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Journal

The American Journal of Psychiatry, 179(11)

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Publication Date

2022-11-01

DOI

10.1176/appi.ajp.21101051

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Am J Psychiatry. Author manuscript; available in PMC 2023 November 01.

Published in final edited form as:

Am J Psychiatry. 2022 November 01; 179(11): 833–843. doi:10.1176/appi.ajp.21101051.

Charting the landscape of genetic overlap between mental disorders and related traits beyond genetic correlation

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Abstract

Introduction: Mental disorders are heritable and polygenic. Genome-wide genetic correlations (r_g) have indicated widespread shared genetic risk across multiple disorders and related traits,

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Disclosures

O.A.A. has received speaker's honorarium from Lundbeck and is a consultant for Healthlytix. A.M.D. is a founder of and holds equity interest in CorTechs Labs and serves on its scientific advisory board. He is also a member of the Scientific Advisory Board of Healthlytix and receives research funding from General Electric Healthcare (GEHC). The terms of these arrangements have been reviewed and approved by the University of California, San Diego in accordance with its conflict of interest policies. Remaining authors have nothing to disclose.

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mirroring their overlapping clinical characteristics. However, r_g may underestimate the shared genetic underpinnings of mental disorders and related traits since it does not differentiate mixtures of concordant and discordant genetic effects from an absence of genetic overlap.

Method: We applied the bivariate causal mixture model (MiXeR) to summary statistics for four mental disorders, four related mental traits, and height from genome-wide association studies (n=53,293–766,345). MiXeR estimates the number of 'causal' variants for a given trait ('polygenicity'), the number of variants shared between traits, and the genetic correlation of shared variants (r_{gs}). We investigated local r_g using LAVA.

Results: Among mental disorders, ADHD was least polygenic (5.6K), followed by bipolar disorder (8.6K), schizophrenia (9.6K) and major depression (14.5K). Most variants were shared across mental disorders (4.4K-9.3K) and between mental disorders and related traits (5.2K-12.8K), but with disorder-specific variations in r_g and r_{gs}. Overlap with height was small (0.7–1.1K). MiXeR estimates correlated with LAVA local r_g ($r=0.88, p<0.001$).

Discussion: There is extensive genetic overlap across mental disorders and related traits, with mixed effect directions and few disorder-specific variants. This suggests that genetic risk for mental disorders is predominantly differentiated by divergent effect distributions of pleiotropic genetic variants rather than disorder-specific variants. This represents a conceptual advance in our understanding of the landscape of shared genetic architecture across mental disorders, which may inform genetic discovery, biological characterization, nosology, and genetic prediction.

Introduction

Mental disorders are among the most heritable complex human disorders. For schizophrenia, bipolar disorder (BIP), major depression (MD) and attention-deficit hyperactivity disorder (ADHD), twin studies have estimated broad sense heritabilities of 40–80%.[1–4] Genome-wide association studies (GWAS) have since shown that approximately one third is driven by thousands of common genetic variants, each with individually small effect.[5] As ever-expanding GWAS sample sizes bring genetic prediction and stratification tools closer to the clinic,[6] a better understanding of the complex genetic architecture of mental disorders is needed to address questions regarding disease classification and the potential for precision medicine in psychiatry.

Larger GWAS sample sizes have also revealed extensive shared genetic risk variants across diagnostic categories, mirroring their overlapping clinical characteristics.[7] A meta-analysis of eight mental disorders identified 109 independent genetic loci associated with two or more disorders.[8] Interestingly, 11 of these had "discordant" effects, i.e. increased the risk of one disorder but decreased the risk of a second.[8] This is supported by findings from pair-wise analyses,[9,10] which have identified hundreds of shared loci between mental disorders and related traits such as intelligence[11,12] and personality traits,[13] with a mixture of concordant and discordant effects (fig. 1a). Such extensive "pleiotropy" calls into question the traditional conceptualisation of genetic risk, in which a specific set of genes are implicated for a specific disorder.[14]

Nonetheless, most 'causal' genetic variants are yet to be discovered at genome-wide significance."Genome-wide" approaches have therefore been developed which quantify

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genetic overlap beyond genome-wide significance, providing a “bird’s eye view” of the landscape of shared genetics across disorders and traits. For example, linkage disequilibrium score regression (LDSC) genetic correlation (r_g) returns a summary measure of the correlation of all SNP effect sizes.[15] When applied to 10 mental disorders, this revealed widespread weak-to-moderate positive correlations, with strong positive correlations between schizophrenia and BIP, and anxiety disorders and MD.[16]

Although r_g is an informative measure of the genetic similarity between two phenotypes, it does not capture all dimensions of genetic overlap. Shared genetic variants can have either concordant or discordant effects.[12,17,18] However, since r_g is a genome-wide summary measure, it does not differentiate genetic overlap with a mixture of concordant and discordant effects from an absence of genetic overlap, returning an estimate close to 0 in both scenarios (fig. 1a). It is necessary to capture this “missing dimension” of genetic overlap to comprehensively describe the shared genetic underpinnings of polygenic mental disorders.[17] Overlap despite minimal genetic correlation may indicate shared molecular mechanisms with implications for how we conceptualise genetic risk for mental disorders.

The bivariate causal mixture model (MiXeR)[19] and local analysis of covariant association (LAVA) can shed light on this “missing dimension”. MiXeR circumvents the need to identify all ‘causal’ variants by inferring the total number of ‘causal’ variants for each trait (univariate), and the total number of shared and unique ‘causal’ variants for a pair of traits (bivariate).[19] MiXeR also estimates the genetic correlation of shared variants (r_{gs}), in addition to r_g (fig. 1b). Using MiXeR, we have demonstrated extensive genetic overlap across several mental disorders and related traits with mixed effect directions.[13,18,21] The relevance of mixed effects has been further emphasised by LAVA, which calculates local genetic correlations across the genome.[22] Despite employing a distinct statistical framework, LAVA revealed widespread local genetic correlations across somatic and mental traits with mixed effect directions, even in the presence of minimal r_g.[22] However, neither MiXeR nor LAVA have been systematically applied across mental disorders, cognitive and personality traits using largest-to-date GWAS.

We applied MiXeR and LAVA to large-scale GWAS of ADHD, BIP, schizophrenia, MD, cognitive and personality traits, to characterise their genetic overlap beyond r_g. We aimed to map a) polygenicity, b) genetic overlap allowing mixed effect directions c) r_{gs}, and d) local genetic correlations, using height as a comparator. We compared MiXeR estimates of mixed effect directions to LAVA local correlations to validate our findings across two distinct statistical frameworks. By charting the landscape of genetic overlap beyond r_g, we provide insights into the unique and shared genetic architectures underlying psychiatric disorders, with implications for how we conceptualise genetic risk for mental disorders and related traits.

Methods

Samples

We acquired summary statistics from large-scale GWAS of major mental disorders ADHD, BIP, MD, schizophrenia, as well as educational attainment (EDU), general intelligence

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(hereafter “intelligence”), neuroticism, subjective well-being (SWB), and height (table 1, supplementary table 1).[15,21–31] Phenotypes were selected based on available sample size and the quality of phenotyping procedures (supplementary methods, supplementary tables 2-3). The final sample included 268,241 individuals with mental disorder and a combined sample size of 3,571,567, although there was participant overlap across samples.[32] Due to the confounding effect of ancestral differences in LD structure and the lack of sufficiently powered multi-ancestry samples, samples were restricted to European ancestry. The Regional Committee for Medical Research Ethics – Southeast Norway evaluated the current protocol and found that no additional institutional review board approval was necessary as no individual data were used.

Modelling polygenicity and shared ‘causal’ variants using MiXeR

We applied MiXeR v1.3 to evaluate the unique and shared genetic architecture across our included phenotypes.[19] MiXeR infers characteristics of the genetic architecture of complex traits based on GWAS summary data using Gaussian mixture models, a probabilistic model which assumes that a given dataset can be modelled as a “mixture” of pre-defined components, each with their own Gaussian (normal) distribution.

MiXeR constructs a univariate mixture model for each trait followed by a bivariate mixture model for cross-trait analysis, incorporating minor allele frequency (MAF), sample size, effects of LD structure, genomic inflation due to cryptic relatedness and sample overlap into the model. Firstly, univariate MiXeR assumes that, for each trait, common genetic variants are a mixture of: 1) ‘causal’ variants and 2) non-causal variants. Under this assumption, MiXeR estimates the polygenicity (π – fraction of causal variants) and discoverability (σ^2 – variance of effect size per causal variant) for a given trait using maximum likelihood estimation. SNP-based heritability h^2_{SNP} is derived from these estimates. To aid interpretation, polygenicity is presented as the number of causal variants with strongest effects required to explain 90% h^2_{snp}. A threshold of 90% is applied to prevent extrapolating model parameters into variants with infinitesimally small effects.

MiXeR is extended to a bivariate context by assuming that, for a pair of traits, common genetic variants can be described as a mixture of four components – shared ‘causal’ variants (1), unique ‘causal’ variants for trait 1 (2) and trait 2 (3), and non-causal variants (4). Informed by the model parameters from univariate MiXeR for each trait, bivariate MiXeR estimates the shared component’s polygenicity irrespective of effect directions and correlation of effect sizes (r_{gs}). The genome-wide genetic correlation (r_g) and proportion of shared variants with concordant effects are derived from these model parameters. See supplementary methods and supplementary fig. 1 for further details.

Analogous to traditional significance testing, model fit is evaluated by calculating the difference between the Akaike Information Criterion (AIC) for best-fitting MiXeR estimates and a “reference” model. Positive AIC differences are interpreted as evidence that the best-fitting MiXeR estimates are distinguishable from the reference model. For univariate MiXeR, an “infinitesimal model” in which all variants are assumed to be ‘causal’ is used as the reference. For bivariate MiXeR, the best-fitting model is compared to minimum possible

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overlap and maximum possible overlap. We provide log-likelihood plots in figure S2 to visualise the parameter estimation procedure.

Computing local genetic correlations with LAVA

We estimated pairwise local r_g using LAVA.[22] LAVA complements MiXeR by estimating local r_g across 2495 semi-independent genetic loci of approximately equal size (~1Mb), thus capable of identifying mixed effect directions despite minimal r_g. LAVA differs from MiXeR because it 1) uses a distinct statistical framework based on a fixed effects model, rather than MiXeR's random effects model, 2) identifies specific shared loci, and 3) is only a proxy measure of genome-wide genetic overlap since the number of significantly correlated loci is, in part, influenced by the statistical power of input GWAS.[22] After computing local h^2_{SNP} estimates for each trait, LAVA computes the matrix of local genetic covariance for each locus using the method of moments. Sample overlap was controlled using LDSC.[23] Significance testing was performed using simulation-based p-values. We used the false discovery rate (FDR) to adjust for multiple testing, reporting loci with FDR<0.05.

Comparing MiXeR and LAVA estimates of effect direction

To test the hypothesis that MiXeR and LAVA-derived measures of mixed effect directions were correlated, we calculated the Pearson correlation coefficient for a) MiXeR-estimated proportion of shared 'causal' variants with concordant effects and b) LAVA-estimated proportion of significantly correlated genetic loci with positive correlation. These measures are comparable since both are proportions quantifying mixed genetic effects between two traits, with 0 indicative of completely discordant effects, 1 completely concordant effects, and 0.5 a balance of concordant and discordant effects. These measures differ since MiXeR estimates the effect directions of all shared 'causal' variants, whereas LAVA only captures significantly correlated loci.

Data availability

All data are publicly available or available on request (supplementary table 1). MiXeR and LAVA code are available at https://github.com/precimed/mixer and https://github.com/josefin-werme/LAVA.

Results

Polygenicity

ADHD was the least polygenic mental disorder (N=5,600 'causal' variants explaining 90% of ADHD's h^2_{SNP}, SD=400), followed by BIP (n=8,600, sd=200) and schizophrenia (n=9,600, sd=200). Intelligence, neuroticism, and subjective well-being were estimated to be associated with 11,200–12,500 variants at 90% h^2_{SNP}, while EDU (n=13,200, sd=300) and MD (n=14,500, sd=700) were most polygenic (fig. 2). Height was less polygenic (n=4,000, sd=100). This pattern of polygenicity was distinct from h^2_{SNP} estimates (fig. 2). Heritability, discoverability and power analyses are described in supplementary results, supplementary table 4 and supplementary fig. 2.

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Genome-wide genetic overlap beyond genetic correlation

Genetic overlap across mental disorders—When applying bivariate MIXeR to mental disorders, there was a pattern of extensive genetic overlap between the four mental disorders, with almost complete genetic overlap across all disorders (fig. 2, supplementary table 5). Further, AIC differences indicated that MiXeR-modelled overlap was not distinguishable from maximum overlap (supplementary results). This pattern was most evident for schizophrenia and BIP which were almost completely overlapping, with 8.5K (sd=0.3K) shared variants, 0.1K (sd=0.2K) unique BIP variants and 1.1K (sd=0.4K) unique schizophrenia variants. Since the number of shared variants was almost equal to the total number of 'causal' variants, r_{gs} (0.78, SD=0.03) was similar to r_g (0.73, sd=0.006), providing further evidence of the highly similar genetic architectures of these two psychotic disorders.

Extensive genetic overlap was also observed in the presence of weak r_g. For example, schizophrenia and ADHD also shared large numbers of 'causal' variants (5.4K, sd=0.4K), with only 0.1K unique ADHD variants, despite possessing the weakest r_g (0.19, sd=0.010) and r_{gs} (0.26, sd=0.02). This pattern of extensive genetic overlap but weak r_g is indicative of mixed effect directions, supported by the MiXeR-estimated proportion of shared 'causal' variants with concordant effects (0.58, sd=0.006).

LAVA local correlations provided further evidence of mixed effect directions across mental disorders (fig. 2). This was most evident between schizophrenia and MD (35 positively/9 negatively correlated loci), although even schizophrenia and BIP were found to share a mixture of effect directions despite strong positive r_g (123 positively/5 negatively correlated loci). Local correlations for schizophrenia and ADHD were not consistent with MiXeR estimated mixed effect directions (10 positively correlated loci).

Given MD's high polygenicity compared to less polygenic disorders like ADHD and BIP, there were large differences in the number of shared and unique 'causal' variants. For example, MD and ADHD shared the smallest number of variants (4.4K, sd=0.4K), with many more unique-MD variants (10.1K, 0.6K) than unique-ADHD variants (1.2K, sd=0.5K). While they were moderately correlated at the genome-wide level (r_g=0.45, sd=0.011), shared variants were strongly correlated (r_{gs}=0.93, sd=0.07). AIC differences indicated that this analysis was underpowered to provide precise estimates (supplementary results). Nonetheless, there would still be strong r_{gs} even in a scenario of complete genetic overlap (r_{gs}-max=0.72, supplementary methods). A similar, although less pronounced, relationship was evident between MD and BIP. LAVA results supported these findings. All five significantly correlated loci for ADHD and MD were positively correlated, while 20 out of 22 (91%) were positively correlated between MD and BIP.

Mental disorders and cognitive and personality traits

Mental disorders displayed similarly pronounced genetic overlap with intelligence, EDU, neuroticism, and SWB (fig. 3). As for mental disorders, AIC differences indicated that the MiXeR-modelled overlap was indistinguishable from maximum possible overlap for all analyses besides MD and NEUR, which displayed poor model fit (supplementary fig. 4,

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supplementary tables 6-7*)*. Prominent mixed effect directions among shared 'causal' variants were supported by LAVA local correlations (supplementary results).

Genetic overlap with height

Relative to height's polygenicity (4.0K, sd=0.1K), there was minimal genetic overlap (0.7–1.1K) with large numbers of unique height (2.9K-3.3K) and mental disorder variants (4.9K-13.5K) (fig. 3, supplementary table 8). AIC differences indicated reliable estimates for all analyses. See supplementary results for more details.

Comparing MiXeR estimated effect directions with LAVA local correlations

The proportion of loci with positive genetic correlations was significantly correlated with the proportion of MiXeR estimated 'causal' variants with concordant effects ($r=0.88$, $p<0.001$), supporting the validity of MiXeR estimates of mixed effect directions (fig. 4). Complete LAVA results are presented in supplementary table 9.

Discussion

In this cross-trait genetic analysis of ADHD, BIP, MD, schizophrenia, and cognitive and personality traits, we systematically quantified genetic architecture beyond genome-wide genetic correlations. We found marked differences in polygenicity but extensive genetic overlap across all mental disorders, cognitive, and personality traits, with few disorder-specific variants. These findings were supported by LAVA local correlations which also revealed patterns of mixed effect directions concealed by estimates of genome-wide genetic correlations. This indicates that, rather than a predominance of disorder-specific risk variants, there may be a set of highly pleiotropic variants which influence the risk of diverse mental disorders and related traits. By extension, phenotypic specificity may be largely driven by the distribution of effect sizes and effect directions across this pool of pleiotropic variants rather than variants unique to each phenotype.[17] Building on previous work highlighting extensive overlap across mental disorders,[13,17] this represents a conceptual advance in our understanding of the genetic architecture of mental disorders, which may inform strategies for genetic discovery, biological characterization, and psychiatric nosology, providing the foundations for the development of precision psychiatry and treatment stratification across diagnostic boundaries.

First, we used univariate MiXeR to show that the genetic architectures of mental traits exhibit fundamental differences beyond heritability, with differences in polygenicity across the eight included traits. Among mental disorders, this was most pronounced between ADHD and MD, although lower polygenicities have recently been reported for migraine[24], cortical MRI measures, and other somatic traits.[24–26] While the neurobiological and clinical implications of these findings are currently speculative, it is possible that polygenicity is a marker of heterogeneity at the neurobiological and/or clinical level. For example, ADHD may represent a more neurobiologically and/or clinically homogenous population than MD. By extension, polygenicity may be a useful marker of genetic heterogeneity, which could be used to test the effect of biomarkers or clinically defined sub-groups on the genetic make-up of a given disorder. Differences in polygenicity may also be due to differences

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in biological complexity or negative selection.[27,28] More deeply-phenotyped samples and improved functional characterisation of genetic loci are required to provide further insights.

Using bivariate MiXeR, we found extensive genetic overlap across mental disorders and cognitive and personality traits. This pattern was present in scenarios of weak genome-wide genetic correlation, such as MD and cognition, as well as strong genome-wide correlations, such as BIP and schizophrenia. The former is indicative of a balance of shared variants with concordant and discordant effect directions on each trait, a pattern we replicate using LAVA. These findings build on previous evidence demonstrating extensive genetic overlap between SCZ, BIP, MD and intelligence, with widespread mixed effect directions.[11,17] Together, this indicates that most common variants which influence the genetic risk for diverse mental phenotypes are highly pleiotropic and may have both risk-enhancing and risk-reducing effects on different disorders and traits. Consequently, it may be the specific distribution of effect sizes of highly pleiotropic variants which predominantly contribute to the development of a given mental disorder rather than a set of phenotype-specific variants.

This conceptual insight extends the current theories of genetic susceptibility for mental traits and disorders. These are traditionally based on the assumption that a specific set of genes are implicated for a given mental disorder with varying degrees of genetic overlap across disorders, reflected by their genetic correlations.[8,16,29] However, this is inconsistent with the extent of genetic overlap observed when accounting for mixed effect directions, which may provide a better conceptual framework for the neurobiology of mental traits and disorders. The brain is a complex organ with abundant pleiotropy across different brain regions,[30] brain functions,[31] and mental traits.[32] Thus, it is likely that differences in activity in the same neurobiological systems alter diverse mental traits and disorders but the magnitude and direction of effect may differ across and within diagnostic categories, exemplified by evidence of increased glutamatergic neurotransmission in schizophrenia[33] but decreased transmission in MD.[34] This is also consistent with the fact that most genetic variants associated with mental disorders reside within regulatory elements rather than coding regions.[35] Allelic variation may therefore “tune” neurobiological pathways in different directions, resulting in phenotypic differences mediated by the same pathways.[36] By applying statistical tools that allow for mixed effect directions and estimation of effects sizes, new insight into neurobiological substrates for mental disorders is possible.

These findings also have clinical implications. Firstly, evidence of extensive genetic overlap with limited trait specificity underscores the limited extent to which our current categorical diagnostic system maps on to underlying biological processes.[37] These findings may therefore be more consistent with dimensional approaches to psychiatric nosology which allow for specific combinations of symptoms as well as interactions with other mental traits, as proposed by the RDoC or HiTOP taxonomies.[38,39] This may also help to explain the large degree of comorbidity and the prominence of overlapping clinical characteristics observed across mental disorders. Alternatively, once greater proportions of the SNP-based heritability of mental disorders have been characterized, it may be possible to parse the heritable component into constituent biological processes. This may enable construction of a personalised, biologically-informed diagnostic system, similar to the “palette model” proposed for diabetes.[40] As the era of large-scale case control GWAS transitions towards

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deeply phenotyped clinical and population samples,[41] it will be of great interest whether sub-phenotyping results in more specific genetic signals. This will also be highly relevant for the clinical application of polygenic risk scores, which not only require improved explained variance but also the ability to discriminate across diagnostic groups or clinically relevant decisions.

Despite the pervasive overlap, the number of shared and unique 'causal' variants varied across phenotypic pairs, sometimes revealing the presence of strongly correlated shared variants despite moderate genome-wide genetic correlation. This pattern was most evident between ADHD and MD, a finding supported by LAVA. This suggests that, although a large proportion of MD associated variants are not associated with ADHD, those which are shared have highly similar effects. This mirrors recent findings from a genomic structural equation modelling (Genomic SEM) approach that clustered MD with neurodevelopmental disorders including ADHD.[8] This may indicate distinct clinical sub-groups with higher rates of co-morbidity, or shared involvement of specific molecular mechanisms with similar effects on both disorders. Further investigation of the shared genetic architecture of ADHD and MD may prove fruitful for the identification of underlying biological mechanisms and new treatment targets.[42–44]

There was substantially less genetic overlap between mental disorders and height, with approximately one thousand shared 'causal' variants across all pair-wise analyses. This may represent non-specific "background" genetic overlap observed across all polygenic traits, or alternatively may capture highly pleiotropic transcription factors or regulatory elements which influence diverse traits across distinct tissues and systems. Please refer to supplementary discussion for an extended discussion on the relevance of our findings to the p-factor hypothesis.

This study had limitations. Only samples of European ancestry and common genetic variants were included due to limited availability of trans-ancestral and sequenced samples. Both EDU and SWB are influenced by social factors, and neither can be considered direct measures of cognition or personality. Nonetheless, there is a lack of well-powered GWAS of more specific measures within either domain and they provide useful insights alongside intelligence and neuroticism. We also cannot exclude the possibility of co-morbidity or misdiagnosis across psychiatric samples. However, the extent of the overlap observed and its consistency across mental traits indicate that this alone cannot explain our findings. In addition, for all pair-wise analyses of mental disorders and related traits, besides MD and neuroticism, the AIC differences were negative when compared to maximum possible overlap. This indicates that MiXeR modelled estimates of genetic overlap are indistinguishable from maximum overlap as measured by AIC, and so must be interpreted with caution. It is important to note, however, that the overlaps presented are still the best-fitting estimates as determined by maximum likelihood estimation. Finally, given the need to maximise sample sizes, it was not possible to perform replication analyses in independent samples. Nonetheless, we use both MiXeR and LAVA to triangulate our findings using different statistical frameworks. Our univariate measures are further supported by recent findings using Fourier Mixture Regression (FMR),[45] which predicts required sample sizes for a given proportion of explained heritability, like MiXeR (supplementary material). For

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schizophrenia, BIP and neuroticism, which were common to both analyses, there was high concordance of predicted sample sizes required to explain 90% SNP-heritability.

In summary, we have used advanced statistical modelling to demonstrate both considerable similarities yet also fundamental differences in the genetic architecture of ADHD, BIP, schizophrenia and MD, alongside cognitive and personality traits. Despite extensive genetic overlap and few trait-specific variants, there were distinct patterns of genetic correlations with widespread mixed effect directions. This suggests that it is the specific distribution of effect sizes of highly pleiotropic variants that predominantly contribute to the development of mental disorders and related traits, rather than a set of disorder-specific variants. This represents a conceptual advance in our understanding of the genetic risk of mental disorders, suggesting that normative and pathological mental traits, and the biological processes underlying them, exist on the same dimensions in genomic space. These findings place greater emphasis on efforts to improve the specificity of psychiatric diagnostic categories, potentially offering a means to test the genetic heterogeneity of hypothesized sub-groups through estimates of polygenicity. This may aid efforts to refine the current nosological system, with potential for improved translation of genetic findings into clinically meaningful prediction and stratification tools, and improved drug target identification.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We thank the research participants, employees and researchers of the Schizophrenia, Depression, BIP and ADHD Working Groups of the Psychiatric Genomics Consortium, 23andMe, UK Biobank, CTG, SSGAC and GIANT for making this research possible. This work was partly performed on the TSD (Tjeneste for Sensitive Data) facilities, owned by the University of Oslo, operated and developed by the TSD service group at the University of Oslo, IT-Department (USIT). (tsd-drift@usit.uio.no). Computations were also performed on resources provided by UNINETT Sigma2—the National Infrastructure for High Performance Computing and Data Storage in Norway. We gratefully acknowledge support from American National Institutes of Health (NS057198, EB000790, 1R01MH124839), the Research Council of Norway (229129, 213837, 223273, 324252, 248980), the South-East Norway Regional Health Authority (2017–112, 2019–108), and KG Jebsen Stiftelsen (SKGJ-MED-021). This project has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement nos. 847776, 964874, and 801133 (Marie Skłodowska-Curie grant agreement).

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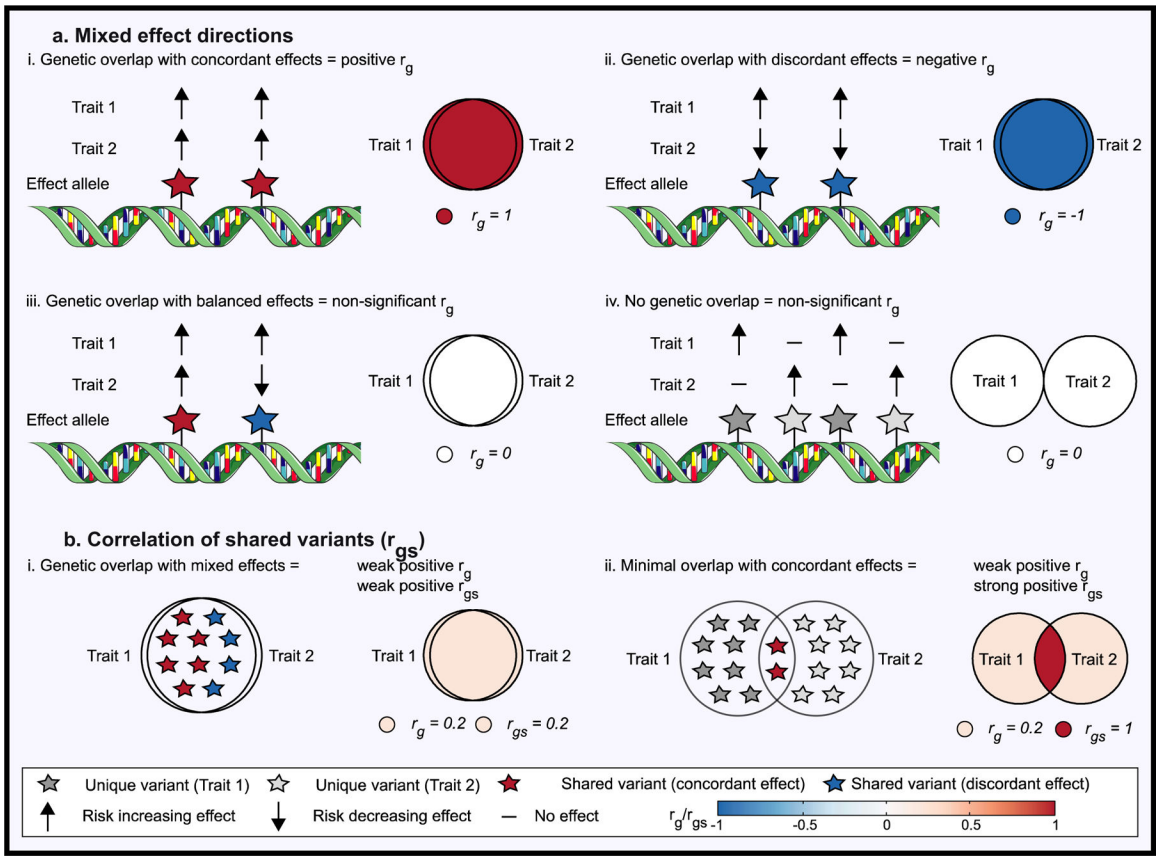

Figure 1.

MiXeR model concepts. Features of genetic overlap beyond genetic correlation (r_g) characterized by MiXeR (Venn diagrams). **a) Mixed effect directions.** While r_g captures genetic overlap with (i.) predominantly concordant or (ii.) discordant effects, it is incapable of differentiating (iii.) genetic overlap with a balance of concordant and discordant effects from (iv.) an absence of genetic overlap, returning an estimate of 0 in both scenarios. In contrast, MiXeR quantifies the number of shared 'causal' variants (Venn diagrams) and so identifies genetic overlap also in the presence of mixed effect directions. **b) Correlation of shared variants (r_{gs}).** r_g does not differentiate (i.) extensive genetic overlap with a small majority of concordant effect directions from (ii.) smaller overlap with a majority of concordant effect directions, returning weak positive r_g in both scenarios. In contrast, MiXeR-estimated r_{gs} returns an equivalent estimate to r_g in scenario i) but a higher estimate in scenario ii) (same concept applies to weak negative r_g / discordant scenarios).

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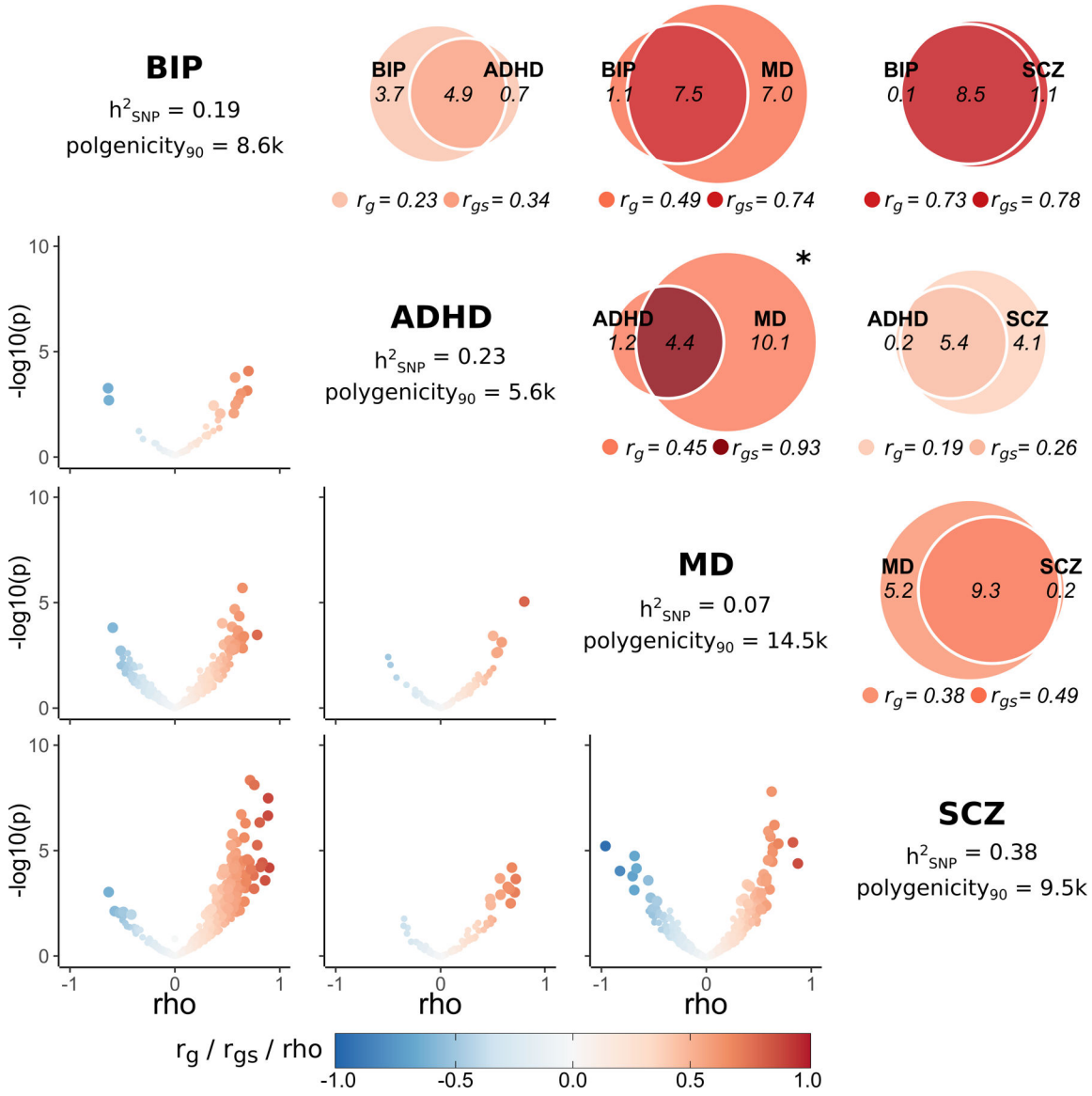

Figure 2:

Along the diagonal, univariate MiXeR estimates for each mental disorder. h^2_{SNP}=SNP-based heritability estimate; polygenicity^{90}= number (in thousands) of causal variants with strongest effects required to explain 90% SNP-based heritability. MiXeR-modelled genome-wide genetic overlap and genetic correlations (top right) and LAVA local correlations (bottom left) across bipolar disorder (BIP), attention-deficit hyperactivity disorder (ADHD), major depression (MD) and schizophrenia (SCZ). **Top right:** MiXeR Venn diagrams showing the number of shared and disorder-specific 'causal' variants in thousands for each pair of disorders. Genome-wide genetic correlation (r_g) and genetic correlation of shared variants (r_{gs}) are represented by the colour of the disorder-specific (r_g) and shared regions (r_{gs}), respectively. All analyses besides MD and ADHD had positive AIC differences when comparing modelled estimates to minimum possible overlap but negative compared to maximum overlap, indicating that MiXeR estimates were indistinguishable from maximum

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overlap. * For MD and ADHD, both AICs were negative, indicating that the analysis was not sufficiently powered to provide precise estimates of genetic overlap. Variation in polygenicity estimates for SCZ are due to variation in univariate MiXeR results across the 20 iterations. **Bottom left:** Volcano plots of LAVA local genetic correlation coefficients (rho, y-axis) against -$\log_{10}$-p values for each pairwise analysis per locus. Larger dots represent significantly correlated loci after FDR-correction. MiXeR estimated r_g and r_{gs}, and LAVA estimated rho are represented on the same blue to red colour scale.

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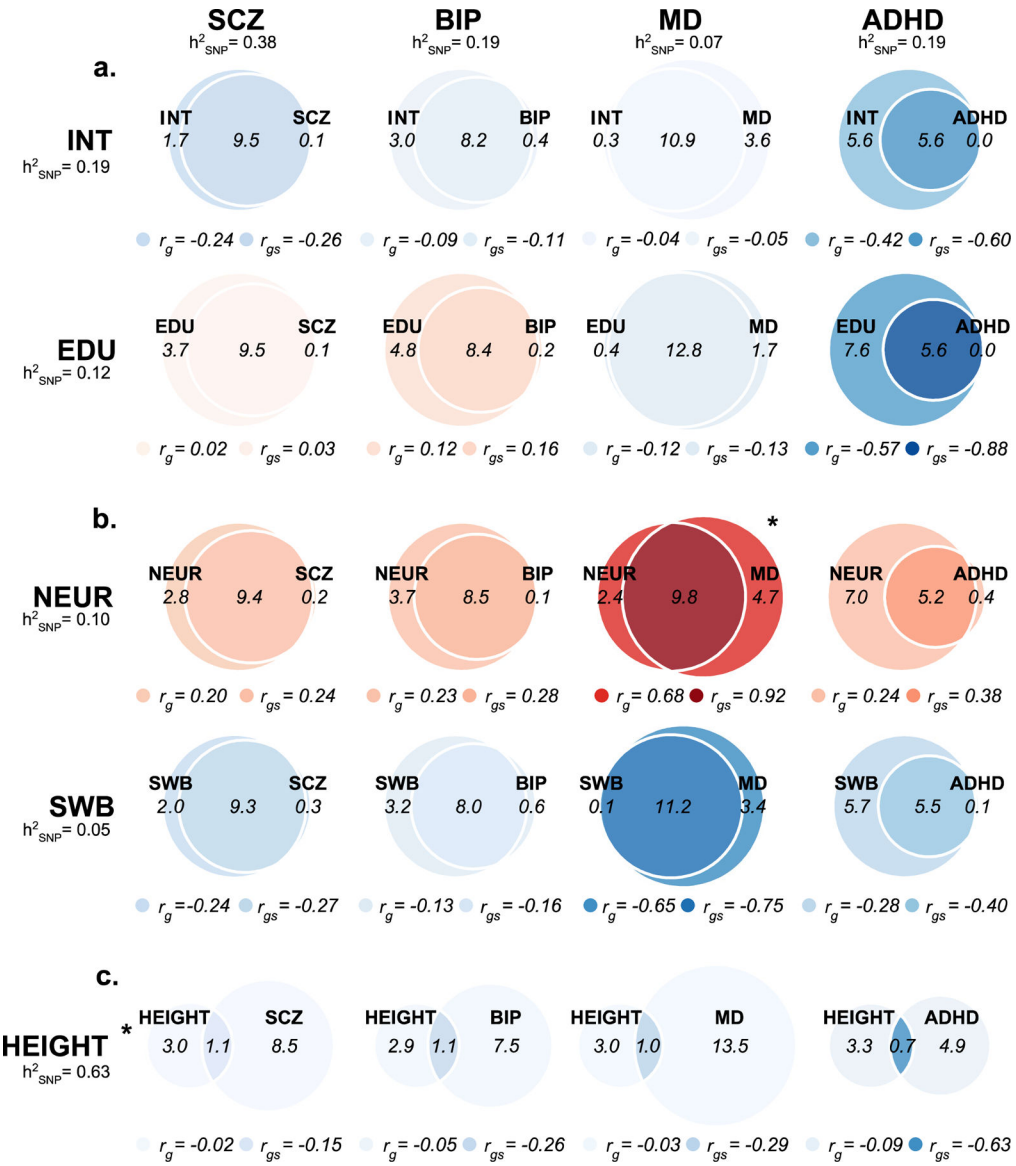

Figure 3:

MiXeR Venn diagrams illustrating MiXeR modelled genetic overlap, genome-wide genetic correlation (rg) and genetic correlation of shared variants (r_{gs}) between mental disorders and **a. cognitive traits**: intelligence (INT) and educational attainment (EDU), **b. personality traits:** neuroticism (NEUR) and subjective well-being (SWB), and **c. height.** The number of unique and shared 'causal' variants are presented in thousands and illustrated by the size of the unique and shared regions of the Venn diagrams. Rg and r_{gs} are provided beneath each diagram and are represented by the shading of the unique (rg) and shared (ρβ) regions, ranging from −1 (dark blue) to +1 (dark red). The SNP-based heritability (h^2_{SNP}) for each trait is provided beneath each trait label. All analyses besides NEUR and major depression (MD) and all height analyses had positive AIC differences when comparing modelled estimates to minimum possible overlap but negative compared to maximum possible overlap, indicating that the estimates were indistinguishable from maximum overlap. *For

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NEUR and MD and all analyses involving height, both AIC differences were positive. However, there was unstable model fit for NEUR and MD compared to minimum possible overlap. These results should be interpreted with caution. Variation in polygenicity estimates for SCZ and SWB are due to variation in univariate MiXeR results across the 20 iterations.

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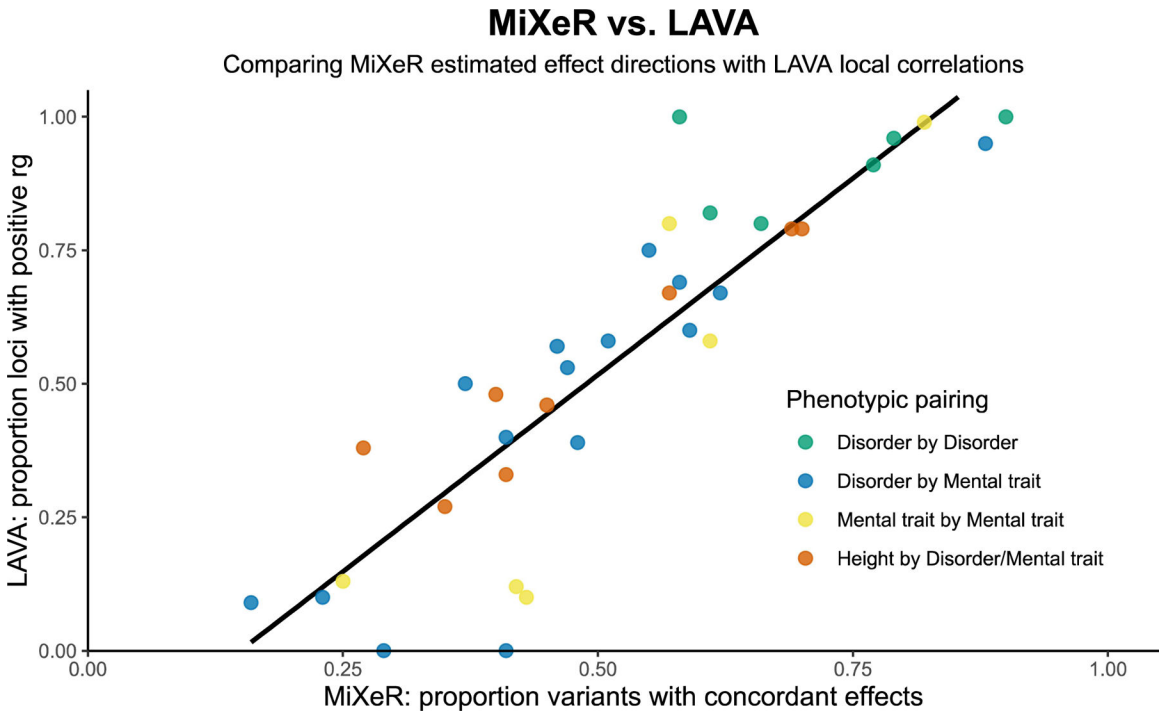

Figure 4:

Scatter plot comparing the proportion of LAVA-estimated independent genetic loci with significant positive genetic correlation against MiXeR-estimated proportion of shared 'causal' variants with concordant effects. Each individual point represents an individual pairwise analysis. Mental disorder by mental disorder (yellow) are clustered around high concordance consistent with higher genetic correlation, height by mental disorders/mental traits are clustered around 0.5 concordance, consistent with minimal genetic correlation and mixed effects, while disorders by mental traits and mental traits by mental traits ("Other mental traits") are distributed across the spectrum of concordance. Both methods emphasise the presence of mixed effect directions across most analyses. However, note that LAVA local correlations were generally more extreme than MiXeR, possibly due to LAVA's tendency to identify the most strongly correlated loci which are most likely to be significant.

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Table 1:

Overview of included samples.

Phenotype	Source	Phenotyping strategy	n cases (n controls)	Genome-wide loci[1]
Mental disorders				
Schizophrenia	PGC-SCZ 3[46]	Clinical diagnosis, structured diagnostic interviews, or health registry review	53,386 (77,258)	177
Bipolar disorder	PGC-BIP 3[47]	Structured diagnostic interviews or health registry diagnoses	41,917 (371,549)	61
Major depression	PGC-MDD 2 + 23andMe[48]	Structured diagnostic interviews or health registry diagnoses of MDD or self-report of Depression or clinical Depression	135,458 (344,901)	44
ADHD	PGC-ADHD 2[49]	Structured diagnostic interviews or health registry diagnoses	19,099 (34,194)	12
Mental traits				
Intelligence	CTG[50]	Neurocognitive test of intelligence or sub-domains	269,867	213
Educational attainment	SSGAC (including UKB)[51]	Self-reported years of completed education	766,345[2]	448
Neuroticism	CTG[52]	Questionnaire response to psychometric scale	390,278[2]	107
Subjective well-being	23andMe[53]	Questionnaire response to ordinal item “how satisfied are you with your life?”	252,053	4
Somatic comparator				
Height	GIANT (including UKB)[54]	Anthropometric measurement	709,706	1292

PGC=Psychiatric Genomics Consortium, SCZ=schizophrenia, BIP=bipolar disorder, MDD=major depressive disorder, ADHD=attention-deficit hyperactivity disorder, CTG=Complex trait genetics, SSGAC=social science genetic association consortium; UKB=UK Biobank, GIANT=The genetic investigation of anthropometric traits consortium.

1 Since the original studies used different procedures for locus definition, we present the number of genome-wide loci using a standardized FUMA-based procedure for locus definition to enable cross-phenotype comparison (see supplementary methods).[35]

2 Original samples for educational attainment and neuroticism included 23andMe sub-cohorts which are not publicly available and so sample sizes are smaller than the original samples.