

Genetic and Environmental Influences on Behavioral Disinhibition

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Comorbidity among childhood disruptive behavioral disorders is commonly reported in both epidemiologic and clinical studies. These problems are also associated with early substance use and other markers of behavioral disinhibition. Previous twin research has suggested that much of the covariation between antisocial behavior and alcohol dependence is due to common genetic influences. Similar results have been reported for conduct problems and hyperactivity. For the present study, an adolescent sample consisting of 172 MZ and 162 DZ twin pairs, recruited through the Colorado Twin Registry and the Colorado Longitudinal Twin Study were assessed using standardized psychiatric interviews and personality assessments. DSM-IV symptom counts for conduct disorder and attention deficit hyperactivity disorder, along with a measure of substance experimentation and novelty seeking, were used as indices of a latent *behavioral disinhibition* trait. A confirmatory factor model fit to individual-level data showed a strong common factor accounting for 16–42% of the observed variance in each measure. A common pathway model evaluating the genetic and environmental architecture of the latent phenotype suggested that behavioral disinhibition is highly heritable ($a^2 = 0.84$), and is not influenced sig-

nificantly by shared environmental factors. A residual correlation between conduct disorder and substance experimentation was explained by shared environmental effects, and a residual correlation between attention deficit hyperactivity disorder and novelty seeking was accounted for by genetic dominance. These results suggest that a variety of adolescent problem behaviors may share a common underlying genetic risk. *Am. J. Med. Genet. (Neuropsychiatr. Genet.)* 96:684–695, 2000. © 2000 Wiley-Liss, Inc.

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INTRODUCTION

Conduct disorder (CD) and attention deficit hyperactivity disorder (ADHD) are among the most common clinical syndromes manifested in childhood and adolescence and are frequently comorbid [Biederman et al., 1991; Caspi and Moffitt, 1995; Crowley and Riggs, 1995; Farrington and Van Kammen, 1990; Hinshaw, 1987]. It has been estimated that among delinquent youth, 30–50% also have been diagnosed with ADHD [Szatmari et al., 1989]. Similarly, among children referred for ADHD treatment at least half also show signs of a burgeoning antisocial career [Biederman et al., 1987; McConaughy and Achenbach, 1994]. Moreover, youth with *both* CD and ADHD exhibit more severe [Forehand et al., 1991; McArdle et al., 1995; Walker et al., 1987] and persistent behavioral problems [Caspi and Moffitt, 1995] than those with CD or ADHD alone. Whether or not the symptom patterns, psychosocial correlates, or developmental consequences of ADHD and CD constitute manifestations of a single disorder or two separable disorders has been widely debated. There is accumulating evidence from factor analytic studies [Fergusson et al., 1993; Hinshaw, 1987] that these are highly correlated, yet dis-

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tinct dimensions of childhood externalizing behavior. Findings suggest that CD and ADHD can be distinguished by parental psychopathology [Faraone et al., 1991], cognitive/learning deficits [Fergusson et al., 1993], and response to stimulant medications [Barkley et al., 1989].

Children with CD are at an increased risk for early substance experimentation, and the subsequent development of substance use disorders [Loeber, 1988; Robins and McEvoy, 1990; Van Kammen et al., 1990; Young et al., 1995]. Not only have hyperactivity [Weiss et al., 1985] and attentional difficulties [Pogge et al., 1992] been linked to alcohol and other substance use disorders, but Wilens et al. [1998] report that ADHD is associated with a longer duration of substance use problems and a significantly slower rate of remission. When CD and ADHD co-occur, the risk is compounded [Thompson et al., 1996].

This clustering of behavior problems has also been associated with personality dimensions, such as high levels of novelty seeking (NS). According to Cloninger's Tridimensional Personality Theory, NS is a heritable tendency to exhibit exploratory activity in pursuit of rewards and avoidance of monotony [Cloninger, 1987a]. Evidence suggests that a high level of NS is associated with early-onset drinking and alcohol problems [Cloninger et al., 1988; Kendler et al., 1998], increased relapse [Meszaros et al., 1999], and treatment dropout [Kravitz et al., 1999]. NS has also been linked to delinquency and antisocial personality [Hesselbrock and Hesselbrock, 1992; Ruchkin et al., 1998], and can discriminate between antisocial and nonantisocial alcoholics [Howard et al., 1997]. Increasing evidence suggests that children with hyperactivity or a diagnosis of ADHD also show elevated levels of NS [Downey et al., 1997; Johnson et al., 1997].

Genetics, Environment, and Comorbidity

Not only have the clinical and developmental characteristics of these behavioral patterns been well described, but there have been a number of studies examining their biological and social etiology. For more than 30 years data have been published suggesting that heritable factors play a role in the genesis of antisocial behavior. Results from three adoption samples studied in Denmark [Mednick et al., 1984], Sweden [Bohman et al., 1982], and the United States [Cadoret, 1987, 1995] provided early support for the influence of genetic factors underlying criminality. Estimates of the relative importance of genetic and environmental factors have varied, depending on definition of the phenotype, sample selection, and whether prospective or retrospective reports are considered [Dilalla and Gottesman, 1989; Lyons et al., 1995; Rutter et al., 1990], and a majority of the data have come from studies of adult criminality. Recently, large community-based twin studies of adolescent CD have reported that between 37–68% of the variance in adolescent CD is due to genetic factors [Eaves et al., 1997; Slutske et al., 1997], and that there is little contribution from shared environmental influences. Twin studies of ADHD symptoms tell much the same story. Parent- and

teacher-reported hyperactivity and inattentiveness have also shown substantial heritabilities, ranging from 0.32 to 0.80 [Eaves et al., 1997; Gjone et al., 1996; Sherman et al., 1997; Stevenson, 1992; Thapar et al., 1995], with nonsignificant effects of the shared environment.

There is now considerable support for genetic influences underlying risk for smoking and nicotine dependence [Carmelli et al., 1992; Madden et al., 1997; Maes et al., 1999; True et al., 1999], as well as alcohol use [Heath et al., 1991; Jardine and Martin, 1984; Prescott et al., 1994a], abuse and dependence [Cadoret et al., 1995; Heath et al., 1997; Kendler et al., 1992; McGue et al., 1992; Pickens et al., 1991; Prescott et al., 1994b]. Twin studies of illicit substance use disorders are more sparse, but similar conclusions about the pathways to abuse and dependence are drawn [Tsuang et al., 1998]. Although a majority of this research focuses on adult substance use disorders, reports on adolescent twins suggest that both genetic and shared environmental influences are important in the onset of experimentation as well as the quantity and frequency of consumption [Koopmans and Boomsma, 1996], and that the importance of genetic factors increases with the severity of substance use [Maes et al., 1999].

Extensive data from twin and adoption studies also confirm the importance of genetic factors in explaining individual differences in personality [Bouchard, 1994; Eaves et al., 1989; Loehlin, 1992; Pedersen et al., 1988]. Generally, the findings demonstrate that there are substantial genetic influences on almost all personality traits, accounting for between 40% and 60% of the phenotypic trait variance; the influence of shared environmental influences are minimal. Twin studies of NS have estimated the broad sense heritability of NS between 0.30 and 0.40 [Heath et al., 1994; Stallings et al., 1996], suggesting that genetic factors explain a substantial proportion of the variance in this personality dimension. Consistent with other personality traits, both of these studies found no evidence for shared environmental influences underlying twin resemblance. Heath et al. [1994] report substantial non-additive genetic effects for NS in their Australian adult sample, while an additive genetic model was sufficient to explain twin resemblance in an older adult American sample studied by Stallings et al. [1996].

Importantly, the *co-occurrence* of these psychiatric syndromes and personality characteristics also show familial aggregation [Biederman et al., 1987; Faraone et al. 1991; Stallings et al., 1997; Young et al., 1997]. Recent evidence suggests that this familial comorbidity may be best explained by genes with pleiotropic effects. Slutske et al. [1998] studied adult twins who retrospectively reported on juvenile CD and lifetime alcohol dependence. Genetic factors accounted for most of the correlation between CD and alcohol dependence liability, indicating that common genetic risk factors may underlie these disorders or that CD may be an important, genetically influenced risk factor for alcohol dependence. Reports on a large Australian twin sample suggests that the genetic risk for alcoholism may be mediated, in part, though NS [Heath et al., 1994]. Likewise, results from the Virginia Twin Study of Ado-

lescent Behavioral Development [VTSABD; Silberg et al., 1996] suggest that the covariation between hyperactivity and CD is largely attributable to genetic factors, particularly at preadolescent ages.

The Present Study

The aims of the present study are to extend the findings described above by addressing the following questions. First, do individual differences in CD, ADHD, substance experimentation and NS overlap to the extent that they can be represented as a latent factor? In other words, is the variance shared among these measures substantial enough for them to be treated as indices of a common phenotype, which can then be studied from an etiological point of view? We label this latent factor *behavioral disinhibition* (BD), suggesting that the shared vulnerability underlying these traits could be characterized as an inability to resist expressing inappropriate or restricted behavior. Second, do each of these individual characteristics contribute to this factor to the same extent? Finally, what proportion of the variance in behavioral disinhibition is due to genetic and environmental factors? That is, is the comorbidity among these behavioral patterns driven by biological risk, environmental risk, or both?

MATERIALS AND METHODS

Twin Sample

We report on 668 adolescents from 334 pairs of twins participating in the Colorado Drug Research Center, an ongoing, multicomponent, collaborative study under way at the Institute for Behavioral Genetics (IBG) and the Addiction Research and Treatment Services, operating on two campuses of the University of Colorado. The goals of the center include the identification of chromosomal regions which may be linked to antisocial substance dependence and the development of treatment modalities appropriate and effective with these persistent behavioral problems. The aims of the twin-family component (P.I.: Hewitt) are to identify early indicators of risk for early substance use problems and antisocial behavior, in part by developing maximally heritable phenotypes associated with liability for these disorders.

Twins were recruited from two sources: the Colorado Longitudinal Twin Sample (LTS) and the Colorado Twin Registry (CTR), both community-based samples of adolescents residing in Colorado. The LTS twin sample consists of same-sex twins whose emotional, cognitive, and behavioral development has been studied since birth. These twins were originally recruited through the Colorado Department of Health's Division of Vital Statistics [for a detailed description of recruitment procedures and family demographics, see Plomin et al., 1990]. LTS twins currently at or beyond their 12th birthday are eligible for participation in the Drug Research Center (DRC) study. To date, 104 of the 400 twin pairs in the target LTS sample have aged into the study and completed the assessments. Adolescent twins in the CTR sample are identified both through the Department of Health and through 170 of the 176 school districts in Colorado. The CTR twins ranged in

age from 12–18 years at time of contact, and include MZ, DZ same-sex, and DZ opposite-sex pairs. Informed parental consent and subject assent (for twins under age 18) were obtained and twins were paid \$30 for participation.

Zygoty Determination

Zygoty for same-sex pairs was determined by two methods. During interview sessions, interviewers rated each twin pair on a nine-item assessment of physical characteristics [Nichols and Bilbro, 1966]; ratings were used to make a judgment of zygoty. A second zygoty rating is based on genotyping each individual at a minimum of 11 highly informative short tandem repeat polymorphisms (STRPs) using standard polymerase chain reaction (PCR) methods and ABI 377 genotyping technology. Marker discordance for members of a twin pair indicates their dizygotic (DZ) origin, while marker concordance across all genotyped markers indicates their monozygotic (MZ) origin. The average heterozygosity of the markers exceeds 0.75, and gives a posterior probability of MZ misdiagnosis of less than 0.0001. DNA is extracted from epithelial cells collected by noninvasive cheek swabbing [Meulenbelt et al., 1995]. DNA extraction, storage, and genotyping was carried out by the Molecular Core of the Center for CRT twins and by IBG faculty for the LTS sample. Only twins whose tester ratings and genotypic data agree on zygoty determination were used in the current analyses. Any discrepant cases were reevaluated and, if necessary, resampled.

Psychiatric Assessment

Twins were administered the Diagnostic Interview Schedule for Children – IV [DISC-IV; Shaffer et al., 1997], a structured psychiatric interview which assesses DSM-IV [APA, 1994] symptoms and diagnoses for Axis I disorders. Computer algorithms, based on the instructions provided by the instrument's authors, were used to determine the presence or absence of each symptom/behavioral pattern. Lifetime symptom counts were derived by a simple sum of the criteria met.

Data on substance experimentation were obtained using the Composite International Diagnostic Interview-Substance Abuse Module [CIDI-SAM; Cottler et al., 1989]. The CIDI-SAM assesses quantity, frequency, and onset of use, as well as symptoms of substance abuse and dependence according to DSM-IV criteria. For the purposes of this study, substance experimentation (SUB) was defined as the number of substances, including nicotine, alcohol, and 13 classes of illicit substances used on more than five occasions. Thus, SUB represents *breadth* of experimentation, rather than severity or duration of use.

Personality Assessment

Each twin also completed a series of questionnaires requiring approximately 30 min. To assess personality characteristics, we used the Tridimensional Personality Questionnaire [TPQ; Cloninger, 1987b] for twins who were at least 16 years old. For twins age 15 years or younger, the Junior Temperament and Character Inventory [J-TCI; Cloninger et al., 1994] was used. Be-

cause an occasional item is left blank (or both “true” and “false” answers are circled), the mean of the items endorsed is computed for each scale, rather than the sum of endorsements. If more than half of the items are left blank, the scale score is coded as missing. For the current analyses, only the NS scale was utilized. NS can be characterized as high levels of exploratory behavior, enjoyment of novel experiences, and seeking immediate rewards. Two example items for the NS scale are “I often try new things just for fun or thrills, even if most people think it is a waste of time” and (reversed) “I hate to make decisions based only on my first impressions” [TPQ; Cloninger, 1987b].

Statistical Methods and Models

Phenotypic “comorbidity” factor model. A confirmatory common factor model was used to examine the phenotypic overlap in CD, ADHD, SUB, and NS. In this model, the variance in each measure was partitioned into that which is shared among measures (represented as a single common factor), and residual variance that is measure-specific. Thus, factor loadings on each measure, when squared, represent the proportion of variance in the measure accounted for by the common factor. If the measures were uncorrelated, we would expect zero loadings on the common factor portion of the model, and significant factor loadings on the measure-specific portion of the model. Alternatively, if the measures were highly intercorrelated (i.e., approaching $r = 1.0$), we would expect substantial factor loadings from the ‘common’ factor, and trivial or zero loadings from the measure-specific factors. If the estimated factor loadings on the common factor are significant, the data support a hypothesis that there is a latent factor, which may in this case represent an underlying vulnerability or risk identified by CD, ADHD, SUB, and NS.

Univariate twin model. Figure 1 shows the classic twin path model for a univariate analysis. In this case, squares represent observed behavioral phenotypes for a pair of twins. The circles represent unmeasured latent influences on the observed measures; the A’s represent latent additive genetic effects, C’s represent latent shared environmental effects (i.e., environmental influences which by definition make twins more similar), D’s represent genetic dominance effects, and

E’s represent latent unique (individual) environmental effects and measurement error. Double-headed arrows represent the correlations between the latent factors. MZ twins are genetically identical; thus, correlations are fixed at unity for both their additive (A) and genetic dominance (D) effects. On average, DZ twins share half of their additive genetic effects, and 25% of their genetic dominance effects, so correlations among these sources are fixed at 0.50 and 0.25, respectively. The correlation between the shared environmental effects is fixed at 1.0 for both MZ and DZ twins, implying equal shared environmental effects for the different twin types. Other implicit assumptions of the model are that additive genetic and shared environmental effects are uncorrelated and random mating is operating in the parent generation (not shown).

The effects of shared environment (C) and genetic dominance effects (D) are confounded in studies of twins raised together [Neale and Cardon, 1992], and cannot be estimated simultaneously. Thus, in any given analysis the influence of one of these sources of variation must be assumed to be absent (i.e., fixed to zero). The model was chosen based on the plausibility of the source’s influence and the pattern of observed twin correlations.

Independent pathway model. The independent pathway model shown in Figure 2 posits that a single genetic factor, A, a single shared environmental factor, C (or genetic dominance factor, D), and a single non-shared environmental factor, E, together explain the covariation among the four measures. For simplicity, only Twin 1 is depicted, but the same correlations among the latent factors between twins, as shown in Figure 1, are implied. The model decomposes both the variance of each measure and covariance among measures into their genetic and environmental sources.

Common pathway model. The common pathway model, shown in Figure 3, is a restricted submodel of the independent pathway model, in that the covariance

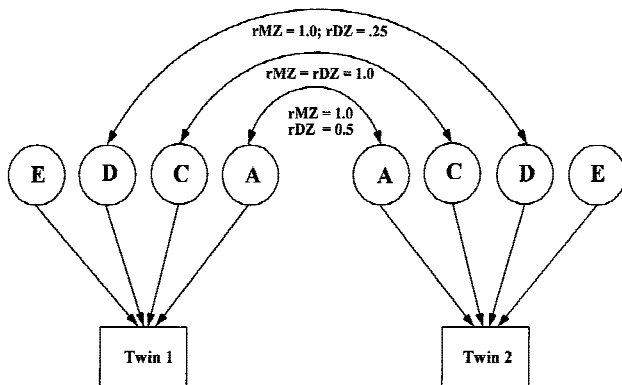


Fig. 1. Univariate twin path model.

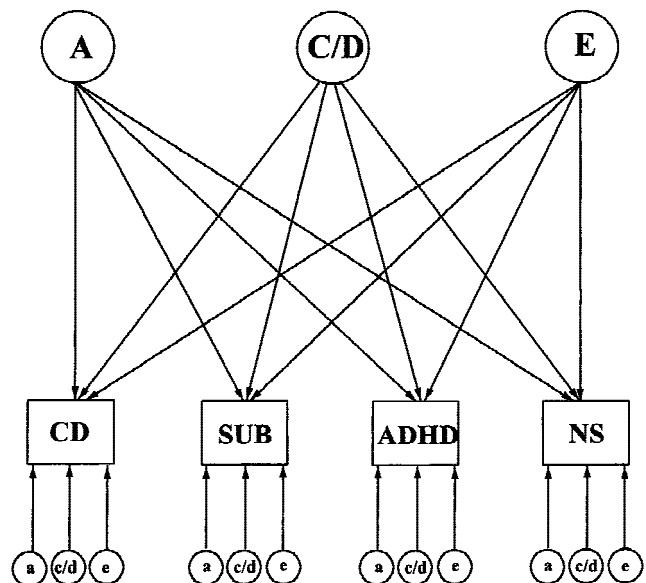


Fig. 2. Independent pathway model; Twin 1 only depicted.

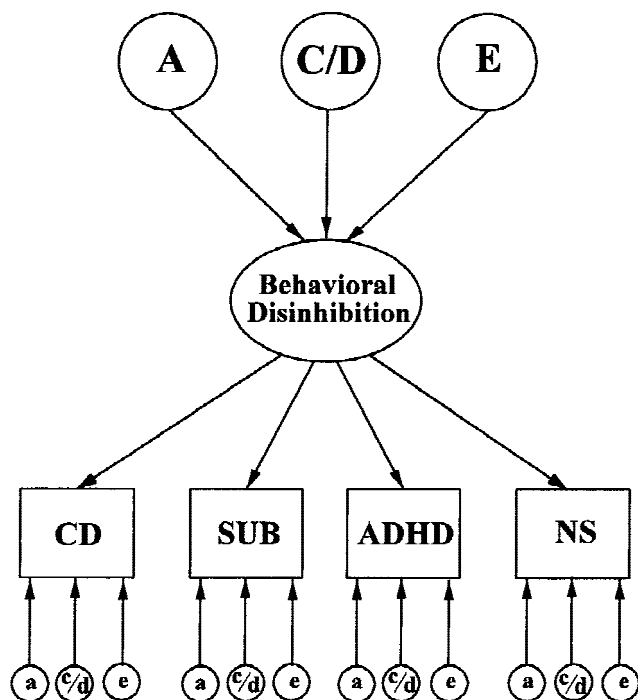


Fig. 3. Common pathway model; Twin 1 only depicted.

among the measures is represented as a latent phenotype (*BD*). The latent phenotype is partitioned into genetic and environmental factors, represented in the model as *A*, *C/D*, and *E*. Likewise, residual variance, that which is unique to each measure, is also partitioned into genetic and environmental components, shown as *a*, *c/d*, and *e*, as it was in the previous model. As in the phenotypic model, factor loadings on each measure will be estimated in order to evaluate the contribution of each measure to the latent phenotype.

Maximum likelihood estimation procedures operationalized in Mx, software designed for structural equation modeling of genetically informative data [Neale, 1999], provide estimates for each parameter specified in the model. Chi-square (χ^2) goodness-of-fit statistics were used to assess how well the models fit the data. A smaller χ^2 value and corresponding higher *P* value indicate better correspondence between the model and the observed variances and covariances. To evaluate the relative fit of nonnested independent and common pathway models, we used Akaike's Information Criterion [AIC; Akaike, 1987], an index of goodness-of-fit for which a larger negative value indicates greater parsimony of the model. Significance tests of the individual path coefficients are carried out by constraining paths to zero and applying a χ^2 difference test, or by estimating the 95% confidence intervals on individual parameters.

RESULTS Descriptive Statistics

Table I presents the means and standard deviations of the endorsement rates for CD, SUB, ADHD, and NS separately for males and females in the eight age groups after the raw scores were rescaled to have means of 50 and standard deviations of 10. This transformation was carried out to increase interpretability across measures, and was not used in subsequent analyses. As shown, there were higher endorsement rates at older ages for the psychiatric symptom counts as well as for NS. Significant correlations with age ranged from 0.16 for ADHD in females to 0.51 for substance experimentation in females. Males reported significantly higher scores than females for each of the four variables when age groups were collapsed. In addition to age and sex effects, an age-x-sex interaction

TABLE I. Rescaled* Mean Scores (SD) by Age and Gender

	<i>N</i> =	12 yrs 218	13 yrs 88	14 yrs 66	15 yrs 80	16 yrs 54	17 yrs 80	18 yrs 82	<i>r</i> _{age}
CD	Males	47.45 (6.97)	52.03 (12.18)	49.92 (8.02)	54.60 (15.13)	54.97 (11.43)	58.04 (13.29)	58.50 (16.55)	0.33 ^a
	Females	45.08 (3.74)	47.26 (5.81)	47.16 (6.04)	47.82 (5.56)	50.38 (8.91)	51.88 (10.39)	50.33 (7.48)	0.34 ^a
SUB	Males	45.99 (3.88)	47.44 (5.68)	47.03 (6.64)	51.43 (9.09)	53.42 (8.62)	54.92 (12.36)	59.62 (17.62)	0.45 ^a
	Females	45.15 (1.20)	46.70 (4.14)	46.52 (3.49)	50.51 (8.72)	52.15 (10.73)	55.94 (13.51)	59.32 (14.79)	0.51 ^a
ADHD	Males	50.68 (11.51)	50.46 (10.05)	47.40 (5.93)	51.95 (11.43)	52.65 (13.49)	51.33 (12.84)	52.48 (11.53)	0.06
	Females	47.67 (5.69)	48.09 (6.30)	46.68 (5.24)	50.50 (12.09)	53.89 (11.43)	52.01 (12.01)	49.45 (7.31)	0.16 ^a
NS	Males	49.28 (9.64)	50.97 (9.50)	48.50 (8.48)	52.46 (11.41)	56.00 (8.17)	52.08 (9.11)	55.27 (9.92)	0.21 ^a
	Females	44.67 (8.93)	49.34 (8.93)	45.75 (11.60)	50.32 (9.00)	54.81 (11.69)	53.73 (9.71)	50.63 (9.28)	0.29 ^a

*Variables were standardized to a mean of 50 and a standard deviation of 10 for the complete sample.

^a*P* < 0.01.

TABLE II. Twin Correlations*

MZ Twins (n = 172)				
	CD ₁	SUB ₁	ADHD ₁	NS ₁
CD ₂	0.35	0.34	0.24	0.15
SUB ₂	0.31	0.69	0.19	0.18
ADHD ₂	0.32	0.37	0.48	0.20
NS ₂	0.12	0.26	0.18	0.40
DZ Twins (n = 162)				
CD ₂	0.17	0.28	0.06	0.15
SUB ₂	0.42	0.61	0.17	0.13
ADHD ₂	0.15	0.18	0.16	0.16
NS ₂	0.23	0.21	0.02	0.02

*Within-trait twin correlations on the diagonals; cross-trait twin correlations on off-diagonals.

was detected. Thus, each variable was corrected for these effects using standard regression methods and residualized scores were rank normalized [Blom, 1958] to reduce skewness. No significant differences in mean endorsement rates were found for MZ and DZ twins.

Phenotypic Comorbidity Model Results

The common factor model of comorbidity was fit to 8 × 8 covariance matrices for MZ and DZ twins. Within-person correlations were equated for MZ and DZ twins as well as for Twin 1 and Twin 2 to test for violations of the assumptions of comparable phenotypic associations. Cross-twin correlations were allowed to vary between zygoty groups for the phenotypic analysis. The proportion of phenotypic variance in each measure explained by the “comorbidity” factor was 16% for NS, 27% for ADHD, 36% for SUB, and 42% for CD. The model fit the data well ($\chi^2_{32} = 24.08, P = 0.84$). Factor loadings could not be equated for the four measures without a significant decrement in model fit ($\Delta \chi^2_3 = 13.50, P < 0.01$). These results provide initial support for viewing the covariation among these measures as a latent phenotype, although the behaviors assessed by these measures are influenced to different degrees by this underlying phenotype.

Twin Correlations

The within-pair correlations for CD, SUB, ADHD, and NS in the MZ and DZ groups are presented in Table II. The within-trait correlations are shown on the main diagonal of the upper and lower portions of the table. The MZ correlations ranged from 0.35 to 0.69 for CD and SUB, respectively. The DZ correlations were

consistently lower, ranging from 0.02 to 0.61 for NS and SUB, respectively. For CD, the MZ correlation was approximately twice the DZ correlation, suggesting that twin resemblance was due primarily to additive genetic effects. A similar pattern of correlations was found for ADHD. For NS, the DZ correlation was substantially less than half the MZ correlation, suggesting there may be genetic nonadditivity or sibling interaction operating. In contrast, SUB showed relatively high correlations for both MZ and DZ pairs, indicative of both genetic and shared environmental influences underlying substance experimentation. Within-pair cross-trait correlations, which provide information regarding the etiology of the covariation among the measures, are shown above and below the main diagonals. With few exceptions, the greater MZ correlations suggest that genetic influences underlie comorbidity.

Univariate Genetic Model Results

Univariate twin models (Fig. 1) were fit to 2 × 2 covariance matrices for each measure separately. Table III summarizes the full and best-fitting models, the variance components due to genetic (a², d²) and environmental (c², e²) influences, and the corresponding statistics evaluating goodness of fit. Standard χ^2 difference tests were applied in order to compare the fit of nested models.

An ADE model of CD provided a good fit to the data. However, the contribution of genetic dominance was estimated at zero. Thus, a simplified model which allowed for only additive genetic and nonshared environmental influences did not result in a poorer fit to the data (ADE vs. AE: $\Delta\chi^2_1 = 0.00, P > 0.99$). The AE model estimated that 34% of the variance in CD could be attributed to additive genetic influences and 66% due to nonshared environmental influences. The etiological structure of SUB appeared to be somewhat different. While the full ACE model fit the data well, the influences of additive genetic factors were nonsignificant by χ^2 change (ACE vs. CE: $\Delta\chi^2_1 = .50, P = .48$). The reduced CE model suggested that 68% of the variation was due to shared environmental factors and 32% due to nonshared environment.

A full ADE model was also tested for ADHD, and fit the data well. When the effects of nonadditive genetic factors (D) were constrained to zero, no significant change in χ^2 resulted (ADE vs. AE: $\Delta\chi^2_1 = 0.88, P > 0.25$). Based on this more parsimonious model (AE), 49% of the variance in ADHD could be attributed to additive genetic effects, and the remaining 51% was

TABLE III. Full and Best-Fitting Univariate Models

		a ²	c ²	d ²	e ²	χ^2	df	p	AIC
CD	(ADE)	0.35	—	0.00	0.65	4.45	4	0.35	-3.55
	(AE)	0.34	—	—	0.66	4.45	5	0.49	-5.55
SUB	(ACE)	0.07	0.62	—	0.31	3.51	4	0.48	-4.49
	(CE)	—	0.68	—	0.32	4.01	5	0.55	-5.99
ADHD	(ADE)	0.19	—	0.32	0.49	3.14	4	0.55	-4.86
	(AE)	0.49	—	—	0.51	4.02	5	0.55	-5.98
NS	(ADE)	0.00	—	0.42	0.58	2.95	4	0.57	-5.05
	(AE)	0.37	—	—	0.63	7.42	5	0.19	-2.58

TABLE IV. Model Series Results

	Compare	χ^2	df	<i>P</i>	AIC ^a	$\Delta\chi^2_{(df)}$	df	<i>P</i>
1. Independent Pathway		68.64	48	0.03	-27.37			
2. Drop C/D Specifics	2 vs. 1	68.67	52	0.06	-35.33	0.03	4	>0.99
3. Drop A Specifics	3 vs. 2	72.68	56	0.07	-39.32	4.01	4	>0.25
4. Drop C Common	4 vs. 3	118.38	58	<0.01	2.38	45.70	2	<0.01
5. Drop D Common	5 vs. 3	93.34	58	<0.01	-22.66	20.66	2	<0.01
6. Drop A Common	6 vs. 3	146.77	60	<0.01	26.77	74.09	4	<0.01
7. Drop E Common	7 vs. 3	81.55	60	0.03	-38.45	8.87	4	>0.05
8. Common Pathway	8 vs. 3	74.19	59	0.09	-43.81	1.51	3	>0.50

due to nonshared environmental effects. Finally, an ADE model was fit to the NS data, yielding an adequate fit. Additive genetic effects were estimated at 0.00; however, nonadditive genetic effects operating in the absence of additive genetic effects is not highly plausible for polygenic traits [Eaves, 1988]. Thus, the AE model, although technically providing a poorer fit than the full ADE model, does provide an acceptable fit to the data ($\chi^2_{55} = 7.42, P = 0.19, AIC = -2.58$). Under the AE model, the broadsense heritability was estimated at 0.37.

Independent Pathway Model Results

An independent pathway model (Fig. 2) was fit to 8 × 8 covariance matrices (four measures for Twin 1, four measures for Twin 2). The full model decomposed the covariation among the measures into a common additive genetic factor, *A*, a common nonshared environmental factor, *E*, a shared environmental factor, *C*, which loaded only on CD and SUB, and a nonadditive (dominance) factor, *D*, which loaded only on ADHD and NS. Measure-specific effects of *A*, *C*_(CD,SUB), *D*_(ADHD,NS), and *E* were also estimated. Table IV summarizes the results for the full model and a series of nested sub-models.

The full model (1) did not provide an adequate fit to the data. Comparisons with Models 2 and 3 reveal non-significant effects of the measure-specific genetic (both additive and nonadditive) and shared environmental influences. Model 3, dropping all specifics for *a*, *c*, and *d* provided an acceptable fit to the data. All of the additive genetic variance and covariance could be explained by a single common factor. Nonadditive genetic influences were common to ADHD and NS only, and shared environmental influences were common to CD and SUB only. Models 4 through 6 suggest that the *A*, *C*, and *D* common factors could not be eliminated from the model without a significant decrement in fit. Although Model 7 showed that nonshared environmental factors common to the measures were nonsignificant, the model had an overall poor fit to the data ($\chi^2_{60} = 81.55, P = 0.03, AIC = -38.45$). Thus, the best fitting independent pathway model (Model 3: $\chi^2_{56} = 72.68, P = 0.07, AIC = -39.32$), included a common *A* factor with heritabilities ranging from 14% to 36% for the individual measures. The shared environmental factor explained 7% of the variance in CD and 45% of the variance in SUB, and the dominance factor common only to ADHD and NS, accounted for 5% and 20% of the variances, respectively.

Common Pathway Model Results

The structure of the common pathway model (Fig. 4) was derived from the pattern of results described above. Variance in the latent phenotype (BD) was partitioned into additive genetic influences (*A*) and non-shared environmental influences (*E*). Residual variance was decomposed into shared environmental influences (*c*) loading only on CD and SUB (and allowed to correlate); genetic dominance (*d*) loading on ADHD and NS only (and allowed to correlate); and non-shared environmental influences (*e*) specific to each of the four measures. The overall fit of the model was acceptable ($\chi^2_{59} = 74.19, P = 0.09, AIC = -43.81$).

Figure 4 shows the parameter estimates obtained for the common pathway model. Because this is a more parsimonious model than the independent pathway model and shows no significant decrement in fit by χ^2 difference test (see Table IV), this model was accepted

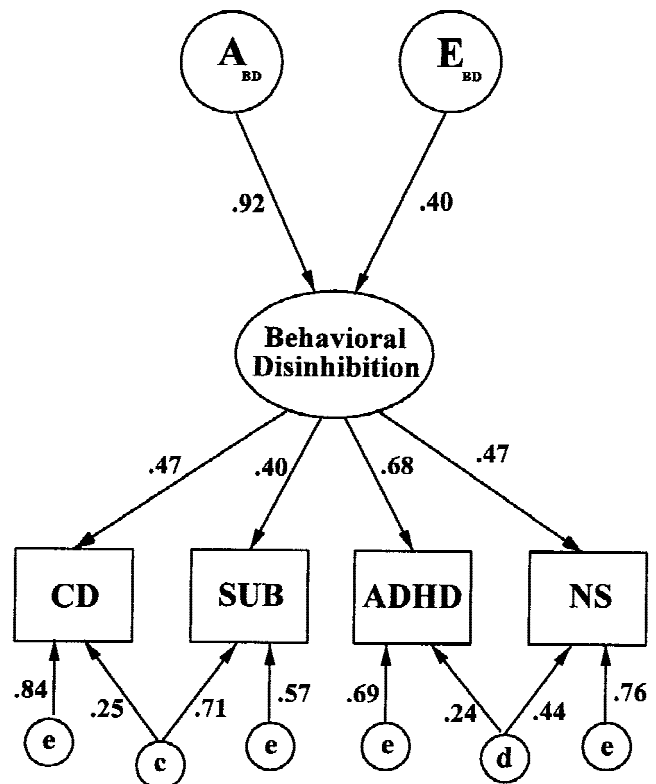


Fig. 4. Common pathway model results.

as the final model. Table V presents the variance components derived from the model. Additive genetic factors explained 84% of the variance in BD, while non-shared environmental factors explained the remaining 16%. Thus, the variance shared among CD, SUB, ADHD, and NS is highly heritable. BD explained 16% to 46% of the phenotypic variance in the individual measures. Note that the common factor loads most highly on ADHD, but also substantially on the other three measures. No significant contribution of shared environmental factors were evident for the latent phenotype. However, the decomposition of measure-specific variance revealed that while the contribution of *c* to the variance in CD was modest (6%), it explains 51% of the variance in SUB. The common *d* factor accounted for 6% and 19% of the variance in ADHD and NS, respectively.

DISCUSSION

The aim of the present study was to evaluate the nature of the overlap or covariation among childhood disruptive behavior (CD, ADHD), early substance experimentation (SUB), and novelty seeking (NS), commonly associated markers of risk, in a community-based sample of male and female adolescent twins participating in the Colorado Drug Research Center studies. Phenotypic correlations suggested there were significant associations between each of the four measures of interest, and a more formal analysis of these associations, utilizing confirmatory factor analysis, suggested that the covariation among these characteristics can be characterized as a latent phenotype. Although this result has not been previously reported, associations between ADHD and CD have been well supported in both clinical and nonclinical populations [Biederman et al., 1991; Caspi and Moffitt, 1995; Hinshaw, 1987]. Similar convincing evidence has connected childhood disruptive behavior with risk for sub-

stance use problems [Loeber, 1988; Robins and McEvoy, 1990; Thompson et al., 1996; Young et al., 1995] and higher levels of NS [Downey et al., 1997; Hesselbrock and Hesselbrock, 1992; Howard et al., 1997; Johnson et al., 1997]. We present results that confirm substantial associations among these characteristics, and suggest that this overlap may represent a single underlying vulnerability.

Our findings are consistent with previous reports of moderate genetic influences on conduct problems and weak evidence of any shared environmental influences [Eaves et al., 1997; Slutske et al., 1997]. However, our measure of the *breadth* of substance experimentation showed much weaker evidence of heritability, and substantial influences of the shared environment, much like findings reported by Maes et al. [1999], who found that adolescent alcohol and marijuana use was largely influenced by environmental factors. Previous research on adolescent substance involvement suggests that these shared environmental factors are not limited to family influences, but may be strongly driven by peer interactions [Rowe and Gulley, 1992]. Interestingly, Maes et al. [1999] found quite different results for adolescent tobacco use and “harder” illicit drug use, which showed substantial heritability.

Because the age range of our sample is from 12 to 18, not all of the twins had completely aged through what we might consider the period of risk, particularly for exposure to substances. While large-scale studies of adolescent substance use [Johnston et al., 1998] suggest that it is relatively common for youth to begin experimentation at early ages, they may not complete the range of experimentation until later in adolescence. Moreover, recent reports suggest that genetic influences on alcohol consumption may increase from early to late adolescence [Dick et al., in press], and that persistent use is more influenced by genetic factors than initiation of substance use [Stallings et al., in press]. Thus, studies of possible genetic overlap between substance use *problems* and associated markers of risk (e.g., ADHD) would be a valuable addition to the current work; however, such studies would require a twin sample of older, more experienced users.

The present study is the first twin analysis to examine factors underlying *self-reported* ADHD symptoms. While it is likely that adolescents are the most valid informants for their own substance use and delinquency (given the covert nature of these behaviors), teens may be less able to recognize and report on their hyperactivity or attentional problems, particularly when they must report retrospectively. Despite possible underreporting that could result in poor estimates of symptom severity, this does not necessarily reduce twin similarity, nor bias our estimates of the sources of variation in ADHD. Despite method differences our data show quite comparable findings to those reported on other large-scale community-based twin studies [Eaves et al., 1997; Sherman et al., 1997] which analyzed parent and/or teacher ratings of ADHD symptoms, and reported substantial heritable influences.

Individual differences in NS in our sample appear to be partially influenced by genetic dominance. This finding is in line with mounting support for nonaddi-

TABLE V. Parameter Estimates From Common Pathway Model

	Estimate	C.I. (95%)
Latent B.D. factor variance components		
a^2	0.84	0.70–0.96
e^2	0.16	0.04–0.30
Squared factor loadings		
λ^2_{CD}	0.22	0.15–0.31
λ^2_{SUB}	0.16	0.09–0.25
λ^2_{ADHD}	0.46	0.34–0.58
λ^2_{NS}	0.22	0.12–0.33
Squared residual common factor loadings		
c^2_{CD}	0.06	0.03–0.12
c^2_{SUB}	0.51	0.43–0.60
d^2_{ADHD}	0.06	0.01–0.18
d^2_{NS}	0.19	0.06–0.34
Measure-specific variance components		
e^2_{CD}	0.71	0.64–0.78
e^2_{SUB}	0.32	0.26–0.39
e^2_{ADHD}	0.48	0.36–0.60
e^2_{NS}	0.58	0.46–0.73

tive genetic effects on personality [Finkel and McGue, 1997; Pedersen et al., 1988] and NS in particular [Heath et al., 1994]. The near zero correlation for DZ twins is intriguing, and may suggest contrast effects as an alternative explanation. However, given the sample size and corresponding standard error of the correlation ($C.I._{.95} = \pm 0.16$), it is well within the expected range of DZ correlations based on previous twin research.

The purpose of the multivariate twin analysis was to investigate the etiological nature of covariation among these characteristics. A common pathway model, which provided the most parsimonious explanation of these data, suggested that the covariation among CD, SUB, ADHD, and NS is largely due to additive genetic factors, with heritability of our latent phenotype estimated at 0.84. This estimate is markedly higher than the heritabilities for the individual measures. Interestingly, there was little evidence of residual additive genetic influences on individual measures. There were no significant shared environmental influences on behavioral disinhibition. Our findings confirm those described by Silberg et al. [1996], who found genetic factors explained much of the phenotypic correlation between parent-rated hyperactivity and CD in the VT-SABD sample. Their bivariate analyses also provided evidence of shared environmental influences specific to CD in their older cohort. Our findings suggest that these shared environmental factors are also involved in adolescent substance use, possibly manifesting as peer influences, neighborhood effects, or poor parental monitoring.

One central goal of the Drug Research Center is the search for regions of the genome which are associated with vulnerability to substance use problems and antisocial behavior. In contrast to studies which use 'pure' disorders as the target phenotypes, the current results suggest that using a composite or factor score which captures shared variance among comorbid behavioral problems may be a useful strategy in the search for genetic factors underlying these problems.

Recent bivariate analyses have supported a genetic link between conduct problems and both alcohol dependence [Slutske et al., 1997] and marijuana use [Grant et al., in press]. We used a broad measure of substance experimentation, which does not discriminate among particular substances. That is, a score of 2 may reflect experimentation with nicotine and alcohol (1 point each), or with cocaine and marijuana (1 point each). This approach was taken because of the relatively few severe substance users in our population-based sample of adolescent twins. However, it may prove useful to examine possible genetic links between specific substances and problem behavior, or to address these relationships using a severity measure of substance use and associated problems in an older, more experienced group of users. As the sample increases, we also plan to address possible sex-specific effects. We know from epidemiological studies that adolescent males have greater prevalence of CD and ADHD, and tend to experiment with substances at somewhat younger ages. We don't know, however, if there are differences in the

etiological structure of these behavioral patterns for adolescent boys and girls.

We labeled the hypothesized vulnerability underlying these characteristics *behavioral disinhibition*. With this label, we imply that one common thread among these characteristics may be the inability to inhibit behavior, despite its social undesirability and cascade of familial, educational, psychological, and possible legal consequences. This theoretical perspective has been examined in the context of the link between components of executive cognitive function (ECF) and these behavioral outcomes. Newman [1987] showed that antisocial adults exhibit an inability to inhibit previously rewarded behavior after contingencies are changed to a punishing consequence, a finding replicated in adolescents [Shapiro et al., 1988]. Performance on neuropsychological tests which are believed to measure frontal lobe function show robust discrimination between delinquents and nondelinquents [Moffitt, 1993]. Barkley et al. [1992] reviewed 22 neuropsychological studies of frontal lobe function in children with attention deficits with and without hyperactivity. These researchers found that the patterns of deficits clustered around problems with sustained concentration on cognitive tasks and poor inhibitory control. Importantly, studies of comorbid CD and ADHD suggest that executive function deficits are more extensive in children with both disorders than in children with either CD or ADHD alone [Moffitt and Silva, 1988; Aronowitz et al., 1994]. The examination of ECF links to substance use problems is more complex. Particularly in adults, it is difficult to discriminate between cognitive *risks* and cognitive *consequences* of persistent use [Tarter and Alterman, 1984]. However, one study reports that adolescent boys who themselves were not abusers, but had a paternal history of alcoholism, performed poorly on neuropsychological tests of frontal lobe function [Harden and Pihl, 1995].

While these findings support the notion that deficits in ECF may underlie comorbidity of CD, ADHD, and substance use problems, there are many alternative lines of research which target biological markers of these disorders. Neurotransmitter systems [Coccaro, 1996; Fishbein et al., 1989], hormone levels [Virkkunen et al., 1994], brain electrophysiology [Cohen et al., 1997], and cardiovascular factors [Raine, 1996] have all been implicated in the risk for one or more of these disorders. Whether or not heritable factors shared among CD, ADHD, SUB, and NS are linked to one of these biological explanations remains an empirical question worthy of further investigation.

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