

Unique prediction of developmental psychopathology from genetic and familial risk

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Background: Early detection is critical for easing the rising burden of psychiatric disorders. However, the specificity of psychopathological measurements and genetic predictors is unclear among youth. **Methods:** We measured associations between genetic risk for psychopathology (polygenic risk scores (PRS) and family history (FH) measures) and a wide range of behavioral measures in a large sample ($n = 5,204$) of early adolescent participants (9–11 years) from the Adolescent Brain and Cognitive Development StudySM. Associations were measured both with and without accounting for shared variance across measures of genetic risk. **Results:** When controlling for genetic risk for other psychiatric disorders, polygenic risk for problematic opioid use (POU) is uniquely associated with lower behavioral inhibition. Attention deficit hyperactivity disorder (ADHD), depression (DEP), and attempted suicide (SUIC) PRS shared many significant associations with externalizing, internalizing, and psychosis-related behaviors. However, when accounting for all measures of genetic and familial risk, these PRS also showed clear, unique patterns of association. Polygenic risk for ASD, BIP, and SCZ, and attempted suicide uniquely predicted variability in cognitive performance. FH accounted for unique variability in behavior above and beyond PRS and vice versa, with FH measures explaining a greater proportion of unique variability compared to the PRS. **Conclusion:** Our results indicate that, among youth, many behaviors show shared genetic influences; however, there is also specificity in the profile of emerging psychopathologies for individuals with high genetic risk for particular disorders. This may be useful for quantifying early, differential risk for psychopathology in development. **Keywords:** Genetics; behavioural; family history; psychopathology.

Introduction

Psychiatric disorders place a huge burden on those affected, their families, and society. Identifying risk for psychopathology in developmental samples may offer an opportunity for early detection and intervention. Nearly all psychiatric disorders have a heritable component, with twin heritability estimates ranging from 33% to 84% across affective, psychotic, and developmental disorders (Kendler, 2001). Lifetime prevalence rates of several disorders are higher among first-degree biological relatives of individuals with a psychiatric diagnosis (Kendler, Davis, & Kessler, 1997). Therefore, estimating genetic liability for psychiatric disorders presents one avenue for identifying at-risk individuals and probing differential and transdiagnostic risk factors. Here, we sought to determine: (a) if increased genetic risk within a large, typically developing sample would be associated with symptoms of psychopathology, related individual difference factors, and cognitive function; and (b) whether there was any evidence for specificity

in behavioral measures predicted by different genetic markers.

Large-sample analyses of results from genome-wide association studies (GWAS) have revealed the highly polygenic architecture of complex behavioral phenotypes, with many variants in the genome additively accounting for substantial heritability, but individually exerting only very small effects. Models using effect sizes at single nucleotide polymorphisms (SNPs) estimated from large-scale independent GWAS can be used to compute polygenic risk scores (PRS), which estimate an individual's genetic risk for a trait. Recent powerful, cross-disorder meta-analyses (Brainstorm Consortium et al., 2018; Lee et al., 2019) reveal high genetic correlation and widespread pleiotropy across psychiatric disorders, consistent with overlapping genetic architecture. Indeed, polygenic risk for depression has been shown to positively associate with childhood psychopathology across behavioral domains (Akingbuwa et al., 2020).

Family history (FH) is a clinically used factor for predicting psychiatric risk (Blacker, Racette, Sklar, & Smoller, 2010), yet there have been few direct comparisons of associations between PRS and FH of psychopathology in childhood and adolescence. SNP heritabilities (h_{SNP}^2) based on effects across the

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genome are lower than twin heritabilities, suggesting there are genetic factors driving psychiatric phenotypes which are not fully captured with common variants at current GWAS sample sizes. Indeed, FH likely reflects a complex combination of genetic and environmental factors. Due to the differential information that PRS and FH measures may provide, it is important to determine whether they explain independent or overlapping variance in developmental psychopathology and cognition. For example, in a joint model, PRS and FH of schizophrenia were shown to be independent risk factors for schizophrenia (Lu et al., 2018). Here, we aim to further understand the unique contribution of polygenic risk above and beyond FH in a typically developing sample across multiple measures of psychopathology.

For this study we used behavioral and genetic data from 9- to 11-year-old children from the Adolescent Brain and Cognitive Development (ABCD) StudySM. We generated eight PRS that were trained on large independent datasets. We used these PRS and measures of FH of psychopathology both independently and within the same models to predict a large array of both caregiver and youth-reported behaviors thought to reflect risk for developing psychiatric disorders. Measures included both dimensional and diagnostic assessments of psychopathology, individual difference measures of impulsivity and behavioral approach and inhibition, prodromal psychosis, and behaviors associated with mania and prosocial behavior. Given documented associations and genetic overlap between cognitive impairment and schizophrenia and bipolar disorder (Davies et al., 2018; Smeland et al., 2020), we additionally measured associations with cognitive measures from the NIH Toolbox®. Using this approach, we aimed to uncover variability across early signs of psychopathology that are uniquely associated with each genetic/familial predictor. This research is an essential first step in this large longitudinal study to determine whether we can identify early signs of specificity in genetic-behavior associations in development, which can then be tracked to determine their potential predictive power for future diagnoses.

Methods

Sample

The ABCD study is a longitudinal study across 21 data acquisition sites in the United States following 11,880 children starting at 9–11 years. This study uses baseline data from the NIMH Data Archive ABCD Collection Release 2.0.1 (DOI: 10.15154/1504041). The ABCD cohort was recruited to ensure the sample was as close to national representative as possible, and therefore exhibits large sociodemographic diversity (Garavan et al., 2018). There is an embedded twin cohort and many siblings. As the chosen PRS were trained predominantly on European individuals, the main associations in this study were conducted in a European ancestry sample ($n = 5,204$). Supplementary analyses were conducted on those with non-European ancestry ($n = 3,964$) and the full sample

($n = 9,168$). Table S1 outlines the demographics of the three samples.

ABCD baseline mental health battery

The Mental Health Battery in ABCD is an extensive battery of questionnaires and semi-structured interviews assessing diagnostic and dimensional measures of psychopathology and individual difference factors. Both youth and their caregivers provided responses at baseline using divergent and overlapping measures. The motivation behind selecting these assessments is outlined elsewhere (Barch et al., 2018). Table S2 lists variables used from the ABCD public release.

Diagnostic assessments

Kiddie schedule for affective disorders and schizophrenia (KSADS). Participants completed a semi-structured, self-administered, computerized version of the validated and reliable KSADS-5 (Kaufman et al., 1997). Research Assistants had extensive training to support youth completing this assessment. Caregivers and youth completed modules on depression, bipolar disorder, generalized anxiety disorder, social anxiety disorder, suicidality, and sleep. Only caregivers completed psychosis, obsessive-compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), conduct disorder (CD), panic disorder, and eating disorders modules. Symptom scores were the sum of symptoms endorsed in each module. The total symptom score was a sum across modules.

Dimensional assessments

Child Behavior Checklist (CBCL). Caregiver-reported CBCL (Achenbach, 2009) has eight syndrome scales: anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems, rule-breaking behavior, and aggressive behavior, and a total problems score.

General behavior inventory. Caregiver-report 10-item Mania Scale (Youngstrom, Frazier, Demeter, Calabrese, & Findling, 2008) was derived from the 73-item General Behavior Inventory (PGBI) for Children and Adolescents (Youngstrom, Findling, Danielson, & Calabrese, 2001).

Prosocial behavior survey. Caregivers and youth were asked three questions about how helpful and considerate the youth was in general, with summed scores for both caregiver and youth.

Prodromal questionnaire brief (PQ-B). Youth-report measure, modified for use in children in our age range, consisted of a 21-item scale assessing subclinical manifestations of psychosis (Ising et al., 2012; Karcher et al., 2018). The prodromal psychosis severity score is the sum of the number of symptoms endorsed weighted by how distressing the symptoms were.

UPPS-P for children short scale. Youth-report impulsive behavior scale, which includes five subscales that measure four factors of impulsivity: positive and negative urgency, lack of perseverance, premeditation, and sensation seeking (Whiteside, Lynam, Miller, & Reynolds, 2005).

Behavioral inhibition and behavioral activation (BISBAS scale). Youth-report measure of approach and

avoidance behaviors (Carver & White, 1994; Jorm et al., 1998) that produces scores for a drive, fun-seeking, reward responsiveness, and behavioral inhibition.

NIH toolbox cognition battery®. NIH toolbox cognition battery is the widely used battery of cognitive tests that measures a range of different cognitive domains (Gershon et al., 2013; Luciana et al., 2018; Palmer et al., 2021). We analyzed the uncorrected composite scores broadly measuring fluid and crystallized intelligence that are generated from the NIH Toolbox® and have validated against gold-standard measures (Akshoomoff et al., 2013; Heaton et al., 2014). The fluid composite score includes performance on the flanker task, picture sequence memory task, list sorting memory task, pattern comparison processing speed, and dimensional change card sort task. The crystallized composite score includes performance on the oral reading recognition task and picture vocabulary task.

Genetic and familial measures

Polygenic risk scores (PRS). PRS were estimated from summary statistics for ADHD (Demontis et al., 2019), autism spectrum disorder (ASD) (Grove et al., 2019), bipolar disorder (BIP) (Mullins et al., 2021), schizophrenia (SCZ) (The Schizophrenia Working Group of the Psychiatric Genomics Consortium et al., 2020), depression (DEP) (Howard et al., 2019), problematic opioid use (POU) (Sanchez-Roige et al., 2021), attempted suicide (SUIC) (Mullins et al., 2022), and psychotic experiences (PSYEXP) (Legge et al., 2019). Although we pruned SNPs, the results in the main text result do not apply *p*-value thresholds when calculating PRS in an attempt to guard against overfitting. Figures S1–S6 shows these main results are consistent and often outperform using more stringent *p*-value thresholds. In supplementary analysis, we also present results controlling for polygenic prediction of intelligence (Savage et al., 2018). Additional details of preprocessing genetic data and PRS estimation are in the Appendix S1 of Supporting Information.

Family history assessment. Caregivers were given a questionnaire asking about family history (FH) of 10 behaviors associated with psychopathology: alcohol use; drug use; depression; mania; psychosis; conduct problems; nerves; seen a therapist; hospitalized for a mental health problem; and suicide. For each question, the caregivers were asked if any blood relative had experienced any of the described behaviors (see Table S3). Importantly, these variables do not indicate clinical diagnoses of these behaviors.

Statistical analysis

Generalized linear models (GLMs) were fit to measure the association between i) each of the 41 behavioral phenotypes and ii) FH and PRS. Univariate models included one independent variable of interest (PRS or FH) in each model (i.e., $behavior \sim PRS_i + covariates$ or $behavior \sim FH_i + covariates$). Multivariable models included all PRS and FH measures in the same model (i.e., $behavior \sim PRS_1 + PRS_2 + \dots + FH_1 + FH_2 + \dots + covariates$). Fixed nuisance covariates included age, sex, top 10 genetic principal components, household income, highest parental education, and data collection site. ΔR^2 was reported as change in R^2 from a reduced model (covariates only) to a full model (including the predictor of interest) (Nagelkerke, 1991). Supplementary analyses were conducted without controlling for socioeconomic status (SES) – that is, household income and parental education. Family relatedness was controlled for by taking median effect across 100 subsamples of singletons. False discovery (FDR) rate correction was used to determine significance and derive adjusted *p*-values (*p*-adj).

Although the main results are presented in the European ancestry sample, we also show results from the full and non-European ancestry samples in Figure S7. Figure S8 displays the discordance between European and non-European ancestry associations motivating our decision to present the European ancestry results in the main text. Additional models were implemented to measure pairwise spearman correlations across all dependent variables (DVs) and independent variables (IVs) in the European ancestry sample after residualizing for the covariates of no interest (Figures S9 and S10). Behavioral measures were categorized by the behavioral domain (see Table S2) to determine whether associations with each genetic predictor were enriched for measures within domains. See the Supporting Information for further details of statistical analysis.

Results

Unique behavioral associations with PRS across domains

For univariate models (measuring the association between each PRS and each behavior), controlling for SES, the ADHD, DEP, and SUIC PRS showed the largest and greatest number of associations across internalizing, externalizing, and psychosis-related measures (Figure 1, left panel). The ADHD PRS was significantly associated with CBCL rule-breaking ($\Delta R^2=0.0071$, *p*-adj = 6.8×10^{-6}), inattentive ($\Delta R^2=0.0063$, *p*-adj = 7.3×10^{-8}), aggressive ($\Delta R^2=0.0031$, *p*-adj = 6.8×10^{-4}) behaviors, prodromal psychosis severity ($\Delta R^2=0.0063$, *p*-adj = 3.0×10^{-5}), caregiver-reported KSADS oppositional/conduct disorder ($\Delta R^2=0.0041$, *p*-adj = 1.3×10^{-4}), and ADHD ($\Delta R^2=0.0030$, *p*-adj = 1.2×10^{-3}) symptoms, followed by multiple youth- and caregiver-reported measures of impulsivity, depression, and suicidality symptoms, bipolar- and psychosis-related measures, and developmental social problems. The DEP PRS showed strongest associations with CBCL somatic complaints ($\Delta R^2=0.0053$, *p*-adj = 3.3×10^{-6}), KSADS symptoms of oppositional/conduct disorder ($\Delta R^2=0.0039$, *p*-adj = 1.9×10^{-4}), and CBCL anxious/depressive ($\Delta R^2=0.0031$, *p*-adj = 3.2×10^{-4}), aggressive ($\Delta R^2=0.0030$, *p*-adj = 8.4×10^{-4}), and rule-breaking ($\Delta R^2=0.0029$, *p*-adj = 5.7×10^{-3}) behaviors. These were followed by caregiver-reported KSADS symptoms of suicidality ($\Delta R^2=0.0027$, *p*-adj = 2.2×10^{-3}), bipolar disorder ($\Delta R^2=0.0027$, *p*-adj = 2.4×10^{-3}), and anxiety ($\Delta R^2=0.0020$, *p*-adj = 9.1×10^{-3}) and youth-reported KSADS depression symptoms ($\Delta R^2=0.0027$, *p*-adj = 2.5×10^{-3}), as well as other measures of negative urgency, developmental social problems, behavioral inhibition, and bipolar- and psychosis-related behaviors. The SUIC PRS showed the strongest significant associations with CBCL rule breaking ($\Delta R^2=0.0065$, *p*-adj = 1.7×10^{-5}), aggression ($\Delta R^2=0.0035$, *p*-adj = 2.6×10^{-4}), prodromal psychosis severity ($\Delta R^2=0.0041$, *p*-adj = 1.0×10^{-3}), CBCL social problems ($\Delta R^2=0.0031$, *p*-adj = 2.4×10^{-3}), youth-reported depression symptoms ($\Delta R^2=0.0030$, *p*-adj = 1.3×10^{-3}), CBCL inattention ($\Delta R^2=0.0022$,

$p\text{-adj} = 2.3 \times 10^{-3}$), and CBCL thought problems ($\Delta R^2=0.0017$, $p\text{-adj} = 1.6 \times 10^{-2}$).

In addition, the ASD PRS associated with some of the same behaviors as the ADHD, DEP, and SUIC PRS, such as youth-reported KSADS depression symptoms ($\Delta R^2=0.0024$, $p\text{-adj} = 3.9 \times 10^{-3}$), suicidality symptoms ($\Delta R^2=0.0013$, $p\text{-adj} = 4.0 \times 10^{-2}$), and ADHD symptoms ($\Delta R^2=0.0014$, $p\text{-adj} = 3.7 \times 10^{-2}$), as well as CBCL inattention ($\Delta R^2=0.0016$, $p\text{-adj} = 1.0 \times 10^{-2}$). The ADHD, ASD,

DEP, and SUIC PRS were all associated with the youth-reported KSADS Total Symptoms score, and the ADHD, DEP, and SUIC PRS were also associated with the caregiver-reported CBCL Total Problems and KSADS Total Symptoms scores.

The BIP and SCZ PRS were not significantly associated with any bipolar or psychosis-related measures; however, they did significantly associate with CBCL rule breaking with a smaller effect size compared to ADHD, DEP, and SUIC (BIP:

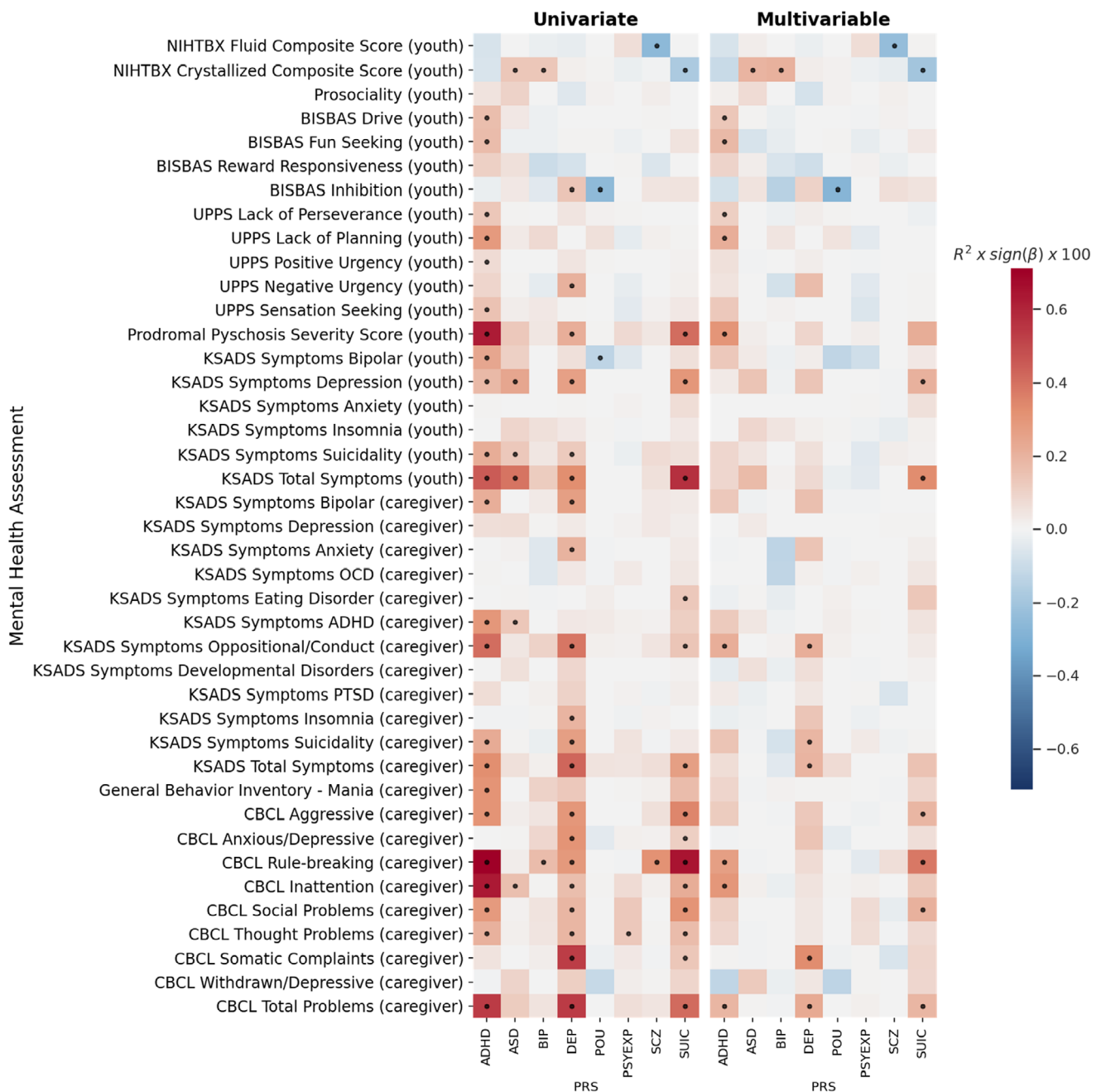


Figure 1 Univariate (left) and multivariable (right) associations for each behavior predicted by PRS. Effect sizes for each association are displayed as the partial variance explained, R^2 (as a percentage) multiplied by sign of beta coefficient (red = positive, blue = negative). Response variable for each model is shown on y-axis. In univariate models (left), only a single genetic predictor was included in each model (each cell = 1 model) – that is, $\text{behavior} \sim \text{PRS} + \text{covariates}$. In multivariable models (right), all genetic/familial predictors were included in each model including all PRS and FH measures (each row = 1 model) – that is, $\text{behavior} \sim \text{PRS}_1 + \text{PRS}_2 \dots + \text{FH}_1 + \text{FH}_2 \dots + \text{covariates}$. ADHD: Attention Deficit Hyperactivity Disorder, ASD: Autism Spectrum Disorder, BIP: Bipolar Disorder, DEP: Depression, POU: problematic Opioid Use, PSYEXP: Psychotic Experience, SCZ: Schizophrenia, SUIC: Suicide Attempt. Dots indicate FDR significant associations

$\Delta R^2=0.0017$, $p\text{-adj} = 4.0 \times 10^{-2}$; SCZ: $\Delta R^2=0.0032$, $p\text{-adj} = 3.5 \times 10^{-3}$). In contrast, the PSYEXP PRS were significantly associated with CBCL thought problems ($\Delta R^2=0.0013$, $p\text{-adj} = 3.5 \times 10^{-2}$). The POU PRS were significantly negatively associated with youth-reported behavioral inhibition ($\Delta R^2=0.0025$, $p\text{-adj} = 3.3 \times 10^{-3}$) and KSADS bipolar symptoms ($\Delta R^2=0.0013$, $p\text{-adj} = 3.9 \times 10^{-3}$).

For associations with cognitive performance, the SCZ PRS negatively associated with the fluid composite score from the NIH Toolbox® ($\Delta R^2=0.0026$, $p\text{-adj} = 3.2 \times 10^{-3}$). Whereas the BIP and ASD PRS positively associated with the crystallized composite score from the NIH Toolbox® (BIP & ASD: $\Delta R^2=0.0014$, $p\text{-adj} = 3.6 \times 10^{-2}$); and the SUIC PRS negatively associated with the crystallized composite score ($\Delta R^2=0.0018$, $p\text{-adj} = 1.7 \times 10^{-2}$).

Multivariable models determined the specificity of these associations by covarying for all PRS and FH predictors simultaneously. In these models, PRS associations were attenuated and showed greater specificity for the ADHD, DEP, and SUIC PRS (Figure 1, right panel). Each of these PRS predicted unique variability across a different pattern of externalizing, internalizing, and psychosis-related measures not predicted by other measures of genetic risk (PRS or FH). For the ASD, BIP, and SCZ PRS, only the associations with cognitive performance remained significant in the multivariable models. Controlling for an intelligence polygenic score (IPS) attenuated these cognitive associations such that they were no longer significant (Figure S11). For the POU PRS, the negative association with behavioral inhibition remained significant when controlling for other measures of genetic risk ($\Delta R^2=0.0027$, $p\text{-adj} = 1.0 \times 10^{-2}$) and the magnitude of the effect was not attenuated. The PSYEXP showed no significant associations in the multivariable models.

When not controlling for SES, behavioral associations were slightly larger and the overall pattern of associations was similar (Figure S12 and S13). However, there was an additional significant negative association between the ADHD PRS and the crystallized composite score ($\Delta R^2=0.0021$, $p\text{-adj} = 2.5 \times 10^{-2}$). Appendix S2 contains regression results from all PRS associations with behavior.

We categorized each behavior into a domain to highlight different types of behavioral measures predicted by each PRS (Figure 2; domains defined in Table S2). Across both univariate and multivariable models, the largest associations with the ADHD PRS were with externalizing and psychosis-related measures; whereas the DEP and SUIC PRS associations encompassed a mix of internalizing and externalizing measures. In multivariable models, the specificity in the unique pattern of behaviors predicted by these PRS across domains was clarified due to the removal of shared variance across the genetic predictors.

Unique behavioral associations with FH across domains

Behavioral associations with FH measures were larger than with PRS (Figure 3, left panel) in the univariate models. Given a large number of overlapping univariate associations, we focus on the associations from the multivariable models (i.e., controlling for all other FH and PRS predictors). In multivariable models, FH of conduct problems, depression, and anxiety/stress showed the largest effects with some specificity across the behavioral measures (Figure 3, right panel). FH of conduct problems significantly associated with the CBCL subscales, particularly with rule-breaking ($\Delta R^2=0.0079$, $p\text{-adj} = 2.8 \times 10^{-5}$), as well as KSADS symptoms related to both externalizing and internalizing disorders ($\Delta R^2\text{range} = 0.0022\text{--}0.0071$) and mania ($\Delta R^2=0.0055$, $p\text{-adj} = 1.1 \times 10^{-3}$). FH of depression was significantly associated with total problems scales from the CBCL ($R^2 = 0.0045$, $p\text{-adj} = 6.1 \times 10^{-4}$) and KSADS ($\Delta R^2=0.0044$, $p\text{-adj} = 6.9 \times 10^{-4}$), as well as internalizing and externalizing measures across the KSADS and CBCL ($\Delta R^2\text{range} = 0.0018\text{--}0.0039$). This pattern was similar to DEP PRS, however, unlike the DEP PRS, FH of depression was only associated with caregiver-reported measures in the multivariable models. FH of anxiety/stress showed several associations across domains with the largest effects for caregiver-reported KSADS anxiety symptoms ($\Delta R^2=0.0083$, $p\text{-adj} = 9.3 \times 10^{-7}$) and the CBCL anxious/depressive subscale ($\Delta R^2=0.0069$, $p\text{-adj} = 9.7 \times 10^{-7}$).

FH of use of professional health services was most strongly associated with CBCL somatic complaints ($\Delta R^2=0.0037$, $p\text{-adj} = 1.3 \times 10^{-3}$), thought problems ($\Delta R^2=0.0026$, $p\text{-adj} = 1.0 \times 10^{-2}$), and the total problem score ($\Delta R^2=0.0036$, $p\text{-adj} = 3.0 \times 10^{-3}$), and also showed a positive association with the crystallized composite score ($\Delta R^2=0.0027$, $p\text{-adj} = 1.1 \times 10^{-2}$). Interestingly, when controlling for all other measures of genetic risk, FH of drug and alcohol abuse was associated with differential behaviors, with FH of drug abuse explaining unique variance in CBCL rule-breaking ($\Delta R^2=0.0035$, $p\text{-adj} = 1.1 \times 10^{-2}$) and KSADS PTSD symptoms ($\Delta R^2=0.0030$, $p\text{-adj} = 8.4 \times 10^{-3}$), and FH of alcohol abuse explained unique variance in CBCL social problems ($\Delta R^2=0.0021$, $p\text{-adj} = 5.0 \times 10^{-2}$) and anxious/depressive behaviors ($\Delta R^2=0.0018$, $p\text{-adj} = 3.2 \times 10^{-2}$). FH of hospitalization showed several negative associations with caregiver-reported internalizing behaviors, which were positive in the univariate models. This sign flip of effects may be due to collinearity across the genetic risk measures (Figure S10) when used in a single model. Appendix S2 contains regression results from all FH associations with behavior.

For univariate models, the FH measures were associated with behaviors across several domains –

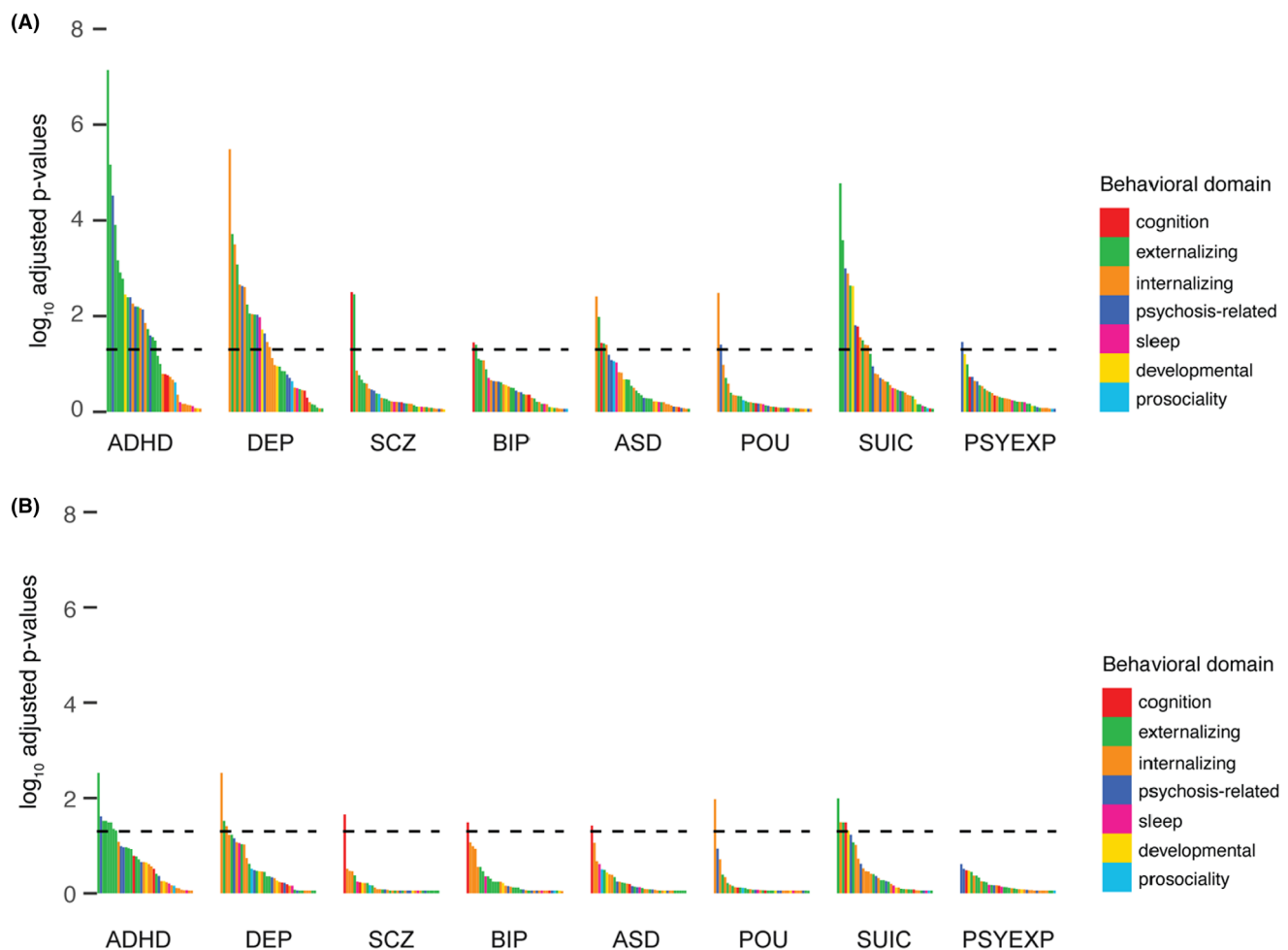


Figure 2 Enrichment of PRS associations across behavioral domains. $\text{Log}(p\text{-adj})$ for all the associations shown in Figure 1 for: (A) univariate and (B) multivariable models. Bars are colored by behavioral domain (see Table S4). Horizontal line represents $p\text{-adj} = .05$

see Figure 4. These patterns became more specific toward particular domains in multivariable models (controlling for other FH measures and the PRS). For example, FH of depression or anxiety/stress was significantly associated with internalizing behaviors, whereas FH of conduct disorder was significantly associated with externalizing behaviors.

Total variance in behavior explained by PRS and FH

We quantified the variance in each behavior predicted by the set of PRS and set of FH measures when controlling for the other set of genetic predictors. Table S4 shows that, in all cases, each set independently predicted unique variance over and above the other set of genetic predictors. The maximum variance explained by the FH and PRS measures combined was $\Delta R^2 = 0.066$ of CBCL Total Problems scale, of which $\Delta R^2 = 0.055$ was uniquely predicted by FH, and $\Delta R^2 = 0.0088$ was uniquely predicted by PRS. The maximum unique variance explained collectively by PRS was $\Delta R^2 = 0.011$ of the variability in CBCL rule breaking. These results further demonstrate that PRS and FH predict unique, nonoverlapping variance across different

domains of behavior in youth with PRS predicting a smaller proportion of variability than FH.

Discussion

Polygenic risk and FH of psychopathology predicted both overlapping and unique variability in behavior across domains in 9- to 11-year-old youth. Several externalizing and internalizing behaviors were associated with multiple measures of genetic risk highlighting shared genetic influences underlying variability in developmental psychopathology. However, when controlling for shared variance across PRS and FH measures, polygenic risk for ADHD, depression, and attempted suicide predicted unique variance across differential externalizing, internalizing, and psychosis-related behaviors. Moreover, polygenic risk for problematic opioid use was uniquely negatively associated with behavioral inhibition, and polygenic risk for ASD, BIP, SCZ, and attempted suicide uniquely predicted variability in cognitive performance. FH of psychopathology explained additional unique variance in behavior, independent of the PRS, indicating additional genetic and environmental influences on behavior



Figure 3 Univariate (left) and multivariable (right) associations for each behavior predicted by FH. Effect sizes for each association are displayed as the partial variance explained, R^2 (as a percentage) multiplied by sign of beta coefficient (red = positive, blue = negative). Response variable for each model is shown on y-axis. In univariate models (left), only a single genetic predictor was included in each model (each cell = 1 model) – that is, $\text{behavior} \sim FH + \text{covariates}$. In multivariable models (right), all genetic/familial predictors were included in each model including all PRS and FH measures (each row = 1 model) – that is, $\text{behavior} \sim PRS_1 + PRS_2 \dots + FH_1 + FH_2 \dots + \text{covariates}$. Dots indicate FDR significant associations

and recapitulating results in adults demonstrating the complementary information provided by PRS and FH (Agerbo et al., 2021; Lu et al., 2018). Using combined information across these genetic and familial measures and the dense behavioral

phenotyping in the ABCD study, we identified several, specific patterns of behavior associated with genetic risk for psychopathology that may be useful for quantifying early risk across different disorders.

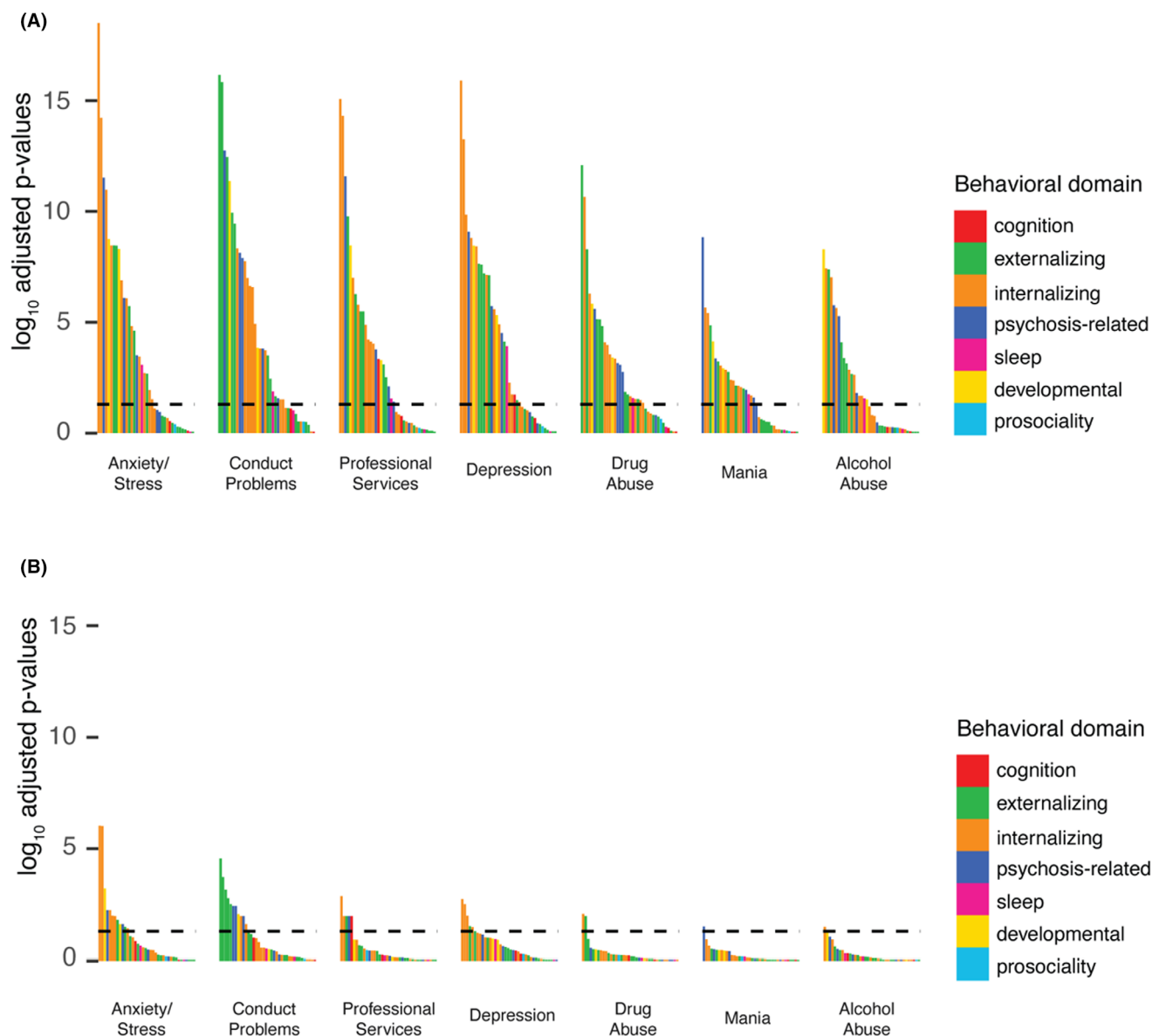


Figure 4 Enrichment of FH associations across behavioral domains. Log (p -adj) for all the associations shown in Figure 1 for: (A) univariate and (B) multivariable models. Bars are colored by behavioral domain (see Table S4). Horizontal line represents p -adj = .05

In this developmental, drug-naïve sample, we interestingly found a negative association between polygenic risk for problematic opioid use and behavioral inhibition that remained significant when controlling for all other PRS and FH measures. This behavioral measure is thought to interrogate the behavioral avoidance system that regulates our motivation to move away from something unpleasant (Carver & White, 1994; Jorm et al., 1998). This negative association highlights that children with a high genetic propensity for misuse of prescription opioids are already showing reduced behavioral avoidance of negative situations at 9–11 years. The direction of this effect is consistent with associations between behavioral inhibition (using the same scale) and drug and/or alcohol use/abuse reported in adults (Franken & Muris, 2006; Kimbrel, Nelson-Gray, & Mitchell, 2007). The specificity of this

association when controlling for polygenic risk for other psychiatric disorders suggests this may be a useful marker specifically for early risk for substance abuse in children.

Of the PRS analyzed, the ADHD, DEP, and SUIC PRS showed univariate associations across largely overlapping behavioral measures. All of these PRS predicted variability in externalizing behaviors (e.g., rule-breaking, aggression, and conduct problems), internalizing behaviors (e.g., youth-reported depression), psychosis-related behaviors (e.g., prodromal psychosis, bipolar symptoms, and thought problems), and inattentive and social problems. Given the correlation between behavioral problems in youth, this supports the evidence that these frequently comorbid behaviors across different behavioral domains have shared genetic influences (Akingbuwa et al., 2020; Cosgrove et al., 2011). This indicates a

common pathway that may contribute to the development of psychopathology. Indeed, suicidality and depression are common across individuals with several different psychiatric disorders and there is evidence that externalizing behaviors in childhood may indicate risk for both externalizing and internalizing disorders in adulthood (Kwong et al., 2019). However, there is variability across all the behavioral measures in terms of measurement error, construct validity, and endorsement across participants; therefore, these common associations across genetic measures may be biased by the behaviors with the largest signal to noise.

Despite this, we did detect some specificity in the behaviors predicted by these different PRS. The ADHD PRS were specifically associated with behavioral approach subscales, impulsivity, and prodromal psychosis; whereas the DEP PRS were associated with somatic complaints and suicidality. Many of the associations between the DEP PRS and internalizing behaviors were no longer significant in the multivariable model likely due to shared variance between the DEP and SUIC PRS. However, there were several specific, unique associations between the SUIC PRS and youth-reported depression symptoms, aggression, and social problems in these multivariable models. This highlights a complex and unique pattern of behaviors associated with genetic risk for attempting suicide specifically compared to depression. These results may point toward potentially distinct pathways associated with the development of unique profiles of behaviors.

Our results replicated previous findings, with a similar magnitude of effects, showing that ADHD PRS were significantly associated with hyperactive and inattentive traits in a developmental sample (Brikell et al., 2020; Jansen et al., 2018). Across the PRS, ADHD and ASD were moderately correlated, and when controlling for the other genetic predictors, ASD was no longer associated with behavioral problems on the CBCL, and neither ASD nor ADHD uniquely predicted ADHD symptoms highlighting the genetic overlap between these disorders in development (Pinto, Rijdsdijk, Ronald, Asherson, & Kuntsi, 2016). There may be additional factors that contributed to the lack of a unique relationship of ASD PRS to youth behaviors. Exclusion criteria of not attending mainstream school classes and an inability to carry out the ABCD protocol would have made low-functioning ASD individuals ineligible for the study. Indeed, we did find a unique positive association between cognitive performance and the ASD PRS in our sample. This suggests that the prevalence of ASD symptoms in the ABCD cohort is likely small and restricted to only part of the autism spectrum, which may have greater overlap with ADHD and associated with higher cognitive functioning. Moreover, rare de novo mutations which are thought to play an important role in ASD (Satterstrom et al., 2020) were not tagged in our analysis.

Interestingly, in our sample, ADHD PRS predicted many bipolar-related behaviors and psychotic-like symptoms. Symptom profiles for pediatric BIP and ADHD are similar and there is high comorbidity across these disorders (Frías, Palma, & Fariols, 2015). Other studies have shown that childhood ADHD is often premorbid to later development of schizophrenia and relatives of individuals with schizophrenia have higher rates of ADHD than the general population (Dalsgaard et al., 2014; Dalteg, Zandelin, Tuninger, & Levander, 2014). Given low correlations among ADHD, SCZ, and BIP PRS in this study, the ADHD PRS may highlight individuals at risk for developing psychosis-related disorders that may be etiologically distinct from those with high SCZ or BIP scores.

Despite previous studies showing SCZ PRS associated with markers of general psychopathology in adolescence (Jansen et al., 2018; Nivard et al., 2017), we did not find any associations of SCZ or BIP PRS with psychopathology; however, we did find a univariate association between PSYEXP and caregiver-reported thought problems. The lack of SCZ/BIP associations with psychopathology in our analysis could be driven by differences in statistical approach, demographics of the samples, or the phenotypes measured – which can impact the stability of results across adolescent samples (Akingbuwa, Hammerschlag, Bartels, & Middeldorp, 2022). The high demands of the study may reduce participation from families with parents or siblings diagnosed with schizophrenia or bipolar disorder; therefore, the prevalence of those with high genetic risk of psychosis may be restricted in this study. Nevertheless, we did identify an expected significant negative association between the SCZ PRS and the fluid composite score from the NIH Toolbox® (which remained after controlling for sociodemographic factors), and an unexpected positive association between BIP and the crystallized composite score from the NIH Toolbox®. Cognitive impairment is a core feature of several psychiatric disorders, particularly those that include psychotic symptoms. Neurodevelopmental studies have highlighted premorbid cognitive impairment across domains in patients with schizophrenia and bipolar disorder (Mollon & Reichenberg, 2018). However, despite this, students who achieve high academically have been shown to have an increased risk of bipolar disorder (MacCabe et al., 2010), supporting the positive association found here. Indeed, there is a large genetic overlap across schizophrenia, bipolar disorders, and general intelligence (Davies et al., 2018; Smeland et al., 2020), suggesting shared etiological mechanisms affecting psychopathology and cognition. In a supplementary analysis controlling for polygenic risk for intelligence, these cognitive associations were attenuated and no longer significant. This suggests our cohort of individuals with any genetic risk for psychosis may be restricted to those with an overlap

in genetic markers also associated with cognition. Studying risk for psychosis in this typically developing sample may, therefore, be biased toward a specific sub-type psychosis. Future research should aim to probe this further using longitudinal data and comparisons with other large samples enriched for psychosis risk.

There were differences in associations across caregiver- and youth-reported behaviors, particularly with genetic risk for depression and suicidality. For multivariable models, youth-reported depression symptom scores were more associated with the SUIC and DEP PRS, while caregiver-reported depression was associated with a FH of depression. Informant discrepancies between caregiver- and child-reported measures have been widely reported (De Reyes & Kazdin, 2005) and we found relatively low correlations between youth- and caregiver-reported measures. Negative biases from caregivers, particularly due to caregiver depression, can also impact behavioral reports (Youngstrom et al., 2001). An awareness of a history of depression within the youth's family may have biased the informant's report about the youth's depression, possibly generating a stronger relationship between FH of depression and caregiver-compared to youth-reported measures. Future time points may indicate which informant-reported measure is most predictive of later diagnosis.

FH of anxiety/stress and conduct problems showed the greatest number of associations across different behavioral domains, supporting the role of anxiety and delinquent behavior as transdiagnostic traits. However, there were subtle differences in the pattern of FH-behavior associations across domains, particularly for multivariable models. For example, FH of drug abuse explained unique variance in rule-breaking behaviors, whereas FH of alcohol abuse explained unique variance in social problems and anxious/depressive behaviors – indicating differential behavioral profiles for specific FHs. Inherent to FH measures are implicit genetic and environmental influences that are difficult to separate. It remains to be seen whether additional variance in behavior explained by FH measures above and beyond PRS reflects environmental or additional genetic influences. Together FH and PRS measures predicted ~7% of the variability in the CBCL Total Problems score. These analyses highlight the utility of measuring multiple markers of genetic risk.

Limitations

PRS association strength is limited by the phenotype's heritability and the training sample used (Dudbridge, 2013). DEP had the largest discovery sample (Figure S14) and a relatively low SNP heritability, yet displayed some of the largest associations in our sample. This may be due to depression having a relatively greater population prevalence compared to the other psychiatric disorders

measured, therefore compared to other disorders risk alleles may be well represented in our sample. Correlations between PRS generated in this study were much lower than the genetic correlations determined in the original GWAS, which may be because this cohort is not enriched for individuals with risk alleles. Many psychiatric disorders have increased penetrance during adolescence, therefore the lack of variance in psychopathology symptoms at this age may explain the limited associations between behavior and the SCZ/BIP PRS. Moreover, the GWAS used to produce the PRS in this study were conducted in predominately European ancestry samples. The ABCD sample is demographically diverse, however, PRS trained and tested in different ancestry groups do not validly predict phenotypes. This highlights the limited predictive capacity of European-only GWAS for non-European populations and emphasizes the need for conducting GWAS in different ancestry groups. Finally, the magnitude of the genetic-behavior effects detected was very small; the development of psychopathology is complex and genetic risk as estimated with polygenic predictors appears to only account for a small proportion of variability in behavior at this age.

Here, we have shown that different PRS and FH measures predicted unique patterns of symptoms of psychopathology, related individual difference factors and cognitive function in a large sample of 9- to 11-year-old children. Unique associations, controlling for other genetic measures, provide encouraging evidence that genetic data may be useful alongside FH in identifying specific risk for psychiatric disorders. Longitudinal analyses will further elucidate the specificity of these associations and may track these patterns of behavior to determine the differential predictive utility for PRS and FH measures.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Appendix S1. Supplementary methods.

Table S1. Sociodemographic breakdown for the samples analyzed in this study.

Table S2. DEAP variable names for all behavioral variables analyzed in this study.

Table S3. Description of the family history variables used and the questions asked.

Table S4. Unique and shared variance across behaviors predicted by PRS and FH.

Figure S1. Univariate Behavior PRS associations for PSYEXP (controlling for covariates including SES) at different p value thresholds in European ancestry sample.

Figure S2. Univariate Behavior PRS associations for SUIC (controlling for covariates including SES) at different p value thresholds in European ancestry sample.

Figure S3. Univariate Behavior PRS associations for BIP (controlling for covariates including SES) at different p value thresholds in European ancestry sample.

Figure S4. Univariate Behavior PRS associations for ASD (controlling for covariates including SES) at different p value thresholds in European ancestry sample.

Figure S5. Univariate Behavior PRS associations for SCZ (controlling for covariates including SES) at different p value thresholds in European ancestry sample.

Figure S6. Univariate Behavior PRS associations for ADHD (controlling for covariates including SES) at different p value thresholds in European ancestry sample.

Figure S7. Behavioral associations across ancestry strata.

Figure S8. Signed Effect Sizes for all multivariable PRS associations for the European sample (X-axis) and non-European sample (Y-axis), controlling for covariates of no interest and SES.

Figure S9. Pairwise spearman correlations between all of the behavioral phenotypes in the European sample pre-residualized for covariates of no interest including socioeconomic status (SES).

Figure S10. Pairwise spearman correlations between all of the genetic risk measures in the European sample pre-residualized for covariates of no interest including SES.

Figure S11. Behavioral associations in the European sample controlling for an intelligence polygenic score (IPS).

Figure S12. Behavioral associations in the European sample without controlling for SES.

Figure S13. $-\log(P\text{-values})$ for all multivariable associations after controlling for SES (Y-axis) and before controlling for SES (X-axis) in the European sample.

Figure S14. Plot of SNP heritability (h^2_{snp}) and log (effective sample size) for each discovery GWAS sample, as reported in discovery papers, used to calculate PRS.

Appendix S2. Regression data tables from all associations between PRS/FH and behavior.

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Key points

- This work quantifies the association between genetic/familial risk and psychopathology in a large socioeconomically diverse sample of typically developing young adolescents aged 9–11.
- We find that genetic risk and family history contribute unique variance across a range of behaviors, with or without controlling for socioeconomic status.
- Genetic risk for developing problematic opioid use was associated with lower behavioral inhibition. Genetic liability for depression and attempted suicide showed stronger associations with both internalizing and externalizing symptoms; whereas genetic risk for ADHD showed stronger associations with ADHD symptoms, impulsivity, and prodromal psychosis. Additionally, genetic risks for schizophrenia, autism, bipolar disorder, and attempted suicide were each uniquely associated with cognitive performance.
- Family history for behaviors related to psychopathology displayed associations with many behavioral measures, overall explaining a greater proportion of unique variance compared to genetic risk predictors.
- ~7% of the variability in a general measure of psychopathology was explained using both genetic risk and family history measures.
- This work demonstrates the complementary information that genetic risk and family history provide in explaining variability in psychopathology at this early age.

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