Alcoholism: Clinical and Experimental Research
Vol. 34, No. 3
March 2010

Common Genetic Contributions to Alcohol and Cannabis Use and Dependence Symptomatology

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Background: Despite mounting evidence that use of and dependence on alcohol and cannabis are influenced by heritable factors, the extent to which heritable influences on these phenotypes overlap across the 2 substances has only rarely been explored. In the current study, we quantified cross-substance overlap in sources of variance and estimated the degree to which within-substance associations between use and dependence measures are attributable to common genetic and environmental factors for alcohol and cannabis.

Methods: The sample was comprised of 6,257 individuals (2,761 complete twin pairs and 735 singletons) from the Australian Twin Registry, aged 24 to 36 years. Alcohol and cannabis use histories were collected via telephone diagnostic interviews and used to derive an alcohol consumption factor, a frequency measure for cannabis use, and DSM-IV alcohol and cannabis dependence symptom counts. Standard genetic analyses were conducted to produce a quadrivariate model that provided estimates of overlap in genetic and environmental influences across the 4 phenotypes.

Results: Over 60% of variance in alcohol consumption, cannabis use, and cannabis dependence symptoms, and just under 50% of variance in alcohol dependence (AD) symptoms were attributable to genetic sources. Shared environmental factors did not contribute significantly to the 4 phenotypes. Nearly complete overlap in heritable influences was observed for within-substance measures of use and dependence symptoms. Genetic correlations across substances were 0.68 and 0.62 for use and dependence symptoms, respectively.

Conclusions: Common heritable influences were evident for alcohol and cannabis use and for AD and cannabis dependence symptomatology, but findings indicate that substance-specific influences account for the majority of the genetic variance in the cannabis use and dependence phenotypes. By contrast, the substantial correlations between alcohol use and AD symptoms and between cannabis use and cannabis dependence symptoms suggest that measures of heaviness of use capture much of the same genetic liability to alcohol- and cannabis-related problems as dependence symptomatology.

Key Words: Alcohol Dependence, Cannabis Dependence, Genetics, Twins.

INTRODUCTION

Alcohol and Cannabis: Use, Dependence, and Comorbidity

Seventy-five percent of U.S. adults over the age of 18 have consumed alcohol (National Center for Health Statistics, 2009). One in three of those individuals have met criteria for at least 1 dependence symptom over their lifetimes (McBride et al., 2009) and the evidence suggests there is a dose–response effect between levels of consumption and risk of dependence. Alcohol use disorder symptomatology is in fact so strongly associated with heaviness of use that integration of a quantifiable indicator of excessive consumption into diagnostic criteria has been proposed (Li, 2008; Li et al., 2007; O'Neill et al., 2001; Saha et al., 2007). Although less commonly used than alcohol, cannabis has long been the most frequently used illicit drug (Johnston et al., 2003; Substance Abuse and Mental Health Services Administration, 2002), with estimated prevalence of lifetime (i.e., ever) use of 20.5 to 42.8% for adults (Grucza et al., 2007) and 47.4% for 12th graders (Johnston et al., 2009) in the U.S. DSM-IV cannabis dependence criteria are met by 10% to 18% of cannabis users (Anthony et al., 1994; Hall and Pacula, 2003; Teesson et al., 2006) and in a recent study of adolescent cannabis users, over one third had at least 1 dependence symptom (Nocon et al., 2006). Like alcohol, severity of symptomatology increases steadily with heaviness of use (Coffey et al., 2002; Nocon et al., 2006). For example, in an Australian sample of young adults, 13% of

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Received for publication July 2, 2009; accepted October 23, 2009.

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DOI: 10.1111/j.1530-0277.2009.01120.x

those who used cannabis once or twice per week met cannabis dependence criteria, compared with 53% of those who used cannabis 3 or more times per week (Coffey et al., 2002).

Lifetime history of alcohol use is nearly universal among adolescents and adults who have used cannabis (Degenhardt and Hall, 2003; Pape et al., 2009; Sartor et al., 2009). As might be expected, problem drinking also frequently co-occurs with cannabis dependence symptomatology: AD criteria are met by approximately 70% of individuals with cannabis dependence (Agosti et al., 2002; Stinson et al., 2006). Likelihood of developing cannabis dependence is similarly elevated in alcohol-dependent individuals: Degenhardt and Hall (2003) reported that the odds of meeting cannabis dependence criteria were 5.81 times higher in those who met criteria for AD than in those who did not. Many of the same risk factors associated with alcohol-related problems have also been linked to cannabis use and related symptomatology. For example, externalizing disorders, deviant peer affiliation and family history of substance use disorders are all well-documented correlates of problem use of both alcohol and cannabis (Elkins et al., 2007; Fergusson et al., 2002, 2008; Gillespie et al., 2009; Hayatbakhsh et al., 2008; Kuperman et al., 2001; Marshal et al., 2003; Monshouwer et al., 2006; Slutske et al., 1998), suggesting that the association may be attributable at least in part to common sources of risk.

Genetic Influences on Alcohol and Cannabis Use and Related Symptomatology

The influence of genes on alcohol dependence (AD) and related symptomatology is well established. Results from twin studies indicate that approximately half of the variance in AD (50% to 60%) is accounted for by genetic factors and heritability does not vary significantly by gender (Heath et al., 1997; Knopik et al., 2004; Reed et al., 1996; True et al., 1996; van den Bree et al., 1998b). Twin studies have also produced evidence for genetic contributions to alcohol consumption (Grant et al., 2009; Heath and colleagues 1991; King et al., 2005; Whitfield et al., 2004), but the literature on consumption phenotypes is more limited than the AD literature and heritability estimates appear to vary by both age and sex. An early study by Heath and colleagues (1991) found that in females 57% of variance in quantity consumed was attributable to genetic factors, but results were less clear in males: an equally good fit was found for models in which 24% and 61% of variance was accounted for by genetic factors. In a longitudinal study by King and colleagues (2005), heavy drinking was assessed at ages 17 and 20 and heritability in females was estimated at 18% and 30%, respectively; for males heritability was 57% at age 17 and 39% at age 20.

Genetically informative studies of cannabis use and related symptomatology have consistently produced evidence for substantial genetic influences on both use and dependence phenotypes (Agrawal and Lynskey, 2006). In a sample of female twins, Kendler and Prescott (1998) found that 79% of variance in heavy cannabis use and 62.3% of variance in cannabis dependence could be explained by genetic factors. A twin study of illicit drug use in males by the same group produced nearly identical heritability estimates: 84% for heavy use and 58% for dependence (Kendler et al., 2000). Similar results have been reported in 2 other twin studies: Lynskey and colleagues (2002) found that 64.3% of variance in heavy use and 53% to 68% of variance in dependence was attributable to genetic factors and van den Bree and colleagues (1998a) estimated heritability of dependence at 44.7%.

Despite mounting evidence that both use of and dependence on alcohol and cannabis are influenced by heritable factors, there is relatively little information on the extent to which heritable influences on these phenotypes overlap across the 2 substances. Results from one such study, which examined use and problem use of alcohol, cannabis and cigarettes in an adolescent twin sample, revealed a genetic correlation of 0.62 between problem alcohol use and problem cannabis use (Young et al., 2006). An investigation of cannabis dependence symptoms and AD symptoms along with conduct disorder in an all-male adult twin sample identified a common genetic factor that accounted for 44.7% of variance in AD symptoms, but only 7.6% of variance in cannabis dependence symptoms (True et al., 1999). Another study using this same sample examined AD and cannabis dependence in combination with nicotine dependence and found that 42.4% of the variance in AD and 33.7% of the variance in cannabis dependence was attributable to a shared genetic factor (Xian et al., 2008). By contrast, when examined in combination with cocaine, caffeine, and nicotine dependence in a study of male and female adult twins, AD and cannabis dependence loaded on 2 different—but correlated ($r = 0.82$)—genetic factors, one encompassing the illicit substances, the other comprised of the licit substances (Kendler et al., 2007). Taken together, the literature suggests that there are some common genetic contributions to alcohol and cannabis-related phenotypes, but differences in samples and measurements of outcomes across studies do not allow for clear conclusions to be drawn about the magnitude of those overlapping influences. (Differences in the manifestation of genetic risk by developmental stage or gender, for example, could explain variations in findings, as might the shift in estimates of overlapping influences specific to alcohol and cannabis that can result from the addition of other phenotypes to genetic models.)

Furthermore, the limited research in this area has not addressed the similarities (and distinctions) in the underlying variance structures of use and dependence for cannabis—and only rarely for alcohol (Grant et al., 2009; Whitfield et al., 2004). Such a pursuit is highly relevant to gene association studies, as a large degree of genetic overlap between heaviness of use and dependence symptoms suggests that gene-finding studies for 1 phenotype can be directed by results from investigations of the other, perhaps even allowing for the integration of findings from studies of heavy use with those focused on dependence. The significant implications for etiological models of alcohol and cannabis dependence and the utility of global versus substance-specific intervention strategies further

highlight the importance of investigating commonality in sources of influence on alcohol and cannabis use and related symptomatology.

The primary aim of our study was to determine the degree to which the (lifetime) co-occurrence of heavy alcohol and cannabis use and the comorbidity of alcohol and cannabis dependence symptomatology are explained by common heritable and environmental factors. In addition, we sought to quantify the overlap in sources of variance between consumption and dependence symptomatology in these 2 substances of abuse. To address these aims, a series of genetic models were fitted, producing estimates of the magnitude of genetic and environmental influences on alcohol consumption and dependence symptoms and cannabis use and dependence symptoms as well as the associations between these influences across the 4 phenotypes.

MATERIALS AND METHODS

Participants

The sample for the current study was comprised of members of the Australian Twin Registry. Twins born in Australia between 1964 and 1971 were recruited for the registry through school systems and mass media appeals. They were registered by their parents from 1980 to 1982 and initially contacted in 1989 through mailed questionnaires, then interviewed by telephone with standard psychiatric assessments between 1996 and 2000, when twins ranged in age from 24 to 36 years (mean = 29.9 years). Approximately 73% of the targeted sample was successfully recruited into the study. Interviews were conducted with 6,257 individuals, representing 2,761 complete twin pairs and 735 respondents whose co-twins did not take part in the study. Breakdown by sex and zygosity of complete pairs are as follows: 698 monozygotic (MZ) female, 494 MZ male, 513 dizygotic (DZ) female, 395 DZ male, and 661 DZ opposite sex twin pairs. Informed consent was obtained prior to the start of interviews, as approved by the Human Research Protection Offices of Washington University School of Medicine in the United States and the Queensland Institute of Medical Research in Australia. Additional details regarding sample ascertainment and data collection are reported in related publications (Heath et al., 2001; Lynskey et al., 2003; Nelson et al., 2002).

Assessment

Data were collected with a modified Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA-OZ) (Bucholz et al., 1994; Hesselbrock et al., 1999), adapted for administration via telephone and updated for DSM-IV diagnostic criteria. Detailed histories of alcohol, cannabis and other substance use were gathered through SSAGA-based interviews, as were diagnostic criteria for substance use, mood, conduct, and anxiety disorders.

Operationalization of Alcohol and Cannabis Use and Dependence Variables

Alcohol Consumption. Alcohol consumption was measured as a composite of 5 indicators of heaviness of alcohol use over the lifetime, represented by a single factor derived through factor analysis (see Agrawal et al., 2009; Grant et al., 2009). Items comprising the factor and their corresponding factor loadings are as follows: density (i.e., quantity per week multiplied by frequency per week) of consumption during period of heaviest drinking (0.92), frequency of intoxication during period of heaviest drinking (0.68), maximum number of drinks ever consumed (0.76), frequency of heavy episodic drinking during period of heaviest drinking (0.79), and maximum number of drinks consumed before having an effect during period of heaviest drinking (0.73). (To adjust for skewness, the natural logarithm of the tolerance, density of heaviest use, and maximum drinks measures were used in the factor analysis.) The resulting continuous factor score was divided at 20% intervals (separately for females and males) and recoded into a 5-level ordinal variable. Alcohol use was nearly universal in the sample, with 98.9% of women and 98.7% of men reporting consumption of one or more drinks over the lifetime.

Cannabis Use. Cannabis use was operationalized as a 6-level categorical variable reflecting number of times used over the lifetime, with the lowest level being all nonusers and the remaining levels representing 20% intervals (quintiles) for frequency of use. Given that males had higher rates of initiation (68.8% of males versus 53.2% of females reported ever use) and reported heavier use, quintiles were calculated separately by sex. As in the case of alcohol consumption, the cannabis use variable is therefore an indicator of heaviness of use relative to same-sex peers. Frequency of use is reported by sex in Table 1.

Alcohol dependence symptoms were assessed in all individuals who reported ever drinking to intoxication or consuming alcohol at least once a month for 6 months or longer. Those who did not meet these criteria but reported some alcohol consumption were coded 0 for dependence symptoms.

Cannabis dependence symptoms were queried in all individuals who reported having used cannabis on at least a monthly basis (and 11 or more times over the lifetime) and coded 0 for those who had used cannabis but did not meet this minimum frequency. Drug dependence was not the primary focus of the interview, so to reduce respondent burden, an abbreviated cannabis dependence assessment based on the following 4 criteria was conducted: (i) using more frequently or over a longer period of time than intended, (ii) needing larger amounts to achieve the same effect (tolerance), (iii) continued use despite cannabis-induced emotional problems, and (iv) recurrent desire to cut down on use. (Analyses examining these modified criteria against full DSM-IV diagnostic criteria have yielded sensitivity and specificity estimates of 96.7 and 94.6%, respectively; Lynskey et al., 2002.)

Dependence symptom variables for both alcohol and cannabis were operationalized as ordinal variables with 4 levels: 0, 1, 2, and 3 or more symptoms. Distributions of alcohol and cannabis dependence symptoms are reported by sex in Table 2.

Data Analysis

Twin Modeling. Data from MZ and DZ twins can be utilized to estimate the relative contribution of additive genetic (A), nonshared environmental (E), and either shared environmental (C) or nonadditive genetic (including dominance, and thus denoted as D) influences on population variation in a given behavior. C and D cannot

Table 1. Frequency of Cannabis Use by Sex

Females n = 3,436		Males n = 2,772	
Number of times used		Number of times used	
Never	46.8%	Never	31.2%
1–2	13.2%	1–3	15.3%
3–5	10.5%	4–10	13.4%
6–12	9.2%	11–50	13.6%
13–100	9.4%	51–500	12.1%
101 or more	10.9%	501 or more	14.3%

Table 2. Rates of Alcohol and Cannabis Dependence Symptoms by Sex

	Alcohol		Cannabis	
Dependence symptoms	Females n = 3,422	Males n = 2,769	Females n = 1,825	Males n = 1,904
0	35.0%	17.2%	76.5%	65.3%
1	26.3%	23.5%	8.8%	12.7%
2	21.0%	24.9%	6.7%	9.1%
3+	17.7%	34.4%	8.1%	12.9%

be jointly estimated when data from twins alone are used, so we fitted models incorporating C and D separately (i.e., ACE and ADE models) to the data.

In all genetic models, consumption/use was set to missing for a given substance if the individual reported 3 or more dependence symptoms for that substance (3 symptoms being the cut-off for a dependence diagnosis). This was the case for 17.7% of female drinkers and 34.4% of male drinkers and for 8.1% of female and 12.9% of male cannabis users, respectively. By using this technique (see Grant et al., 2009; Heath et al., 2002) we were able to examine the genetic correlation between heaviness of use and dependence symptomatology with the effects of dependence on consumption/use removed. (As dependence itself leads to increasing use, an artificial inflation of genetic correlation would occur if such an adjustment were not made.) All 4 measures were tested for assumptions of underlying multivariate normality. Fit statistics for the alcohol measures are available in Grant and colleagues (2009). For cannabis-related measures, with the exception of MZ twins for cannabis use, all other groups showed evidence for multivariate normality.

Quadrivariate Model. A quadrivariate triangular decomposition (also known as a Cholesky decomposition) was fitted to assess the degree of overlap in genetic and environmental influences between alcohol consumption, AD symptomatology, cannabis use, and cannabis dependence symptomatology. Models were fitted in Mx (Neale et al., 2003) using full information maximum likelihood estimation with raw categorical data. Cannabis use and alcohol consumption variables were recoded into ordinal variables, as Mx requires that all variables be in the same format (and dependence symptoms are ordinal in nature). Thresholds were adjusted for age at the time of interview using 3 dummy variables to represent ages 28 to 29, 30 to 31, and 32 to 35, with 24 to 27 years as the comparison group.

A series of sub-models examining the statistical significance of A, C, and E were compared with the full model to derive the best-fitting quadrivariate model. Sub-models were tested by calculating the difference between the −2 log-likelihood fit of the full model and nested sub-model, which is distributed as chi-square for the given degrees of freedom.

RESULTS

Level of Use and Risk for Dependence

As seen in Fig. 1, a linear relationship between alcohol consumption and AD was observed in males, with each 20% incremental increase in heaviness of use corresponding to approximately a 10% increase in rates of AD. By contrast, rates of AD in women increased dramatically from the 60th to 80th percentile and from the 80th percentile to the highest consumption levels (see Fig. 2). Although overall prevalence of AD in women was half that of men (17.7% vs. 34.4%), the prevalence of AD in the heaviest drinking females was considerably higher than in the heaviest drinking males (58.1% vs. 39.9%). The association between frequency of cannabis use and cannabis dependence in women paralleled the association in males (see Fig. 2). The prevalence of cannabis dependence was very low (0 to 6.9%) for individuals in the low to average frequency use groups (i.e., fewer than 13 times for females and fewer than 51 times for males), but rates of cannabis dependence rose substantially as use increased to moderately high (15.4% and 38.8% for females and males, respectively) and again to the highest frequency of use, at which 58.7% of females and 65.5% met full cannabis dependence criteria.

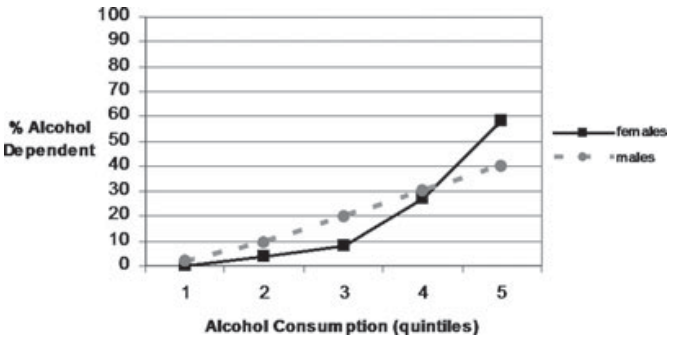

Fig. 1. Rates (%) of alcohol dependence across varying levels of alcohol consumptions by sex.

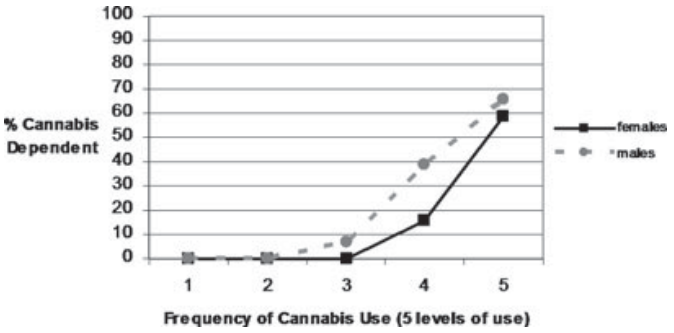

Fig. 2. Rates (%) of cannabis dependence across varying levels of cannabis use by sex.

Co-Occurrence of Alcohol Dependence and Cannabis Dependence

Rates of cannabis dependence were substantially higher in individuals who met criteria for AD compared with those who did not. For women, the corresponding prevalences were 14.3% and 5.8% for AD positive and AD negative, respectively [odds ratio (OR): 2.71; 95% confidence interval (CI): 1.94–3.80]; for men, they were 20.4% and 7.6% (OR: 3.10; 95% CI: 2.33–4.13).

Quadrivariate Model

The sub-models tested and their corresponding model fit statistics are reported in Table 3. Models 1 and 2 were full

Table 3. Model Fit Statistics for Quadrivariate Cholesky Decomposition

	Model	Compared with	$\Delta\chi^2$	Δdf	Significance
1	Full ACE model, women and men equated[a]	–	–	–	–
2	Full ADE model, women and men equated[b]	–	–	–	–
3	AE model, women and men equated[c]	Model 1	4.231	10	0.94
4	AE model, women and men estimated separately[d]	Model 3	**−16.795**	**−20**	**0.66**

[a]−2LL = 48,134.641.
[b]−2LL = 48,138.872.
[c]Final model.
[d]Freeing female and male parameter estimation did not result in a significant improvement in fit.

Cholesky ACE and ADE models respectively. Parameter estimates for women and men were equated in these models. Because the log-likelihood of the ACE model was marginally better than that for the ADE model, the ACE model (Model 1) was selected for further examination. Model 3 tested an AE model with parameter estimates equated for women and men. This model resulted in a nonsignificant decrement in fit compared with Model 1, indicating that shared environmental influences were not significant. Model 3 therefore became the base model for additional analyses. In Model 4, we tested whether the parameters for women and men should be estimated separately. The improvement in fit when women and men were estimated separately was not significant, indicating that the parameter estimates can be equated across sex. Model 3 was therefore selected as the best-fitting model. (We were unable to estimate CIs because of the computational intensity of the calculations for the models, so we present only the point estimates for the proportion of variance attributable to A and E and for the correlations between A and E variance components.)

Under the best-fitting model (shown in Table 4), heritable influences accounted for over 60% of the variance in alcohol consumption, cannabis use, and cannabis dependence symptoms (61.0%, 67.1%, and 72.2%, respectively). The heritability estimate was lowest—but still quite substantial—for AD symptoms: 46.8% of variance could be attributed to genetic factors. As noted above, we did not find evidence that shared environmental factors exert a significant influence on use or dependence symptomatology for alcohol or cannabis.

Table 4. Proportion of Variance Attributable to Additive Genetic and Environmental Sources for Alcohol and Cannabis Use and Dependence Symptoms[a]

	Alcohol		Cannabis	
Source of variance	Dependence symptoms	Consumption	Dependence symptoms	Use
Additive genetic	0.468	0.610	0.671	0.722
Shared environmental	–	–	–	–
Nonshared environmental	0.532	0.390	0.329	0.278

[a]Under the best-fitting quadrivariate model.

Phenotypic correlations among alcohol consumption, cannabis use, AD symptoms, and cannabis dependence symptoms are reported in Table 5. Additive genetic and unique environmental correlations among the 4 phenotypes are shown in Table 6. As is evident from Table 6, our results provide strong support for within-substance and cross-substance overlap in heritable influences. For alcohol consumption and dependence symptoms, $r_G = 0.953$; 90% of the genetic variance in alcohol consumption was shared with AD symptoms. A similarly high overlap in heritable factors was observed for cannabis use and dependence symptoms: $r_G = 0.979$. Cross-substance genetic correlations were more modest, but still highly significant. Genetic correlations of 0.675 and 0.613 were found for alcohol consumption and cannabis use and

Table 5. Phenotypic Correlations Between Alcohol and Cannabis Use and Dependence Symptoms

	Alcohol		Cannabis	
	Dependence symptoms	Consumption	Dependence symptoms	Use
Alcohol				
Dep symptoms	–			
Consumption	0.600	–		
Cannabis				
Dep symptoms	0.330	0.164	–	
Use	0.426	0.440	0.847	–

Dep, dependence.

Table 6. Additive Genetic and Unique Environmental Correlations[a] Between Alcohol and Cannabis Use and Dependence Symptoms[b]

	Alcohol		Cannabis	
	Dependence symptoms	Consumption	Dependence symptoms	Use
Alcohol				
Dep symptoms	–	0.546	0.246	0.230
Consumption	0.953	–	0.250	0.298
Cannabis				
Dep symptoms	0.613	0.655	–	0.889
Use	0.621	0.675	0.979	–

[a]Genetic correlations are shown below the diagonal; correlations between unique environmental factors are shown above the diagonal.
[b]Under the best-fitting quadrivariate model.
Dep, dependence.

for AD and cannabis dependence symptoms, respectively. As expected, given the high within-substance genetic correlation between use and dependence symptoms, genetic correlations were very similar for AD symptoms and cannabis use, $r_G = 0.621$ and for alcohol use and cannabis dependence symptoms, $r_G = 0.655$ as they were for cross-substance correlations of the same measure.

The proportion of genetic variance attributable to various sources was calculated using unstandardized path coefficients for the 4 phenotypes. (Coefficients for each pathway and the method for apportioning variance are reported in Fig. 3, which is included in Appendix 1.) A total of 90.9% of genetic variance in alcohol consumption was attributable to a source common to all 4 phenotypes. For cannabis dependence symptoms, 37.5% of genetic variance was attributable to influences common to all 4 phenotypes, 5.5% to influences shared by alcohol consumption, cannabis dependence symptoms, and cannabis use (but not AD symptoms), and 57.0% to influences shared with cannabis use. For cannabis use, the genetic variance was distributed as follows: 38.6% to influences common to all 4 phenotypes, 7.5% to influences shared by alcohol consumption, cannabis dependence symptoms, and cannabis use (but not AD symptoms), 50.0% to influences shared by cannabis use and cannabis dependence symptoms (but not AD symptoms or alcohol consumption), and 3.9% to phenotype-specific influences.

Analyses revealed both within- and cross-substance overlap in nonshared environmental factors as well, but unlike the associations observed with genetic factors, the degree of overlap differed substantially between alcohol and cannabis. The r_E for cannabis use and cannabis dependence symptoms was 0.889; for alcohol consumption and AD symptoms, $r_E = 0.546$. The cross-substance correlations were also more modest than those observed with genetic factors. Nonshared environmental influences on alcohol consumption and cannabis use were correlated at $r_E = 0.298$, AD symptoms and cannabis dependence symptoms at $r_E = 0.246$.

DISCUSSION

Our investigation of genetic and environmental contributions to use and dependence symptomatology for alcohol and cannabis revealed significant associations both across and within substances. On the phenotypic level, it produced further support for the strong link between heaviness of use and dependence symptoms for both substances as well as the high degree of comorbidity between AD and cannabis dependence. Through biometrical modeling we estimated heritability for each of the 4 phenotypes as well as both within- and cross-substance overlap in genetic and environmental influences on use and dependence symptoms, revealing the substantial role of common heritable factors in observed associations.

The correspondence between heaviness of alcohol consumption and level of risk for dependence in the current study is consistent with the dose–response effect described in the literature (Li et al., 2007; O'Neill et al., 2001; Saha et al., 2007). The overall trend did not vary by sex but the fact that nearly 60% of the heaviest drinking females compared with only 40% of the heaviest drinking males met AD criteria suggests some intriguing potential gender-related differences, for instance, that deviation from the norms for drinking behaviors confers greater risk for AD in women than in men. The parallel analysis with cannabis use and dependence symptomatology revealed a similar association that was consistent across sexes, with negligible rates of dependence for the lowest 60% and dramatic increases in prevalence for the next 2 levels of frequency of use. Although previous studies have measured heaviness of cannabis use in terms of number of days used per week or month, whereas we queried total number of times used, our results mirror the patterns reported in the literature: substantial elevations in risk occur as frequency of use moves from experimentation to moderate to heavy use (Coffey et al., 2002; Nocon et al., 2006). Our finding that 21.8% of women with AD and 27.1% of men with AD met cannabis dependence criteria also coincides with previous reports of elevated rates of cannabis dependence among alcohol-dependent individuals (Degenhardt and Hall, 2003; Xian et al., 2008).

Genetic modeling revealed that just under half of the variance in AD symptoms and over 60% of variance in the other 3 phenotypes could be accounted for by heritable sources of influence. Our estimated heritability of 46.8% for AD symptoms is slightly lower but within the expected range for dependence symptomatology. The majority of studies in this area have examined AD as a dichotomous outcome and produced heritability estimates of 50% to 60% (Heath et al., 1997; Knopik et al., 2004; Reed et al., 1996; True et al., 1996; van den Bree et al., 1998b). Far fewer genetically informative investigations have focused on heaviness of alcohol consumption and results have varied widely. Compared with the few published studies, our results fall at the high end of the range (Heath et al., 1991; King et al., 2005; Whitfield et al., 2004). By contrast, our findings for cannabis use and dependence symptoms closely match those from prior studies, which have estimated heritability at 45% to 85%, with little distinction between estimates for use and dependence phenotypes (Agrawal and Lynskey, 2006; Kendler and Prescott, 1998; Kendler et al., 2000; Lynskey et al., 2002; van den Bree et al., 1998a). Also consistent with the existing literature (Heath et al., 1997; Kendler and Prescott, 1998; Kendler et al., 2000; Knopik et al., 2004), there was no evidence that the underlying variance structure for any of the 4 phenotypes under study varied significantly across sex.

We found a high degree of within-substance overlap in heritable influences on use and dependence. In contrast to the more moderate genetic correlation of 0.63 reported by our group for AD and *average alcohol intake* (Whitfield et al., 2004), we found that 90.9% of genetic contributions to heaviness of alcohol consumption (during heaviest period of use) were shared with AD symptoms (see also Grant et al., 2009). For cannabis phenotypes, the genetic correlation was 0.979. The nearly perfect correlation between genetic contributions

to use and genetic contributions to dependence for both alcohol and cannabis suggests that an indicator of heaviness of use may act as a proxy for dependence symptomatology (and vice versa). The implications for linkage and association studies of alcohol and cannabis use and dependence are far-reaching. Data collected on one of the 2 phenotypes can be highly informative for investigations focusing on the other phenotype; it may even be possible to integrate findings from studies examining heavy use with those examining dependence. Furthermore, the substantial genetic overlap in dependence symptomatology across the 2 substances suggests that samples ascertained based on AD risk capture a subpopulation at high genetic risk for cannabis dependence and thus can be useful in linkage and association studies of cannabis-related phenotypes as well.

With respect to individual-specific environmental influences, the degree of overlap across use and dependence symptoms was considerably higher for cannabis than for alcohol: nonshared environmental factors were correlated at 0.889 for cannabis versus 0.546 for alcohol. Given that nonshared environmental sources of variance include error, interpretations must be made with caution, but the higher strength of the association for the illicit drug raises some interesting possibilities. For example, it could be argued that use of a common licit drug is normative and is therefore shaped by different environmental factors than pathological use, whereas use of an illicit drug is somewhat more deviant and access is more limited, so the role of environmental factors in use and misuse of an illicit drug may not be as distinct.

In addition to the high within-substance correlations, we found a moderate degree of overlap in genetic influences across alcohol and cannabis in the respective use and dependence symptom phenotypes. Genetic factors were correlated at 0.675 for use and 0.613 for dependence symptomatology, but over half of inherited vulnerabilities to heavy use and to dependence symptoms were explained by substance-specific influences (57% for cannabis dependence symptoms and 53.9% for cannabis use) This etiological model is consistent with the high—but far from 100%—rate of co-occurrence for alcohol and cannabis-related problems (Degenhardt and Hall, 2003; Xian et al., 2008). The genetic correlation of 0.675 for use in our sample also coincides closely with the genetic correlation of 0.62 between problem alcohol use and problem cannabis use reported by Young and colleagues (2006), who examined these phenotypes in combination with nicotine dependence symptoms. Our estimates of overlap in heritable influences on dependence symptoms are highly consistent with Xian and colleagues (2008), who found that 42.4% of the variance in AD and 33.7% of the variance in cannabis dependence were accounted for by a shared genetic factor (that also loaded on nicotine dependence), but less so with 2 other known studies in this area. Notably, these 2 investigations included additional phenotypes not examined in studies that produced results more similar to ours, which likely influenced the identification of common factors in these models and thus the estimated overlap in genetic influences specific to AD and cannabis dependence. For example, Kendler and colleagues' (2007) study in which 2 distinct but correlated genetic factors emerged, with alcohol loading on one and cannabis on the other, included cocaine and caffeine dependence. Similarly, True and colleagues' (1999) finding that the genetic factor common to AD symptoms and cannabis dependence symptoms accounted for only 7.6% of the total variance (and 17% of the genetic variance) in cannabis dependence symptoms may be attributable in part to the inclusion of conduct disorder in the models. In short, our study adds to a limited literature that has thus far produced mixed results regarding the degree of genetic overlap in AD and cannabis dependence symptomatology, with findings that match the highest estimates of common genetic influences to date (i.e., Xian et al., 2008).

In contrast to the high genetic correlations, the overlap across substances in nonshared environmental factors was negligible for both use and dependence symptoms (r_E = 0.298 and 0.246, respectively), indicating that the individual-specific environmental conditions that promote use and related problems vary across the 2 substances. This conclusion does not appear to be in keeping with evidence in the larger literature of common risk factors for alcohol and cannabis-related behaviors. The apparent discrepancy has 3 likely explanations. First, the low degree of overlap in nonshared environmental factors may be attributable to substance-specific measurement error. Second, many of the well-established risk factors, including externalizing behaviors and parental substance-related problems (Elkins et al., 2007; Fergusson et al., 2008; Hayatbakhsh et al., 2008; Kuperman et al., 2001; Monshouwer et al., 2006; Slutske et al., 1998) are themselves highly heritable (Knopik et al., 2005; Krueger et al., 2002; McGue et al., 2006; Sherman et al., 1997; Slutske et al., 1998). Moreover, they share a substantial proportion of genetic variance with alcohol and cannabis-related phenotypes (Hicks et al., 2004; Miles et al., 2002; Slutske et al., 1998; True et al., 1999), so they cannot be viewed as primarily environmental. Finally, heritability estimates—and consequently, genetic correlations—may also reflect gene-by-environment interactions or gene–environment correlations (i.e., seeking out environments that promote behaviors for which one is at high genetic risk). Deviant peer affiliation, which has consistently been linked to alcohol and cannabis-related problems (Fergusson et al., 2002; Gillespie et al., 2009; Marshal et al., 2003) is one such example of gene–environment correlation: adolescents with externalizing problems, who are at high risk for substance misuse, seek out like-minded peers that encourage experimentation with substances. Exploration of gene-by-environment interplay in future studies is critical to fostering our understanding of the development of problem use of alcohol and cannabis.

Limitations and Future Directions

Our findings provide a foundation for further investigation of the genetics of alcohol- and cannabis-related phenotypes,

both gene-mapping and studies of the interaction of inherited vulnerabilities with environmental influences that lead to these outcomes. However, there are possible limitations that need to be kept in mind. One is the potential for retrospective reporting biases to influence results, for example, for greater lag time from the event to the time of reporting to translate into systematic underreporting of use and symptoms (Carney et al., 1998; Stockwell et al., 2004). Given the relatively narrow age range (and thus the relatively narrow range in lag times) in the sample and our adjustment for age at the time of interview, it is unlikely that such a bias greatly influenced results, but reports from prospective studies would be more accurate. To the extent to which the relative influences of heritable and environmental factors vary across cultures, the generalizability of our findings may also be somewhat limited. Conducting investigations similar to ours in other populations would reveal the nature of cross-cultural distinctions and commonalities in the degree to which these phenotypes are shaped by genes versus environment (and gene-by-environment interplay). Such studies will lead to the next critical step in this line of research: the exploration of specific environmental contributions to heavy use and dependence on alcohol and cannabis, which, if they are not consistent across cultural groups, may call for differing approaches to intervention and prevention. Similarly, the modest associations between nonshared environmental influences on the 2 substances indicate that there are substance-specific environmental risk factors. The development of effective strategies for preventing misuse of alcohol and cannabis will therefore depend in part on identifying the influences on problem use that are unique to each of the 2 substances.

ACKNOWLEDGMENTS

This study was funded by grants AA007728, AA017688, AA010248, AA013320, AA13321, and AA011998 from the National Institute on Alcohol Abuse and Alcoholism and grants DA018660 and DA018267 from the National Institute on Drug Abuse.

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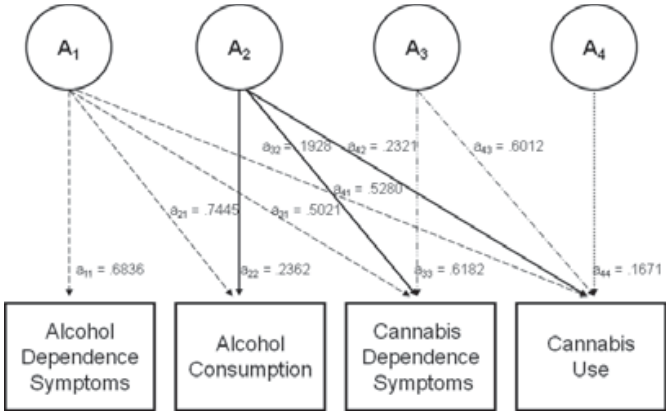
APPENDIX 1



Unstandardized Additive Genetic Path Estimates for the 4 Phenotypes.

Raw path estimates are shown.

Calculation of genetic variance from common and specific sources is illustrated below for cannabis dependence symptoms:

Total genetic variance $= (0.6182)^2 + (0.1928)^2 + (0.5021)^2 = 0.6715$.

Variance explained by A1 (genetic influences common to all 4 phenotypes) $= (0.5021)^2/0.6715 = 0.3754$*.

Variance explained by A2 (genetic influences shared by alcohol consumption, cannabis dependence symptoms, and cannabis use) $= (0.1928)^2/0.6715 = 0.0554$**.

Variance explained by A3 (genetic influences common to cannabis dependence symptoms and cannabis use) $= (0.6182)^2/0.6715 = 0.5691$.

*From Table 6, the genetic correlation between *alcohol dependence symptoms* and *cannabis dependence symptoms* is 0.6128, which is computed as $\sqrt{0.3754}$.

**From Table 6, the genetic correlation between *alcohol consumption* and *cannabis dependence symptoms* is 0.6558. This is NOT equal to $\sqrt{0.0554}$. To calculate this correlation, we compute the total genetic covariance across the 2 measures, including variance shared with *alcohol dependence symptoms*, and divide it by the product of the square root of the total genetic variance in *alcohol consumption* and *cannabis dependence symptoms*.

Therefore, $0.6558 = (0.2362 \times 0.1928) + (0.7445 \times 0.5021)/[(\sqrt{0.6715}) \times (\sqrt{0.6100})]$, where $0.6100 = (0.2362)^2 + (0.7445)^2 =$ the total genetic variance in alcohol consumption explained by A1 and A2.