Conduct disorder (CD) symptoms and substance dependence commonly co-occur. Both phenotypes are highly heritable and a common genetic influence on the covariation has been suggested. The aim of this study was to determine the extent to which genes and environment contribute to the covariance between CD and drug dependence using twins from the Colorado Longitudinal Twin Sample and the Colorado Twin Registry. A total of 880 twin pairs (237 monozygotic [MZ] female, 195 MZ male, 116 dizygotic [DZ] female, 118 DZ male and 214 DZ opposite-sex) aged 13 to 18 (mean = 15.65) were included in the analysis. CD was assessed by lifetime Diagnostic and Statistical Manual of Mental Disorders (4th ed.; DSM-IV; American Psychiatric Association, 1994) symptom count and a polysubstance dependence vulnerability index was developed from responses to the Composite International Diagnostic Interview — Substance Abuse Module. A bivariate Cholesky Decomposition model was used to partition the cause of variation and covariation of the two phenotypes. No sex-limitation was observed in our data, and male and female parameter estimates were constrained to be equal. Both CD symptoms and dependence vulnerability were significantly heritable, and genes, shared environment and nonshared environment all contributed to the covariation between them. Genes contributed 35% of the phenotypic covariance, shared environment contributed 46%, and nonshared environmental influences contributed the remaining 19% to the phenotypic covariance. Therefore, there appears to be pleiotropic genetic influence on CD symptoms and dependence vulnerability.

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between them (Slutske et al., 1998). Other twin studies have demonstrated a substantial genetic contribution to the covariance of CD with tobacco use (Silberg et al., 2003), marijuana use (Miles et al., 2002), and other illicit drug use (Grove et al., 1990). An underlying latent factor has also been proposed to explain the covariation between CD and substance use (Young et al., 2000) or dependence (Hicks et al., 2004; Krueger et al., 2002), as well as a number of other externalizing disorders. This factor has been called Behavioral Disinhibition, is substantially heritable, and contributes to the variance of both CD and substance use disorder.

There is evidence that comorbid CD negatively impacts the outcome of treatment for substance abuse (Fischenscher & Novins, 2003; Rowe et al., 2004). Understanding the causes of this comorbidity may aid development of effective techniques for each disorder, occurring alone or jointly. Knowledge of the cause of comorbidity will also aid the search for genetic or environmental risk factors specific to each as well as those that potentially influence both. This will lead to a better understanding and diagnosis of these clinical disorders.

The aim of the current study was to determine the extent to which genes and environment contribute to the covariance between CD and drug dependence, using a large, population-based twin study. We hypothesize that both genes and environmental factors contribute to the covariance of the two phenotypes.

Materials and Methods

Participants

Twins were recruited from the Colorado Longitudinal Twin Sample (LTS; Emde & Hewitt, 2001) and the Colorado Twin Registry (CTR; Young et al., 2000). The LTS twins were recruited through the Colorado Department of Health’s Division of Vital Statistics and were included in the Center for the Genetics of Antisocial Drug Dependence (CADD) sample as they reached their 12th birthday. The CTR were recruited through the Department of Health and 170 of the 176 school districts in Colorado. Written informed consent or assent (from minor participants) was obtained and assessments were administered by trained interviewers. Twins used in this analysis were aged 13 to 18 (mean = 15.65, SD = 1.65). Of the 881 twin pairs aged 13 to 18 years, one twin pair was eliminated due to uncertain zygosity, resulting in a total of 880 twin pairs (1760 individuals: 432 monozygotic [MZ] pairs — 237 female, 195 male; 448 dizygotic [DZ] pairs — 116 female, 118 male, 214 opposite-sex).

Zygosity

Zygosity was determined using a 9-item assessment questionnaire (Nichols & Bilbro, 1966) and by genotyping for 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 both twins.
of effect of genetic, shared environmental and non-shared environmental influences on the phenotypic variance of both symptoms of CD and symptoms of DV. Furthermore, the Cholesky model enables us to decompose the genetic, shared environmental and nonshared environmental influences on DV (Neale & Cardon, 1992) into those in common with CD, as well as those specific to DV. Therefore, the full model tests the influence of nine pathways; a genetic influence on both CD symptoms (CD: r = .076, p < .001; female r = .109, p < .001; DV: r = .193, p < .001; male r = .175, p < .001; female r = .228, p < .001). Both CD symptoms and DV scores were first regressed on age and age² separately within sex and the residual deviance scores were standardized. As the scores were skewed they were then log-transformed to approximate a normal distribution using the equation \( x = \ln(2 + x) \), where \( x \) is the original raw score, \( x \) is the transformed score, and a constant of 2 is added to each score as some scores were negative.

MZ and DZ correlations both prior to and after splitting by sex are presented in Table 2. As the MZ correlations are higher than the DZ for both CD symptoms and DV they suggest a genetic influence on each.

The phenotypic correlation between CD symptoms and DV is .489. The cross-twin cross-trait correlations were higher for MZ twins than for DZ twins, indicating the importance of genetic influences on the association between the two.

The results of model fitting are presented in two ways. First, the models were fit to the full set of five separate zygosities and sex groups, and the results of this series of models are presented in Table 3. All the models in this series fit the data poorly. The source of the poor overall fit was that the variance of DV for opposite-sex DZ twins was significantly lower in both male and females. We explored a number of post hoc models, including sex-limited sibling interaction models, but could not provide an adequate rationale for this observation. Our current interpretation is that the result reflects sampling variation leading to an attenuated range of dependence symptoms in this group. Despite the poor overall fit, hierarchical nested \( \chi^2 \) tests indicate that parameters of our models can be constrained to be equal across sex, but otherwise, only the shared environment specific to DV could be dropped. Because of the poor overall fit of the first series of models, together with the indication of homogeneity across sexes, we refit the series of models to data collapsed over sex groups, and results of this series of models are presented in Table 4. In this case the models provided a good fit to the data, \( \chi^2(d) = 8.804 \) (11); \( p = .640 \), as well as resulting in

Table 1

<table>
<thead>
<tr>
<th>Age</th>
<th>Conduct Disorder symptoms</th>
<th>Dependence Vulnerability</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>13</td>
<td>1.14 (2.04)</td>
<td>0.47 (1.16)</td>
</tr>
<tr>
<td>14</td>
<td>1.77 (2.59)</td>
<td>0.72 (1.52)</td>
</tr>
<tr>
<td>15</td>
<td>2.76 (2.90)</td>
<td>0.98 (1.56)</td>
</tr>
<tr>
<td>16</td>
<td>2.76 (2.88)</td>
<td>1.06 (1.45)</td>
</tr>
<tr>
<td>17</td>
<td>2.39 (2.44)</td>
<td>1.01 (1.23)</td>
</tr>
<tr>
<td>18+</td>
<td>2.04 (2.23)</td>
<td>1.00 (1.13)</td>
</tr>
</tbody>
</table>

Tanya M. M. Button, John K. Hewitt, Soo Hyun Rhee, Susan E. Young, Robin P. Corley, and Michael C. Stallings

Figure 1

A Bivariate Cholesky Decomposition model decomposing the relative contribution of genetic, shared environmental and nonshared environmental influences on the variances and covariance of conduct disorder symptoms (CD) and dependence vulnerability (DV).

Variances components: \( A_1 \), genetic effects common to both disorders; \( A_2 \), genetic effects specific to DV. \( C_1 \), shared environmental effects common to both disorders; \( C_2 \), shared environmental effects specific to DV. \( E_1 \), shared environmental effects specific to DV; \( E_2 \), nonshared environmental effects specific to DV. Path coefficients: \( a_1 \), effect of \( A_1 \) on CD; \( a_2 \), effect of \( A_1 \) on DV; \( a_3 \), effect of \( A_2 \) on DV; \( c_1 \), effect of \( C_1 \) on CD; \( c_2 \), effect of \( C_1 \) on DV; \( c_3 \), effect of \( C_2 \) on DV; \( e_1 \), effect of \( E_1 \) on CD; \( e_2 \), effect of \( E_1 \) on DV; \( e_3 \), effect of \( E_2 \) on DV.
Conduct Disorder and Drug Dependence Covariation

Table 2
Cross-Twin and Cross-Twin Cross-Trait Correlations for Conduct Disorder Symptoms and Dependence Vulnerability Split First by Zygosity and Then by Zygosity and Sex

<table>
<thead>
<tr>
<th></th>
<th>CD</th>
<th>DV</th>
<th>CD1–DV2</th>
</tr>
</thead>
<tbody>
<tr>
<td>MZ</td>
<td>.562</td>
<td>.610</td>
<td>.392</td>
</tr>
<tr>
<td>DZ</td>
<td>.400</td>
<td>.387</td>
<td>.293</td>
</tr>
<tr>
<td>MZ male</td>
<td>.585</td>
<td>.576</td>
<td>.357</td>
</tr>
<tr>
<td>DZ male</td>
<td>.453</td>
<td>.423</td>
<td>.350</td>
</tr>
<tr>
<td>MZ female</td>
<td>.540</td>
<td>.640</td>
<td>.426</td>
</tr>
<tr>
<td>DZ female</td>
<td>.512</td>
<td>.359</td>
<td>.393</td>
</tr>
<tr>
<td>DZ opposite-sex</td>
<td>.291</td>
<td>.396</td>
<td>.329 (male CD, female DV)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>.129 (female CD, male DV)</td>
</tr>
</tbody>
</table>

almost identical parameter estimates for the best fitting model as the first series.

In both series, with the exception noted above, it was not possible to drop any of the genetic or environmental influences on either phenotype without significantly reducing the fit of the model. This indicates a significant influence of all parameters. The best fitting model was one which did not drop any of the correlation pathways. However, as noted, it was possible to drop the shared environment specific to DV, thereby constraining the shared environment correlation to 1, $\Delta \chi^2 = 0.000; p = 1.000$, indicating that all the shared environmental influences are common to both phenotypes.

The genetic correlation was estimated to be .50, explaining approximately 39% of the phenotypic covariance between the two. Shared environmental influences had a correlation of 1.0 and contributed the greatest proportion (43%) to the phenotypic covariance. Nonshared environmental influences correlated .22 and contributed 18% to the phenotypic covariance.

Discussion

A number of studies have identified a significant correlation between the occurrence of conduct and substance use disorders, as well as identifying the possibility of common etiology for the two. The current study examined the etiology of the comorbidity between symptom counts for CD and the vulnerability to develop dependence on drugs of abuse, including alcohol and tobacco, in a large population-based twin study.

Bivariate model fitting provided parameter estimates for the univariate components of CD symptoms and DV, both of which were found to be moderately heritable, with heritability estimates of .35 (95% confidence intervals [CI]: 0.18–0.51) and 0.40 (95% CI: 0.24–0.55) respectively. Furthermore, our study also demonstrated a significant influence of the shared environment contributing towards the between twin pair covariances for both disorders (.22; 95% CI: 0.08–0.36) for CD symptoms and .19 (95% CI: 0.06–0.33) for DV. Nonshared environmental influences including error were found to account for 43% (95% CI: 0.37–0.49) of the variance of CD and 41% (95% CI: 0.36–0.47) of the variance of dependence vulnerability. These findings are consistent with other studies of similar phenotypes (Jacobson, Prescott et al., 2000; Tsuang et al., 1996).

There was a substantial and significant phenotypic correlation of approximately .49. Results of bivariate analysis showed that the two traits shared approximately half their genetic influence in common ($r_G = .50$), as well as all their shared environmental influences ($r_C = 1.00$) and a small but significant proportion of their nonshared environment influences ($r_E = .22$). The contribution of genes, shared environment and nonshared environment to the phenotypic covariance were 39%, 43% and 18% respectively. Consequently, it appears that CD symptoms and DV share substantial genetic influences, and thus genes and shared environment contribute to the co-occurrence of the two traits, whereas disorder-specific genes and also nonshared environment influences account for the etiological differences and thus the development of two distinct disorders. Again, these findings are generally consistent with those from adult studies (Miles et al., 2002).

Age trends and sex differences for CD symptoms and DV in this sample have previously been noted (Young et al., 2002). These mean effects were regressed out of the data prior to analysis and age effects on genetic and environmental parameters were not tested for here. We tested for sex differences in etiology using this sample but found that genetic and environmental parameters could be constrained to be the same for males and females for both the individual disorders and for the covariance between the two disorders. Consequently, we conclude that the relative influences of genetic and environmental risk factors on CD symptoms, DV and their covariation are the same in male and female adolescents despite different degrees of manifestation in the observed variables. This is in contrast to the conclusions drawn from retrospective studies (Slutske et al., 1998).

There are a number of limitations of this study. The overall fit of models to the five zygosity and sex groups was poor. This occurred because the variance in the opposite-sex twin pairs for DV was significantly lower than those for the same-sex groups. A number of post hoc tests were conducted to explain this observation, such as fitting a sex-limited sibling imitation model. However, these did not improve the fit of the model. Despite this, nested models in which male and female parameter estimates were equated did not result in a worsening of the fit. Consequently, we conducted a second series of analyses in which matrices were collapsed across sex. This resulted in good fitting models and resulted in the same parameter estimates. Our conclusion is that the opposite-sex DZ twins have been subject to some unusual sampling variance for DV, resulting in an attenuated range of scores.

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Table 3
Results of Fitting a Sex-Limitation Model

<table>
<thead>
<tr>
<th>Conduct Disorder symptoms</th>
<th>Dependence Vulnerability</th>
<th>Correlation</th>
<th>Fit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>C</td>
<td>E</td>
</tr>
<tr>
<td>1.1 M</td>
<td>.27</td>
<td>.30</td>
<td>.43</td>
</tr>
<tr>
<td>F</td>
<td>.46</td>
<td>.12</td>
<td>.42</td>
</tr>
<tr>
<td></td>
<td>(.02–.49)</td>
<td>(.11–.51)</td>
<td>(.35–.53)</td>
</tr>
<tr>
<td>1.2*</td>
<td>.35</td>
<td>.22</td>
<td>.43</td>
</tr>
<tr>
<td></td>
<td>(.18–.51)</td>
<td>(.08–.36)</td>
<td>(.38–.49)</td>
</tr>
<tr>
<td>1.3*</td>
<td>.18</td>
<td>.35</td>
<td>.47</td>
</tr>
<tr>
<td></td>
<td>(.05–.29)</td>
<td>(.26–.45)</td>
<td>(.41–.53)</td>
</tr>
<tr>
<td>1.4*</td>
<td>.53</td>
<td>.05</td>
<td>.42</td>
</tr>
<tr>
<td></td>
<td>(.35–.63)</td>
<td>(.00–.12)</td>
<td>(.37–.49)</td>
</tr>
<tr>
<td>1.5*</td>
<td>.39</td>
<td>.19</td>
<td>.42</td>
</tr>
<tr>
<td></td>
<td>(.22–.57)</td>
<td>(.03–.33)</td>
<td>(.37–.48)</td>
</tr>
<tr>
<td>1.6*</td>
<td>.17</td>
<td>.35</td>
<td>.46</td>
</tr>
<tr>
<td></td>
<td>(.00–.45)</td>
<td>(.13–.50)</td>
<td>(.40–.55)</td>
</tr>
<tr>
<td>1.7*</td>
<td>.35</td>
<td>.22</td>
<td>.43</td>
</tr>
<tr>
<td></td>
<td>(.18–.54)</td>
<td>(.08–.36)</td>
<td>(.38–.49)</td>
</tr>
</tbody>
</table>

Note: 1.1: Full model with sex limitation; 1.2: full model with parameter estimates equated across sex; 1.3: sex-equated parameters testing the significance of the genetic correlation; 1.4: sex-equated parameters testing the significance of the shared environment correlation; 1.5: sex-equated parameters testing the significance of the nonshared environment correlation; 1.6: sex-equated parameters testing the significance of the dependence vulnerability (DV) specific genetic effects; 1.7: sex-equated parameters testing the significance of the DV specific shared environment effects; A: genetic contribution to the (co)variance; C: shared environment contribution to the (co)variance; E: nonshared environment contribution to the (co)variance; χ² = chi-square; df: degrees of freedom; p = probability; AIC = Akaike’s Information Criterion; RMSEA = Root Mean Square Error of Approximation; Δχ² = chi-square difference between full and nested models.

#Fit compared to model 1.1; *Fit compared to model 1.2; best fitting model is in bold; 95% confidence intervals in parentheses.
Another possible limitation of this study is that it was conducted using a population-based sample, and thus the findings may not be applicable to those from clinical samples who will likely display greater prevalence of both disorders, and may be subject to unusual combinations of genetic and environmental risks. However, it has also been suggested that the use of population-based samples may be advantageous in the determination of causes of comorbidity (Caron & Rutter, 1991). Moreover, Stallings et al. (2005) report evidence for pleiotropic genetic influences on CD symptoms and DV in clinical probands and their siblings, indicating the possibility of a specific antisocial drug dependence phenotype.

Despite these limitations, our study finds evidence in favor of a substantial genetic influence on the comorbidity of CD and DV symptomatology in adolescents. Another conclusion from this study is that 43% of the phenotypic covariance is attributable to common environment effects. This indicates that some of the shared environmental risk factors that have previously been associated with conduct problems in adolescents may also contribute to the development of DV and, consequently, account for the co-occurrence of the two disorders. This conclusion reflects previous literature, which has identified similar putative environmental risk factors for the development of both disorders (Guo et al., 2002; Hawkins et al., 1992; Rutter et al., 1998).

In summary, this study provides further evidence that both CD and dependence vulnerability in adolescence are heritable and that the comorbidity between these traits in adolescence is due, in part, to shared genetic influences, and shared environment and nonshared environment influences also contribute. Furthermore, the etiology of this comorbidity is similar in males and females.

**Acknowledgments**

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