Genetic Predisposition vs Individual-Specific Processes in the Association Between Psychotic-like Experiences and Cannabis Use

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Importance Previous research indicates that cannabis use is associated with psychotic-like experiences (PLEs). However, it is unclear whether this association results from predispositional (i.e., shared genetic) factors or individual-specific factors (e.g., causal processes, such as cannabis use leading to PLEs).

Objectives To estimate genetic and environmental correlations between cannabis use and PLEs, and to examine PLEs in twin and nontwin sibling pairs discordant for exposure to cannabis use to disentangle predispositional from individual-specific effects.

Design, Setting, and Participants In this cross-sectional analysis, diagnostic interviews and self-reported data were collected from 2 separate population-based samples of twin and nontwin sibling pairs. Data from the Human Connectome Project were collected between August 10, 2012, and September 29, 2015, and data from the Australian Twin Registry Cohort 3 (ATR3) were collected between August 1, 2005, and August 31, 2010. Data were analyzed between August 17, 2017, and July 6, 2018. The study included data from 1188 Human Connectome Project participants and 3486 ATR3 participants, totaling 4674 participants.

Main Outcomes and Measures Three cannabis-involvement variables were examined: frequent use (i.e., ≥100 times), a DSM-IV lifetime cannabis use disorder diagnosis, and current cannabis use. Genetic and environmental correlations between cannabis involvement and PLEs were estimated. Generalized linear mixed models examined PLE differences in twin and nontwin sibling pairs discordant for cannabis use.

Results Among the 4674 participants, the mean (SD) age was 30.5 (3.2) years, and 2923 (62.5%) were female. Data on race/ethnicity were not included as a covariate owing to lack of variability within the ATR3 sample; among the 1188 participants in the Human Connectome Project, 875 (73.7%) were white. Psychotic-like experiences were associated with frequent cannabis use (β = 0.11; 95% CI, 0.08-0.14), cannabis use disorder (β = 0.13; 95% CI, 0.09-0.16), and current cannabis use (β = 0.07; 95% CI, 0.04-0.10) even after adjustment for covariates. Correlated genetic factors explained between 69.2% and 84.1% of this observed association. Within discordant pairs of twins/siblings (Npairs, 308-324), Psychotic-like experiences were more common in cannabis-exposed individuals compared with their relative who used cannabis to a lesser degree (β ≥ .23, P < .05; e.g., frequent and infrequent cannabis-using relatives significantly differed, z = −5.41; P < .001).

Conclusions and Relevance Despite the strong contribution of shared genetic factors, frequent and problem cannabis use also appears to be associated with PLEs via person-specific pathways. This study’s findings suggest that policy discussions surrounding legalization should consider the influence of escalations in cannabis use on trait-like indices of vulnerability, such as PLEs, which could contribute to pervasive psychological and interpersonal burden.
Since first finding a 6.0 relative risk of schizophrenia in heavy cannabis users, researchers have debated the role of cannabis use in the development of psychotic disorders.2-7 Some posit that cannabis use causally affects risk for psychosis, either via direct pharmacologic pathways or by potentiating genetic susceptibility. For instance, a recent case-control study found that cannabis users with first-episode psychosis were more likely to have used a high-potency form of cannabis relative to controls, suggesting direct causation.8 In contrast, epidemiologists have demonstrated that, although the prevalence of cannabis use has increased worldwide, the incidence of psychotic disorders remains largely stable9 and, furthermore, that attributable risk is small.10 Unmeasured confounders, including common genetic and environmental contributors, have also been inconsistently accounted for in causal calculations.11

Cannabis involvement is also linked to psychotic-like experiences (PLEs), which are more prevalent and easily assessed via self-report.12-16 Lifetime PLEs are associated with mental health problems9 and independently increase risk for disability attributable to deficits in cognition, social interactions, and role functioning.18 Owing to greater prevalence of PLEs (approximately 7%)19 compared with psychotic disorders (approximately 1% for schizophrenia), any causal effects of cannabis use on PLEs may have significant public health consequences.

Cannabis involvement (additive genetic heritability [h²], approximately 51%),20 schizophrenia (h², approximately 80%)21 and PLEs (h², approximately 43%-77%)24 are heritable. Until recently, the low prevalence of psychotic disorders precluded examination of the extent to which shared genetic factors were important (although see Carey et al.,22 whose study found an association between polygenic risk for schizophrenia and cannabis dependence). Using results from large genome-wide association studies (GWASs) of schizophrenia, investigators have now found evidence for pleiotropic effects of schizophrenia loci on aspects of cannabis involvement.22-25 Other investigators have interpreted this genetic commonality as evidence for causation,26,27 which is also consistent with the dopamine hypothesis of schizophrenia, because acute cannabis use releases dopamine,28 thus offering a biologically plausible pathway for cannabis use to lead to increased psychosis risk.

An alternative and frequently untested possibility is that both shared genetic influences and individual-specific factors of a causal nature might be implicated. One twin study reported a genetic correlation (r_g) of 0.55 between cannabis use disorder (CUD) and PLEs and found that a model in which CUD causally influenced PLEs fit better than the reverse.14 However, the relative fits of the correlational and causal models were extremely close, precluding a definitive conclusion.

The present study examined the association between cannabis and PLEs in 2 large population-based samples from twin and nontwin sibling pairs, the Human Connectome Project (HCP) and the Australian Twin Registry Cohort 3 (ATR3). First, we examined whether measures of cannabis use were associated with PLEs. Second, we estimated the extent to which additive genetic and individual-specific environmental factors contributed to their covariance. Finally, we compared PLEs across twin and nontwin sibling pairs varying in cannabis exposure, including twins discordant for cannabis involvement. Because twin and sibling pairs share at least 50% of their segregating loci identical by descent, any excess presence of PLEs in the cannabis-exposed twin compared with the unexposed co-twin may be viewed as evidence in favor of putatively causal individual-specific influences.

Methods

Participants

Participants were drawn from 2 sources: the HCP SI200 participants’ data release (1206 participants, whose data were collected between August 10, 2012, and September 29, 2015, and retrieved for the present study on August 4, 2017; mean age, 29.3 [range, 22-35] years); and ATR3 (3856 participants whose data were collected between August 1, 2005, and August 31, 2010, and retrieved for the present study on December 4, 2017; mean age, 30.9 [range, 24-36] years) (eMethods and eTable 1 in the Supplement). Four hundred thirty-two participants were excluded from the current analyses for missing relevant interview or questionnaire data (eTable 1 in the Supplement), resulting in a combined sample size of 4674 individuals. Data were analyzed between August 17, 2017, and July 6, 2018. For twin and nontwin sibling pair analyses, only individuals with a similarly aged full sibling (±2 years’ age difference) or twins with complete data were included, leaving 1733 pairs (758 monozygotic [MZ] twins, 780 dizygotic [DZ] twins, and 195 nontwin sibling pairs). Only same-sex sibling pairs were included in analyses of exposure effect (eMethods in the Supplement). Institutional review board approvals for the studies were obtained from Washington University in St Louis, Missouri, and from the Queensland Institute of Medical Research for the ATR3, and all participants provided written informed consent, including permission for the public release of data.

Outcome Measures

Psychotic-like Experiences

In the HCP sample, participants completed the Achenbach Adult Self-report (ASR).29 The ASR assesses aspects of adap-
tive functioning and mental health–relevant behaviors in adults. As in previous research, 30 4 questions were identified within the ASR as measuring PLEs. Although the ASR was not administered in the ATR3 sample, 4 questions mapping onto the ASR questions were assessed using items from a broad measure of personality (eTable 2 in the Supplement). To equate PLE scores in the HCP and ATR3 samples, ASR responses were binarized (ie, any answer of yes [answering “somewhat/sometimes true” or “very true/often true”] = 1, or not answered yes [answering “not true”] = 0), yielding a range of scores from 0 to 4. Answers of yes to these 4 psychosis questions were summed to yield a PLE score (eMethods in the Supplement). One thousand thirty of 4674 participants (22.0%) reported experiencing at least 1 PLE.

Cannabis Involvement
Cannabis involvement in both HCP and ATR3 was assessed using the Semi-structured Assessment for the Genetics of Alcoholism.31 Specifically, we examined 3 variables: (1) frequent cannabis use (1 = cannabis use ≥100 times, 0 = cannabis use <100 times in lifetime; 712 of 4674 [15.2%] met criteria for frequent use), (2) CUD (1 = met criteria for DSM-IV abuse or dependence, 0 = no CUD diagnosis; 666 of 4674 [14.2%]; eMethods in the Supplement), or (3) current cannabis use (1 = positive cannabis screening results on either day of testing, 0 = no positive cannabis screening results [because the ATR3 sample did not conduct urine screens, current cannabis use was defined as cannabis use during the past year]; 659 of 4674 [14.1%]).

Statistical Analysis
Statistical analyses were performed using R, version 3.4.3 (R Foundation).32 Analyses were conducted individually for each of the 3 cannabis-involvement variables using the combined HCP and ATR3 samples. Unless otherwise stated, the analyses used generalized linear mixed models (R package lme4),33 nesting individuals within families, and included the following covariates: sex (1 = female, 0 = male); age; MZ twin status (1 = MZ twin, 0 = not); DZ twin status (1 = DZ twin, 0 = not); sample (1 = ATR3, 0 = HCP); total household income (eMethods in the Supplement); lifetime regular cigarette use (1 = ≥100 cigarettes, 0 = <100 cigarettes); lifetime regular alcohol use (1 = average ≥2 drinks/d during heaviest period, 0 = average <2 drinks per day, during heaviest 12-month period); and lifetime noncannabis illicit drug use (1 = illicit drug use, 0 = not). Race/ethnicity was not included as a covariate owing to the lack of variability within the ATR3 sample; results in the HCP sample remained consistent when race/ethnicity was included (eTable 3 in the Supplement). The significance threshold was set at P = .05 (corrected for multiple comparisons). All P values are 2-sided.

Estimation of Genetic and Environmental Correlation
The variance in and covariance between each cannabis involvement measure and PLEs were parsed into additive genetic (A), shared environmental (C), and individual-specific environmental (E) sources (eMethods in the Supplement). Models were fitted to raw data using full information maximum likelihood estimation using the OpenMx34 and umx35 packages in R. These models also allowed for estimation of additive genetic (rA) and individual-specific environmental (rE) correlations between PLEs and cannabis involvement.36 The Akaike information criterion was used to compare model fit.37

Twin/Sibling Pair Analyses of Exposure Effect
All possible same-sex twin and nontwin sibling pairs were drawn from the data (Npairs: 2022-2041; eMethods in the Supplement). For each cannabis-involvement measure, twin and nontwin sibling pairs were assigned to 4 groups: concordant unexposed pairs, discordant exposed pairs, unexposed individuals from discordant pairs, and exposed individuals from discordant pairs.38 Lifetime never users were included in the unexposed groups.

First, we used Helmert contrast coding to conduct sibling analyses by cannabis exposure and examined the association between cannabis involvement and PLEs using generalized linear mixed models after nesting individuals within twin and nontwin sibling pairs and nesting pairs within families.39 Three hypotheses were tested (eTable 4 in the Supplement). The first, the causal hypothesis, that cannabis involvement and PLEs are associated via person-specific, potentially causal factors. Information regarding the onset of PLEs was not available for either data set, precluding conclusions regarding the direction of causality (ie, whether cannabis causes PLEs or vice versa), by testing whether cannabis-exposed twins and siblings from discordant pairs differed in PLE scores from their unexposed co-twin or nontwin sibling. We tested the second hypothesis, the predispositional hypothesis (ie, that PLEs result from factors shared by members of twin and nontwin sibling pairs, including segregating loci), by testing whether the unexposed member of discordant pairs showed a similar susceptibility to PLEs when compared with the exposed co-twin or sibling and with individuals from concordantly exposed pairs. The third hypothesis was graded liability, a variation of the predispositional model (ie, exposure does not lead to changes in PLEs within discordant pairs). For this hypothesis, we tested whether unexposed individuals from discordant pairs exhibit increased liability to PLEs compared with unexposed members from discordant pairs. These contrasts allowed examination of support for all 3 hypotheses because the likelihood of causation and correlated liabilities are not mutually exclusive. Post hoc analyses examined cannabis-exposure effects and whether each of the cannabis-exposure groups showed significantly different PLEs that were Bonferroni-corrected for multiple comparisons.

Second, we focused on the discordant pairs alone. We examined whether mean PLE scores were higher in the exposed twin or nontwin sibling compared with their genetically related co-twin or nontwin sibling while accounting for covariates. Interaction terms between each cannabis-exposure variable and zygosity (MZ vs DZ; twin vs nontwin sibling) were used to assess differences in the magnitude of the association between discordant MZ pairs and DZ twin or nontwin sibling pairs. Absence of a significant interaction term indicated equality of effect sizes in the MZ and DZ twin or nontwin sibling pairs. Significantly elevated PLE scores in MZ twins exposed to canna-
bis compared with their unexposed co-twin might be viewed as evidence in favor of putatively causal individual-specific environmental factors. Monozygotic twins are fully matched for their segregating loci; therefore, any excess association between cannabis and PLEs in these pairs cannot be associated with segregating loci (or to environmental factors that are shared by twins and nontwin siblings) and is therefore attributed to person-specific influences, including causal processes.

**Results**

**Associations Between PLEs and Cannabis Use**
Analyses were performed on 4674 participants. Among the 4674 participants, mean (SD) age was 30.5 (3.2) years, and 2923 (62.5%) were female. Data on race/ethnicity were not included as a covariate in the ATR3 study owing to lack of variability within that sample; among the 1188 participants in the Human Connectome Project, 875 (73.7%) were white. Psychotic-like experiences were associated with frequent cannabis use ($\beta = 0.11$; 95% CI, 0.08-0.14), cannabis use disorder ($\beta = 0.13$; 95% CI, 0.09-0.16), and current cannabis use ($\beta = 0.07$; 95% CI, 0.04-0.10), even after adjustment for covariates (Table 1). Those reporting frequent use, CUD, and current use were 1.21 to 1.26 times more likely to report at least 1 PLE than their counterparts who used cannabis to a lesser extent or not at all. Associations persisted after including covariates, which of younger age, nontwin status, lower household income, lifetime regular smoking, and lifetime illicit drug use were also associated with greater PLEs. Interactions between cannabis exposure and sex were nonsignificant (for all comparisons, $\beta \leq .13$ and $P > .21$; eTable 5 in the Supplement). Interactions with sample were significant (frequent cannabis use: $\beta = 0.03$, $P = .04$; CUD: $\beta = 0.04$, $P < .01$; interaction with current cannabis use was not significant, $\beta = -0.03$, $P = .06$), with the HCP sample showing a smaller effect size with PLEs but in the same direction (eTable 3 in the Supplement). Age at onset of cannabis use was not related to PLEs ($\beta = 0.013$, $P = .44$).

**Estimation of Genetic and Environmental Correlation**
Cannabis involvement ($h^2$, 0.69-0.77) and PLEs ($h^2$, 0.38) were heritable. The best-fitting twin models did not include shared environmental influences (eTable 6 in the Supplement). The observed association between frequent use, CUD, and current cannabis use measures and PLEs was generally attributable to genetic factors, and genetic correlations ($r_g$) ranged from 0.41-0.56 (Table 2). These genetic factors accounted for 69.2% to 84.1% of the observed association, with the remainder of covariance attributable to individual-specific environmental factors. Heritability remained significant, although both heritability and the extent of $r_g$ were reduced ($r_g = 0.26-0.46$) when models were rerun after adjustment for significant covariates (eTable 7 in the Supplement). Genetic factors continued to con-
tribute to much of the covariance, approximately 69.2% to 82.5%.

**Twin/Sibling Pair Analyses of Exposure Effect**

Psychotic-like experiences were commonly reported by exposed members of discordant pairs (eTable 8 in the Supplement for N pairs) and by members of concordant exposed pairs compared with unexposed members from discordant and concordant unexposed pairs, showing a robust main effect of exposure ($\beta = 0.08-0.13$, $P < .001$ for all; Figure and Table 3). Use of Helmhert contrast coding indicated support for both the causal and graded liability contrasts (the predispositional contrast was also significant for the frequent cannabis and CUD variables; eTable 9 in the Supplement).

Second, when we focused on discordant pairs alone (eTable 10 in the Supplement; with interactions, eTable 11 in the Supplement; N pairs, 308-324), reports of PLE were more common in cannabis-exposed individuals compared with their relative who used cannabis to a lesser degree ($\beta = 0.23-0.41$, $P < .05$); for example, frequent and infrequent cannabis-using relatives significantly differed in mean PLE score, $z = -5.41$, $P < .001$, Table 3). This suggests that, even within twin and non-twin sibling pairs matched for 50% or 100% of their segregating loci and for familial environment, frequent or current use and CUD contributed to more frequent reports of PLE. Interaction terms with zygosity were nonsignificant (MZ vs DZ; twin vs non-twin sibling; $z = -1.24$, $P = .22$), indicating equality of effect sizes in MZ and DZ sibling pairs. These significant associations in discordant MZ pairs provided evidence in favor of person-specific effects of a potentially causal nature.

**Effect of Co-occurring Tobacco Smoking and Illicit Drug Use**

All previous analyses accounted for lifetime history of regular tobacco smoking and illicit drug use. Use of other illicit drugs (22.3%-43.5%) and regular tobacco smoking (27.3%-41.5%) was not uncommon (eTable 12 in the Supplement). Within discordant pairs (eMethods in the Supplement), individuals who were exposed to cannabis were more likely to report use of other illicit drugs and regular tobacco smoking than their cannabis-unexposed relatives (eTable 13 in the Supplement). The likelihood of PLEs was elevated in those reporting regular tobacco smoking (eTable 14 in the Supplement) and use of other illicit drugs more than 11 times (eTable 15 in the Supplement) more than their cannabis exposure. However, there was also evidence that those reporting use of comorbid tobacco or illicit drugs were also likely to have significantly more CUD symptoms and somewhat more frequent use.

**Discussion**

After combining 2 US and Australian data sets, we found that cannabis involvement (ie, frequent or current use and CUD) was associated with a greater number of PLEs, even when we included a variety of demographic variables and other substance use measures (eg, lifetime tobacco, alcohol, other illicit drug use). Although shared genetic influences were major contributors to their association, there was evidence of the role of person-specific influences (ie, those in addition to factors that twins and siblings are matched for) that might be of a causal nature on the association between cannabis involvement and PLEs.

Our study supports a growing body of literature outlining the extent of genetic overlap between cannabis involvement and psychotic disorders as well as PLEs. Our estimates of $\sigma_g$ are also consistent with those from 1 previous twin study. It is too early to speculate the exact nature of the loci that might contribute to this genetic correlation because adequately powered GWASs of cannabis involvement are pending. Promising evidence arises from a recent GWAS of CUD in a Danish cohort that implicates a locus on chromosome 8, which is an expression quantitative trait locus for $CHRNA2$ and is also significant genome-wide in the current largest schizophrenia GWAS. In contrast to 1 other study, we did not find support for the role of shared environmental influences on either PLEs or cannabis involvement or their covariance. Unlike the previous study, which focused on cannabis use (ever trying cannabis) in adolescents, we focused on indices of more involved forms of use (eg, CUD) in adults. Thus, our finding of no shared environment is consistent with the broader twin literature on the etiology of heavier cannabis use, including 1 previous study of CUD. Nonetheless, disentangling additive genetic from shared environmental influences requires very large sample sizes, and we cannot discount the role of shared environment, especially early life exposures (eg, prenatal exposures, childhood adversity) as a contributor. Still, because twin pairs are matched for these factors, our discordant pair analyses are likely unaffected by the extent of shared environmental overlap.

Within pairs of individuals who share between 50% (DZ twins and non-twin siblings) and 100% (MZ twins) of their segregating loci and early environmental influences, cannabis involvement was associated with more frequent reports of PLE. Although we cannot unequivocally ascribe this residual association to causal mechanisms (especially given the lack of data...
on PLE onset age), we can speculate that differences in participant reports of PLE attributable to cannabis exposure, at least within related pairs (and as associations were of a similar magnitude in MZ pairs who share all their segregating loci, on average), can be viewed as evidence of causal processes. Potential causal pathways from cannabis involvement to PLEs may be associated with dopaminergic dysfunction. Long-term drug use has been shown to modify the density and availability of dopamine D2/D3 receptors, although results for cannabis are mixed. Dopaminergic variants, including those in DRD2, have been implicated in schizophrenia, and dopamine receptor antagonists are generally effective in treating positive symptoms of schizophrenia, with the endocannabinoid system being involved in the modulation of dopamine neurotransmission. Therefore, increased sensitivity to the psychotomimetic effects of cannabis or further alteration of dopaminergic functioning on significant cannabis use might lead to increased PLEs. On the other hand, purely environmental factors (eg, early trauma) might also shape these potentially causal pathways.

Limitations

Our data are cross-sectional and age at first PLE was not assessed. World Mental Health surveys indicate that PLEs have a mean age at onset of 24 to 25 years. In our data sets, the mean (SD) cannabis dependence age at onset was 18.6 (2.4) years for HCP and 21.4 (4.1) years for ATR3. Thus, cannabis use may precede PLEs, although we cannot rule out reverse causation (especially given other evidence of onset of PLEs in childhood and adolescence). Unmeasured confounders (eg, stressful life events) cannot be excluded. Although underpowered, our descriptive analyses suggest that there might be an independent association of tobacco and other drug use with PLEs beyond the association with cannabis severity. We were unable to test for associations with variability in amount smoked or for varying strengths of Δ-9-tetrahydrocannabinol. Although tetrahydrocannabinol is associated with psychotic experiences, cannabinoid may be associated with antipsychotic properties. Our twin and nontwin sibling pair analyses treated never users of cannabis and less frequent/nondisordered users similarly, which does not adequately address whether associations extended beyond a simple effect of ever using cannabis. However, the association between using cannabis fewer than 11 times during one’s lifetime (vs never using it) and PLEs was not significant (P = .75), suggesting that casual use may not be solely responsible for the observed association. In addition, PLE measures were limited, although findings were generally consistent with extant literature.

Although we covaried for sample, sample-specific differences cannot be discounted. For instance, HCP excluded participants for extended psychiatric hospitalization, which may have limited the severity of substance use and PLEs. Also, the definition of current cannabis use varied by sample (ie, HCP defined it as positive test results for tetrahydrocannabinol on either day of testing; ATR3 defined it as past-year cannabis use). However, results remained unchanged when current use was defined as past-year use in both samples. Likewise, it is possible our study was underpowered to detect nuanced sex differences, although interactions with sex were not significant.

Conclusions

Psychosis is a major adverse health correlate of cannabis use. However, there is a lack of a consensus on the pathways underlying this robust association. Although the association is primarily attributable to genetic overlap, the individual-specific component might serve as a target for intervention. If this person-specific pathway is causal, then policies that result in escalations in cannabis involvement should be further scrutinized. If they represent noncausal factors, such as severe early life stress, then such factors are critical to identify. Targeting cannabis use may be a key strategy in preventing exacerbation of PLEs among individuals at increased genetic susceptibility to cannabis use and PLEs, should we be able to reliably identify those individuals in the future.
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Research Original Investigation

Influence of Schizophrenia on Cannabis Use: Genetic Overlap with Mental Health, and a Causal Pathway to Lifetime Cannabis Use (N=184,765) Identifies New Risk Loci


