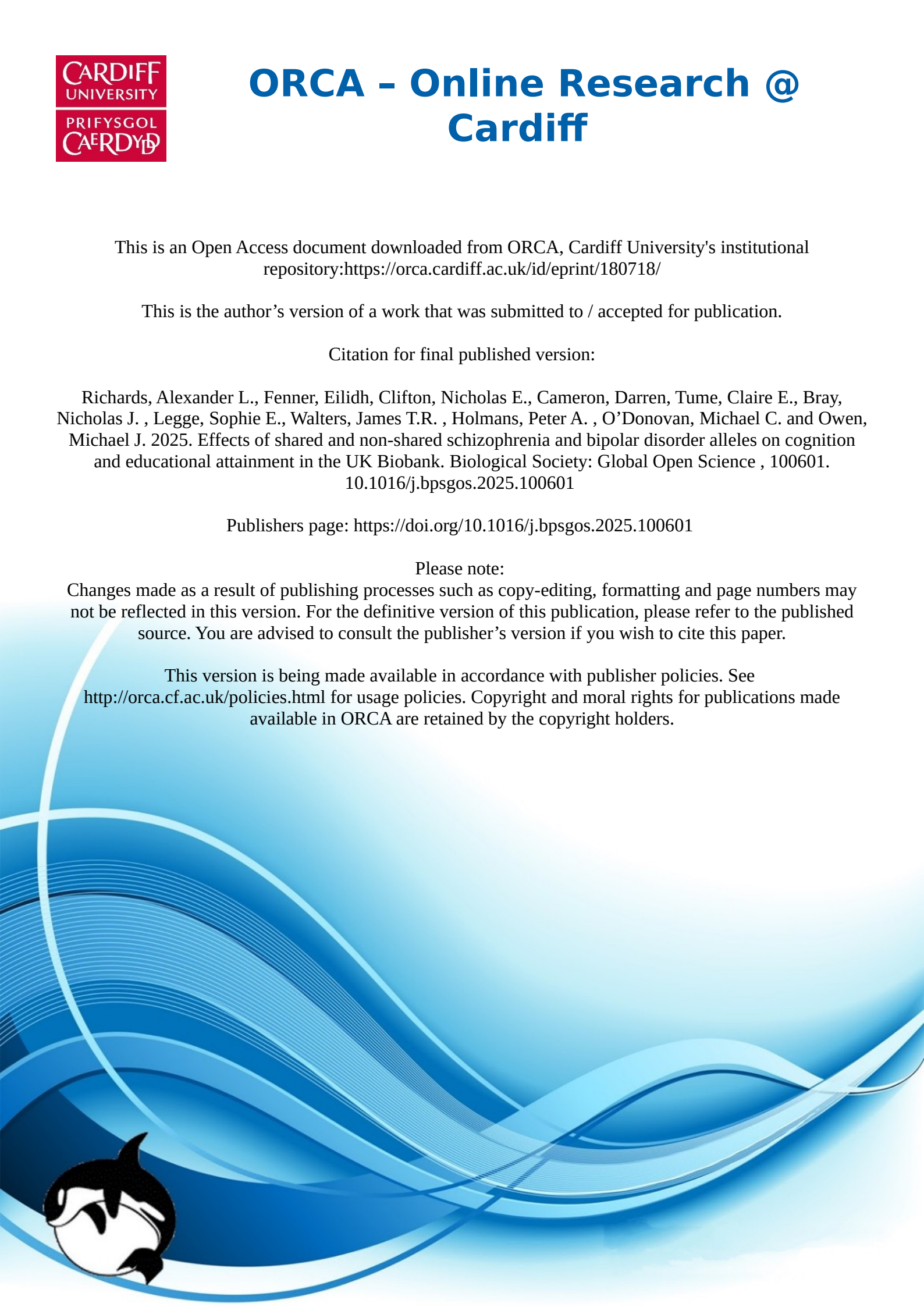

Effects of shared and non-shared schizophrenia and bipolar disorder alleles on cognition and educational attainment in the UK Biobank.

Running title: Schizophrenia and bipolar liability in UKBB

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Keywords: Genomics, schizophrenia, bipolar disorder, cognition, education, enrichment.

Abstract

Background: Cognitive impairment is typically more severe in schizophrenia (SZ) than bipolar disorder (BD). We explored the underlying genetics and biology of this difference and its relationship to educational attainment (EA) using Genomic Structural Equation Modelling (gSEM).

Methods: Shared and differentiating fractions of liability for SZ and BD were derived and tested for association with general intelligence (g, 93541 participants), fluid intelligence (FI, 160465 participants), and EA (354609 participants) in the UK Biobank. Liabilities were tested for enrichment in genes with high expression specificity (HES) for developmental stages, cell types, and functional categories.

Results: Shared liability was associated with poorer cognition but higher EA. The SZ differentiating fraction (SZ_{diff}) was associated with poorer cognition and lower EA. Adjusting for cognition, the effects of SZ_{diff} on EA were attenuated but significant. The differentiating fraction was enriched for HES genes for young adulthood (20-30 years), mid-adulthood (30-60 years), and dentate gyrus.

Conclusions: Shared liability for SZ and BD is enriched for alleles conferring risk to poorer cognitive function in the general population, but is associated with noncognitive traits that enhance EA. In contrast, SZ_{diff} is enriched for alleles that confer risk to poorer EA through both cognitive and non-cognitive mechanisms, which has implications for interventions. The enrichment of the differentiating fraction for HES genes in early and mid-adulthood and in the dentate gyrus highlights developmental stages and cell types important for further research.

Word count: 3251 words.

Introduction

Schizophrenia (SZ) and bipolar disorder (BD) are highly heritable polygenic conditions(1). Distinct entities in major diagnostic systems(2, 3), their clinical features nevertheless overlap(4) as do their genetic liabilities, with a genetic correlation (rg) of around 0.7(5). This is consistent with SZ and BD occupying different, but overlapping, positions on several dimensions of psychopathology rather than being fully independent categories of disorder(6). This hypothesis is further supported by findings that risk alleles influencing major dimensions of symptomatology (e.g. psychosis, depression, mania) are partly distinct, and influence those dimensions across diagnoses(7–10).

Cognitive impairment is typically more severe in SZ than BD(11–13), involves many aspects of cognitive function(14) including general intelligence (*g*) and is qualitatively similar(15–17). While consistent with a dimensional view, this suggests that there may be pathogenic processes manifested by cognitive impairment that are more prominent in those diagnosed with SZ. Cognitive impairment is strongly associated with functional outcomes(14) and therefore of considerable importance. Understanding its aetiology in SZ and BD may point to potential interventions that can improve outcomes(18) or even prevent illness onset should low cognitive ability be established as a causal risk factor.

It has been postulated that cognitive impairment seen in SZ reflects an underlying perturbation of neurodevelopment, that is more prominent in SZ than in BD(19, 20). This implies that alleles that preferentially increase liability to SZ over BD will be enriched for variants associated with poorer cognition and in genes whose expression characterises early brain development.

Genomic structural equation modelling (gSEM) (21) is an adaptation of SEM that allows genetic liability that is shared between two or more genetically correlated traits to be extracted from input genome-wide association study (GWAS) summary statistics of the individual traits. It then allows the fraction of liability to each individual trait that is not included in the shared component to be isolated from the input GWAS, which is the component of liability that is specific to each trait. Here, to test our predictions, we applied gSEM to GWAS of SZ and BD to isolate the fraction of common variant liability that is shared between these two disorders as well as that fraction that differentiates between them. We used genetic correlation and polygenic risk score (PRS) methods to examine the relationships between these fractions and cognition in a population sample without SZ or BD. We also sought to identify functional gene sets, cell populations and developmental time points that are enriched for the differentiating fraction of liability.

Finally, we examined the relationships between genetic liability to SZ and BD, cognitive ability and educational attainment (EA). Our motivation here was two-fold. First, EA is often used as a proxy measure of cognitive ability in genomic studies. Second, some(22–25) though not all(26–28) studies have reported the surprising finding that genetic liability to SZ shows a small positive association with genetic liability for educational outcomes despite the robust evidence for both lower cognitive ability and poorer educational outcomes in SZ(29).

Methods and Materials

See Supplementary Methods for additional information.

Genomic SEM

GWAS summary statistics were from studies of SZ and BD conducted by the Psychiatric Genomics Consortium (PGC)(30, 31) (Table S1; all input samples of European ancestry). Single nucleotide polymorphisms (SNPs) present in both studies (minor allele frequency > 1% in HapMap 3(32), imputation score > 0.7, MHC region excluded) were retained (N=7,334,582). We ran gSEM in R (The R Foundation, version 4.0.3) using the GenomicSEM package(21) to apply a common factor model to the GWAS summary statistics. For each SNP, the loading on the common factor was extracted to produce a statistic corresponding to the effect shared between disorders. We then applied a model extracting the loading of each SNP on the residual variance from each input GWAS that was not explained by the common factor so that the residual effect sizes for each SNP indexes its influence on the probability of having one phenotype over the other (see lavaan models in Supplementary Methods).

For the SZ differentiating fraction (SZ_{diff}), alleles with effects signed above zero increase the probability of SZ over BD, while those below zero indicate the converse. For the bipolar differentiating fraction (BD_{diff}), alleles with effects signed above zero increase the probability of BD over SZ, while those below zero indicate the reverse. As there are only two phenotypes in the model, SZ_{diff} and BD_{diff} are perfectly negatively correlated. We use the terms SZ_{diff} and BD_{diff} when we are presenting results where a direction of effect is meaningful, for example testing against *g* or EA so that it can be understood whether the alleles that favour development of one of the disorders are associated with higher or lower *g* or EA. For gene set enrichment, direction of effect does not affect the results, and therefore we use the term 'differentiating' (abbreviated to Diff) to refer to the results for the differentiating factors.

SNP-based heritabilities (SNPh2) and genetic correlations were calculated using linkage disequilibrium score regression (LDSC)(33, 34).

Cognitive and Education datasets.

We tested for genetic correlations between the input GWAS and gSEM fractions and summary statistics(35, 36) for *g* and educational attainment (EA). We also used a PRS approach(37) to test for association between gSEM fractions of liability and measures of cognition and EA in the UK Biobank, a UK prospective volunteer study of around 500,000 participants aged 40-69 at the time of recruitment (www.ukbiobank.ac.uk). The North-West Multi-Centre Ethics Committee granted ethical approval to UK Biobank, and all participants provided written informed consent. This study was conducted under UK Biobank project number *13310.*

Genotyping and Phenotyping in UK Biobank

See Supplementary Methods for full variant and individual exclusion criteria.

Individuals with a diagnosis of BD, SZ, or a psychotic disorder were excluded(38). *g* was derived as a measure of general intelligence from the standardised first principal component of four cognitive measures (numeric memory, reaction time, pairs matching, and trail making test B; Table S2). We used the measures of FI and highest EA provided in the Biobank data. The EA variable was transformed into an ordinal measure(26).

Polygenic Risk Score (PRS) Analyses

PRS were derived as described(37) on clumped SNPs without thresholding on p-values. We tested standardised PRS for association with *g* (93541 participants, Table S3) and FI (160465 participants)

using linear regression. PRS were also tested for association with EA using ordinal regression (354609 participants).

Developmental Stage Enrichment Analyses

Transcriptomic data from the human dorsolateral prefrontal cortex and hippocampus, aged between 12 post-conception weeks and 84 years, were obtained from BrainSeq Phase II(39). Samples were divided into 10 developmental stages and, for each gene, a t-statistic calculated as a measure of expression specificity in one stage relative to all other ages (Table S4)(40, 41). The top 10% genes, ranked by their specificity t-statistics, were selected to define high expression specificity (HES) gene sets for each stage, which were then tested for enrichment of SNP heritability in the gSEM fractions (as well as source GWAS data for comparison) using stratified LD score regression v1.2(33, 42). The one-sided coefficient z-score p-value, accounting for 53 baseline genomic annotations, was used to indicate significance.

Cellular Enrichment Analyses

Cellular gene expression specificity scores were obtained for cell populations from human fetal brain(43), human prefrontal cortex spanning gestation to adulthood(44, 45), adult human frontal cortex and hippocampus(46), entire adult human brain(47, 48) and mouse brain(49) (Table S5). Specificity scores were calculated in the cited studies by dividing each gene's expression in a given cell type by the sum of that gene's expression across all cell types. As above, the top 10% of HES genes for each cell type were tested for heritability enrichment using stratified LD score regression v1.2(31, 48).

Gene Ontology Enrichment Analyses

We tested for enrichment of gSEM and GWAS associations in Gene Ontology (GO) term gene sets using MAGMA (v1.10)(50). GO terms were downloaded from the Gene Ontology Consortium(51, 52). One-sided competitive p-values for each GO term were extracted as the primary test statistics.

Results

Heritabilities and Genetic Correlations

Estimated SNP heritabilities and genetic correlations (rg) are given in Table 1 and Figure 1. As expected from the known strong genetic correlation between SZ and BD, most heritability from gSEM derived components was assigned to the shared fraction.

SZ liability was negatively correlated with that for *g*, as was, less strongly, BD liability. Despite the negative correlations with cognition, SZ liability was not associated with EA liability while BD liability was associated with that for higher EA. Similar estimates have been reported using a different methodology(27).

Shared liability also showed discordant effects, being negatively correlated with that for *g* but positively correlated with higher EA liability (0.07). In contrast, the SZ_{diff} fraction showed congruent

effects, being negatively associated with liabilities to higher cognition and higher EA. It follows the BD_{diff} fraction is correlated with liabilities to better cognition and higher EA.

Polygenic Risk Score Analyses

The results of PRS analyses are given in Figure 2a and b, and in Tables S6 and S7.

The SZ, BD, and shared PRS were negatively associated with *g* (SZ beta -0.075, p=4.16e-51; BD beta -0.035, p=9.05e-17; shared beta -0.079, p=7.51e-51). The SZ_{diff} fraction was weakly associated with lower *g* (SZ_{diff} beta -0.009, p=3.74e-3), and reciprocally BD_{diff} with higher *g*. The pattern of associations with FI was similar to those for *g*, but with a stronger effect for the differentiating fraction (Figure 2a, Table S6).

SZ PRS was associated with lower EA (beta -0.013, p=2.46e-5) while the BD PRS was associated with higher EA (beta 0.043, p=9.07e-44). Consistent with genetic correlation analysis, the shared PRS was associated with higher EA (beta 0.016, p=5.08e-7) while the SZ_{diff} fraction was associated with lower EA (beta -0.049, p=1.84e-58). Reciprocally, the BD_{diff} PRS was associated with higher EA.

***Cognitive and non-cognitive effects on Education*.**

Associations of shared liability with low cognition but higher EA suggest that it is enriched for alleles that promote EA through non-cognitive mechanisms. In contrast, the concordant effects of SZ_{diff} on cognition and EA suggest that these alleles affect EA through effects on cognition. However, the effects of SZ_{diff} PRS on EA covarying for cognition (primary test FI as we have more data and power than for *g*) while attenuated remained significantly associated with poorer educational attainment (unadjusted beta on subset of UKBB with FI data: -0.042, se=0.005, p=2de.55e-17; adjusted for FI: beta -0.025, se=0.005, p=1.28e-6) indicating that SZ_{diff} is enriched for alleles that have negative non-cognitive as well as cognitive effects on EA.

Enrichment analyses

High expression specificity genes (HES genes) for young (age 20-30 years) and mid (age 30-60 ranges) adulthood were significantly enriched for heritability that differentiates SZ from BD (Figure 3, Table S8). In these two age groups the HES genes only modestly overlap each other as do the genes with evidence for association with the differentiating fraction, indicating that the enrichments at these stages are largely independent (Figure S1). BD showed stronger evidence for enrichment than SZ for heritability in these gene sets. SZ showed stronger evidence than BD for heritability enrichment in HES genes for early infancy, but this was not accompanied by enrichments in either gSEM fraction.

Details of the cellular heritability enrichments are provided in Figures S2-S6 and Tables S9-S13. Differentiating liability was not significantly enriched in HES genes for cell populations from human second trimester fetal brain(43), prefrontal cortex from gestation to adulthood(44, 45), or from adult human prefrontal cortex and hippocampus(46). We did find significant enrichment of the differentiating fraction in HES genes for granule cells of the dentate gyrus in a more comprehensive dataset from adult human brain(47, 48) (Figure S6, Table S13). This set also showed significant evidence for enrichment in BD and nominally significant evidence in SZ and the shared liability fraction. In cell types from mouse brain(49) (Figure S3, Table S10), heritability in the differentiating

fraction was enriched for HES genes for pyramidal neurons from somatosensory cortex and the CA1 region of hippocampus, and for medium spiny neurons (MSN) of the striatum, but these findings were not recapitulated in the tested datasets from human brain (Figures S2, S6). Moreover, these sets were also enriched for shared liability as well as liability to both source disorders.

GO enrichment analyses (Table S15) of differentiating liability identified no significant findings while that of shared liability highlighted similar biological processes and molecular functions as the GWAS of SZ and of BD, albeit more categories were significant (N=58 in shared, N= 38 in SZ, N= 11 in BD).

Discussion

Our findings are consistent with our primary hypothesis that alleles that preferentially increase liability to SZ over BD are associated with lower cognitive performance in the general population, whereas genetic liability that increases liability to BD over SZ is associated with higher performance. We also show the fraction shared between the two disorders is associated with poorer cognition, consistent with observations that both disorders are associated with cognitive impairment. The opposing effects of the differentiating fractions provide a partial explanation for the greater cognitive impairments in SZ compared to BD(30, 53), but their relatively modest effects are also in line with evidence that non-familial factors, such as environmental exposures and de novo mutations, rather than familial ones (including inherited genetic variation) are the main cause of cognitive impairments in SZ(29). Together with evidence that non-familial factors play a greater role in SZ than BD(54), our findings support the hypothesis that these are more important than common genetic variation in the greater cognitive impairment seen in SZ than BD.

As far as we are aware, ours is the first study to compare the relationships between shared and specific fractions of genetic liability to SZ and BD with direct measures of cognitive function. Our results are, however, consistent with those from studies using different methods to compare genetic liability to SZ with that for BD. These include a study(55) that reported most alleles shared between SZ and *g* were associated with poorer cognition whereas most BD alleles shared with *g* were associated with better cognition. Another study(27) using a bivariate causal mixture model showed high overlap between variant sites that influence *g* and those that confer liability to BD and SZ but, like us, found low to moderate genetic correlations. Extensive overlapping sites but modest genetic correlations implies that risk alleles to the psychiatric disorders include a mixture of alleles associated with higher and lower intelligence. Further analyses using LAVA(56) also showed prominent mixed directions of effect between BD, schizophrenia, and cognitive traits.

Our secondary aim was to examine the relationships between fractions of liabilities to SZ and BD and liability to EA and to measured EA. Shared liability was weakly but significantly correlated with liability to higher EA (Figure 1) and with higher measured EA (Figure 2b) while the SZ_{diff} fraction was negatively correlated with liability to higher EA but was associated with lower measured EA. SZ liability therefore includes a greater proportion of risk alleles that negatively influence EA than does liability to BD, which might explain why despite the high genetic correlation between the two disorders, we find liability to BD is associated with better EA and liability to SZ with poorer EA.

Our study also extends work on the relationships between the cognitive and non-cognitive components of educational attainment and the shared and specific fractions of liability to SZ and BD(21, 57, 58) by incorporating direct measures of cognition and of educational attainment. The counter-intuitive observation that, while shared liability is associated with poorer cognition (Figure 2a), it is also associated with higher EA (Figure 2b), implies that the effects of shared liability on EA

comes from alleles associated with *noncognitive* traits that promote higher EA. In contrast, the observations that SZ_{diff} is associated with poorer cognition and with poorer EA, and that the association to EA is attenuated after conditioning on cognitive ability, suggests this fraction of liability exerts effects on EA through *cognitive* mechanisms. However, this association was only partially attenuated suggesting that SZ_{diff} also exerts effects on *noncognitive* traits that promote *lower* EA. Nevertheless, given that overall liability to SZ shows little association with liability to, or measured EA performance, the opposing effects of alleles from the shared and SZ_{diff} fractions must largely cancel each other out. These findings have important implications for interventions designed to improve educational outcomes in SZ which we suggest may need to focus on noncognitive as well as cognitive mechanisms. They also suggest that there are important shortcomings associated with using EA in genomic studies as a proxy for cognitive function.

Our finding that, in the general population, genetic liability to SZ conferred by common heritable alleles is associated with better EA than expected given their effects on cognitive ability (Figures 2a and b) is surprising given that overall risk of the disorder is associated with poorer EA(59). It is, however, consistent with evidence that SZ is more strongly associated with the extent to which EA in people deviates from that of their family members, and that this deviation is not explained by heritable liability to SZ(60).

SZ is more strongly associated than is BD with cognitive impairment, leading us to predict differentiating liability would be enriched for HES genes for prenatal and early childhood developmental stages and cells of the developing brain, but this was not observed. This is consistent with the hypothesis that non-familial factors play a larger role than common genetic variation in the greater neurodevelopmental impairment seen in SZ than BD. Contrary to our expectation, differentiating liability was enriched in HES genes for early and mid-adulthood, an age range likely to index later, rather than early, neurodevelopmental processes. This stage of development does, however, correspond to the typical age at onset of psychotic symptoms, the severity of which was reported to be associated with the SZ_{diff} fraction in people with bipolar disorder(7). Using cell-specific gene expression data from adult human brain, we additionally observed an enrichment of the differentiating fraction in HES genes for granule cells of the adult dentate gyrus, the function of which has been proposed as central to the genesis of psychotic symptoms(61). The same set of HES genes was also more strongly enriched in the GWAS for BD than that of SZ (Figure S6). Studies of the dentate gyrus and the relevant associated genes might therefore offer a window into biology that is potentially more important for BD; indeed, a hyperexcitable phenotype has been reported in induced pluripotent stem cell (iPSC)-derived granule neurons from people with BD(62).

Strengths and Limitations

We studied cognition in individuals without severe mental illness to reduce the impact of medication effects and reverse causation. We used both fluid intelligence and a measure of *g*, which we formed from a principal components analysis of four other cognitive tests. We chose these to ensure that our findings went beyond the analysis of a single cognitive measure. *g* also gives a more robust measure of general cognitive ability(63, 64) and psychotic disorders are associated with broad, multi-domain cognitive impairments(14) including in *g*. Moreover, the source GWASs showed associations with cognitive function that were in line with expectations based on the degrees of cognitive impairment seen in the two disorders and seen in previous correlational studies between the disorders and intelligence. This reassures us that the cognitive measures we used were comparable to those used in previous studies demonstrating impaired cognitive function in these disorders. In

addition, our results were consistent across the two measures of cognition that we used. Our interpretation that the discordant findings between effects of liability on measures of cognition and EA point to effects on noncognitive traits that influence EA is that these findings could be explained by aspects of cognition that are not captured by *g* or FI. Individuals in the UK Biobank differ from individuals in the general population, and in particular they have higher than average levels of educational attainment and cognitive function(23), which may result in underestimation of the effect sizes of associations to these traits. In addition, the single nuclei RNA-Seq datasets from human post-mortem brain that we tested in this study are likely to under-represent synaptic genes(49), which are known to be relevant to psychiatric disorders(30, 31) .

Conclusion

Liability that is shared between SZ and BD is enriched for alleles that confer risk to poorer cognitive function in the general population, but is associated with noncognitive traits that enhance EA. In contrast, SZ_{diff} is enriched for alleles that confer risk to poorer EA through both cognitive and non-cognitive mechanisms. Establishing the relevant non-cognitive traits may afford opportunities for intervention. Alleles that differentiate between SZ and BD are enriched for genes with high expression specificity for early and mid-adulthood and for granule cells of the dentate gyrus. Follow-up studies focussing on genes with high expression specificity for these timepoints and brain region may provide insights into the biology distinguishing these two major psychiatric disorders.

Tables

GWAS	SNP Heritability	S.E heritability
Schizophrenia	0.35	0.01
Bipolar Disorder	0.28	0.01
Shared	0.26	0.01
Differentiating	0.14	0.01

Table 1. SNP heritability of schizophrenia(31) and disorder GWAS(30) and gSEM fractions. SNP heritability reported on the observed scale as the absence of population prevalence data for the latent gSEM constructs preclude deriving values on the liability scale.

Figures

Figure 1. Heatmap showing genetic correlation for schizophrenia(31) (SZ) and bipolar disorder (BD) GWAS(30), gSEM shared and schizophrenia differentiating (SZ_{Diff}) fractions (derived in the present study) and published *g(35) and Educationa*l Attainment (EA)(36) GWAS from general population samples. Correlations were calculated using LDSC. Genetic correlation (rg) values are below the diagonal with standard errors in brackets. Genetic correlation p-values are given above diagonal.

Figure 2. (a) Association of gSEM fractions and source GWAS PRS with *g* and fluid intelligence in UK Biobank (fluid intelligence N= 160465; *g* N= 93541). Point estimates for beta with standard errors. Note that the relative magnitudes of effects for different PRS are not meaningful as they are dependent not only on the degree of shared genetic liability with the cognitive measures, but also on the power of relevant input GWAS. The beta coefficient indicates the number of standard deviations fluid intelligence or *g* will increase or decrease by when the PRS increases by 1 standard deviation. (b) Association of gSEM PRS and source PRS with Educational Attainment (EA) in UK Biobank. Point estimates for beta with standard errors are given. Negative beta values indicate higher liability to the relevant trait is associated with lower EA. Note that the relative magnitudes of effects for different PRS are not meaningful as they are dependent not only on the degree of shared genetic liability with EA, but also on the power of relevant input GWAS

Figure 3. Enrichment of fractions of liability in genes with high specificity for developmental stages. -log10 p shows the significance level for SLDSR enrichment tests. The black line represents the corrected significance threshold (Bonferroni corrected for 10 developmental stages). EarlyMidfetal samples are between 10 post-conception weeks (pcw) and 16 pcw, Midfetal between 16 pcw and 17 pcw, LateMidfetal from between 17 pcw and 24 pcw, EarlyInfancy between birth and 6 months of age, EarlyChildhood between 1 and 6 years, LateChildhood between 6 and 13 years, Adolescence between 13 and 20 years, YoungAdulthood between 20 and 30 years, MidAdulthood between 30 and 60 years, and OlderAdult over 60 years.

Acknowledgements

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Author Contributions: Dr Richards had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Richards, Walters, O'Donovan, Owen.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Richards, Fenner, Clifton, Cameron, Bray, Walters, O'Donovan, Owen.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Richards, Fenner, Clifton, Cameron, Holmans, O'Donovan.

Obtained funding: Walters, O'Donovan, Owen.

Administrative, technical, or material support: Richards, Clifton, Cameron, Tume, Bray, Legge, O'Donovan, Owen.

Study supervision: O'Donovan, Owen.

Funding/Support: This work supported by UKRI Grant 10039251 under Horizon Europe Guarantee for Project Gene Environment interactions in Mental health trajectories of Youth (YOUTH-GEMS), a Medical Research Council grant (MR/L010305/1) and programme grants (MR/P005748/1 and MR/Y004094/1), and the Brain and Genomics Hub of the Mental Health Platform (MR/Z503745/1). NC is funded by MRC grant MR/W017156/1. DC and NJB were supported by MRC project grant MR/T002379/1.

Disclosures: MJO, MCO and JW reported grants from Akrivia Health and Takeda Pharmaceuticals outside the submitted work. All other authors reported no biomedical financial interests or potential conflicts of interest.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Information: A previous draft of this paper is available as a pre-print online (https://doi.org/10.1101/2025.02.13.25322048). Summary statistics for the Shared and Diff gSEM fractions are available at the Cardiff University Data Repository (https://research-data.cardiff.ac.uk/).

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