ORIGINAL ARTICLE

Specificity of Genetic and Environmental Risk Factors for Symptoms of Cannabis, Cocaine, Alcohol, Caffeine, and Nicotine Dependence

Kenneth S. Kendler, MD; John Myers, MS; Carol A. Prescott, PhD

Context: Although genetic risk factors have been found to contribute to dependence on both licit and illicit psychoactive substances, we know little of how these risk factors interrelate.

Objective: To clarify the structure of genetic and environmental risk factors for symptoms of dependence on cannabis, cocaine, alcohol, caffeine, and nicotine in males and females.

Design: Lifetime history by structured clinical interview.

Setting: General community.

Participants: Four thousand eight hundred sixty-five members of male-male and female-female pairs from the Virginia Adult Twin Study of Psychiatric and Substance Use Disorders.

Main Outcome Measure: Lifetime symptoms of abuse of and dependence on cannabis, cocaine, alcohol, caffeine, and nicotine.

Results: Controlling for greater symptom prevalence in males, genetic and environmental parameters could be equated across sexes. Two models explained the data well. The best-fit exploratory model contained 2 genetic factors and 1 individual environmental factor contributing to all substances. The first genetic factor loaded strongly on cocaine and cannabis dependence; the second, on alcohol and nicotine dependence. Nicotine and caffeine had high substance-specific genetic effects. A confirmatory model, which also fit well, contained 1 illicit drug genetic factor—loading only on cannabis and cocaine—and 1 licit drug genetic factor loading on alcohol, caffeine, and nicotine. However, these factors were highly intercorrelated ($r = +0.82$). Large substance-specific genetic effects remained for nicotine and caffeine.

Conclusions: The pattern of genetic and environmental risk factors for psychoactive substance dependence was similar in males and females. Genetic risk factors for dependence on common psychoactive substances cannot be explained by a single factor. Rather, 2 genetic factors—one predisposing largely to illicit drug dependence, the other primarily to licit drug dependence—are needed. Furthermore, a large proportion of the genetic influences on nicotine and particularly caffeine dependence appear to be specific to those substances.

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A CRITICAL ISSUE IN THE ETIology of psychoactive drug dependence is the degree to which genetic and environmental risk factors for these substances are specific to individual pharmacological classes or nonspecific in predisposing a person to dependence on a range of psychoactive drugs.[1,2] Two large population-based twin studies have examined this question for illicit psychoactive substances.[2,3] The first was by Tsuang et al,[2] who examined the abuse of 5 classes of illicit drugs (marijuana, sedatives, stimulants, heroin or opiates, and psychedelics) in 3372 male twin pairs from the Vietnam Era Twin Registry. They found that most genetic and environmental risk factors were shared among these substances, though modest amounts of drug-specific genetic and environmental influences were also seen.[2] The second was by Kendler and colleagues,[3] who examined the abuse or dependence of 6 illicit psychoactive drug classes (cannabis, sedatives, stimulants, cocaine, opiates, and hallucinogens) in 1196 male-male twin pairs from the Virginia Adult Twin Study of Psychiatric and Substance Use Disorders (VATSPSUD). They found that all the genetic influences on abuse/dependence of these 6 substance classes were nonspecific and shared across substances.

These important studies, however, both had 2 limitations. First, they examined only illegal psychoactive substances. They were therefore unable to elucidate the degree to which genetic and environmental risk factors for dependence were shared between illicit and the more commonly used licit psychoactive drugs. Second, both reports included only male subjects.

Author Affiliations: Virginia Institute of Psychiatric and Behavioral Genetics (Dr Kendler and Mr Myers), and Departments of Human Genetics (Dr Kendler) and Psychiatry (Dr Kendler and Mr Myers), Medical College of Virginia, Virginia Commonwealth University, Richmond; and Department of Psychology, University of Southern California, Los Angeles (Dr Prescott).

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In this report, we examine, in both male and female personally interviewed twins from VATSPSUD, the interrelationship of genetic and environmental risk factors for abuse/dependence of the 3 common licit psychoactive substances (alcohol, caffeine, and nicotine) and 2 of the more frequently used illicit psychoactive drugs (cannabis and cocaine). Caffeine is included in these analyses because it is the most widely used psychoactive substance in the world and has substantial addictive potential.[4] We address the following questions:

1. Does the structure of genetic and environmental risk factors for the abuse/dependence of common psychoactive drugs differ in males and females?
2. Can genetic risk for the liability to abuse/dependence for all common psychoactive substances be explained by a single common genetic factor?
3. If there is evidence for multiple common genetic factors for psychoactive drug abuse/dependence, can the pattern of findings be explained by 1 common factor for illicit and 1 common factor for licit substances?

METHODS

SAMPLE

Participants in this study come from 2 interrelated studies in white, same-sex twin pairs who participated in VATSPSUD.[5] All subjects for VATSPSUD were ascertained from the Virginia Twin Registry, a population-based registry formed from a systematic review of birth certificates in Virginia. Female-female twin pairs, from birth years 1934 through 1974, became eligible if both members previously responded to a mailed questionnaire in 1987-1988, to which the response rate was approximately 64%. Data on psychoactive substance abuse and dependence used in this report were collected at the fourth wave of interviews, conducted in 1995-1997. For this wave, we succeeded in interviewing 85% of the eligible sample. Data on the male-male pairs from a sample (birth years 1940-1974) initially ascertained directly from registry records, which contained all twin births, came by a phone interview, which had a 72% response rate. Data on alcohol, cannabis, cocaine, and nicotine were collected at the second wave of interviews conducted in 1994-1998 with a response rate of 83%, while caffeine data were collected at the third wave of interviews conducted in 1998-2004 with a response rate of 75%. Zygosity was determined by discriminate function analyses using standard twin questions validated against DNA genotyping in 269 female-female and 227 male-male twin pairs.[6] The mean (SD) age and time of education was, respectively, 36.3 (8.2) and 14.3 (2.2) years at the fourth wave of interviews for females and 37.0 (9.1) and 13.6 (2.6) years at the second wave of interviews for males.

The total sample size on which we had data for cannabis abuse and dependence was 4865 individuals consisting of 2027 complete pairs and 811 twins whose co-twins did not participate. Of these subjects, 3569 (73.4%) had complete data on all 4 of the other substances. Of the 1296 subjects with incomplete data, 1277 (98.5%) were missing data on a single substance, usually caffeine. There were 1666 monozygotic male twins, 1269 dizygotic male twins, 1151 monozygotic female twins, and 779 dizygotic female twins. The sample size was virtually the same for cocaine use and differed only slightly for nicotine and alcohol use. For caffeine, the number of female twins was nearly identical to those for cannabis, but the male sample was smaller (1030 monozygotic and 671 dizygotic twins).

This project was approved by the human subject committees at Virginia Commonwealth University. Written informed consent was obtained prior to face-to-face interviews and verbal consent was obtained prior to telephone interviews. Interviewers had master's degrees in a mental health–related field or bachelor's degrees in this area plus 2 years of clinical experience. At each wave, members of a twin pair were questioned by different interviewers who were blind to clinical information about the co-twin.

MEASURES

To maximize information, we used ordinal measures for psychoactive drug dependence. We summed the total number of endorsed *DSM-IV* criteria[7] for lifetime alcohol, cannabis, and cocaine abuse/dependence. For alcohol, we divided all subjects into 4 categories: those meeting 0, 1 to 2, 3 to 4, and 5 to 11 criteria for abuse or dependence. For cocaine abuse/dependence—owing to the rarity of those endorsing 5 or more symptoms—we divided subjects into only 3 categories: those meeting 0, 1 to 2, and 3 to 11 criteria. Lifetime nonusers of alcohol, cannabis, and cocaine were included with a score of 0.

Lifetime nicotine dependence was measured by the Fagerstrom Test for Nicotine Dependence[8] from the period of heaviest tobacco use. Four classes were constructed with scores of 0, 1 to 3, 4 to 6, and 7 to 11. Lifetime nonsmokers were included with a score of 0.

Caffeine dependence was defined as the sum of reported symptoms of caffeine tolerance and caffeine withdrawal during the period of lifetime maximal caffeine intake. Tolerance was assessed by the 2 items from the psychoactive substance abuse section of the Structural Clinical Interview of *DSM-IV*,[9] which operationalized the criteria 1a and 1b for substance dependence (ie, need for more of a substance to obtain same effect or diminished effect with same amount).[7] Caffeine withdrawal was assessed using the following 4 symptoms identified in *DSM-IV*[7]: headaches, marked fatigue or drowsiness, marked anxiety or depression, and nausea or vomiting. Five classes for caffeine dependence were constructed for those having 0, 1, 2, 3, or 4 or more symptoms of tolerance or withdrawal.

Given empirical evidence in this[10] and other samples[11,12] that *DSM-IV* symptoms of abuse and dependence form a single dimension of liability, herein we will refer to it as *dependence* for all substances. (Recent studies have also suggested that patterns of substance abuse or dependence can be well explained by mixture models that combine dimensional and categorical approaches.[13,14])

STATISTICAL ANALYSIS

Our models divide the sources of individual differences in liability to substance dependence into 3 classes: additive genetic effects (A), shared family environment (C), and unique environment (E).[5] Shared environment reflects family and community experiences that increase similarity in siblings who are raised together. Unique environment included environmental experiences not shared by siblings as well as measurement error.

Our multivariate twin models determine the degree to which genetic and environmental influences on dependence are shared across 5 different psychoactive substances or are specific to individual substances. This is done by including in the model both genetic and environmental common factors that influence risk for more than 1 substance as well as substance-specific influences.

Model fitting to raw data, using the method of full information maximum likelihood, was conducted using the program Mx.[15] Given that 5 variables were involved, we were limited to multivariate models with 2 common factors. We adopted the independent pathway approach because these models make

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Table 1. Prevalence of Symptoms of Alcohol, Cannabis, Cocaine, Nicotine, and Caffeine Abuse or Dependence in Male and Female Twins

	Cannabis[a]			Cocaine[a]			Alcohol[a]			Caffeine[b]			Nicotine[c]		
Liability Class	No. of Criteria Met[a]	Male, %	Female, %	No. of Criteria Met[a]	Male, %	Female, %	No. of Criteria Met[a]	Male, %	Female, %	No. of Criteria Met[b]	Male, %	Female, %	No. of Criteria Met[c]	Male, %	Female, %
0	0	79.5	90.6	0	93.8	96.1	0	54.2	81.0	0	52.1	63.3	0	42.4	66.2
1	1-2	11.0	5.2	1-2	2.1	0.9	1-2	11.0	6.5	1	23.9	19.3	1-3	18.9	19.3
2	3-4	5.2	2.4	3-11	4.1	3.0	3-4	12.7	6.7	2	12.7	9.9	4-6	20.4	9.9
3	5-11	4.3	1.9	0	0	0	5-11	22.1	5.7	3	7.4	5.7	7-11	18.3	5.7
4										4-6	3.9	1.7			

[a] *DSM-IV* criteria for abuse or dependence.[7]
[b] Sum of *DSM-IV* tolerance and caffeine withdrawal criteria.[7]
[c] Score on Fagerstom Test for Nicotine Dependence.[8]

Table 2. Polychoric Correlations Between Symptoms of Alcohol, Cannabis, Cocaine, Nicotine, and Caffeine Abuse or Dependence in Male and Female Twins[a]

Substance	Cannabis	Cocaine	Alcohol	Caffeine	Nicotine
Cannabis		0.76[b]	0.57[b]	0.24[b]	0.52[b]
Cocaine	0.76[b]		0.66[b]	0.16[c]	0.42[b]
Alcohol	0.54[b]	0.58[b]		0.21[b]	0.44[b]
Caffeine	0.11[c]	0.14[c]	0.16[b]		0.10[c]
Nicotine	0.36[b]	0.39[b]	0.41[b]	0.07[d]	

[a] Results for males are below the diagonal; females are above.
[b] $P < 0.001$.
[c] $P < .01$.
[d] $P < .05$.

the fewest assumptions.[16] However, evidence permitting, we were also interested in testing an a priori model—independent but correlated common genetic factors indicated by loadings on licit and illicit psychoactive drugs.

Because of concerns about the stability and run times for our models, we began with the simple 1-1-1 model with specifics (where the first, second, and third numbers reflect the number of genetic, shared environmental, and unique environmental common factors). We first sought to determine if we could detect evidence for any second common genetic or environmental factors. Then we sought to simplify the resulting model by deleting all the common factors and then the substance-specific loadings one by one. We did not attempt to eliminate the substance-specific unique environmental loadings, as these included errors of measurement, which would be unrealistic to assume to be 0.

When fitting models with 2 common factors, we identified the solution by arbitrarily setting the loading of 1 substance to 0 on the second factor and then submitting the resulting parameter estimates to a varimax rotation in SAS (SAS Institute Inc, Cary, North Carolina), which renders the factors independent. We confirmed the stability of these solutions by picking a different substance for the 0 loading and found the results to be within the rounding error.

Our analyses included male and female same-sex twin pairs, thereby enabling us to test for quantitative sex effects, that is, differences in males and females in the magnitude of genetic and environmental influences. We did not include opposite-sex dizygotic twins, so that these analyses are not informative about qualitative sex effects, ie, the degree to which genetic risk factors for psychoactive substance dependence are the same in the sexes.

The goal of our model fitting is to achieve the best possible balance of explanatory power and simplicity. This goal is operationalized by Akaike's information criterion (AIC),[17] which equals $\chi^2 - 2\,df$. We seek to minimize the AIC value.

RESULTS

PREVALENCES

The number of male and female twins in each symptom class for cannabis, cocaine, alcohol, caffeine, and nicotine dependence are presented in **Table 1**. Compared with females, males have higher rates of dependence for all substances. Therefore, our models allowed for sex-dependent thresholds. The prevalence of any symptoms of dependence was lowest for cocaine in both sexes and highest for nicotine in males and caffeine in females.

CORRELATIONS

The polychoric correlations between our measures of cannabis, cocaine, alcohol, caffeine, and nicotine dependence are presented in **Table 2** for males (below diagonal) and females (above diagonal). The pattern of correlations was similar in the sexes, though a number of correlations were slightly higher in females than in males. The highest correlation in both sexes is between cannabis and cocaine dependence. The correlations between dependence on caffeine and on the remaining 4 psychoactive substances are consistently low in both males and females.

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Table 3. Results of Model Fitting for Lifetime Symptoms of Abuse or Dependence on Alcohol, Caffeine, Cannabis, Cocaine, and Nicotine in Male and Female Twins

Model	Sex-Specific Parameter	General Factor			Substance-Specific Factor			Change in *df*[a]	Change in χ^2[a]	Change in AIC[a]
		A	C	E	A	C	E			
I[b]	Y	1	1	1	Y	Y	Y	-	-	-
II	N	1	1	1	Y	Y	Y	25	23.6	−26.4
III	N	2	1	1	Y	Y	Y	21	8.5	−33.5
IV	N	1	2	1	Y	Y	Y	21	19.0	−23.0
V	N	1	1	2	Y	Y	Y	21	14.6	−27.4
VI	N	2	2	1	Y	Y	Y	17	8.7	−25.3
VII	N	2	1	2	Y	Y	Y	17	5.5	−28.5
VIII	N	2	0	1	Y	Y	Y	26	16.4	−35.6
IX	N	2	1	0	Y	Y	Y	26	106.1	+54.1
X	N	2	0	1	N	Y	Y	36	168.4	+96.4
XI	N	2	0	1	Y	N	Y	31	20.6	−41.4[c]
XII[d]	N	2	0	1	Y	N	Y	34	21.2	−46.8[c]
XIII[e]	N	2	0	1	Y	N	Y	35	55.3	−14.7

Abbreviations: A, additive genetic effect; AIC, Akaike's information criterion; C, shared environment; E, unique environment; N, parameter(s) absent; Y, parameter(s) present.

[a] Relative to model I.

[b] $\chi^2_{22\,908}$ = 34 359.6; AIC = −11 456.4.

[c] Best-fit models.

[d] Confirmatory model with the genetic correlation between the 2 genetic factors unconstrained.

[e] Confirmatory model with the genetic correlation between the 2 genetic factors constrained to unity.

MODEL FITTING

We began with a 1-1-1 model that contained 1 common genetic, 1 common shared environmental, and 1 common unique environmental factor along with substance-specific loadings. This model allows for different parameter estimates in males and females (model I, **Table 3**). In model II, we constrained all parameters to equality in the sexes, resulting in a substantial improvement in the AIC (−26.4). In models III, IV, and V, we added a second common genetic, a second common shared environmental, and a second common unique environmental factor, respectively. The best-fitting of these was model III. We then added to model III a second common shared environmental (model VI) or a second common unique environmental factor (model VII). Neither of these further improved the AIC value.

We then eliminated the single common shared environmental factor (model VIII) or the single common unique environmental factor (model IX), which produced, respectively, a modest improvement and a marked deterioration in the AIC value. In models X and XI, we set the genetic and then shared environmental substance-specific loadings to 0. The AIC value for model X was very poor, whereas for model XI, it was substantially better than that seen for model VIII.

Because the best-fit model (model XI) contained 2 genetic factors, we also fit an a priori model (model XII) in which the first, or illicit, common genetic factor only had loadings on cannabis and cocaine dependence, whereas the second, or licit, common genetic factor had loadings only on alcohol, nicotine, and caffeine dependence. These 2 factors, however, were allowed to intercorrelate. This model fit almost as well as model XI (only 0.6 of a χ^2 unit difference). Because it was simpler (3 fewer parameters), it achieved a superior AIC. Finally, to evaluate the degree to which we could discriminate a 1 vs a 2 common factor–a priori genetic model, we fit a final model XIII, which added to model XII the constraint that the correlations between the 2 factors equaled unity. This model (which was equivalent to fitting a 1-0-1 model with genetic and unique environmental specifics) produced a substantial deterioration in AIC values, thereby indicating the strength of the statistical support for a second common genetic factor.

PARAMETER ESTIMATES

As models XI and XII represented 2 different approaches to explicating the same pattern of findings and were similar in their explanatory power, we present parameter estimates for both of them in **Figure 1** and **Figure 2**, respectively. Model XI contained 3 common factors—2 genetic and 1 unique environmental—as well as substance-specific genetic and unique environmental loadings. This model has 5 noteworthy results: (1) The first common genetic factor has quite high loadings on cannabis and cocaine dependence, intermediate loadings on alcohol and nicotine dependence, and very low loadings on caffeine dependence. (2) The second common genetic factor has moderately high loadings on alcohol and nicotine dependence, intermediate loadings on cannabis and cocaine dependence, and rather low loadings on caffeine dependence. (3) Substance-specific loadings are seen for all 5 drugs but are particularly large for nicotine and caffeine dependence. (4) The single common unique environmental factor had moderate loadings on cocaine and alcohol dependence and low to modest loadings on the 3 remaining substances. (5) Individual-specific loadings were present for all sub-

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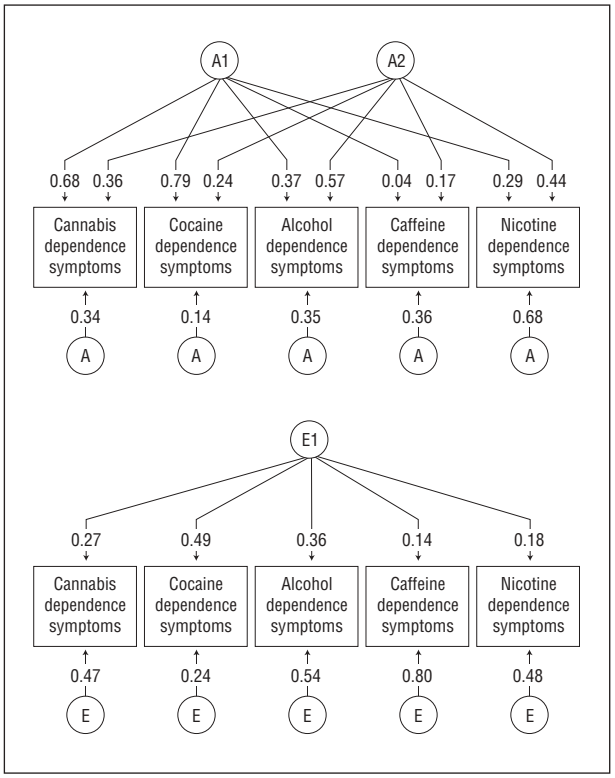

Figure 1. Parameter estimates for the best-fitting exploratory model (model XI) for symptoms of cannabis, cocaine, alcohol, caffeine, and nicotine abuse or dependence (shown as *dependence*). A1, A2, and E1 represent, respectively, the first and second common additive genetic factors and the first and only common unique environmental factor. Individual A and E components below each measure of substance-dependence symptoms represent, respectively, substance-specific genetic and unique environmental factors. Path values are standardized loadings and thus need to be squared to reflect the proportion of variance in the observed variable accounted for by the factor.

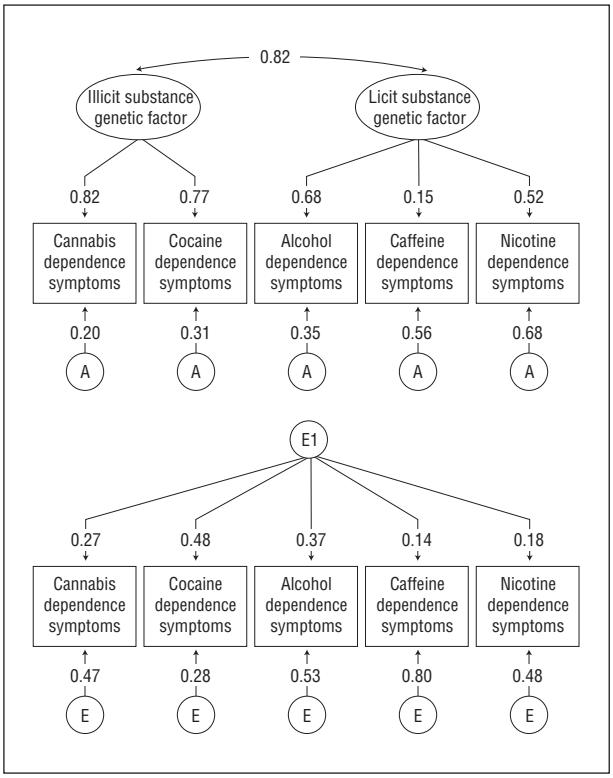

Figure 2. Parameter estimates for the best-fitting confirmatory model (model XII) for symptoms of cannabis, cocaine, alcohol, caffeine, and nicotine abuse or dependence (shown as *dependence*). The double-headed arrow connecting the illicit and licit substance genetic factors represents the genetic correlation between these factors. A1, A2, and E1 represent, respectively, the first and second common additive genetic factors and the first and only common unique environmental factor. Individual A and E components below each measure of substance dependence symptoms represent, respectively, the substance-specific genetic and unique environmental factors. Path values are standardized loadings and thus need to be squared to reflect the proportion of variance in the observed variable accounted for by the factor.

stances and ranged from quite high for caffeine dependence to very low for cocaine dependence.

Because of the complexity of the genetic results for model XI, we summarized these findings in **Table 4**. The total heritability varied widely from 34% for caffeine dependence to 73% for nicotine dependence. Each of the 5 substances demonstrated a relatively unique pattern of sources of genetic variance. Cocaine and cannabis dependence was most similar with the bulk of genetic variance coming from the first genetic factor, though that proportion was higher for cocaine than for cannabis. Alcohol dependence was the only substance with most genetic variance originating from the second common genetic factor; it also had similar proportions coming from the first common factor and substance-specific sources. While nicotine dependence was more strongly influenced by the second common genetic factor than the first common factor, nearly two-thirds of its genetic variance was substance specific. Finally, liability to caffeine dependence was largely unrelated to those of other substances with more than 90% of the genetic liability shown to be substance specific.

Model XII differs from model XI in that the choice of paths is influenced by a priori (or confirmatory) concepts. The 2 common genetic factors are now conceptualized as representing, respectively, illicit- and licit-substance dependence. The common and substance-specific unique environmental loadings are nearly identical between the 2 models (we will not comment on them further here). Four main points are noteworthy about the genetic loadings in model XII. First, the genetic correlation between the licit and illicit common factors is high. However, we know from the poor fit of model XIII that our results cannot be explained by a single common genetic factor. Second, cannabis and cocaine dependence load quite strongly and approximately equally on the illicit common genetic factor. Third, loadings on the licit common genetic factor are highest for alcohol dependence, intermediate for nicotine dependence, and quite low for caffeine dependence. Fourth, the substance-specific loadings of model XII are very similar to those seen for model XI except for modest changes for cocaine and cannabis dependence.

COMMENT

MAJOR QUESTIONS

We sought, in these analyses, to address 3 main questions. The first was whether the pattern of genetic and environmental risk factors for psychoactive substance de-

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Table 4. Proportion of Genetic Variance in Liability to Symptoms of Abuse or Dependence of Licit and Illicit Drugs in Best-Fitting Model XI

	Cannabis		Cocaine		Alcohol		Caffeine		Nicotine	
Model Factor	Variance	Total Genetic Variance, %	Variance	Total Genetic Variance, %	Variance	Total Genetic Variance, %	Variance	Total Genetic Variance, %	Variance	Total Genetic Variance, %
Factor 1	0.46	65	0.62	88	0.14	24	0.00	0	0.08	11
Factor 2	0.13	18	0.06	9	0.32	55	0.03	9	0.19	26
Substance-specific	0.12	17	0.02	3	0.12	21	0.31	91	0.46	63
Total heritability	0.71		0.70		0.58		0.34		0.73	

pendence differed between the sexes. When we controlled for the differences in level of symptoms of dependence between males and females, we could easily constrain all of the genetic and environmental parameters to equality in the sexes. In our sample, the pattern of comorbidity between licit and common illicit substance dependence appears to be the same in males and females. We are unaware of prior parallel studies on sex differences in multiple drug dependences with which to compare our findings, though 2 prior reports did find evidence for sex differences in problem drug and alcohol use assessed by a self-report questionnaire[18] and for problem tobacco use in adolescence.[19] However, 1 population-based study of nicotine dependence[20] failed to find significant sex effects, and another study of cannabis dependence was unable to distinguish between a model that assumed no sex differences and one that assumed genetic effects on cannabis dependence in men but not in women.[21] Prior analyses in this sample of both initiation and abuse/dependence of illicit drugs and alcohol dependence found no evidence for quantitative sex effects.[22,23]

The second question we addressed was whether genetic risk for the liability to dependence for all common psychoactive substances could be explained by a single common genetic factor, as has been found previously for illicit drugs.[22] Our results were unambiguous. The structure of genetic risk factors for the common legal and illegal psychoactive drugs is more complex than previously seen solely for illicit compounds. Not only do both best-fit models contain 2 common genetic factors, but dependence on 2 of the licit substances, caffeine and nicotine, is substantially influenced by genetic factors unique to those individual substances.

Our third question was whether an a priori model, in which genetic risk factors for drug dependence were divided into 1 factor for illicit drugs and 1 for licit substances, would provide a good fit to the data. Indeed, such a model explained our results well with 2 important caveats. First, the 2 factors were strongly intercorrelated. Second, substantial substance-specific genetic factors were also needed.

OTHER ISSUES

We found no consistent evidence for shared environmental effects for dependence of common psychoactive drugs. These results are consistent with most but not all prior studies of drug dependence in adults[24-28] in contrast with twin studies of drug use, which typically show an important shared environmental influence.[27-31]

These results are not consistent with the hypothesis that most genetic variation that influences risk for dependence in humans occurs in the primary sites of action of the psychoactive drugs themselves.[32] If this were the case, we would expect stronger and more pervasive substance-specific genetic variation, as current evidence suggests that the principal receptor sites for cocaine, cannabis, alcohol, caffeine, and nicotine are largely distinct.[33] Rather, these results suggest that the genetic variants that influence human drug dependence likely include psychological traits and/or brain systems that impact a wide range of substance classes. These might include personality, which probably influences risk for experimentation with most psychoactive compounds[34,35]; frontal inhibitory systems, which modulate impulsive, reward-related behaviors[33]; and brain systems, which subserve the hedonic response to a wide variety of substances of abuse.[33]

What are the implications of this work for gene-finding studies? First, as shown clearly in the confirmatory model (Figure 2), our results support the plausibility of finding genes that underlie multiple drug dependencies (as suggested, for example, by Uhl et al[36]). Although the relationship between a genetic correlation and the effect of specific susceptibility alleles is approximate at best,[37] the genetic correlation between the common genetic factors for licit and illicit drugs is high enough to suggest that most alleles that impact 1 of the 2 factors will also impact the other factor. Second, it will not be possible to capture all genetic variations that influence psychoactive drug dependency in this manner. In particular, anyone looking for genetic effects on caffeine dependence should examine that substance alone. Furthermore, most genetic risk for nicotine dependence is also substance specific. Third, our model would predict a modest number of genes that differ substantially in their impact on liability to dependence of licit vs illicit psychoactive substances.

Our analyses provide no direct insight into what underlies the partially distinct genetic liabilities to dependence on licit vs illicit drugs. Two broad classes of models seem worthy of consideration. First, 2 distinct biological processes could underlie the vulnerability to dependence on cannabis and cocaine on the one hand and alcohol, nicotine, and caffeine on the other. Second, the 2 liabilities could result from nonspecific factors, such as personality and impulsivity, which relate to the willingness to experiment with illegal substances. Our review of the literature suggests that the second hypothesis is more plausible than the first.

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LIMITATIONS

These results need to be interpreted in the context of 11 potential methodological limitations. First, this sample is restricted to white males and females born in Virginia. Although the rates of substance abuse and dependence are typical of other US populations,[27,30] these findings may not be generalizable. Second, these models assume that exposure to environmental factors that influence twin similarity for substance dependence is approximately equal in monozygotic and dizygotic pairs. We have examined this assumption previously in this sample and found it to be supported.[27,30] Third, diagnostic assessments were done at a single interview and include the effects of measurement error. In multivariate models, such error is confounded with true disorder-specific, unique environmental effects and produces a downward bias on other parameter estimates. We have shown elsewhere[27,30] that our measures of drug abuse and dependence in this sample have good to excellent test-retest reliability. In any case, measurement error would not be expected to alter the structure of the common factors, only the magnitudes of the loadings. Fourth, our twin model assumes that comorbidity results from the impact of latent genetic and environmental risk factors. Comorbidity could arise from other causal processes,[38] but these were not examined here. Fifth, although drug dependence is a conditional process in that it requires prior initiation,[39] this conditionality was not incorporated into current modeling owing to the complexity of implementing it with so many variables. Therefore, individuals who never tried a substance and those who tried it but developed no symptoms of abuse or dependence were treated the same. The validity of this approach is supported by prior analyses in this sample, which have shown a high degree of sharing between risk factors for initiation and subsequent dependence.[22,39] Sixth, while it would be desirable to include dependences on other illicit substances, such as sedatives or stimulants, in our modeling, their prevalence was too low in our female twins to allow for stable estimation. Seventh, because of our need to maximize statistical power, our analyses examined symptoms of abuse/dependence rather than dichotomous diagnoses. However, recent analyses of criteria for drug abuse and dependence suggest that underlying these categorical diagnoses is a single continuum of liability.[10-12] We were unable to include items for the abuse of nicotine and caffeine, as the abuse construct is not well defined for these substances. Eighth, we used the Fagerstrom Test for Nicotine Dependence[8] instead of *DSM-IV* criteria for nicotine dependence. However, substantial evidence suggests that the Fagerstrom Test for Nicotine Dependence or the closely related Fagerstrom Tolerance Questionnaire[40,41] provides a valid measure for nicotine dependence that has been successfully used in a number of genetic studies.[42,43] Ninth, because caffeine is rarely studied as a drug of abuse, we re-ran our key analyses eliminating this substance. Parameter estimates were very similar to those seen in Figures 1 and Figures 2. For example, in the confirmatory model, the genetic correlation between the illicit and licit genetic factors remained +0.82 and the genetic loadings on the individual substances differed no more than ±0.01. Tenth, although our cooperation rates were high, subjects with a history of drug problems may have been underrepresented in our sample. To evaluate this, in our male-male twin sample controlling for education and zygosity, we examined whether a history of alcohol, nicotine, cannabis, or cocaine abuse/dependence or heavy caffeine use reported at the second wave of interviews predicted cooperation at the third wave. Only results for alcohol were significant ($P=.03$) and its effect was modest (odds ratio, 0.84). Those with a history of drug problems are not likely to be substantially unrepresented in our sample. Finally, multivariate analysis of categorical outcomes can be limited by insufficient power to reject group differences or alternative models. The correlations in Table 2 support the similarity of males and females and suggest that our rejection of sex differences was not because of insufficient power. Furthermore, our model-fitting results in Table 3 show sufficient power to reject a number of alternative structures for the covariation among these substances.

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Correspondence: Kenneth S. Kendler, MD, Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University Medical School, Box 980126, 800 E Leigh St, Room 1-123, Richmond, VA 23298-0126 (kendler@vcu.edu).
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