

Rapid Publication

Genetic and Environmental Influences on Adolescent Substance Use and Abuse

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The inheritance of substance use and abuse among adolescents was investigated in a sample of 626 male and female 17-year-old twin pairs. Both licit (tobacco) and illicit (e.g., marijuana, amphetamines) substance use and abuse was assessed and analyzed using standard biometric methods. The heritability of use and abuse of illicit substances was modest (25% or less), whereas the heritability of tobacco use and nicotine dependence was substantial (40% to 60%). There was no evidence that gender moderated the strength of genetic influences. Shared environmental influences were substantial for all substance use measures. The finding of greater genetic influence on the use and abuse of a licit substance than on the use and abuse of illicit substances suggests that inherited risk to drug abuse is considerably moderated by environmental control, at least in adolescence. The finding of significant environmental influences on all substance use measures underscores the importance of intervention on early adolescent substance use, a known predictor of adult substance abuse and dependence. *Am. J. Med. Genet. (Neuropsychiatr. Genet.)* 96: 671–677, 2000. © 2000 Wiley-Liss, Inc.

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INTRODUCTION

Substance use is alarmingly common during late adolescence. The Monitoring the Future study (MFS)

[O'Malley et al., 1995], a large epidemiological sample of American adolescents, found that 61.9% of twelfth-graders had tried cigarettes, and 87% had tried alcohol. The MFS also found that marijuana was by far the most prevalent illicit drug used—26% of twelfth-graders reported having used marijuana in the past year. Although use of other illicit substances is less common (e.g., 8.4% of twelfth-graders had used amphetamines in the past year in the MFS), such illicit drugs as methamphetamine account for a disproportionate amount of police contact or medical emergencies [Falkowski, 1996]. Moreover, an early onset of illicit drug use in adolescence is associated with a substantially increased risk of drug problems in adulthood [Anthony and Petronis, 1995]. Efforts aimed at preventing early adolescent substance use are likely to benefit from an understanding of the developmental pathways that underlie the initiation of substance use in adolescence and the subsequent progression to substance abuse in early adulthood [cf. Loeber and Farrington, 1994]. Genetically informative designs (twin and adoption studies) are particularly useful for elucidating the source of influences on substance use and abuse as individuals move through adolescence [McGue, 1994].

Unfortunately, as several researchers have recently noted [McGue et al. 1996; Maes et al., 1999], compared with the expanding body of research on genetic influences on substance disorders in adults, there is a relative paucity of such research on adolescent samples. One of the few studies to investigate heritable effects on adolescent drug use is the Virginia Twin Study of Adolescent Behavioral Development, a study of 1,412 male and female twin pairs aged 8 to 16 [Maes et al., 1999]. In this study, heritable effects were strong for lifetime tobacco (heritability of 84%) and alcohol (72%) use, moderate for lifetime drug use (45%), and modest for lifetime marijuana (22%) use. The difference in heritability estimates for licit (tobacco and alcohol) versus illicit (marijuana) drug use in the Virginia study suggests that the relative accessibility of drugs may moderate the strength of genetic and environmental influences on their use. Consistent with this explanation, Rose et al. [1999] found heritable effects on 16-year-old adolescents' alcohol use were greater among twins living in urban Helsinki, where it is relatively

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easy to gain access to alcohol, than among twins living in primarily rural northern Finland, where alcohol access is limited.

Age and gender also may moderate the strength of genetic influences on substance use in adolescence. For example, in a sample of 1,582 Dutch male and female twin pairs aged 13–22, Koopmans and Boomsma [1996] found that the heritability of alcohol use increased, while the importance of shared environmental factors decreased with age, a finding that is consistent with the moderate to strong heritability estimates that are typically observed for alcohol use measures in adulthood [McGue, 1999]. In an earlier report from the present project, based on a subset of the adolescent twin sample reported here, estimates of the heritability of tobacco, alcohol, and illicit drug use were larger in male (59%, 60%, and 33%, respectively) compared with female (11%, 10%, and 11%, respectively) twins [Han et al., 1999]. Despite the magnitude of the observed differences, the male–female heritability estimates were not significantly different, given the sample sizes.

The present study is an investigation of genetic and environmental influences on lifetime substance use and abuse in a sample of 17-year-old male and female twins. Our study not only adds to the limited behavioral genetic research literature on adolescent substance use but also is the first to investigate the heritability of substance abuse and dependence in an adolescent sample. The primary aims of the study were to examine the following questions: What is the degree of genetic and environmental influence on substance use and abuse in late adolescence? Are there gender differences in the relative magnitude of these influences? Does the magnitude of genetic and environmental influences differ for the use and abuse of a licit substance (tobacco) compared with the use and abuse of illicit substances (marijuana)?

METHODS

Participants

The sample consisted of late-adolescent twin participants from the Minnesota Twin Family Study (MTFS). The MTFS is a prospective study of a community-based sample of adolescent twins and their parents. Adolescent twins were identified through Minnesota birth records, with more than 90% of twin births in a given year located using various public databases. To be eligible to participate, twins needed to live within a day's drive of Minneapolis, have at least one living biological parent eligible to participate, and not have a physical or mental condition that precluded their completing the daylong intake assessment. Among eligible twin families, approximately one-sixth declined our invitation to participate, two-thirds completed the intake assessment, and the remaining one-sixth were still in the recruitment pool after recruitment targets had been achieved. Comparing the information gathered from brief interviews and self-reports from participating and nonparticipating families, we found that participating parents were slightly better educated than nonparticipating parents (a difference of 0.3 years or less for both mothers and fathers). The two groups could not be dis-

tinguished based on rates of self-reported mental health and substance abuse, however. Consistent with demographic patterns for the state of Minnesota in the birth years sampled, over 97% of the MTFS families were white. Iacono et al. [1999] give a detailed description of the MTFS recruitment and assessment procedures.

The MTFS consists of two twin cohorts, an “11-year old” cohort assessed at an average age of 11.7 (SD = 0.43) at intake and a “17-year old” cohort assessed at an average age of 17.5 (SD = 0.45). Since our focus here is on early-onset substance use and abuse (both of which are limited in our 11-year old cohort), our analyses were restricted to the 17-year-old cohort. The 626 twin pairs in this cohort consisted of 188 MZ male, 101 DZ male, 223 MZ female, and 114 DZ female twin pairs. The greater number of MZ versus DZ twins in the sample does not necessarily reflect a sampling bias, because there was a greater number of MZ than DZ twin births in the years sampled [Hur et al., 1995].

Zygoty Determination

An initial determination of zygosity was based on three sources of information: a standard zygosity questionnaire completed by parents, a diagnosis based on various physical measures obtained at the time of assessment (ponderal index, cephalic index, and fingerprint ridge count), and a subjective evaluation of the physical similarity of the twins made by an experienced staff member. If the results of these three methods agreed, no further zygosity testing was carried out. If there was a discrepancy, however, serological confirmation was sought. In an analysis of 50 twin pairs, we found that when there was agreement among the questionnaire, physical similarity, and staff judgment measures, this agreement was always confirmed by serological analysis.

Assessment and Measures

The intake MTFS assessment took place at our laboratories at the University of Minnesota and consisted of approximately 8 hours of interview, testing in a psychophysiology lab, and completion of self-report questionnaires. The assessment of substance use and abuse used in the present study was based on an expanded substance abuse module developed by Robins et al. [1987]. We have modified the substance abuse module by adding questions to update the instrument. Lifetime use and abuse were analyzed for the following substances: tobacco, marijuana, amphetamines, cocaine, hallucinogens, inhalants, opiates, PCPs, and sedatives.

Lifetime use was scored as positive if the twin reported ever having used the substance in his or her lifetime. The diagnosis of substance use disorders was based on DSM-III-R criteria for substance abuse and substance dependence, the diagnostic system in place when the MTFS was begun. All diagnoses cover the lifetime of the participants. Substance dependence diagnoses were made at two levels of certainty. A definite substance dependence diagnosis was made when all relevant DSM-III-R criteria were met; a probable diagnosis was given when all but one symptom was pres-

ent. Substance abuse diagnoses, which require only one positive symptom in DSM-III-R, were made only at the definite level of certainty. Our analyses focused on only those substance use and abuse phenotypes having a prevalence of at least 5% in our epidemiological sample of 17-year-olds. This included lifetime tobacco use and nicotine dependence, lifetime marijuana use and DSM-III-R cannabis abuse or dependence, lifetime amphetamine use, and lifetime use of any illicit substance (excluding tobacco), number of illicit substances ever used, and any DSM-III-R illicit substance abuse or dependence diagnosis.

Statistical Methods

The twin data were analyzed assuming that the various substance use and abuse phenotypes followed a liability-threshold model [Falconer, 1965]. Before modeling analyses, twin tetrachoric (in the case of a single threshold) and polychoric (multiple threshold) correlations were estimated by maximum likelihood. For each categorical phenotype, modeling analyses involved estimating three components of liability variance: additive genetic (a^2 , or heritability), shared environmental (c^2 , the effect of those environmental factors that are shared by reared-together relatives), and nonshared environmental (e^2 , the effect of those environmental factors that differ among reared-together relatives). Under the standard assumptions of the twin method (i.e., all genetic effects are additive, there is no assortative mating for the phenotype in question, and the environmental contribution to twin similarity is the same for MZ and DZ twins), the expected MZ and DZ twin correlations are, respectively, $r_{MZ} = a^2 + c^2$, and $r_{DZ} = 1/2a^2 + c^2$.

Models were fit to the observed twin data using the method of maximum likelihood, as implemented in the Mx software system [Neale, 1997]. Two models were fit: a model that estimated the three variance components (a^2 , c^2 , e^2) separately in the male and female samples (designated the *free model*) and a model that constrained the variance component estimates to be the same in the two samples (termed the *constrained model*). The fit of each model was evaluated using the chi-square goodness-of-fit test statistic. The relative fit of the free and constrained models was evaluated using the Akaike information criterion ($AIC = \chi^2 - 2 df$), a measure of model fit relative to model parsimony. For each phenotype the "best fitting" model was identified as the model having a large negative AIC value and a nonsignificant goodness-of-fit test statistic.

RESULTS

Prevalences and Twin Correlations

Lifetime prevalence rates for tobacco and drug use and DSM-III-R substance abuse or dependence diagnoses are given in Table I by sex and zygosity group. In general, prevalence rates are comparable in the MZ and DZ samples and between boys and girls. The only exceptions were lifetime tobacco use, where the prevalence was significantly greater among boys than girls (69.2% versus 57.1%), and nicotine dependence, where the rate was significantly higher in DZ than MZ twins.

It is interesting to note that despite the sex difference in rate of lifetime tobacco use, the rate of DSM-III-R nicotine dependence did not differ appreciably in boys (15.4%) and girls (15.9%). In any case, our finding of minimal sex differences in adolescent substance use rates is consistent with the observation that rates of drug dependence have become increasingly similar for men and women in younger cohorts [Grant, 1996]. These findings are also in agreement with those of other epidemiological studies of adolescents that show similar rates of marijuana and drug use in boys and girls [Boyle et al., 1992]. Moreover, the overall levels of substance use in our sample are in general agreement with normative rates reported in the MFS [O'Malley et al., 1995] but are substantially higher than the rates of substance use reported by Maes et al. [1999] in their sample of adolescent twins from Virginia. For example, in the MFS, 26% of twelfth-graders reported using marijuana in the past year; 23% of our male and 24% of our female twins reported ever having used marijuana; and 13% of the male and 11% of the female 16-year-old Virginia twins reported ever having used marijuana.

The twin proband-wise concordances and the tetrachoric and polychoric correlation estimates for the substance use and abuse phenotypes also are reported in Table I. Although the MZ correlation in every case is larger than the corresponding DZ correlation, suggesting the importance of genetic factors, the difference in correlations is generally small and in only three instances (all involving nicotine) statistically significant. The correlations thus suggest that heritable effects are modest for most of the substance use and abuse phenotypes.

Biometric Model Fitting

Table II reports the parameter estimates and model-fit test statistics both when the three variance components (a^2 , c^2 , e^2) were estimated separately in the male and female samples (the free model) and when they were constrained to be equal in males and females (the constrained model). Table II also shows the 95% confidence intervals for the three variance components estimated under the constrained models. These confidence intervals were computed using the method described by Neale and Miller [1997]. Several consistent patterns emerge. First, in no case did the free model fit significantly better than the constrained model. For every phenotype, the AIC is smaller for the constrained compared with the free model, and in no case is the difference in the goodness-of-fit test statistic between the two models statistically significant. Consequently, our data do not provide statistical support for gender moderation of the magnitude of genetic or environmental effects.

Second, except for tobacco use and nicotine dependence, the heritability estimates for the substance use and abuse phenotypes are modest to moderate (ranging from about 10% to 25% under the constrained model). We observed no consistent difference in heritability between substance use and substance abuse phenotypes. For tobacco use and nicotine dependence, the heritability estimates were substantial, on the order of 50%.

TABLE I. Lifetime Prevalences, Proband-Wise Concordances, and Twin Correlations for Tobacco and Drug Use and DSM-III-R Substance Abuse or Dependence in 17-Year-Old Twins, by Sex and Zygosity*

	Male			Female		
	MZ (n = 188 pairs)	DZ (n = 101 pairs)	Total (n = 289 pairs)	MZ (n = 223 pairs)	DZ (n = 114 pairs)	Total (n = 337 pairs)
Ever used tobacco (%)	69.1	69.3	69.2	54.9	61.4	57.1
Concordance	0.89	0.81	—	0.85	0.76	—
r_t	0.84 ^b	0.60	—	0.87 ^b	0.56	—
(95% Confidence interval)	(0.72, 0.92)	(0.32, 0.80)	—	(0.77, 0.93)	(0.30, 0.75)	—
Nicotine dependence (%)	11.4	22.8	15.4	14.3	18.9	15.9
Concordance	0.60	0.57	—	0.59	0.42	—
r_t	0.83	0.67	—	0.79*	0.49	—
(95% Confidence interval)	(0.63, 0.93)	(0.39, 0.85)	—	(0.62, 0.90)	(0.15, 0.74)	—
Ever used marijuana (%) ^a	17.3	26.2	20.4	23.3	25.4	24.0
Concordance	0.65	0.60	—	0.62	0.59	—
r_t	0.82	0.69	—	0.74	0.67	—
(95% Confidence interval)	(0.66, 0.92)	(0.43, 0.86)	—	(0.58, 0.85)	(0.42, 0.84)	—
Cannabis abuse/dependence (%)	6.1	8.9	7.1	6.1	7.9	6.7
Concordance	0.52	0.33	—	0.44	0.44	—
r_t	0.81	0.54	—	0.74	0.71	—
(95% Confidence interval)	(0.53, 0.94)	(0.06, 0.84)	—	(0.44, 0.90)	(0.31, 0.92)	—
Ever used amphetamines (%) ^c	3.7	8.4	5.4	5.2	5.8	5.4
Concordance	0.29	0.35	—	0.27	0.17	—
r_t	0.60	0.58	—	0.55	0.34	—
(95% Confidence interval)	(0.11, 0.89)	(0.11, 0.87)	—	(0.13, 0.82)	(-0.29, 0.80)	—
Ever used any illicit drug (%)	18.1	27.2	21.3	24.2	25.9	24.8
Concordance	0.65	0.65	—	0.59	0.58	—
r_t	0.82	0.76	—	0.70	0.65	—
(95% Confidence interval)	(0.65, 0.92)	(0.52, 0.90)	—	(0.52, 0.82)	(0.39, 0.83)	—
Number of illicit drugs used (%)						
One only	13.6	15.3	14.2	15.9	17.5	16.5
Two or more	4.5	11.9	7.1	8.3	8.3	8.3
r_p	0.72	0.64	—	0.66	0.60	—
(95% Confidence interval)	(0.55, 0.84)	(0.40, 0.81)	—	(0.50, 0.78)	(0.36, 0.78)	—
Any drug abuse/dependence (%) ^d	6.4	9.4	7.4	6.5	8.3	7.1
Concordance	0.50	0.42	—	0.41	0.42	—
r_t	0.78	0.65	—	0.69	0.67	—
(95% Confidence interval)	(0.50, 0.93)	(0.23, 0.89)	—	(0.39, 0.88)	(0.26, 0.90)	—

*Concordances were calculated using the proband-wise method. r_t , tetrachoric correlation; r_p , polychoric correlation. Percentages are based on the number of individual twins within each sex and zygosity group who are positive for each substance variable, not on the number of twin pairs who are positive. Abuse and dependence diagnoses include both probable and definite levels of certainty.

^aIncluded hashish, pot, grass, bhang, and ganja.

^bMZ correlation significantly greater than DZ correlation at $P < 0.05$.

^cIncludes uppers, speed, stimulants, khat, betel nut, white cross, crystal meth, ice, and crank.

^dIncludes amphetamine, cannabis, cocaine, hallucinogens, inhalants, opiates, PCP, sedatives, or other drug abuse or dependence.

The difference in heritability estimates for tobacco versus illicit substance use and abuse is consistent with our conjecture that genetic influences are minimal and, conversely, that environmental influences are maximal for the use and abuse of substances that are relatively easy for a 17-year-old adolescent to obtain. Finally, for all phenotypes, the proportion of variance associated with shared environmental factors is substantial, falling generally in the 0.40 to 0.60 range. This latter finding is especially intriguing, given the general finding that shared environmental influences are modest to nonexistent for most behavioral phenotypes [Plomin and Daniels, 1987].

DISCUSSION

The present study extends our earlier research on illicit drug use in adolescence [Han et al., 1999] by including a sample of same-sex twin pairs that is 25% larger than the original sample and by considering sub-

stance abuse/dependence as well as substance use. Our finding of modest heritability for illicit substance use is consistent with findings of our earlier study as well as those of other studies of adolescent twins [Maes et al., 1999]. On the other hand, our finding of a similar modest heritability for illicit drug disorders extends this previous research in showing that genetic influences are also minimal for illicit substance abuse and dependence in adolescence. The lack of strong genetic effects on illicit substance use and abuse in adolescence may reflect developmental stage. Studies of adult twins have tended to find stronger genetic influences on illicit substance use and abuse than those found here. For example, Kendler et al. [1999] reported moderate to strong heritability estimates for hallucinogen (49%), opiate (52%), sedative (60%), but not stimulant (21%) use in a large sample of adult female twins. Kendler and Prescott [1998] reported heritability estimates of 65% to 79% for cocaine abuse and dependence in the

TABLE II. Biometric Model Fitting Results*

	Parameter estimates			Model fit			
	a ²	c ²	e ²	χ ²	df	P	AIC
Ever used tobacco							
Males	0.48	0.36	0.16				
Females	0.62	0.25	0.14	3.91	4	0.42	-4.09
Constrained	0.56	0.30	0.15	4.11	7	0.77	-9.89
	(0.23, 0.89)	(0.00, 0.60)	(0.09, 0.22)				
Nicotine dependence							
Males	0.31	0.52	0.17				
Females	0.60	0.19	0.21	1.52	4	0.82	-6.48
Constrained	0.44	0.37	0.19	2.51	7	0.93	-11.49
	(0.03, 0.87)	(0.00, 0.71)	(0.11, 0.32)				
Ever used marijuana							
Males	0.26	0.56	0.18				
Females	0.13	0.61	0.26	5.15	4	0.27	-2.85
Constrained	0.18	0.59	0.23	5.93	7	0.55	-8.07
	(.00, .57)	(.23, .80)	(.15, .34)				
Cannabis abuse/dependence							
Males	.54	.27	.19				
Females	.06	.68	.26	5.98	4	.20	-2.02
Constrained	.28	.49	.23	6.61	7	.47	-7.39
	(.00, .86)	(.00, .82)	(.11, .42)				
Ever used amphetamines							
Males	0.05	0.55	0.40				
Females	0.41	0.14	0.55	3.41	4	0.49	-4.59
Constrained	0.16	0.41	0.43	3.89	7	0.79	-10.11
	(0.00, 0.78)	(0.00, 0.72)	(0.21, 0.69)				
Ever used any illicit drug							
Males	0.12	0.69	0.19				
Females	0.09	0.61	0.30	5.92	4	0.21	-2.08
Constrained	0.09	0.66	0.25	7.83	7	0.35	-6.17
	(0.00, 0.47)	(0.31, 0.80)	(0.16, 0.36)				
Number of illicit drugs used							
Males	0.16	0.56	0.28				
Females	0.12	0.54	0.34	33.28	20	0.03	-6.72
Constrained	0.13	0.56	0.32	33.74	23	0.07	-12.26
	(0.00, 0.51)	(0.21, 0.73)	(0.22, 0.42)				
Any illicit drug abuse/dependence							
Males	0.26	0.52	0.22				
Females	0.05	0.65	0.30	3.94	4	0.41	-4.06
Constrained	0.15	0.59	0.26	4.24	7	0.75	-9.76
	(0.00, 0.78)	(0.01, 0.82)	(0.13, 0.44)				

*See footnote to Table I for an explanation of the specific substance variables. Two models were fit: a free model, where the percentage of liability variance associated with additive genetic (a²), shared environmental (c²), and nonshared environmental factors (e²) were estimated independently in the two sexes, and a constrained model, where the three parameters were constrained to be equal in males and females. Parameter estimates for the free model are given in the rows labeled Males and Females; fit statistics for the free model are given in the row labeled Females. The 95% confidence interval estimates of the variance components under the constrained model are given in parentheses.

same sample. Heritability estimates from other twin studies of substance abuse in adulthood [Pickens et al., 1991, Tsuang et al., 1996] are also higher than those reported here, even if they are not as high as those reported by Kendler and colleagues.

These findings from adult twin studies thus suggest that the heritability of substance use and abuse in our sample may grow stronger as the twins age into adulthood. That is, we expect that some of the adolescents we classified as “unaffected” at age 17 will ultimately be affected by a substance disorder once they pass completely through the period of greatest risk, which could substantially change the relative contributions of genetic and environmental factors that we have reported here. Preliminary findings from the first 3-year follow-up of our 17-year-old twins are consistent with this expectation. Specifically, for those male twins in the present sample who completed a follow-up assessment

at age 20, the heritability of illicit drug dependence was estimated at 52% [Iacono et al., 1999]. (The female assessments lagged the male assessments, so that we do not as yet have much follow-up data on our female sample.) In any case, because an early onset of substance use is a strong predictor of later substance-related problems in adulthood [Hawkins et al., 1997], from a developmental behavior genetic perspective, it will be important to understand how these disorders evolve. As follow-up data from ages 20–26 become available, we will be able to explore possible changes in the salience of these different factors during development.

The low heritability values we found for illicit drug use and abuse also could be related to differences between illicit and licit substance use and abuse. Previous research suggests that genetic influences on drug abuse may be greater for licit compared with illicit sub-

stances. For example, in a recent review of behavioral genetic research on smoking, Heath and Madden [1995] found high heritability values for current smoking (approximately 50% to 60%) that are consistent with those for tobacco use and nicotine dependence reported here. Although Kendler and colleagues have reported heritability estimates for illicit drug use and abuse that are comparable to the figures for tobacco, other researchers have documented lower heritability estimates. For example, in a large sample of male veteran twins from the Vietnam era, Tsuang et al. [1996] found a heritability estimate of 34% for any illicit drug disorder, while in a relatively small sample of male and female adult twins, Pickens et al. [1991] cited heritability estimates in the 20% to 30% range for any illicit substance abuse or dependence.

One explanation for the relatively low heritability for illicit substance use and abuse may be the somewhat greater importance of environmental control on illicit drug use compared with licit drug use. Indirect support for this contention is provided by the findings of recent epidemiological surveys that rates of alcohol and drug disorders vary widely across different birth cohorts [Kessler et al., 1994; Grant, 1996] or regions [Rose, 1998]. These cohort and regional effects suggest that environmental factors (such as those that affect the availability of a specific substance) that fluctuate substantially over a period of years or vary based on degree of urbanization may affect rates of drug disorders greatly.

Based on our preliminary findings, we had expected to discover greater heritability of substance use and abuse in male twins compared with female twins [Han et al., 1999], but we found no significant gender differences. Given the size of the observed sex differences, our failure to document significant sex differences in heritability may be due to low statistical power. As with the earlier findings of Pickens et al. [1991] regarding drug disorders, shared environmental factors appeared to have a slightly greater role for female than for male twins. Nonetheless, the observed sex differences in estimates of shared environmental effects also were not statistically significant.

The most striking finding in our study was that shared environmental factors (e.g., sharing a household where drugs are available through parents or siblings or sharing the same circle of acquaintances) seem to exert a considerable influence on illicit drug use and abuse in adolescence. In our sample, shared environmental factors accounted for 41% to 66% of the variance in liability to illicit substance use and abuse. Our findings are clearly consistent with the estimates of shared environmental influence of 47% for lifetime drug use and from 68% to 85% for lifetime marijuana use in the Virginia study of adolescent twins [Maes et al., 1999]

Although the behavioral genetic literature suggests that there is little effect of shared environment on many characteristics in adults [Plomin and Daniels, 1987], behavioral genetic studies of parental and sibling relationships during childhood and adolescence [Elkins et al., 1997; Bussell et al., 1999] indicate moderate shared environmental influence during these ear-

lier developmental stages. In a study of adolescent adoptees [McGue et al., 1996], there were significant effects of unrelated siblings on each other's substance use, even though the environment that reared-together adoptees shared was relatively unimportant for most aspects of adolescent adjustment. Twin studies also have found that degree of closeness or socialization between members of a twin pair has at least a modest influence on initiation of substance use [Kendler and Gardner, 1998] and development of drug (but not alcohol) disorders [LaBuda et al., 1997]. Finally, another often-shared environmental influence that can affect whether underlying risk factors are translated into actual substance use initiation and abuse may be attendance at religious services, with more frequent attendance being associated with lower likelihood of substance use in twin [Maes et al., 1999] and nontwin [Cochran, 1991] samples.

Although our finding of modest genetic and strong environmental influences on adolescent illicit substance use and abuse is impressively consistent across the multiple substances studied, any conclusions we draw must be tempered by the relatively modest size of the twin sample studied. As indicated in Table II, the 95% confidence interval estimates of the genetic and environmental parameters are quite broad. The relative width of these interval estimates reflects, in part, our decision to include all three parameters in the fitted model (in contrast to the typical practice of estimating confidence intervals for a reduced parameter model, in which case the interval widths would be markedly narrower), and not simply the size of our sample. Nonetheless, with our sample we cannot say with complete assurance that the substance use and abuse phenotypes we studied are moderately heritable. Our findings also do not imply that the search for genetic markers of risk for substance disorders is unimportant. As we noted previously, modest heritable effects in adolescence may transform to moderate to strong heritable effects in adulthood.

Moreover, as we have shown in earlier analyses, the heritable component of risk for drug disorders overlaps substantially with heritable tendencies toward antisocial behavior as well as with certain personality and psychophysiologic characteristics [Iacono et al., 1999]. Determining how these genetically influenced predispositions toward drug abuse interact developmentally with environmental factors will be important to understanding at what point specific interventions are most likely to be effective. For example, in our younger cohort of male twins, we recently found that low levels of environmental risk at age 11 seemed to mitigate the effects of inherited vulnerabilities on substance use at age 14, whereas high levels of environmental risk increased the likelihood that inherited risk would be translated into substance use [Legrand et al., 1999]. Along with the current results from our 17-year-old twin cohort, these findings suggest that interventions are likely to be most efficacious if environmental modifications are targeted to a biologically vulnerable subgroup in early adolescence (or even pre-adolescence).

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