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Genetic and Environmental Influences on the Covariation Between Hyperactivity and Conduct Disturbance in Juvenile Twins

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Structural equation models were applied to the maternal ratings of 265 MZ and 163 DZ male–male, 347 MZ and 160 DZ female–female, and 262 male–female twin pairs, aged 8–16 years, who participated in the Virginia Twin Study of Adolescent Behavioral Development (VTSABD). Substantial additive genetic influences and contrast effects were found for hyperactivity, and additive genetic and shared environmental effects or positive comparison effects (particularly for the girls) for oppositional/conduct disturbance. Bivariate model fitting showed that the covariation between hyperactivity and oppositional/conduct problems in both younger and older boys and girls is almost entirely attributable to genetic factors. However, whereas in the younger males and females the same set of genes explain all the variation in hyperactivity and conduct disturbance, in the older cohort at least some of the genetic effects are behavior- and gender-specific.

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Introduction

The classification of behaviors into discrete diagnostic classes or categories represents an important goal for understanding the underlying causes of psychiatric problems and for devising effective preventative and ameliorative interventions for many disabling psychological conditions. Numerous epidemiological and clinical studies, however, have demonstrated the high frequency with which supposedly separate child psychiatric disorders co-occur (Biederman, Newcorn, & Sprich, 1991; Caron & Rutter, 1991). For example, the co-occurrence between oppositional/defiant or conduct disorders and hyperkinetic/attention deficit disorders, and the symptoms that comprise these diagnoses (Biederman et al., 1991; Fergusson & Horwood, 1993; Fergusson, Horwood, & Lloyd, 1991; Szatmari, Boyle, & Offord, 1989) is so strong that many commentators have questioned the reality of the distinction between them (see Hinshaw, 1987; Loeber & Keenan, in press for a review). Behavior ratings of the two different forms of

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psychopathology by the same informant typically intercorrelate at about the .5 level and, even using different raters in different settings correlations are usually at the .3 level, which is as great as the between-rater agreement for the same type of psychopathology (Fergusson et al., 1991).

There is also evidence for concluding that there are meaningful differences between oppositional/conduct and hyperkinetic/conduct problems. The distinctiveness of separate diagnostic conditions needs to be determined, not by the degree of overlap between symptoms but rather by the extent to which they differ in their patterns of associations with correlates external to the symptoms that comprise them (Achenbach, 1981; Cantwell & Rutter, 1994; Farone, Biederman, Keenan, & Tsuang, 1991; Rutter, 1978; Szatmari et al., 1989;), such as psychosocial factors (Faraone et al., 1991; Sandberg, Rutter, & Taylor, 1978), responsiveness to treatment (Loney, Langhorne, & Paternite, 1978; Wood, Reimherr, Wender, & Johnson, 1976) and long-term outcome (August, Stewart, & Holmes, 1983; Fergusson & Horwood, 1993; Gittelman, Manuzza, Shenker, & Bonagura, 1985; Loney, Kramer, & Milich, 1981; Paternite & Loney, 1980; Weiss, Hechtman, Milroy, & Perlman, 1985). For example, longitudinal data indicate that the two constructs show a different developmental progression, with early conduct problems serving as a precursor to future offending, and early attentional problems a precursor for poor scholastic performance (Fergusson & Horwood, 1993). Several groups of investigators have shown that hyperkinetic/attentional disorders are more likely than conduct disorders to be associated with cognitive impairment and developmental delay, and more likely to be responsive to stimulant medication (Szatmari et al., 1989; Taylor et al., 1987). There are also differences between the two groups of disorders with respect to psychosocial correlates and later outcome (Farrington, Loeber, & Van Kammen, 1990; Taylor, Chadwick, Heptinstal, & Kankaerts, in press).

The evidence that the two disorders are distinct does not address the reasons for their co-occurrence or overlap at a phenotypic level. The systematic investigation of comorbid patterns, using methods that can test competing hypotheses, can be very informative in excluding (or showing) artifactual association, and in elucidating the possible mechanisms underlying true comorbidity (Caron & Rutter, 1991).This can be addressed using two different strategies, ideally in combination. The first strategy examines the developmental progression of the two types of psychopathology. It has been demonstrated, for example, that early hyperactivity increases the risk for later oppositional/conduct problems, but that the reverse is not true to any marked extent (Taylor, Sandberg, Thorley, & Giles, 1991; Taylor et al., in press). The second approach seeks to uncover the discrete causes of the separate conditions and the possible causal influences on their overlap. This strategy is founded upon the assumption that useful categorizations are ones that point to unique etiological processes (Biederman et al., 1991; Klein & Riso, 1994; Taylor, 1988), and group symptoms based upon shared genetic or environmental factors, rather than the degree to which they may co-occur clinically or phenotypically.

Biederman and colleagues (Biederman et al., 1986; Biederman, Faraone, Keenan, Knee, & Tsuang, 1990; Faraone et al., 1991) have used the latter type of approach on categorical data in their examination of the nature of the association between symptoms of Attention Deficit, Oppositional Defiant and Conduct Disorder, using the models of familial transmission developed by Pauls et al. (1986). The analysis of dimensional twin data can also make important contributions to the understanding of comorbidity by identifying etiologically distinct subtypes of symptoms. This approach allows the partitioning of genetic and environmental variance on hyperactivity and conduct problems separately, and the comorbid pattern of hyperactivity and conduct problems together. Further, by using structural equation models, estimates of these genetic and environmental effects, as well as the genetic and environmental correlation between two behaviors, can be obtained. In the family studies described above, these correlations can be derived only by including all forms of comorbidity (i.e. ADD with Conduct, ADD without Conduct, Conduct without ADD, etc.) which becomes prohibitive unless a very large number of cases are ascertained. In the dimensional approach that is adopted here, all permutations of symptom expression are represented.

In the present analysis, the nature of the association between hyperactivity and antisocial behaviors is further explored by applying structural equation models (cf. Heath, Neale, Hewitt, Eaves, & Fulker, 1989; Neale & Cardon, 1992) to data on both boys and girls from a large epidemiological sample of juvenile twins ascertained through the Virginia Twin Study of Adolescent Behavioral Development (VTSABD). The VTSABD was designed to address questions of comorbidity, one of its most important aspects being the combination of the twin design and the collection of longitudinal data. It also has the advantage of using a sample and a set of measures that allows the contrasting of categorical and dimensional approaches (Eaves et al., 1993a, 1993b). The adequate examination of comorbidity between hyperactivity and conduct problems requires all these features but will first be addressed analyzing a dimensional measure of the two constructs on a cross-sectional sample of male and female juvenile twin pairs between the ages of 8 and 16 years. The inclusion of dizygotic opposite sex twin pairs allows us to test differences in the causes of variation and covariation in boys and girls, and the inclusion of both younger and older twin groups provides an opportunity to begin to explore the impact of age/cohort on comorbidity. Given the developmental changes in the pattern of association between hyperactivity and conduct problems from early childhood to adolescence (Gittelman et al., 1985; Weiss et al., 1985) we expect differences in the genetic and environmental structure of these behaviors at different ages. Hence, the analysis of comorbidity of symptoms of hyperactivity and conduct problems is analyzed separately in a younger (8–11 years) and older (12–16 years) cohort of male and female twins. Furthermore, the reciprocal influence of one twin's behavior on his/her cotwin, referred to as sibling interaction (Carey, 1986, 1992; Eaves, 1976; Heath, 1990) as well as rater bias effects

(Hewitt, Silberg, Neale, & Erickson, 1992; Neale & Stevenson, 1989), both of which can significantly influence twin similarity, the foundation upon which genetic and environmental inferences are based, are also evaluated for explaining the causes of behavioral variation and covariation between the two traits.

Method

Ascertainment of Juvenile Twins

In the year 1987–1988, just prior to the formal approval date of the Virginia Twin Study of Adolescent Behavioral Development (VTSABD) in May 1989, all superintendents of both the public and private schools in the Commonwealth State of Virginia were contacted and asked to provide the names and addresses of those children who had a common last name and date of birth. Eliminating those twins the superintendents requested us not to contact, a target population of 3264 putative twin pairs between the ages of 8 and 16 years was obtained. These families were sent a twin brochure requesting information on zygosity, date of birth, race, and number of siblings in the family. After one to three re-mails and/or telephone follow-ups, 2791 of the 3264 families eventually returned the brochure, a 86% co-operation rate. By 1 November 1990, 1894 of these families (which also included a subsample of twin pairs who returned the twin brochure that was distributed directly by the superintendents of the schools and those ascertained independently through a toll free number at the Medical College of Virginia) continued to meet the study's age, residence and race (i.e. Caucasian) requirements, and were assigned for the first wave of data collection. Using census-derived indices of neighborhood income and urbanicity, Meyer, Silberg, Simonoff, Kendler, and Hewitt (in press) report slight departures from population representativeness, specifically an abundance of families living in high-income urban neighborhoods, and an under-representation of those residing in urban neighborhoods of lower income. It is unknown whether these demographic biases arose at the time of ascertainment or when the families were contacted. Regardless, they have been shown to have a negligible effect on the prevalence rates of childhood diagnoses (Meyer et al., in press). Throughout the study we have made every attempt to obtain interviews on those families who initially refused to participate because of time or scheduling conflicts, thereby extending the length of the waves of data collection. As of 1 May 1994, 1412 of the 1894 assigned families had participated in the interview study, resulting in an overall co-operation rate of 74.6%.

The present analyses included mothers' ratings (i.e. both biological and adoptive) of 265 MZ males (106 younger/159 older), 163 DZ males (82/81), 347 MZ females (162/185), 160 DZ females (77/83) and 262 opposite sex DZ twins (130/132) from the first wave of data collection.

VTSABD Protocol

The behavioral and emotional functioning of the children is assessed using the Child and Adolescent Psychiatric Assessment (CAPA), (Angold et al., 1995) a semi-structured clinical interview that provides sufficient information for the diagnosis of psychopathology according to DSM-III-R and ICD-10 criteria. Dimensional measures of the twins' behavior were also obtained by having the children and their parents complete a series of questionnaires under the supervision of a trained field interviewer. Included in the packet of instruments was the Rutter Parent 'A' scale (Rutter, Tizard & Whitmore, 1970), a 31-item questionnaire consisting of behaviors that comprise the formal DSM-III-R diagnoses of and Oppositional Defiant and Conduct Disorder and ICD-10 diagnosis of Hyperkinetic Disorder. Each item reflects one aspect of the child's behavior, and is rated either '0', '1' or '2', depending upon the extent to which the behavior applies or has occurred in the last 3 months.

Zygosity Determination

For like-sex twins, zygosity was determined using three sources of information. The most definitive source is blood antigen or DNA typing. To date, the zygosity of 237 like-sex twin pairs have been diagnosed by this method. The remaining pairs have received zygosity diagnoses by considering parental responses to three questions regarding the physical similarity of the twins and the ratings of pictures of the twins by two experienced judges.

Data Analysis

Factor analysis of the Rutter 'A' scale. In a factor analysis, variables are grouped into superordinate factors based upon the degree to which the individual items co-occur. This procedure was used to assess the extent of symptom overlap in this population, as well as provide a rationale for constructing the hyperactivity and conduct disturbance subscales. To examine the pattern of association among the individual symptoms of conduct disorder and hyperactivity, a varimax rotated factor analysis was performed on the product-moment correlations of the responses of mothers to the 31 items of the Rutter 'A' scale on both of their twins, and those factors with eigenvalues of approximately 1.0 or greater extracted. (Although we are primarily interested in the covariation between hyperactive behaviors and problems of conduct, all the items of the scale were included in this preliminary analysis.) To evaluate the impact of gender and age on the pattern of associations among the various behaviors, the linear effects of age were first partialled out of the inter-item correlations for younger and older boys and girls, and the factor analysis was then conducted on these four groups separately.

Phenotypic correlations. The extent of overlap among the hyperactivity and antisocial subscales is dependent upon the the actual correlation between them as well as their baseline rate in the population. In addition to calculating the phenotypic correlations between hyperactivity and conduct disturbance, differences in the mean vectors of these behaviors in the four groups were tested by comparing the average antisocial and hyperactivity scores for the younger (aged 8–11 years) and older (12–16 years) boys and girls using a multivariate analysis of variance (MANOVA).

Twin correlations. A comparison of the twin correlations between monozygotic and dizygotic twins provides an estimate of genetic and environmental influences on the observed (phenotypic) variation of a particular behavior. In general, a DZ twin correlation less than the MZ correlation is indicative of additive genetic influences on a trait, whereas a DZ correlation less than half the MZ correlation suggests genetic effects that operate non-additively (e.g. dominance genetic effects or epistasis). The influence of the shared environment (those environmental experiences that are common to twins of a pair) is denoted by a DZ correlation greater than half the MZ correlation. Because dominant (or epistatic) genetic influences have the effect of lowering the dizygotic twin correlation, and the shared environment, to increase this correlation, the two are confounded allowing the estimation of only one of these parameters. The effect of the

environment specific to individual twins within a pair is indicated by an MZ correlation less than 1.0.

Other phenomena can also signficantly affect twin similarity. For example, the tendency to rate twins as more or less similar than they really are, referred to as 'rater bias', can significantly influence twin resemblance and, in turn, conclusions regarding the relative importance of genetic and environmental factors. Another potentially important influence on twin similarity is sibling interaction, or the degree to which the twins actually do influence one another's behavior. This can result in greater similarity between the twins as one twin imitates his/her cotwin's behavior (co-operation), or less similarity as one twin attempts to individuate from his/her cotwin (contrast). Without ratings from both same and different informants rating each twin, we are unable to disentangle sibling interaction from rater bias. Hence, for the present analysis, we will refer to both types of phenomena under the general heading of comparison effects.

Univariate model fitting. Whereas a comparison of the twin correlations can provide a broad picture of the causes underlying behavioral variation, structural modelling procedures yield more precise estimates of genetic and environmental parameters. Furthermore, these approaches provide the opportunity for testing specific competing hypotheses about the causes of behavioral variation. For a more complete description of the application of structural equation models to twin data, and its advantages for estimating genetic and environmental influences on behavioral variation, refer to Heath et al. (1989) and Neale and Cardon (1992).

To summarize the data for model fitting, each constituent item of the hyperactivity and conduct problems subscale was summed and then log-transformed to approximate normality. Based upon the observed twin correlations, a univariate structural equation model was fitted to the 3 × 3 covariance matrices (the unstandardized correlation matrices) comprised of age and mothers' ratings of Twin 1 and Twin 2's hyperactivity and conduct problems separately. Theoretically, a model that includes additive genetic effects (*A*) fixes the additive genetic correlation between Twin 1 and Twin 2 to be unity in identical twins, and .50 in DZ twins. To include non-additive genetic effects (*D*) in the model (as implied by the very low DZ correlations), an additional parameter is required that specifies that dominance effects correlate .25 in DZ twins and 1.0 in MZ twins. Because non-shared environmental influences (*E*) affect only one twin of a pair, this correlation is zero. For this modelling procedure, we also added an additional parameter for the regression of the phenotype on age. Since age is perfectly correlated in twins, its effect would otherwise be included in the estimate of the shared environment. All models are fitted by maximum likelihood using the statistical program MX (Neale, 1994). The adequacy of different models are evaluated by likelihood ratio χ^2, or using Akaike's information criteria (AIC).

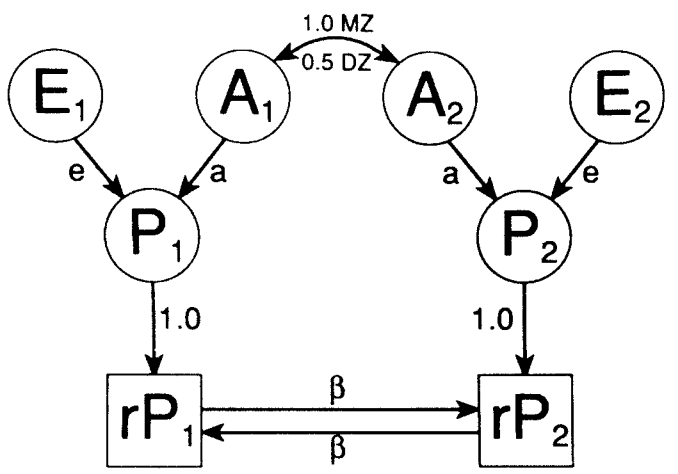

Figure 1. Univariate path model incorporating sibling interaction–rater bias.

Comparison effects: rater bias–sibling interaction. The tendency of an informant to rate the twins as more or less similar than they really are, or the actual influence of one twin's behavior on his/her cotwin, can affect twin correlations and variances, resembling the effects of genetic non-additivity or the shared environment. Alternative hypotheses regarding the relative influence of rater bias or sibling interaction, vs genetic non-additivity and the shared environment, can be accomplished with structural equation modelling. For example, a model that includes a shared environmental parameter to account for a DZ correlation greater than half the MZ correlation has similar implications to one that parameterizes a positive path from the rating of one twins' phenotype to his/her twin. Similarly, the relative fit of a model that specifies non-additive genetic effects based upon a DZ twin correlation signficantly lower than half the MZ twin correlation, and lower DZ variances can be compared against a model that includes a negative or contrasting influence of one twin's rating (behavior) on his/her cotwin (i.e. a negative path). It is easier, however, to distinguish negative comparison effects from genetic non-additivity than positive comparison effects and the non-shared environment. Whereas a very high DZ correlation can be accounted for by either shared environmental influences or positive sibling interaction–rater bias, the only tenable explanation for an extremely low DZ correlation is negative comparison effects, since a DZ correlation that approximates zero is not consistent with any genetic model. For illustration purposes, a univariate path model with sibling interaction–rater bias is shown in Fig. 1.

Bivariate model fitting. Whereas univariate model fitting yields estimates of the causes of *variation* in *one* phenotype, it is with bivariate structural equation models that we can estimate the causes of *covariation* between *two* phenotypes. To uncover the underlying causes of covariation in this population, bivariate twin models were fitted to the 5 × 5 covariance matrices comprised of age and the maternal ratings of *both* conduct problems and hyperactivity in the two twins. If the association can be explained by a common set of genetic–environmental factors (i.e. a genetic–environmental correlation of 1.0 between the two behaviors) this would indicate that the two disorders may be best considered a unitary phenomenon. Alternatively, if specific genetic–environmental factors influence differences among individuals in one behavior, but not the other, this would suggest that the two may be best classified as separate psychiatric conditions.

The bivariate approach recognizes that traits may be correlated for both genetic and environmental reasons, and the analysis is founded upon estimating the covariance or correlation between genetic or environmental effects on the two behaviors. The 'Cholesky decomposition model' (cf. Neale & Cardon, 1992) provides a convenient parameterization of both common *and* behavioral specific genetic and environmental effects as well as the genetic and environmental correlation between the two behaviors. Consequently, we can address whether the expression of the two constructs is attributable to the same (or different) set of genes or environmental factors.

Testing for gender effects. Structural equation modelling

Table 1
Factor Loadings for Rutter Parent Questionnaire for all Twins

Variable	Factor 1	Factor 2	Factor 3
Headache	−.10	**.32**	.08
Stomach ache	.09	**.36**	.11
Asthma	.02	.10	.03
Enuresis	.07	.01	.11
Encopresis	.14	.01	.06
Temper	**.49**	.25	.12
Tears	.11	.28	.06
Truant	.24	.14	.04
Stammer	.03	.12	.17
Steal	**.40**	.00	.15
Eat	.09	.33	.11
Sleep	.09	.33	.14
Accidents	.09	.16	.16
Restless	.26	.11	**.82**
Fidgety	.24	.14	**.80**
Destroy	**.55**	.11	.22
Fights	**.63**	.26	.17
Not liked	**.40**	.26	.14
Worries	.14	**.58**	.13
Solitary	.16	.34	.04
Irritable	**.54**	.38	.14
Miserable	.36	**.55**	.10
Twitches	.03	.13	.16
Sucks thumb	.07	.06	.08
Bites nails	.14	.07	.17
Disobeys	**.65**	.17	.30
Not settled	.34	.12	**.61**
Fearful	.07	**.56**	.18
Fussy	.20	**.48**	.05
Lies	**.63**	.09	.19
Bully	**.56**	.18	.08

also allows us to construct tests of significance of alternative hypotheses concerning the differential effects of genes and environment on behavioral covariation in boys and girls. Such effects may be conceptualized in terms of the genetic and environmental correlation between opposite sex twin pairs. In our application we accomplished this goal by using the 'Cholesky decomposition' applied to the genetic and environmental matrices across both traits and genders. Models that constrain the magnitude of the paths from the latent genetic and environmental factors to the trait to be equivalent for boys and girls are compared to models that estimate gender specific parameters. Moreover, if the same genetic or environmental factors affect the trait in boys and girls, we expect the cross-sex genetic or environmental correlation to be unity. The inclusion of opposite-sex pairs represents a powerful method for testing for heterogeneity in the magnitude of genetic and environmental effects across the sexes, in which the male twin is consistently identified as Twin 1 and the female Twin 2, and their parameters equated to the like-sex males and like-sex females, respectively.

To obtain the most parsimonious explanation of the data, we begin by fitting a bivariate model that specifies separate genetic and environmental factors for each behavior for boys and girls separately. We then proceed to build up the model by systematically examining: (1) the relative fit of comparison effects vs genetic non-additivity/shared environment; (2) whether a single genetic factor model can account for both behaviors; and (3) if the genetic parameters can be constrained to be equal in both boys and girls, i.e. r_g between opposite-sex pairs can be fixed to unity.

Results

Factor Analysis

Table 1 presents the results of a varimax rotated factor analysis for the age-regressed maternal ratings of each item of the Rutter 'A' scale for all twins. The combined factor analysis is presented, since no significant differences in the factor structure was evident by conducting the factor analyses separately by age and gender. Thus, at least phenotypically, the pattern of association among the hyperactivity, conduct problems and anxiety/depression items appears to be the same across age and gender. Factor loadings equal to or greater than .40 are underscored for clarification of the factor structure. All three regressions of the hyperactive behaviors on age and five of the eight conduct disturbance item regressions on age were significant, $p < .05$.

The factor analysis of the Rutter Parent Scale results in a solution that provides three coherently defined phenotypic factors, consistent with previous factor analyses of this instrument (Goodman & Stevenson, 1989a; Schachar, Rutter, & Smith, 1981). The first factor is characterized by oppositional/conduct problems. This factor includes all but the truancy item which has a factor loading of less than .40. However, since truancy is typically considered a problem of conduct, and since it has a higher loading on the first factor compared to the latter two factors, it was included as part of the conduct disturbance subscale. Behaviors reflecting depressed affect and anxiety comprise the second factor and the third factor, a hyperactivity factor, is characterized by high loadings on restlessness, fidgetiness and difficulty settling. Based upon this factor analytic procedure, the maternal ratings of the three items that reflect symptoms of hyperactivity, that is: (1) very restless, has difficulty staying seated for long; (2) squirmy, fidgety child; and (3) cannot settle to anything for more than a few moments—and eight items representing oppositional and conduct problems: (1) has temper tantrums (that is, complete loss of temper); (2) truants from school; (3) steals things; (4) often destroys own or others' property; (5) frequently fights or is extremely quarrelsome with other children; (6) often disobedient; (7) often tells lies; and (8) bullies other children were selected for subsequent data analysis.

Descriptive Statistics

For both sexes in both age groups, the intercorrelations between hyperactivity and opposition/conduct problems were substantial, the Pearson correlation coefficients all in the region of .50. The mean hyperactivity score was found to be significantly higher in the younger children compared with the older ones ($F = 35.03$, $p < .0001$) and in males compared with females ($F = 8.29$, $p < .004$), but there was no significant interaction between age and gender. The scores for oppositional/conduct problems were significantly higher in younger children ($F = 16.19$, $p < .0001$), but the gender difference was not significant.

Table 2
Phenotypic Correlations Among Symptoms of Hyperactivity and Conduct Problems in Younger and Older Male MZ and DZ Twins

	Twin-a MZ-a			Twin-b MZ-b		
	Age	Hypera	Conda	Hyperb	Condb	Age
Hypera	.049		.551[1]	.468[2]	.437[3]	.031
Conda	.043	.501[1]		.312[3]	.700[2]	.034
Hyperb	−.062	.579[2]	.366[3]		.385[1]	−.126
Condb	.143	.500[3]	.680[2]	.522[1]		.001
	DZ-a			DZ-b		
	Age	Hypera	Conda	Hyperb	Condb	Age
Hypera	−.173		.467[1]	−.107[2]	.235[3]	−.002
Conda	.079	.379[1]		−.033[3]	.327[2]	−.090
Hyperb	−.124	−.006[2]	.180[3]		.379[1]	−.089
Condb	−.054	.137[3]	.362[2]	.329[1]		.114

Note: younger twins in lower triangle matrix; older twins in upper triangle matrix.[1]Cross-trait within twin correlation.[2]Cross-twin within trait correlation.[3]Cross-twin cross-trait correlation.

Table 3
Phenotypic Correlations Among Symptoms of Hyperactivity and Conduct Problems in Younger and Older Female MZ and DZ Twins

	Twin-a MZ-a			Twin-b MZ-b		
	Age	Hypera	Conda	Hyperb	Condb	Age
Hypera	−.006		.343[1]	.471[2]	.249[3]	.050
Conda	.109	.577[1]		.259[3]	.693[2]	−.102
Hyperb	−.111	.570[2]	.519[3]		.414[1]	−.041
Condb	.011	.509[3]	.682[2]	.552[1]		−.091
	DZ-a			DZ-b		
	Age	Hypera	Conda	Hyperb	Condb	Age
Hypera	−.091		.365[1]	.100[2]	.051[3]	−.325
Conda	−.079	.371[1]		.208[3]	.494[2]	−.054
Hyperb	.002	.212[2]	.343[3]		.52[1]	−.102
Condb	−.203	.272[3]	.532[2]	.414[1]		−.087

Note: younger twins in lower triangle matrix; older twins in upper triangle matrix.[1]Cross-trait within twin correlation.[2]Cross-twin within trait correlation.[3]Cross-twin cross-trait correlation.

Table 4
Phenotypic Correlations Among Symptoms of Hyperactivity and Conduct Problems in Younger and Older DZ Opposite-sex Twins

	Twin-a DZO-a			Twin-b DZO-b		
	Age	Hypera	Conda	Hyperb	Condb	Age
Hypera	.056		.518[1]	−.058[2]	.128[3]	−.120
Conda	.146	.413[1]		−.037[3]	.395[2]	−.186
Hyperb	−.101	−.105[2]	.097[3]		.422[1]	−.006
Condb	.054	.215[3]	.413[2]	.409[1]		.017

Note: younger twins in lower triangle matrix; older twins in upper triangle matrix.[1]Cross-trait within twin correlation.[2]Cross-twin within trait correlation.[3]Cross-twin cross-trait correlation.

Twin Correlations

The within-pair correlations for both hyperactivity and conduct problems (and correlations with age) in the younger and older same-sex MZ and DZ, and DZ opposite-sex twins are presented in Table 2–4, respectively. In the younger boys, a DZ correlation less than half the MZ correlation (.579 MZ vs −.006 DZ) for hyperactive behavior is indicative of genetic non-additivity or the contrasting effects of rater bias or sibling interaction, and the influence of the non-shared environment. The same pattern and inference applies to

Table 5
Genetic and Environmental Components of Variance, Comparison Effects and Age on Mother's Ratings of Twins' Hyperactivity and Conduct Problems

	Hyperactivity						
	VA	VE	β	Age	χ^2	*df*	*p*
Young boys	.70	.27	−.156	−.05			
Young girls	.67	.32	−.082	−.03	24.8	20	.210
Older boys	.70	.25	−.224	.06			
Older girls	.70	.26	−.183	−.04	32.9	20	.03
	Conduct problems						
	VA	VC	VE	Age	χ^2	*df*	*p*
Young boys	.57	.10	.33	.08			
Young girls	.25	.42	.33	.02	10.94	21	.964
Older boys	.66	.04	.30	−.08			
Older girls	.48	.23	.29	−.04	8.71	21	.991

VA, Additive Genetic Variance; VC, Shared Environmental Variance; VE, Non-Shared Environmental Variance; β, Comparison Effects (sibling interaction/rater bias).

the older groups for boys and girls. In the young girls, the DZ correlation (.212) is almost half the MZ correlation (.57), indicating genetic effects that are additive in nature.

The twin correlations for conduct problems present a different etiological profile from hyperactivity. The MZ:DZ ratio is approximately 2:1 for the younger and older boys, pointing to additive genetic influences (together with non-shared environmental effects), whereas in the girls, the effect appears to be due primarily to additive genetic effects, non-shared environmental influences and environmental effects that are shared by the twins (or positive comparison effects).

The correlations between unlike-sex twin pairs (presented in Table 4) provide important information regarding gender differences in the causes of variation. For hyperactivity, any comparison between the DZ opposite-sex twin pairs and the DZ same-sex pairs is limited by a floor effect, in that the same-sex twin correlation is nearly zero. However, the correlations for conduct problems are more informative. For example, in the younger group, the opposite-sex twin correlation (.41) is intermediate between the young boys' DZ correlation (.36) and the young girls' correlation (.53). This pattern is consistent with a model in which boys and girls share a similar set of genes for the expression of conduct problems, and shared environmental effects (or positive comparison effects) are also influential, particularly in the girls.

Whereas the cross-twin, within trait, correlation between MZ and DZ twins provide a broad estimate of the influence of genetic and environmental factors on behavioral *variation*, it is the cross-twin, cross-trait, correlation (denoted by superscript ^{3}) that provides information regarding the causes of *covariation*. For example, in the older MZ boys, the average correlation between twin 1's hyperactivity and twin 2's conduct problems is .37. In the DZ boys, twin 1's hyperactivity correlates only at the .101 level with twin 2's conduct. In older MZ girls, the cross-twin, cross-trait correlations average .25, and in DZ girls .12. These differences point to stronger genetic influences on covariation in boys than in girls. However, more extensive and rigorous testing of these differences in behavioral variation and covariation is only accomplished with the application of structural equation models to the covariances of hyperactivity and conduct disturbance, which are presented below.

Univariate Results: Models Fitted to the Individual Variables Separately

Results from modelling hyperactivity and conduct disturbance separately for younger and older male and female twins are presented in Table 5. Included are the full univariate models, their χ^2, degrees of freedom and probability, the genetic and environmental components of variance for the younger and older cohorts, and β, the parameter estimate of sibling interaction–rater bias.

For hyperactive behaviors, a contrast model provides a relatively better fit to the data than a model including genetic non-additivity, particularly in the older cohort. Overall, however, a very similar pattern of causality characterizes the data on all the twin groups (consistent with the presentation of twin correlations by themselves). According to these models, approximately 70% of the phenotypic or observed variation in hyperactivity in boys and girls in the 8–16-year age range can be explained by additive genetic effects, 1–5% attributable to contrast effects, and the remaining to the non-shared environment (and/or measurement error).

The univariate model fitting results for conduct disturbance reveal important differences in the pattern of causality observed for hyperactivity, specifically less influence of hereditary factors and greater importance of the shared environment, especially for the girls. For all the twin groups, a model that includes the shared environment provides a better fit to the data than one estimating rater bias–sibling interaction.

These model fitting results underscore potential differences in the causes of variation in the hyperactivity and conduct problems, as well as possible gender-related differences for at least conduct disturbance. Whereas in hyperactivity genetic influences and contrast effects predominate, it is the influence of genetic factors and the

Table 6
Bivariate Model Fitting Results for Younger and Older Cohort

Model	A	E	D_{sp}	C_{sp}	β	χ^2	df	p	AIC
				Younger twins					
I	Sat	Sat	—	—	—	68.37	54	.09	−39.63
II	Sat	Sat	—	—	Sat	48.89	48	.437	−47.11
III	Sat	Sat	—	Specific	Hyp	55.39	49	.246	−42.61
IV	Sat	Sat	Specific	Specific	—	63.92	50	.089	−36.08
V	1	Sat	—	—	Sat	55.76	54	.408	−52.24
				Best fitting model					
VI	1 M = F	Sat	—	—	Sat M = F	69.30	62	.225	−54.7
				Older twins					
I	Sat	Sat	—	—	—	75.62	54	.028	−32.38
II	Sat	Sat	—	—	Sat	48.75	48	.443	−47.25
III	Sat	Sat	—	Specific	Hyp	48.55	49	.491	−49.45
IV	Sat	Sat	Specific	Specific	—	66.21	50	.062	−33.79
V	1	Sat	—	Specific	Hyp	74.09	55	.044	−35.91
VI	Sat M = F	Sat	—	Specific	Hyp	171.1	56	.000	59.1
				Best fitting model					
VI	Sat	Sat	—	Specific	Hyp M = F	51.32	54	.578	−56.68

A, additive genetic factor(s). E, non-shared environmental factor(s).
D_{sp}, dominant genetic effects specific to hyperactivity. C_{sp}, shared environmental effects specific to conduct disturbance.
Sat A/E, additive genetic (A)/non-shared environmental (E) factors common to the two behaviors and additive genetic/non-shared environmental factors specific to each behavior.
1 Factor, one factor genetic model; additive genetic factor common to both behaviors; no behavioral specific additive genetic effects; $r_g = 1.0$.
Sat β, comparison effects; contrast for hyperactivity, positive comparison effects for conduct disturbance.
M = F, no gender-specific effects. AIC, Akaike's Information Criteria.

Table 7
Genetic Correlation Matrix Between Hyperactivity and Conduct Disturbance in Younger (Lower Triangle) and Older (Upper Triangle) Males and Females

	Males		Females	
	A_{Hyp}	A_{Cond}	A_{Hyp}	A_{Cond}
A_{Hyp}	1.00	0.58	0.83	0.56
A_{Cond}	1.00	1.00	0.20	0.84
A_{Hyp}	1.00	1.00	1.00	0.46
A_{Cond}	1.00	1.00	1.00	1.00

Table 8
Non-shared Environmental Correlation Matrix Between Hyperactivity and Conduct Disturbance in Younger (Lower Triangle) and Older (Upper Triangle) Males and Females

	Males		Females	
	E_{Hyp}	E_{Cond}	E_{Hyp}	E_{Cond}
E_{Hyp}	1.00	0.23	0.00	0.00
E_{Cond}	0.08	1.00	0.00	0.00
E_{Hyp}	0.00	0.00	1.00	0.32
E_{Cond}	0.00	0.00	0.07	1.00

shared environment, particularly in females, that is paramount for explaining conduct disturbance.

The phenotypic correlations between hyperactivity and conduct problems, as well as the results from the factor analysis, indicate that the pattern of covariance or comorbidity is quite similar among the younger and older boys and girls. Based upon what we observe so far in this population, we conclude that there is a similar pattern of symptom expression across age and gender. However, as the univariate model fitting results have shown, there is no reason to assume that the causes of variation are necessarily comparable in these four groups. Moreover, we cannot assume that the causes of their covariation are the same. To explore the nature of the co-occurrence of hyperactivity and conduct disturbance and test more complex models regarding age- and gender-related differences in the causes of their covariation, bivariate structural equation models were fitted to the twin data. The covariance matrices for this analysis are provided in Appendix A.

Bivariate Model Fitting Results: Models Fit to Both Hyperactivity and Conduct

Table 6 presents the results of fitting a series of bivariate models to hyperactivity and conduct problems together in the younger and older cohort. Included is the likelihood ratio χ^2 for each model, and the relative goodness of fit of the different models. To illustrate differences in the genetic and environmental architecture underlying covariation in the two age groups, the genetic and non-shared environmental correlation matrices for

the Cholesky factors under the best fitting bivariate models are presented in Table 7 and Table 8.

Younger cohort. For younger males and females, a single genetic factor model, provided the best fit to the data, $\chi^2_{(62)} = 69.30$, $p = .225$, pointing to a single set of genes influencing hyperactivity and conduct problems in both the boys and girls. In this age group the genetic correlation between the two traits and the two sexes is unity (Table 7). The non-shared environmental correlation (Table 8) between the two behaviors was quite small (.08 for males and .07 for females), underscoring that the covariation between hyperactivity and conduct disturbance is accounted for almost entirely by hereditary factors. This model, which estimates a negative path between the twins' ratings of hyperactivity, −.1622 and a positive path for conduct disturbance, .2164, represented a significantly better fit than a model with genetic non-additivity or the shared environment. Since the same set of genes influence the two behaviors in both males and females, we conclude that hyperactivity and conduct disturbance probably reflect a unitary psychiatric construct in early childhood.

Older cohort. A very different picture emerges from modelling the covariation between hyperactivity and conduct disturbance in adolescence. A single genetic factor model provided a relatively poorer fit to the data, $\chi^2_{(55)} = 74.09$, $p = .044$, as compared to a model comprised of separate genetic factors for hyperactivity and conduct disturbance, $\chi^2_{(49)} = 48.55$, $p = .20$. In contrast to the younger twins, these results indicate that there are specific genetic influences on hyperactive behavior and conduct disturbance in this age group, and, further, that different genes influence the expression of each behavior in males and females. As in the younger cohort, the non-shared environment played a small role in explaining covariation. Similar to the univariate results, a model including contrast effects for hyperactivity and shared environmental influences on conduct disturbance fits better than a model with comparative effects for both behaviors, or one including genetic non-additivity for hyperactivity and the shared environment for conduct disturbance. The fit of this model and the genetic correlations, marked, but significantly different from 1.0 (see Table 7), provides evidence that hyperactive behavior among male and female adolescents represents quite a different psychiatric condition than conduct disturbance.

In summary, both the univariate and bivariate modelling results point to significant differences in the causes of variation and covariation in hyperactivity and conduct disturbance, and heterogeneity in the mechanisms of causation underlying their co-occurrence in the two age groups. In the younger cohort, the covariation between hyperactivity and conduct disturbance is attributable to a common set of genetic influences, whereas in the older cohort, different sets of genes contribute to the two behaviors independently.

Discussion

The identification of causative factors in the comorbidity of symptoms of conduct disorder and hyperactivity was investigated through an application of structural equation models to mothers' ratings of their juvenile twins' behavior. This approach was adopted to examine whether the co-occurrence of hyperactivity and conduct problems observed phenotypically could be attributed to a common etiology, or whether these two behaviors are best construed as distinct patterns of psychopathology based upon behavior specific genetic and/or environmental factors.

A necessary requirement of any methodology using cofamiliality as a criterion for identifying distinct homogenous subgroups of behaviors is that the relevant behavior is at least familial. The present analyses confirmed the importance of genetic factors in the expression of hyperactivity and conduct problems in this population. Our findings are consistent with a growing body of evidence from a number of family (Cantwell, 1972; Stewart, DeBlois, & Cummings, 1980; Welner, Welner, Stewart, Palkes, & Wish, 1977), twin (Eaves et al., 1993a; Gillis, Gilger, Pennington, & DeFries, 1992; Goodman & Stevenson, 1989b; Graham & Stevenson, 1985; Rhee, Waldman, Hay, & Levy, 1995; Stevenson & Graham, 1988; Thapar, Hervas, & McGuffin, 1995) and adoption studies (Cantwell, 1975; Cunningham, Cadoret, Loftus, & Edwards, 1975), that support a substantial genetic component to both hyperactivity and conduct disturbance, as well as other 'externalizing' behaviors in childhood and adolescence (Cloninger & Gottesman, 1987; DiLalla & Gottesman, 1989; Grove et al., 1990; Graham & Stevenson, 1985; McGuffin & Thapar, 1992; Rutter et al., 1990; Silberg et al., 1994). In fact, the 0.6 MZ/−0.08 DZ correlation for mothers' ratings of hyperactivity reported in the study of 13-year-old male twins by Goodman and Stevenson (1989b) and the pattern of twin correlations presented by investigators from the Cardiff Birth Survey of 8–16-year-old twins (Thapar, Hervas, & McGuffin, 1995) are nearly identical to those in the VTSABD sample. In the latter report, the very low DZ correlations for hyperactivity are accounted for using a sibling interaction model. However, there is not a systematic comparison of this model with a model that includes genetic non-additivity, nor is the possible importance of negative rater bias effects fully explored. As mentioned previously, it is only with data from both the same and different informants rating the twins that one can distinguish sibling interaction from rater bias. One of the essential features of the VTSABD protocol is having collected data from both same and different teachers, offering the opportunity for evaluating the relative fit of these models for explaining unusually high DZ differences.

Another potentially important influence on twin resemblance is the non-shared environment. This can include measurement error, transient environmental effects and the more salient factors in the environment that create differences between identical twins. One approach for separating error variance from the more informative factors in the twins' environment that influence the expression of behavioral problems is to compare the test–retest reliability coefficient with the correlation among identical twins for the trait in question. Since any difference from unity in the test–retest correlation reflects measurement error, an MZ correlation that is lower than the reliability coefficient

indicates there are differences between identical twins that are accounted for by experiences of the individual of a pair that are enduring over time (Eaves & Eysenck, 1976; Silberg & Heath, 1991). The average test–retest correlation over a 1.5-year interval for all the twins is estimated at .57 for hyperactivity and .69 for conduct disturbance, based upon preliminary data from the second wave of data collection. The comparison with an average MZ correlation of .52 and .68, respectively, indicates that at least for hyperactivity, there is a small proportion of environmental effects, other than measurement error, that influences behavior. For conduct disturbance, error variance accounts for nearly all of the non-shared environment.

In addition to underscoring the importance of hereditary factors to variation in hyperactive behavior and conduct problems individually, the most compelling finding of the present analyses is the influence of hereditary factors on comorbidity. The comparison of covariances between the two behaviors in identical and non-identical twins enables us to determine whether hyperactivity can be distinguished from conduct problems on the basis of distinct etiological factors, or represents different (phenotypic) manifestations of a generalized syndrome, shown to be due to the same set of genes (or environment). Particularly in the younger cohort, there is strong evidence that the genes that influence variation in hyperactivity are also responsible for individual differences in the expression of conduct problems in both boys and girls.

The demonstrable common genetic mechanism between hyperactivity and conduct disturbance in younger children provides empirical support that these behaviors do represent a single behavioral dimension. Although the pattern of covariances is not unequivocal evidence for the existence of a biologically based subgroup of individuals manifesting both hyperactivity and conduct disturbance, these results are not inconsistent with the existence of such a group of comorbid children. Thus, for generating homogenous samples of subjects for a linkage or association study for uncovering candidate loci in hyperactivity, it may be children with multiple symptoms that are most informative. To elucidate the existence of a biologically based group of children manifesting both hyperactivity and conduct problems more precisely, latent class analytic methods applied to twin data (Eaves et al., 1993a, b; Silberg et al., in press) can provide information for grouping individuals with specific symptom profiles and the causal mechanisms underlying group membership.

Although there is also substantial genetic overlap between the two behaviors in the older children, there is also marked etiological specificity suggesting that the two behaviors cannot be construed as representing the same latent psychiatric condition. The finding of a distinct set of genes for hyperactivity and conduct disturbance in the older group suggests that those factors that influence the expression of hyperactivity and conduct problems in childhood cannot fully account for their continuity into adolescence. Numerous studies (Borland & Heckman, 1976; Gittelman et al., 1985; Klein & Manuzza, 1991; Loney, Whaley-Klahn, Kosier, & Conboy, 1983; Stewart, Mendelson, & Johnson, 1973; Weiss & Hechtman, 1986; Weiss, Hechtman, Perlman, Hopkins, & Wener, 1979; Weiss, Minde, Werry, Douglas, & Nemeth, 1971) have shown that a substantial number of adolescents with a history of childhood hyperactivity do retain symptoms of psychomotor overactivity and inattentiveness from childhood, and exhibit additional impairments in several areas of functioning including school performance, relationships with peers, self-esteem, substance abuse and antisocial behavior. This could represent one endpoint of a genetically influenced developmental pathway that begins with the presentation of multiple symptoms in early childhood. However, the present findings indicate there may also be another developmental process taking place in which specific genes (for conduct problems) are 'switched on' in adolescence, e.g. an 'adolescence limited' conduct disturbance (Moffitt, 1993).

Clearly, the present design requires extension to confirm the rater effects identified and to address the nature of the changes that may be occurring developmentally. The availability of teacher reports and the recent completion of the second wave of VTSABD data collection will allow both these issues to be addressed more fully in this sample, allowing us to distinguish, for example, whether the continuity of symptoms is mediated by the same or different etiological process

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Appendix

Table A1
Covariance Matrices of Maternal Ratings of Twins' Hyperactivity and Conduct Problems With Age for Younger Cohort

Young cohort (8–11 years)				
Hypera	Conda	Hyperb	Condb	Age
MZM				
0.779369161	0.420986232	0.481213916	0.400442647	0.047607821
0.420986232	0.907465079	0.328084797	0.588202281	0.044866647
0.481213916	0.328084797	0.887018609	0.445969785	−0.064117379
0.400442647	0.588202281	0.445969785	0.824420189	0.143430436
0.047607821	0.044866647	−0.064117379	0.143430436	1.223450135
DZM				
0.832858807	0.307042522	−0.004882945	0.117959416	−0.156259790
0.307042522	0.786396447	0.133260302	0.302627635	0.069296977
−0.004882945	0.133260302	0.699643436	0.259077426	−0.102973558
0.117959416	0.302627635	0.259077426	0.888017299	−0.050809147
−0.156259790	0.069296977	−0.102973558	−0.050809147	0.980311489
MZF				
0.717709548	0.459403703	0.406372893	0.400747991	−0.005207455
0.459403703	0.884255078	0.410842010	0.596063424	0.102796995
0.406372893	0.410842010	0.707917690	0.431708770	−0.093545234
0.400747991	0.596063424	0.431708770	0.864744090	0.010577595
−0.005207455	0.102796995	−0.093545234	0.010577595	1.006883136
DZF				
0.747204395	0.284714389	0.179281441	0.211562598	0.085112204
0.284714389	0.789271233	0.297703779	0.425473407	−0.075805845
0.179281441	0.297703779	0.957017811	0.364378179	0.002460943
0.211562598	0.425473407	0.364378179	0.809773752	−0.197515405
0.085112204	−0.075805845	0.002460943	−0.197515405	1.172248804
DZO				
0.871176020	0.363703275	−0.081146406	0.185284625	0.056934330
0.363703275	0.890113559	0.076589860	0.359854594	0.147937720
−0.081146406	0.076589860	0.686886106	0.312609097	−0.090313846
0.185284625	0.359854594	0.312609097	0.852577915	0.053709688
0.056934330	0.147937720	−0.090313846	0.053709688	1.157364341

Continued

Table A2
Covariance Matrices of Maternal Ratings of Twins' Hyperactivity and Conduct Problems With Age for Older Cohort

Older cohort (12–16 years)				
Hypera	Conda	Hyperb	Condb	Age
MZM				
0.734939504	0.430085427	0.324190563	0.333503593	0.037775341
0.430085427	0.830293636	0.229546709	0.567492144	0.044005429
0.324190563	0.229546709	0.652645453	0.276973162	−0.145986924
0.333503593	0.567492144	0.276973162	0.791144917	0.001878413
0.037775341	0.044005429	−0.145986924	0.001878413	2.072204969
DZM				
0.820535781	0.393847517	−0.092131217	0.196614758	−0.002673471
0.393847517	0.866137002	−0.029500237	0.281787305	−0.116459190
−0.092131217	−0.029500237	0.908755890	0.334675190	−0.117197878
0.196614758	0.281787305	0.334675190	0.856530829	−0.146615596
−0.002673471	−0.116459190	−0.117197878	−0.146615596	1.918827160
MZF				
0.576179478	0.226942436	0.254216044	0.160577389	0.053875572
0.226942436	0.758532711	0.160095832	0.513218296	−0.126815560
0.254216044	0.160095832	0.504576409	0.250074520	−0.041123590
0.160577389	0.513218296	0.250074520	0.723631848	−0.111147672
0.053875572	−0.126815560	−0.041123590	−0.111147672	2.042420682
DZF				
0.766962385	0.289287219	0.083223618	0.041759160	−0.395710844
0.289287219	0.816832448	0.178251511	0.420954693	−0.068397972
0.083223618	0.178251511	0.902361622	0.465818717	−0.134800436
0.041759160	0.420954693	0.465818717	0.890235016	−0.114710263
−0.395710844	−0.068397972	−0.134800436	−0.114710263	1.931531002
DZO				
0.779037033	0.42136712	−0.040170287	0.100420009	0.071258210
0.421262211	0.849397116	−0.027118934	0.323634767	−0.251837790
−0.040170287	−0.027118934	0.617227192	0.294626850	−0.006671785
0.100394699	0.323634767	0.294626850	0.789723498	0.022544002