

Neuroticism and cognitive ability partially account for genetic overlap across major psychiatric disorders

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Abstract

Introduction:

Psychiatric disorders show substantial genetic overlap, but the mechanisms underlying this shared liability remain poorly understood. Biobehavioral traits such as neuroticism and cognitive ability are heritable and genetically correlated with multiple psychiatric disorders, and may contribute to shared genetic risk. We investigated whether these traits account for genetic correlations among nine major psychiatric disorders; anorexia nervosa, anxiety, attention deficit hyperactivity disorder, autism spectrum disorder, bipolar disorder, depression, obsessive-compulsive disorder, post-traumatic stress disorder and schizophrenia.

Methods

We analysed summary statistics from the largest available genome-wide association study (GWAS) of these nine psychiatric disorders, two neuroticism subtypes ('depressed affect' and 'worry') and four cognitive measures (verbal-numerical reasoning, reaction time, memory and educational attainment). Genomic Structural Equation Modelling was used to determine whether biobehavioural traits influenced pairwise genetic correlations between psychiatric disorders.

Results

Accounting for a biobehavioural trait significantly altered genetic correlations between 54 of 168 pairs of psychiatric disorders (32%). The neuroticism dimension of 'worry' produced the largest average change and, in some cases, almost completely accounted for genetic correlation between psychiatric disorders, such as between depression and obsessive-compulsive disorder. Educational attainment accounted for the greatest number of significant changes overall, indicating a broad contribution to shared genetic risk across psychiatric disorders.

Conclusions

The transdiagnostic biobehavioural traits neuroticism and cognitive ability partially explain genetic overlap between psychiatric disorders in this study, although effects vary across traits and disorders. This heterogeneity highlights distinct biological pathways underlying psychiatric comorbidity and may inform psychiatric classification, future genetic studies, and transdiagnostic intervention strategies.

Introduction

Psychiatric disorders are heritable, genetically correlated and share biobehavioural traits, which may account for their genetic overlap.

There is widespread overlap across major psychiatric disorders, with many disorders sharing clinical characteristics, genetic risk and pathophysiology (Bourque et al., 2024). Whether this biological similarity across disorders is due to shared symptoms and features is an open and important question. Here, we addressed that question using genomic structural equation modelling (SEM) (Grotzinger et al., 2019) a statistical framework that uses GWAS summary statistics to study the genetic relationships between multiple traits or disorders, to examine whether genetic overlap between psychiatric disorders is due to genetic variants influencing a common biobehavioural trait.

Large GWAS of major psychiatric disorders indicate that most have substantial SNP-based heritability (range 0.02–0.27; (Grove et al., 2019; Howard et al., 2019; International Obsessive Compulsive Disorder Foundation Genetics & Studies, 2018; Mullins et al., 2021; Nievergelt et al., 2019; Trubetskoy et al., 2022; Watson et al., 2019) and that there is high genetic correlation between disorders (Anttila et al., 2018; O'Donovan & Owen, 2016), which may underlie their overlapping clinical characteristics. Many biobehavioural traits, 'sub-phenotypes' which are common across disorders, are heritable and genetically correlated with at least two different psychiatric disorders. Examples include impulsivity (Sanchez-Roige et al., 2019), risk tolerance (Karlsson Linner et al., 2019), loneliness (Sanchez-Roige & Palmer, 2020), cognitive functions (Davies et al., 2016), neuroticism (Nagel, Jansen, et al., 2018) and socio-economic status (Marees et al., 2021).

Previous work used Genomic SEM to model the latent factors underlying the shared genetic architecture of 11 major psychiatric disorders and proposed a four-factor model encompassing neurodevelopmental, compulsive, psychotic, and internalizing domains (Grotzinger et al., 2022). The extent to which these four factors explained the genetic correlations between the individual psychiatric disorders and 49 different biobehavioural traits was variable and the authors suggested that the broadness of the four factor model may obscure patterns of genetic correlations with external biobehavioral traits. Another study of socio-economic status (SES) found that genetic correlates of SES significantly changed the genetic correlations between psychiatric disorders and substance use phenotypes, but not between any pairs of psychiatric disorders (Marees et al., 2021).

We hypothesised that biobehavioural traits which may be closer to the underlying biology of the psychiatric disorders would account for some of the genetic correlation between them. We chose two well established biobehavioral traits which demonstrated genetic correlations with the broadest range of psychiatric disorders (Anttila et al., 2018)- (i) the personality trait neuroticism and (ii) cognitive ability.

Neuroticism is a heritable personality trait associated with increased risk of psychiatric disorders.

Neuroticism is a well-established personality trait characterized by a tendency toward negative emotions such as anger, anxiety, irritability, and depression (Goldberg, 1993; Leary, 2009). It is associated with psychiatric disorders such as depression (DEP) and schizophrenia (SCZ) (Kendler & Myers, 2010; Van Os & Jones, 2001). Neuroticism has a SNP-based heritability of ~ 30% (Hill et al., 2018; Lo et al., 2017; Luciano et al., 2018) and significant genetic correlation with multiple psychiatric disorders, particularly DEP, SCZ, attention deficit hyperactivity disorder (ADHD) and anorexia nervosa (AN) (Anttila et al., 2018;

Luciano et al., 2018). Studies estimating causal relationships using GWAS summary statistics have largely shown a positive, bidirectional causal relationship between neuroticism and psychiatric disorders – increased neuroticism increases risk of DEP, ANX and SCZ and visa versa (Gupta et al., 2024; Jones et al., 2018; Jones et al., 2020; Speed et al., 2019).

Although considered relatively stable, neuroticism can be reduced through both pharmacological treatments such as selective serotonin reuptake inhibitors (SSRIs) (Jylha et al., 2012; Quilty et al., 2008; Tang et al., 2009) and non-pharmacological treatments such as cognitive behavioural therapy (CBT) (Roberts et al., 2017). Given that higher neuroticism occurs across diagnostic categories, the unified protocol (UP), a transdiagnostic cognitive behavioural therapy (CBT) explicitly developed to target neuroticism was developed (Ellard et al., 2010), which may outperform disorder-specific CBT protocols in lowering neuroticism levels (Sauer-Zavala et al., 2021).

Cognitive impairments are diverse, heritable and a robust feature of many psychiatric disorders.

Cognitive function is central to overall health and is composed of both general (*g*) and domain-specific abilities (Carroll, 1993). Cognitive impairments are a core feature of many psychiatric disorders (Millan et al., 2012) although the pattern of cognitive impairments tends to differ between diagnoses (Green et al., 2020; Pu et al., 2018; Wenzel et al., 2024). There is, however, some evidence of a transdiagnostic, cognitive deficit subtype, particularly in affective and psychotic illness (Cotrena et al., 2017; Green et al., 2020; Wenzel et al., 2024).

Like neuroticism, cognitive functions are heritable (SNP-based heritability estimates range 20% – 70% (Davies et al., 2015; Deary et al., 2010; Haworth et al., 2010; Plomin & Deary, 2015; Tucker-Drob et al., 2013)) and significantly genetically correlated with many psychiatric disorders (Anttila et al., 2018; Carey et al., 2021; McCarthy et al., 2018). Studies estimating causal relationships using GWAS summary statistics have shown a negative, bidirectional relationship with many psychiatric disorders - increased cognitive ability reduces the risk of ADHD (Ahn et al., 2022), DEP (Hao et al., 2025), SCZ (Guo et al., 2024; Ohi et al., 2021) and autism spectrum disorder (ASD) (Hope et al., 2023) and visa versa.

Despite their impact on quality of life and persistence even during remission, cognitive deficits remain poorly treated. Pharmacological treatments have had limited success (Millan et al., 2012). ‘Cognitive remediation’, an umbrella term for behavioural training interventions, shows promise but the diversity of approaches has limited definitive conclusions about best practices (Keshavan et al., 2014; Trapp et al., 2022).

Do the biobehavioural traits cognitive ability and neuroticism account for the genetic correlation between nine major psychiatric disorders?

We examined nine psychiatric disorders for which summary statistics from large GWAS were available at the time of analysis – AN, anxiety (ANX), ADHD, ASD, bipolar disorder (BIP), DEP, obsessive compulsive disorder (OCD), post-traumatic stress disorder (PTSD) and SCZ. We tested whether partialling out the

genetic variance attributable to the biobehavioural trait significantly changed the genetic correlation between each pair of psychiatric disorders. The amount of genetic correlation accounted for by the biobehavioural trait could theoretically range between all of it (if two psychiatric disorders share a set of variants all of which also influence the shared biobehavioural trait) and none of it (the two psychiatric disorders each share separate sets of genetic variants with the biobehavioural trait and with each other) (Fig. 1).

Methods

Biobehavioural trait measures:

We used the results of the largest GWAS which had been conducted on cognition and neuroticism at the time of analysis, which analysed the following specific measures of these traits:

Neuroticism: 'depressed affect' (NeuDA) and 'worry' (NeuW) measures.

Neuroticism is a heterogenous trait which is often measured using the 12-item Eysenck Personality Questionnaire-Revised Short Form (Eysenck et al., 1985). Hierarchical clustering of these 12 items has shown that they can be divided into two genetically homogenous clusters, 'depressed affect' and 'worry', each comprising different questionnaire items and each significantly genetically correlated with multiple psychiatric disorders (Nagel, Watanabe, et al., 2018).

Neuroticism 'depressed affect' cluster (NeuDA): scores were obtained by summing the scores on the four items: 'Do you often feel lonely?', 'Do you ever feel 'just miserable' for no reason?', 'Does your mood often go up and down?', and 'Do you often feel 'fed-up'?'

Neuroticism 'worry' cluster (NeuW): scores were obtained by summing the scores on the four items: 'Are you a worrier?', 'Do you suffer from nerves?', 'Would you call yourself a nervous person?', and 'Would you call yourself tense or highly strung?'.

Cognition: verbal-numerical reasoning (CogVNR), reaction time (CogRT), memory (CogM) and educational attainment (CogEA) measures.

All three measures of cognition, plus educational attainment, from the GWAS (UK Biobank) data were used. These measures are described in detail in the original publication (Davies et al., 2016).

Verbal–numerical reasoning (CogVNR): measured using a 13-item test presented on a touchscreen computer.

Reaction time (CogRT): measured using a computerized 'Snap' game.

Memory (CogM): measured using a 'pairs matching' task on a touchscreen computer.

Educational attainment (CogEA): used as a proxy for general cognitive ability, acknowledging that educational attainment is also influenced by factors beyond cognitive ability. A binary education variable indicating whether each participant had attained a college or university-level degree.

Details of GWAS summary statistics and power calculations:

For all nine psychiatric disorders and six biobehavioural traits, the largest GWAS with publicly available summary statistics at the time of analysis was used.

Power calculations for the GWAS studies used in these analyses were performed using the R package 'genpwr' (version 1.0.4) (Moore et al., 2020)). Power was calculated for $\alpha:0.05$, true model:additive, test model:additive, minor allele frequency (MAF):0.05, odds ratio (OR):1.05 (or equivalent for quantitative traits) for all psychiatric disorders and biobehavioural traits.

Details about the study sample size, power, SNP-based heritability, references and download sources for each phenotype are shown in Table 1.

LD Score regression used to generate a genetic covariance matrix and sampling covariance matrix:

Multivariable Linkage Disequilibrium (LD) Score regression (Bulik-Sullivan et al., 2015) implemented in Genomic SEM R package v0.0.3 (Nivard, 2021) was used to generate a genetic covariance matrix from the GWAS summary statistics, containing the genetic variance and covariance of the phenotypes (all psychiatric disorders and biobehavioural traits). To estimate the uncertainty in the genetic covariance matrix, LD Score regression also constructs a corresponding sampling covariance matrix, containing standard errors of genetic variances (how noisy each estimate is) and covariances (how errors are related), calculated from jackknife (leave-one-out) resampling. The error covariances capture sample overlap between contributing GWAS (sample overlap leads to correlation in estimation errors). The sampling covariance matrix is used by Genomic SEM to weight the genetic covariances by their precision, making Genomic SEM robust to sample overlap. The premise of LD Score regression is that if SNPs with higher LD tend to have larger GWAS test statistics, that is considered evidence of a real polygenic signal (higher heritability) (Bulik-Sullivan et al., 2015). The method is robust to confounding factors like population stratification because they do not typically correlate with LD scores, while polygenic inheritance does.

Mismatches between the sample used to compute the LD Scores and the GWAS sample can bias the output of LD Score regression. As the GWAS samples were predominantly of European ancestry, LD scores pre-computed from 1000 Genomes European reference data (eur_w_ld_chr) were used (for details, see <https://github.com/bulik/ldsc/wiki/Heritability-and-Genetic-Correlation>). The heritabilities (standardised genetic variance) and genetic correlations (standardised genetic covariance) between all psychiatric disorders and biobehavioural traits were calculated by LD Score regression. For dichotomous outcomes, disease prevalence from the literature (listed in Table 1) was used to convert heritabilities to the liability scale.

Genetic multivariable regression in Genomic SEM:

We specified the structural equation model shown in Figure 2 to investigate if a biobehavioural trait accounted for the genetic correlation between two psychiatric disorders using genomic SEM as implemented in the R package v0.0.3 (Nivard, 2021). We only included in this analysis psychiatric disorders and biobehavioural traits which met the following criteria: (i) both psychiatric disorders and the biobehavioural trait had significant heritability ($p < 0.05$) and (ii) there was significant genetic correlation between the two psychiatric disorders ($p < 0.05$). Genomic SEM estimated the parameters (Partial r_g , se) by minimizing the discrepancy between the model-implied genetic covariance matrix and the empirical covariance matrix obtained using multivariable LD Score regression.

Significance of change in genetic correlations:

For all 'trios' (comprising two psychiatric disorders and one biobehavioural trait) which met the heritability and genetic correlation criteria, we tested whether partialling out the genetic variance led to a significant change in genetic correlation between the psychiatric disorders. To assess significance while accounting for the covariance between estimates, we used the Monte Carlo random sampling technique to calculate empirically-derived p values, as published in detail previously (Marees et al., 2021).

Briefly, we used the R function `mvrnorm` (MASS package) to estimate 1000 random covariance matrices (simulated datasets), which followed the error covariance structure of our actual dataset, and used the simulated datasets to recalculate genetic correlations with and without the biobehavioural traits. We counted the number of times the change in genetic correlation in the 1000 simulated datasets was in the opposite direction to that in the actual data and the p-value was this number divided by the 1000 simulations, multiplied by two (for two-sided testing). The process was repeated for each set of trios separately. For example, accounting for NeuDA *reduced* the genetic correlation between AN and ASD in our actual data. In 2/1000 of the simulated datasets, accounting for NeuDA *increased* the genetic correlation between AN and ASD. Therefore the Monte Carlo p value for the observed change in genetic correlation between AN and ASD after accounting for NeuDA was calculated as $2/1000 \times 2 = 0.004$. We then performed FDR correction of these empirically-derived Monte Carlo p values to account for multiple testing across different trios.

Results

Genetic correlations between the psychiatric disorders and the biobehavioural traits were substantial and widespread.

Heritabilities calculated from the GWAS summary statistics were significant for all nine psychiatric disorders and six biobehavioural traits ($p < 0.05$). Heritability estimates ranged from 0.024 for PTSD to 0.273 for OCD (Table 1). Some of the heritabilities and genetic correlations are novel and others have been reported previously (Figure 2 and Supplementary Table 1). Of the 36 unique pairings between the nine psychiatric disorders, 28 were significantly genetically correlated ($p < 0.05$). For these 28 pairs, mean

(absolute) genetic correlation was 0.34 (sd 0.16). Only one pair, OCD/ADHD, had negative genetic correlation. All nine psychiatric disorders had significant genetic correlations with at least five other psychiatric disorders except for ANX which had significant genetic correlations with just three; ADHD, DEP and PTSD. Each of the biobehavioural traits was significantly genetically correlated with at least two of the psychiatric disorders ($p < 0.05$; Figure 2). The largest positive and negative genetic correlations were between SCZ/CogM (0.30), and ADHD/CogEA (-0.52).

Overall, accounting for the genetic variance due to the biobehavioural trait significantly changed the genetic correlation between pairs of psychiatric disorders 32% of the time.

We assessed whether including any of the biobehavioural traits led to a significant change in genetic correlation between the 28 pairs of psychiatric disorders, resulting in 168 unique trios (28 pairs of psychiatric disorders x six biobehavioural traits). For 54 of these 168 trios (32%), accounting for the biobehavioural trait significantly changed the genetic correlation (FDR-corrected Monte Carlo $p < 0.05$; Figure 4, Figure 5 and Supplementary Table 1). All biobehavioural traits except for CogRT changed the genetic correlation between at least one pair of psychiatric disorders; CogM changed the least ($n=3$) and CogEA the most ($n=17$) (Figure 4).

For most (32) trait pairs, genetic correlation decreased after accounting for the biobehavioural trait. The biobehavioural trait which caused the largest mean absolute change in genetic correlation was NeuW (average $r_g = 0.15$ (se 0.02) over 15 pairs; Figure 4). For the remaining 22 pairs, genetic correlation between them was increased after accounting for the biobehavioural trait (only CogEA and CogVNR increased genetic correlation). In all cases, the trait had genetic correlation with the psychiatric disorders with discordant directions of effect (Figure 3-5, and Supplementary Table 1).

The amount of genetic correlation between psychiatric disorders which was accounted for by the biobehavioural trait varied by both trait and disorder pair.

Although many changes were significant, most only accounted for a fraction of the overall genetic correlation between disorder pairs. However we show that in some cases, biobehavioural traits shared between psychiatric disorders accounted for much of the observed genetic correlation between the disorders, consistent with the first scenario represented in Figure 1. NeuW, which caused the largest mean absolute change in genetic correlation, almost completely accounted for the genetic correlation between some pairs of disorders, such as DEP/AN, DEP/OCD, and PTSD/AN (Figure 5, corresponding numeric values presented in Supplementary Table 1).

Some disorder pairs were particularly robust to changes in their genetic correlation. For example,

the disorder pair SCZ and BIP had one of the highest genetic correlations between them, which was only changed by NeuW and CogM, and the magnitude of the change was small compared to other pairs of psychiatric disorders (r_g between SCZ/BIP = 0.68, r_g unique of NeuW = 0.61, r_g unique of CogM = 0.61; Figure 5 and Supplementary Table 1). CogVNR, CogRT, CogEA and NeuDA were all significantly

genetically correlated with both SCZ and BIP (Figure 3), but did not significantly change the genetic correlation between them (Supplementary Table 1).

Discussion

Evidence that biobehavioural traits underlie shared genetic risk across psychiatric disorders.

We used genomic SEM to comprehensively examine whether genetic overlap with the shared biobehavioural traits cognition and neuroticism explains the genetic correlation between pairs of psychiatric disorders. We found that overall, 32% of the 28 pairs of psychiatric disorders with significant genetic correlation between them was significantly changed by accounting for one of the six biobehavioural traits included in this study (FDR-corrected Monte Carlo $p < 0.05$). This is in contrast to a previous study of SES, which found that although SES was heritable and genetically correlated with the nine psychiatric disorders they examined (the same disorders as this study except they looked at Tourette's syndrome, where we looked at PTSD), it did not significantly change the genetic correlation between any pairs of psychiatric disorders (Marees et al., 2021). To our knowledge this study represents the first evidence that a shared biobehavioural trait accounts for pairwise shared genetic correlation between major psychiatric disorders.

Shared Biobehavioural Traits Do Not Always Explain Psychiatric Genetic Correlations.

This study revealed heterogeneous mechanisms of shared genetic liability between psychiatric disorders. Despite many cases where accounting for a shared biobehavioural trait significantly changed the genetic correlation between pairs of psychiatric disorders, in some cases, the biobehavioural trait failed to significantly change the genetic correlation between psychiatric disorders despite having substantial genetic correlation with each of them, more consistent with the final scenario represented in Fig. 1. For example, both CogRT and CogEA had significant positive genetic correlations with SCZ and BIP, but did not significantly account for any of the genetic correlation between them (Supplementary Table 1). One explanation for this finding is that different biological pathways may be involved in explaining the genetic correlation between each disorder and the shared biobehavioural trait (Fig. 1 final scenario).

However, previous work elucidating the relationship between SCZ, BIP and EA did show evidence for genetic overlap, whereby the observed genetic correlation between SCZ and higher EA can be fully explained by SCZ's genetic correlation with BIP, and SZ-specific genetic liability is actually correlated with lower EA (Bansal et al., 2018; Grotzinger et al., 2019; Hindley et al., 2022; Richards et al., 2025; Smeland et al., 2020; Watson et al., 2026; Wu et al., 2024). One possibility is that the proportion of the (substantial) genetic correlation between SCZ and BIP responsible for this shared relationship with EA is small - not sufficient in this study to significantly change the genetic correlation (r_g before/after accounting for CogEA was 0.678/0.672, $p = 0.77$; Supplementary Table 1). Only NeuW and CogM significantly reduced the genetic correlation between SCZ and BIP in this study and the reduction was small, meaning that the question of what traits (if any) do intersect with the strong genetic correlation between SCZ and BIP is outstanding.

Even biobehavioural traits which account for a small proportion of the genetic correlation may be useful in guiding treatment approaches, however. For example, there is consistent evidence that cognitive remediation is effective in improving global cognition and functioning in SCZ (Vita et al., 2021), but does not affect functional outcomes in BIP (Samamé et al., 2023), in keeping with the consistent observation that SCZ is negatively genetically correlated with EA when BIP is accounted for. Similarly, for CogRT there is evidence that reaction time is improved with antipsychotic medication in SCZ (Plesnicar et al., 2003), but may not be beneficial in treating BIP.

Some findings are hypothesis-generating, and may help direct future research directions.

One interesting finding in this study is that CogEA reduced the negative genetic correlation between OCD and ADHD to close to zero. CogEA has a positive genetic correlation with OCD ($r_g=0.273$), and a larger negative genetic correlation with ADHD ($r_g=-0.523$) (Supplementary Table 1). The fact that CogEA accounts for the negative genetic correlation between OCD and ADHD could be explained by a situation where the same CogEA genetic variants are positively correlated with OCD, and negatively correlated with ADHD. Previous work has shown that the negative genetic correlation between ADHD and EA is independent of cognitive ability (Dardani et al., 2021), which also seemed to be the case in this study where ADHD was not genetically correlated with most cognitive traits (only CogVNR - not CogM or CogRT; Fig. 3). In this study, OCD was not significantly correlated with any cognitive measures other than CogEA, suggesting that the positive genetic correlation between OCD and EA may be similarly independent of cognitive ability. Taken together, this suggests that for both OCD and ADHD, their shared aetiology with EA may be due to non-cognitive features associated with EA. Further studies will be needed to formally explore the mechanisms underlying this relationship between OCD, ADHD and CogEA, which may have implications for what types of cognitive remediation, if any, are likely to be beneficial in these disorders.

Implications for genetic discovery, psychiatric nosology, and treatment approaches.

The results of studies such as these could be used to facilitate more informative and powerful genetic analyses - genetically correlated traits can be jointly analysed to increase power and identify shared genetic factors ('clumping'), or the genetic contribution of one trait can be 'partialled out' to identify genetic influences specific to a particular disorder ('splitting') (Sanchez-Roige & Palmer, 2020). Joint analyses of genetically correlated psychiatric disorders that partial out the genetic influence of shared biobehavioural traits will more specifically reflect the genetic contributions to the disorders unique from those of the biobehavioural trait, which could provide insight into disease-specific biological mechanisms and increase their clinical utility.

This work also has implications for the classification of psychiatric disorders, and the biological basis of existing diagnostic and therapeutic approaches. High levels of psychiatric comorbidity complicate efforts to differentiate among psychiatric disorders. We show that the genetic comorbidity between psychiatric disorders and their relationship to biobehavioural traits is complex – in some cases, the

biobehavioural trait likely shared the same biological underpinnings across psychiatric disorders, in other cases, these causal pathways are likely distinct. This type of information may lead to further subtyping of psychiatric disorders based on their underlying genetic architecture, facilitating more personalised treatment approaches.

Finally, multi-trait methods can show where aetiology is shared between psychiatric disorders and biobehavioural traits. Identifying shared aetiology can inform where existing treatments should be broadly applied across one or more psychiatric disorders, or tailored to specific diagnoses. For example, this study showed that NeuW has large, significant genetic correlation with both DEP ($r_g=0.523$) and OCD ($r_g=0.604$) and almost completely accounted for the genetic correlation between them (r_g change from 0.257 to -0.059; Supplementary Table 1), suggesting it may share biological pathway(s) with both DEP and OCD. This is in line with the finding from the most recent OCD GWAS, that the most significant SNP is also associated with both depressive symptoms and neuroticism (Strom et al., 2025). The shared aetiology we are proposing between NeuW and DEP/OCD suggests that existing CBT protocols to treat neuroticism (particularly those targeting the 'worry' subtype) should be broadly targeted to one or more psychiatric disorders, versus tailored to a specific diagnosis.

Study limitations and future directions: variable power, lack of generalizability, limited insights into genetic architecture.

There are several limitations to this study. One is that our ability to detect a significant change in genetic correlation by accounting for a biobehavioural trait is affected by the power of the original GWAS (how much of the true genetic variance has been captured). Although we used the largest available GWAS, none of the GWAS account for all of the estimated heritability. It is important therefore to consider these results in the context of the power of the GWAS from which the summary statistics were taken. Biobehavioural traits with smaller or less powerful GWAS are less well powered to cause a change in the genetic correlation between two psychiatric disorders. Similarly, if GWAS for the psychiatric disorders are underpowered, the genetic correlation between them will be underestimated and overlap with the biobehavioural may not be fully captured. In addition, the size of GWAS tends to affect se, so even when effect sizes were large, a change in genetic correlation may not meet significance.

As is the case for most genetic studies of psychiatric disorders, the summary statistics in this study are based on samples with an overrepresentation of participants from Western, Educated, Industrialized, Rich, and Democratic (WEIRD) populations. This means that our findings may not be generalizable outside of these populations. As GWAS summary statistics from other populations become available, future studies should be focused on exploring the relationships between biobehavioural traits and psychiatric disorders in other populations.

Finally, as the results are based on common variants captured by GWAS, the genetic relationships described are based on additive, common variant effects only. Rare variants and non-additive effects may contribute to these relationships but are not captured in these analyses. An additional caveat to

these results is that although genetic correlation is an informative measure of the genetic similarity between two phenotypes, it captures net direction of effect only and is likely missing pleiotropy between phenotypes which is masked by bidirectional effects. Previous work in psychiatric disorders has shown that genetic overlap *is* more extensive than that estimated by overall genetic correlation across mental disorders and related traits, with mixed effect directions and few disorder-specific variants (Hindley et al., 2022). Follow-up studies using methodologies such as LAVA (Werme et al., 2022) to investigate local and bidirectional effects and MiXeR, which can differentiate between lack of genetic correlation due to no genetic overlap vs extensive genetic overlap with discordant directions of effect (Hindley et al., 2022), may be illuminating.

Conclusion

Our findings demonstrate that the genetic correlation between psychiatric disorders is sometimes, but not always, attributable to shared genetic overlap with the biobehavioural traits we examined; two neuroticism subtypes and four cognitive traits. The heterogeneity in how biobehavioural traits account for genetic correlations across disorder pairs reflects the complex and varied biological mechanisms underlying psychiatric comorbidity. These insights have implications for treatments targeting these biobehavioural traits, suggesting that some transdiagnostic traits may benefit from shared treatment approaches, while others may require disorder-specific interventions. Future research should extend this work as larger and more diverse GWAS results become available, and incorporate methodologies to investigate local and bidirectional effects.

Consultation with people with lived experience.

Although the importance of input from people with lived experience as research partners is now widely acknowledged, it is not always done well, particularly in mental health research where inequities in lived experience inclusion and support are well established. We were fortunate to have as a member of our team a person with lived experience, who is an author on this paper and was involved across all stages of the research as a valued voice. As suggested in some recent recommendations (Carras et al., 2023), she has provided a lived experience commentary on this article, which can be found below.

Comment from a person with lived experience of a mental health disorder, Susie Hincks:

Questions: Do you see this type of research as being important, and why? Does this type of research raise any concerns for you?

Answer: All psychiatric genetics research is important to me. Scientific research gives people living with psychiatric illness hope for the future. It also means someone cares enough to devote their working life to help treat these complex and devastating illnesses. That cannot be underestimated.

This research could provide groundwork for more specifically targeted treatment - personalised treatment which should lead to more effective treatment outcomes. One of the great problems with

current medications for mental illness is the side effects. If you have schizophrenia, as I do, you may suffer from anhedonia. Many medications for schizophrenia can flatten your mood and your experience of life. So, it can be “The devil or the deep blue sea.” One size does not fit all. We need more research like this that aims to prioritise personalised medical treatment.

It may also challenge the current diagnostic methods and labels we use for psychiatric illnesses. In terms of the stifling stigma associated with psychiatric illness, this shakeup of labels could be a productive step forward, and in doing so, change some of the approaches to psychiatric treatment, and the public perception of what mental illness actually is.

This research is bold and, I believe, is exploring important and potentially productive areas in psychiatric genetic research. Let’s get research results out there, not just in scientific journals but in a translational way so society can understand the importance, relevance and urgency of this sort of scientific research.

Declarations

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Ethical standards: The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. This study was assessed as exempt from ethics review at the University of Western Australia by the Human Ethics Office (RA/4/20/5359), because it involves secondary analysis of de-identified, publicly available, aggregate GWAS summary statistics. The analysis results are low risk to individuals (investigating aggregate statistical relationships), and the study makes no attempt to re-identify individuals.

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Competing interests: All authors declare that they have no competing interests relevant to the content of this article.

Data availability statement: All datasets used in this paper are publicly available from the sources listed in Table 1 of this paper. The code used for the analyses is available here:

https://github.com/nmc24/GenomicSEM_cognition_neuroticism_psych_disorders. All results from these analyses are available in the Supplementary information.

Author Contribution

Authors NMc and GC designed the study, with input from JB and SH. NMc and GC wrote the protocol and conducted the analyses. NMc and GC drafted the manuscript, with input from JB and SH. All authors contributed to and have approved the final manuscript.

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Table

Table 1 is available in the Supplementary Files section.

Figures

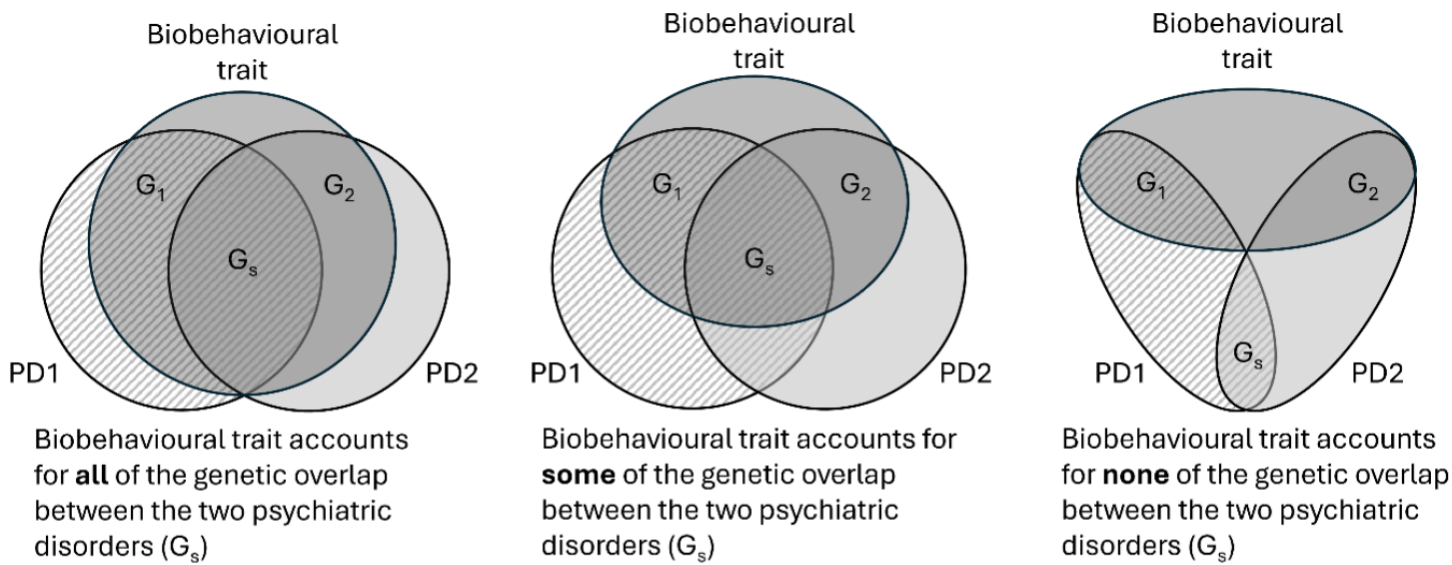


Figure 1

The genetic mechanisms which might underlie the relationships between psychiatric disorders and their shared biobehavioural traits. In each of these scenarios, two psychiatric disorders (PD1 and PD2) are genetically correlated with each other, and both are also genetically correlated with the same biobehavioural trait. The circles in the diagram depict the sets of genetic variants contributing to each phenotype.

In the first scenario, shown on the left, the two psychiatric disorders share a set of pleiotropic genetic variants (G_s), **all** of which also influence the common biobehavioural trait. Therefore, all of the genetic correlation between the psychiatric disorders is accounted for by the shared biobehavioural trait. Another possibility, shown in the centre, is that **some** of the pleiotropic genetic variants (G_s) shared between the two psychiatric disorders also influence the shared biobehavioural trait, however a proportion of the shared genetic variants (G_s) influence both psychiatric disorders but not the

biobehavioural trait. Therefore some, but not all, of the genetic correlation between the psychiatric disorders is accounted for by the shared biobehavioural trait. For both the first and second scenario, the genetic correlation between the biobehavioural trait and each psychiatric disorder may be comprised of the genetic correlation with the pleiotropic genetic variants, G_s AND the 'unique' genetic contribution to the disorder (shown in the figure as G_1 and G_2 for PD1 and PD2, respectively) as shown OR may be entirely accounted for by the shared genetic component, G_s (this possibility is not shown). In the last scenario, shown on the right, the two psychiatric disorders each share separate sets of genetic variants with the biobehavioural trait, shown in the figure as G_1 and G_2 for PD1 and PD2, respectively. The genetic correlation between the psychiatric disorders is explained by a set of genetic variants (G_s) which does not influence the shared biobehavioural trait. Therefore **none** of the genetic correlation between the psychiatric disorders is accounted for by the shared biobehavioural trait.

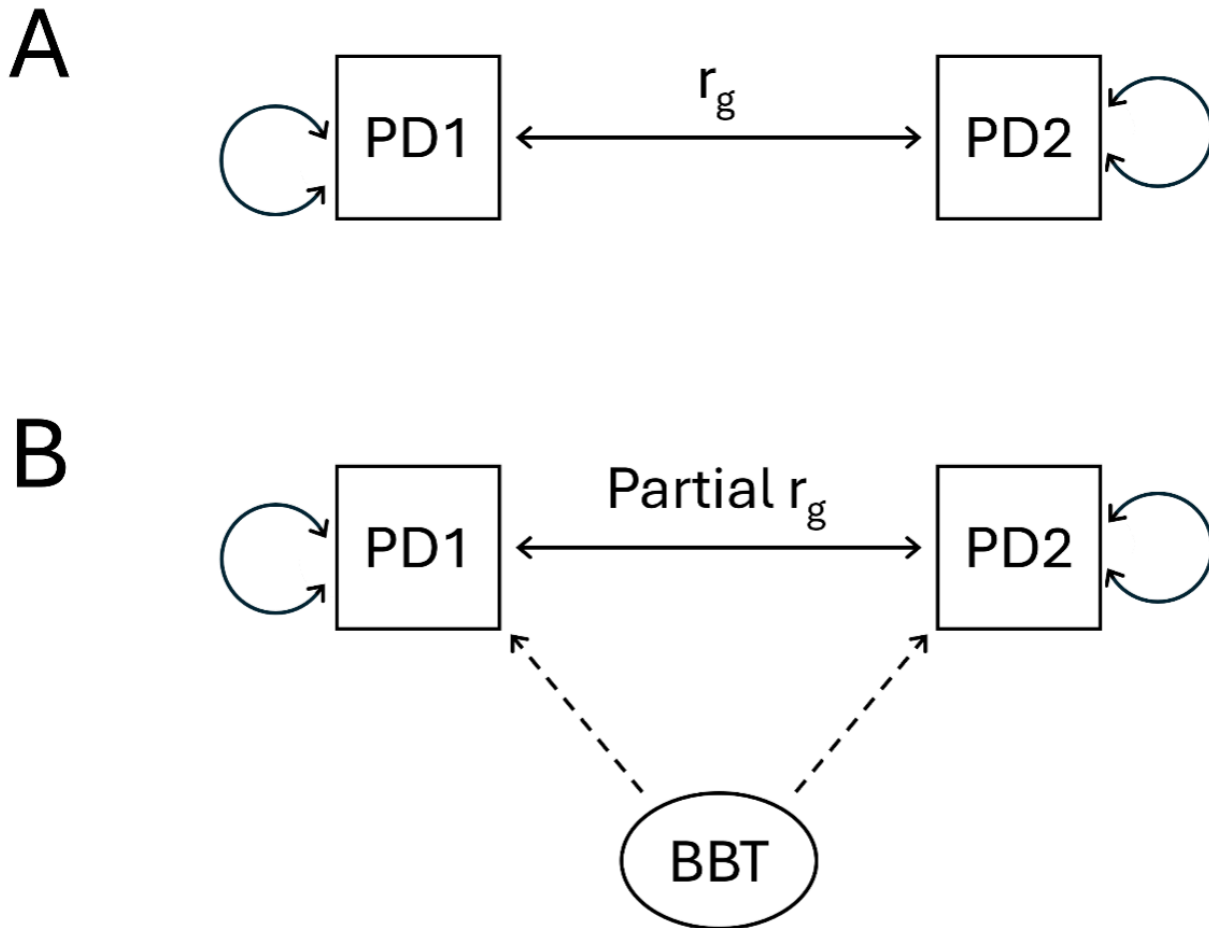


Figure 2

Path diagram.

The genomic SEM path model fitted on the genetic covariation matrices estimates the genetic correlation, r_g (solid bidirectional arrow) between two psychiatric disorders (PD1, PD2). (A) path model of

the simple bivariate genetic correlation using LD Score regression. (B) The model including the genetic variance of the biobehavioural trait (BBT) which is regressed out from the variance of PD1 and PD2 (dashed arrows) affecting the estimate for genetic correlation (Partial r_g).

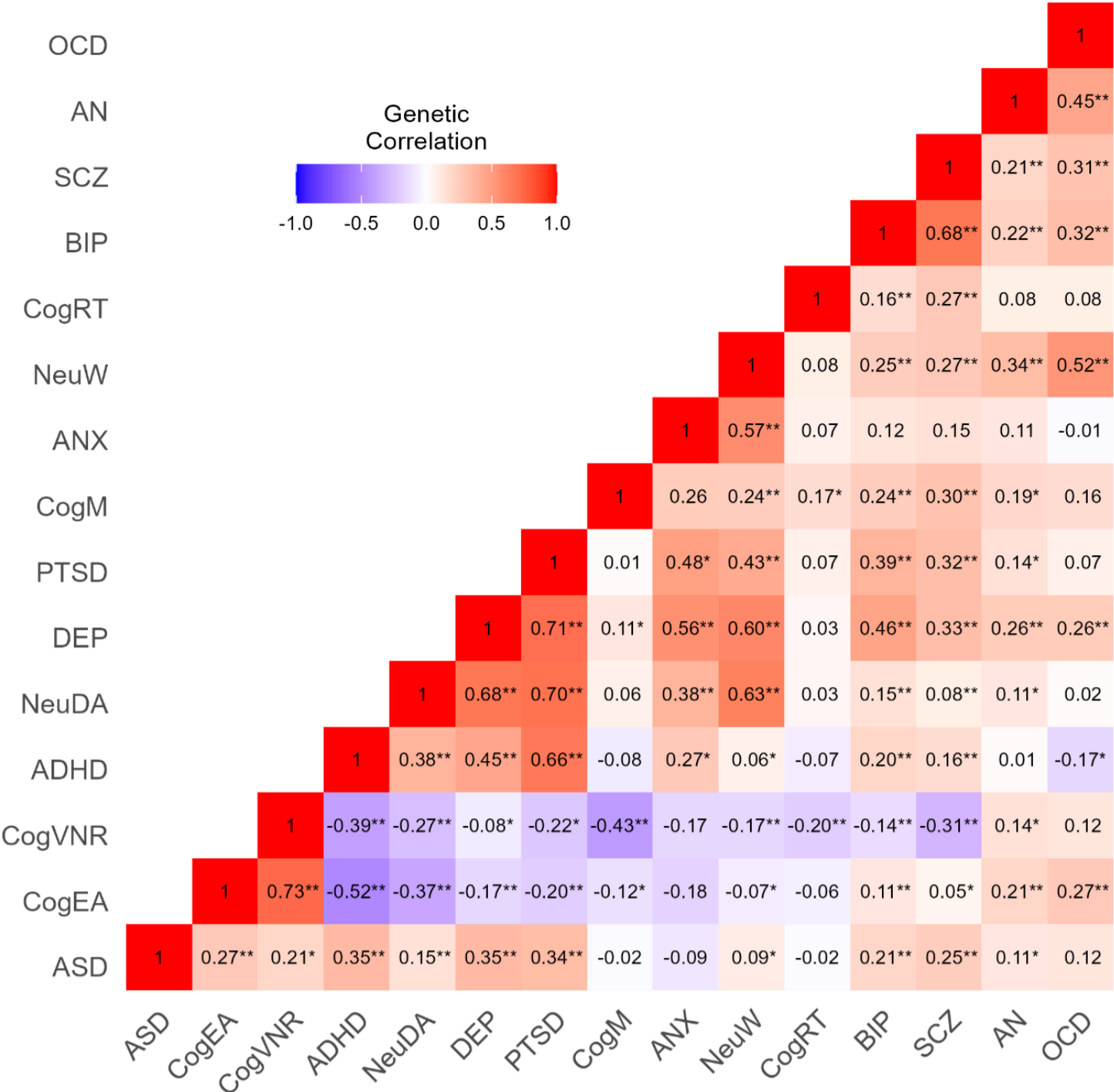


Figure 3

Heat map illustrating the genetic correlations between the nine psychiatric disorders and six biobehavioural traits included in this study, based on the GWAS summary statistics used. The values in the coloured squares are genetic correlations, with the colour corresponding to the direction of the

genetic correlation and the shade to its magnitude. Asterisks denote genetic correlations significantly different from 0: * $P < 0.05$; ** $P < 0.00047$ (Bonferroni correction threshold). Biobehavioural traits: neuroticism 'depressed affect' cluster (NeuDA), neuroticism 'worry' cluster (NeuW), cognition verbal-numerical reasoning (CogVNR), cognition reaction time (CogRT), cognition memory (CogM), cognition educational attainment (CogEA). Psychiatric disorders: anorexia (AN), anxiety (ANX), attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), bipolar disorder (BIP), depression (DEP), obsessive compulsive disorder (OCD), post-traumatic stress disorder (PTSD) and schizophrenia (SCZ).

Mean Change in r_g Between Pairs of Psychiatric Disorders
Significantly Changed by the Addition of a Biobehavioural Trait

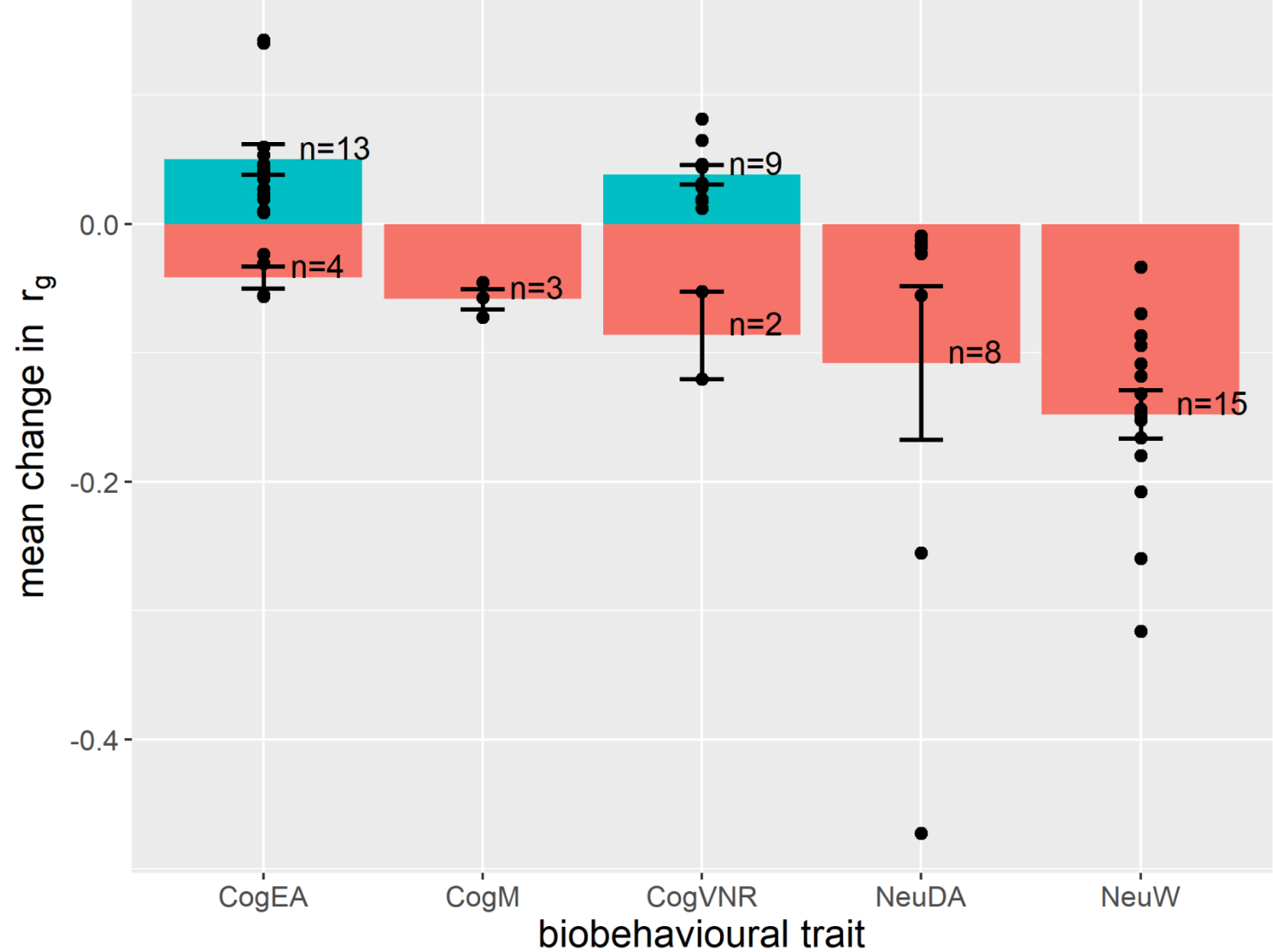


Figure 4

The mean change in genetic correlation between the 54 pairs of psychiatric disorders for which accounting for the biobehavioural trait significantly changed the genetic correlation between them. Each dot point is the change in genetic correlation (before/after accounting for the biobehavioural trait). 'n' is

the number of pairs of psychiatric disorders for which the biobehavioural trait significantly changed the genetic correlation (increased and decreased genetic correlation counted separately). Biobehavioural traits: neuroticism 'depressed affect' cluster (NeuDA), neuroticism 'worry' cluster (NeuW), cognition verbal–numerical reasoning (CogVNR), cognition reaction time (CogRT), cognition memory (CogM); cognition educational attainment (CogEA). Error bars denote standard error (se). Mean changes in genetic correlation(se) were as follows: increased CogEA 0.050(0.012), decreased CogEA -0.041(0.008), decreased CogM -0.058(0.008), increased CogVNR 0.038(0.008), decreased CogVNR -0.086(0.034), decreased NeuDA -0.108(0.060), decreased NeuW -0.148(0.019). Mean absolute changes: CogEA 0.048(0.009), CogM 0.058(0.007), CogVNR 0.047(0.010), NeuDA 0.108(0.060), NeuW 0.148(0.019).

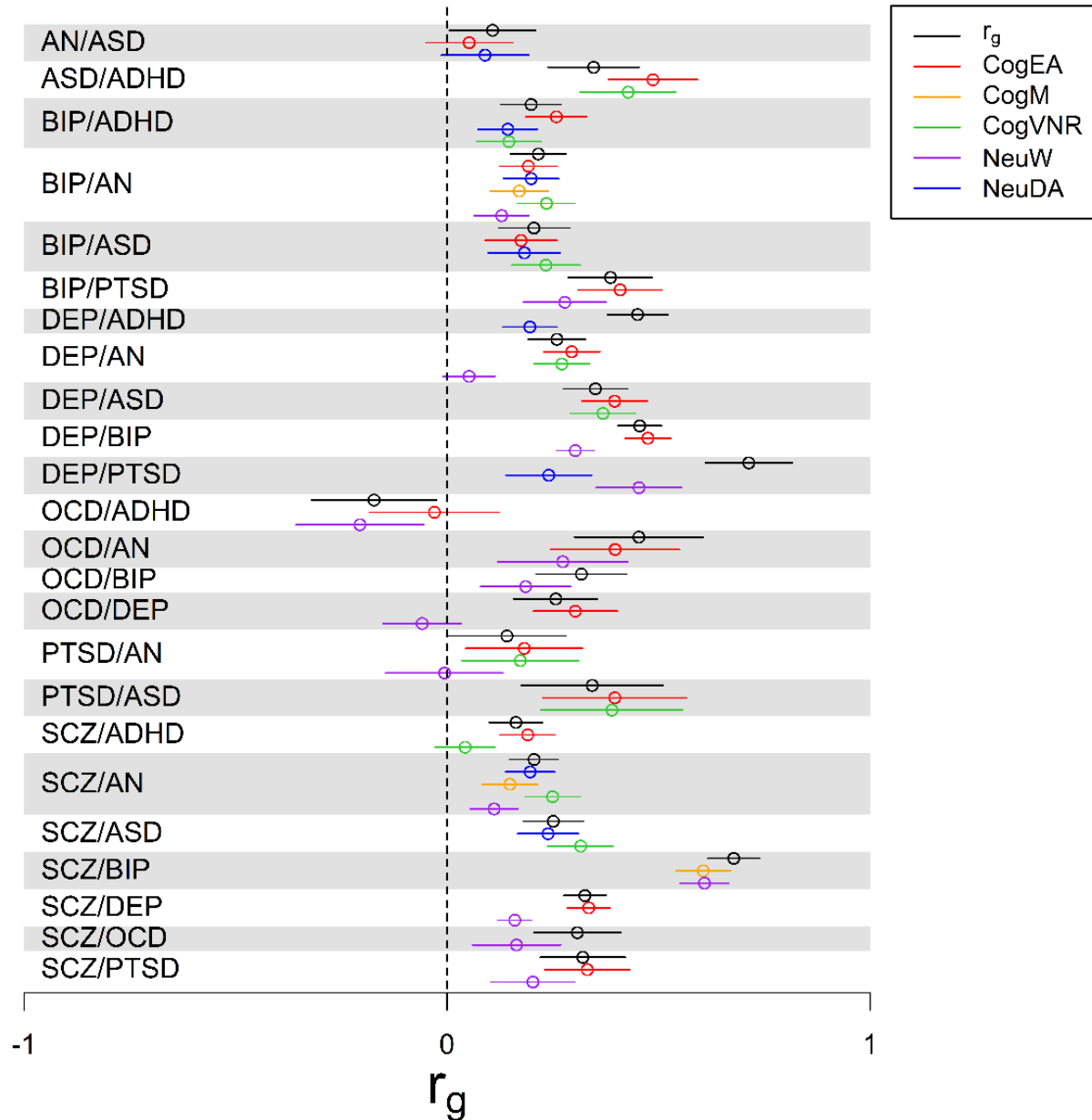


Figure 5

Genetic correlation between pairs of psychiatric disorders before and after accounting for biobehavioural traits. The genetic correlation (r_g) before (black) and after partialling out the biobehavioural trait (coloured) is shown for the 54 pairs of psychiatric disorders for which including the biobehavioural trait in the model significantly changed the genetic correlation between them. The circle indicates the genetic correlation and the horizontal line the 95% confidence intervals ($1.96 \times SE$) for each genetic correlation. Biobehavioural traits: neuroticism 'depressed affect' cluster (NeuDA), neuroticism

‘worry’ cluster (NeuW), cognition verbal–numerical reasoning (CogVNR), cognition reaction time (CogRT), cognition memory (CogM); cognition educational attainment (CogEA). Psychiatric disorders: anorexia (AN), anxiety (ANX), attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), bipolar disorder (BIP), depression (DEP), obsessive compulsive disorder (OCD), post-traumatic stress disorder (PTSD) and schizophrenia (SCZ). All values are shown in Supplementary Table 1.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryTable1CADBYBG.xlsx](#)
- [Table1.docx](#)