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Associations between cognition and polygenic liability to substance involvement in middle childhood: Results from the ABCD study

Sarah E. Paul [a,*], Alexander S. Hatoum [b], Deanna M. Barch [a,b,c], Wesley K. Thompson [d], Arpana Agrawal [b], Ryan Bogdan [a], Emma C. Johnson [b]

[a] Department of Psychological and Brain Sciences, Washington University in St. Louis, 6411 Forsyth Blvd, St. Louis, MO 63105, USA
[b] Department of Psychiatry, Washington University School of Medicine, 660 S Euclid Ave., St Louis, MO 63110, USA
[c] Department of Radiology, Washington University School of Medicine, 510 S Kingshighway Blvd, St. Louis, MO 63110, USA
[d] Division of Biostatistics and Department of Radiology, UCSD, La Jolla, CA 92093, USA

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ABSTRACT

Background: Cognition is robustly associated with substance involvement. This relationship is attributable to multiple factors, including genetics, though such contributions show inconsistent patterns in the literature. For instance, genome-wide association studies point to potential positive relationships between educational achievement and *common* substance use but negative relationships with *heavy and/or problematic* substance use.
Methods: We estimated associations between polygenic risk for substance involvement (i.e., alcohol, tobacco, and cannabis use and problematic use) and cognition subfacets (i.e., general ability, executive function, learning/memory) derived from confirmatory factor analysis among 3205 substance naïve children (ages 9–10) of European ancestry who completed the baseline session of the Adolescent Brain Cognitive Development (ABCD) Study.
Findings: Polygenic risk for lifetime cannabis use was positively associated with all three facets of cognitive ability ($Bs \geq 0.045$, $qs \leq 0.044$). No other substance polygenic risk scores showed significant associations with cognition after adjustment for multiple testing ($|Bs| \leq 0.033$, $qs \geq 0.118$).
Conclusions: Polygenic liability to lifetime cannabis use, but not use disorder, was positively associated with cognitive performance among substance-naïve children, possibly reflecting shared genetic overlap with openness to experience or the influence of genetic variance associated with socioeconomic status. Our lack of findings for the other polygenic scores may reflect ascertainment differences between the genome-wide association study (GWAS) samples and the current sample and/or the young age of the present sample. As longitudinal data in ABCD are collected, this sample may be useful for disentangling putatively causal or predispositional influences of substance use and misuse on cognition.

1. Introduction

A wealth of literature demonstrates that cognition and substance involvement (i.e., initiation/common use and heavy/problematic use) are intimately related, but the source of this relationship remains unclear. Substance involvement longitudinally precedes worst performance across broad cognitive domains (Conrod and Nikolaou, 2016; Morin et al., 2019; Peeters et al., 2015; Squeglia and Gray, 2016), but cognitive deficits also appear to confer susceptibility to substance use initiation (Heitzeg et al., 2015; Khurana et al., 2013). Theories speculate that negative associations between substance use and cognition may be attributable to chronic substance use resulting in cognitive impairment (neurotoxicity model; Morin et al., 2019), deficits in working memory and response inhibition increasing overall risk of substance use and misuse (cognitive vulnerability model), and/or common genetic and environmental underpinnings (hereafter referred to as the "shared predispositions model"). Evidence from longitudinal and twin studies generally supports the shared predispositions model, wherein links

* Correspondence to: CB 1125 Psychological and Brain Sciences, Washington University in St. Louis, One Brookings Drive, Bldg Room 453, St. Louis, MO 63130, USA.
E-mail addresses: spaul24@wustl.edu (S.E. Paul), ashatoum@wustl.edu (A.S. Hatoum), dbarch@wustl.edu (D.M. Barch), wes.stat@gmail.com (W.K. Thompson), arpana@wustl.edu (A. Agrawal), rbogdan@wustl.edu (R. Bogdan), emma.c.johnson@wustl.edu (E.C. Johnson).

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between cognitive phenotypes and substance use may be attributable to genetically-influenced shared vulnerability (e.g., Gustavson et al., 2017a; Jackson et al., 2016; Latvala et al., 2016; Morin et al., 2019). Below, we outline the existing literature on the source and directionality of the association between cognitive ability and the use of commonly used and studied substances (alcohol, tobacco, and cannabis), before introducing the present study. Better elucidating the causal and/or shared etiological nature of these relationships may critically inform targeted interventions for the development of substance use and related problems.

1.1. The relationship between substance use and cognition

In terms of directionality, negative associations between cognitive ability, such as executive function, and adolescent substance use have been attributed to genetic factors (Gustavson et al., 2017). Further, discordant twin and longitudinal population- and family-based studies have found that negative associations between global domains of cognition (e.g., IQ) and substance use have a largely genetic basis (Jackson et al., 2016; Latvala et al., 2016; Schaefer et al., 2021).

However, in contrast to the above literature, some epidemiological (Müller et al., 2013) and genetically-informed (W. Johnson et al., 2009) studies suggest a positive relationship between cognition and substance use. National survey and cohort-based data have documented positive associations between intelligence and ever having experimented with substances (Wilmoth, 2012), and between childhood cognitive ability and later problematic alcohol use (Batty et al., 2008). Higher intelligence and greater educational attainment have been associated with greater substance use in young adulthood, after accounting for genetic and shared environmental influences (W. Johnson et al., 2009). Similarly, data from two independent samples show that co-twins with higher early verbal ability reported more frequent drinking in adolescence (Latvala et al., 2014) but see (Woodward et al., 2019). These discrepant findings—of both positive and negative associations between cognition and substance use—may be partially explained by phenotypic heterogeneity. That is, the directionality of associations may differ according to severity of substance use and/or cognitive domain assessed.

1.2. Genetic correlations between substance use and cognition

Genome-wide association studies (GWAS) depict a complex pattern in shared genetic influences on cognition and substance use depending on the substance use severity. For example, both substance *use* and *initiation* tend to have positive genetic correlations (r_g) with educational attainment and general cognitive ability/IQ, whereas *heavy and/or problematic* substance use has negative correlations with these traits. For example, an index of broad alcohol use, the consumption subscale of the Alcohol Use Disorders Identification Test (AUDIT-C) is positively correlated with educational attainment and childhood IQ (r_gs = 0.18–0.25), while an index of problematic use (i.e., AUDIT-P) is not significantly associated with either (r_gs = -0.017–0.022; Kranzler et al., 2019; Sanchez-Roige et al., 2019). Similarly, whereas alcohol consumption in the UK Biobank is positively correlated with years of schooling (r_g=0.18; Clarke et al., 2017) and drinks per week is not significantly correlated with educational attainment (Liu et al., 2019), problematic alcohol use, alcohol use frequency, and alcohol dependence have negative r_gs with educational attainment, cognitive performance, and executive function (Hatoum et al., preprint; Kranzler et al., 2019; Liu et al., 2019; Walters et al., 2018). Polygenic risk for alcohol dependence has also been linked to lower verbal fluency even after adjustment for education (Clarke et al., 2016). Similarly, whereas the r_g between lifetime cannabis use and educational attainment is positive (r_g = 0.30; Pasman et al., 2018), the r_gs and polygenic risk associations between cannabis use disorder (CUD) and educational attainment and intelligence are negative ($r_g \sim 0.40$ for CUD and educational attainment; Demontis et al., 2019; Johnson et al., 2020). In contrast, nicotine shows little evidence of a pattern of divergence for initiation vs. severity of use: both smoking initiation and number of cigarettes per day (which is highly correlated [rg = 0.95] with the Fagerström Test for Nicotine Dependence; Quach et al., 2020) show negative r_gs with educational attainment (r_gs = -0.40 and −0.26; Liu et al., 2019). Furthermore, ever smoking shows a negative r_g with executive function (r_g = −0.08; Hatoum et al., preprint), and being a former smoker (i.e., cessation) is positively correlated with both executive function (r_g = 0.19; Hatoum et al., preprint) and intelligence (r_g = 0.33; Savage, Jansen et al., 2018). Because nicotine has higher addictive potential than alcohol and cannabis, those who initiate cigarette use are more likely to escalate to heavy use. This higher addictive potential may explain why cognitive ability and educational attainment are consistently negatively correlated with genetic liability for tobacco use across *all* stages of tobacco involvement, from initiation to heavy use and dependence, unlike the patterns of divergence seen for alcohol and cannabis initiation vs. problematic use. There may also be other mechanisms at play; for example, in many societies, alcohol is used socially, but this is less true for cigarettes and tobacco, and this difference in use may contribute to differential correlations with educational attainment.

1.3. Introduction to the present study

The general pattern suggests that initiation of or common substance use is positively, and heavy and/or problematic substance use negatively, genetically correlated with cognition. However, GWAS have not extensively explored the multiple correlated but separable facets that comprise cognition, due to reliance on widely available, simple measures are easily collected and enable convergence across multiple large-scale data sets (e.g., educational attainment, IQ). As such, evidence for the pattern by which genetic factors account for shared variance between substance use and specific facets of cognition is unclear. Complementary approaches, such as the use of polygenic risk scores (PRS), may help overcome these challenges if applied in target samples with detailed cognitive measures. PRS offer a way to test theories about overlap between cognition and risk for substance use and use disorder in deeply phenotyped samples when they are substance naive, prior to possible neurotoxic contamination by substance exposure.

The present study examined whether polygenic liability for aspects of substance involvement—ranging from initiation to dependence—are differentially associated with the three facets of cognition previously identified in the first release of data from the Adolescent Brain Cognitive Development (ABCD) Study (i.e., General Ability, Executive Function, and Learning/Memory; Thompson et al., 2019) among substance-naïve children in the same sample. Importantly, by limiting our analyses to substance-naïve children, we circumvent any possible confounding by neurotoxic effects. We hypothesized that PRS for stages of substance use that are more common and less indicative of problematic use—hereafter referred to as *common* substance *use/initiation* (i.e., smoking initiation, drinks per week, lifetime cannabis use)—would be *positively* associated with each cognitive subtype, while PRS for stages of substance involvement that are indicators of heavy, prolonged use and/or problem—hereafter referred to as *heavy or problematic* substance use (i.e., cigarettes per day,[a] problematic alcohol use, CUD)—would be *negatively* associated with these cognitive domains. Because the existing literature has focused on global cognitive metrics (e.g., IQ, education), we believe it is critical to examine—but do not make separate predictions

[a] Because of the high genetic correlation between cigarettes per day and nicotine dependence (r_g=0.95, vs. 0.40 for smoking initiation and nicotine dependence; Quach et al., 2020) and the substantially smaller sample size of the existing GWAS of nicotine dependence relative to that for cigarettes per day (i.e., 46,213 vs. 337,334 participants of European ancestry; Liu et al., 2019; Quach et al., 2020), we chose to use the summary statistics for cigarettes per day as a proxy index of heavy or problematic tobacco use to maximize power.

about—specific cognitive domains. Similarly, it is possible that the relationship between substance use and cognitive ability may differ by type of substance, but given recent evidence of shared genetic architecture across substance phenotypes (e.g., Hatoum et al., 2021; Karlsson Linnér et al., 2019) we do not make separate hypotheses for each substance.

2. Methods

2.1. Participants

Data came from 11,875 children (mean ± SD age=9.91 ± 0.62 years; 47.85% girls; 74.13% White) who completed the baseline assessment of the ongoing longitudinal Adolescent Brain Cognitive Development℠ (ABCD) Study (release 2.0.1; https://abcdstudy.org/) (Volkow et al., 2018). The study includes a family-based design in which twin (n = 2108), triplet (n = 30), non-twin siblings (n = 1589), and singletons (n = 8148) were recruited. Parents/caregivers provided written informed consent, and children verbal assent, to a research protocol approved by the institutional review board at each of 21 data collection sites across the United States (https://abcdstudy.org/sites/abcd-sites.html). For the present analyses, data from substance-naïve participants of genetically confirmed European ancestry were used (n = 3371; see Table 1 for a description of this subsample and Supplemental Table 1 for a description of substance involvement that was the basis for exclusion). Due to missing data, the final analytic sample included 3179 participants from 2720 families.

Table 1
Sample Characteristics.

	N (%) / Mean ± SD
Demographics	
Female	1610 (47.8%)
Age (months)	119 ± 7.47
Caregiver Education	
Less than High School	28 (0.83%)
High School or Equivalent	175 (5.19%)
Some College/Associate's Degree	903 (26.8%)
College	1270 (37.7%)
Graduate Degree	994 (29.5%)
Combined Income	
$0-$49,999	400 (12.3%)
$50k-$74,999	466 (14.4%)
$75k-$99,999	614 (18.9%)
$100k-$199,999	1315 (40.6%)
$200k or more	447 (13.8%)
Caregiver Marital Status	
Married	2821 (83.7%)
Widowed	22 (0.65%)
Divorced	267 (7.92%)
Separated	80 (2.37%)
Never Married	88 (2.61%)
Living with Partner	92 (2.73%)
Prenatal Substance Exposure	
Tobacco	391 (11.7%)
Alcohol	864 (25.9%)
Cannabis	118 (3.53%)
Parental History of Substance Problems	1395 (41.8%)
Cognition	
Flanker	94.8 ± 8.06
List Sort	99.3 ± 10.8
Card Sort	94.0 ± 8.58
Picture Sequence	104.5 ± 11.9
Pattern Comparison	88.9 ± 13.8
Picture Vocabulary	86.9 ± 7.25
Oral Reading	91.8 ± 6.23

Note. N = 3371.

2.2. Measures

2.2.1. Cognition

2.2.1.1. National Institutes of Health Toolbox Cognition Battery (NIH Toolbox). The NIH Toolbox consists of seven tests assessing executive function, attention, processing speed, working memory, episodic memory, and language (Luciana et al., 2018; Weintraub et al., 2013). The Flanker Test of Executive Functioning-Inhibitory Control and Attention, List Sorting Working Memory Test, Dimensional Change Card Sort Test of Executive Function-Cognitive Flexibility, Picture Sequence Memory Test, and Pattern Comparison Processing Speed Test index fluid cognition, and the Picture Vocabulary Test and Oral Reading Recognition Test index crystalized cognition. Age- and gender-uncorrected scores were used for each measure.

2.2.1.2. Rey Auditory Verbal Learning Test (RAVLT). The RAVLT assesses auditory learning, memory, and recognition by orally presenting participants with 15 words over five trials and requiring participants to verbally recall as many words as possible after presentation of a distractor list and short delays (Rey, 1958; Schmidt, 1996). Following Thompson et al. (2019), the total number of words correctly recalled after a short delay were summed together to form a composite RAVLT score.

2.2.1.3. Little Man Task. The Little Man Task assesses visuospatial processing by requiring participants to identify what hand a man is holding a briefcase in following presentations of the man in various positions (Acker and Acker, 1982). Following Thompson et al. (2019), the percentage correct of all 32 presented trials on the *Little Man Task* was used.

2.2.2. Polygenic risk scores

Summary statistics from the most well-powered publicly-available genome-wide association studies (GWAS) of each of our substance use phenotypes (Smoking Initiation (N = 632,802, 311,629 cases; Liu et al., 2019), Cigarettes Per Day (N = 263,954; Liu et al., 2019), Drinks per Week (N = 537,349; Liu et al., 2019), Problematic Alcohol Use (N = 435,563; Zhou et al., 2020), Lifetime Cannabis Use (N = 184,765; Pasman et al., 2018) and Cannabis Use Disorder (N = 384,032, 20,916 cases; E.C. Johnson et al., 2020)) were used to generate PRS in the European ancestry subsample of ABCD (n = 4650). To calculate PRS, we used a Bayesian approach, PRS-CS (Ge et al., 2019), which incorporates all SNPs (i.e., no p-value thresholding) and utilizes an external linkage disequilibrium (LD) reference panel to account for correlations between SNPs. The "auto" function within the PRS-CS software package was used to compute PRS (see Supplement for further details).

2.2.2.1. Genotyping, quality control, and imputation. The Rutgers University Cell and DNA repository genotyped saliva samples on the Smokescreen array. Genotyped calls were aligned to GRCh37 (hg19).

The genetic data underwent typical quality control procedures following the Ricopili pipeline (Lam et al., 2020). Analyses were restricted to individuals of genetically-confirmed European ancestry, to match the ancestry makeup of the discovery GWAS. Further details are provided in the Supplement.

2.2.3. Covariates

The following variables were considered as covariates in all analyses (see **Statistical Analyses**): caregiver-reported biological sex assigned at birth, age, age^2, age x sex, age^2 x sex, caregiver education, combined annual household income, parent marital status, and the first 10 ancestrally informative principal components (PCs). Prenatal exposure to tobacco, alcohol, and cannabis (each measured as separate dichotomous variables), as well as parental history of alcohol and drug problems

(a single composite dichotomous indicator), were also included as covariates; supplemental analyses excluded these covariates to account for possible over-correction by including contributions of both parental genotypes (i.e., through PRS) and parental behavior, as parental genotypes partially contribute to both parental substance use and offspring cognition (see Supplemental Methods). Age was measured in months. Caregiver education was an ordinal variable roughly mapping onto total years of education (see **Supplement** for further information). Combined annual household income was an ordinal variable ranging from 1 ($0-$49,999) to 5 ($200,000 or more). Parent marital status indicated whether the parent was married, divorced, separated, widowed, living with a partner, or never married at the time of the baseline assessment. These demographic variables have previously been associated with offspring cognitive outcomes (Bacharach and Baumeister, 1998; Zhang et al., 2020) and were thus included as covariates. Ancestrally informative genetic PCs were used to account for potentially confounding effects of population stratification, or systematic differences in allele frequencies due to ancestry.

2.3. Statistical analyses

Analyses were preregistered on OSF (https://osf.io/sg3n4/, finalized 04/13/2020) and are detailed below. We sought to confirm the factor structure that was identified by Thompson and colleagues (2019) in the first data release of ABCD (i.e., the first half of the baseline sample; n = 4093, mean age=10.00 years) among the present substance-naïve sample of European ancestry and to then relate these subdomains to PRS of each substance phenotype. We departed from our preregistered analysis in the following ways: (1) we tested alternative confirmatory models in order to determine whether the original factor structure best fit the data; (2) we included prenatal exposure to alcohol, tobacco, and cannabis, as well as parental history of problems with alcohol or drugs, as covariates, while removing genotype batch as a covariate given concerns that batch effects represent noise rather than systematic bias at such a small sample size; and (3) we included post hoc analyses to control for polygenic scores for Educational Attainment, a frequently used proxy for socioeconomic status in genetic studies, as SES has been shown to influence the correlations between substance use and mental health traits (Marees et al., 2020).

Individual values on continuous predictor and outcome variables were winsorized (to ± 3 SD) to minimize the influence of extreme values. These variables were then standardized to have a mean of 0 and standard deviation of 1. Linear mixed-effects models with random intercept parameters were used to account for site and family membership with the lme4 package in Rv4.0.1 (Bates et al., 2015).

2.3.1. Confirmation of three factor structure for cognition

Confirmatory factor analysis (CFA) was used to generate the three-factor structure of cognition (General Ability, Executive Function, Learning/Memory) previously identified in the first wave of ABCD (Thompson et al., 2019) by applying the *cfa()* function within the lavaan package in R (Rosseel, 2012).

Specifically, Picture Vocabulary, List Sorting, Reading, and Little Man Task scores were specified to load onto the General Ability factor; Flanker, Card Sort, and Pattern Comparison onto the Executive Function factor; and List Sorting, Picture Sequence Memory, and RAVLT onto the Learning and Memory factor. The three cognition factors were allowed to covary/correlate. Model fit was assessed via the Comparative Fit Index (CFI), Tucker-Lewis Index (TLI), Root Mean Square Error of Approximation (RMSEA), and Standardized Root Mean Square Residual (SRMR). CFI and TLI values around 0.95, and RMSEA and SRMR values below 0.06 and 0.08, respectively, were interpreted as evidence for good model fit (Hu and Bentler, 1999).

To find the best-fitting model of the relationships between facets of cognition, a series of CFA model comparisons were conducted. First, a model in which the three cognition factors were *not* allowed to covary (i.e., orthogonal factors) was conducted as an explicit test of the Thompson et al. (2019) structure. Second, a model in which all cognition indicators loaded onto a unitary dimension of cognitive ability was compared to the three correlated factors model described above. Third, the three correlated factors model was compared to a hierarchical model in which the common variance between the three factors was captured by a higher-order *g* factor. For all CFA models, the loadings onto each latent factor were scaled to the indicator with the highest loading, and the residual variances of each of the cognition factors were freely estimated (see Fig. 1 for an overview). In order to account for the nested structure of the data, the random effects for family and research site were residualized out of the cognition indicators. The function *lavPredict()* was used to extract factor scores for the three latent cognition factors.

2.3.2. Primary models: substance involvement PRS and cognition

A total of 18 linear mixed effects models were conducted to assess whether each of six substance involvement PRS were associated with each of three cognition factors, using the best-fitting model. To correct for multiple testing, Benjamini-Hochberg False Discovery Rate (FDR) correction was conducted across the three cognitive factors and six PRS (i.e., six tests for each of the three cognition outcomes).

2.3.3. Covarying for educational attainment PRS

Finally, in order to account for the possibility that associations between cognitive factors and PRS for substance phenotypes were partly due to the influence of SES, we covaried for Educational Attainment PRS (Lee et al., 2018) in analyses that yielded significant effects. FDR correction was applied to the p-values resulting from these analyses.

2.3.4. Supplemental analyses

Supplemental post-hoc analyses were conducted for analyses that yielded significant effects to examine the specificity with which substance PRS relate to each of the three cognitive factors.

3. Results

3.1. Confirmation of three factor structure for cognition

The factor structure identified by Thompson and colleagues (2019) was tested via a CFA in which the three cognition factors were not allowed to covary (i.e., were orthogonal), as this most closely matched the original procedure. Although each indicator (with random effects for site and family residualized out) loaded significantly onto its specified latent factor, model fit was poor (CFI = 0.789, TLI = 0.708, RMSEA = 0.112, SRMR = 0.138; Supplemental Table 2). A model in which the three cognition factors were allowed to covary fit the data well (CFI = 0.973, TLI = 0.958, RMSEA = 0.043, SRMR = 0.028), better than the orthogonal model (χ^2_{diff} (3) = 955.02, $p < 2.2e\text{-}16$) and a model in which all indicators loaded onto a unitary dimension of cognition (χ^2_{diff} (4) = 1053.2, $p < 2.2e\text{-}16$; Supplemental Table 2). The hierarchical model fit was identical to that of the three correlated factors model, but in order to maintain more consistency with Thompson and colleagues' (2019) factor structure and examine differential associations between PRS and cognition facets, we allowed the three latent factors to covary for our final model rather than load on a higher order factor The three latent factors were significantly correlated with one another (General Ability and Executive Function $r = 0.45$; General Ability and Learning/Memory $r = 0.56$; Executive Function and Learning/Memory $r = 0.51$; all $ps < 0.001$). All cognition indicators loaded positively and significantly onto their respective latent factors (see Supplemental Table 3 for standardized loadings).

3.2. Primary models: substance involvement PRS and cognition

Random effects of research site and family were residualized out of the indicators used to compute the cognition factor scores. When

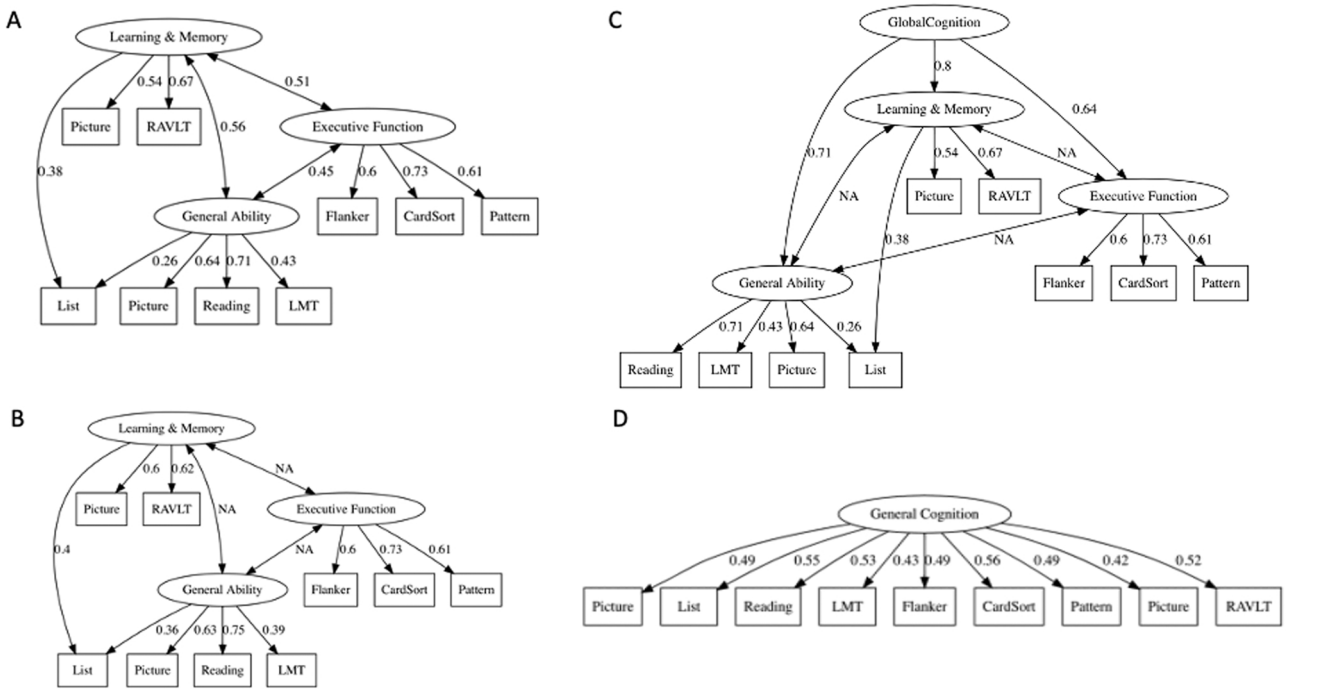

Fig. 1. Cognition Factor Structure Model Testing. This figure presents a series of models used to determine the appropriate factor structure of cognitive abilities. (A) Three correlated factors model. Each of the three cognition factors were allowed to correlate. (B) Three orthogonal factors model. The three cognition factors were specified to be orthogonal. (C) Hierarchical factor model. Each of the three cognition factors loaded onto a higher-order global cognition factor. (D) One factor model. All indicators were specified to load onto a single general cognition factor.

included in the linear mixed effect models that regressed the cognition factor scores onto the PRS and covariates, the random effect of family ID no longer explained any variance and was thus removed from the models. Site still explained a negligible portion of variance and was retained in the final models; removal of this random effect did not alter results.

After correcting for multiple testing, PRS for lifetime cannabis use was positively and significantly associated with factor scores for General Ability (B = 0.0792, FDR-corrected *q-value* = 4.12e-06), Executive Function (B = 0.0451, q = 0.0437), and Learning/Memory (B = 0.0594, q = 0.00219; Table 2). No other PRS was significantly associated with any of the cognition factor scores ($|Bs| \leq 0.0329$, $ps \geq 0.0393$, $qs \geq 0.118$). Analyses in which parental history of substance problems and prenatal substance exposure were removed as covariates recapitulated these results, with the exception that the association between lifetime cannabis use PRS and executive function was no longer significant after correction for multiple testing (B = 0.0442, q=0.0538; **Supplement;** Supplemental Table 4). Post-hoc analyses examining the specificity of these associations revealed that lifetime cannabis use PRS remained significantly associated only with general ability when the other cognitive factors were included in the same model (**Supplement;** Supplemental Fig. 1).

3.3. Covarying for educational attainment PRS

Educational Attainment PRS was significantly associated with the cognition factor scores (General Ability: B=0.156, $p < 2.22e-16$; Executive Function: B=0.0779, p = 3.42e-06; Learning/Memory: B=0.117, p = 4.52e-12). Inclusion of educational attainment PRS (correlation with lifetime cannabis use PRS = 0.15) attenuated the associations between lifetime cannabis use PRS and General Ability (B=0.0570, q=9.96e-04), Executive Function (B=0.0339, q=0.0451), and Learning/Memory (B=0.0431, q=0.0152).

4. Discussion

Based upon evidence from GWAS depicting differences in how early, non-problematic stages of substance use versus later stages of heavy, problematic use and use disorder genetically relate to educational attainment and intelligence, we tested hypotheses that polygenic liability for *common* substance *use/initiation* would be positively associated with three facets of cognition, and that polygenic liability for *heavy or problematic* substance use would be negatively associated with these same facets, among a population-based sample of 3205 substance-naïve children. Two primary findings emerged. First, consistent with our hypotheses, polygenic risk for lifetime cannabis use was associated with higher general ability, executive function, and learning/memory factor scores in primary analyses ($Bs \geq 0.045$), although post-hoc analyses indicated that only the association with general ability was consistently robust to alternative models (**Supplement;** Supplemental Table 4; Supplemental Fig. 1). Second, contrary to our hypotheses, no other significant associations between substance involvement PRS (i.e., smoking initiation, drinks per week, cigarettes per day, problematic alcohol use, and CUD) and cognition factor scores emerged. Collectively, these data suggest that polygenic scores for substance use and misuse explain small amounts of variance in cognitive factors in the ABCD sample.

There are several possible explanations for our finding that genetic propensity to lifetime cannabis use, but not the use or misuse of other substances, was positively associated with cognitive ability. The lifetime cannabis use PRS was derived from a GWAS of lifetime ever-use of cannabis (Pasman et al., 2018). In that study, lifetime cannabis use was positively genetically correlated with educational attainment and openness to experience, which is linked with higher IQ. Further, follow-up analyses in the same study showed that, phenotypically, lifetime cannabis use was positively associated with both fluid intelligence and household income, in line with other studies in which cannabis use was associated with higher childhood SES (Patrick et al., 2012) and in which higher childhood IQ was positively associated with

Table 2
Associations between substance PRS and cognitive outcomes.

	Smoking Initiation			Cigarettes Per Day			Drinks Per Week			Problematic Alcohol Use			Cannabis Use			Cannabis Use Disorder		
	B	R^2	*q**	*B*	R^2	*q**	*B*	R^2	*q**	*B*	R^2	*q**	*B*	R^2	*q**	*B*	R^2	*q**
General Ability	-5.7e-3	3.2e-5	0.854	-3.0e-3	9.0e-6	0.854	0.0329	0.001	0.118	8.2e-3	6.7e-5	0.854	**0.0792**	**0.006**	**4.1e-6**	0.0181	3.3e-4	0.516
Executive Function	4.5e-3	2.0e-5	0.966	0.0190	3.6e-4	0.520	0.0227	5.2e-4	0.520	-1.1e-4	1.2e-8	0.966	**0.0451**	**0.002**	**0.0437**	-7.2e-4	5.2e-7	0.966
Learning & Memory	-0.0191	3.6e-4	0.630	6.2e-3	3.8e-5	0.854	9.8e-3	9.6e-5	0.834	-0.0168	2.8e-4	0.630	**0.0594**	**0.004**	**2.2e-3**	8.4e-4	7.1e-7	0.960

Note. n = 3179. *Bs* represent standardized betas. R^2 represent partial R^2. *p-values were FDR-corrected (q-values) for the associations between PRS and the three cognitive outcomes. PRS = Polygenic Risk Score. Bolded cells indicate significant associations (FDR $q < 0.05$) between PRS and cognitive outcomes.

cannabis and other illegal drug use in adolescence and young adulthood (White and Batty, 2012). The authors speculated that those with higher SES are more likely to experience environments (e.g., academic settings) in which cannabis may be more accessible (Pasman et al., 2018). Thus, it is possible that this particular GWAS partially indexes genetic propensity to substance experimentation that does not develop into problematic use, in the context of protective factors such as higher SES and cognitive ability. In the present study, polygenic liability to cannabis use disorder was not linked with cognitive ability, although the GWAS of CUD found that genetic liability to CUD is correlated with lower educational attainment and SES; the positive associations between lifetime cannabis use PRS and cognition phenotypes may be specific to use that does not progress to misuse.

Our hypotheses were largely based on findings from GWAS that have measured educational attainment or intelligence (e.g., Lee et al., 2018; Savage et al., 2018). However, these measures may not directly map onto the facets of cognitive ability included in the present study. For instance, our PRS for educational attainment was only modestly associated with the cognition factor scores, explaining between 1% and 4% of variance. That said, these effect sizes are in line with other cross-trait PRS associations in the ABCD sample (e.g., Hatoum et al., 2021; Ohi et al., 2021). Furthermore, caregiver-reported grades were only moderately correlated with cognitive abilities (*r*s ranging from 0.29 to 0.42; **Supplement**), suggesting some distinction between cognitive ability and educational performance that may reflect different genetic and sociocultural influences. Relatedly, there have been few large GWAS of cognitive function or performance, and very few GWAS for cognitive phenotypes of the same degree of granularity as studied in the ABCD sample, limiting our ability to generate hypotheses based directly on genetic data for cognitive ability. This may be one possible explanation for the discrepancy between our findings and published genetic correlations between substance involvement and educational attainment. However, this explanation seems unlikely to be fully explain null findings for alcohol and executive function, at least, given evidence that both alcohol use frequency and alcohol dependence are negatively genetically correlated with more a more fine-grained cognitive measure of executive function (Hatoum et al., preprint). Still, it may be that future large GWAS of cognitive abilities will identify patterns of correlation with substance use and misuse that diverge from those reported in GWAS of educational attainment.

Another potential reason for our null results is simply that the effect sizes may be too small to detect significant associations in this sample. While the sample sizes for our discovery GWAS are seemingly large (Ns=184,765–948,452), even well-powered PRS tend to explain less than 5% of the variance for most complex traits in independent samples (Bogdan et al., 2018). The effect sizes for cross-trait PRS analyses like the ones we conducted in the present study (i.e., testing whether PRS for *substance* phenotypes are associated with *cognitive* phenotypes) tend to be even smaller, and we may have been underpowered to detect these associations (based on a range of estimates of heritability, prevalence, and genetic correlations from prior literature (Dudbridge, 2013), we estimate our power was between 20% and 60% to detect associations in this study). It is thus plausible that the significant associations we observed with lifetime cannabis use PRS are false positives; replication of these findings will be necessary before stronger conclusions can be made. Further, the discovery GWAS were primarily conducted in ascertained samples that differ substantially from the population based ABCD sample of children. Relatedly, selection effects of discovery GWAS may result in biased estimates of PRS associations, such that participants in a GWAS of problematic substance use may not be reflective of the overall population of those with SUDs. Finally, it is possible that associations between substance misuse PRS and cognitive abilities may emerge as these children age; genetic influences on cognition tend to grow over time, as individuals can select environments (e.g., hobbies, employment, friends) that may be correlated with their genes and that also can affect their cognitive performance. For instance, those with high

polygenic liability toward substance misuse may choose friends and environments that foster the initiation and problematic use of substances and not cognitive pursuits.

Some limitations of the current study include that the PRS were derived from GWAS studies with relatively small sample sizes, particularly for cannabis use disorder, and thus explain a relatively small proportion of variance in the relevant phenotype and thereby limit power to detect significant effects. Further, although there are now relatively large GWAS of alcohol use disorder and dependence available in non-European ancestries populations, this is not the case for tobacco or cannabis; thus, we confined our analyses to individuals in the ABCD sample who were of European genetic ancestry, to avoid potential biases. However, we note that limiting our analyses to individuals of European ancestry means that these findings may not be generalizable across all ancestries. In addition, our data are cross-sectional. As the ABCD study accumulates more waves of data, it would be interesting to examine longitudinal trajectories of these PRS associations with cognition phenotypes that may be more robust as these children age, and to explore the ways in which substance use initiation in these children influences these associations.

Overall, the data presented here suggest that genetic predisposition to lifetime cannabis use is positively linked with cognitive ability in middle childhood, but we found no other significant associations between substance use and misuse PRS and cognitive factors. These data set the stage for future research to better disentangle the longitudinal development of these relationships as substance use is initiated and when problems with such use may be encountered.

Author Disclosures

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Contributors

SEP and ECJ had full access to the data used and take responsibility for the accuracy of analyses. SEP, ASH, and ECJ conceptualized and designed the study. SEP, ASH, ECJ, RB, and AA analyzed and/or interpreted the data. SEP and ECJ drafted the manuscript, and ASH, DMB, WKT, AA, and RB provided critical revisions relevant to intellectual content.

Conflict of Interest

No conflicts declared.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.drugalcdep.2022.109277.

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