Family Transmission and Heritability of Externalizing Disorders

A Twin-Family Study

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Background: Antisocial behavior and substance dependence disorders exact a heavy financial and human cost on society. A better understanding of the mechanisms of familial transmission for these “externalizing” disorders is necessary to better understand their etiology and to help develop intervention strategies.

Objectives: To determine the extent to which the family transmission of externalizing disorders is due to a general vs a disorder-specific vulnerability and, owing to the genetically informative nature of our data, to estimate the heritable vs environmental nature of these transmission effects.

Design: We used structural equation modeling to simultaneously estimate the general and specific transmission effects of 4 externalizing disorders: conduct disorder, adult antisocial behavior, alcohol dependence, and drug dependence.

Setting: Participants were recruited from the community and were interviewed in a university laboratory.

Participants: The sample consisted of 542 families participating in the Minnesota Twin Family Study. All families included 17-year-old twins and their biological mother and father.

Main Outcome Measures: Symptom counts of conduct disorder, the adult criteria for antisocial personality disorder, alcohol dependence, and drug dependence.

Results: Transmission of a general vulnerability to all the externalizing disorders accounted for most familial resemblance. This general vulnerability was highly heritable ($h^2=0.80$). Disorder-specific vulnerabilities were also detected for conduct disorder, alcohol dependence, and drug dependence.

Conclusions: The mechanism underlying the familial transmission of externalizing disorders is primarily a highly heritable general vulnerability. This general vulnerability or common risk factor should be the focus of research regarding the etiology and treatment of externalizing disorders.

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though women may require greater familial loading before expressing the disorder.\textsuperscript{6,10-14}

Twin studies, however, tend to show substantial genetic overlap among disinhibitory syndromes, including conduct disorder and alcohol dependence,\textsuperscript{15-17} child and adult antisocial behavior,\textsuperscript{15,16,18} adult antisocial behavior and alcohol and drug dependence,\textsuperscript{15,16,19} and dependence among different classes of illicit drugs.\textsuperscript{30,31} Twin studies\textsuperscript{15,16} also tend to show the same pattern of genetic and environmental effect for men and women. Although twin studies\textsuperscript{13-21} consistently reveal genetic overlap among these disorders, they also find evidence of genetic and environmental risk factors that are specific to each disorder. Analyses\textsuperscript{15,16,18} that examine the patterns of comorbidity in large epidemiologic samples consistently identify a broad dimension of risk underlying antisocial personality disorder (ASPD), conduct disorder, alcohol dependence, and drug dependence. This general vulnerability factor is typically referred to as externalizing (EXT)\textsuperscript{15,16,22-24} and findings from recent twin studies\textsuperscript{15,16,25} indicate that the source of the comorbidity in these externalizing disorders can be largely attributed to common genetic factors.

Rare are twin-family studies that integrate the 2 literatures,\textsuperscript{20-28} allowing for the simultaneous estimation of general and specific transmission and the genetic and environmental contributions to these effects. Although family studies tend to show specificity of transmission and twin studies tend to show generality, a recent critique\textsuperscript{29} of family studies concluded that analyses typical of family studies do not provide valid tests of alternative comorbidity models. As a remedy, the authors recommended a model-fitting approach, which we use in the present investigation. The present study is also unique in that, to our knowledge, it is the first twin-family study that incorporates the assessment of multiple externalizing disorders in both biological parents and their twin offspring. Such a study provides an opportunity to clarify whether familial resemblance (both parental and sibling) is due to general vs disorder-specific vulnerabilities while also estimating the genetic and environmental contributions to these general and specific risk factors.

## METHODS

### PARTICIPANTS

Participants were members of 542 families participating in the Minnesota Twin Family Study (MTFS), a longitudinal epidemiologic study investigating the development of substance abuse and related disorders. A comprehensive description of the goals, design, and sample characteristics of the MTFS is available elsewhere.\textsuperscript{32-33} Families were identified using public birth records of twins born in Minnesota between January 1, 1972, and December 31, 1979, and were recruited the year the twins turned 17 years old. For this investigation, each family consisted of the biological mother and father and their same-sex twin offspring (N = 2,168). All but 1 biological mother was also the rearing mother. At the time of the assessment, 464 biological fathers (85.6%) resided with their twin offspring, 36 biological fathers (10.3%) had joint custody or visitation rights but did not currently live with their twin offspring, and 22 biological fathers (4.0%) had little or no contact with their twin offspring but did participate in the assessment. Of the 542 families, 357 included a monozygotic (MZ) twin pair (169 male and 188 female pairs) and 185 included a dizygotic (DZ) twin pair (87 male and 98 female pairs). Zygosity was determined by the agreement of 3 estimates: parental responses to a standard zygosity questionnaire, MTFS staff evaluation of physical similarity, and comparison of ponderal and cephalic indexes and fingerprint ridge counts. A serologic analysis was conducted if the 3 estimates did not agree. Twins ranged in age from 16.6 to 18.5 years (mean ± SD age, 16.9 ± 0.6 years), mothers from 33 to 59 years (mean ± SD age, 43.9 ± 4.8 years), and fathers from 32 to 66 years (mean ± SD age, 46.2 ± 5.4 years). Consistent with the demographics of Minnesota during the years the twins were born, 98% of the families were white. All twins and parents gave informed assent or consent as appropriate, and all study protocols were reviewed by an internal review board.

### ASSESSMENT

Externalizing disorders were assessed in person at the Department of Psychology, University of Minnesota, via structured clinical interviews administered by trained interviewers with either a bachelor’s or a master’s degree in psychology. Lifetime symptoms of DSM-III-R\textsuperscript{34} alcohol and drug dependence were assessed using the Substance Abuse Module of the Composite International Diagnostic Interview.\textsuperscript{35} Drug assessment covered amphetamines, cannabis, cocaine, hallucinogens, inhalants, opioids, phencyclidine, and sedatives. The drug class for which a participant reported the most symptoms was used as their number of drug dependence symptoms. The DSM-III-R symptoms of conduct disorder and adult antisocial behavior (the adult criteria for ASPD) were assessed using a structured interview designed by MTFS staff.\textsuperscript{36} The twin offspring were also assessed for adult antisocial behavior despite most not yet reaching age 18 years, as is required for a diagnosis of ASPD. This was done for 2 reasons. First, despite most twins being younger than 18 years, they reported engaging in a substantial amount of adult antisocial behavior, with 5.7% of male twins and 1.8% of female twins reporting 4 or more adult symptoms (the number necessary for a diagnosis of ASPD in DSM-III-R), which is consistent with previous prevalence rates of ASPD in adult community samples.\textsuperscript{37} Second, a previous work by our group\textsuperscript{38} has shown that adult antisocial behavior has the highest loading on a general externalizing factor and so is the best single measure of the vulnerability to externalizing disorders.

 Mothers also reported on the presence of conduct disorder and substance dependence symptoms in their children using the parent version of the Diagnostic Interview for Children and Adolescents.\textsuperscript{39} A symptom was considered present if it was reported by either the mother or a twin. Previous studies\textsuperscript{40} using the MTFS sample have shown that each informant contributes unique and valid information and that this best-estimate approach provides the most comprehensive assessment of psychiatric symptoms. All interview data were reviewed (referring to audiotapes of the interview when necessary) in a case conference consisting of at least 2 clinical psychology graduate students with extensive training in descriptive psychopathology and differential diagnosis. Consensus between the diagnosticians regarding the presence or absence of symptoms was reached before assigning symptoms. The consensus process yielded k reliabilities ranging from 0.81 for conduct disorder to 0.95 for adult antisocial behavior.

### DATA ANALYSIS

Structural equation modeling was used to investigate the transmission of externalizing disorders from parents to their offspring. In particular, we sought to determine the extent to which
a general vulnerability to all externalizing disorders could account for familial resemblance and to identify any disorder-specific vulnerability factors (ie, effects that contributed to familial resemblance that were independent of or unaccounted for by a general transmission effect). A general vulnerability to externalizing disorders was conceptualized as the latent phenotype EXT and was operationalized as the covariance among symptoms of alcohol and drug dependence, conduct disorder, and adult antisocial behavior, that is, the vulnerability factors common to all the disorders. For each member of a family, the 4 diagnostic variables were allowed to load on an EXT variable. General transmission effects were operationalized as the latent correlations between the parent and offspring EXT phenotypes. The specific transmission effects of a given disorder were estimated by allowing the residuals (ie, the variance unaccounted for by EXT) of the parental symptom count variables to covary with the residuals of the twins’ symptom count variables. Heritability estimates for the general and specific vulnerabilities were estimated by allowing the correlation between members of the twin pair to vary across zygosity (with greater similarity in MZ twins being indicative of a genetic effect) and by doubling the parent-to-child effect (because children receive 50% of their genetic material from each parent). Because MZ twins would be expected to be more similar than DZ twins, for the initial model, the latent correlation between twin A and twin B EXT was allowed to vary across zygosity.

Owing to positive skew in the distributions of the symptom count variables that is typical of a community sample, we used a normalizing (Blom) transformation that has been shown to optimize model selection when analyzing psychiatric symptom count data. Symptom counts were used primarily to increase statistical power because the number of persons meeting full criteria for psychiatric diagnoses in a community sample such as the MTFS is lower than that in clinically referred samples. Model fitting was conducted in Mplus 2 using a robust maximum-likelihood estimator, which is appropriate when analyzing nonnormal variables. The fit of models was evaluated using the mean-adjusted (Satorra-Bentler) $\chi^2$ fit statistic, the Bayesian information criterion (BIC) ($\chi^2$–df*ln N), and the root-mean-square error of approximation (RMSEA). The mean adjusted $\chi^2$ provides an overall estimate of model fit for nonnormal data. The BIC is a function of a model’s $\chi^2$ value and df, penalizing model fit for the retention of unnecessary parameters. Models that provide the best fit while retaining the fewest parameters yield lower (more negative) BIC values. The RMSEA provides an estimate of discrepancy in model fit per 1 df: values less than 0.08 indicate a good fit to the data, and values less than 0.05 indicate a very good fit to the data.

### RESULTS

Before model fitting, we examined sex differences by testing the null hypothesis that the correlation matrix for families with a male twin pair ($n=256$) did not differ from the correlation matrix for families with a female twin pair ($n=286$). Because there was no evidence to reject the null hypothesis that the correlation matrices were the same ($\chi^2=120.18$, $P=.08$, BIC = –611.2, RMSEA = 0.015), the sample was collapsed across the sex of the twin pair.

#### GENERAL VS SPECIFIC TRANSMISSION OF EXTERNALIZING DISORDERS

Results of the model fitting are provided in the Table. An initial model that allowed for only general transmission of externalizing disorders from parents to offspring provided an adequate fit to the data ($\chi^2=491.97$, BIC = –1113.3, RMSEA = 0.059). Next, we tested for any disorder-specific transmission effects by allowing the residual variance of each parental disorder to covary with the residual variance of the corresponding disorder in the offspring. A significant effect would indicate that parents and offspring were more similar than would be expected given only a general transmission of the disorders. To maximize our ability to detect specific effects, we conducted 1 df tests separately for each paternal and maternal disorder. Results of these tests are given in the Table under “Specific transmission effects” and are delineated from the general transmission—only model by a reduction of 1 df (from 255 to 254; df; the loss of 1 df is necessary to estimate the additional parameter) and subsequent changes in model fit indexes. A specific effect was retained in the model if it yielded a lower BIC value than the initial general transmission—only model. We did not detect any form of disorder-specific transmission from parents to offspring (Table).

We also examined whether siblings were more similar than would be expected given their general vulnerability to all the externalizing disorders (ie, their similarity on the latent EXT phenotype) by allowing the residual variance of each disorder to correlate across members of the twin pair. The same 1 df tests were conducted for each disorder. Cross-twin specific effects were detected for conduct disorder, alcohol dependence, and drug dependence (Table). This finding indicates that there...
are familial vulnerability factors to these disorders that are independent of the general vulnerability but that are not due to parental externalizing disorders.

The **Figure** displays parameter estimates for the best-fitting model, which entailed general transmission only from parents to offspring (mother and father EXT to child EXT), general transmission across siblings (twin A EXT to twin B EXT), and specific transmission effects across siblings for conduct disorder, alcohol dependence, and drug dependence (ie, the residual variances for each disorder were allowed to correlate across twin A and twin B). Maternal and paternal general transmission effects were estimated as the latent correlation between parent and child EXT. The latent correlations between mother and father EXT and child EXT were $r=0.30$ (95% CI, 0.22-0.38) (Figure).

The resulting latent correlation between parent and child EXT was moderate and represents the general transmission of externalizing disorders from parents to offspring ($r=0.30$; 95% CI, 0.22-0.38) (Figure). The magnitude of the specific cross-twin effects, which represent risk factors for a particular disorder independent of the general vulnerability, did not differ across zyosity (ie, allowing the parameters to differ across zyosity did not improve the fit of the model as indexed by the BIC). Therefore, parameter estimates for the entire sample are presented in the figure. AAB indicates adult antisocial behavior.

The latent externalizing (EXT) variables represent the general vulnerability factors common among the 4 disorders. The circular latent variables associated with each disorder represent the residual variance of that disorder, that is, the variance unaccounted for by the general EXT vulnerability. The residual variance represents vulnerability factors that are specific to the disorder. Twin A refers to the firstborn of the twin pair. Double-headed arrows linking mother and father EXT to twin A and twin B EXT represent the general transmission effect for the 4 disorders and are expressed in a correlation metric. All parent-to-offspring effects were constrained to be equal because model-fitting results indicated that there was not a statistically significant difference in the strength of maternal and paternal transmission, nor did the parental effects differ for members of the twin pair. The double-headed arrow that links twin A and twin B EXT indexes twin similarity for the general vulnerability to the 4 disorders. This effect was significantly greater for monozygotic (MZ) than for dizygotic (DZ) twins, indicating a genetic effect; therefore, it was allowed to differ across zyosity. The double-headed arrows linking the residual variances of conduct disorder (CD), alcohol dependence (ALD), and drug dependence (DD) across members of the twin pair represent disorder-specific vulnerabilities that increase sibling similarity but that are independent of the general EXT vulnerability. These disorder-specific effects did not differ across zyosity; therefore, parameter estimates for the whole sample are presented in the figure. AAB indicates adult antisocial behavior.
rately for male and female twins. The results were consistent with those given in the Table, that is, we did not detect any specific transmission from parents to offspring for either male or female twins. In addition, the genetic transmission effects could be equated for male and female twins without a loss in model fit.

HERITABILITY OF THE GENERAL VULNERABILITY TO EXTERNALIZING DISORDERS

The design of a twin-family study allows 2 ways to estimate the heritability of the general vulnerability to externalizing disorders. Comparing the similarity of MZ and DZ twins yields an estimate of the broad-sense heritability \( h^2 \), which includes additive and nonadditive genetic effects. Because nonadditive effects involve the interaction of genetic effects, MZ twins are necessary to estimate the broad-sense heritability. Examining the similarity of parents and offspring yields an estimate of the narrow-sense heritability \( a^2 \), which includes additive genetic effects only and is the extent to which a trait “breeds true” from one generation to the next.43,44

The latent correlation between mother and father EXT revealed substantial assortative mating (the tendency for like to mate with like) for the general vulnerability to externalizing disorders \( (r=0.51; 95\% \text{ CI}, 0.41-0.61) \). Assortative mating tends to increase the similarity of DZ twins, thereby decreasing the heritability estimate when comparing the similarity of MZ and DZ twins.44 Despite this finding, there was a significant difference in the latent correlation between the twins of MZ and DZ pairs for EXT, as constraining the latent correlation between twin A and twin B EXT across zygosity yielded an increase in the BIC value \( (\Delta \text{BIC}=28.4) \). The latent correlation between twin A and twin B EXT was \( r=0.80 \) (95% CI, 0.72-0.88) for MZ twins and \( r=0.31 \) (95% CI, 0.08-0.53) for DZ twins. Because the MZ correlation was greater than twice that of the DZ correlation, an \( h^2 \) of 0.80 provides a reasonable estimate of the broad-sense heritability for the general vulnerability to externalizing disorders.43,44 In addition, because the MZ correlation is more than twice that of the DZ correlation, there is no evidence of shared environmental effects on the general vulnerability to externalizing disorders, including cultural or environmental transmission from parents to offspring. In the absence of shared environmental effects, the heritability can also be estimated by doubling the parent-child effects, as children receive 50% of their genetic material from each parent.43,44 Using the equated parent-to-child effect, this approach yielded a narrow-sense heritability estimate of \( a^2 = (2 \times 0.30) = 0.60 \) for the general vulnerability to externalizing disorders.

Last, to ensure that the latent EXT phenotype was measuring the same construct for mothers, fathers, and adolescent twins, we tested a model that equated the factor loadings across the different family members. This model yielded a lower BIC value while maintaining a good overall fit to data \( (\chi^2_{261}=386.12; \text{ BIC}=1256.9; \text{ RMSEA}=0.042) \), indicating that the latent EXT phenotype measures an equivalent construct across family members; that is, the general vulnerability to the 4 externalizing disorders has the same meaning for mothers, fathers, and their offspring. Equating the factor loadings did not change any results regarding the generality and specificity of transmission or the parent-child associations and heritability estimates for the general vulnerability to externalizing disorders.

This investigation sought to answer basic questions regarding the familial resemblance of 4 externalizing disorders: conduct disorder, adult antisocial behavior, alcohol dependence, and drug dependence. Specifically, we sought to determine the extent to which familial resemblance for externalizing disorders could be attributed to general transmission, that is, risk factors common to all the disorders, and the extent to which family resemblance was due to risk factors that were specific to each disorder, that is, factors that increased risk for only 1 disorder.

Regarding parents and offspring, our results suggest that general transmission and not disorder-specific transmission can account for familial resemblance. This result was obtained despite an analytic strategy that maximized the likelihood of detecting specific effects (a 1 df test for each maternal and paternal disorder) after controlling for the general transmission effect. These results indicate that rather than increased risk of a particular disorder, what parents pass on to the next generation is a vulnerability to a spectrum of disorders, with each disorder representing a different expression of this general vulnerability.

The general vulnerability to externalizing disorders was estimated to be highly heritable (broad-sense \( h^2=0.80 \)), which is consistent with findings from twin studies16,25 that have explicitly modeled the genetic and environmental components of variance of this general vulnerability. The slightly lower estimate for the narrow-sense heritability \( (a^2=0.60) \) suggests the contribution of certain nonadditive genetic factors and underscores the importance of including MZ twins when attempting to detect genetic effects.13 The heritability of the general vulnerability is greater than that reported for individual disorders in the spectrum \( (h^2=0.35-0.60) \),17-21,46-48 which suggests that the common variance among externalizing disorders may be the most appropriate target for molecular genetic research.

Our results, however, are not incompatible with disorder-specific risk factors, and, in fact, such effects were detected for conduct disorder, alcohol dependence, and drug dependence but for sibling rather than parental resemblance. The fact that these specific effects were detected for horizontal (ie, sibling-to-sibling) but not vertical (ie, parent-to-child) transmission suggests that this distinction may be important when examining familial resemblance among first-degree relatives, as it may reconcile evidence for the generality and specificity of familial transmission. Also, these disorder-specific effects did not differ in magnitude for MZ and DZ twins, suggesting that they are due more to environmental than genetic factors and that they are present after accounting for the presence of parental externalizing disorders. This
suggests that there are environmental factors (eg, peers, neighborhoods, and sibling cooperation) that act independently of parental externalizing disorders and increase the risk of and sibling resemblance for conduct disorder, alcohol dependence, and drug dependence in adolescence.

Although we detected substantial assortative mating for the general externalizing vulnerability, this did not seem to affect the heritability estimates. Assortative mating tends to increase similarity between DZ twins, thereby decreasing the heritability estimate. However, because the heritability estimate cannot exceed the correlation between MZ twins reared together, assortative mating will not decrease the heritability estimate if, as in the present case, the DZ twin correlation remains less than half the MZ correlation.

Finally, there was no evidence to suggest that the family transmission of externalizing disorders differed for men and women. This is also consistent with twin and adoption studies that do not detect sex differences in the genetic architecture and structural relations among externalizing disorders, despite mean level differences in externalizing symptoms.

The present work should be interpreted in the context of its strengths and limitations. First, we did not explicitly model and estimate components of genetic and environmental variance. Although multivariate twin-family models exist, their analytic complexity and requisite sample sizes make such models prohibitive, and, as yet, only bivariate models have been reported in the literature. The additional requirements of modeling the general vulnerability as a latent phenotype while also estimating the genetic and environmental components of variance for the general and specific transmission effects would be problematic in terms of model identification and power to detect effects; such an approach is also unlikely to yield results of any substantive difference from the current model.

Regarding its strengths, this study is one of few that entailed the in-person assessment of both biological parents and a twin pair for multiple disorders. Also, because families were recruited from the community rather than through a clinically referred proband, the results are likely to generalize to the population. However, future investigations will be needed to determine whether these results also generalize to other racial and ethnic groups. In addition, as with any cross-sectional study, the results are limited to a particular developmental period, in this case late adolescence. Future investigations are needed to determine whether the same relations hold at both earlier (childhood and middle adolescence) and later ( adulthood) developmental epochs.

In conclusion, results of the present investigation indicate that most familial resemblance for externalizing disorders is due to a highly heritable general vulnerability. The mechanism, then, for most genetic factors that contribute to externalizing disorders is most likely through a broad behavioral system or psychopathologic process characterized by behavioral undercontrol that underlies all the disorders in the externalizing spectrum. Because this general vulnerability contributes to the risk of a host of disorders, a greater understanding of this broad behavioral system (its genetic architecture, developmental course, and affective and cognitive mechanisms) is most likely to have the greatest impact on public health and the remediation of the deleterious effects of externalizing disorders.

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REFERENCES


