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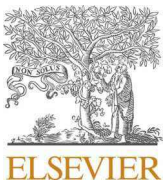

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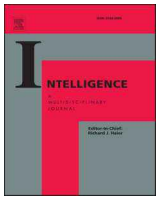

Polygenic influences associated with adolescent cognitive skills

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ABSTRACT

Genes play an important role in children's cognitive ability through adolescence and into adulthood. Recent advances in genomics have enabled us to test the effect of various genetic predispositions on measured cognitive outcomes. Here, we leveraged summary statistics from the most recent genome-wide association studies of eleven cognitive and mental health traits to build polygenic prediction models of measured intelligence and academic skills in a cohort of Australian adolescent twins ($N = 2335$, 57% female). We show that polygenic risk scores for educational attainment, intelligence, and cognitive performance explained up to 10% of the variance in academic skills and 7% in intelligence test scores in our cohort. Additionally, we found that a genetic predisposition for ADHD was negatively associated with all cognitive measures and a genetic predisposition for schizophrenia was negatively associated with performance IQ but no other cognitive measure. In this study, we provide evidence that a genetic vulnerability to some mental health disorders is associated with poorer performance on a variety of cognitive and academic tests, regardless of whether the individual has developed the disorder.

1. Introduction

It is well known that different people learn at different levels of ease and speed. Cognitive ability or intelligence can be broadly defined as an individual's ability to learn, reason, and infer when presented with new situations. In 1904, Charles Spearman first described a general intelligence factor, termed '*g*', to describe the observation where individuals that score highly in one type of intelligence test, will be likely to score high in others (positive inter-correlation) (Spearman, 1904). General intelligence can be measured through a variety of cognitive tests that output a standardized IQ score (Intelligence Quotient). Higher general intelligence is correlated with a wider range of variables, cognitive and other, than any other trait (Krapohl et al., 2016) including increased mortality (Batty, Deary, & Gottfredson, 2007), reduced fertility (Barban et al., 2016; Day et al., 2016) and increased risk of mental and physical disease (Deary, Strand, Smith, & Fernandes, 2007; Hill et al., 2018). For more than a century, scientists have attempted to understand and identify factors that correlate with general intelligence.

A large body of literature has shown that cognitive ability is influenced by genetics and furthermore, that the influence of genetic factors on individual intelligence changes from childhood to adulthood (Bartels, Rietveld, Van Baal, & Boomsma, 2002; Deary, Whalley, Lemmon, Crawford, & Starr, 2000; Von Stumm & Plomin, 2015). Heritability estimates for intelligence increase dramatically as we age. Heritability is estimated to be 20% in childhood, 40% during adolescence and between 60 and 80% in adulthood (Finkel, Pedersen, & McGue, 1995; Hansell et al., 2005; Haworth et al., 2009; Plomin & von Stumm, 2018). Genome-wide association studies (GWAS) of cognitive ability have greatly increased our understanding of the polygenic genetic architecture underpinning these traits and have led to the discovery of variants, genes, and biological pathways that play a role in cognition (Visscher et al., 2017). To date, more than 200 independent variants have been associated with general intelligence (IQ) (Davies et al., 2018; Hill et al., 2019; Savage et al., 2018).

Intelligence is generally understood to be the ability to learn and apply knowledge to adapt to or alter the environment (Sternberg, 2012). Two commonly proposed types of intelligence are that of crystalized (the ability to learn and recall) and fluid (the ability to infer and reason in

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new situations) intelligence (Cattell, 1963). Intelligence is sometimes parsed into verbal IQ (the ability to acquire and apply verbal information and skills to solve problems) and performance IQ (the ability to fluently manipulate visual-spatial information to solve problems) (Blaha & Wallbrown, 1982). The widely used tests of intelligence developed by Wechsler assess performance in several domains, including verbal comprehension, non-verbal reasoning, working memory, and processing speed, which generally cluster together to provide an intelligence score (Wechsler, 1955). Despite the identification of genetic variants associated with general intelligence, GWAS sample sizes are currently not large enough to detect unique genetic variation specific to cognitive domains.

The need for such large sample sizes is a result of the complex nature of intelligence as a genetic trait, meaning that it is influenced by the culmination of many genetic variants that each have small effect. A commonly used proxy for intelligence is that of educational attainment (EA)—the number of years of formal education. EA is correlated both phenotypically (~0.50) (Plomin & von Stumm, 2018) and genetically (~0.72) (Hagenaars et al., 2016; Lee et al., 2018; Okbay et al., 2016; Sniekers et al., 2017; Trampush et al., 2017) with intelligence. Intelligence is regarded as a combination of both cognitive and non-cognitive factors, and is influenced by both genes and the environment (Belsky et al., 2018; Krapohl & Plomin, 2016). Though a coarser measure than traditional intelligence tests, the highest level of education is a common question asked in almost all recruiting studies, and this has allowed researchers to rapidly gain large enough sample sizes to detect genetic variants (Single Nucleotide Polymorphisms; SNPs) with small effect. The most recent GWAS of EA (N = ~1.1 million) identified 1271 variants and estimated the heritability explained by common SNPs, i.e. the SNP-based heritability, to be 30% (Lee et al., 2018). Using a large GWAS of cognitive performance, a recent study used genomic structural equation modelling (gSEM) to partition genetic variants associated with EA, the most well-powered cognitive trait, into two factors representing cognitive and non-cognitive components (Demange et al., 2021). This novel approach has produced a well-powered proxy GWAS for the non-cognitive EA factor associated with educational attainment.

The wealth of genetic information produced from GWAS has led to the production of genetic predictors (polygenic risk scores; PRS). Polygenic risk scores have created the opportunity to operationalise an indicator of an individual's genetic predisposition for complex traits. Such studies have shown that PRS for intelligence or EA are able to significantly predict educational attainment (Selzam et al., 2017a), IQ test scores (Allegrini et al., 2019) as well as university entrance exam scores and university enrolment (Smith-Woolley, Ayorech, Dale, von Stumm, & Plomin, 2018) in independent samples. Aligned with the increasing role of genetics in cognitive abilities during puberty and adolescents, PRS have been shown to account for a cumulatively larger proportion of variance in cognitive test scores and educational attainment between the ages of 7 and 16 (Allegrini et al., 2019; Selzam et al., 2017b).

To date, few studies have examined the domain or subject-specific genome-wide associations of cognitive or academic abilities (Donati, Dumontheil, Pain, Asbury, & Meaburn, 2021; Gialluisi et al., 2019; Lee et al., 2018; Luciano et al., 2013; Price et al., 2020), and most have small samples for GWAS. Phenotypically, education has been associated with improvement in particular domains of intellectual ability, such as working memory and vocabulary, rather than gains in general intelligence (Melby-Lervåg & Hulme, 2013; Ritchie, Bates, & Deary, 2015). Several studies report high, but imperfect, genetic correlations (~60%) between achievement in reading and mathematics (Davis et al., 2014) as well as performance in various school subjects including English, art, mathematics and science (Rimfeld, Kovas, Dale, & Plomin, 2015). Additionally, it has been shown that differences in EA genetic scores are associated with word reading ability (Belsky et al., 2016) and reading comprehension (Selzam et al., 2017b). Genetic variation associated with EA also differentially influences A-level subject choice and achievement in the United Kingdom (Rimfeld, Ayorech, Dale, Kovas, & Plomin, 2016) and has a stronger association with English rather than mathematics in early adolescence (Ward et al., 2014). Polygenic scores for EA and cognitive performance have also been found to predict variation in math, science, and verbal performance at the end of schooling (Lee et al., 2018). Both PRS for EA and for cognitive performance have been reported to predict variation in several measures of intelligence or related cognitive domains (Davies et al., 2016; Lee et al., 2018), although not statistically significant, the vocabulary domain was reported to have a stronger qualitative association with both an EA and a cognitive performance PRS (Davies et al., 2016). Although PRS are as yet imperfect measures of genetic predisposition, these studies demonstrate that PRS derived from GWAS of cognitive measures may be useful for differential statistical prediction of domain-specific cognitive abilities and academic performance.

The Queensland Core Skills Test (QCST) is a test of academic achievement that was administered to the majority of Year 12 students in Queensland, Australia between 1992 and 2019. The test was used to assess individual achievement and core skills and the results were used for university entrance applications. Instead of testing subject-specific knowledge, the QCST comprises a set of five 'baskets' that represent core academic skills. These baskets are aimed to assess higher-order cognitive skills such as comprehension and communication, reasoning, synthesis and integration of information, creating and presenting, and applying techniques and procedures. Prior work using the classic twin design has identified that these core skills have moderate to high heritability estimates, ranging from 0.43 to 0.73 (Wainwright, Wright, Luciano, Geffen, & Martin, 2005). Although shared genetic variation across baskets and verbal and performance IQ accounted for most of the genetic influences on three of these baskets, two were significantly influenced by independent genetic factors. In addition, both verbal and performance IQ were influenced by specific genetic factors, indicating some differences in the genetic influences across these core skills and intelligence. The QCST represents a unique resource to assess PRS associations of general academic achievement but also whether differential associations between academic skills exist (Authority, Q. S, 2003).

Poorer cognitive performance is often associated with many mental health disorders, such as schizophrenia, bipolar and major depressive disorder, and has been shown to persist even after episodic and symptom remission (Robinson et al., 2006; Rock, Roiser, Riedel, & Blackwell, 2014). In fact, a recent study reported that cognitive functions declined in individuals with psychotic disorders over the twenty years following their first hospitalization (Fett et al., 2020). Impaired performance in specific cognitive domains has also been associated with mental health disorder status when compared to age-matched controls. Examples include decreased working memory, vocabulary and verbal fluency in individuals with schizophrenia (Fett et al., 2020; Trivedi, 2006) and deficits in working memory and executive function in individuals with depression (Rock et al., 2014). However, after the onset of a mental health disorder, it is difficult to distinguish whether these observed associations are as a result of the subsequent environment or more innate and biological processes that precede disease onset.

The genetic relationship between cognitive ability, educational attainment, and mental health disorders are also heterogeneous. Table 1 details the average of significant genetic correlations between intelligence, educational attainment and several mental health disorders that have been derived from GWAS studies. Intelligence has been found to have significant negative genetic correlations with schizophrenia, depression or depressive symptoms, and attention-deficit/hyperactivity disorder (ADHD), significant positive genetic correlations with autism, and anorexia, and genetic correlations with bipolar disorder have been non-significant across several studies (Davies et al., 2018; Hagenaars et al., 2016; Hill, Davies, Liewald, McIntosh, & Deary, 2016; Lam et al., 2017; Savage et al., 2018). While the genetic correlations between educational attainment and depression, ADHD, autism, and anorexia nervosa were in the same direction as with intelligence, the correlations were slightly stronger. In contrast to intelligence, educational

Table 1
Significant mean genetic correlations between intelligence, educational attainment and several mental health disorders reported in previous studies.

Mental Health Disorder	Intelligence	References	Educational Attainment	References
Autism Spectrum Disorder	0.21	(Davies et al., 2018; Hagenaars et al., 2016; Hill et al., 2019; Lam et al., 2017; Savage et al., 2018; Sniekers et al., 2017; Trampush et al., 2017)	0.31	(Hagenaars et al., 2016; Hill et al., 2016; Lam et al., 2017)
Anorexia Nervosa	0.06	(Hill et al., 2019)	0.19	(Hill et al., 2016; Lam et al., 2017; Watson et al., 2019)
Bipolar Disorder	ns		0.28	(Hill et al., 2016; Lam et al., 2017; Okbay et al., 2016; Stahl et al., 2019)
Schizophrenia	−0.21	(Davies et al., 2018; Hagenaars et al., 2016; Hill et al., 2016; Hill et al., 2019; Lam et al., 2017; Savage et al., 2018; Sniekers et al., 2017; Trampush et al., 2017)	0.10	(Hagenaars et al., 2016; Lam et al., 2017; Okbay et al., 2016)
Depression	−0.28	(Barban et al., 2016; Davies et al., 2018; Savage et al., 2018; Sniekers et al., 2017)	−0.32	(Lam et al., 2017)
ADHD	−0.39	(Davies et al., 2018; Hill et al., 2019; Lam et al., 2017; Savage et al., 2018)	−0.53	(Lam et al., 2017)

attainment has been found to have significant positive genetic correlations with bipolar disorder and with schizophrenia. Moreover, when educational attainment was parsed into cognitive and non-cognitive factors, the non-cognitive component of educational attainment was found to have a stronger positive genetic relationship with schizophrenia (0.26) (Demange et al., 2021). This positive genetic correlation between schizophrenia educational attainment, which contrasts with both phenotypic associations and genetic correlations with cognition, might result from heterogeneity in both schizophrenia and educational attainment phenotypes (Bansal et al., 2018; Demange et al., 2021). These findings highlight the potential complexity of relationships that underpin the correlation between traits.

Although genetic correlations provide information on the similarity of allelic effects on two traits averaged across the genome, the extent that those genetic effects are evident in a phenotype depends on the heritability of those phenotypes and the accuracy of the measured allelic effects. Increasing sample sizes have increased the power to detect common genetic effects in GWAS and the precision in estimating those effects (Howard et al., 2019; Wray et al., 2012), which in turn has increased the power of PRS derived from those GWAS (Dudbridge, 2013). Although the power of PRS is still limited, they provide an opportunity to test for measured genetic effects on traits that might be measured in samples too small for GWAS. They also provide a test of whether a genetic predisposition to one trait has a measurable impact on the phenotypic expression of another. PRS have been employed to explain variation in cognitive trajectories in the subgroups of individuals with schizophrenia (Dickinson et al., 2020). A higher PRS for schizophrenia has been associated with lower cognition scores but not lower academic achievement scores in healthy individuals (Shafee et al., 2018). In the reverse direction, higher PRS for EA has been associated with some domains of cognition in individuals with schizophrenia, including working memory and crystallised IQ, but not other domains, including processing speed and cognitive flexibility (Comes et al., 2019). Similarly, a PRS of ADHD has been associated with poorer performance on word reading, nonword reading, and spelling but was not associated with other skills including phoneme awareness, rapid naming tasks, and a working memory task (Gialluisi et al., 2019). This suggests that a genetic predisposition to ADHD does not uniformly contribute to poorer performance across cognitive tasks and academic skills; however, a review of PRS of ADHD did show a general pattern of poorer educational or cognitive performance with a higher genetic liability for ADHD (Ronald, de Bode, & Polderman, 2021). Krapohl et al. (2016) conducted a systematic examination of the association of genetic predisposition for several traits, including mental health disorders, on various outcomes, including cognitive and academic skills. They did not detect any significant association between a genetic predisposition for either ADHD, autism, depression, bipolar disorder, or schizophrenia and cognitive performance or academic achievement in an adolescent sample (N ~ 3 k); although, the association between a predisposition and English was nominally positive. Meanwhile, Hagenaars et al. (2016) used the same training GWAS summary data to build PRS and predicting intelligence (N ~ 36 k) and educational attainment (N ~ 111 k) in an older adult sample. They found genetic predisposition to autism to predict higher cognitive scores while a genetic predisposition for depression and one for schizophrenia each predicted lower cognitive scores. They also found a genetic predisposition for ADHD predicted poorer educational attainment, while a predisposition for autism, or bipolar, or schizophrenia were all associated with higher educational attainment. The different findings of Hagenaars et al. and Krapohl et al. might reflect the vastly different target sample size and subsequent power differences or it might be due to the difference in cognitive phenotypes and age of the sample.

Here, we leveraged GWAS summary statistics from the most recent genome-wide association studies of intelligence, EA, cognitive and non-cognitive EA factors, as well as seven mental health disorders, to build prediction models of IQ test scores, core academic skills, and academic achievement in a cohort of Australian adolescent twins.

2. Methods

2.1. Participants

A cohort of 2335 adolescent twins (57% female) from the Brisbane Longitudinal Twin study (BLTS) were used in these analyses (Wright & Martin, 2004). Each individual completed the Multiple Aptitude Battery (MAB) test at approximately the age of 16 (mean age = 16.6, s.d. = 1.4). Each participant also completed a standardized test of academic achievement, the Queensland Core Skills Test (QCST), in August of their Year 12 of formal schooling (mean age = 17.4, s.d. = 0.4), for which we were granted consent to access their results. The mean family socioeconomic status, assessed using the Australian Socioeconomic Index 2006 (AUSEI06) occupational status scale, was 59.65 (s.d. = 24.0; scale 0–100) indicating a slightly higher than average socioeconomic standing in this cohort. Standard genotyping and quality control procedures for

the BLTS have been described previously (Colodro-Conde et al., 2018). Imputation was conducted using the Haplotype Reference Consortium 1.1 reference panel.

Written informed consent was obtained from each participant and from a parent or legal guardian for participants under the age of 18. The BLTS study was approved by the Human Research Ethics Committees of the QIMR Berghofer Medical Research Institute. Access to QCST results was approved by the Queensland Department of Education given participant and parent consent.

2.2. Cognitive Performance Instruments

2.2.1. Multidimensional Aptitude Battery (MAB)

The MAB, based on the Wechsler Adult Intelligence Scale (WAIS-R; Purves et al., 2020; Wechsler, 1981) (Jackson, 1998), is a multiple-choice test of general intelligence that yields three scores: Verbal IQ, Performance IQ and Full-scale (VIQ, PIQ and FIQ respectively). FIQ is computed as a weighted sum of VIQ and PIQ. Verbal IQ is designed to measure an individual's ability to solve problems using language-based reasoning, which includes things such a vocabulary, arithmetic and general knowledge. Performance IQ is designed to measure visuospatial intellectual abilities and includes tasks like spatial arrangement, object assembly and attentiveness to detail. Further details regarding these subtests have been described previously (Luciano et al., 2001; Wainwright, Wright, Geffen, Luciano, & Martin, 2005).

2.2.2. Queensland Core Skills Test (QCST)

Substantial additional detail regarding the QCST has been described previously (Wainwright, Wright, Luciano, Geffen and Martin, 2005). Briefly, the QCST is composed of four test papers, one writing task, one short response paper, and two multiple-choice test papers. Test items from across the multiple choice and short response paper contribute to five core academic skills and the writing task contributes to one of the core skills, *Create and Present*. These core skills which are summed to give a total score that represents general academic achievement. These core skills, termed baskets, are as follows: *Comprehend and Collect* which entails comprehending facts, extracting, and interpreting and displaying meaning from various sources of information including poetry, prose, diagrams, tables, and graphs. *Structure and Sequence* involves selecting and organizing information, and discerning patterns and relationships in pictures, graphs, tables, and text. *Analyse, Assess and Conclude* assesses the ability to deduce key messages, make inferences, evaluate assumptions, and draw conclusions. *Create and Present* involves the use of written language to clearly present ideas in response to provided stimulus materials. Lastly, *Apply Techniques and Procedures* assesses the ability to select and apply mathematical problem solving techniques.

The total QCST score is scaled by the calendar year in which the test was written. However, individual baskets scores do not undergo any type of scaling. Therefore, we controlled for the test year by creating residuals of the basket scores, thereby removing the variance associated with which year the test was taken from the regression.

2.3. Correlations and polygenic risk score calculation

We estimated the pairwise phenotypic and genetic correlations between seven psychiatric disorders and four cognitive traits (Table 2) using Pearson correlations and linkage-disequilibrium score (ldsc) regression (Bulik-Sullivan et al., 2015) respectively.

All traits selected had a significant SNP-based heritability in the reference GWAS, though the predictive power of PRS calculated from the identified common SNPs into the target traits differed substantially (Table 2). For example, a PRS of Educational Attainment explained between 11 and 13% of variance in EA in Lee et al. (2018) where a PRS for anxiety only explained 0.5% of variance in anxiety in Purves et al. (2020). Only SNPs passing quality control (minor allele frequency $>$ 0.01, call rate $>$ 0.9 and imputation score $>$ 0.6) were used for PRS calculation. Summary statistics for our 11 traits of interest in Table 2 were used for polygenic risk score calculation. These traits were selected as they were reasonably powered GWAS summary statistics on mental health disorders that were available to download from the Psychiatric Genomic Consortium. To improve accuracy, the summary statistics used as input for PRS calculation were refined by discarding all ambiguous markers, indels and restricting SNPs to those with INFO $>$ 0.6 and MAF $>$ 0.01. Importantly, as participants at QIMR have participated in studies that contributed to several of these GWAS studies, PRS for these traits were calculated using summary statistics that excluded any QIMR cohorts. PRS were calculated using SBayesR, a Bayesian analysis that was used to approximate the results of a conditional GWAS (Lloyd-Jones et al., 2019). Polygenic risk scores were estimated by multiplying the multivariate effect size (obtained from SBayesR) with the allelic dosage of the effect allele and summing across all loci for each participant and then standardised. For the LD reference, we used the same sparse LD matrix as used in Lloyd-Jones et al. (2019).

The effect of each PRS on the three IQ measures (performance, verbal, and full-scale) and on the six QCST measures (total and the 5 baskets) was estimated using a linear mixed model regression with the PRS as a predictor variable while accounting for sex, age and the first 10 genetic ancestry principal components included as covariates. Relatedness between participants was accounted for as a random effect with a genetic relatedness matrix, using GCTA 1.91.7 (Yang, Lee, Goddard, & Visscher, 2011; Yang, Zaitlen, Goddard, Visscher, & Price, 2014). A partial R^2 was calculated and variance explained by the PRS was estimated as the difference in Pearson correlation coefficient between the full model (i.e. including the PRS) and a reduced model including only covariates. All significance values were corrected to account for multiple testing using FDR $<$ 5%.

Table 2
Traits and their sources used for PRS construction using SBayesR.

Trait	Source	N cases	N controls	SNP-based heritability (SE)	Phenotypic Variance explained (%) in source study
Depression †	Howard et al., 2019	246,819	561,485	0.09 (0.003)	1.5–3.2
Anxiety	Purves et al., 2020	25,453	58,113	0.26 (0.011)	0.5
Bipolar Disorder †	Mullins et al., 2021; Purves et al., 2020	41,917	371,549	0.19 (0.006)	4.6
Schizophrenia	Pardiñas et al., 2018	40,675	64,643	0.25 (0.007)	5.7
ADHD	Demontis et al., 2019	20,183	35,191	0.22 (0.014)	5.5
Anorexia Nervosa†	Watson et al., 2019	16,992	55,525	0.17 (0.01)	1.7
Autism	Grove et al., 2019	18,381	27,969	0.12 (0.01)	2.5
Educational Attainment †	Lee et al., 2018	1,100,000	NA	0.15 (0.009)	11–13
Intelligence †	Savage et al., 2018	269,867	NA	0.19 (0.01)	5.2
Cognitive skills	Demange et al., 2021	*510,795	NA	0.19 (0.006)	Not reported
Non-Cognitive skills	Demange et al., 2021	*257,700	NA	0.06 (0.002)	Not reported

* Sample sizes for the cognitive and non-cognitive skill factors are estimates using the output of genomicSEM. The traits themselves were not measured.
† QIMR samples removed from GWAS summary statistics.

3. Results

3.1. Cohort descriptives

The cohort consists of 827 monozygotic (MZ) and 1247 dizygotic (DZ) twins and 261 twin siblings. All participants are of European ancestry. Demographic information is summarized in Table 3.

3.2. Correlations between cognitive traits and mental health disorders

All cognitive test measures in our cohort were positively correlated ($p < 0.01$; Supplementary Table 1). Total QCST scores were highly (>0.7) correlated with all five core skill tests, as well as verbal IQ. The correlation between total QCST score and performance IQ was lowest at 0.49.

While the genetic correlations among the mental health disorders were all positive, we found that the genetic correlations between our mental health and cognitive traits were highly heterogeneous (Fig. 1; Supplementary Table 2). Anorexia and Autism were positively associated with EA, IQ as well as the cognitive and non-cognitive EA factors. Conversely, ADHD, depression and anxiety were negatively associated with these four traits (albeit, the correlation between depression and the cognitive skills factor did not survive multiple testing correction). We also observed several contrasting correlations with the cognitive and non-cognitive factors. For example, schizophrenia was negatively associated with IQ and the cognitive EA factor, but was positively correlated with the non-cognitive EA factor. Likewise, bipolar disorder was negatively correlated with cognitive EA factor, but positively correlated with EA and the non-cognitive EA factor (Fig. 1).

3.3. Cognitive and educational attainment PRS prediction of cognitive and academic skills

A PRS for EA explained 10% of variance in total QCST scores ($p = 4.5 \times 10^{-40}$), 4.5% in FIQ ($p = 7.9 \times 10^{-20}$) and explained approximately 3× more variance in VIQ than PIQ (6.8% and 2.1% respectively). Comparatively, a PRS for intelligence explained approximately 9.4% of variance in total QCST ($p = 4.8 \times 10^{-40}$), 6.5% ($p = 5.2 \times 10^{-27}$) in VIQ and 4.8% ($p = 2.2 \times 10^{-10}$) in PIQ. The cognitive EA factor PRS had a highly similar association pattern to that of the IQ PRS. In contrast, the non-cognitive EA factor PRS only explained a small amount of variance in total QCST (2.2%; $p = 1.1 \times 10^{-9}$), FIQ (0.4%; $p = 0.008$) and VIQ (1.2%; $p = 4.9 \times 10^{-6}$) and was not associated with PIQ ($p = 0.51$) (Fig. 2). The IQ PRS and cognitive skills PRS were more strongly associated with performance IQ ($p = 0.016$) than the EA PRS ($p = 0.029$) (Paternoster, Brame, Mazerolle, & Piquero, 1998).

Next, we tested the association between different QCST academic skills and the PRS from the four cognitive and educational attainment traits. Association results were largely similar across the different academic skills, indicating that a genetic predisposition to these cognitive and educational attainment traits does not differentially impact acquisition and performance of these academic skills (Fig. 3; Supplementary Table 3).

3.4. Mental Health Disorder PRS prediction of cognitive and academic skills

Only the ADHD PRS was significantly associated with all IQ and academic measures whereby a higher genetic predisposition for ADHD is predictive of lower outcome scores with effect sizes ranging from −0.05 and − 0.11. A genetic vulnerability to bipolar disorder was negatively associated with PIQ and the academic skills *Comprehend and Collect* as well as the *Application of Techniques and Procedures* (β = −0.07, −0.05 and − 0.03 respectively). Several PRS showed association with only one cognitive outcome: depression and anxiety PRS were associated with lower scores for the academic skill *Applying Techniques and Procedures* (β-0.06), and schizophrenia PRS was associated with lower performance IQ (β = −0.09;Fig. 3; Supplementary Table 3).

All remaining mental health PRS had non-significant associations with all IQ and academic measures, indicating that we did not find evidence that a genetic predisposition to these mental health disorders were associated with performance on these tests. Though non-significant, anorexia nervosa had a non-trivial association effect size with PIQ (β = −0.05) and the academic skill *Analyse, Assess and Conclude* (β = 0.05), albeit the effect was in the opposite direction.

4. Discussion

Intelligence is important to both individuals and society as a whole. Understanding the mechanisms influencing intellectual ability is crucial to better understand relationships between cognitive abilities and psychosocial, educational and economic outcomes. This study had two main objectives: First, to test the association between PRS for EA, intelligence, the cognitive and non-cognitive EA factors and IQ scores, as well as unique measures of academic skills assessed during the QCST. Second, we explored the associations between genetic predispositions to seven mental health disorders and the same cognitive and academic scores as above.

In line with previous findings, we found that individuals with higher PRS for EA, intelligence and the cognitive EA factor performed better in all IQ and academic tests. The PRSs for EA and intelligence explained roughly the same amount of variance in total QCST and full-scale IQ test scores, despite the greater statistical power of the EA GWAS (Table 2). This implies that the genetic architecture of the QCST is more similar to the genetics of intelligence than educational attainment. However, while EA may be a good proxy for full-scale IQ, it did not perform as well for performance IQ, which was better predicted by intelligence PRS or cognitive EA factor PRS. In fact, intelligence PRS explained approximately twice as much variance in performance IQ than EA PRS. PRS for the non-cognitive EA factor significantly predicted total QCST scores, as well as the five individual core academic skills, albeit more weakly than the cognitive EA factor. This indicates that there are genetic influences independent of intelligence that contribute to higher educational attainment that also capture variance in these higher-order academic skills. When it comes to intelligence scores, it appears that genetic influences on the cognitive component of educational attainment contribute almost equally to both performance and verbal IQ. Interestingly, genetic influences on the non-cognitive EA factor (i.e. independent of intelligence) contribute to verbal IQ. This probably results from using a full-scale IQ or first principal component in the GWAS on

Table 3
Summary of demographic and phenotypic measures of the BLTS cohort used in this study.

	Mean (s.d.) [min - max]	State Average[a]
Age at IQ testing	16.6 (1.4) [15.7–28.9]	
Age at QCST	19.9 (0.4) [16.2–19.9]	
Sex		
Females (N)	1331	
Males (N)	1002	
IQ Test Scores		
FIQ	111.9 (12.8) [77–153]	
VIQ	109.9 (11.5) [77–153]	
PIQ	112.4 (15.9) [64–151]	
QCST Test Scores		
Total QCST	125.37 (29.8) [42–212]]	117 (26.4)
Comprehend and Collect	23.2 (7) [5–44.5]	23.2 (5.7)
Structure and Sequence	20.4 (6.7) [2.5–45]	18.4 (4.9)
Analyse, Assess and Conclude	25.4 (8.1) [5.5–53.5]	14.8 (5.9)
Create and Present	40.9 (10.2) [1–73]	37.9 (8.7)
Apply Techniques and Procedures	14.5 (6.7) [1–38.5]	23.4 (7.0)

[a] The state means and SD were calculated from the weighted means and SD from four calendar years, 2007–2010 (McLeod & Davidson, 2012).

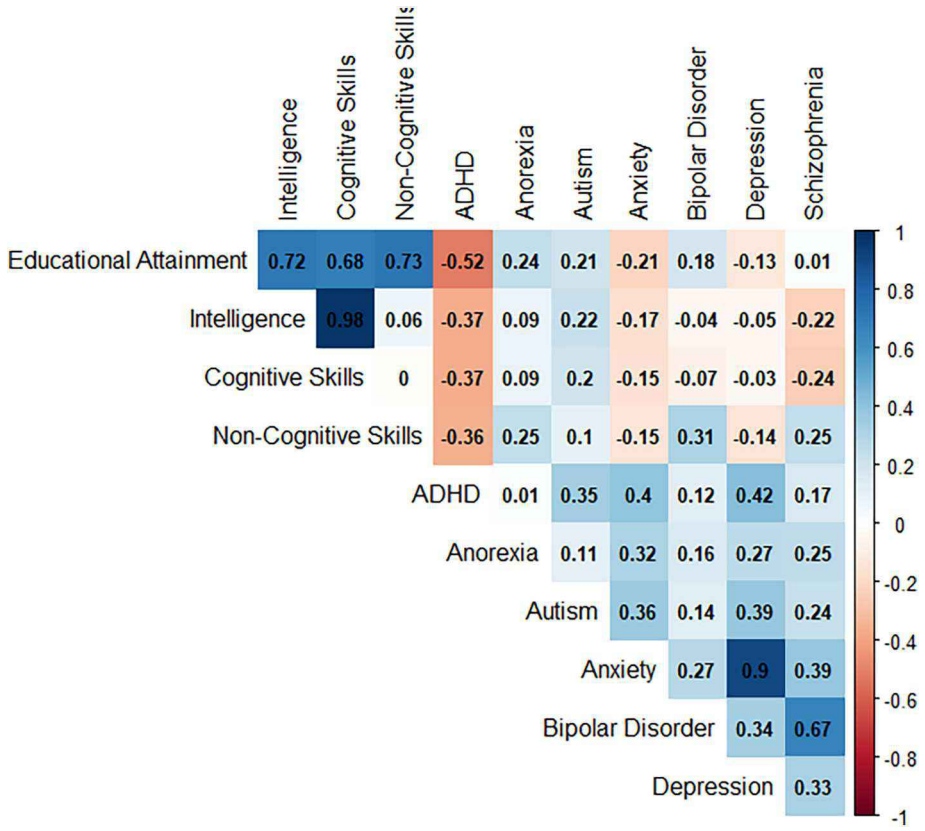

Fig. 1. Genetic correlations between cognitive and psychiatric traits reveals highly heterogeneous genetic associations between mental health disorders and cognitive phenotypes.

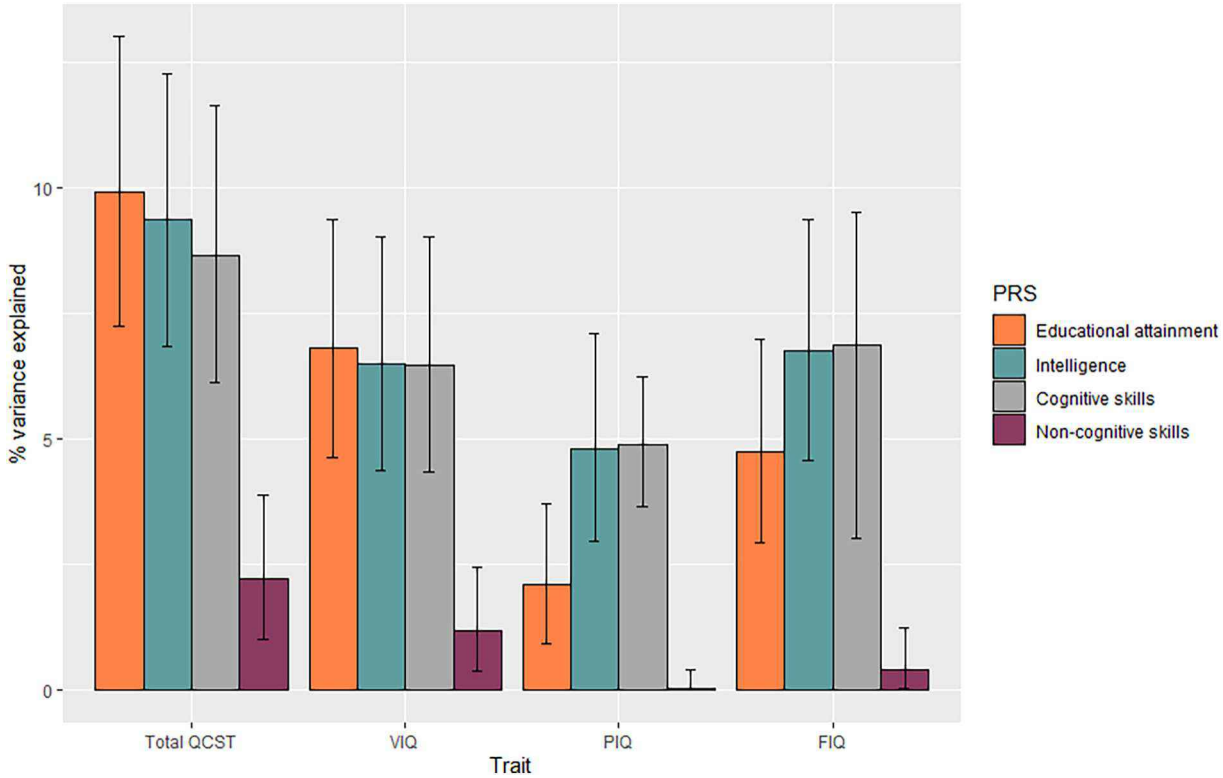

Fig. 2. Barplot depicting percentage variance explained in total QCST, full IQ (FIQ), performance IQ (PIQ) and verbal IQ (VIQ) scores by the respective PRSs. PRS were constructed for educational attainment, intelligence, cognitive skills and non-cognitive skills. Error bars represent 95% Confidence Intervals.

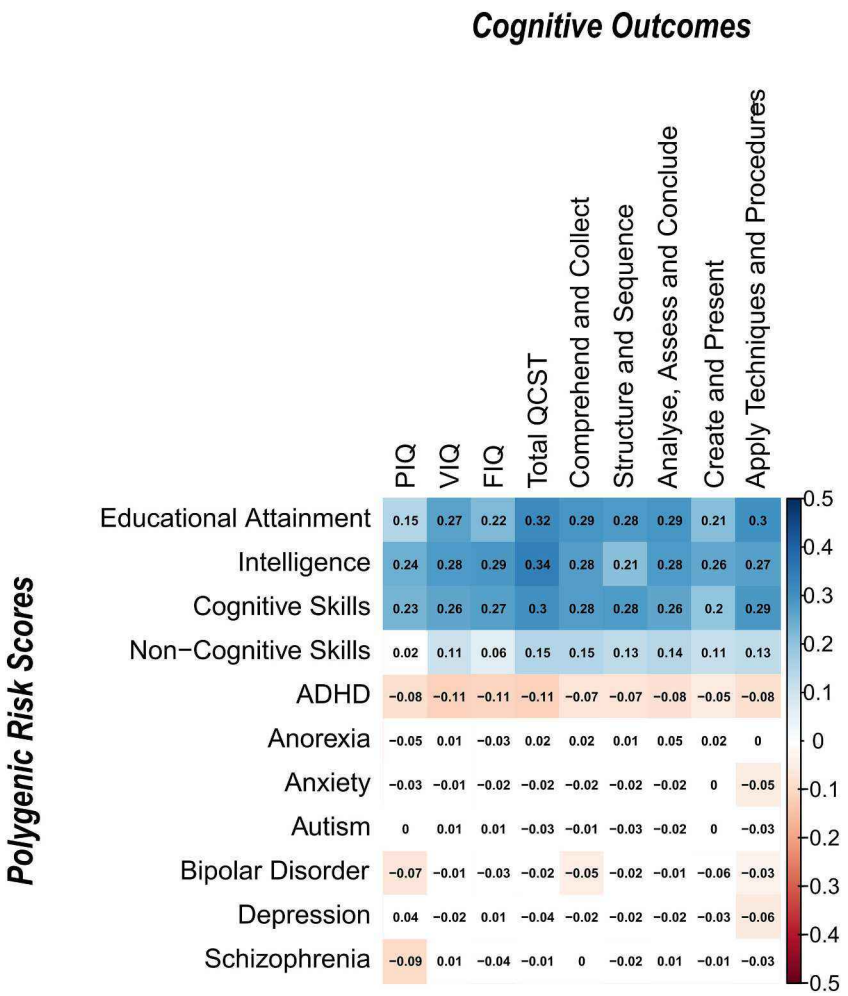

Fig. 3. Beta coefficients of association results between PRS and cognitive outcomes. Associations in white did not survive multiple testing correction (FDR < 5%).

intelligence, which does not fully capture the genetic influences on each of the performance and verbal IQ domains. It suggests that if there are unique genetic influences on these IQ domains, those influencing educational attainment are more strongly associated with verbal IQ than performance IQ.

We found that a genetic predisposition for ADHD was negatively associated with all IQ and academic outcomes, despite the limited statistical power of the ADHD PRS compared to other mental health traits. These findings are in line with previous studies that found that a higher PRS for ADHD was associated decreased working memory in children aged 7–11 (Aguilar-Lacasaña et al., 2020), and were associated with lower educational and IQ test scores in a sample of 6900 adolescents in the UK (Stergiakouli et al., 2017), and studies where PRS for EA and IQ predicted ADHD traits (de Zeeuw et al., 2014; Krapohl et al., 2016). Our results demonstrate the pervasiveness of this association across five academic skill domains that are rarely measured in tests of achievement and are representative of higher-order skills that are thought to generalise across academic subjects. It is possible that the genetic effects that have been captured by the ADHD PRS are predicting these academic skills via an association with a general factor. This would be consistent with the common genetic factor identified by Wainwright, Wright, Luciano, et al. (2005). These findings point to genetic overlap between ADHD and cognitive abilities and highlight the importance of recognizing that ADHD risk may functionally contribute to poorer cognitive outcomes across numerous domains.

Although cognitive impairment is a frequent observation in those at risk of schizophrenia, only the association between schizophrenia PRS and performance IQ maintained statistical significance after multiple testing correction. Our results replicate previous reports of an association between schizophrenia and adolescent performance IQ on both the phenotypic level (Hubbard et al., 2016) and using genetic risk scores (Riglin et al., 2017), where a higher PRS for schizophrenia has been associated with lower performance IQ and language fluency, and supports evidence of impaired spatial functioning in individuals with schizophrenia (Piskulic, Olver, Norman, & Maruff, 2007) or with a genetic vulnerability for schizophrenia (Glahn et al., 2003). Together, these findings suggest that specific domains, namely performance or fluid intelligence, may be compromised in individuals at higher genetic risk of schizophrenia rather than general intellectual ability. In a similar vein, a genetic predisposition for schizophrenia was not associated with compromised performance in the higher-order academic skills assessed with the QCST.

A genetic vulnerability for bipolar disorder was also negatively associated with performance IQ, perhaps driven by the high genetic correlation between bipolar disorder and schizophrenia. None of the remaining mental health trait PRSs had significant associations with IQ measures or total QCST scores. However, ADHD, anxiety, depression and bipolar disorder PRS were all negatively associated with the *Applying Techniques and Procedures* basket. This basket tests the academic skill of information integration and problem-solving (Wainwright, Wright, Luciano, et al., 2005). Bipolar disorder PRS was also significantly negatively associated with the *Comprehend and Collect* QCST basket. Together this points towards domain-specific impairment in individuals with genetic risk for these disorders, and sheds light on

possible mechanisms underlying the observed relationship between these disorders and impaired cognitive ability.

It is important to note that PRS associations do not necessarily imply causality but rather highlight how genetic relationships and associations express in phenotypic variability. However, a causal relationship between intelligence and some of these mental health traits has been demonstrated previously in the latest IQ GWAS (Savage et al., 2018). The authors used Mendelian Randomization to assess the causal relationships of some of these observations and found a significant protective effect of intelligence on schizophrenia and ADHD and intelligence was shown to be a risk factor for autism. Lastly, despite significant genetic correlations, we found no significant influence of PRS for anorexia or autism spectrum disorder on our cognitive outcomes, though this might be because of limited statistical power rather than the absence of a true effect.

Our study has several limitations. First, the GWASs used to create the PRS only explain a small fraction of variance in each respective trait in the general population. Additionally, the statistical power of each GWAS is substantially different and therefore the absence of a significant association for some traits may be due to lack of power and not the absence of a true association. Additionally, the QCST participants may be regarded as a biased sample of the cohort because less academically able students escape ascertainment by not sitting the test. While we have attempted to account for this through the inclusion of IQ measures, it is possible these individuals are also not truly representative of the general population given biases involved in the voluntary participation in research studies. Lastly, participants in this cohort are mostly of British and Irish ancestries, have higher-than-average IQ scores and are, on average, from families with an above-average socio-economic status. Therefore, once again, these results may not generalize to the general population.

Overall, our results support the hypothesis of a general cognitive factor for which the genetic underpinnings are being measured through various proxies in GWAS studies. Additionally, we show that biological risk of mental health disorders may influence cognitive test outcomes in the general population from an early age, before the onset of any adult forms of psychopathology and may effect individual developmental trajectory.

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Author contributions

B.L.M and K.L.G designed and supervised the study. B.L.M performed the analyses, with support and input from K.L.G. and M.E.R. M.J.W., N. K.H., K.M. and N.G.M. were responsible for the cohort design, genotyping, and data acquisition, processing and quality control. B.L.M. wrote the first draft of the manuscript, and integrated input and feedback from all co-authors. All authors read and approved the final manuscript.

Data availability

Data used in this analysis and described in this article are available to all interested researchers through collaboration. Please contact the corresponding author for enquiries.

Declaration of Competing Interest

All authors report no conflicts of interest in relation with this study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.intell.2022.101680.

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