Investigating associations between genetic risk for bipolar disorder and cognitive functioning in childhood

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Abstract

Introduction

Identifying phenotypic manifestations of genetic risk for bipolar disorder (BD) in childhood could increase our understanding of aetiological mechanisms.

Aims

To examine whether BD genetic risk is associated with childhood (age 8 years) cognitive function.

Methods

Using data from the Avon Longitudinal Study of Parents and Children, we examined associations between polygenic risk scores for BD (BD-PRS) derived using Psychiatric Genomics Consortium summary data at p-thresholds (P_T) ≤ 0.01 (primary) and ≤ 0.5 (secondary) and several cognitive domains (sample sizes 5,613 to 5,936). We also examined whether associations were due to SNPs that have shared risk effects on schizophrenia (SZ).

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Results

At $P_T \leq 0.01$, the BD-PRS was associated with poorer executive functioning (ß= -0.03, 95%CI -0.06, -0.01; p=0.013), and, more weakly with poorer processing speed (ß = -0.02, 95%CI -0.05, 0.02; p=0.075). Evidence of association with both poorer processing speed (p=0.016) and performance IQ (p=0.018) was stronger at $P_T \leq 0.5$. Associations with performance IQ and processing speed were primarily driven by genetic effects that are shared with SZ risk, but there was some evidence of bipolar-specific genetic effects on childhood executive functioning.

Limitations

The BD-PRS still explains only a small proportion of the variance for BD which will have reduced power to detect associations.

Conclusions

Genetic risk for BD manifests as impaired cognition in childhood, and this is driven by risk SNPs that are also shared with SZ genetic risk. Further elucidation of which cognitive domains are most affected by genetic risk for BD could help understanding of aetiology and improve prediction of BD.

Key words ALSPAC, Polygenic Risk Score, Bipolar Disorder, Genetics, Cognition

1. Introduction

Cognitive deficits in childhood have been identified as a possible precursor of BD in both familial high-risk and cohort studies (Bora et al., 2017; Bora and Ozerdem, 2017). However, unlike in schizophrenia (SZ), it is unclear whether deficits are present in the premorbid phase of those who eventually go on to develop BD (Bortolato et al., 2015; Martino et al., 2015). A number of studies suggest equivocal (Kendler et al., 2016; Zammit et al., 2004) or higher cognitive abilities and scholastic achievement in those who develop BD compared to controls (Gale et al., 2013; MacCabe et al., 2010), whilst others report deficits (Meyer et al., 2004; Sharma et al., 2017). It is possible that the relationship between cognitive ability and BD is non-linear, with increased risk of BD being present both in those with lower, and those with higher than average cognitive ability (Kendler et al., 2016).

Approximately 40-60% of adults with BD exhibit cognitive deficits which appear to be independent of mood state (Arts et al., 2008; Bora et al., 2009). Several meta-analyses in adults with BD have found impairments in intelligence quotient (IQ), processing speed, working memory, problem solving, verbal learning, visual learning, executive functioning, and social cognition (Bora and Ozerdem, 2017; Bora et al., 2009; Bortolato et al., 2015).

In contrast to SZ, there is no consensus on the optimal assessment of cognition in BD. However, the International society for BD have suggested using the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) consensus cognitive battery (MCCB) (Yatham et al., 2010) that was developed for assessing cognitive functioning in SZ (Marder and Fenton, 2004), and this has now been used by a number of studies examining cognition in BD (Bo et al., 2017; Sperry et al., 2015).

Twin, adoption and molecular genetic studies suggest that BD is a highly heritable disorder, with heritability estimates ranging between 60-85% (Barnett and Smoller, 2009). Through genome wide association studies (GWAS), single nucleotide polymorphisms (SNPs) occurring more frequently in BD cases relative to controls

have been identified (Sklar et al., 2011; Stahl et al., 2019). On an individual level, risk SNPs typically have small effects on disease risk. However, by summing trait-associated alleles across many genetic loci into a polygenic risk score (PRS), a greater proportion of genetic variation for BD can be explained (approximately 4% on the liability scale in a recent GWAS) (Stahl et al., 2019). Using this approach it is then possible to examine the effect of multiple disease-risk SNPs on phenotypes in other samples (Cross-Disorder Group of the Psychiatric Genomics, 2013; Purcell et al., 2009).

There is a limited understanding of how genetic risk for BD is manifest during childhood/adolescence in the general population, as most studies have relied on studying relatively small numbers of offspring of adults with BD to characterize genetically high-risk individuals (de la Serna et al., 2017; Nurnberger et al., 2011). To date, only one study has assessed the associations between a BD-PRS and cognitive measures in childhood in the general population. The authors found no association between a BD-PRS and social cognition (Coleman et al., 2017).

In this study, we therefore examine whether genetic risk for BD, using a BD-PRS, is associated with measures of IQ, processing speed, working memory, problem solving, executive function, attention, verbal learning, and emotion recognition during childhood in a large general population birth cohort. We also examine the extent to which any associations with cognitive deficits are due to risk alleles for BD that overlap with SZ given the high genetic correlation between these two disorders (Bulik-Sullivan et al., 2015).

2. Methods

2.1 Participants

We use data from the Avon Longitudinal Study of Parents and Children (ALSPAC) that recruited expectant mothers in the South West of England (Avon) with an expected delivery date between 1st April 1991 and 31st December 1992. The initial cohort contained 14,062 live births (Boyd et al., 2013; Fraser et al., 2013), and when the oldest children were age 7 years, any eligible children who did not join the study were invited. The parents and their children have been followed up regularly since then (see www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/ for details of data collected). Informed consent for the use of data collected via questionnaires and clinics was obtained from the participants following the recommendations of the ALSPAC Ethics and Law Committee and Local Research Ethics Committees at the time (http://www.bristol.ac.uk/alspac/researchers/research-ethics/).

2.2 Cognitive assessments

The cognitive domains we assessed in this study (IQ, processing speed, working memory, problem solving, attention, executive function, verbal learning, and social cognition) were selected *a priori* based on the literature of cognitive deficits in people with BD. These measures cover most of the domains described in the MCCB, although they do not map precisely onto them. All cognitive measures were assessed at age 8 years, and all cognitive domain scores were re-coded where needed so that higher scores always reflect better cognitive performance.

The Wechsler Intelligence Scale - III (WISC-III) (Wechsler et al., 1992) was used to assess the following cognitive domains:

General intelligence: We examined associations with Verbal IQ (VIQ) (derived from the information, similarities, arithmetic, vocabulary, comprehension, and forward and backward digit span subtests), Performance IQ (PIQ) (derived from the picture

completion, picture arrangement, block design, coding and object assembly subtests), and Total IQ (TIQ) (VIQ and PIQ combined) scores.

Processing speed: This was assessed using the coding subtest of the WISC-III which required the children to place the correct symbol above each number as quickly as possible within a set time period.

Working memory: This was assessed using the Freedom From Distractibility index score that combined scores from the arithmetic subtest (which required the children to solve mathematical problems without the use of pen and paper), and the digit span task (which required the children to repeat lists of numbers of increasing length in chronological and reverse order).

Problem solving: The block design subtest of the WISC-III was used to assess problem solving. The children were required to copy specific patterns of blocks seen on a picture and replicate these patterns using real blocks.

Other cognitive domains assessed included:

Executive function: This was assessed using the opposite world's task from the Test of Everyday Attention for Children (TEACh) (Robertson et al., 1996), whereby the children were presented with a number (either 1 or 2), and required to verbalise the non-presented number as quickly as possible.

Attention: This was assessed using the sky search task from the TEACh. The task required the children to distinguish identical from non-identical spaceships and draw a circle around only identical spaceships. The score was calculated as the time to identify all identical spaceships minus the time taken for the child to circle all pairs when only identical pairs were presented.

Verbal learning: This was assessed using the nonword repetition task from the Children's Test of Nonword Repetition (CTNWR) (Gathercole and Adams, 1994).

The task required the child to listen to 12 nonsense words and repeat each word back.

Emotion recognition: This was assessed using the Diagnostic Analysis of Nonverbal Accuracy (DANVA) (Nowicki and Duke, 1994). Children were presented with 24 faces representing emotions of happiness, sadness, fear or anger, and were required to make judgements and verbalise their interpretation of the emotion being shown on the screen. As a measure of social cognition, a total emotion errors score was derived by summing the errors on each of the emotions.

2.3 Genetic data in ALSPAC

Genetic data from 9,912 participants were obtained using the genome wide single-nucleotide polymorphism genotyping platform (HumanHap550-Quad; Illumina). Following quality control, imputation, and restriction to 1 young person per family, genetic data were available on 8,230 individuals (see Supplementary methods available online for more detail). Consent for biological samples has been collected in accordance with the Human Tissue Act (2004).

Prior to construction of the PRS, single nucleotide polymorphisms (SNPs) were removed from the analysis if they had a minor allele frequency (MAF) of <0.01, their imputation quality (INFO) score was <0.8, if there was a mismatch of alleles between the GWAS summary statistics and ALSPAC, and if there were any palindromic SNPs.

2.4 Construction of the Polygenic Risk Scores (PRS)

Using summary statistics from the second PGC-BD GWAS (20,352 BD cases and 31,358 controls) (Stahl et al., 2019), second PGC SZ GWAS (n = 36,989 cases and 113,075 controls) (Ripke et al., 2014), and the second SZvsBD GWAS (20,129 BD cases and 33,426 SZ cases) (Ruderfer et al., 2018), polygenic risk scores were created for each individual in ALSPAC.

Using PLINK v1.9, SNPs were linkage disequilibrium (LD) clumped using the --clump command at r^2 <0.2 within 1MB windows. For our primary analyses we derived a PRS using SNPs with a P_T≤0.01, as this is the threshold which maximally captured BD liability in the second PGC-BD GWAS (Stahl et al., 2019). However, as a secondary analysis, we also examined associations between a BD-PRS and cognitive domains at a less stringent P_T≤0.5.

For the SZ PRS, we retained SNPs with a P_T≤0.05, as this is the threshold which maximally captures SZ liability (Ripke et al., 2014), and for the SZvsBD PRS, we used SNPs with a P_T≤0.5 (Ruderfer et al., 2018).

To generate a PRS for each individual in ALSPAC, the --score command in PLINK was used. This score is the sum of the total number of risk alleles present for each SNP (0, 1, 2) weighted by the log of its odds ratio (OR) for BD from the second PGC-BD/SZ/SZvsBD GWASs.

2.5 Statistical analysis

Data for all cognitive tasks were standardized, and individuals with scores >3 standard deviations from the mean were omitted. Linear regression was used to determine associations between the BD-PRS and continuous outcomes. These results are presented as beta coefficients per standard deviation (SD) increase in PRS. The residuals for all outcomes were normally distributed. We tested for quadratic effects of the BD-PRS by inclusion of quadratic terms in the models, with p-values derived from likelihood ratio tests comparing models with linear and quadratic terms to models with linear terms only. As a more explicit test of whether both higher and lower genetic risk for BD is associated with cognitive performance, we also derived tertiles of the BD-PRS, and compared cognitive performance in those with higher/lower BD-PRS compared to the middle (reference category) tertile. To help address the issue of multiple testing, we also used a multivariate approach in which all cognitive domain outcomes were included in a single model, with a single p-value reported that tests the null hypothesis that the associations between the BD-PRS and cognitive outcomes are equal to 0.

For the strongest association(s), we used three approaches to determine the extent to which the association between genetic risk for BD and cognitive performance was due to risk alleles for BD that are also risk alleles for SZ:

1. First, we used a multivariable model to adjust for the SZ-PRS to determine the extent to which the effect of the BD-PRS is due to shared effects with SZ.
2. Second, we conducted a principal components analysis (PCA) to obtain 2 orthogonal factors that described: i) shared variance (i.e. what is similar genetically) between the BD-PRS and SZ-PRS, and ii) non-shared variance (what is genetically different) between the two risk scores. From herein, the former will be referred to as the shared component and the latter as the difference component.
3. Third, we used summary statistics from the second PGC GWAS of SZ cases vs BD cases to generate a PRS to determine whether common genetic variants associated with increased risk of being a SZ case relative to a BD case were associated with cognition. From herein, this PRS will be referred to as the SZvsBD PRS.

Whilst genetic variation is often associated with geographical and historical populations, the ALSPAC sample has been shown to be homogeneous with no significant population stratification, and genome-wide analyses of phenotypes indicate a low lambda (Martin et al., 2015; Zammit et al., 2014). Therefore, in our analyses, we have not adjusted for population stratification using PCA.

Data were analysed using STATA statistical software version 14.1 SE (StataCorp LP).

3. Results

3.1 Sample characteristics

Of the 8,230 ALSAPC individuals whose genetic data passed quality control checks (51.2% male), 6,555 to 7,405 participated in cognitive assessments at age 8 years (ST1). Cognitive domains assessed using the WISC-III were the most strongly correlated measures (correlations ranged between 0.25 and 0.89), with other cognitive domain measures showing weaker correlations (correlations ranged from 0.08 to 0.38) (see ST2).

Associations between the BD-PRS at both P_T's and cognitive domains are shown in Figure 1, ST3 and ST4.

3.2.1 IQ

Using our primary $P_T \leq 0.01$, there was little or no evidence that higher genetic risk for BD was associated with PIQ (p=0.204), VIQ (p=0.922) or TIQ (p=0.485) (ST3). However, there was some weak evidence to support quadratic effects of BD-PRS on both PIQ (p=0.066) and TIQ (p=0.077), but not for VIQ (p=0.229), indicating that any association is driven primarily by those at the higher end of the spectrum of genetic (ST5).

At the less stringent $P_T \leq 0.5$, there was evidence that the BD-PRS was associated with poorer PIQ (β= -0.03, 95%CI -0.06, -0.01; p=0.018), but not with VIQ (p=0.858) or TIQ (p=0.147) (ST4). Similar to the findings at the more stringent P_T, there was weak evidence to support quadratic effects of the BD-PRS on both PIQ (p=0.063) and TIQ (p=0.075), but not VIQ (p=0.229), again providing evidence that the association is primarily driven by those at the higher end of the spectrum of genetic risk (ST6).

3.2.2 Processing speed

At our primary P_T, we found weak evidence of association between the BD-PRS and poorer processing speed (ß = -0.02, 95%CI -0.05, 0.02; p=0.075), and no evidence of a quadratic effect of the BD-PRS (p=0.961).

There was stronger evidence for an association with processing speed at our secondary P_T (ß = -0.03, 95%CI -0.04, -0.01; p=0.016), and no evidence to support a quadratic effect of the BD-PRS (p=0.943).

3.2.3 Working memory

We found no evidence of association between higher genetic risk for BD and working memory at both our primary (p=0.959) or secondary (p=0.329) P_T, and no evidence of a quadratic effect at either P_T (both p=0.638).

3.2.4 Problem solving

A higher BD-PRS was not associated with problem solving at both the primary (p=0.513) and secondary (p=0.570) P_T's. Similarly, there was no evidence of a quadratic at either P_T (both p>0.289).

3.3.1 Executive function

The BD-PRS was associated with poorer executive functioning at both P_T's (β= -0.03, 95%CI -0.06, -0.01; p=0.013) and (β= -0.03, 95%CI -0.06, -0.01; p=0.014) (ST4). There was weak evidence of a quadratic effect of the BD-PRS at both primary (p=0.089) and secondary (p=0.083) P_T's.

3.3.2 Attention

There was little evidence of association between the BD-PRS and attention at either P_T (both p>0.115) and no evidence of a quadratic effect (both p>0.466).

3.3 Verbal learning

We found little evidence of association between the BD-PRS and verbal learning at either P_T (both p>0.173), or evidence of a quadratic effect (both p>0.284).

3.4 Emotion recognition

There was little evidence of association between the BD-PRS and greater number of errors on the total emotion score at either P_T (both p>0.134) or in recognizing happy, sad, angry or fearful faces (all p>0.116) (ST7), and no evidence of quadratic effects (all p>0.758).

3.5 Tertiles of genetic risk and associations with cognitive outcomes

We examined the association between tertiles of genetic risk and our cognitive outcomes to help clarify the non-linear patterns of association identified by evidence of quadratic effects as described above. Analyses using our primary P_T (ST8 and SF1), and particularly using our secondary P_T, showed evidence that the associations between genetic risk for BD and performance IQ, total IQ and executive function were driven by those in the highest genetic risk tertile, whilst those in the lowest tertile had similar scores on these tasks to those in the middle tertile (ST9 and SF2). In contrast, the association with processing speed was observed across the whole spectrum of genetic risk, with those in the lowest tertile having better, and those in the highest tertile worse, performance compared to the middle tertile. A pattern of poorer performance on emotion recognition both in those with higher and in those with lower genetic risk compared to the middle tertile was not consistent with the model that included quadratic terms (ST6), and nor was it robust when changing the cut-off for genetic risk to examine patters across quartiles or quintiles.

3.6 Multivariate analysis

There was little evidence to support an association between the genetic risk scores and cognitive outcomes at either the primary P_T (p=0.116) or secondary P_T (p=0.184) when examining all cognitive domain associations within a multivariate model to help address multiple testing.

3.7 Shared and non-shared effects of BD-PRS and SZ-PRS on cognition

In the unadjusted (univariable) models, evidence of association with performance IQ and processing speed was stronger for the SZ-PRS than for the BD-PRS, whereas that for executive function was stronger for the BD-PRS. After adjusting for the SZ-PRS in the multivariable model, effect sizes for the association between the BD-PRS and performance IQ and processing speed weakened substantially, though the association with executive function remained relatively unchanged (Table 1).

Following the principal components analysis of the BD-PRS and SZ-PRS, we found strong evidence of association between the shared component and performance IQ (ß = -0.03, 95%CI -0.06, -0.01; p=0.004), processing speed (ß = -0.04, 95%CI -0.06, -0.01; p = 0.001), and more weakly with executive function (ß = -0.03, 95%CI -0.04, 0.00; p=0.027), but little evidence of association between the difference component and these measures (Table 2).

Finally, there was strong evidence of association between the SZvsBD PRS and performance IQ (ß= -0.03, 95%CI -0.06, -0.01; p=0.009), but no evidence of association with processing speed or executive function (both p>0.499) (Table 1).

4. Discussion

4.1 Summary of findings

Using a large population-based cohort study, we found consistent evidence that higher genetic risk for BD in healthy children from the general population at age 8 years was associated with impaired executive functioning, and more weakly with poorer performance IQ and poorer processing speed. However, there was no or little evidence of association with verbal IQ, attention, working memory, verbal learning or social cognition. The associations between genetic risk for BD and both performance IQ and processing speed seem to be primarily due to the genetic component that is shared with that for SZ risk, rather than genetic effects that differ across these disorders. However, executive functioning deficits appear to be associated with risk alleles for BD that are not shared with SZ.

4.2 Interpreting findings in the context of previous work

Epidemiological studies examining associations between cognition and BD suggest that cognitive deficits occur in between 40-60% of adults with BD (Bora, 2018; Szmulewicz et al., 2015). Whilst the cognitive deficits in adults with BD compared to adults with SZ are qualitatively similar, the severity of these deficits is typically less in those with BD (Bortolato et al., 2015). Nevertheless, these deficits are still of importance as they contribute to the level of functional impairment and impact on quality of life for individuals with BD (Bora, 2016).

Our results for IQ implicate effects of genetic risk for BD on fluid but not crystalised intelligence, a finding similar to that in SZ (Hubbard et al., 2016). Our findings also suggest that genetic effects of BD on fluid intelligence is driven by risk SNPs that are shared between the BD-PRS and SZ-PRS. with a substantially greater proportion of the variance in PIQ explained by such shared SNPs or SNPs that are specific to SZ, rather than ones that have risk effects specifically on BD. This is consistent with the observation that IQ deficits are greater in adults with SZ compared to adults with BD (Bora and Ozerdem, 2017), and that it is the severity rather than the profile of

cognitive deficits that differentiates these two disorders in adulthood (Vöhringer et al., 2013). Furthermore, greater severity of IQ deficits in people with BD has been linked to the presence of psychotic symptoms (McCarthy et al., 2016; Tsitsipa and Fountoulakis, 2015), whilst individuals with BD who had a manic psychosis had higher SZ-PRS scores compared to those with BD and no history of psychosis (Markota et al., 2018). These studies, in conjunction with our findings, suggest that both cognitive deficits and presence of psychotic phenomena in people with BD are primarily driven by risk SNPs that are shared across BD and SZ.

We previously reported that higher IQ was associated with greater hypomania features, assessed using the Hypomania Checklist-32 (HCL-32), in young adults in the ALSPAC cohort (Smith et al., 2015). This does not appear to be consistent with our findings for BD genetic risk in this study. It is possible that hypomanic features, as captured by measures such as the HCL-32 in community samples, do not accurately index individuals with high propensity to develop BD. Consistent with this thesis, we found little evidence that the BD-PRS was associated with hypomania scores in ALSPAC, although there was some evidence of association with binary measures of hypomania when these were defined by cut-offs at higher extremes of the score (Mistry et al., 2018).

The BD-PRS was more strongly associated with executive function than the SZ-PRS was in our study, and this didn't change when adjusting for the SZ-PRS. Executive functioning is often used as a general umbrella term that captures 3 core domains: response inhibition, interference control, and cognitive flexibility (Diamond, 2013). Meta-analyses from systematic reviews show medium to large effect size deficits in executive functioning in both SZ (Fioravanti et al., 2012) and BD cases (Torres et al., 2007) as well as their first-degree relatives (Bortolato et al., 2015). The strongest evidence of deficits in executive functioning in people with SZ described in that review was within the domain of cognitive flexibility, whereas the review of BD described deficits across all 3 domains. As the Opposite World's task that we used to assess executive functioning in our study primarily assesses response inhibition, this might explain why we observed a stronger association with the BD-PRS than the SZ-PRS. Whilst deficits in different aspects of executive functioning might be more strongly related to genetic risk for BD than for SZ (or vice versa), and one study

reported a BD-specific association with response inhibition compared to other psychotic disorders (Ethridge et al., 2014), deficits in response inhibition have also been described in people with SZ (Ettinger et al., 2018).

We found some evidence of association between the BD-PRS and poorer processing speed, which was stronger at the less stringent P_T. Moreover, when examining associations whilst adjusting for the SZ-PRS, associations attenuated substantially. Processing speed is often reported as one of the most impaired domains in adults with BD, evidenced by large effect size from meta-analysis (Bora, 2018; Bora et al., 2009), and evidence in young people at high familial risk of BD (Bora et al., 2017). In our study, children within the general population at high genetic risk for BD do not appear to be as impaired in this cognitive domain as they are in executive functioning. It is possible however, that deficits in processing speed develop at a later time point compared to executive functioning as maturation of different cognitive processes can occur at different stages of development (Kail, 1991; Luna et al., 2004).

A previous study in the ALSPAC sample, but using the smaller PGC-1-BD GWAS to derive the PRS, also found no evidence of association between the BD-PRS and emotion recognition (Coleman et al., 2017). Our results, using a more powerful BD-PRS, similarly provides little evidence for such a relationship. It is possible that other neurocognitive domains mature at an earlier time point in development, and that in general, social cognition measures develop at a later time point (Chronaki et al., 2015). It is possible therefore that deficits in relation to genetic risk for BD become manifest only later in adolescent or early adult development. Furthermore, whilst deficits in social cognition more broadly are reported in the literature in adults with BD, deficits may be more pronounced for Theory of Mind rather than emotion recognition, which was the only measure of social cognition that we were able to examine here (Mitchell and Young, 2016).

4.3 Strengths and limitations

This study has a number of strengths. Firstly, we have used the most recent and largest BD GWAS (Stahl et al., 2019) and the most recent SZvsBD GWAS (Ruderfer et al., 2018) as training sets from which to derive the PRSs, thus maximising power and minimising measurement error (Dudbridge, 2013). Second, we have used a large, well characterized general population-based sample for analyzing neurocognitive phenotypes at an early age, well before onset of BD. This means we can be confident the associations are not biased by presence of cognitive deficits arising as a result of BD or treatment effects. Third, we used well validated measures for assessing our neurocognitive phenotypes, reducing information bias in our results.

However, there are also several limitations. Firstly, as with any longitudinal study, there was a large degree of attrition which might have led to selection bias. A previous study reported that genetic risk for SZ was associated with non-participation by both mothers and children in the ALSPAC sample (Martin et al., 2016), whilst lower cognitive ability is also associated with greater attrition in ALSPAC (Boyd et al., 2013). We cannot rule out the possibility therefore of selection bias affecting the validity of our results, although such attrition generally has a minimal impact on estimates of association in contrast to estimates of prevalence (Wolke et al., 2009).

Second, we were unable to examine all aspects of cognitive function due to the lack of availability of some measures in the ALSPAC sample, although we nevertheless assessed multiple cognitive domains that provided a reasonably comprehensive coverage of cognitive function.

Third, the PRS approach captures information from common variants conferring risk for BD, but does not capture the effects of rare variants. This means our results only reflect common variant influences on childhood neurocognitive outcomes rather than the effects of all genetic risk.

Fourth, the assessment of multiple cognitive domain outcomes may lead to an increase in type I error. Whilst the cognitive domains we examined were selected *a priori* based on prior literature, the strength of evidence of the associations we report should be interpreted in the context of the study limitations, including the testing of multiple cognitive outcomes. In our multivariate analysis there was little evidence to support an association between genetic risk scores and cognitive outcomes, and replication of our findings in other large population-based samples is required.

Fifth, we did not have data on whether parents of the participants had bipolar disorder. However, given the low lifetime risk of bipolar disorder it seems unlikely that this would have had any significant impact on our results.

Finally, as the BD-PRS only explains a small proportion of variance in BD, the lack of evidence of association we observed for some cognitive measures might result from our analyses being under-powered to detect smaller effect sizes, despite our use of the largest BD GWAS to date to derive the genetic risk score.

4.4 Implications

We believe this work has several implications. The severity of deficits in cognitive domains of performance IQ and processing speed are similar to those observed in children at high genetic risk for SZ in the general population (Hubbard et al., 2016). Our evidence of cognitive deficits in genetically higher risk children in the general population supports other evidence suggesting that BD, like SZ, should also be considered as being on the neurodevelopmental spectrum (Fioravanti et al., 2012), and this is particularly so for more severe forms of BD characterized by psychotic symptoms in childhood (Arango et al., 2014).

Overall, our findings are more consistent with epidemiological studies that have reported an increased risk of BD in those with lower cognitive ability in childhood (Meyer et al., 2004; Sharma et al., 2017) than studies reporting increased BD risk in those with higher cognitive ability (Gale et al., 2013; MacCabe et al., 2010). Nevertheless, there is some evidence that risk alleles for BD may include both

alleles that increase, and some that decrease, cognitive ability (Smeland et al., 2019). This could lead to low levels of genetic correlation between BD and cognition and hence less consistent evidence of association between BD genetic risk and cognition compared to SZ genetic risk, as well as less consistent evidence of association between childhood cognition and BD compared to that for SZ.

4.5 Conclusions

Within this study of children from a prospective population-based birth cohort, we found associations between increased genetic risk for BD and poorer executive functioning, performance IQ and processing speed, but less consistent/no evidence of association with other cognitive domains. Our results for performance IQ and processing speed suggest that these associations appear to be driven primarily by genetic risk that is shared between BD and SZ, and those for executive functioning driven primarily by genetic risk that is independent of SZ. Nevertheless, using the largest GWAS to derive our polygenic risk scores still explains little of the variance in these cognitive phenotypes.

Further work using both population-based longitudinal studies and clinical samples are required to determine the cognitive profiles of those at high genetic risk of BD, to inform studies of prediction, improve detection, and facilitate early intervention where appropriate.

5. Funding

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