

The role of conduct disorder in explaining the comorbidity between alcohol and illicit drug dependence in adolescence

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Received 20 December 2005; received in revised form 25 July 2006; accepted 26 July 2006

Abstract

Background: Conduct disorder (CD), alcohol dependence (AD), and illicit drug dependence (IDD) frequently co-occur. This paper describes the result of an investigation of the extent to which comorbid alcohol and illicit drug dependence in adolescents are explained by etiological factors in common with conduct disorder.

Methods: Participants were 645 MZ twin pairs, 702 DZ twin pairs, 429 biological sibling pairs, and 96 adoptive sibling pairs, aged 12–18 years, from a community based sample. Conduct disorder was measured using the Diagnostic Interview Schedule for Children-IV. Alcohol and illicit drug dependence were assessed using the Composite International Diagnostic Interview-Substance Abuse Module (CIDI-SAM). For each outcome, subjects were categorized into those with no symptoms, those with one or more symptoms but no diagnosis, and those with a diagnosis.

Results: The heritability estimates for CD, AD, and IDD were 58, 66, and 36%, respectively. The genetic correlation between AD and IDD was partially explained by the genetic risk they both share with conduct disorder.

Conclusions: We conclude that conduct disorder in adolescents explains, in part, the co-occurrence of alcohol and illicit drug dependence. Specifically, the genetic contribution to their covariation is explained partially by the genetic contribution in common with conduct disorder.

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Keywords: Conduct disorder; Alcohol; Substance dependence; Genetic; Comorbidity

1. Introduction

There are substantial genetic influences on disorders associated with both alcohol (Heath et al., 1997; Kendler et al., 1994; Rhee et al., 2003) and illicit drug use (Rhee et al., 2003; Tsuang et al., 1996). Alcohol dependence and illicit drug dependence are highly comorbid (Bierut et al., 1998; Kendler et al., 1997; Kessler et al., 1997; Merikangas et al., 1998; Pickens et al., 1995; True et al., 1999), and there is evidence that correlated genetic vulnerability may contribute to the comorbidity between them (Grove et al., 1990; Tsuang et al., 2001).

Conduct problems are also substantially heritable (Jacobson et al., 2000; Miles et al., 2002; Simonoff et al., 1998; Slutske et al., 1997), and commonly co-occur with alcohol and drug problems in adolescence (Neighbors et al., 1992; Reebye et al.,

1995). Again, comorbidity between conduct problems and alcohol problems may result from a genetic vulnerability common to both (Pickens et al., 1995; Slutske et al., 1998), and a correlation of 0.50 between the genetic influences on lifetime alcohol dependence and retrospective conduct problems has been reported (Slutske et al., 1998). Similarly, a common genetic liability for conduct problems and illicit drug problems appears to explain much of the covariation between them (Grove et al., 1990; Miles et al., 2002). Although research on illicit drug dependence and its correlates in adolescents is limited, one study has reported a genetic correlation of 0.28 and non-shared environment correlation of 0.14 between conduct disorder and marijuana use in an adolescent sample (Miles et al., 2002).

One suggested reason for the substantial genetic correlation between conduct problems, alcohol use problems, and illicit drug use problems is that they are all alternative manifestations of a highly heritable common latent variable (Hicks et al., 2004; Iacono et al., 1999; Young et al., 2000). This single latent variable, frequently referred to as behavioral disinhibition (Iacono

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et al., 1999; Young et al., 2000), accounts for the covariation between a number of externalizing-spectrum disorders (Krueger et al., 2002). Differential manifestation of each of the disorders is attributable to the influence of trait specific genetic and environmental risks.

Furthermore, Fu et al. (2002) have shown, in a sample of adult male twins, that the etiology of the comorbidity among antisocial personality disorder, alcohol use problems, and marijuana use problems is largely genetic, and that the genetic correlation between alcohol and marijuana use problems is explained by the genetic liability they share in common with antisocial personality disorder (Fu et al., 2002). Similar to the behavioral disinhibition model described previously, trait-specific genetic influences were demonstrated, accounting for the differential manifestation of the three phenotypes.

The current study was a large sample of twins, biological sibling pairs and adoptive sibling pairs, to investigate the extent to which comorbid alcohol and illicit drug dependence in adolescents may be explained by etiological factors in common with conduct disorder. We will also examine whether the etiological factors common to substance dependence and conduct disorder are genetic, shared (family), environmental, or non-shared (individual) environmental influences.

2. Method

2.1. Participants

The participants were 645 MZ twin pairs (352 female pairs, 293 male pairs), 702 DZ twin pairs (214 female pairs, 274 opposite sex pairs, 214 male pairs), 429 biological sibling pairs (48 female pairs, 196 opposite sex pairs, 185 male pairs) and 96 adoptive sibling pairs (13 female pairs, 75 opposite sex pairs, 8 male pairs) with an overall age range of 12–18 years (mean = 15.08 years, $IDD = 2.12$). Twin pairs were drawn from the Colorado Longitudinal Twin Study (LTS; Emde and Hewitt, 2001) and the Colorado Twin Registry (CTR; Young et al., 2002), adoptive siblings were from the Colorado Adoption Project (CAP; DeFries et al., 1994) and biological siblings were ascertained from both the CAP and control families from the Adolescent Substance Abuse Family Study (Miles et al., 1998). All participants were assessed as part of the Center on Antisocial Drug Dependence (PI: T. Crowley) and all interviews were face-to-face structured diagnostic interviews administered by non-clinician interviewers either in the laboratory at the Institute for Behavioral Genetics, or in the participants' home or school.

2.2. Procedure

Twins' zygosity was determined using a nine-item assessment questionnaire (Nichols and Bilbro, 1966) and by genotyping a minimum of 11 informative short tandem repeat polymorphisms (STRPs) using DNA from cheek swabs. Zygosity was assigned as MZ if at least nine STRPs were identical in the two twins and no discrepancies were detected.

Lifetime symptoms of conduct disorder (CD) were assessed using the Diagnostic Interview Schedule for Children-IV (DISC-IV) (Shaffer et al., 1997), a structured psychiatric interview that assesses DSM-IV symptoms (APA, 1994). This measure has demonstrated acceptable reliability and validity (Shaffer et al., 2000). Alcohol dependence (AD) and illicit drug dependence (IDD) were assessed using the Composite International Diagnostic Interview-Substance Abuse Module (CIDI-SAM) (Cottler et al., 1989), a structured diagnostic interview, which assesses the symptoms of dependence associated with the use of tobacco, alcohol, marijuana, cocaine, amphetamines, sedatives, inhalants, hallucinogens, opiates, and PCP. This measure has been shown to be valid and reliable in clinical, epidemiological and community based samples (Cottler and Keating, 1990; Crowley et al., 2001; Horton et al., 2000; Young et al., 2002).

Subjects who report having used alcohol or any illicit drug 'more than five times' were queried regarding each DSM-IV symptom of dependence (subjects using alcohol or illicit drugs fewer than five times are considered to have insufficient use to be queried regarding symptoms of dependence; these individuals received a zero on our measures of alcohol and illicit drug dependence).

Given that the DSM-IV symptom counts of CD, AD, and IDD are highly skewed with many zero counts, a threshold model that treats the variables as ordinal indices is appropriate (Stallings et al., 2001). For the CD and AD variable, an individual falls into one of three categories: no symptoms or diagnosis, in which the individual has not endorsed any of the DSM symptoms for that variable; symptoms but no diagnosis, in which the individual has endorsed one or more symptoms but not enough to lead to a clinical diagnosis; and positive diagnosis, in which the individual has endorsed enough symptoms (three or more) to lead to a dependence diagnosis. Illicit drug dependence was categorized as: endorsing no symptoms of dependence for any of the illicit drugs; endorsing one or more symptoms for dependence for one or more of the illicit drugs, but not ascertaining a diagnosis for any; and endorsing enough symptoms for one or more of the illicit drugs to get a DSM-IV diagnosis (three or more symptoms of a single substance). A dependence diagnosis for combined illicit drug dependence, rather than for individual drugs was used because adolescents rarely specialize in one drug. Also, there is evidence of a common vulnerability factor underlying the abuse of different illicit drugs (Tsuang et al., 1998). Clustering, in which the symptoms were expressed simultaneously or within a short time of one another, was not required for diagnosis.

2.3. Analyses

Basic statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS) (SPSS Inc., 2004). All genetic analyses were conducted on raw, ordinal, data, using the structural equation modeling package Mx (Version 1.61c) (Neale, 2004). We employed a threshold model, and assumed a normal, continuous liability distribution. In this model, individuals who fall below a pre-defined threshold are unaffected whilst those who exceed it are affected. In the case described here there are two thresholds: a person who falls below both thresholds will be unaffected, someone who exceeds only the first threshold will be symptomatic, and someone who exceeds both thresholds will have a diagnosis. Polychoric correlations were estimated for the association between conduct disorder, alcohol dependence, and illicit drug dependence. Consistent with results from previous analyses of these data, using different phenotype categories (Ehringer et al., 2006; Rhee et al., 2003), preliminary analyses found no evidence of sex limitation in this sample for CD, AD, or IDD. It was possible to constrain the magnitude of the effects of genes, shared environment and non-shared environment to be the same for males and females, without a significant reduction in the fit of the model compared with one in which the magnitude of these parameters was allowed to differ across sex (CD: $\Delta\chi^2 = 0.905$, d.f. = 3, $P = 0.824$; AD: $\Delta\chi^2 = 5.862$, d.f. = 3, $P = 0.118$; IDD: $\Delta\chi^2 = 1.037$, d.f. = 3, $P = 0.792$). Consequently, sex limitation was not examined in our analyses. However, to accommodate prevalence differences across age and sex, thresholds were estimated separately for males and females for each age (e.g., separate thresholds for 12-year-old males, 12-year-old females, 13-year-old males, 13-year-old females, etc.) prior to conducting model fitting, based upon symptom and diagnosis prevalences, and corresponding z-scores. As expected, thresholds were higher for females than males and decreased with increasing age in both sexes. The thresholds were fixed separately for individuals of each age and sex and these thresholds were read into the model fitting analyses.

Extensions of classical twin analyses can be used to estimate the relative contributions of additive genetic effects (A), shared environmental effects (C), and non-shared environmental effects (E) to the phenotypic variance for each variable. The basic principle of the classical twin study is that MZ twins are genetically identical and DZ twins share on average approximately 50% of their alleles. Consequently, the covariance between MZ twin pairs is due to shared genes and shared environment (A + C), and the covariance between DZ twin pairs, and also full biological siblings, is due to the 50% of alleles that they share and their shared environment (0.5A + C). Furthermore, the covariance between adoptive siblings results only from the environment they share (C) as they do not share any of their genes. Hence, if genes contribute towards liability for a phenotype, MZ twins will tend to be more similar than DZ twins and full biological

Table 1
Prevalence of conduct disorder, alcohol dependence, and illicit drug dependence for males and females from age 12 to 18 years

	Age (years)	Male		Female		Total	
		Symptoms	Diagnosis	Symptoms	Diagnosis	Symptoms	Diagnosis
Conduct disorder	12	25.30	4.40	23.90	0.50	24.58	2.37
	13	36.50	14.90	33.30	3.20	35.04	9.49
	14	41.30	12.30	34.00	3.80	37.63	8.03
	15	44.30	19.50	40.80	4.90	42.49	12.01
	16	48.50	17.40	39.30	8.50	44.01	13.07
	17	43.20	27.40	44.70	6.90	43.92	17.91
	18	47.00	27.60	44.00	12.00	45.45	19.51
	Total	40.09	17.29	36.47	5.44	38.29	11.39
Alcohol dependence	12	0.00	0.30	0.00	0.00	0.00	0.16
	13	2.90	0.00	1.70	0.00	2.35	0.00
	14	5.30	0.40	2.20	0.40	3.74	0.44
	15	10.90	3.50	7.80	1.80	9.07	2.63
	16	13.90	3.80	16.20	4.10	15.03	3.97
	17	33.60	7.80	23.60	5.20	28.90	6.59
	18	30.60	11.20	27.10	5.70	28.83	8.38
	Total	16.41	4.46	12.67	2.80	14.56	3.64
Illicit drug dependence	12	0.30	0.60	0.30	0.00	0.32	0.32
	13	1.40	0.70	1.80	0.00	1.59	0.40
	14	2.30	1.40	1.80	0.90	2.01	1.12
	15	9.10	2.00	8.00	1.90	8.54	1.95
	16	10.30	3.40	12.90	7.90	11.60	5.70
	17	2.06	13.90	14.90	8.60	17.95	11.41
	18	18.10	14.30	16.70	6.10	17.43	10.17
	Total	10.37	6.39	8.83	4.22	9.61	5.31

(symptoms only) and 1.0% (diagnosis) for amphetamines, 1.3% (symptoms only) and 0% (diagnosis) for sedatives, 0.2% (symptoms only) and 0% (diagnosis) for inhalants, 2.9% (symptoms only) and 1.1% (diagnosis) for hallucinogens, 0.8% (symptoms only) and 0.1% (diagnosis) for opiates, and 0.1% (symptoms only) and 0% (diagnosis) for PCP. More details regarding the percentage of people meeting the definitions of illicit drug symptoms and diagnosis who have symptoms and diagnoses of each of the individual illicit drugs are presented in Table 2.

All three phenotypes were highly correlated, and after pooling across age and sex (but allowing for age- and sex-dependent thresholds on the liability distribution), the polychoric correlations were 0.48 (0.42–0.54) for CD with AD, 0.60

(0.56–0.65) for CD with IDD, and 0.72 (0.67–0.75) for AD with IDD.

3.2. Sib-pair similarity and univariate model fitting

Table 3 shows the cross-pair-within-trait correlations separately for MZ twins, DZ twins, full siblings and adoptive siblings. The MZ twin correlations are higher than those for DZ and full siblings, which are in turn higher than those for adoptive siblings, for all three phenotypes, indicating a genetic influence on each. Furthermore, the cross-pair-cross-trait correlations, also presented in Table 3, show a similar pattern, indicating a possible genetic contribution to the comorbidity between all pair wise combinations of the phenotypes.

The results of univariate model fitting showed that all three phenotypes were substantially heritable (CD = 58% (50–65%), AD = 66% (56–76%), and IDD = 36% (12–60%)). The remainder of the variance of CD and AD was due to non-shared environmental variance, but both shared and non-shared environmental influences contributed to IDD (C = 36% (17–53%) and E = 27% (19–39%)).

3.3. Bivariate model fitting

The results of bivariate model fitting can be seen in Table 4, and the standardized path coefficient estimates from the best fitting model are presented in Fig. 3. It was possible to drop all the shared environmental influences on AD from the bivari-

Table 2
The percentage of people meeting the criteria for illicit drug dependence symptoms or diagnosis with symptoms and diagnoses of each of the individual illicit drugs

Drug	Illicit drug dependence symptoms (%)	Illicit drug dependence diagnosis	
		Symptoms (%)	Diagnosis (%)
Marijuana	91.8	12.8	83.0
Amphetamine	5.6	10.6	18.6
Cocaine	3.8	9.6	11.2
Hallucinogen	15.0	27.7	20.7
Inhalant	0.9	1.6	0.0
Opioid	2.6	10.1	2.1
PCP	0.9	0.5	0.0
Sedative	1.8	3.2	0.5

Table 3
Sibling-pair correlations for conduct disorder (CD), alcohol dependence (AD), and illicit drug dependence (IDD), and cross-pair-cross-trait correlations

	MZ twins	DZ twins	Biological siblings	Adoptive siblings
Univariate				
CD	0.57 (0.48–0.65)	0.33 (0.22–0.43)	0.23 (0.03–0.40)	0.01 (–0.78–0.79)
AD	0.63 (0.49–0.74)	0.51 (0.34–0.64)	0.24 (0.00–0.47)	–0.05 (–0.30–0.22)
IDD	0.72 (0.59–0.81)	0.65 (0.51–0.76)	0.51 (0.28–0.68)	0.22 (–0.05–0.46)
Bivariate				
CD/AD	0.41 (0.30–0.50)	0.27 (0.15–0.38)	0.21 (0.03–0.38)	–0.019 (–0.42–0.08)
CD/IDD	0.57 (0.46–0.65)	0.34 (0.23–0.45)	0.30 (0.13–0.46)	–0.03 (–0.36–0.31)
AD/IDD	0.52 (0.39–0.62)	0.47 (0.34–0.57)	0.32 (0.14–0.47)	–0.05 (–0.25–0.17)

Table 4
Goodness-of-fit results from bivariate model fitting for covariation of alcohol dependence (AD) and illicit drug dependence (IDD)

Model	Model fit			Comparative fit		
	–2ll	d.f.	AIC	χ^2	d.f.	P
(1) Full	4704.26	7481	–10257.74	NA	NA	NA
(2) ^a Drop c_{AD}	4706.77	7483	–10259.23	2.51	2	0.285
(3) ^b Drop a_{12}	4821.01	7484	–10146.99	114.24	1	>0.001
(4) ^b Drop e_{12}	4723.76	7484	–10244.24	16.99	1	>0.001
(5) ^b Drop a_{22} [#]	4706.79	7484	–10261.21	0.03	1	0.872
(6) ^b Drop c_{22}	4718.40	7484	–10249.60	11.63	1	>0.001

Abbreviations: –2ll, minus twice the log likelihood fit function; AIC, Akaike's Information Criterion fit function; c^2 d.f., degrees of freedom; P, probability; c_{11} , path coefficient for shared environment common to AD and IDD on AD; c_{12} , path coefficient for shared environment correlation between AD and IDD (dropping c_{11} and c_{12} simultaneously eliminates the influence of all shared environment associated with AD); a_{12} , path coefficient for genetic correlation between AD and IDD; e_{12} , path coefficient for non-shared environment correlation between AD and IDD; a_{22} , path coefficient for the unique genetic influences on IDD; e_{22} , path coefficient for the unique non-shared environment influences on IDD.

^a Goodness-of-fit compared with model 1, this model tests whether it is possible to drop, from the bivariate model, all the parameters found to be non-significant in the univariate model, before testing for the influence of further path coefficients.

^b Goodness-of-fit compared with model 2.

[#] Best fitting model.

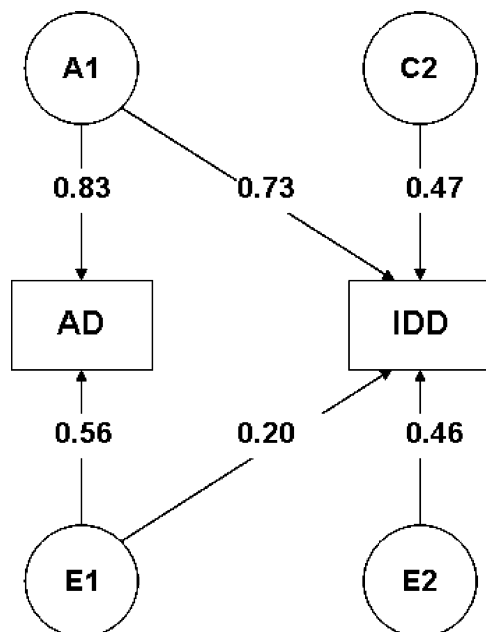


Fig. 3. Cholesky bivariate decomposition results for the covariance between alcohol dependence (AD) and illicit drug dependence (IDD). A1, additive genetic effects common to AD and IDD; C2, shared environmental effects specific to AD and IDD; E1, non-shared environmental effects common to AD and IDD; E2, non-shared environmental effects specific to IDD.

ate model without a significant deterioration in fit ($\Delta\chi^2 = 2.51$, d.f. = 2, $P = 0.285$). It was not possible to drop either the genetic or non-shared environment correlation paths between AD and IDD without a significant reduction in fit, indicating that genetic and non-shared environmental influences, but not shared environmental influences, contribute to the comorbidity between the two. Finally, it was possible to drop the genetic influences unique to IDD without a significant deterioration in the fit of the model, indicating that all the genetic influence on IDD is shared in common with AD.

Non-shared environmental effects common to AD and IDD accounted for 4% of the total variance and 16% of the total non-shared environmental variance on IDD, and non-shared environmental effects unique to IDD contributed 21% of the total phenotypic variance, and 84% of the total non-shared environmental variance of IDD.

3.4. Trivariate model fitting

As the best fitting univariate model for CD and AD were ones in which the shared environmental influences were fixed at 0, and the best fitting bivariate model also included fitting the unique genetic effects on IDD to zero, these parameters were also initially dropped from the trivariate model; dropping these parameters did not significantly reduce the fit compared with

Table 5

Goodness-of-fit results from trivariate model fitting for covariation of conduct disorder (CD), alcohol dependence (AD), and illicit drug dependence (IDD)

Model	Model fit			Comparative fit		
	–2ll	d.f.	AIC	χ^2	d.f.	<i>P</i>
(1) Full	9197.94	10289	–11380.06	NA	NA	NA
(2) ^a Drop $C_{CD}/C_{AD}/(unique)A_{IDD}$ [#]	9198.34	10295	–11391.66	0.40	6	0.999
(3) ^b Drop a_{22}	9212.41	10296	–11379.59	14.07	1	<0.001
(4) ^b Drop e_{22}	9216.60	10296	–11375.40	18.26	1	<0.001
(5) ^b Drop c_{31}	9218.41	10296	–11373.59	20.07	1	<0.001

Abbreviations: –2ll, minus twice the log likelihood fit function; AIC, Akaike's Information Criterion fit function; d.f., degrees of freedom; *P*, probability.

^a Goodness-of-fit compared with model 1, this model tests whether it is possible to drop, from the trivariate model, all the parameters found to be non-significant in the bivariate model, before testing for the influence of further path coefficients.

^b Goodness-of-fit compared with model 2.

[#] Best fitting model.

the full model ($\Delta\chi^2 = 0.400$, d.f. = 6, $P = 0.999$). Consequently, the goodness-of-fit of all further nested models were compared with the model containing no C influence on CD or AD or unique genetic effect on IDD. Results of these analyses can be seen in Table 5.

When the genetic correlation specific to AD and IDD was fixed to 0, there was significant reduction in the fit of the model ($\Delta\chi^2 = 14.07$, d.f. = 1, $P < 0.001$). Furthermore, fixing the non-shared environment correlations specific to AD and IDD to 0 also significantly reduced the goodness-of-fit of the model ($\Delta\chi^2 = 18.26$, d.f. = 1, $P < 0.001$). Genetic influences common to AD and CD appear to play a significant role in the correlation of AD and IDD independent of the genetic association of both with CD. Finally, to determine the most parsimonious model, we tested a further nested model in which the IDD-specific shared environment influence was fixed to 0, which again resulted in a significant reduction in the fit of the model. The parameter estimates from the best fitting model can be seen in Fig. 4.

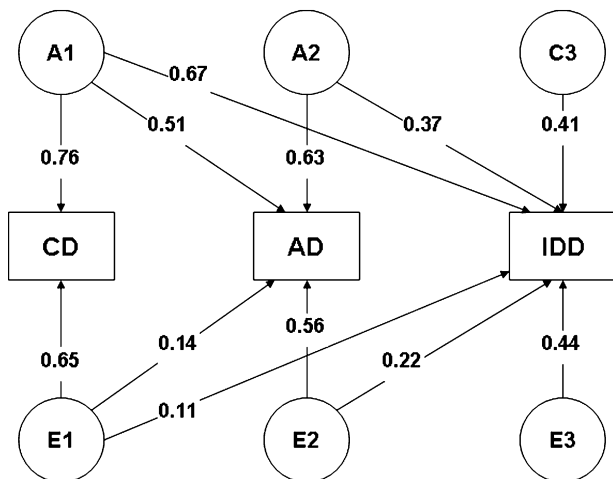


Fig. 4. Best-fitting Cholesky trivariate decomposition model for the partitioning the covariance between conduct disorder (CD), alcohol dependence (AD), and illicit drug dependence (IDD). A1, additive genetic effects common to CD, AD, and IDD; A2, additive genetic effects common to AD and IDD (but not CD); C3, shared environmental effects unique to IDD; E1, non-shared environmental effects common to CD, AD, and IDD; E2, non-shared environmental effects common to AD and IDD (but not CD); E3, non-shared environmental effects unique to IDD.

After inclusion of CD in the model, the genetic covariance between AD and IDD, conditional on CD, is reduced from 0.61 to 0.23. Genetic effects shared in common with CD accounted for approximately 60% of the genetic liability shared by AD and IDD. The shared environment correlation does not contribute to the covariation among the three outcomes. However, inclusion of CD in the analysis did not impact the non-shared environment correlation between AD and IDD. These analyses were repeated using marijuana rather than combined illicit drug dependence, since marijuana contributed the majority of the dependence phenotype, and the same pattern of results was demonstrated.

4. Discussion

The results of this study show that the genetic vulnerability for conduct disorder in adolescent males and females accounts for a large percentage of the genetic contribution to the comorbidity between symptoms of alcohol dependence and illicit drug dependence. The results of the present study are consistent with previous studies providing evidence for a genetic and non-shared environmental contribution to the comorbidity between CD and AD, CD and IDD, and AD and IDD.

As the genetic correlation specific to AD and IDD decreased after inclusion of CD in the model, we concluded that the genetic contribution to the comorbidity between AD and IDD was partially explained by the genetic vulnerability they both share in common with CD. The common genetic influence on all three phenotypes lends further support to the hypothesis of a single latent variable, such as behavioral disinhibition, with a strong genetic component, underlying a wide range of problem behaviors in adolescence (Krueger et al., 2002).

These results are consistent with those reported by Fu et al. (2002), who conducted a similar analysis in adult males from the Vietnam Era Twin Registry. They also showed that genetic vulnerability to Antisocial Personality Disorder almost fully explains the genetic correlation between Alcohol and Marijuana Dependence. We believe that the current study is the first to address this question in adolescents and extend the conclusion to females.

In addition to these genetic influences, there are non-shared environmental influences common to all three phenotypes, a

non-shared environment vulnerability common to AD and IDD, and also non-shared environmental influences unique to IDD. In terms of risk for development of AD and IDD, this result suggests that although some of the non-shared environmental risk factors may be common to all three (e.g. antisocial peers), there are others that account for the development of alcohol and illicit drug dependence independent of conduct disorder symptomatology (e.g. peer pressure to use, or being exposed to alcohol and other substances) and still others that will lead to the development of illicit drug dependence regardless of alcohol dependence. Whether this latter reflects environmental differences, such as illicit drug availability, or simply a random process (including measurement error), we cannot determine from these data. However, there are also shared environmental risks specific for illicit drug dependence, which may also be responsible for the development of dependence independent of the development of other problems. This is best illustrated in the data by the significant correlation for adoptive siblings for IDD. It seems plausible that this reflects family or neighborhood differences in availability or access, quite separate from the individual vulnerability that is captured in the genetic comorbidity across CD, AD, and IDD. This observation is consistent with other studies showing significant shared environmental influences on marijuana or other illicit drug use and dependence (Rhee et al., 2003).

The results of univariate analyses presented by here are similar to those presented previously for analyses of a single threshold representing endorsement of a single item of either dependence or abuse for alcohol and marijuana (Rhee et al., 2003), demonstrating a significant genetic contribution to the liability. Moreover, results for the univariate model fitting for conduct disorder in this twin/sibling/adoptive sibling design were remarkably similar to those from an analysis utilizing using the twins described in this study, and the twins' closest in age siblings. Our best-fitting AE model yielded a heritability of 0.58, similar to the 0.53 reported using this slightly smaller dataset (Ehringer et al., 2006).

There are some limitations in this study. The participants were from an unselected community sample, and we do not know the extent to which these results can be generalized to clinical samples. However, unselected samples may be advantageous in the determination of causes of comorbidity, in part because clinical samples will typically over sample comorbid cases (Caron and Rutter, 1991). Furthermore, the data analyzed in the current study were cross sectional and did not enable us to test models implicating causal relationships between the phenotypes. Another limitation may be that the association between CD, AD, and IDD, and therefore possibly the genetic association, may vary with development. Therefore, these results may be limited to adolescents only, and further studies looking into similar association in adults would be useful. However, our results were comparable to those of Fu and colleagues' examination of the covariation among antisocial personality disorder, alcohol use problems, and marijuana use problems in an adult sample (Fu et al., 2002), suggesting that the genetic relationship between CD, AD, and IDD is stable across age. Finally, in any model fitting analysis, we make a number of simplifying assumptions that are not tested by the analysis. One such assumption is that

there are only additive effects of genes and environment on the phenotypic variance. However, in practice, there may be interactive effects. These interactive effects become incorporated into the estimates of genetic liability (for interactions between shared environmental and genetic risk) or non-shared environment estimates (for interactions between non-shared environmental and genetic risks). Consequently, the estimates of genetic and non-shared environmental variance may include these types of gene by environment interaction variance.

The results aid the understanding of the biological and environmental contributions to the development of CD, AD, and IDD, and the co-occurrence among them, which in turn can aid development of effective interventions and treatments. Approximately one-half of the genetic influence on AD is shared with conduct disorder, and the remaining one-half is unique to AD. Thus, whilst many of the genes identified with a role in CD in children are also likely to influence AD, and vice versa, there are also likely to be genes with an effect on AD only. We found no evidence of genetic influences unique to IDD; all of the genetic influences on IDD were those that also influence vulnerability to CD and AD. Thus, the results suggest that genes identified as candidates for IDD also should influence CD or AD; as predicted, quantitative trait loci with a pleiotropic influence on these two traits have recently been reported (Stallings et al., 2005).

Acknowledgements

This work was supported by grants DA-011015, DA-13956, DA-05131, MH-43899, and HD-010333. An earlier version of this paper was presented at the meeting of the Behavior Genetics Association on July 1, 2005 in Hollywood, CA.

References

- Akaike, H., 1987. Factor analysis and AIC. *Psychometrika* 52, 317–332.
- APA, 1994. *Diagnostic and Statistical Manual of Mental Disorders*, Fourth ed., American Psychiatric Association, Washington, DC.
- Bierut, L.J., Dinwiddie, S.H., Begleiter, H., Crowe, R.R., Hesselbrock, V., Nurnberger Jr., J.I., Porjesz, B., Schuckit, M.A., Reich, T., 1998. Familial transmission of substance dependence: alcohol, marijuana, cocaine, and habitual smoking: a report from the Collaborative Study on the Genetics of Alcoholism. *Arch. Gen. Psychiatry* 55, 982–988.
- Caron, C., Rutter, M., 1991. Comorbidity in child psychopathology: concepts, issues and research strategies. *J. Child Psychol. Psychiatry* 32, 1063–1080.
- Cottler, L.B., Keating, S.K., 1990. Operationalization of alcohol and drug dependence criteria by means of a structured interview. *Recent Dev. Alcohol.* 8, 69–83.
- Cottler, L.B., Robins, L.N., Helzer, J.E., 1989. The reliability of the CIDI-SAM: a comprehensive substance abuse interview. *Br. J. Addict.* 84, 801–814.
- Crowley, T.J., Mikulich, S.K., Ehlers, K.M., Whitmore, E.A., MacDonald, M.J., 2001. Validity of structured clinical evaluations in adolescents with conduct and substance problems. *J. Am. Acad. Child Adolesc. Psychiatry* 40, 265–273.
- DeFries, J.C., Plomin, R., Fulker, D.W., 1994. *Nature and Nurture During Middle Childhood*. Blackwell Publishers, Oxford, UK.
- Ehringer, M.A., Rhee, S.H., Young, S.E., Corley, R.P., Hewitt, J.K., 2006. Genetic and environmental contributions to common psychopathologies of childhood and adolescence: a study of twins and their siblings. *J. Abnorm. Child Psychol.*

- Emde, R.N., Hewitt, J.K., 2001. *Infancy to Early Childhood: Genetic and Environmental Influences on Developmental Change*. Oxford University Press, Oxford.
- Fu, Q., Heath, A.C., Bucholz, K.K., Nelson, E., Goldberg, J., Lyons, M.J., True, W.R., Jacob, T., Tsuang, M.T., Eisen, S.A., 2002. Shared genetic risk of major depression, alcohol dependence, and marijuana dependence: contribution of antisocial personality disorder in men. *Arch. Gen. Psychiatry* 59, 1125–1132.
- Grove, W.M., Eckert, E.D., Heston, L., Bouchard Jr., T.J., Segal, N., Lykken, D.T., 1990. Heritability of substance abuse and antisocial behavior: a study of monozygotic twins reared apart. *Biol. Psychiatry* 27, 1293–1304.
- Heath, A.C., Bucholz, K.K., Madden, P.A., Dinwiddie, S.H., Slutske, W.S., Bierut, L.J., Statham, D.J., Dunne, M.P., Whitfield, J.B., Martin, N.G., 1997. Genetic and environmental contributions to alcohol dependence risk in a national twin sample: consistency of findings in women and men. *Psychol. Med.* 27, 1381–1396.
- Hicks, B.M., Krueger, R.F., Iacono, W.G., McGue, M., Patrick, C.J., 2004. Family transmission and heritability of externalizing disorders: a twin-family study. *Arch. Gen. Psychiatry* 61, 922–928.
- Horton, J., Compton, W., Cottler, L.B., 2000. Reliability of substance use disorder diagnoses among African-Americans and Caucasians. *Drug Alcohol Depend.* 57, 203–209.
- Iacono, W.G., Carlson, S.R., Taylor, J., Elkins, I.J., McGue, M., 1999. Behavioral disinhibition and the development of substance-use disorders: findings from the Minnesota Twin Family Study. *Dev. Psychopath.* 11, 869–900.
- Jacobson, K.C., Neale, C.A., Prescott, M.C., Kendler, K.S., 2000. Cohort differences in genetic and environmental influences on retrospective reports of conduct disorder among adult male twins. *Psychol. Med.* 30, 775–787.
- Kendler, K.S., Davis, C.G., Kessler, R.C., 1997. The familial aggregation of common psychiatric and substance use disorders in the National Comorbidity Survey: a family history study. *Br. J. Psychiatry* 170, 541–548.
- Kendler, K.S., Neale, M.C., Heath, A.C., Kessler, R.C., Eaves, L.J., 1994. A twin-family study of alcoholism in women. *Am. J. Psychiatry* 151, 707–715.
- Kessler, R.C., Crum, R.M., Warner, L.A., Nelson, C.B., Schulenberg, J., Anthony, J.C., 1997. Lifetime co-occurrence of DSM-III-R alcohol abuse and dependence with other psychiatric disorders in the National Comorbidity Survey. *Arch. Gen. Psychiatry* 54, 313–321.
- Krueger, R.F., Hicks, B.M., Patrick, C.J., Carlson, S.R., Iacono, W.G., McGue, M., 2002. Etiologic connections among substance dependence, antisocial behavior, and personality: modeling the externalizing spectrum. *J. Abnorm. Psychol.* 111, 411–424.
- Merikangas, K.R., Stolar, M., Stevens, D.E., Goulet, J., Preisig, M.A., Fenton, B.T., Zhang, H., O'Malley, S.S., Rounsaville, B.J., 1998. Familial transmission of substance use disorders. *Arch. Gen. Psychiatry* 55, 973–979.
- Miles, D.R., Stallings, M.C., Young, S.E., Hewitt, J.K., Crowley, T.J., Fulker, D.W., 1998. A family history and direct interview study of the familial aggregation of substance abuse: the adolescent substance abuse study. *Drug Alcohol Depend.* 49, 105–114.
- Miles, D.R., van den Bree, M.B., Pickens, R.W., 2002. Sex differences in shared genetic and environmental influences between conduct disorder symptoms and marijuana use in adolescents. *Am. J. Med. Genet.* 114, 159–168.
- Neale, M.C., 2004. *Mx: Statistical Modeling*. 6th ed., Richmond, VA, Box 980126 MCV.
- Neighbors, B., Kempton, T., Forehand, R., 1992. Co-occurrence of substance abuse with conduct, anxiety, and depression disorders in juvenile delinquents. *Addict. Behav.* 17, 379–386.
- Nichols, R.C., Bilbro Jr., W.C., 1966. The diagnosis of twin zygosity. *Acta Genet. Stat. Med.* 16, 265–275.
- Pickens, R.W., Svikis, D.S., McGue, M., LaBuda, M.C., 1995. Common genetic mechanisms in alcohol, drug, and mental disorder comorbidity. *Drug Alcohol Depend.* 39, 129–138.
- Reebye, P., Moretti, M.M., Lessard, J.C., 1995. Conduct disorder and substance use disorder: comorbidity in a clinical sample of preadolescents and adolescents. *Can. J. Psychiatry* 40, 313–319.
- Rhee, S.H., Hewitt, J.K., Young, S.E., Corley, R.P., Crowley, T.J., Stallings, M.C., 2003. Genetic and environmental influences on substance initiation, use, and problem use in adolescents. *Arch. Gen. Psychiatry* 60, 1256–1264.
- Shaffer, D., Fisher, P., Lucas, C.P., Dulcan, M.K., Schwab-Stone, M.E., 2000. NIMH Diagnostic Interview Schedule for Children Version IV (NIMH DISC-IV): description, differences from previous versions, and reliability of some common diagnoses. *J. Am. Acad. Child Adolesc. Psychiatry* 39, 28–38.
- Shaffer, D., Fisher, P.J., Lucas, C., 1997. *The Diagnostic Interview Schedule for Children IV*. Ruane Center for Early Diagnosis. Division of Child Psychiatry Columbia University, New York.
- Simonoff, E., Pickles, A., Meyer, J., Silberg, J., Maes, H.H., 1998. Genetic and environmental influences on subtypes of conduct disorder behavior in boys. *J. Abnorm. Child Psychol.* 26, 495–509.
- Slutske, W.S., Heath, A.C., Dinwiddie, S.H., Madden, P.A., Bucholz, K.K., Dunne, M.P., Statham, D.J., Martin, N.G., 1997. Modeling genetic and environmental influences in the etiology of conduct disorder: a study of 2682 adult twin pairs. *J. Abnorm. Psychol.* 106, 266–279.
- Slutske, W.S., Heath, A.C., Dinwiddie, S.H., Madden, P.A., Bucholz, K.K., Dunne, M.P., Statham, D.J., Martin, N.G., 1998. Common genetic risk factors for conduct disorder and alcohol dependence. *J. Abnorm. Psychol.* 107, 363–374.
- SPSS Inc., 2004. *SPSS for Windows*, Release 12.0.2. Chicago, IL, SPSS Inc.
- Stallings, M.C., Corley, R.P., Dennehey, B., Hewitt, J.K., Krauter, K.S., Lessem, J.M., Mikulich-Gilbertson, S.K., Rhee, S.H., Smolen, A., Young, S.E., Crowley, T.J., 2005. A genome-wide search for quantitative trait loci that influence antisocial drug dependence in adolescence. *Arch. Gen. Psychiatry* 62, 1042–1051.
- Stallings, M.C., Hewitt, J.K., Lessem, J.M., Young, S.E., Corley, R.P., Mikulich, S.K., Crowley, T.J., 2001. Modeling the familial transmission of alcohol dependence symptom counts in clinical and control family pedigrees. *Behav. Genet.* 31, 470.
- True, W.R., Heath, A.C., Scherrer, J.F., Xian, H., Lin, N., Eisen, S.A., Lyons, M.J., Goldberg, J., Tsuang, M.T., 1999. Interrelationship of genetic and environmental influences on conduct disorder and alcohol and marijuana dependence symptoms. *Am. J. Med. Genet.* 88, 391–397.
- Tsuang, M.T., Bar, J.L., Harley, R.M., Lyons, M.J., 2001. The Harvard Twin Study of Substance Abuse: what we have learned. *Harv. Rev. Psychiatry* 9, 267–279.
- Tsuang, M.T., Lyons, M.J., Eisen, S.A., Goldberg, J., True, W., Lin, N., Meyer, J.M., Toomey, R., Faraone, S.V., Eaves, L.J., 1996. Genetic influences on DSM-III-R drug abuse and dependence: a study of 3372 twin pairs. *Am. J. Med. Genet.* 67, 473–477.
- Tsuang, M.T., Lyons, M.J., Meyer, J.M., Doyle, T., Eisen, S.A., Goldberg, J., True, W., Lin, N., Toomey, R., Eaves, L.J., 1998. Co-occurrence of abuse of different drugs in men: the role of drug-specific and shared vulnerabilities. *Arch. Gen. Psychiatry* 55, 967–972.
- Young, S.E., Corley, R.P., Stallings, M.C., Rhee, S.H., Crowley, T.J., Hewitt, J.K., 2002. Substance use, abuse and dependence in adolescence: prevalence, symptom profiles and correlates. *Drug Alcohol Depend.* 68, 309–322.
- Young, S.E., Stallings, M.C., Corley, R.P., Krauter, K.S., Hewitt, J.K., 2000. Genetic and environmental influences on behavioral disinhibition. *Am. J. Med. Genet.* 96, 684–695.