CNS+ genes" (2,725 genes representing 547 Mb), SNPs in "other genes" (14,804 genes representing 1,069 Mb) and the remaining SNPs "not in genes". Gene boundaries as ± 50kb from 3' and 5' UTRs of each gene and the CNS+ genes were the four sets identified by Raychaudhuri *et al*.[34] (one set comprised genes expressed preferentially in the brain compared to other tissues and the other three sets comprised genes annotated to be involved in neuronal activity, learning and synapses). The CNS+ set was found to explain more of the SNP-heritability than expected by

chance for schizophrenia[35]. All methods have been implemented into the freely available GCTA software[67].

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Jonathan Pimm[145], Joseph Piven[207], Danielle Posthuma[208,209,210], James B Potash[47],

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