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Associations Between Cannabis Use, Polygenic Liability for Schizophrenia, and Cannabis-related Experiences in a Sample of Cannabis Users

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***Background and Hypothesis*: Risk for cannabis use and schizophrenia is influenced in part by genetic factors, and there is evidence that genetic risk for schizophrenia is associated with subclinical psychotic-like experiences (PLEs). Few studies to date have examined whether genetic risk for schizophrenia is associated with cannabis-related PLEs. *Study Design*: We tested whether measures of cannabis involvement and polygenic risk scores (PRS) for schizophrenia were associated with self-reported cannabis-related experiences in a sample ascertained for alcohol use disorders (AUDs), the Collaborative Study on the Genetics of Alcoholism (COGA). We analyzed 4832 subjects (3128 of European ancestry and 1704 of African ancestry; 42% female; 74% meeting lifetime criteria for an AUD). *Study Results*: Cannabis use disorder (CUD) was prevalent in this analytic sample (70%), with 40% classified as mild, 25% as moderate, and 35% as severe. Polygenic risk for schizophrenia was positively associated with cannabis-related paranoia, feeling depressed or anhedonia, social withdrawal, and cognitive difficulties, even when controlling for duration of daily cannabis use, CUD, and age at first cannabis use. The schizophrenia PRS was most robustly associated with cannabis-related cognitive difficulties ($\beta = 0.22$, SE = 0.04, $P = 5.2e{-}7$). In an independent replication sample ($N = 1446$), associations between the schizophrenia PRS and cannabis-related experiences were in the expected direction and not statistically different in magnitude from those in the COGA sample. *Conclusions*: Among individuals who regularly use cannabis, genetic liability for schizophrenia—even in those without clinical features—may increase the likelihood of reporting unusual experiences related to cannabis use.**

Introduction

The relationship between cannabis use and psychosis has long been a question of interest.[1,2] Heavy cannabis use itself has been linked to features of schizophrenia, notably psychotic-like experiences (PLEs), cognitive difficulties, and negative symptoms such as social withdrawal and depressed mood.[3–6] In challenge paradigms, it has been shown that administration of delta-9-tetrahydrocannabinol (THC; the principal psychoactive constituent in cannabis)

Table 1. Cannabis-Related Experience Items From the SSAGA Interview

Phrasing in SSAGA: "Because of Your Marijuana Use, Did You Ever Experience:"	Term Used in Current Manuscript
Hearing, seeing, or smelling things that weren't really there?	Hallucinations
Feeling paranoid or suspicious of people for more than 24 h to the point that it interfered with your relationships?	Paranoia
Feeling depressed or uninterested in things for more than 24 h to the point that it interfered with your functioning?	Depression/anhedonia
Decreased contact with friends or family?	Decreased social contact
Having trouble concentrating or having such trouble thinking clearly for more than 24 h to the point that it interfered with your functioning?	Cognitive difficulties

Note: SSAGA, Semi-Structured Assessment for the Genetics of Alcoholism.

can induce acute, transitory PLEs[7–9] that often include forms of unusual thought content, paranoia, and disorganized thinking; auditory and visual hallucinations are rarer.[3,8,9] While self-reported PLEs are often transitory, subclinical, and much more common in the general population than psychotic disorders,[10] they are considered indices of psychopathology and are associated with impairment. Some risk factors appear to make it more likely that cannabis users will report these PLEs, including early age of cannabis initiation,[4] heavy cannabis use,[6] and consumption of high-potency strains of cannabis.[5]

Risk for cannabis use and schizophrenia is influenced by genetic factors, and genome-wide association studies (GWASs) and polygenic risk score (PRS) studies have shown that cannabis use and schizophrenia share genetic overlap.[11–13] There is also evidence that genetic factors contribute to risk for PLEs,[14–16] and studies have found that cognitive symptoms of schizophrenia (eg, disorganized thought patterns) show the most robust associations with polygenic risk for schizophrenia.[17–19] Furthermore, a recent study from Wainberg et al.[20] showed that the relationship between cannabis use and PLEs in the UK Biobank was moderated by a schizophrenia PRS, with cannabis use having a larger influence on the risk of PLEs for individuals with a higher genetic vulnerability for schizophrenia. It is plausible that individuals with greater polygenic vulnerability to schizophrenia may be particularly sensitive to the psychotomimetic and mood-altering effects of THC and thus, are at greater likelihood of experiencing schizophrenia-related symptoms after cannabis use—including PLEs and cognitive difficulties. Empirical evidence on the association between genetic risk for schizophrenia and cannabis-related experiences, including paranoia, hallucinations, and cognitive difficulties, is scarce. Our study sought to understand whether genetic predisposition to schizophrenia, even in individuals without schizophrenia, could contribute to how individuals respond to cannabis.

In this study, we examined the extent to which genetic risk for schizophrenia is associated with 5 self-reported cannabis-related experiences: hallucinations, paranoia, depression and anhedonia, cognitive difficulties, and decreased social contact. We used data from a sample partially ascertained for alcohol use disorders (AUDs)[21–23] (74% of the analytic sample met lifetime criteria for AUD, while 70% met lifetime criteria for cannabis use disorder) and tested whether polygenic liability for schizophrenia was associated with cannabis-related experiences in individuals who reported using cannabis at least 11 times during their life.

Methods

Target Sample Description

The Collaborative Study on the Genetics of Alcoholism (COGA) was designed to investigate the genetic underpinnings of AUDs and related mental health conditions[21–24] (details in online supplementary material and related publications[22,23]). Individuals were assessed using the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA)—only those using cannabis at least 21 times in a year (SSAGA I, II), or at least 11 times (lifetime; SSAGA IV), were asked follow-up questions about their cannabis-related experiences and were included in the current study. These cutoffs were a component of the SSAGA assessment instrument, similar to other diagnostic schedules. Diagnoses of schizophrenia and bipolar disorder were early exclusions for the COGA cohort[21]; thus, few, if any, individuals in this sample have a psychotic disorder diagnosis. Genotype data, covariates, and response to at least one cannabis-related experience were available on 4832 subjects (3128 of European ancestry and 1704 of African ancestry, determined via genetic principal components analysis; 42% female). The Institutional Review Boards at all sites approved this study, and all participants provided informed consent at every assessment.

Replication Sample Description

The Comorbidity and Trauma Study (CATS) sample[25] (N = 1446; 39.8% female; all of the European-Australian descent) consists of individuals with opioid use disorder and genetically unrelated control individuals with little or no lifetime opioid misuse. Active psychosis was an exclusion criterion. The Institutional Review Boards at Washington University School of Medicine and the Queensland Institute of Medical Research approved the study and all participants provided informed consent.

Cannabis-Related Experiences

Cannabis-related experiences were assessed for the following binary (yes/no) measures in the SSAGA[26,27] (table 1)

- Auditory, visual, or olfactory hallucinations
- Paranoia
- Depression or anhedonia
- Decreased social contact
- Cognitive difficulties

If items were assessed at multiple timepoints for an individual in COGA, we used a lifetime measure (ie, if an individual reported a cannabis-related experience at any timepoint, they were coded as having endorsed the experience [a "yes"].)

Decreased social contact was not assessed in CATS (details in supplementary table 1).

Genotype Data

The COGA sample was genotyped using multiple arrays, details of which have been reported.[28] Briefly, a set of 47 000 high-quality variants that were typed on multiple arrays and duplicate individuals was used for the initial phase of data alignment. The full set of variants was imputed for each array using the appropriate ancestry-matched 1000 Genomes Phase 3 reference panel. Imputed SNPs with INFO scores <0.30 or individual genotype probability scores <0.90 were excluded, as were SNPs that did not pass Hardy-Weinberg equilibrium (HWE $P < 10^{-6}$), and SNPs with a minor allele frequency less than 0.05%. Details on the genotyping QC and imputation of the CATS sample are described in detail elsewhere[25,29] and in the online supplementary material.

Statistical Analyses

Calculating Polygenic Risk Scores. PRS in European ancestry individuals from the COGA and CATS studies were calculated using summary statistics from the most recent Psychiatric Genomics Consortium (PGC) GWAS of schizophrenia (N = 306 011)[30] https://www.med.unc.edu/pgc/download-results/) using PRS-CS[31] (using the "auto" function).

To maximize prediction, we used a variation of PRS-CS, PRS-CSx[32] (https://github.com/getian107/PRScsx) in the African ancestries subset of COGA. We used GWAS summary statistics from both the PGC GWAS of European ancestry and a GWAS meta-analysis of schizophrenia in African ancestry individuals[33] (N_{cases} = 7509, $N_{controls}$ = 8337, from the Cooperative Studies Program (CSP) #572 and the Genomic Psychiatry Cohort) to create meta-analyzed combined weights.

We also created a PRS for cannabis use disorder (CUD) in the European ancestry individuals in COGA using a "leave-one-out" version (N = 356 763) of a CUD GWAS[11] that excluded the COGA sample. We only performed the leave-one-out analysis in the European ancestry GWAS, and thus only created PRS in the European ancestry subset of COGA, due to the severely limited statistical power of the African ancestry GWAS with the COGA sample excluded from the discovery GWAS (with COGA removed, remaining cases = 3035).

The PRS was scaled using the scale() function in R, such that the PRS followed a distribution with mean = 0 and variance = 1.

Regression Models. In separate mixed effect logistic regression models, we tested whether age at first cannabis use, DSM5 cannabis use disorder (CUD) diagnosis,[34] and maximum duration of daily cannabis was associated with cannabis-related experiences, controlling for sex, age, genotyping array, lifetime use of any other illicit substances (including hallucinogens, stimulants, sedatives, opioids), and 10 genetic ancestry principal components as fixed effects, and for family ID as a random intercept. We also tested whether these risk factors were associated with reporting at least 1 of the 5 cannabis-related experiences (hereafter referred to as "any" cannabis-related experience). Next, we tested whether the schizophrenia PRS was associated with cannabis-related experiences; we controlled for the same covariates as above, and CUD diagnosis (a binary variable) as another fixed effect. Statistical analyses were conducted in R.[35]

We conducted several secondary analyses: first, we tested whether the PRS for schizophrenia was associated with the severity of CUD diagnosis and whether CUD severity predicted greater endorsement of cannabis-related experiences. We also tested whether age at first cannabis use influenced the associations between the schizophrenia PRS and cannabis-related experiences. Given the ascertained nature of the COGA sample, we also tested whether controlling for AUD diagnosis influenced associations. Given prior evidence of genetic overlap between schizophrenia and CUD,[11,36] we also tested whether including a PRS for CUD in the model attenuated associations between the schizophrenia PRS and cannabis-related experiences. For cannabis-related experiences that were nominally associated ($P < .05$) with the schizophrenia PRS, we tested whether there were significant interactions between the schizophrenia PRS and duration of daily cannabis use, age of first cannabis use, or CUD. We controlled for all moderator-by-covariate and PRS-by-covariate cross-terms[37] but did not control for CUD in interaction analyses of duration or age of first use. Finally, we also tested whether the schizophrenia PRS was associated with the use of illicit substances, or with the number of cannabis-related experiences endorsed.

Due to potential cross-ancestry differences in linkage disequilibrium patterns and minor allele frequencies, we calculated PRS and analyzed the initial regression models in each ancestry group separately to avoid possible confounding. To maximize sample size and power, we then used a fixed-effects model to meta-analyze these results across the European and African ancestries.[38] We corrected for a total of 61 tests (details in

online supplementary materials). Using a conservative Bonferroni correction, we consider P-values < .05/61 = 8.2e−4 to be statistically significant.

Replication in the CATS sample[25] was carried out using regression analyses that controlled for CUD, opioid use disorder (ascertainment criterion), lifetime use of illicit drugs other than cannabis, age, sex, and the first 9 genetic principal components. To assess differences in findings across the COGA and CATS samples, we used the following formula to calculate a z score for each outcome: $Z = |\beta_{COGA} - \beta_{CATS}| / \sqrt{(SE_{COGA}{}^2 + SE_{CATS}{}^2)}$, where β_{COGA} is the association between the schizophrenia PRS and the outcome in COGA, and SE_{COGA} is the standard error of the regression coefficient.

Results

The average age of first cannabis use in the COGA analytic sample was 16 years (table 2), consistent with national trends.[39] Lifetime CUD was prevalent in this subsample (70%), although most were classified as "mild" (40% of sub-sample; 25% "moderate", 35% "severe"). Use of other illicit drugs was common in the analytic sample (75%). 74% of the analytic sample met lifetime criteria for an AUD. Between 12% (hallucinations) and 31% (decreased social contact; table 2) of the sample endorsed a cannabis-related experience with 46% reporting experiencing at least 1 of the 5 cannabis-related experiences. There were few significant differences between the European and African ancestry samples (online Supplementary materials). There were very minor to no differences in endorsement in those who were assessed with the SSAGA I vs those who were assessed with later SSAGAs (eg, the largest difference was for cognitive difficulties, which was endorsed by 23% of those who were assessed with SSAGA I vs 26% of those who were assessed with other SSAGAs.) In the CATS replication sample, 81% of individuals had a lifetime diagnosis of opioid use disorder (further details in supplementary table 1).

Phenotypic correlations between the 5 cannabis-related experiences ranged from 0.51 (between hallucinations and depression/anhedonia) to 0.84 (between cognitive difficulties and depression/anhedonia; supplementary figure 1) in COGA. Correlations were slightly lower in the CATS replication sample (0.37–0.64; supplementary figure 1). Overall, the hallucinations item showed the lowest correlations with the other 4 cannabis-related experiences in both samples.

In meta-analyzed cross-ancestry findings from the primary regression models, lifetime CUD diagnosis was strongly associated with reporting cannabis-related experiences (P < 8.3e−26; table 3). Similar associations were noted for earlier age at first cannabis use and cannabis-related experiences (P < 2.2e−4). Duration of daily cannabis use was significantly associated with all experiences (P < 2.9e−5) except hallucinations and paranoia. We also found that CUD severity (as coded in the DSM-5: mild, moderate, severe, or none) was strongly associated with endorsement of a greater number of cannabis-related experiences (ANOVA F-statistic = 783.1 (3, 3039.1), P < 2e−16 in the European ancestry sample; F-statistic = 351.7 (3, 1639.0), P < 2e−16 in the African ancestry sample; note: degrees of freedom are not always integer values because they were estimated using Satterthwaite's method of approximation).

In models that controlled for CUD, the schizophrenia PRS was significantly associated with all cannabis-related experiences (maximum P < 6.8e−4) except hallucinations (P = .47; figure 1; table 4). The association between the schizophrenia PRS and reporting *any* cannabis-related experience did not pass our statistical significance threshold (P = .001), but the schizophrenia PRS was associated with endorsing a greater number of cannabis-related experiences

Table 2. Descriptive Statistics of COGA Sample

	African-ancestry Sample (Total N = 1704)	European-ancestry Sample (Total N = 3128)	Total Trans-ancestral Sample (Total N = 4832)
Age at last interview	32.2 (9.8)	32.6 (9.4)	32.4 (9.6)
Females	716 (1704); 42%	1321 (3128); 42%	2037 (4832); 42%
AUD diagnosis	1084 (1704); 64%	2480 (3128); 79%	3564 (4832); 74%
Age at first cannabis use	15.7 (3.4)	15.7 (3.2)	15.7 (3.2)
CUD diagnosis	1224 (1704); 72%	2163 (3128); 69%	3387 (4832); 70%
Lifetime use of other illicit drugs	989 (1704); 58%	2635 (3128); 84%	3624 (4832); 75%
Lifetime report of *any* cannabis-related experiences	752 (1665); 45%	1458 (3,068); 48%	2210 (4733); 47%
Hallucinations	204 (1704); 12%	360 (3128); 12%	564 (4832); 12%
Paranoia	340 (1665); 20%	506 (3068); 16.5%	846 (4733); 18%
Depression/anhedonia	370 (1701); 22%	708 (3125); 23%	1078 (4826); 22%
Cognitive difficulties	428 (1701); 25%	837 (3125); 27%	1265 (4826); 26%
Decreased social contact	431 (1701); 25%	1042 (3125); 33%	1473 (4826); 31%

Note: AUD, alcohol use disorder; CUD, cannabis use disorder.
Mean (SD) provided for continuous variables. N affected (N total); % provided for binary variables.

Table 3. Associations Between Measures of Cannabis Involvement (Age at First Cannabis Use, Duration of Daily Cannabis Use, and Cannabis Use Disorder) and Cannabis-Related Experiences in the COGA Sample, Both Ancestry-Specific and Meta-Analyzed

Outcome	Beta (SE) of AFU in AAs	Beta (SE) of AFU in EAs	Beta (SE) of AFU (meta-analyzed)	Meta-analysis AFU p-value
Any cannabis-related experience	−0.308 (0.063)	−0.326 (0.047)	−0.320 (0.038)	2.20e−17*
Hallucinations	−0.293 (0.093)	−0.156 (0.069)	−0.205 (0.055)	2.22e−4*
Paranoia	−0.238 (0.079)	−0.289 (0.062)	−0.270 (0.049)	3.26e−8*
Depression/anhedonia	−0.378 (0.077)	−0.339 (0.056)	−0.353 (0.045)	7.08e−15*
Cognitive difficulties	−0.469 (0.075)	−0.301 (0.053)	−0.357 (0.043)	1.63e−16*
Decreased social contact	−0.311 (0.072)	−0.294 (0.050)	−0.300 (0.041)	3.02e−13*
	Beta (SE) of Duration of Daily Use in AAs	Beta (SE) of Duration of Daily Use in EAs	Beta (SE) of Duration of Daily Use (Meta-analyzed)	Meta-analysis Duration of Daily Use *P*-value
Any cannabis-related experience	0.209 (0.057)	0.218 (0.045)	0.215 (0.035)	1.25e−9*
Hallucinations	0.070 (0.079)	−0.049 (0.065)	−0.001 (0.050)	0.985
Paranoia	0.052 (0.430)	0.100 (0.051)	0.099 (0.051)	0.050
Depression/anhedonia	0.179 (0.060)	0.185 (0.047)	0.183 (0.037)	7.88e−7*
Cognitive difficulties	0.203 (0.059)	0.192 (0.046)	0.196 (0.036)	6.40e−8*
Decreased social contact	0.156 (0.059)	0.146 (0.045)	0.150 (0.036)	2.87e−5*
	Beta (SE) of CUD in AAs	Beta (SE) of CUD in EAs	Beta (SE) of CUD (meta-analyzed)	Meta-analysis CUD *P*-value
Any cannabis-related experience	3.236 (0.224)	3.221 (0.149)	3.226 (0.124)	4.93e−149*
Hallucinations	2.649 (0.425)	1.971 (0.230)	2.125 (0.202)	8.34e−26*
Paranoia	3.067 (0.370)	3.099 (0.312)	3.086(0.239)	2.79e−38*
Depression/anhedonia	4.568 (0.713)	3.693 (0.325)	3.844 (0.296)	1.27e−38*
Cognitive difficulties	2.999 (0.307)	3.683 (0.278)	3.375 (0.206)	2.78e−60*
Decreased social contact	3.314 (0.365)	3.293 (0.201)	3.298 (0.176)	2.78e−78*

Note: AAs, African genetic ancestry individuals; EAs, European genetic ancestry individuals; AFU, age at first use of cannabis; CUD, DSM 5 cannabis use disorder.
These separate models controlled for sex, age, array type, lifetime use of other illicit drugs (including hallucinogens), and 10 genetic ancestry principal components as fixed effects, and accounted for family ID as a random effect. * indicates a result passed our statistical significance threshold of $\alpha = 8.2e{-}4$.

(meta-analysis beta = 0.11, $P = 1.3e{-}6$). Associations between the schizophrenia PRS and paranoia and depression/anhedonia were weaker in the African ancestry (AA) sample of COGA (betas = 0.03–0.04, SEs = 0.07–0.08) than in the European ancestry (EA) sample (betas = 0.24–0.25, SEs = 0.06), with significant heterogeneity in the meta-analysis. Across both ancestries, cognitive difficulties after cannabis use were most robustly associated with the schizophrenia PRS (AA beta = 0.14 [SE = 0.07]; EA beta = 0.27 [SE = 0.06]; meta-analysis beta = 0.22, $P = 5.2e{-}7$). The schizophrenia PRS was not significantly associated with the use of other illicit substances (meta-analyzed beta = 0.027, $P = .57$).

We found that CUD severity and the schizophrenia PRS were not significantly associated in the European ancestry nor the African ancestry samples of COGA (ANOVA F-statistic = 1.73 [3, 2919.7], $P = .158$ in the European ancestry sample; *F*-statistic = 0.86 [3, 1596.7], $P = .462$ in the African ancestry sample). Associations between the schizophrenia PRS and cannabis-related experiences were attenuated but still significant when controlling for age at first use, except for paranoia, which no longer passed our statistical significance threshold ($P = 8.5e{-}4$; supplementary table 2). Similarly, previous associations were still significant when controlling for AUD diagnosis except for the association with cannabis-related paranoia ($P = .001$; supplementary table 3). When we controlled for a PRS for CUD in the models, none of the associations with the schizophrenia PRS were attenuated (supplementary table 4; note, this sensitivity analysis was only performed in the European ancestry subset of COGA). None of the interactions between the schizophrenia PRS and duration of daily cannabis use passed our significance threshold of $\alpha = 9.8e{-}4$ ($P > .42$). The same was true for interactions between the schizophrenia PRS and age at first cannabis use ($P > .01$) and between the schizophrenia PRS and CUD

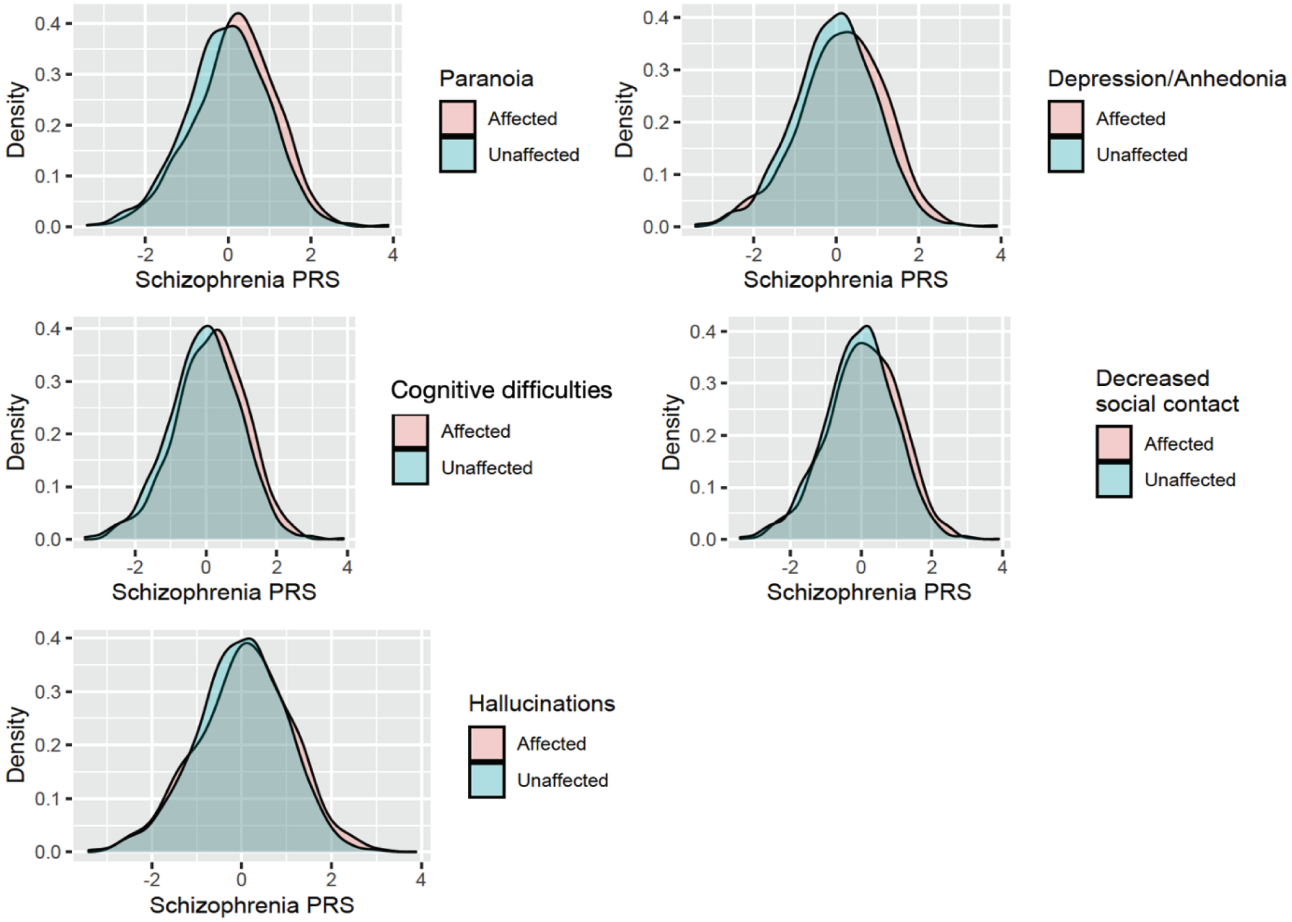

Fig. 1. Density plots showing the distribution of schizophrenia polygenic risk scores (PRS) in affected and unaffected European genetic ancestry individuals for cannabis-induced psychotic-like experiences. The schizophrenia PRS was significantly associated with all cannabis-induced psychotic-like experiences except for hallucinations.

Table 4. Associations Between Schizophrenia PRS and Cannabis-Related Experiences in the COGA Sample, Both Ancestry-Specific and Meta-Analyzed

Outcome	Total *N* Affected	Beta (SE) of PRS in AAs	Beta (SE) of PRS in EAs	Beta (SE) of PRS (meta-analyzed)	Meta-analysis *P*-value
Any cannabis-related experience	2210	0.113 (0.066)	0.149 (0.053)	0.135 (0.041)	0.001
Hallucinations	564	0.033 (0.086)	0.043 (0.070)	0.039 (0.054)	0.472
Paranoia	846	0.042 (0.076)	0.244 (0.062)	0.163 (0.048)**	6.77e−4*
Depression/anhedonia	1078	0.031 (0.069)	0.248 (0.056)	0.162 (0.044)**	1.98e−4*
Cognitive difficulties	1265	0.137 (0.069)	0.266 (0.055)	0.216 (0.043)	5.18e−7*
Decreased social contact	1473	0.077 (0.065)	0.216 (0.054)	0.159 (0.042)	1.26e−4*

Note: AAs, African genetic ancestry individuals; EAs, European genetic ancestry individuals; PRS, polygenic risk scores.
*indicates a result passed our statistical significance threshold of $\alpha = 8.2e{-}4$. ** indicates that the meta-analysis test for heterogeneity ($Q[df = 1]$) was significant ($P < .05$) for these models.
Regression models controlled for sex, age, array type, DSM 5 cannabis use disorder (CUD) diagnosis, lifetime use of other illicit drugs (including hallucinogens), and 10 genetic ancestry principal components as fixed effects, and accounted for family ID as a random effect.

diagnosis, although the interaction effect between the PRS and CUD on any cannabis-related experience was the strongest ($P > .003$; supplementary table 5).

No associations between the schizophrenia PRS and cannabis-related experiences were significant in the smaller CATS replication sample ($N = 1446$). However, none of the estimates were significantly different from those in the European ancestry sub-sample of COGA (z scores of the difference between betas = 0.13–0.88, $P > .38$; supplementary table 6), suggesting a similar pattern of results.

Discussion

The current findings suggest that heavy and early-onset cannabis users are more likely to report unusual cannabis-related experiences and that higher genetic vulnerability to schizophrenia may place regular cannabis users at even greater risk for these experiences, especially cognitive difficulties. Even accounting for aspects of cannabis involvement, including polygenic risk for CUD, the schizophrenia PRS was significantly associated with all cannabis-related experiences except for hallucinations. This suggests a role for genetic vulnerability to schizophrenia in cannabis-related experiences, even in those without psychotic disorders. Interestingly, we find that accounting for a PRS for CUD does *not* dampen the associations between the PRS for schizophrenia and cannabis-related experiences, suggesting that these cannabis-related experiences are more strongly related to genetic liability for schizophrenia in this sample. Despite nonsignificant effects in the replication models, the magnitude of association for the schizophrenia PRS was comparable (supplementary table 6), implying that the much smaller sample size for CATS is the primary factor behind the null results in this replication sample. Notably, these findings are from samples that were partly ascertained for AUD or opioid use disorder and generally had high levels of other substance use; therefore, these results may not generalize to the overall population.

In COGA, there was especially robust support across ancestries for an association between the schizophrenia PRS and cognitive difficulties (meta-analyzed beta = 0.22, SE = 0.04, P = 5.2e−7). This is consistent with previous studies which have found that schizophrenia PRS are associated with increased disorganized symptom scores and lower cognitive ability,[17,18] while weaker associations are reported with other symptom domains. In the European ancestry sample, we created a categorical variable representing quartiles of polygenic risk for schizophrenia; when we regressed cognitive difficulties on this categorical variable of risk, we found that individuals in the top 25% of polygenic risk for schizophrenia had 2 times greater odds of reporting cognitive difficulties after using cannabis, relative to individuals in the lowest quartile of risk (supplementary figure 2). We note that while this may seem like a large increase in risk, there is great uncertainty in PRS models and individual-level prediction is unlikely to be accurate. Of the 5 cannabis-related experiences studied in this report, hallucinations were the least common and the least strongly correlated with the other reported experiences (supplementary figure 1). This is consistent with most reports of cannabis-related PLEs, which more often implicate delusions, paranoia, and cognitive dysfunction than hallucinations.[7,8,40,41]

We found little evidence to support multiplicative interactions between the schizophrenia PRS and duration of daily use or age at first cannabis use (supplementary table 5). However, we note that the ascertained nature of the COGA sample and the fact that the overwhelming majority of individuals who endorse cannabis-related experiences in COGA have met the criteria for a lifetime CUD diagnosis (eg, 98% of individuals who report cognitive difficulties have met criteria for a CUD diagnosis) may have influenced our findings. The exclusion of individuals with schizophrenia, by study design, may also have impacted our results. It is likely that this range restriction (ie, few individuals who report cannabis-related experiences without heavy cannabis use and few individuals at the highest end of the spectrum of risk for schizophrenia), coupled with a small sample size, limited our statistical power to identify interactions. It is worth noting that the strongest interaction effect observed, which suggested that polygenic liability for schizophrenia has a greater effect on risk for any cannabis-related experiences in individuals with a CUD diagnosis, was actually stronger in the model that controlled for all covariate-by-PRS and covariate-by-CUD interactions[37] compared to the model without these terms (beta = 0.43, SE = 0.14, P = .003 vs beta = 0.29, SE = 0.12, P = .01). Our primary interaction models were on the multiplicative scale, a test of whether the combined effect of the PRS and moderator differs from the product of their individual effects. However, in light of these null findings, we subsequently tested interactions on the additive scale, which tests whether the combined effect of the PRS and moderator differs from the *sum* of their individual effects. Some have argued that departures from additivity may be more meaningful biologically than multiplicative models.[42,43] Supporting this theory, several of the interactions were stronger in the additive models (eg, PRS-by-age at first use predicting cognitive difficulties P = .004, PRS-by-CUD predicting cognitive difficulties P = .0011), though none of the interaction effects passed our statistical significance threshold (α = 9.8e−4). Our findings are most consistent with a multifactorial model,[44,45] wherein polygenic risk for schizophrenia combines additively with environmental risk factors, including early and heavy cannabis use, to increase an individual's vulnerability to unusual cannabis-related experiences. Relatedly, while we found that CUD severity and polygenic risk for schizophrenia were both associated with the endorsement of a greater number of cannabis-related experiences, the schizophrenia PRS and CUD severity were *not* related, suggesting that these factors independently contribute to the risk of cannabis-related experiences in this sample.

There were few statistically significant differences in the prevalence of cannabis-related experiences across ancestries: self-reported cannabis-related paranoia was more common in the African ancestry sample than in the European ancestry sample, while cannabis-related social withdrawal was more commonly reported in the European ancestry sample. While there was no difference in associations with the measures of cannabis

involvement (table 3), the schizophrenia PRS was more weakly associated with cannabis-related experiences in the African ancestry subsample of COGA relative to the European ancestry subsample, a divergence supported by significant heterogeneity tests in the meta-analysis of 2 of the 4 significant outcomes (table 4). One potential explanation for this divergence is the relatively small sample size of the African ancestry GWAS. While multi-ancestry methods like PRS-CSx have been shown to improve the predictive power of PRS in diverse samples,[32] these methods still fall short of having a large, fully ancestry-matched discovery GWAS to construct SNP weights for PRS.[46] It may also be the case that the relative importance of different risk factors (eg, readiness to report hallucinations and other PLEs[47–49]; the likelihood of living in an urban area[50,51]; and the cumulative effects of racism and discrimination[52–54]) for cannabis-related experiences varies across these 2 ancestry groups in COGA. However, our study was not designed to address this question; more studies of cannabis-related psychosis risk in multi-ancestry samples and large-scale discovery of GWAS in non-European ancestries are needed.

Our findings should be viewed with some limitations in mind. First, it is unclear how the timing of the self-reported cannabis-related experiences relate to the period of heaviest cannabis use, limiting causal inferences that can be drawn from our data. Second, although these experiences were self-reported to have occurred "because of" one's marijuana use, assessments were retrospective, and it is unclear how tightly these experiences were temporally linked to cannabis use. We cannot determine whether individuals were acutely intoxicated when these experiences occurred. We did not have data available on the persistence of these experiences, nor whether they were considered distressing. However, the polygenic risk for schizophrenia was associated with a greater number of cannabis-related experiences endorsed (meta-analyzed beta = 0.11, SE = 0.02, P = 1.3e−6); this provides some evidence that genetic risk for schizophrenia is associated with greater severity of cannabis-related experiences as indexed by a greater number of experiences endorsed. Third, we analyzed a variable assessing duration of daily cannabis use—self-reported the longest period of time an individual used marijuana almost every day—but this may not be an ideal measure of the heaviness of use. Beyond limitations associated with self-report, this measure does not capture quantity nor potency, and any "noise" captured by this variable may have contributed to its weaker associations with cannabis-related experiences. Fourth, no data on the potency of cannabis used was available, and there is evidence that the ratio of THC to cannabidiol can vary widely in available cannabis across the US[55,56]; there is a possibility that varying levels of cannabis potency and THC:cannabidiol ratio could have affected our results. Fifth, we only examined the genetic risk for schizophrenia, but some of the cannabis-related experiences analyzed—psychosis, anhedonia, and social withdrawal—are common features of other disorders, including bipolar disorder and depression, for which we did not examine polygenic liability. Sixth, while individuals with psychotic disorder diagnoses were excluded from the COGA cohort,[21] new onsets of psychotic disorders may have been missed as the SSAGA does not evaluate these diagnoses. However, these are expected to be rare. Finally, the cannabis-related experiences were only queried in individuals who reported using cannabis at least 11 times (or 21 times in a year) in SSAGA assessments. Thus, our subsample excludes any individuals who may have had these experiences at lower levels of cannabis use.

In conclusion, we found that polygenic liability for schizophrenia was associated with an increased risk of cannabis-related paranoia, depression and anhedonia, decreased social contact, and cognitive difficulties, even when accounting for the effects of other pertinent risk factors including CUD, age at first use of cannabis, and lifetime use of other illicit substances. As noted above, our findings come from ascertained samples with a high prevalence of CUD and use of other substances; thus, it is unclear whether these findings will generalize to population-based samples. Our results support the hypothesis that individuals who have a preexisting genetic vulnerability for schizophrenia are more likely to report unusual experiences, especially cognitive difficulties, when using cannabis.

Supplementary Material

Supplementary material is available at https://academic.oup.com/schizophreniabulletin/.

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Author Contributions

ECJ and AA conceptualized and planned the study. ECJ, SMCC, PWJ, and RT performed statistical analyses. AA supervised analyses. PWJ, LD, NGM, and ECN contributed replication data and analyses. ECJ wrote the first draft of the manuscript. SMCC, TB, NRK, SK, JIN, CK, MS, DMD, HJE, MHP, RMM, DCD, MDF, ECN, and AA critically revised and edited the manuscript. All authors reviewed and approved the final manuscript.

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A detailed COGA acknowledgement is available in the supplement. The authors have declared that there are no conflicts of interest in relation to the subject of this study.

Data Availability

CATS and COGA are available upon application to dbGaP, stored under accession numbers phs000277.v2.p1 (CATS) and phs000125.v1.p1, phs000763.v1.p1, phs000976.v2.p1, and phs001208.v2.p1 (COGA).

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