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Genetic effects on the variation and covariation of attention deficit-hyperactivity disorder (ADHD) and oppositional-defiant disorder/conduct disorder (ODD/CD) symptomatologies across informant and occasion of measurement

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ABSTRACT

Background. Previous studies have shown that the presence of conduct disorder may contribute to the persistence of attention deficit-hyperactivity disorder (ADHD) symptomatology into adolescence; however, the aetiological relationship between the two phenotypes remains undetermined. Furthermore, studies utilizing multiple informants have indicated that teacher ratings of these phenotypes are more valid than maternal reports.

Methods. The genetic structure underlying the persistence of ADHD and oppositional-defiant disorder/conduct disorder (ODD/CD) symptomatologies as rated by mothers and teachers at two occasions of measurement was investigated on a sample of 494 male and 603 female same sex adolescent twin pairs participating in the Virginia Twin Study of Adolescent Behavioral Development (VTSABD).

Results. Using structural modelling techniques, one common genetic factor was shown to govern the covariation between the phenotypes across informants and occasion of measurement with additional genetic factors specific to ODD/CD symptomatology and persistence of symptomatology at reassessment. Genetic structures underlying the phenotypes were, to some extent, informant dependent.

Conclusions. The findings indicate that it is unlikely that the co-morbidity between ADHD and ODD/CD is due to environmental influences that are independent of ADHD. Rather it is likely to be due to a shared genetic liability either operating directly, or indirectly through gene–environment correlations or interactions. The covariation between phenotypes across informants and time is governed by a common set of genes, but it seems that ODD/CD is also influenced by additional genetic factors. Developmentally, different forms of genetic liability control ADHD in males and inattention in females.

INTRODUCTION

Numerous studies have shown a high level of co-morbidity between attention deficit-hyperactivity disorder (ADHD) and both oppositional-defiant and conduct (ODD/CD) symptomatology and disorders (see Biederman *et al.* 1991; Fergusson *et al.* 1991; Silberg *et al.* 1996*a*; Tannock, 1998; Angold *et al.* 1999). The clinical and theoretical implications necessarily vary according to the meaning of the co-morbidity and to the mechanisms involved. The first possibility is that the diagnostic distinction

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between ADHD and ODD/CD is artefactual, both forms of psychopathology representing varied manifestations of the same general syndrome of disruptive behaviour. Three main sets of findings make this explanation unlikely. First, the longitudinal course and correlates of the two are relatively distinct, as shown, for example, by the Christchurch longitudinal findings (Fergusson & Horwood, 1993; Fergusson *et al.* 1991, 1993). The association arises in early to middle childhood and, after this age period, the two patterns show a different developmental course if co-morbidity has not been established already (Fergusson *et al.* 1993). ADHD mainly predicts poor scholastic attainment whereas ODD/CD mainly predicts criminal offending. Early ADHD carries risks for later ODD/CD but the reverse is not the case (Taylor *et al.* 1996) and there is little risk for late onset antisocial behaviour associated with ADHD (Loeber *et al.* 1995; McArdle *et al.* 1995). Secondly, genetic influences on ADHD are much higher than those for ODD/CD that is not co-morbid with ADHD (Silberg et al., 1996*a*, *b*; Eaves *et al.* 1997; Thapar *et al.*, 1999; Levy & Hay, 2001). Thirdly, whereas there is a marked sex difference in the rate of ADHD, there is a much smaller sex difference in the case of ODD/CD that is not accompanied by ADHD (Moffitt *et al.* 2001).

However, although there is good reason to suppose that ADHD and ODD/CD are meaningfully different, it should not be assumed that either psychopathological pattern is homogeneous. In particular, there is much evidence to indicate that early onset antisocial behaviour that persists into adulthood (life course persistent varieties) is rather different from later onset syndromes in which the manifestations are mainly evident in adolescence – adolescence-limited variety (see Moffitt, 1993; Moffitt *et al.* 2001; Rutter *et al.* 1998). The chief possible heterogeneity within ADHD concerns the contrast between hyperactivity/impulsivity and inattention, with the latter tending to be more persistent over time but less likely to be associated with conduct problems (Hart *et al.* 1995; Wolraich *et al.* 1996), and possibly reflecting a somewhat different genetic liability (Nadder *et al.* 2001).

By contrast, although ODD and CD are treated as separate categories in psychiatric classification systems, the bulk of the evidence suggests that ODD represents an earlier onset, milder, variety of the same disorder later manifest as CD (Cohen & Flory, 1998; Loeber *et al.* 1998; Rutter *et al.* 1998; Pickles *et al.* 2001). Also, the evidence suggests that ODD and CD reflect the same genetic liability (Eaves *et al.* 2001).

The three other possibilities (beyond the suggestion that the distinction is artefactual) with respect to the co-morbidity between ADHD and ODD/CD are: first, that they represent the same underlying genetic liability with different peak ages of manifestation; secondly, that ADHD behaviour provokes negative reactions from other people and that it is this negativity that predisposes to ODD/CD; and thirdly, that ODD/CD develops in children with ADHD only when they encounter psychosocial adversity.

The first possibility accepts the validity of phenotype differences between ADHD and ODD/CD, but hypothesizes that, when the two co-occur, the co-morbidity reflects the same genetic liability. The parallel here would be the association between early anxiety symptoms and the later development of depression (Silberg *et al.* 2001). The prediction with this hypothesis is that there are no environmental factors specific to ODD/CD that are implicated in the co-morbidity.

The second possibility is similar to the first in proposing that genetically influenced ADHD is the driving force underlying the development of ODD/CD, but differs fundamentally in proposing that the crucial mechanism for the co-morbidity lies in the negative environment brought about by the ADHD rather than in the genetic liability as such (see Caron & Rutter, 1991; Rutter 1997). The predisposing environment could involve either evoked negativity in parents, peers, or teachers, or scholastic failure (Rutter *et al.* 1977*a*, *b*).

The third possibility is similar to the second in proposing an environmental mechanism but differs in its postulate that the risk environments arise for reasons other than the negative effects of ADHD behaviour.

Twin designs are particularly informative in differentiating between the first and third possibilities. Because gene–environment correlations and interactions are ordinarily incorporated in the genetic term, further steps are needed to

differentiate between the first and second possibilities (see Discussion section below). Cross-twin, cross-trait correlations provide the basis of co-morbidity analyses (Neale & Cardon, 1992). Previous reports of studies using genetic analyses of co-morbidity between ADHD and ODD/CD have found a substantial shared genetic liability and a moderate non-shared environmental effect (Silberg *et al.* 1996*a*; Nadder *et al.* 1998). The findings, however, have been limited by reliance on cross-sectional data and, in some cases, reliance on single informant questionnaire measures.

The present investigation provides an advance in three respects: (1) use of two time points of measurement, 19 months apart; (2) use of both questionnaire and interview measures; and (3) the combination of maternal and teacher reports. We imposed three restrictions on our data. Ordinarily, in such analyses, it would be desirable to include child measures, which were available in both questionnaire and interview form. They were excluded, however, because of the evidence that child reports of hyperactivity/inattention lack adequate validity (Angold *et al.* 1995). In order to avoid possible biases due to informant variance across constructs, it was important to use comparable sources of data for both ADHD and ODD/CD. Secondly, opposite sex pairs were excluded because of the evidence that there were twin contrast effects for ADHD (Simonoff *et al.* 1998), and because of the uncertainty over whether they would have the same meaning in same-sex as opposite-sex pairs. Thirdly, on the basis of both epidemiological/longitudinal and genetic findings (see above) we combined ODD/CD symptomatologies rather than treating them as separate psychopathological features.

METHOD

Sample

This analysis was limited to same-sex male and female twin pairs who participated in the home interview study of the Virginia Twin Study of Adolescent Behavioral Development (VTSABD). The protocol of the VTSABD and sample characteristics have been discussed in detail elsewhere (Meyer *et al.* 1996; Eaves *et al.* 1997; Hewitt *et al.* 1997; Simonoff *et al.* 1997). To summarize, initial home visits, which included comprehensive interviews of the twin pairs and parents/guardians and administration of written questionnaires, were completed between 1990 and 1992. Of the 1894 Caucasian families targeted for this first wave of interviews (Wave 1), 1412 (75%) agreed to participate; 1408 families were successfully interviewed. The remaining four families completed only the questionnaires. The families who remained residents of the state of Virginia and whose twins were of school age were revisited in their homes 19 months after the initial visit for follow-up interviews and completion of questionnaires. Seventy-two per cent ($N = 1019$) of the initially interviewed families participated in the second wave of assessment (Wave 2). The effect of attrition on the rates of psychopathology was shown to be minimal (Shillady, 1998). There were no significant differences between the group of families that participated in both waves of study and the 229 families who participated in Wave 1 but did not participate in the second wave. For maternal ratings of ADHD, a significant difference in the prevalence rate was noted only for the ratings in older girls between the ages of 14 and 15 years, with the rate slightly higher in Wave 1 (3·6% *v.* 0%).

The sample used in this analysis consisted of 307 male MZ, 405 female MZ, 187 male–male DZ, and 198 female–female DZ twin pairs between the ages of 8 and 16 at both time points whose families participated in Waves 1 and 2 data collection. Only like-sex twins were included due to the complexity of the genetic multivariate analyses that arises from the incorporation of contrast effects on ADHD symptomatology (see Simonoff *et al.* 1998). The under-representation of DZ twins has been reported in other twin samples (see Hewitt *et al.* 1997 for a further explanation). When compared to the preliminary data collected from the North Carolina twin sample ascertained through birth records, the proportion of MZ pairs is similar to that of this sample, which was based on school records (data available upon request). Thus, there appeared to be no evidence of bias resulting from ascertainment through the school systems.

Measures and informants

To assess ADHD and ODD/CD symptomatologies in the twin pairs, maternal ratings from a comprehensive interviewer-based psychiatric

interview, the Child and Adolescent Psychiatric Assessment (CAPA) (Angold *et al.* 1995; Angold & Fisher, 1999), and teacher ratings from a written questionnaire composed of items from the Rutter B and Conners' scale (Rutter, 1967; Conners, 1969; Elander & Rutter, 1996; Hogg, Rutter & Richman, 1997) were obtained. Informants were instructed to base their ratings on behaviour observed during the prior 3-month period. Symptom counts from the CAPA were subclassified and summed as related to the hyperactivity, inattention, and impulsivity dimensions of the disorder. Though results from an earlier genetic study (Nadder *et al.* 2001) indicated that the three dimensions of ADHD co-aggregate, other studies suggested that symptoms of hyperactivity and impulsivity are more likely than those of inattention to decrease with age (Hart *et al.* 1995) and be associated with conduct problems (Wolraich *et al.* 1996). Therefore, the dimensions were analysed separately, here, to explore their developmental expression and their impact on the expression of ODD/CD symptomatology. The CAPA ADHD subscales comprised four items for hyperactivity, five for inattention, and three items for impulsivity. To assess ODD/CD symptomatology, summed maternal symptom counts of ODD and CD from the CAPA interview were added, giving equal weight to each scale.

Teachers of the twin pairs, selected by the school principals, completed the written Teacher Questionnaire on one or both twins. Seven items on this questionnaire corresponding to ADHD symptomatology and seven items relating to ODD/CD behaviour were summed. To avoid effects from rater bias, this analysis used ratings from teachers different for each twin whenever these were available (as they were in 66% of cases in Wave 1 and 61% in Wave 2). Overall, 82% of the twin pairs utilized in this sample were rated by teachers for ADHD and ODD/CD symptomatology.

It should be noted that, with the exception of the ADHD subscales of the CAPA interview, the summed symptom counts were imputed for those with 75% of the item responses completed. In these cases, an average of the ratings for the completed items was calculated; and the averaged value was substituted for the missing responses. If more than 25% of the items were omitted for any given twin, missing values for the corresponding scale were assigned.

Raw data

To minimize the effects of a skewness of the observed scores as well as age trends and sex differences on mean symptom counts, raw scores were first normalized and then standardized to a mean of 10 and unit variance within each sex and age (in years) of the twin pairs using SAS (1989) RANK and STANDARD procedures. Male and female data were treated separately to account for the growing evidence that genetic heterogeneity exists between sexes (Rhee *et al.* 1999). The transformed raw data were subsequently used to calculate twin correlations and in model-fitting analyses.

Genetic analyses

Genetic model fitting analyses were used to address four main questions: (1) Is the covariation between ADHD and ODD/CD across time governed by the same set of genes?; (2) Are there additional genetic factors that contribute to the covariation at the follow-up assessment?; (3) If so, are these factors specific to one dimension of ADHD?; and (4) Is the best-fitting model stable across the informants who provide the descriptions of behaviour and between males and females?

Phenotypic and twin correlations

A preliminary investigation of the sources of causal effects of variation within symptomatologies was conducted by computing twin correlations for each measure within each zygosity group. A comparison of MZ and DZ (dizygotic) twin correlations provides an estimate of the magnitude of additive and non-additive genetic, shared and non-shared environmental effects. In addition, phenotypic correlations across the 12 variables were estimated to compare the magnitude of correlations across informants and occasions of measurement and between traits. Product-moment correlations were computed for both the phenotypic and twin correlations using the 'PROC CORR' statement in SAS (1989).

Independent pathway models

To determine the degree to which the association between ADHD and ODD/CD across time was

governed by the same genes, structural modelling techniques were applied to the twin data. A series of independent pathway models depicting alternative structures that explain the covariation between maternal and teacher ratings corresponding to ADHD and ODD/CD symptomatologies were conducted separately, then jointly, to delineate the proportion of covariation due to common and specific genetic effects. Furthermore, these models were used to systematically test the significance of occasion-, informant-, and trait-specific effects. The method of maximum likelihood pedigree analysis (Lange *et al*. 1976) was used to fit the structural models to the transformed raw data. Available in the statistical package Mx (Neale, 1997), this method was chosen to allow all collected data in Waves 1 and 2 to be included in this analysis even though data from one or more measures or from one twin were missing at random.

Previous VTSABD analyses (Silberg *et al*. 1996*b*; Eaves *et al*. 1997; Nadder *et al*. 1998; Simonoff *et al*. 1998) and the pattern of twin correlations derived from the current data provided a framework from which the structural models were developed. Independent pathway models in this analysis consisted of one or more common additive genetic factors (A) and variable-specific additive genetic effects (Asp). Sibling contrast effects, a form of rater bias, were incorporated in the models for ADHD symptomatology. In addition, models explaining variance in ODD/CD symptomatology included one or more common shared environmental factors (C) as well as variable-specific effects from this source of variation. The unique environmental effects (E) were triangularly decomposed among the variables in each model, thereby, eliminating any unique environmental effects that were variable specific (Neale & Cardon, 1992). For each model, the first common additive genetic factor (A1) and, when applicable, shared environmental factor (C1) loaded on each of the observed phenotypes assessed during Waves 1 and 2 of the VTSABD. To test whether or not additional genetic or environmental effects influenced the expression of these traits 19 months after the initial assessment, second common factors (A2, C2) were included in the model which loaded only on the variables derived from the second wave of data collection. An additional common genetic factor specific to teacher ratings was added to the model to furnish evidence for teacher-specific effects on behaviour.

Test for goodness-of-fit and parsimony

In order to evaluate the fit of a given structural model using the maximum likelihood pedigree approach, the -2LL (twice the negative log-likelihood) of full and nested models were compared. This provides a likelihood ratio chi-square test of goodness-of-fit. The difference between the two values is distributed as a chi-square (χ^2) with degrees of freedom (df) equivalent to the difference in the number of parameters between the models. A large χ^2 value in comparison to the number of degrees of freedom suggests that the simpler or nested model does not explain the data as well as the more complex model.

Each independent pathway model was compared to a fully saturated model in which all the variances, covariances, and means were estimated as free parameters using Akaike's Information Criteria (AIC) to determine the best-fitting and most parsimonious model. AIC was computed as $\chi^2 - 2$df where the χ^2 is the difference in -2LL between the saturated and more restricted model and df denote the degrees of freedom or difference in number of parameters between the two models. The model with the lowest AIC value is considered to be the most parsimonious by this criterion (Akaike, 1987).

RESULTS

Phenotypic and twin correlations

Table 1 provides the phenotype correlations across each measure of ADHD and ODD/CD symptomatologies assessed during Wave 1 and Wave 2. The similarities in correlations between the sexes are striking. For both male and female twin pairs, there were high correlations (0·57–0·64) between teacher ratings of ODD/CD and ADHD. There were also high correlations between the two teacher ratings of ADHD (males, 0·51; females, 0·46).

Generally, the pattern of correlations between same-sex MZ and DZ twin pairs for ADHD and ODD/CD symptomatologies was consistent across occasions of measurement (see Table 2). For ADHD symptomatology in males and females assessed by mothers, the DZ correlations

Table 1. *Phenotype correlations for measures of ADHD and ODD/CD symptomatology across informant and occasion of measurement* (935 *male twins;* 1133 *female twins*)

	Wave 1						Wave 2					
	MHyp	MInatt	MImp	TADHD	MODD/CD	TODD/CD	MHyp	MInatt	MImp	TADHD	MODD/CD	TODD/CD
Wave 1												
MHyp		0·59	0·55	0·27	0·24	0·18	0·49	0·36	0·32	0·21	0·18	0·13
MInatt	0·57		0·56	0·29	0·21	0·22	0·39	0·48	0·33	0·22	0·16	0·15
MImp	0·44	0·44		0·21	0·24	0·17	0·32	0·36	0·43	0·19	0·18	0·11
TADHD	0·29	0·26	0·21		0·18	0·64	0·25	0·32	0·24	0·51	0·23	0·43
MODD/CD	0·21	0·21	0·29	0·21		0·18	0·24	0·21	0·16	0·19	0·38	0·20
TODD/CD	0·20	0·14	0·15	0·57	0·19		0·15	0·16	0·11	0·34	0·22	0·43
Wave 2												
MHyp	0·39	0·34	0·26	0·26	0·20	0·25		0·54	0·30	0·21	0·20	0·17
MInatt	0·40	0·45	0·34	0·31	0·18	0·21	0·51		0·35	0·25	0·25	0·18
MImp	0·19	0·16	0·37	0·20	0·30	0·16	0·27	0·32		0·18	0·22	0·15
TADHD	0·15	0·09	0·10	0·46	0·11	0·36	0·19	0·24	0·16		0·23	0·58
MODD/CD	0·17	0·12	0·16	0·21	0·39	0·22	0·26	0·22	0·33	0·16		0·28
TODD/CD	0·12	0·08	0·16	0·34	0·14	0·34	0·12	0·20	0·10	0·57	0·10	

Male phenotype correlations are above diagonal; female phenotype correlations are below diagonal.
Underlined value indicates $P > 0{\cdot}05$; all other correlations are statistically significant at $P < 0{\cdot}05$
MHyp, Maternal ratings from hyperactivity subscale of CAPA; MInatt, maternal ratings from inattention subscale of CAPA; MImp, maternal ratings from impulsivity subscale of CAPA; TADHD, teacher ratings of ADHD symptomatology from teacher survey; MODD/CD, maternal ratings of ODD/CD symptomatology from CAPA; TODD/CD, teacher ratings of ODD/CD symptomatology from teacher survey.

Table 2. *Twin correlations for measures of ADHD and ODD/CD symptomatologies*

	Zygosity							
	MZ Males		MZ Females		DZ Males		DZ Females	
	N	*r*	*N*	*r*	*N*	*r*	*N*	*r*
Wave 1								
MHyp	288	0·21	385	0·25	174	−0·16	177	−0·03
MInatt	288	0·39	386	0·31	177	−0·02	179	0·00
MImp	282	0·16	381	0·27	175	−0·11	177	−0·02
TADHD	213	0·62	294	0·54	129	0·29	131	0·31
MODD/CD	288	0·59	378	0·59	176	0·37	172	0·26
TODD/CD	212	0·55	293	0·53	129	0·31	131	0·17
Wave 2								
MHyp	229	0·28	278	0·19	126	−0·09	124	0·01
MInatt	232	0·33	279	0·21	130	−0·10	123	−0·03
MImp	228	0·05	277	0·24	129	−0·11	124	0·04
TADHD	155	0·45	180	0·63	89	0·28	98	0·36
MODD/CD	229	0·57	281	0·59	130	0·35	125	0·31
TODD/CD	154	0·47	180	0·55	89	0·42	99	0·27

MHyp, maternal ratings from hyperactivity subscale of CAPA; MInatt, maternal ratings from inattention subscale of CAPA; MImp, maternal ratings from impulsivity subscale of CAPA; TADHD, teacher ratings of ADHD symptomatology from teacher survey; MODD/CD, maternal ratings of ODD/CD symptomatology from CAPA; TODD/CD, teacher ratings of ODD/CD symptomatology from teacher survey.

were less than one-half the correlations of the MZ twins and negative or zero in value suggesting that contrast effects along with additive genetic ones were influencing the trait. Yet, teacher ratings of ADHD symptomatology in male and female twins at the initial assessment and at Wave 2 appeared not to be affected by contrast effects since the DZ correlations were approximately half the MZ correlations.

Fewer differences were observed between maternal and teacher ratings of ODD/CD symptomatology. In males and females, DZ correlations were greater than one-half the MZ correlations suggesting that the twin's shared environment influenced the expression of ODD/CD symptomatology in addition to additive genetic and specific environmental effects.

Influences on separate forms of psychopathology

For both sexes, the genetic structure for ADHD symptomatology (Tables 3 and 4 and Appendix) could not be reduced to one common additive genetic factor to explain the covariation between the measures as determined by the likelihood ratio chi-square test between the one and two common factor models (males, $\chi^2 = 18{\cdot}90$, 4df; females, $\chi^2 = 28{\cdot}42$, 4df). In males (Table 3), two additional genetic factors were needed to further explain the data. A second common factor was identified that influenced the expression of ADHD symptomatology at follow-up assessment as reported by mothers; the third genetic factor was common to behaviour assessed only by the teachers of the twins at each occasion of measurement. Model-fitting results on the female twin data (Table 4), however, suggested that separate genetic effects did not influence the variation in expression of ADHD symptomatology over time. In fact, a two factor model in which the A1 loaded on all the variables and A2 loaded only on the teacher ratings was favoured over a two factor model in which A2 influenced the ratings from the second assessment wave.

The best-fitting models for male and female twins were further simplified to test for stability of teacher ratings of ADHD symptomatology. Indeed, constraining the common factor loadings on the teacher variables to be equal across waves of assessment indicates that the genetic effects influencing teacher ratings of ADHD symptomatology in males and females were stable over time. Further adjustments to the model suggest that contrast effects did not affect teacher ratings of the twins' behaviour; however, the parameter values representing contrast effects on maternal ratings from the CAPA interview ranged from −0·29 to −0·13 in males and −0·21 to 0·02 in females.

Table 3. *Multivariate model-fitting results for ADHD symptomatology in male twins as reported by mothers and teachers across two occasions of measurement* (N = 307 *MZ and* 187 *DZ pairs*)

Model	−2LL	Parameters	*v.* Model No.	χ^2	df	AIC
(1) Saturated	14161·812	304				
(2) 1 A factor model	14643·396	92	1	481·58*	212	57·58
(3) 2 A factor model A1 loads on all variables A2 loads on Wave 2 variables	14624·493	96	2	18·90*	4	46·68
(4) 3 A factor model A1 loads on all variables A2 loads on Wave 2 variables A3 loads on teacher variables	14608·708	98	3	15·79*	2	34·90
(5) Drop A2	14625·905	94	4	17·20*	4	44·09
(6) Drop teacher interaction effects	14608·812	96	4	0·10	2	31·00
(7) Constrain teacher loadings across waves for A1 and A3	14609·385	94	6	0·57	2	27·57

*$P < 0{\cdot}05$.
Model 7 is the best-fitting and most parsimonious model for ADHD symptomatology in male twins. This model consists of a common genetic factor (A1) with loadings on all the variables and a second common factor (A2) with loadings on variables assessed at the second wave of measurement and a third factor (A3) with loadings affecting only the teacher ratings.

Table 4. *Multivariate model fitting results for ADHD symptomatology in female twins as reported by mothers and teachers across two occasions of measurement* (N = 405 *MZ and* 198 *DZ pairs*)

Model	−2LL	Parameters	*v.* Model No.	χ^2	df	AIC
(1) Saturated	17595·638	304				
(2) 1 A factor model	18121·874	92	1	526·24*	212	102·24
(3) 2 A factor model A1 loads on all variables A2 loads on Wave 2 variables	18119·613	96	2	2·26	4	107·98
(4) 2 A factor model A1 loads on all variables A2 loads on teacher variables	18093·450	94	2	28·42*	4	77·81
(5) Constraint A2 teacher loadings	18093·450	93	4	00·00	2	75·81
(6) Drop teacher interaction effects	18093·958	91	5	0·51	2	72·32
(7) 3 A factor model A1 loads on all variables A2 loads on Wave 2 variables A3 loads on teacher variables	18087·488	98	4	5·96	2	79·85

*$P < 0{\cdot}05$.
Model 6 is the best-fitting, most parsimonious model. This model consists of one common genetic factor (A1) with loadings on all variables and a second genetic factor (A2) with loadings only on teacher ratings.

The genetic structure underlying ODD/CD symptomatology for both male and female twins as assessed by mothers and teachers at two occasions of measurement could be reduced to one common additive genetic factor (A1) and one common shared environmental factor (C1) in addition to the specific environmental factors. Due to this similarity, a test for heterogeneity or differences in the genetic and environmental causes of variation in ODD/CD symptomatology across sex was conducted. Specifically, the parameters of the ACE model were constrained to be equal for both males and females. The result of fitting this homogeneity model ($-2LL = 15196{\cdot}89$, df = 42) was compared to one in which the parameters take on different values for each sex ($-2LL = 15153{\cdot}60$, df = 84). The chi-square difference between the models was not significant ($\chi^2 = 43{\cdot}41$, df = 42) suggesting that the magnitude of the genetic and environmental causes was the same in males and females.

Table 5. *Multivariate model fitting results for ADHD and ODD/CD symptomatologies in male twins as reported by mothers and teachers across two occasions of measurement* (N = 307 *MZ and* 187 *DZ pairs*)

Model	−2LL	Parameters	*v.* Model No.	χ^2	df	AIC
(1) Saturated	20437·109	648				
(2) 3 A factor model A1 loads on all variables A2 loads on Wave 2 variables A3 loads on teacher variables C1 loads on ODD/CD variables	21482·784	170	1	823·22*	478	89·68
(3) 4 A factor model A4 loads on ODD/CD variables	21471·879	174	2	10·91*	4	83·69
(4) Drop A2 effects on TADHD, MODD/CD, TODD/CD	21473·301	171	3	1·42	3	79·24
(5) Constrain A3 across symptom/wave	21475·408	168	4	2·11	3	78·30
(6) Drop C on TODD/CD	21475·408	166	5	0·00	2	74·30
(7) Drop C on MODD/CD	21479·478	164	6	4·07	2	74·37

*$P < 0{\cdot}05$.
Model 7, containing four common genetic factors, is the best-fitting, most parsimonious model.

Table 6. *Multivariate model fitting results for ADHD and ODD/CD symptomatologies in female twins as reported by mothers and teachers across two occasions of measurement* (N = 405 *MZ and* 198 *DZ pairs*)

	−2LL	Parameters	*v.* Model No.	χ^2	df	AIC
(1) Saturated	25434·600	648				
(2) 3 A factor model A1 loads on all variables A2 loads on Wave 2 variables A3 loads on teacher variables C1 loads on ODD/CD variables	26441·197	170	1	1006·60*	478	50·60
(3) Drop A2 effects on Hyp, Imp, MODD	26441·140	167	2	0·06	3	44·54
(4) Constrain A3 across symptom/wave	26443·254	164	3	2·11	3	40·65
(5) Drop C on TODD/CD	26443·255	162	4	0·00	2	36·66
(6) Drop C on MODD/CD	26444·741	160	5	1·49	2	34·14
(7) 4 A factor model A4 loads on ODD/CD variables	26436·399	174	2	4·80	4	53·80

*$P < 0{\cdot}05$.
Model 6, containing three common genetic factors, is the best-fitting, most parsimonious model.

The homogeneity model was modified in two ways to test for significance of the common environmental effects that are specific to the phenotype and a common shared environmental factor on teacher ratings. The results indicated that variable-specific variance due to shared environmental effects could be eliminated from the model ($\chi^2 = 0{\cdot}12$, df = 4, $P = 0{\cdot}9983$). Furthermore, the common shared environmental effect on the teachers ratings were eliminated from the model without significantly altering its fit ($\chi^2 = 0{\cdot}00$, df = 2) thus producing the best fitting and most parsimonious homogeneity model for male and female twin pairs (see Appendix).

Influences on co-morbidity

To resolve the number of common genetic and environmental factors that affect the covariation of ADHD and ODD/CD symptomatologies and to test the significance of a genetic factor specific to conduct problems, models that included three or four common genetic factors and one common shared environmental factor were applied to the male and female twin data separately (see Tables 5 and 6 and Appendix). The results of the likelihood ratio chi-square test indicated that only in the male twins was a separate common factor influential in the expression of ODD/CD. Thus, the best-fitting

model for males consisted of four common additive genetic factors; for the females, the best-fitting model contained only three common genetic factors.

Though not hypothesis-driven, attempts were made to clarify the genetic structure underlying the covariances of the phenotypes of the male and female twins at Wave 2. Low parameter estimates of the four factor model from the male twin data suggested that the additional genetic effects at Wave 2 on maternal and teacher ratings of ODD/CD and teacher ratings of ADHD symptomatology could be eliminated from the model. Indeed, omitting these parameters had a non-significant effect on the overall fit of the model, thereby, producing a model in which only the three dimensions of ADHD were affected by additional genetic effects at follow-up assessment (see Table 5). Similar analyses using the female data (Table 6) indicated that these effects had an impact on the expression of inattention and phenotypes assessed by teachers at Wave 2. It should be noted that for both male and female twins, 39% of the total genetic variation (Tables 7 and 8) for the inattention dimension of ADHD at Wave 2 was attributed to this common genetic factor (A2).

To simplify further the models, the teacher ratings were constrained to be equal across wave and trait. In both males and females, these reduced models produced non-significant chi-square differences and lower AIC values. Indeed, the proportions of the genetic variances due to a genetic factor common only to the teachers' ratings were $> 50\%$ and stable across occasions of measurement, as shown in Tables 7 and 8.

Table 7. *Proportion of genetic variance due to common and specific additive genetic factors: across occasions of measurement in male twins*

	A1(%)	A2(%)	A3(%)	A4(%)	Asp(%)
Wave 1					
MHyp	73·2				26·8
MInatt	67·9				32·1
MImp	51·0				49·0
TADHD	18·4		51·2		30·4
MODD/CD	14·3			39·2	46·5
TODD/CD	13·0		59·6	4·2	23·2
Wave 2					
MHyp	40·0	16·2			43·8
MInatt	36·9	39·2			23·9
MImp	43·0	9·8			47·3
TADHD	19·4		57·3		23·3
MODD/CD	15·4			48·84	35·8
TODD/CD	19·0		56·0	11·5	13·5

MHyp, maternal ratings from hyperactivity subscale of CAPA; MInatt, maternal ratings from inattention subscale of CAPA; MImp, maternal ratings from impulsivity subscale of CAPA; TADHD, teacher ratings of ADHD symptomatology from teacher survey; MODD/CD, maternal ratings of ODD/CD symptomatology from CAPA; TODD/CD, teacher ratings of ODD/CD symptomatology from teacher survey.

Table 8. *Proportion of genetic variance due to common and specific additive genetic factors: across occasions of measurement in female twins*

	A1(%)	A2(%)	A3(%)	Asp(%)
Wave 1				
MHyp	39·7			60·3
MInatt	37·9			62·1
MImp	45·5			54·5
TADHD	23·2		57·6	19·2
MODD/CD	52·9			47·1
TODD/CD	22·8		59·9	17·3
Wave 2				
MHyp	27·4			72·6
MInatt	60·7	39·3		0·0
MImp	56·9			43·1
TADHD	12·0	30·4	53·2	4·4
MODD/CD	53·8			46·2
TODD/CD	2·7	10·0	54·3	33·0

MHyp, maternal ratings from hyperactivity subscale of CAPA; MInatt, maternal ratings from inattention subscale of CAPA; MImp, maternal ratings from impulsivity subscale of CAPA; TADHD, teacher ratings of ADHD symptomatology from teacher survey; MODD/CD, maternal ratings of ODD/CD symptomatology from CAPA; TODD/CD, teacher ratings of ODD/CD symptomatology from teacher survey.

Genetic correlations

Genetic correlations between each of the measures of ADHD and ODD/CD symptomatologies were tabulated (data available upon request) for male and female twins. Patterns were similar for sexes. Highest correlations (0·64–0·82) were consistently observed among teacher ratings within and across symptomatologies and occasions of measurement. Within the dimensions of ADHD symptomatology as rated by the mothers, moderate to high correlations occurred across waves of assessment. However, genetic correlations between the maternal ratings and teacher ratings of ADHD were no higher than those between maternal ratings of ADHD and those of ODD/CD symptomatology. It should be noted that the genetic correlation between the teacher ratings of ADHD and maternal ratings of

inattention in the female twins at Wave 2 was moderately high (0·62).

DISCUSSION

The first question we set was whether the covariation between ADHD and ODD/CD over time was governed by the same set of genes. In keeping with previous research, substantial phenotype correlations were found between ADHD symptomatology and ODD/CD symptomatology. Within teacher ratings they were about 0·6 and across informants they were about 0·2. Also, there was substantial temporal continuity in ratings – about 0·5 for teacher ratings of ADHD features. Model-fitting showed that, to a very considerable extent, the covariation among the phenotypes, across informants and over time, was governed by a common set of genes. However, it is noteworthy that several common genetic factors were implicated, and not just one. Environmental influences did not appear to play a major role in the covariation.

It is important to appreciate just what these findings do and do not indicate. Three main points are crucial. First, the limited importance of environmental factors applies strictly to the covariation between ADHD and ODD/CD. Partitioning of the variance shows that there were substantial environmental effects on ODD/CD, especially when it was not accompanied by ADHD (see Silberg *et al*. 1996*a*; Eaves *et al*. 1997). Also, the heritability of ADHD, although higher than that for ODD/CD, is less than unity and non-genetic factors play a contributory role in liability (Thapar *et al*. 1999; Levy & Hay, 2001). What our findings indicate is that genetic factors predominate in the liability to the co-occurrence of ADHD and ODD/CD. Secondly, the genetic component incorporates the effect of gene–environment correlations (rGE) and interactions ($G \times E$). This means that if environmental influences operate through those mechanisms they will not have been separately identified in the models tested. However, it would be possible to differentiate the direct effects of a shared genetic liability (the first possibility as discussed in the introduction) from the indirect effects arising from rGE and/or $G \times E$ (the second possibility). First, if ADHD is bringing about an adverse environment (E_A), the proportion of children experiencing E_A should be greater in the presence of ADHD than in its absence. Secondly, if E_A accounts for the development of ODD/CD, within a group of children with ADHD, the rate of ODD/CD should be greater in the presence of E_A. Causal effects could be tested by examining the psychopathological developments over time (this would probably require a younger age group than available in VTSABD), and the role of genes could be examined by using modelling methods to test for rGE.

Thirdly, the fact that we found several genetic factors serves as a reminder that the genetic component could operate in several rather different ways. Thus, for example, it could concern shared risk factors (such as a genetically influenced temperamental trait, for example sensation-seeking), or different component of the clinical syndrome. In so far as they concern the latter, it is likely that they apply to psychopathological dimensions rather than just an extreme diagnostic entity (Levy *et al*. 1997), although that does not necessarily rule out the possibility of a different genetic risk that applies to an infrequent subgroup (Eaves *et al*. 1993). What is relevant, however, is that it would be unwise to assume that, because ADHD and ODD/CD are conceptualized as distinct and separate conditions, the genetic liability involved for each will be different. Rather, the findings suggest that, at least for the co-morbid pattern, they overlap considerably. That has implications for molecular genetic research strategies.

The second question to be addressed was whether there were additional genetic factors that contributed to the covariation at the follow-up assessment. The findings on this question were somewhat inconclusive. The results for males showed that the second genetic factor operated only at Wave 2, but it concerned just maternal ratings. The results for females showed that the second factor concerned both maternal and teacher ratings at Wave 2. It remains uncertain whether this sex difference reflects measurement issues or a real difference. The analysis of data on the third wave of data collection will be informative on that point.

The third question concerned the possibility that there might be genetic factors that were specific to one dimension of ADHD. The findings supported this possibility in the case of inattention. In both males and females, the

second genetic factor accounted for two-fifths of the genetic effects on covariance of ADHD and ODD/CD in the second wave. This is in keeping with our earlier findings (Nadder *et al*. 2001) that to some extent a different form of genetic liability underlies inattention than that underlying hyperactivity and impulsivity. What is new here is the evidence that both inattention and ODD/CD are affected by this second factor. Why this factor did not seem to be operative in Wave 1 is unclear, particularly as the overall pattern of phenotype correlations and of MZ-DZ differences were broadly similar in the two waves. Once again, the third-wave findings will be helpful in resolving that issue, both because of the availability of three data points and because the greater time span covered will allow a clearer differentiation between age effects and time effects.

The fourth question asked whether the best-fitting model was stable across informants, over time, and comparable in males and females. Three features stand out. First, the third genetic factor covered both ADHD and ODD/CD as rated by teachers at both waves, and accounted for over half of the genetic influence on covariation. Secondly, the teacher ratings, unlike maternal ratings, showed no evidence of rater contrast bias. Taken together, these findings suggest that the teacher reports may be both more valid (in being freer of bias) and more sensitive to time-stable common genetic liability. The findings are particularly striking given the fact that, in most cases, different teachers rated the twins in the two waves of assessment. They support Fergusson & Horwood's (1993) and Goodman & Stevenson's (1989) claims that teacher reports are to be preferred over maternal reports and the DSM-III instructions with respect to ADHD that primary consideration should be given to teacher reports (American Psychiatric Association, 1980).

The third finding, however, indicates the need for caution in this inference. The inter-correlations between teacher ratings of ADHD and of ODD/CD were substantial (about 0·6) and considerably higher than those between maternal ratings of ADHD and ODD/CD (about 0·2). The query is whether teachers were less good than mothers at differentiating between the two forms of psychopathology or whether, because of the school setting and the lack of rater contrast bias, they were better at identifying co-morbidity. The correlations over time for maternal and for teacher ratings of ODD/CD were broadly comparable (about 0·4) but the temporal stability of teacher ratings of ADHD was higher (about 0·5) than that for maternal ratings (about 0·3) despite the fact that different teachers were usually involved, whereas the mother was the same. It was also notable that the variable-specific genetic effects for all maternal ratings were greater than those for teacher ratings. It is evident that many uncertainties remain over measurement issues in relation to ADHD (see Rutter, 2001).

Finally, we need to return to the finding that, to an important extent, the covariation between ADHD and ODD/CD over time is influenced by the same set of genes. What implications are there for inferences on causative mechanisms underlying co-morbidity? As we noted in the introduction to this paper, three main possibilities have been put forward. First, the behaviours involved in ADHD could predispose to ODD/CD because they lead the children to engage in disruptive or antisocial activities. In so far as that is the case, it may be expected that the ODD/CD that develops for this reason will show the same genetic and environmentally influenced liability as found for ADHD. In short, our findings regarding a shared genetic liability are compatible with this hypothesis. The second possibility is that, rather than an ADHD phenotypic effect on risk, both phenotypes represent varied manifestations of the same genetic liability. This, too, is consistent with our findings. The distinction is important because the first mechanism suggests that therapeutic interventions that reduce ADHD symptomatology should diminish the likelihood that ODD/CD would develop, whereas this would not happen with the second mechanism. Longitudinal studies, especially those incorporating trials of treatment, would help resolve the issue. However, there are also genetic questions that are pertinent. Are the genetic liabilities for ADHD that is not accompanied by ODD/CD, for ODD/CD unassociated with ADHD, and for the co-morbid pattern, the same? That requires a categorical, rather than dimensional approach. Within the constraints of sample size, we will be undertaking such an analysis with the Wave 3 data. The ADHD phenotypic risk

mechanism also predicts that the likelihood of ODD/CD developing should be the same for ADHD predominantly due to environmental influences (as, for example, with institutional rearing – see Kreppner *et al*. 2001; Rutter *et al*. 2001) as for ADHD arising in the usual way. We will be testing that prediction in other samples.

The third mechanism is that the association between ADHD and ODD/CD arises when children with ADHD encounter environmental hazards that do not derive from the effects of ADHD. Our findings would appear to be inconsistent with that hypothesis. However, as noted above, if the environmental hazards either arose as a result of ADHD (implying some form of gene–environment correlation) or if the susceptibility to the hazards was genetically moderated (implying gene–environment interaction), the effect would be incorporated in the genetic terms. We will be exploring this possibility in further analyses using the broader range of environmental risk measures available in Wave 3.

Three main limitations to our findings need to be noted. First, our sample covered only the 8 to 16 year age group; it is likely that the co-morbidity first arose at an earlier age period and study of a younger age group would be informative. Secondly, the development of the co-morbid pattern would have been studied more effectively through the longitudinal analysis of three waves of measurement over a longer time period; this will be available in our analysis of all three waves. Thirdly, in our analyses to date, we could not differentiate between the direct effects of a shared genetic liability for ADHD and ODD/CD, and the indirect effects stemming from a creation of an increased risk of psychosocial adversity. Analyses designed to make this differentiation are planned in relation to the use of Wave 3 data.

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APPENDIX
PARAMETER ESTIMATES FOR BEST-FITTING STRUCTURAL MODELS

	ADHD		ODD/CD	ADHD/ODD	
	Males	Females	Males/Females	Males	Females
$A1_1$	0·72	0·67		0·72	0·37
$A1_2$	0·66	0·62		0·65	0·26
$A1_3$	0·64	0·53		0·65	0·39
$A1_4$	0·30	0·44		0·31	0·36
$A1_5$			0·30	0·29	0·55
$A1_6$			0·64	0·24	0·35
$A1_7$	0·49	0·41		0·54	0·37
$A1_8$	0·43	0·54		0·43	0·24
$A1_9$	0·41	0·27		0·44	0·51
$A1_{10}$	0·30	0·21		0·31	0·27
$A1_{11}$			0·31	0·29	0·57
$A1_{12}$			0·30	0·31	0·12
$A2_4$		0·59			
$A2_7$	0·33			0·34	
$A2_8$	0·45			0·44	0·20
$A2_9$	0·21			0·21	
$A2_{10}$	0·07	0·59			0·42
$A2_{12}$					0·24
$A3_4$	0·53			0·52	0·58
$A3_6$				0·52	0·56
$A3_{10}$	0·53			0·52	0·56
$A3_{12}$				0·52	0·56
$A4_5$				0·48	
$A4_8$				0·14	
$A4_{11}$				0·52	
$A4_{12}$				0·24	
Asp_1	0·43	0·56		0·44	0·46
Asp_2	0·45	0·53		0·45	0·33
Asp_3	0·63	0·54		0·63	0·42
Asp_4	0·44	0·18		0·40	0·32
Asp_5			0·53	0·52	0·52
Asp_6			0·32	0·33	0·30
Asp_7	0·56	0·61		0·56	0·60
Asp_8	0·40	0·42		0·34	0·00
Asp_9	0·46	0·33		0·46	0·44
Asp_{10}	0·31	0·46		0·33	0·16
Asp_{11}			0·48	0·44	0·53
Asp_{12}			0·41	0·26	0·43
$Contrast_1$	−0·29	−0·21		−0·29	−0·09
$Contrast_2$	−0·15	−0·17		−0·14	−0·01
$Contrast_3$	−0·33	−0·13		−0·33	−0·06
$Contrast_7$	−0·25	−0·16		−0·24	−0·15
$Contrast_8$	−0·13	−0·13		−0·11	0·01
$Contrast_9$	−0·17	0·02		−0·18	−0·10
$Environ_5$			0·53		
$Environ_{11}$			0·59		

A1, A2, A3, A4 are common genetic factors; Asp, are variable-specific genetic factors; Contrast, are twin contrast effects; Environ, are shared environmental factors.

Subscripts 1 through 12, respectively, represent the following: maternal ratings of hyperactivity (Wave 1); maternal ratings of inattention (Wave 1); maternal ratings of impulsivity (Wave 1); teacher ratings of ADHD (Wave 1); maternal ratings of ODD/CD (Wave 1); teacher ratings of ODD/CD (Wave 1); maternal ratings of hyperactivity (Wave 2); maternal ratings of inattention (Wave 2); maternal ratings of impulsivity (Wave 2); teacher ratings of ADHD (Wave 2); maternal ratings of ODD/CD (Wave 2); teacher ratings of ODD/CD (Wave 2).