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ORIGINAL ARTICLE

Shared Genetic Etiology between Cortical Brain Morphology and Tobacco, Alcohol, and Cannabis Use

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Abstract

Genome-wide association studies (GWAS) have identified genetic variants associated with brain morphology and substance use behaviors (SUB). However, the genetic overlap between brain structure and SUB has not been well characterized. We leveraged GWAS summary data of 71 brain imaging measures and alcohol, tobacco, and cannabis use to investigate their genetic overlap using linkage disequilibrium score regression. We used genomic structural equation modeling to model a "common SUB genetic factor" and investigated its genetic overlap with brain structure. Furthermore, we estimated SUB polygenic risk scores (PRS) and examined whether they predicted brain imaging traits using the Adolescent Behavior and Cognitive Development (ABCD) study. We identified 8 significant negative genetic correlations, including between (1) alcoholic drinks per week and average cortical thickness, and (2) intracranial volume with age of smoking initiation. We observed 5 positive genetic correlations, including those between (1) insula surface area and lifetime cannabis use, and (2) the common SUB genetic factor and pericalcarine surface area. SUB PRS were associated with brain structure variation in ABCD. Our findings highlight a shared genetic etiology between cortical brain morphology and SUB and suggest that genetic variants associated with SUB may be causally related to brain structure differences.

Key words: alcohol use, cannabis use, genetics, neuroimaging, smoking behavior

Introduction

Heavy use of alcohol, tobacco, or cannabis is associated with serious negative consequences, including increased risk for unemployment (Kendler et al. 2017), psychiatric comorbidity (Hasin et al. 2017; Mammen et al. 2018), substance use disorders (Danielsson et al. 2012), morbidity and mortality (Whitfield et al. 2018). Over the last few decades, noninvasive brain imaging techniques have significantly bolstered our understanding of brain structure and function and their relationship with substance use. In parallel, lower genotyping costs, advancements in statistical genetics methods, and the availability of larger samples have enabled the investigation of genetic influences on both brain structure (Hibar et al. 2017; Satizabal et al. 2019; Grasby et al. 2020) and substance use (Pasman et al. 2018; Liu et al. 2016). Despite significant developments in neuroimaging and molecular genetics technologies, few studies have examined how the genetic architectures of alcohol, tobacco, and cannabis use are associated with neuroanatomical measures.

A substantial body of work has linked brain structural variation to substance use and abuse at the phenotypic level among adults. For instance, cannabis use has been associated with reduced cortical thickness and surface area of the right entorhinal cortex (Paul and Bhattacharyya 2018), and an analysis of subcortical surface morphology identified localized differences in surface area and radial distance of the hippocampus, thalamus, putamen, and amygdala, among persons with alcohol dependence (Chye et al. 2019). The same study found surface area differences in the bilateral hippocampus, right nucleus accumbens, thalamus, and putamen among individuals with alcohol dependence (Chye et al. 2019). In another study, Gillespie et al. (2018) found an association between smaller thalamus volume and nicotine use in middle-aged males and no significant associations between subcortical volumes and cannabis use. Another study reported that higher levels of alcohol use were associated with thinner medial and dorsolateral frontal and parieto-occipital cortical regions, in addition to a larger left ventricle volume (Lange et al. 2017). In 2 of the largest meta-analyses on substance use disorders and neurological structures to date, individuals with alcohol use disorder had lower cortical thicknesses in several brain regions (e.g., insula, precuneus) (Mackey et al. 2016) and smaller cortical volumes of the thalamus, putamen, hippocampus, amygdala, and accumbens (Navarri et al. 2020). Taken together, although these studies vary widely in terms of their image acquisition methods and selection of brain regions, they highlight that alcohol, tobacco, and cannabis use are related to differences in brain morphology. However, it is unclear the extent to which these relationships are due to shared genetic factors.

The heritable nature of brain structure has been well-documented (Kremen et al. 2010; Kremen et al. 2013; Renteria et al. 2014; Swagerman et al. 2014), with genetic influences explaining close to 70% of the variance in global, subcortical, and ventricular volumes; and 45% of the variance in frontal, parietal, occipital, and temporal lobe thickness (Kremen et al. 2010). The genetic variation observed in brain structure and function is driven mainly by polygenic influences (i.e., multiple genetic loci of small individual effect sizes) (Elliott et al. 2018; van der Lee et al. 2019; Biton et al. 2020). Several studies to date have attempted to identify (1) common genetic variants underpinning brain structure, and (2) genetic variants associated with psychiatric conditions and their relationship with variability in brain morphology. In a recent genome-wide association meta-analysis, common genetic variants accounted for 34% and 26% of the variance in total cortical surface area and average cortical thickness, respectively (Grasby et al. 2020). Also, previous studies found either no or small negative genetic correlations between psychiatric phenotypes (e.g., schizophrenia, bipolar disorder) and intracranial volume (Ohi et al. 2020). To date, only one study has investigated genetic correlations between substance use phenotypes and brain structural properties and observed a very small genetic correlation between cigarette smoking frequency and cortical surface area (Grasby et al. 2020).

In addition to the limited work that has examined genetic associations between substance use and brain structure, there is a dearth of work that has investigated whether the genetics of substance use could be used to predict neuroimaging traits. Understanding whether genetic risk for substance use behaviors predicts neuroanatomical structures may elucidate potential mechanisms that contribute to substance use engagement. One study investigated whether substance use polygenic risk scores (PRS), defined as one's aggregate genetic risk for a given phenotype (Maher 2015), was related to differences in cortical volumes; this study found that greater PRS for more frequent smoking was tied to smaller cortical volumes of the right orbitofrontal cortex in a sample of adolescents (Li et al. 2020).

The primary goal of the present study was to investigate potential genetic overlap between substance use and brain morphology by examining genetic correlations between these phenotypes. A significant genetic correlation between 2 traits is typically a sign of pleiotropy (Cho et al. 2020), of which there are 2 types, horizontal and vertical pleiotropy. There are several ways to distinguish between them, but it is an active area of research. Here, we propose PRS can be used in differentially exposed samples. For example, if the PRS derived from one trait is associated with another trait (and vice versa) regardless of whether or not the sample has been exposed to the trait for which the PRS was calculated, this might indicate horizontal pleiotropy. Horizontal pleiotropy refers to the existence of shared genetic factors that affect both traits independently (Cho et al. 2020). Vertical pleiotropy, on the other hand, occurs when there is a causal relationship between the 2 traits, which causes them to be genetically correlated as the genetic effects for the causal trait will be proportionally affecting the other trait (Geiler-Samerotte et al. 2020). Vertical pleiotropy may cause the PRS of an exposure (or causal trait) to predict the outcome trait only in a sample in which there is variance with relation to the exposure such that some proportion of the sample has been exposed for the causal changes in the outcome to occur.

With the goal of examining shared genetic factors underpinning both SUB and neuroimaging traits, we leverage the availability of recent genome-wide association studies (GWAS) summary statistics from large meta-analyses conducted by the Enhancing Neuro-Imaging Genetics through Meta-Analysis (ENIGMA) consortium (Hibar et al. 2017; Thompson et al. 2017; Thompson et al. 2020), the GWAS & Sequencing Consortium of Alcohol and Nicotine use (GSCAN) (Liu et al. 2016), and the International Cannabis Consortium (Spechler et al. 2019) to estimate pairwise genetic correlations between

brain morphology measures (regional cortical surface area and thickness for 34 regions of interest and intracranial volume, total cortical surface area, and mean thickness); and tobacco use measurements (age of smoking initiation, ever being a regular smoker, smoking heaviness, and continuation vs. cessation), alcohol use (number of drinks per week), and lifetime cannabis use. To our knowledge, this is the first study to date to explore these genetic relationships. Furthermore, consistent with the common liability hypothesis (Kendler et al. 2007), genetic variants implicated in multiple substance use behaviors may be associated with specific or global neuroanatomic differences, an empirical question that remains unanswered. To address this gap, we used genomic structural equation modeling (gSEM) (Grotzinger et al. 2019) to model a common genetic factor across substance use phenotypes (i.e., tobacco, alcohol, and cannabis use) and evaluated its genetic correlation with cortical morphology measures.

Lastly, we probed significant genetic associations between substance use behaviors and neuroimaging traits by deriving substance use PRS and examined their associations with brain morphology in the Adolescent Behavior and Cognitive Development (ABCD) study, a sample of drug-naïve children aged 9–10. This work has the potential to determine whether SUB PRS predicts variation in brain structure prior to substance use engagement, thus elucidating neurobiological antecedents that may confer risk for using substances.

Methods

Datasets

Brain Imaging Measures

GWAS summary statistics for 71 neuroimaging measures were obtained through direct application to the ENIGMA Consortium (Thompson et al. 2017; Thompson et al. 2020). We specifically used summary statistics from the principal meta-analyses conducted in European ancestry individuals for 68 bilateral cortical measures (thickness and surface area) and mean cortical thickness and total cortical surface area (Grasby et al. 2020), and a large GWAS conducted on intracranial volume (Adams et al. 2016). These measurements were based on brain magnetic resonance imaging scans and genome-wide genotype data from the largest genetic studies of brain structure (Table 1). Participants in all cohorts from these studies gave written informed consent, and sites involved obtained approval from local research ethics committees or Institutional Review Boards. In the original analysis, GWAS summary statistics from each of the 50 sites had been combined using a fixed-effect inverse variance weighted meta-analysis in METAL (Willer et al. 2010).

Tobacco and Alcohol Use Measures

GWAS summary statistics for alcohol and tobacco use phenotypes were obtained from the repository of their corresponding publication which included over 1 million individuals (Liu et al. 2016). Several GWAS were conducted, including (1) ever regularly smoked; (2) age of smoking initiation; (3) smoking heaviness (i.e., packs per day); (4) smoking cessation (i.e., current smoker versus former smoker); and (5) alcohol frequency (i.e., number of drinks per week). GWAS were conducted among European ancestry individuals and included samples from both the 23andMe and GSCAN cohorts. Summary statistics for the 23andMe cohort were obtained via an application and signing of a data transfer agreement between 23andMe, Inc. and the QIMR Berghofer Medical Research Institute where the genetic analyses were conducted.

Lifetime Cannabis Use

The GWAS summary statistics for lifetime cannabis use were retrieved from a meta-analysis ($N = 184\,765$), which included European ancestry individuals from The International Cannabis Consortium, UK Biobank, and 23andMe (Pasman et al. 2018). Summary statistics excluding the 23andMe cohort were obtained from the International Cannabis Consortium's online repository (https://www.ru.nl/bsi/research/group-pages/substance-use-addiction-food-saf/vm-saf/genetics/international-cannabis-consortium-icc/). Summary statistics for the 23andMe cohort were obtained via application and signing of a data transfer agreement between 23andMe, Inc. and the QIMR Berghofer Medical Research Institute. Across all samples used in the GWAS, participants reported on whether they had ever used cannabis or marijuana (e.g., weed, dope, draw) in their lifetime. The 23andMe summary statistics datasets were meta-analyzed with the corresponding summary statistics from GSCAN and The International Cannabis Consortium's datasets. We used an inverse variance weighted meta-analysis implemented in METALv2011-03-25 (Willer et al. 2010).

Statistical Analyses

Linkage Disequilibrium Score Regression

Linkage disequilibrium score (LDSC) regression (Bulik-Sullivan et al. 2015a; 2015b) was used to assess pairwise genetic correlations between substance use (i.e., tobacco, alcohol, and cannabis use) and intracranial volume, as well as global and regional cortical surface area and thickness. LDSC leverages the expected relationship between the amount of LD that a variant tags and its association with a trait to model heritability and coheritability using only the distribution of variant effect sizes. LDSC regression can then assess whether inflation in GWAS test statistics is due to polygenicity or confounding biases such as cryptic relatedness or population stratification. Likewise, bivariate LDSC regression can be used to distinguish between true genetic correlations between traits and inflation due to sample overlap. For this study, each dataset was filtered to only include markers overlapping with HapMap Project Phase 3 single nucleotide polymorphisms (SNPs) ($N_{overlap} = 1\,217\,312$) as these tend to be well-imputed across datasets, and alleles will match those listed in the data used to estimate the LD score. We used precomputed LD scores for European populations, as provided on the LDSC website (https://github.com/bulik/ldsc). Standard errors were estimated using a block jackknife procedure and used to calculate P values.

Genomic Structural Equation Modeling (GSEM)

To gain insights into the genetic etiology of substance use in general, we performed a common factor GWAS using (gSEM) (Grotzinger et al. 2019) implemented in R. This approach leverages the genetic variance–covariance matrix between the traits under study estimated through LDSC regression. Then, structural equation models are used to partition the covariance structure and estimate latent factors. In the current study, we desired to study the common genetic etiology of substance use phenotypes and thus specified a common factor model. The effect of a genetic variant on the common factor can be estimated by including the SNPs covariance with the

Table 1 Source of GWAS summary statistics datasets for phenotypes analyzed in this study

Study	Phenotypes	N participants	N cohorts
Hibar et al. 2017	Intracranial volume	33 536	65
Grasby et al. 2020	Mean cortical thickness Total cortical surface area Surface area and thickness for 34 ROIs	33 992	50
Liu et al. 2016 [a]	Drinks per week Ever regularly smoked Smoking heaviness Smoking cessation Age at smoking initiation	~1.2 million	29
Pasman et al. 2018 [a]	Lifetime cannabis use	184 765	18

Note: Summary statistics from the studies above only included European ancestry cohorts.
[a]The GWAS summary results also included the 23andMe cohort.

traits studied in the model. Repeating this procedure for all genetic variants yields a GWAS of the common factor. Genetic correlations between this common factor GWAS and the neuroimaging traits of interest were performed using bivariate LDSC regression.

Brain Plots

As shown in Figure 1, the cortical thickness and surface area results are presented by mapping the z-score for the genetic correlation between a given trait and a brain region onto a brain triangular surface plot. These plots were generated using python v.3.5 and the modules matplotlib, numpy, plotly, pandas, and scipy. All of the z-scores in Figure 1 are shown without any filtering. Statistically significant results are displayed in the tables.

Polygenic Risk Scoring

We estimated PRS in the ABCD study, a sample of 9–10 year olds at baseline who were recruited from various sites in the USA (Volkow et al. 2018). The ABCD sample was not included in the GWAS considered in the current study; thus, the inclusion of ABCD not only ensured sample independence, but also a lack of sample exposure to the substances studied here. Only SNPs passing quality control (minor allele frequency > 0.01, call rate > 0.9 and imputation score > 0.6) were included in the PRS analyses. To adjust for linkage disequilibrium, we used a clumping + thresholding approach. Briefly, GWAS summary statistics were clumped using PLINK1.9 using a correlation cutoff of 0.05 and a distance of 500 kilobases. Then, 8 PRS were estimated. Each of these PRS were calculated using an increasingly liberal P value threshold for variant inclusion ($P < 5 \times 10^{-8}$, $P < 1 \times 10^{-5}$, $P < 0.001$, $P < 0.01$, $P < 0.05$, $P < 0.1$, $P < 0.5$, $P < 1$). PRS were estimated by multiplying the effect size (obtained from GWAS) times the allelic dosage of the effect allele and summing across all loci for each participant. To test for the association between PRS and region of interest (ROI) morphology, we used a multiple linear regression implemented in python(v3.5) with the library statsmodels. Additional covariates included in the model were sex, age, sex×age, age^2, sex×age^2, and the first 10 genetic ancestry components to adjust for population stratification. Variance explained was estimated as the difference in Pearson correlation coefficient between the full model (i.e., including the PRS) and a reduced model including only the covariates.

Multiple Testing and Significance Threshold

In all analyses using LDSC regression, we applied Benjamini–Hochberg's False Discovery Rate (FDR < 5%) to account for multiple testing (i.e., the number of cortical neuroimaging traits) within each substance use phenotype (Benjamini and Hochberg 1995). Genetic correlations that were nominally significant (i.e., $P < 0.05$) but did not survive multiple testing corrections are reported in the Supplementary Materials. For the analyses examining the relationship between substance use PRS and the neuroimaging traits, 8 sets of analyses (one for each PRS threshold) were conducted for each brain structure. To account for this multiple testing, we used a Bonferroni-corrected P value of 0.006 (0.05/8 tests) to evaluate statistical significance.

Results

Figure 1 shows an overview of the results as summarized by raw z-scores for all genetic correlations between substance use and brain morphology phenotypes, regardless of their level of statistical significance. Overall, we observed positive associations between alcohol use and cortical surface area. A similar pattern was observed for smoking-related phenotypes, with the exception of a negative association between smoking behaviors and surface area of the inferior temporal lobe.

Alcohol

As shown in Table 2, after correcting for multiple testing, significant positive genetic correlations were observed between alcohol use and total cortical surface area ($r_g = 0.12$; P value = 0.023) and surface area of the postcentral gyrus's regional area ($r_g = 0.17$; P value = 4.3×10^{-4}). A significant negative genetic correlation was observed between alcohol use and global average cortical thickness ($r_g = -0.10$, P value = 0.047).

Smoking

Significant negative genetic correlations (Table 2) were observed between ever regularly smoked and (1) intracranial volume ($r_g = -0.09$, P value = 0.038), (2) average cortical thickness ($r_g = -0.09$, P value = 0.02), and (3) surface area of the inferior temporal lobe ($r_g = -0.13$, P value = 8×10^{-4}). A significant negative genetic correlation was observed between age of smoking initiation and intracranial volume ($r_g = -0.21$, P value = 0.02). Last, a significant positive genetic correlation was observed

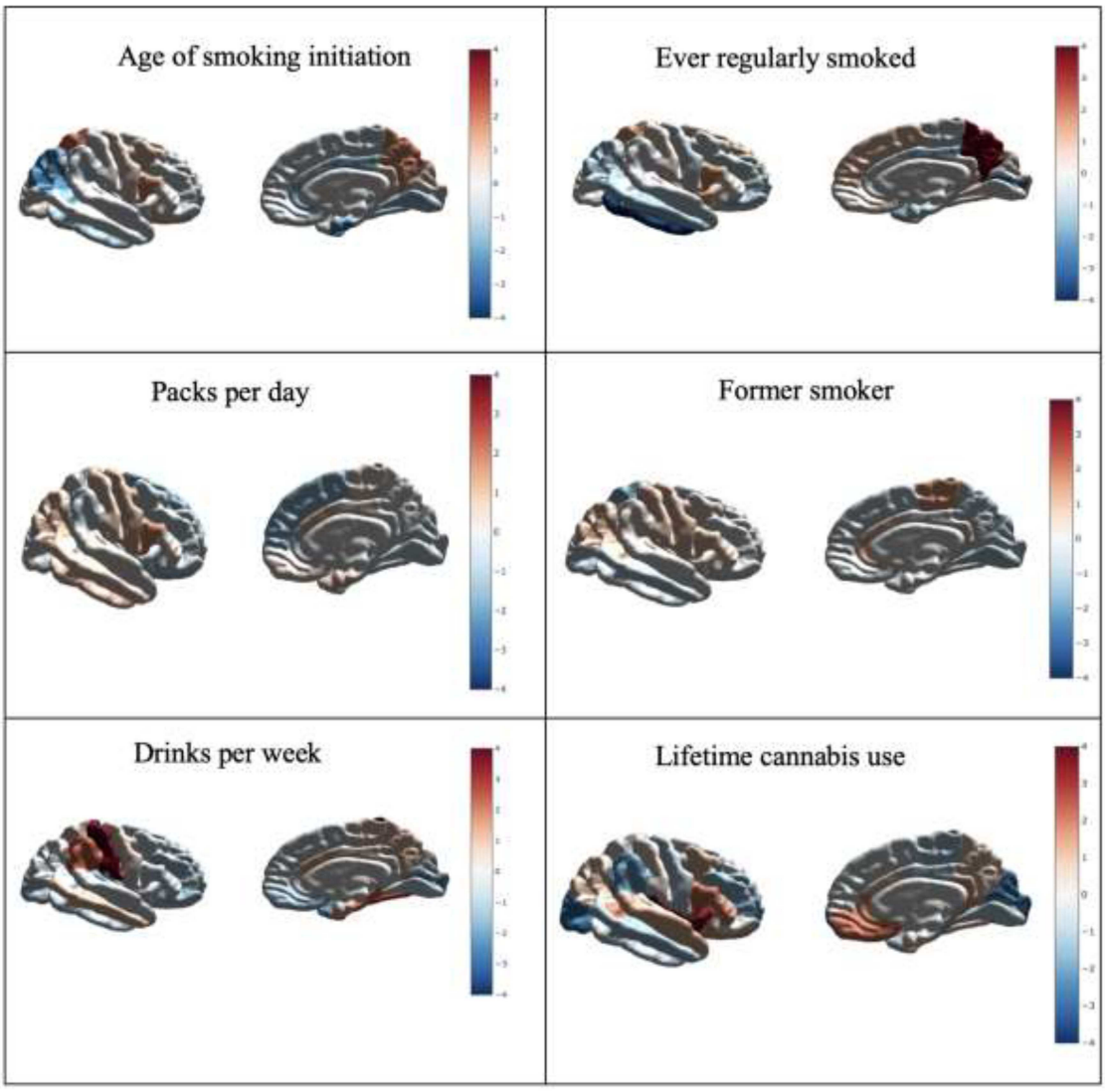

Figure 1. Standardized effect sizes (*z*-scores) reflecting the relationship between genetic risk for the substance use phenotypes and surface area. Positive effects highlighted in red denote increases in surface area and negative effects highlighted in blue denote reductions in surface area for colored regions. Results shown here correspond to all observed genetic correlations regardless of their level of statistical significance. Details for genetic correlations which surpassed multiple testing correction are shown in Table 2.

between ever regularly smoked and precuneus surface area ($r_g = 0.10$, *P* value = 0.002).

Cannabis

As shown in Table 2, a significant positive genetic correlation was found between lifetime cannabis use and insula surface area ($r_g = 0.17$, *P* value = 7.4×10^{-3}). No other associations between cannabis use and neuroimaging traits remained significant after multiple testing correction.

Common Substance Use Genetic Factor

Negative genetic associations were observed between the common substance use genetic factor and the surface areas of the inferior temporal gyrus ($r_g = -0.13$, *P* value = 0.002) and pericalcarine ($r_g = -0.09$, *P* value = 0.012), and cortical thickness ($r_g = -0.09$, *P* value = 0.023) (Table 2). In addition, a positive genetic correlation was observed involving the common substance use genetic factor and the precuneus surface area ($r_g = 0.10$, *P* value = 0.012).

PRS Analyses

A secondary set of analyses assessing the association between substance use PRS with the neuroimaging traits were performed. Briefly, when there was evidence of a genetic association between SUB and neuroimaging traits identified in the LDSC analyses, we derived SUB PRS in the ABCD sample (see methods) and assessed whether they predicted the morphometry of the ROI. As shown in Table 3, several significant PRS associations with brain morphology were observed. Higher PRS for alcohol use predicted greater postcentral gyrus surface area and cortical surface area. Greater PRS for regularly smoking was positively associated with ICV and surface area of the inferior temporal gyrus.

Table 2 Significant genetic correlations after multiple testing correction (FDR < 5%) between brain imaging and substance use phenotypes

Neuroimaging traits	Alcohol (drinks per week)			Ever regularly smoked			Age of smoking initiation			Lifetime cannabis use			Common substance use factor		
	rg	se	P	rg	se	P	rg	se	P	rg	se	P	rg	se	P
Intracranial volume	—	—	—	−0.09	0.03	0.038	−0.21	0.06	0.027	—	—	—	—	—	—
Postcentral gyrus surface rea	0.17	0.04	5.2×10^{-4}	—	—	—	—	—	—	—	—	—	—	—	—
Total cortical surface area	0.12	0.04	0.023	—	—	—	—	—	—	—	—	—	—	—	—
Inferior temporal gyrus surface area	—	—	—	−0.13	0.03	1.01×10^{-3}	—	—	—	—	—	—	−0.13	0.03	1.6×10^{-3}
Precuneus surface area	—	—	—	0.10	0.03	0.002	—	—	—	—	—	—	0.10	0.03	0.012
Insula surface area	—	—	—	—	—	—	—	—	—	0.17	0.05	.009			
Pericalcarine surface area	—	—	—	—	—	—	—	—	—	—	—	—	−0.09	0.03	0.012
Average cortical thickness	−0.10	0.04	0.047	−0.09	0.03	0.020	—	—	—	—	—	—	−0.09	0.03	0.023

There was no evidence of statistically significant associations between (1) age of initiation PRS and ICV, (2) lifetime cannabis use PRS and insula surface area; (3) alcohol use PRS and cortical thickness, (4) ever regularly smoked PRS with inferior temporal gyrus surface area, precuneus surface area, and cortical thickness, and (5) common substance use genetic factor with surface area of the inferior temporal gyrus, precuneus surface area, pericalcarine surface area, and cortical thickness.

Discussion

Although alcohol, tobacco, and cannabis use have previously been linked to brain structural differences (Lange et al. 2017; Paul and Bhattacharyya 2018; Chye et al. 2019), there is a dearth of work that has examined whether the genetic architecture of substance use overlaps with that of brain structure. The present study examined whether genetic liability for alcohol, tobacco, or cannabis use is associated with cortical brain morphology and probed significant genetic associations by creating SUB PRS and examining their association with brain morphology in a substance use naïve sample. Such work has the potential to shed light onto the genetic and neurobiological precursors of substance use behaviors.

In terms of the relationship between alcohol use and brain morphology, we found a genetic correlation between alcoholic drinks per week and a thinner average cortical thickness. These findings are consistent with previous work indicating that individuals with alcohol dependence display decreased cortical thickness compared to nonalcohol dependent individuals (Fortier et al. 2011). There is some evidence that reduced cortical thickness is associated with characteristics such as poorer executive function, which may exacerbate the risk of drinking more frequently (Burzynska et al. 2012). We also found a genetic correlation between drinks per week and larger cortical surface areas and surface areas of the postcentral gyrus, in line with previous work showing that alcohol abuse is associated with structural differences in the bilateral postcentral gyrus (Jang et al. 2007). Future work should investigate the precise mechanisms that account for the association between alcohol consumption and these brain phenotypes.

Regarding the relationship between smoking phenotypes and neuroanatomical traits, intracranial volume was negatively associated with both smoking initiation (i.e., ever being a regular smoker) and age at smoking initiation. Ever being a regular smoker was (a) positively genetically correlated with the precuneus surface area, and (b) negatively genetically correlated with average cortical thickness and surface area of the inferior temporal gyrus. Previous observational studies have identified a relationship between phenotypic smoking and structural variation in the inferior temporal cortex (a region implicated in object and face recognition) (Conway 2018) and the precuneus (a region involved in motor imagery, directing attention, and processing abstract mental images) (Ogiso et al. 2000). For instance, an increased number of years of smoking has been associated with smaller cortical volumes in the left middle temporal gyrus and right inferior temporal gyrus (Thiel and Fink 2007) and cortical perfusion levels in the left precuneus (Durazzo et al. 2015). These findings suggest that the genetic association between brain morphology and tobacco smoking depends mainly on the age at which the behavior started or having a lifetime history of smoking regularly, rather than on its frequency or being a former smoker.

Table 3 Substance use PRS associations with brain imaging traits in the ABCD study

PRS phenotype and threshold	Neuroimaging trait	beta	se	P	rsq
Age of smoking initiation $P < 5 \times 10–8$	ICV	234858.981	140317.946	0.0942175	0.00027157
Age of smoking initiation $P < 5 \times 10–5$	ICV	47480.4985	21525.4542	0.02742835	0.00047153
Age of smoking initiation $P < 0.001$	ICV	362.899012	4812.83657	0.93989656	5.51E-07
Age of smoking initiation $P < 0.01$	ICV	913.671368	2128.03885	0.66768118	1.79E-05
Age of smoking initiation $P < 0.05$	ICV	0.84520238	1343.31729	0.99949799	3.84E-11
Age of smoking initiation $P < 0.10$	ICV	254.083657	1133.04516	0.82256987	4.88E-06
Age of smoking initiation $P < 0.50$	ICV	148.33005	873.235382	0.86512261	2.80E-06
Age of smoking initiation $P < 1$	ICV	258.738116	861.626692	0.7639638	8.74E-06
Lifetime cannabis use $P < 5 \times 10–8$	Insula SA	37.4306302	26.6738751	0.1605766	0.00020745
Lifetime cannabis use $P < 5 \times 10–5$	Insula SA	5.65217963	12.7767595	0.65822678	2.06E-05
Lifetime cannabis use $P < 0.001$	Insula SA	1.01071199	3.12938501	0.74672316	1.10E-05
Lifetime cannabis use $P < 0.01$	Insula SA	1.06632932	1.43571811	0.45767678	5.81E-05
Lifetime cannabis use $P < 0.05$	Insula SA	−0.3878843	0.82967746	0.64014661	2.30E-05
Lifetime cannabis use $P < 0.10$	Insula SA	0.14259272	0.71478884	0.84188525	4.19E-06
Lifetime cannabis use $P < 0.50$	Insula SA	0.11972915	0.55560989	0.82938989	4.89E-06
Lifetime cannabis use $P < 1$	Insula SA	0.17710138	0.54598012	0.74566418	1.11E-05
Alcohol (drinks per week) $P < 5 \times 10–8$	Postcentral gyrus SA	314.0491	241.34794	0.19321851	0.00018698
Alcohol (drinks per week) $P < 5 \times 10–5$	Postcentral gyrus SA	242.191884	157.208433	0.12346028	0.00026207
Alcohol (drinks per week) $P < 0.001$	Postcentral gyrus SA	122.137472	76.1193971	0.10863333	0.00028428
Alcohol (drinks per week) $P < 0.01$	Postcentral gyrus SA	94.2982005	46.2256129	0.04138856	0.0004594
Alcohol (drinks per week) $P < 0.05$	Postcentral gyrus SA	90.5536151	32.4186689	0.00523085	0.00086092
Alcohol (drinks per week) $P < 0.10$	Postcentral gyrus SA	83.2904156	28.6206291	0.00362279	0.00093441
Alcohol (drinks per week) $P < 0.50$	Postcentral gyrus SA	68.464345	24.0737467	0.00446757	0.00089242
Alcohol (drinks per week) $P < 1$	Postcentral gyrus SA	69.2765934	23.7780433	0.00358458	0.00093653
Alcohol (drinks per week) $P < 5 \times 10–8$	Cortical SA	9124.44994	7610.78436	0.23060957	0.00014092
Alcohol (drinks per week) $P < 5 \times 10–5$	Cortical SA	7455.72118	4957.00023	0.13260169	0.00022178
Alcohol (drinks per week) $P < 0.001$	Cortical SA	3792.39809	2400.82514	0.11423406	0.00024461
Alcohol (drinks per week) $P < 0.01$	Cortical SA	4060.76871	1457.95714	0.0053617	0.00075999
Alcohol (drinks per week) $P < 0.05$	Cortical SA	3152.539	1022.41403	0.0020535	0.00093121
Alcohol (drinks per week) $P < 0.10$	Cortical SA	2884.8708	902.673758	0.00139946	0.00100031
Alcohol (drinks per week) $P < 0.50$	Cortical SA	2060.42849	759.34238	0.00667361	0.00072134
Alcohol (drinks per week) $P < 1$	Cortical SA	2053.69802	750.018751	0.00619183	0.00073455
Alcohol (drinks per week) $P < 5 \times 10–8$	Cortical thickness	0.04544648	0.05265596	0.3881184	9.23E-05
Alcohol (drinks per week) $P < 5 \times 10–5$	Cortical thickness	0.05690662	0.0342854	0.09699681	0.0003413
Alcohol (drinks per week) $P < 0.001$	Cortical thickness	−0.0013141	0.01660991	0.93694271	7.76E-07
Alcohol (drinks per week) $P < 0.01$	Cortical thickness	−0.0050523	0.01009038	0.61659566	3.11E-05
Alcohol (drinks per week) $P < 0.05$	Cortical thickness	−0.0043889	0.00707866	0.53526241	4.76E-05
Alcohol (drinks per week) $P < 0.10$	Cortical thickness	−0.0049285	0.00624998	0.43038693	7.71E-05
Alcohol (drinks per week) $P < 0.50$	Cortical thickness	−0.003584	0.00525614	0.49533922	5.76E-05
Alcohol (drinks per week) $P < 1$	Cortical thickness	−0.0045353	0.0051915	0.38236757	9.46E-05
Ever regularly smoked $P < 5 \times 10–8$	ICV	−1978.042	5072.99229	0.69660919	1.47E-05
Ever regularly smoked $P < 5 \times 10–5$	ICV	−3458.9854	3759.51187	0.35756877	8.21E-05
Ever regularly smoked $P < 0.001$	ICV	−4331.9386	2443.59965	0.07630616	0.00030464
Ever regularly smoked $P < 0.01$	ICV	−4509.9739	1860.97659	0.01539681	0.0005691
Ever regularly smoked $P < 0.05$	ICV	−3515.4547	1528.28333	0.02145969	0.00051276
Ever regularly smoked $P < 0.10$	ICV	−4043.4712	1416.89768	0.0043321	0.00078891
Ever regularly smoked $P < 0.50$	ICV	−3683.6723	1277.07865	0.00393175	0.00080596
Ever regularly smoked $P < 1$	ICV	−3629.1407	1270.23747	0.00428726	0.00079074
Ever regularly smoked $P < 5 \times 10–8$	Inferior temporal gyrus SA	−8.4774256	16.8143476	0.61415056	2.76E-05
Ever regularly smoked $P < 5 \times 10–5$	Inferior temporal gyrus SA	−11.001419	12.4625704	0.37739505	8.45E-05
Ever regularly smoked $P < 0.001$	Inferior temporal gyrus SA	−17.476902	8.09826778	0.03095036	0.00050474
Ever regularly smoked $P < 0.01$	Inferior temporal gyrus SA	−17.940266	6.16611144	0.00363043	0.00091696
Ever regularly smoked $P < 0.05$	Inferior temporal gyrus SA	−7.9418555	5.06553519	0.11696357	0.00026647
Ever regularly smoked $P < 0.10$	Inferior temporal gyrus SA	−7.802245	4.69788283	0.09679399	0.000299
Ever regularly smoked $P < 0.50$	Inferior temporal gyrus SA	−6.3497341	4.23451398	0.13377975	0.00024376
Ever Regularly Smoked $P < 1$	Inferior temporal gyrus SA	−6.3576148	4.21178636	0.13121644	0.00024701
Ever regularly smoked $P < 5 \times 10–8$	Precuneus SA	−6.668509	18.5119273	0.71868667	1.39E-05
Ever regularly smoked $P < 5 \times 10–5$	Precuneus SA	−8.3536585	13.7222474	0.54269637	3.96E-05
Ever regularly smoked $P < 0.001$	Precuneus SA	−10.0019	8.91705899	0.26204213	0.00013444
Ever regularly smoked $P < 0.01$	Precuneus SA	−10.59728	6.79150769	0.11871272	0.00026014
Ever regularly smoked $P < 0.05$	Precuneus SA	−3.1817718	5.5778535	0.56840299	3.48E-05

(Continued)

Table 3 Continued

PRS phenotype and threshold	Neuroimaging trait	beta	se	P	rsq
Ever regularly smoked $P < 0.10$	Precuneus SA	−2.7015228	5.17231723	0.60147349	2.92E-05
Ever regularly smoked $P < 0.50$	Precuneus SA	−2.1866766	4.66179669	0.63903775	2.35E-05
Ever regularly smoked $P < 1$	Precuneus SA	−2.1720255	4.63682002	0.6394903	2.35E-05
Ever regularly smoked $P < 5 \times 10–8$	Cortical thickness	−0.0026998	0.00424612	0.52491442	5.01E-05
Ever regularly smoked $P < 5 \times 10–5$	Cortical thickness	−0.000504	0.00314707	0.87277414	3.18E-06
Ever regularly smoked $P < 0.001$	Cortical thickness	0.0001948	0.00204637	0.92416299	1.12E-06
Ever regularly smoked $P < 0.01$	Cortical thickness	−0.0009318	0.00155876	0.55002245	4.43E-05
Ever regularly smoked $P < 0.05$	Cortical thickness	−0.0024819	0.00127979	0.0525028	0.00046586
Ever regularly smoked $P < 0.10$	Cortical thickness	−0.0021716	0.00118668	0.06729459	0.00041484
Ever regularly smoked $P < 0.50$	Cortical thickness	−0.0018017	0.00106948	0.09208759	0.00035161
Ever regularly smoked $P < 1$	Cortical thickness	−0.0018479	0.00106367	0.08236926	0.00037392
Common SUB factor $P < 5 \times 10–8$	Inferior temporal gyrus SA	−285.23808	271.72387	0.29387263	0.00011948
Common SUB factor $P < 5 \times 10–5$	Inferior temporal gyrus SA	−245.08906	168.354548	0.14549085	0.00022976
Common SUB factor $P < 0.001$	Inferior temporal gyrus SA	−106.53498	101.973457	0.2961792	0.00011834
Common SUB factor $P < 0.01$	Inferior temporal gyrus SA	10.6785604	73.5891492	0.88462738	2.28E-06
Common SUB factor $P < 0.05$	Inferior temporal gyrus SA	−18.147942	58.4265476	0.75610453	1.05E-05
Common SUB factor $P < 0.10$	Inferior temporal gyrus SA	−30.149333	53.3313944	0.5718721	3.47E-05
Common SUB factor $P < 0.50$	Inferior temporal gyrus SA	−41.969645	47.3527678	0.37547328	8.52E-05
Common SUB factor $P < 1$	Inferior temporal gyrus SA	−32.905934	47.1182847	0.48496759	5.29E-05
Common SUB factor $P < 5 \times 10–8$	Precuneus SA	−380.97908	299.149805	0.20286484	0.00017331
Common SUB factor $P < 5 \times 10–5$	Precuneus SA	−133.06232	185.367588	0.47288403	5.51E-05
Common SUB factor $P < 0.001$	Precuneus SA	20.2493511	112.278233	0.85688271	3.48E-06
Common SUB factor $P < 0.01$	Precuneus SA	135.433412	80.9894219	0.09451816	0.00029876
Common SUB factor $P < 0.05$	Precuneus SA	144.306263	64.2938244	0.02482955	0.00053806
Common SUB factor $P < 0.10$	Precuneus SA	134.479338	58.6958016	0.02198295	0.00056064
Common SUB factor $P < 0.50$	Precuneus SA	90.548278	52.1227025	0.08238913	0.00032242
Common SUB factor $P < 1$	Precuneus SA	92.6382002	51.8617832	0.07409755	0.00034087
Common SUB factor $P < 5 \times 10–8$	Pericalcarine SA	−106.33581	136.11675	0.43470263	7.47E-05
Common SUB factor $P < 5 \times 10–5$	Pericalcarine SA	−83.22776	84.3292338	0.32370361	0.00011924
Common SUB factor $P < 0.001$	Pericalcarine SA	−72.053948	51.0860628	0.15844919	0.0002435
Common SUB factor $P < 0.01$	Pericalcarine SA	−28.6623	36.8530616	0.43674282	7.41E-05
Common SUB factor $P < 0.05$	Pericalcarine SA	−46.868987	29.2560626	0.10919047	0.00031412
Common SUB factor $P < 0.10$	Pericalcarine SA	−49.474937	26.7060453	0.06398133	0.00042002
Common SUB factor $P < 0.50$	Pericalcarine SA	−57.746032	23.7081432	0.01488518	0.00072581
Common SUB factor $P < 1$	Pericalcarine SA	−56.845659	23.5901382	0.01598784	0.00071042
Common SUB factor $P < 5 \times 10–8$	Cortical thickness	−0.108783	0.06862599	0.11297138	0.00031131
Common SUB factor $P < 5 \times 10–5$	Cortical thickness	−0.0286126	0.04253268	0.50114585	5.61E-05
Common SUB factor $P < 0.001$	Cortical thickness	−0.0035863	0.02575566	0.88926085	2.40E-06
Common SUB factor $P < 0.01$	Cortical thickness	−0.0247286	0.01858003	0.18325307	0.00021948
Common SUB factor $P < 0.05$	Cortical thickness	−0.022517	0.0147516	0.12694879	0.00028866
Common SUB factor $P < 0.10$	Cortical thickness	−0.0228674	0.01346731	0.08954865	0.00035719
Common SUB factor $P < 0.50$	Cortical thickness	−0.021622	0.01195656	0.07058626	0.00040511
Common SUB factor $P < 1$	Cortical thickness	−0.0221886	0.01189683	0.06220768	0.00043091

Note: ICV = intracranial volume; SUB = substance use behavior; SA = surface area.

Lifetime cannabis use was negatively genetically correlated with insula surface area. Individuals who have greater genetic liability for using cannabis may use cannabis more frequently, which has been associated with cortical differences (Chye et al. 2020; De Niz et al. 2020), such as variation in the insula. For example, work by Chye et al. (2019, 2020) indicated that adolescents who used cannabis showed reduced thickness in the bilateral insula, a brain region that has been closely linked to addictive behaviors, including craving and drug-seeking, interoceptive processing, response to reward, and impulsive decision making (Battistella et al. 2014; Naqvi et al. 2014). Other work has shown that individuals who initiate cannabis use had a smaller insula surface area in the right hemisphere (Infante et al. 2018).

The common substance use genetic factor was positively genetically correlated with precuneus surface area and was negatively genetically associated with average cortical thickness and surface areas of the pericalcarine and the inferior temporal gyrus. These findings are in line with the genetic correlations observed between neuroimaging traits and alcohol, tobacco and cannabis use in isolation. However, the correlation with pericalcarine surface area was unique to the common substance use genetic factor. The pericalcarine cortex, which is involved in visual and spatial processing of information (Holmes et al. 2016), has previously been linked to impulsivity and sensation-seeking (Holmes et al. 2016; Kubera et al. 2018) and substance use (Jacobus et al. 2014). A study reported that individuals who use more than one substance (i.e., alcohol and tobacco) had thicker left pericalcarine cortices relative to controls. However, this association did not remain significant upon controlling for alcohol use (Jacobus et al. 2014).

Several substance use PRS were associated with variation in brain structure in the ABCD sample. For example, higher alcohol use PRS were associated with larger postcentral gyrus surface area and cortical surface area, whereas higher genetic propensity to be a regular smoker was positively associated with ICV and inferior temporal gyrus surface area. The fact that these PRS were associated with structural brain morphology differences in a sample of children prior to substance use engagement suggests that these are either shared genetic factors (horizontal pleiotropy) (Solovieff et al. 2013) or potentially causal associations whereby brain morphology differences predispose certain individuals to engage in substance use. For genetic correlations discovered only though LDSC but not observed through PRS, a potential explanation is that substance use behaviors affect the regional brain morphology. As such, these effects would only be observed in samples where there is variance in relation to substance use behaviors, such as the adult discovery samples for substance use and neuroimaging GWAS, but not for the ABCD sample which includes children naïve to substance use.

Limitations regarding the interpretation of the genetic correlations presented here must be acknowledged. These include the potential influence of pleiotropic effects. It is established that genetic variants associated with a given trait can also be related to other attributes as well (Biton et al. 2020). In our case, a potential mediator is that of cognitive ability and educational attainment. Cognitive ability has been robustly linked to increased total surface area and ICV (Cox et al. 2018; Nave et al. 2019; Mitchell et al. 2020), but has also been negatively associated with substance abuse phenotypes (Gustavson et al. 2017; Schepis et al. 2018; Beverly et al. 2019). Recent studies have shown that a genetic predisposition for higher cognitive ability or educational attainment is linked to variation in regional cortical morphology, particularly in the frontal and temporal lobes (Lett et al. 2020; Mitchell et al. 2020). It is thus plausible that the associations we observe may, in part, be mediated by educational attainment—especially as many of the identified regions for both sets of traits are involved in cognitive processing, impulse control, and decision making. For example, one study found that the surface area and thickness of the prefrontal, insula, and medial temporal cortices were significant mediators of the relationship between PRS for intelligence and general cognitive performance in 2 independent cohorts (Lett et al. 2020). Although we cannot exclude the possibility that some of our observations are influenced by cognitive ability, several of our observations are in contrast to what would be expected if the relationship was entirely driven by cognitive ability. For example, we observed a positive genetic correlation between alcohol use and total cortical surface area. Future studies would benefit from examining the relationship among cortical morphology, substance use, and cognitive ability together.

In addition, longitudinal data on substance use or neuroimaging traits were not available; thus, we were unable to investigate the potential effect of prolonged exposure to the substances investigated here. For instance, in analyses where significant genetic correlations were revealed between substance use and neuroimaging traits, it is possible that the associations observed may be due to changes in neural structures as a result of acute or chronic substance use. Indeed, modifications in glial cell number, reductions in the neuronal size and volume of the neuropile, as well as epigenetic alterations may be possible mechanisms through which substance use contributes to changes in brain structure and function (Cecil et al. 2015; Kroenke and Bayly 2018), something the current study was not able to examine. Future longitudinal studies are needed to examine the direction of effects between substance use and brain structure, as well as investigate brain-based pathways and ROI that may influence the gene-substance use relationship.

Nevertheless, this study is one of few studies to examine genetic correlations between tobacco, alcohol, and cannabis use with neuroimaging traits, elucidating the relationship between the genetic architecture of substance use and brain structure. Moreover, to our knowledge, this is one of the only studies to examine whether substance use PRS could be used to predict variation in brain organization in children, elucidating potential neural mechanisms that predispose individuals to engage in substance use. With the increasing emphasis on precision medicine and personalized health initiatives, our work is a first step in helping to elucidate the complex relationship between genes and brain morphology in relation to substance use; however, at this time, clinical or prevention applications are limited as much remains unknown about the biological and molecular pathways through which substance use influences neural structure and vice versa. In terms of next steps, future research should consider examining genetics, brain structure, substance use and related behaviors, and environments over time to help determine the causal relationships among these variables. Such work has the potential to contribute to a better understanding the mechanisms involved in the pathogenesis of substance use, enable the detection of individuals at heightened risk for substance use problems, and aid in more precise diagnosis and treatments.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request. To apply and access 23andMe summary statistics, please visit research.23andme.com/dataset-access/ for more information.

Supplementary Material

Supplementary material can be found at *Cerebral Cortex* online.

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Notes

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more than 10 000 children age 9–10 and follow them over 10 years into early adulthood.

A full list of supporters is available at https://abcdstudy.org/federal-partners.html. A listing of participating sites and a complete listing of the study investigators can be found at https://abcdstudy.org/consortium_members/. ABCD consortium investigators designed and implemented the study and/or provided data but did not necessarily participate in the analysis or writing of this report. This manuscript reflects the views of the authors and may not reflect the opinions or views of the NIH or ABCD consortium investigators.

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