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The genetic relationship between cannabis and tobacco cigarette use in European- and African-American female twins and siblings

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ABSTRACT

Background: Use of cigarettes and cannabis frequently co-occurs. We examine the role of genetic and environmental influences on variation in and covariation between tobacco cigarette and cannabis use across European-American (EA) and African-American (AA) women.
Methods: Data on lifetime cannabis and cigarette use were drawn from interviews of 956 AA and 3557 EA young adult female twins and non-twin same sex female full siblings. Twin modeling was used to decompose variance in and covariance between cigarette and cannabis use into additive genetic, shared, special twin and non-shared environmental sources.
Results: Cigarette use was more common in EAs (75.3%, 95% C.I. 73.8–76.7%) than AAs (64.2%, 95% C.I. 61.2–67.2%) while cannabis use was marginally more commonly reported by AAs (55.5%, 95% C.I. 52.5–58.8%) than EAs (52.4%, 95% C.I. 50.7–54.0%). Additive genetic factors were responsible for 43–66% of the variance in cigarette and cannabis use. Broad shared environmental factors (shared + special twin) played a more significant role in EA (23–29%) than AA (2–15%) women. In AA women, the influence of non-shared environment was more pronounced (42–45% vs. 11–19% in EA women). There was strong evidence for the same familial influences underlying use of both substances (r_A = 0.82–0.89; r_{C+T} = 0.70–0.75). Non-shared environmental factors were also correlated but less so (r_E = 0.48–0.66). No racial/ethnic differences were apparent in these sources of covariation.
Conclusion: Heritability of cigarette and cannabis use is comparable across racial/ethnic groups. Differences in the contribution of shared and non-shared environmental influences indicate that different factors may shape substance use in EA and AA women.

1. Introduction

According to the most recent estimates from the National Survey of Drug Use and Health, 86.8% of lifetime cannabis users aged 12 and older reported a lifetime history of tobacco cigarette use while 61.7% of cigarette smokers also reported smoking cannabis during their lifetime (Substance Abuse and Mental Health Services Administration (SAMHSA), 2014). Adolescents reporting dual use are more likely to experience problems with both drugs, including rapid escalation to more involved stages of use and difficulty quitting (Agrawal et al., 2008; Peters et al., 2012; Timberlake et al., 2007).

Contributors to the co-occurring use of cannabis and cigarettes include risk and protective influences that shape a general liability to experimentation with multiple substances (Hawkins et al., 1992) as well as influences specific to cigarette and cannabis co-use (e.g., shared route of administration; (Agrawal et al., 2012)). Both genetic and environmental influences play a role in the shared vulnerability to cannabis and cigarette use (Agrawal et al., 2010; Han et al., 1999; Young et al., 2006). One study suggested a genetic correlation as high as 0.75 (Agrawal et al., 2010) between cannabis and cigarette use while another suggested a more modest overlap of r = 0.31 (Young et al., 2006). Environmental contributions on these early stages of substance use can be further parsed into those that make members of twin and sibling pairs similar to each other (i.e., shared environment) and those that are individual-specific, with more robust evidence for the shared influences being correlated than the non-shared (Young et al., 2006). However, a study using a

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subset of the data from this study showed that in African American (AA) women, the relationship between timing of onset of cigarette smoking and cannabis use was prominently attributable to overlapping individual-specific environmental factors ($r = 0.95$) (Sartor et al., 2009).

The strong evidence for the heritability of and the co-heritability between lifetime use of cannabis and cigarettes comes almost entirely from international research conducted in twin samples of European origin. In U.S. populations, this is particularly problematic given significant variations in the rates of cannabis and cigarette use across race/ethnicity (Garrett et al., 2008; Griesler and Kandel 1998; Keyes et al., 2015; Wallace et al., 2003; Wu et al., 2014). Racial/ethnic differences are also particularly pronounced in females with AA adolescent girls and young adult women appearing to be less likely than their European American (EA) counterparts to use cigarettes and cannabis (Garrett et al., 2008; Keyes et al., 2015; SAMHSA, 2014; Wallace et al., 2003). In addition, although cigarette use typically predates cannabis use in EAs, reverse gateways (cannabis before cigarettes/alcohol) are somewhat more common in AAs than EAs (Sartor et al., 2013; Vaughn et al., 2008). Notably, these variations in prevalence and sequence may relate to differing societal attitudes towards cannabis and cigarette use, the relative availability and exposure opportunity of the two drugs as well as to putative differences in biological response to anticipation and receipt of drug-related rewards. For cigarette use, we are only aware of 3 studies, including two by us in the sample under study here, that show that additive genetic factors explain similar proportions of variance (40–50%) in AAs and EAs (Sartor et al., 2009, 2015; Whitfield et al., 2007). However, in a recent study by our group (Sartor et al., 2015), the remainder of the variance in cigarette use was solely attributable to individual-specific environmental factors (44%) in AA twins while in EA twins, substantial influence of both individual-specific (10%) and shared environmental factors (34%) was noted for cigarette use. Likewise, we have previously reported that timing to cannabis use is heritable in AA female twins (0.52) and that the role of shared environment is limited (Sartor et al., 2009). However, no study to date has examined the bivariate relationship between lifetime use of cannabis and cigarettes in AA and EA twins.

In the current study, we utilize a large, general population sample of adult female twins and non-twin siblings of self-described AA ($n = 956$) and EA ($n = 3557$) ancestry to examine the role of additive genetic, shared environmental and individual-specific environmental influences on the covariance between lifetime cigarette and cannabis use and the extent to which the magnitude of their contribution varies across race/ethnicity.

We leveraged a sample of females who are notably understudied in addiction research. Importantly, AA females appear to be at low risk for both cannabis and cigarette involvement, relative to EA females, both during adolescence (Keyes et al., 2015; Wallace et al., 2003) and adulthood (SAMHSA, 2014). Thus, access to related individuals of AA ancestry is a unique aspect of the present study – we are also not aware of other datasets of this magnitude with AA twins. Further, by utilizing a young adult sample, we circumvented concerns regarding lack of adequate opportunity for experimentation with cannabis (Wagner and Anthony 2002).

2. Materials and methods

2.1. Participants

The sample was composed of female twins who completed the fourth wave of data collection for the Missouri Adolescent Female Twin Study MOAFTS and female participants from the Missouri Family Study (MOFAM). Data on male twins were not collected in MOAFTS, although male siblings did participate in MOFAM but were not included in the present study.

2.1.1. MOAFTS. The Missouri Adolescent Female Twin Study (MOAFTS; Heath et al., 2002; Knopik et al., 2005) is a population-based longitudinal study of female twin pairs born between July 1, 1975 and June 30, 1985 in Missouri to Missouri-resident parents The sample was demographically representative of the Missouri population at the time the twins were born, with nearly 15% of twins being African-American (AA) and the remainder being of European-American (EA) descent. A baseline interview was conducted with 3258 twins beginning in 1995 (median age = 15 years). All available twins were targeted for three waves of telephone interviews (Waves 1, 4, and 5, at median ages 15, 22, and 24 years, respectively). Between 2002 and 2005, all twins from the target cohort (excluding those who had withdrawn from the study or whose parents asked that the family not be re-contacted) were contacted for Wave 4 interviews. As all twins ($N = 3787$) were 18 years of age or older at the time of recruitment for Wave 4, sensitive questions regarding their illicit substance use was queried. Therefore, we limited the sample to MOAFTS participants who completed Wave 4 interviews, but data from other waves (including the subsequent Wave 5, conducted from 2005 to 2008), which were available for over 95% of Wave 4 participants, were integrated as well. The Wave 4 sample consisted of 1038 monozygotic (MZ) twin pairs, 735 dizygotic (DZ) twin pairs and 241 twins whose co-twins did not participate.

The MOAFTS protocol was approved by the Washington University School of Medicine Human Research Protections Office. All twins 18 years old or older gave informed consent prior to study participation.

2.1.2. MOFAM. MOFAM is a longitudinal family study that included high-risk and low-risk subjects and was designed to investigate the impact of paternal alcoholism on offspring outcomes in an ethnically diverse sample of youth, with oversampling of AA families (55%) to increase the statistical power to detect differences in outcomes by race/ethnicity. As detailed elsewhere (Calvert et al., 2010), between 2003 and 2009, Missouri state birth records were used to identify families with at least one child aged 13, 15, 17 or 19 years (the same age range targeted in MOAFTS) and at least one full sibling aged 13 or older. Biological mothers completed brief telephone screening interviews to determine level of familial risk for alcoholism. Families in which the mother reported that the biological father had a history of excessive drinking were classified as "high risk." All others were classified as "low risk." An additional group of families was selected from men identified through driving records as having 2 or more drunk-driving convictions and classified as "very high risk." Sample enrollment occurred over 6 years. A total of 731 females (of 1461 offspring interviewed) completed at least one interview. For the current analyses, 163 full-sibling pairs, 30 full-sibling trios, and 315 individuals with no female sibling interview data were included – 81% of these women were interviewed at least twice. Of the 511 women who were recruited in the first 3 years and were interviewed at least once, 89% had 2 or more, and 73% had 3 or more follow up interviews. Rates are comparable across EA and AA women. These retention rates are quite good, particularly in light of the high risk nature of the families to which these women belonged.

The MOFAM study protocol was approved by the Washington University School of Medicine Human Research Protections Office and by the Ethics Board of the State Department of Health and Senior Services in accordance with regulations governing the use of vital records in research. All subjects aged 18 and older provided