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Etiology of Inattention and Hyperactivity/Impulsivity in a Community Sample of Twins with Learning Difficulties

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A community sample of 373 8 to 18 year-old twin pairs in which at least one twin in each pair exhibited a history of learning difficulties was utilized to examine the etiology of inattention and hyperactivity/impulsivity (hyp/imp). Symptoms of attention-deficit/hyperactivity disorder (ADHD) were assessed by the DSM-III Diagnostic Interview for Children and Adolescents. Inattention and hyp/imp composite scores were created based on results of a factor analysis. Results indicated that extreme ADHD scores were almost entirely attributable to genetic influences across several increasingly extreme diagnostic cutoff scores. Extreme inattention scores were also highly heritable whether or not the proband exhibited extreme hyp/imp. In contrast, the heritability of extreme hyp/imp increased as a linear function of the number of inattention symptoms exhibited by the proband. This finding suggests that extreme hyp/imp may be attributable to different etiological influences in individuals with and without extreme inattention. If this result can be replicated in other samples, it would provide evidence that the hyp/imp symptoms exhibited by individuals with Combined Type ADHD and Predominantly Hyp/Imp Type ADHD may be attributable to different etiological influences.

KEY WORDS: ADHD; inattention; hyperactivity; twins; etiology.

Previous twin studies of attention-deficit/hyperactivity disorder (ADHD) have suggested that individual differences in symptoms of ADHD are largely attributable to genetic influences (Edelbrock, Rende, Plomin, & Thompson, 1995; Eaves *et al.*, 1997; Gjone, Stevenson, & Sundet, 1996; Levy, Hay, McStephen, Wood, & Waldman, 1997; Nadder, Silberg, Eaves, Maes, & Meyer, 1998; Schmitz, Fulker, & Mrazek, 1995; Sherman, Iacono, & McGue, 1997, Thapar, Hervas, and McGuffin, 1995). Estimates of heritability (h^2), the proportion of individual differences in ADHD symptoms attributable to the influence of genes, have been consistently high in multiple samples utilizing different measures (mean $h^2 \approx 0.75$). Moreover, studies of selected groups have indicated that extreme ADHD scores are also largely attributable to genetic influences, with group heritability estimates ($h^2_g =$ 0.76–0.92) similar to the estimates obtained for individual differences across the entire symptom dimension (Gillis, Gilger, Pennington, & DeFries, 1992; Gjone *et al.*, 1996; Levy *et al.*, 1997; Stevenson, 1992). The similarity of these estimates is consistent with the hypothesis that the same genetic influences may be associated with both extreme ADHD scores and individual differences across the entire distribution of symptoms.

All but one (Sherman *et al.*, 1997) of these studies utilized broad-band measures that combine symptoms of inattention, hyperactivity, and impulsivity to create a single ADHD score. In contrast to this unidimensional conceptualization, exploratory and confirmatory factor analyses have indicated consistently that symptoms of ADHD comprise separate but correlated dimensions of inattention and hyperactivity/impulsivity (Bauermeister, 1992; Burns, Walsh, Patterson, *et al.*, 1997; Burns, Walsh, Owen, and Snell, 1997; Conners, Sitarenios, Parker, & Epstein, 1998a, 1998b; DuPaul *et al.*, 1997, 1998; Healey *et al.*, 1993; Hudziak *et al.*, 1998; Pelham, Gnagy, Greenslade, &

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Milich, 1992; Sherman *et al.*, 1997; Willcutt & Pennington, in press). Consequently, the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.) (*DSM-IV*; American Psychiatric Association, 1994) described three subtypes of ADHD based on elevations of inattention and hyperactivity/impulsivity (hyp/imp). The Predominantly Inattentive Type describes individuals with significant elevations of inattention in the absence of significant hyp/imp; the Predominantly Hyperactive/Impulsive Type (Hyp/Imp Type) includes children with significant elevations of hyp/imp but not inattention; and the Combined Type describes individuals with elevations of both inattention and hyp/imp.

The single twin study (Sherman *et al.*, 1997) that subdivided symptoms of ADHD into factors of inattention and hyp/imp found that individual differences in symptoms of inattention and hyp/imp were each highly heritable. In addition, this study found significant bivariate heritability for the two dimensions, suggesting that the same genetic influences contribute to individual differences in symptoms of inattention and hyp/imp. These results provide preliminary evidence consistent with the *DSM-IV* model of ADHD. However, the sample utilized by Sherman and colleagues was not large enough to examine the etiology of extreme inattention or hyp/imp, an analysis which has essential implications for the validity of the diagnostic taxonomy of *DSM-IV* ADHD.

The Current Study

This report describes a study that replicates and extends previous research in several ways. First, multiple diagnostic cutoff scores for ADHD were utilized to test if the etiology of extreme ADHD scores varied as a function of severity. Symptoms of ADHD were then subdivided into dimensions of inattention and hyp/imp, facilitating the comparison of the etiological influences that contribute to extreme scores on these symptom dimensions. Finally, a series of analyses were conducted to test whether the etiology of extreme inattention or hyp/imp differed as a function of scores on the other dimension. Results of these analyses have implications for the validity of the three subtypes of *DSM-IV* ADHD. Because the *DSM-IV* subtypes are proposed to represent variations of the same disorder, similar etiological influences would be expected to contribute to extreme inattention or hyp/imp scores regardless of the child's score on the other dimension (e.g., the etiology of extreme hyp/imp would be similar among individuals with the Hyp/Imp Type or the Combined Type). On the other hand, if the etiology of extreme scores on one dimension (e.g., inattention) is different among children with extreme hyp/imp (Combined Type) and children with solitary elevations of inattention (Inattentive Type), this finding would be consistent with the hypothesis that the Combined Type and Inattentive Type were attributable to different etiological influences.

METHOD

Participants

A total of 373 same-sex pairs of 8 to 18-year-old twins from the ongoing Colorado Learning Disabilities Research Center (DeFries *et al.*, 1997) were included in these analyses. The total sample included 215 MZ twin pairs (100 female, 115 male) and 158 DZ pairs (70 female, 88 male) selected because at least one member of the pair exhibited evidence of reading or mathematics difficulties in their school records. Such evidence included low standardized test scores, referrals for academic tutoring, or special education placement. Because children with learning difficulties are at increased risk for ADHD (Fergusson & Horwood, 1992; McGee & Share, 1988; Willcutt & Pennington, in press), we anticipated that the prevalence of ADHD would be higher in this enriched sample than in the general population.

Measures

Zygosity Determination

Zygosity of the twins was determined using a modified version of the Nichols and Bilbro zygosity questionnaire (1966), which has been shown to reliably classify 96% of twins. If zygosity classification was ambiguous based on the questionnaire, DNA polymorphisms obtained from blood plasma or cheek samples were compared between twins in order to ensure accurate categorization.

Measure of ADHD

The *DSM-III* (American Psychiatric Association, 1980) version of the Diagnostic Interview for Children and Adolescents, Parent Report Version (DICA, Reich & Herjanic, 1982), was utilized to assess symptoms of ADHD. The Attention Deficit Disorder subscale of the DICA consists of dichotomous items that ask parents to indicate whether or not their child exhibits each of the sixteen symptoms of *DSM-III* ADHD. The inter-interview reliability of the DICA is reported to be 0.82, and diagnoses based on the DICA have been shown to be concordant with blind clinical assessments approximately ninety percent of the time (Welner, Reich, Herjanic, Jung, & Amado, 1987).

Table I. Factor Loading of the DSM-III Symptoms and Comparison to DSM-IV Symptoms

DSM-III item	Factor loading[a]	Comparable *DSM-IV* item	*DSM-IV* factor
Inattention Factor			
Often fails to finish things he or she starts	.79	Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace	Inattention
Often doesn't seem to listen	.71	Often does not seem to listen when spoken to directly	Inattention
Easily distracted	.72	Is often easily distracted by extraneous stimuli	Inattention
Has difficulty concentrating on schoolwork	.79	Often has difficulty sustaining attention in tasks or play activities	Inattention
Shifts excessively from one activity to another	.74	No directly comparable item	
Has difficulty organizing work	.71	Often has difficulty organizing tasks and activities	Inattention
Needs a lot of supervision	.70	No directly comparable item	
Has difficulty sticking to a play activity	.35[b]	Often has difficulty sustaining attention in tasks or play activities	Inattention
Hyperactivity/Impulsivity Factor			
Often acts before thinking	.60	No directly comparable item	
Frequently calls out in class	.58	Often blurts out answers before the questions have been completed	Hyp/Imp
Has difficulty awaiting turn	.62	Often has difficulty awaiting turn	Hyp/Imp
Runs about or climbs excessively	.72	Often runs about or climbs excessively in situations in which it is inappropriate	Hyp/Imp
Has difficulty sitting still or fidgets excessively	.78	Often fidgets with hands or feet or squirms in seat	Hyp/Imp
Has difficulty staying seated	.70	Often leaves seat in the classroom or in other situations in which staying seated is expected	Hyp/Imp
Is always "on the go," or acts as if "driven by a motor"	.76	Is often "on the go" or often acts as if "driven by a motor"	Hyp/Imp
Moves about excessively during sleep	.42[b]	No directly comparable item	

[a]Factor loadings from principal axis factor analysis with direct oblimin rotation.
[b]These two symptoms did not load significantly on either factor, and were not included in either composite score.

Because maternal report was available for many more children than paternal report (93% of all twins vs. 46% of all twins), maternal report was utilized for the analyses described in this report. The DICA was administered as an interview to approximately the first 50% of the participants in the present study ($n = 380$). Because of time constraints, the DICA was administered as a parent questionnaire to the remainder of the participants ($n = 366$). The wording of all items remained identical across these two methods of administration. At the time that this transition was made, 42 mothers completed the interview and the rating scale approximately one month apart. The total number of ADHD symptoms endorsed during these two administrations was highly correlated ($r = .84$), providing support for both the test-retest reliability of the measure and the comparability of these two methods of administration. Additional support for the reliability of the DICA is provided by the high correlation between maternal report and paternal report in the subset of families for whom paternal report was available ($r = .79$).

Assessment of the Symptom Dimensions of ADHD

Results of a principal axis factor analysis reported in a previous paper (Willcutt & Pennington, in press) indicated that symptoms of *DSM-III* ADHD as assessed by the DICA comprise two factors (summarized in Table I). The first factor included seven symptoms similar to the symptoms of inattention described in *DSM-IV*, and the second component included seven symptoms similar to the *DSM-IV* hyp/imp dimension. Based on these results, inattention and hyp/imp composite scores were created by summing the number of positive symptoms among the seven on each component. Estimates of internal reliability were high for both the inattention composite (Cronbach's $\alpha = .88$) and the hyp/imp composite ($\alpha = .84$).

Consistent with *DSM-III* criteria, a cutoff score of eight positive symptoms was utilized as the diagnostic criterion for the overall diagnosis of ADHD. This criterion selected 9.6% of a separate control sample of 542 twins without evidence of learning difficulties in their academic records. In the sample of twins with learning difficulties, this cutoff score selected 84 MZ pairs (27 female, 57 male) and 78 DZ pairs (28 female, 50 male). Extreme cutoff scores were then derived for the inattention and hyp/imp composites by determining the number of symptoms of inattention (6 symptoms) and hyp/imp (3 symptoms) that would also identify the same proportion of the control sample without learning problems. The inattention cutoff selected 83 MZ pairs (32 female, 51 male) and 75 DZ pairs (30 female, 45 male) from the sample of twins with learning difficulties, and the hyp/imp cutoff selected 71 MZ pairs (49 male, 22 female) and 72 DZ pairs (49 male, 23 female) from this sample.

Measures of Cognitive Ability

The revised version of the Wechsler Intelligence Scale for Children (WISC-R; Wechsler, 1974) was utilized to assess the Full Scale IQ (FSIQ) of participants 16 years of age or younger, and the Wechsler Adult Intelligence Scale (WAIS, Wechsler, 1981) was utilized for participants who were 17 or 18 years of age.

Measure of Reading Achievement

The Peabody Individual Achievement Test (PIAT; Dunn & Markwardt, 1970) was utilized to assess academic achievement in reading and spelling.

Data Analyses

Concordance Rates

Monozygotic (MZ) twins share all of their genes, whereas dizygotic (DZ) twins share half of their segregating genes on average. Therefore, if a disorder is attributable to genetic influences, the rate of concordance between twins in a pair would be expected to be significantly higher for MZ twins than for DZ twins. However, the method used to calculate concordance rates depends upon the manner in which the sample was ascertained.

Two different selection procedures can be utilized to ascertain twin pairs in which at least one twin is affected with a disorder (e.g., DeFries & Alarcon, 1996; McGue, 1992). The *single selection* procedure randomly identifies one twin from each pair (e.g., the first-born member of the pair), and only those pairs in which that individual has the disorder are selected. In contrast, the *truncate selection* procedure allows all twins who fall above the cutoff score to be selected as probands, so if both twins in a pair fall above the cutoff they are both considered as probands. Truncate selection was utilized to identify the present sample, with all twins who met criteria for ADHD (or inattention or hyp/imp) selected as probands.

With single selection, only twin pairs in which Twin 1 meets criteria for the diagnosis are included in the sample (the first two rows in Table II), thereby providing a total sample of C + D. The "pairwise" concordance rate estimated from a sample ascertained in this manner would equal C/(C + D). In contrast, truncate selection also ascertains pairs in which Twin 2 has the disorder but Twin 1 does not (third row of Table II). Therefore, truncate selection identifies a total sample of C + 2D. In order to compensate for the greater number of discordant pairs ascertained through truncate selection, the "probandwise" concordance rate is computed by counting each concordant pair twice, once when Twin 1 is the proband and once when Twin 2 is the proband. By including both twins in the first row as probands, this "double entry" procedure effectively increases the sample to 2C + 2D, equating the probandwise concordance rate obtained through truncate selection (i.e., 2C/[2C + 2D]) and the pairwise concordance rate estimated using single selection. Because our sample was ascertained using truncate selection, this double-entry procedure was used to estimate probandwise concordance rates for the present study.

Table II. Calculation of Concordance Rates

Pairs	Twin 1	Twin 2	Number
Concordant	ADHD	ADHD	C
Discordant	ADHD	Not ADHD	D
Discordant	Not ADHD	ADHD	D

The DeFries-Fulker Multiple Regression Method

Whereas a comparison of the rates of concordance in MZ and DZ twin pairs provides a conceptually simple appraisal of the etiology of a discrete disorder, the multiple regression method proposed by DeFries and Fulker (1985, 1988) provides a more powerful and versatile test of the etiology of extreme scores on a continuous dimension. The DeFries and Fulker model (DF model) is based on the regression of MZ and DZ cotwin scores toward the population mean when probands are selected because of extreme scores on a phenotype (e.g., ADHD). Although scores of both MZ and DZ cotwins would be expected to regress toward the population mean, scores of DZ cotwins should regress further toward the mean of the unselected population than scores of MZ cotwins to the extent that extreme ADHD scores are influenced by genes.

Similar to the concordance analyses, all twins who scored above the cutoff on the ADHD measures were selected as probands for the regression analyses. Because the double entry of concordant pairs artificially inflates the sample size, the standard errors of the regression coefficients were corrected prior to tests of significance (e.g., Stevenson, Pennington, Gilger, DeFries, & Gillis, 1993). In order to facilitate the estimation of h_g^2, standardized scores were created prior to conducting the multiple regression analysis based on the mean and standard deviation of the separate control sample of twins without a history of significant learning problems. The obtained standardized scores of the selected sample of MZ probands and cotwins were then divided by the MZ proband mean, and the DZ proband and cotwin scores were divided by the DZ proband mean. This procedure ensures that the MZ and DZ probands are equally divergent from the mean score of the controls prior to the regression analysis.

The basic regression model is as follows:

$$C = B_1 P + B_2 R + K \quad (1)$$

where C is the expected cotwin score, P is the proband score, R is the coefficient of relationship (1 for MZ pairs, 0.5 for DZ pairs), and K is the regression constant. The B_1 coefficient represents the partial regression of the cotwin's score on the proband score, and provides a measure of twin resemblance irrespective of zygosity. The B_2 parameter represents the partial regression of the cotwin's score on the coefficient of relationship, and after appropriate transformation of the data, provides a direct estimate of the heritability of extreme scores on the trait under consideration (h_g^2). After adjustment of the standard errors of the regression coefficients to correct for the double entry of concordant pairs, the significance of the B_2 parameter provides a statistical test of the extent to which extreme scores are attributable to genetic influences.

Evaluation of the Relation Between Extreme Inattention and hyp/imp

The DF model can be elaborated to test for the influence of other independent variables on the etiology of the extreme score under consideration. For the current analyses, extended DF models were utilized to test whether the etiology of extreme inattention or hyp/imp varied as a function of the proband's score on the other dimension. For example, the extended model to test whether the heritability of inattention varied as a function of hyp/imp was as follows:

$$C_{IN} = B_1 P_{IN} + B_2 R + B_3 P_{HYP} + B_4 P_{IN} * P_{HYP} + B_5 R * P_{HYP} + K \quad (2)$$

where C_{IN} is the number of inattention symptoms exhibited by the cotwin, P_{IN} is the number of inattention symptoms exhibited by the proband, R is the coefficient of relationship, P_{HYP} is a dummy code indicating whether or not the proband fell above the extreme score cutoff for hyp/imp, $P_{IN} * P_{HYP}$ is the product of the proband's inattention score and the hyp/imp dummy code, and $R * P_{HYP}$ is the product of the coefficient of relationship and the hyp/imp dummy code. When scores below the hyp/imp cutoff are coded as -0.5 and scores above the hyp/imp cutoff are coded as 0.5, the B_5 parameter estimates the difference between the heritabilities for inattention obtained in individuals with high versus low hyp/imp. Thus, in this case, the significance of the B_5 parameter tests whether the heritability of inattention is significantly different between individuals with high versus low hyp/imp. Alternatively, the actual number of symptoms of hyp/imp can be used as the P_{HYP} covariate in Equation 2 to test if the heritability of inattention differs as a linear function of hyp/imp symptoms.

RESULTS

Demographic Characteristics in the Overall Sample

Table III presents mean scores for the overall sample by zygosity for age, socioeconomic status (SES), IQ, and symptoms of ADHD. MZ and DZ twins did not differ in age or SES as assessed by the Hollingshead (1975) 2-factor inventory. The mean number of ADHD symptoms was also not significantly different by zygosity in the total sample of MZ and DZ twins, and the MZ and DZ variances were virtually identical. The ethnic composition of the overall sample was 84.8% Caucasian, 7.9% Non-white Hispanic, 4.0% African American, 1.7% Asian American, and 1.1% Native American. There were no significant differences in ethnic composition by zygosity.

Etiology of ADHD

When probands were selected for ADHD, MZ cotwins (78%) were significantly more likely than DZ cotwins (38%) to also meet criteria for ADHD, $\chi^2 = 47.02$, $p < .001$, suggesting that ADHD is substantially the result of genetic influences. These MZ and DZ concordance rates are similar to those obtained using another DSM-III measure of ADHD in an unselected twin sample (Levy *et al.*,

Table III. Mean Scores by Zygosity on Demographic Measures and Dimensions of ADHD[a]

Measure	MZ Twins *M*	MZ Twins *SD*	DZ Twins *M*	DZ Twins *SD*
Age	11.4	2.6	11.3	2.4
Socioeconomic status	37.5	14.6	35.0	14.9
Full Scale IQ	99.2	10.8	101.2	11.9
Hyp/imp symptoms	1.4	1.9	1.5	2.0
Inattention symptoms	3.4	2.6	3.2	2.5
Total ADHD symptoms	5.1	4.3	5.0	4.3

[a] MZ and DZ means were not significantly different for any variable.

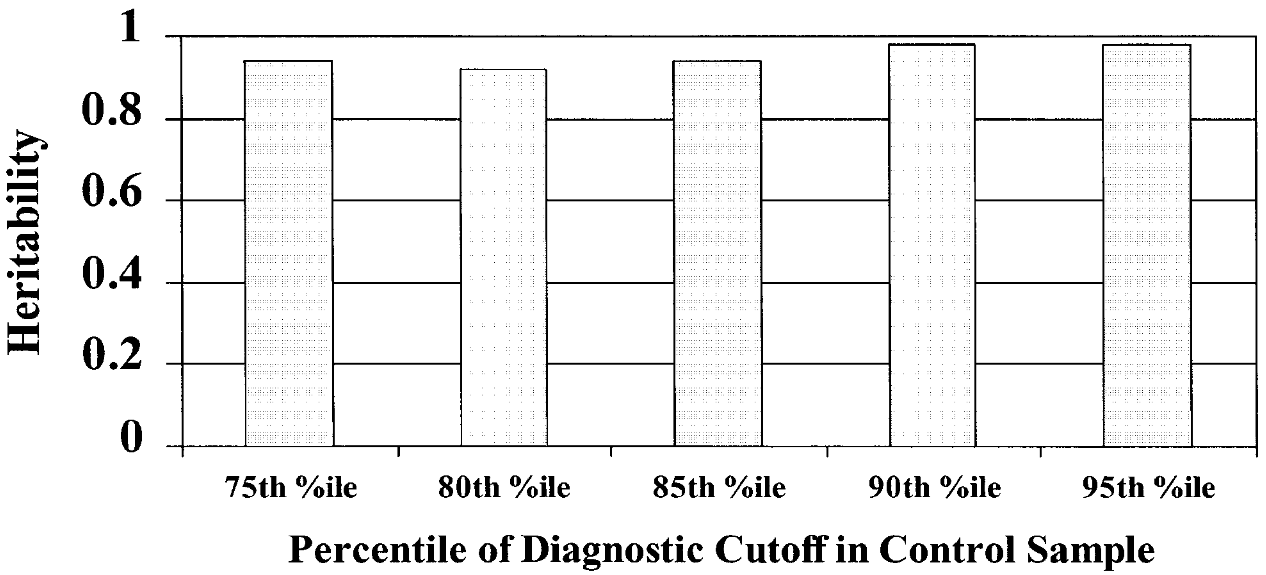

Fig. 1. Heritability of extreme ADHD scores based on a range of diagnostic cutoff scores.

1997), providing support for the generalizability of the current findings.

Whereas concordance analyses provide a rough index of the extent to which genetic and environmental influences contribute to extreme ADHD scores, the DF method provides a more powerful test of the etiology of this condition, and facilitates the comparison of the relative influence of genetic and environmental factors. When probands with eight or more symptoms of ADHD were selected, the mean standardized DICA scores of the MZ and DZ probands fell approximately two and one-half standard deviations above the mean of the comparison sample of twins without learning difficulties (MZ $M = 2.45$, $SD = 0.68$; DZ $M = 2.59$, $SD = 0.73$). As expected, the scores of MZ and DZ cotwins both regress toward the control mean, but the difference between the mean scores of the MZ cotwins (2.19 standard deviations above the control mean) and DZ cotwins (1.02 standard deviations above the mean of the comparison sample) suggests that extreme ADHD scores are highly heritable. Indeed, results of the multiple regression analysis indicated that extreme scores on the DICA are significant and almost entirely attributable to genetic influences, $h_g^2 = 0.98(.16)$, $t = 6.12$, $p < .001$.

Etiology of ADHD at Different Diagnostic Cutoff Scores

In order to test whether the etiology of ADHD differed depending on severity, a series of DF analyses were conducted utilizing a range of diagnostic cutoff scores. As noted previously, the cutoff score of eight positive symptoms specified in the *DSM-III* and the DICA manual selected 9.6% of the separate control sample of twins without evidence of learning difficulties. Additional cutoffs were then derived that selected 25% (5 symptoms), 20% (6 symptoms), 15% (7 symptoms), and 5% (10 symptoms) of the same control sample. Results of analyses using each of these cutoffs indicated that extreme ADHD scores were highly heritable for all five cutoff scores (Fig. 1). Moreover, the similarity of these heritability estimates is consistent with the hypothesis that the same genetic influences contribute to ADHD across a range of diagnostic severity.

Etiology of Extreme Inattention and Hyperactivity/Impulsivity

The rates of concordance for extreme inattention and hyp/imp were both significantly higher for MZ pairs than DZ pairs (Table IV), suggesting that extreme scores on these dimensions are both significantly attributable to genetic influences. Similarly, group heritability estimates (Table V) were significant and substantial for both extreme inattention ($h_g^2 = 0.94$) and extreme hyp/imp ($h_g^2 = 0.78$).

The Relation Between Extreme Inattention and Hyperactivity/Impulsivity

Analyses of the overlap between extreme hyp/imp and inattention were conducted in order to test whether

Table IV. Probandwise Concordance Rates by Zygosity for Extreme Inattention and Hyperactivity/Impulsivity

Measure	Number of pairs MZ	Number of pairs DZ	Probandwise concordance MZ	Probandwise concordance DZ	χ^2
Extreme inattention					
Total sample	83	75	76%	30%	61.71***
High hyp/imp probands	43	30	83%	30%	44.04***
Low hyp/imp probands	40	45	65%	20%	21.65***
Extreme hyperactivity/ impulsivity					
Total sample	71	72	72%	46%	23.88***
High inattention probands	29	31	80%	42%	24.00***
Low inattention probands	42	41	56%	50%	2.71

***= $p < .001$.

extreme scores on the two dimensions co-occurred significantly more frequently than would be expected by chance. Results revealed a substantial correlation between the continuous dimensions of inattention and hyp/imp symptoms ($r = .59$). Similarly, individuals who scored above the extreme score cutoff on the inattention dimension were significantly more likely also to score above the hyp/imp cutoff (54%) than were individuals who scored below the inattention cutoff score (13%), and individuals with extreme hyp/imp scores exhibited a significantly higher prevalence of extreme inattention (61%) than individuals without significant hyp/imp symptoms (15%).

Because the finding that extreme inattention and hyp/imp scores overlapped significantly, follow-up analyses were conducted to test if the etiology of extreme scores on either dimension varied as a function of the proband's score on the other dimension. When probands were selected due to extreme inattention (Table IV), the rate of extreme inattention was significantly higher among MZ cotwins than DZ cotwins whether or not the proband also exhibited extreme hyp/imp. This result suggests that the etiology of extreme inattention is similar whether the proband exhibits both inattention and hyp/imp (e.g., the Combined Type) or inattention alone (the Inattentive Type). The probandwise concordance rate for extreme hyp/imp was also significantly higher among MZ pairs than DZ pairs when probands exhibited both extreme inattention and extreme hyp/imp. In contrast, the probandwise concordance for extreme hyp/imp was almost identical in MZ and DZ pairs when the proband scored above the hyp/imp cutoff in the absence of significant inattention. This unexpected finding suggests that whereas extreme hyp/imp is attributable to genetic influences in individuals that also have significant attention problems, environmental influences largely account for extreme hyp/imp in individuals without significant inattention.

Two sets of analyses were conducted to test if the heritability of extreme inattention or hyp/imp varied significantly as a function of the proband's score on the other dimension. First, a dummy code indicating whether or not the proband exhibited an extreme score on the other dimension was included in an extended DF model (see Equation 2). Results indicated that extreme inattention was highly heritable whether or not the proband also exhibited extreme hyp/imp (Table V). In order to test whether this finding might be limited to the specific cutoff for hyp/imp utilized in this study, the extended model was also fit to the inattention data using the entire dimension of hyp/imp symptoms. The heritability of extreme inattention did not vary significantly as a function of the number of hyp/imp symptoms exhibited by the proband ($p > .50$). In contrast, the heritability of extreme hyp/imp was substantially higher when selected probands also met criteria for inattention ($h_g^2 = 1.10$) than when probands fell below the extreme score cutoff for inattention ($h_g^2 = 0.08$). The inclusion of a dummy code for the inattention diagnosis in the extended multiple regression model revealed that

Table V. Heritability of Extreme Scores on the Inattention and Hyperactivity/Impulsivity Composites

Sample	# Pairs MZ	# Pairs DZ	MZ Proband Mean (*SD*)	DZ Proband Mean (*SD*)	MZ Cotwin Mean (*SD*)	DZ Cotwin Mean (*SD*)	h_g^2 (SE)	*t*
Extreme inattention								
Total sample	83	75	2.35 (0.23)	2.31 (0.24)	1.96 (0.89)	0.84 (1.11)	0.94 (.15)	6.27**
Proband high H/I	40	45	2.43 (0.23)	2.37 (0.25)	2.19 (0.74)	0.91 (1.13)	1.04 (.19)	5.47**
Proband low H/I	43	30	2.26 (0.24)	2.22 (0.23)	1.73 (0.98)	0.73 (1.08)	0.88 (.28)	3.14**
Extreme hyperactivity/impulsivity								
Total sample	71	72	2.71 (1.05)	2.80 (0.95)	2.31 (1.44)	1.28 (1.64)	0.78 (.22)	3.54**
Proband high Inatt.	42	41	2.87 (1.08)	3.21 (0.97)	2.56 (1.42)	1.08 (1.51)	1.10 (.23)	4.78**
Proband low Inatt.	29	31	2.34 (0.90)	2.29 (0.61)	1.75 (1.34)	1.65 (1.76)	0.08 (.32)	0.24

**= $p < .01$.

the difference between the two h_g^2 estimates for hyp/imp is significant ($B_5 = 1.02 \pm 0.38$, $t = 2.72$, $p < .01$), suggesting that the etiology of extreme hyp/imp is different in children who also exhibit extreme inattention versus children with high hyp/imp alone. Moreover, results of the extended model revealed that the heritability of extreme hyp/imp increased as a linear function of the number of symptoms of inattention ($p < .01$), suggesting that this relation is not restricted to a single arbitrary cutoff for extreme inattention.

The Influence of Academic Achievement, FSIQ, and Gender on the Etiology of ADHD

As a final test of the etiology of extreme ADHD symptomatology, the influence of reading and mathematics achievement, FSIQ, and gender was tested by including each of these variables in a separate extended DF model. None of the findings discussed previously differed significantly as a function of academic achievement or FSIQ ($p > .50$). Although none of the heritability estimates differed significantly as a function of gender, the difference between the heritability of hyp/imp in males ($h_g^2 = 0.92$) and females ($h_g^2 = 0.50$) suggested that extreme hyp/imp might be more heritable among males than among females in a larger sample.

DISCUSSION

This study examined the etiology of ADHD in a sample of twins selected because at least one twin in each pair had a history of learning difficulties. Results revealed that extreme scores on a measure of *DSM-III* ADHD were almost entirely attributable to genetic influences, with similar heritability estimates across a range of diagnostic cutoff scores ($h_g^2 = 0.92$–0.98). These heritability estimates are similar to those obtained in a different study (Levy *et al.*, 1997) that utilized the same analytical technique to examine the etiology of symptoms of *DSM-III* ADHD ($h_g^2 = 0.91$), suggesting that the current findings are comparable to results from unselected community samples. The finding that heritability estimates are similar across multiple diagnostic cutoff scores is also consistent with two previous studies (Gjone *et al.*, 1996; Levy *et al.*, 1997), providing converging evidence suggesting that genetic influences account for a similar proportion of the variance in symptoms of ADHD across a range of severity.

Based on the results of a factor analysis (Willcutt & Pennington, in press), symptoms of ADHD were subdivided to form inattention and hyp/imp symptom composites. Extreme inattention scores were highly heritable whether or not the proband also exhibited extreme hyp/imp, consistent with the hypothesis that the etiology of symptoms of inattention is similar whether or not the individual also exhibits elevations of hyp/imp. In contrast, whereas extreme hyp/imp was highly heritable ($h_g^2 = 1.10$) when probands exhibited scores above the cutoff for both hyp/imp and inattention, the heritability of extreme hyp/imp was nonsignificant ($h_g^2 = 0.08$) when probands with extreme hyp/imp did not also exhibit extreme inattention. This unexpected finding suggests that the etiology of extreme hyp/imp may be different for individuals with and without concomitant elevations of inattention.

Implications for the *DSM-IV* Model of ADHD

Although these results should be interpreted with caution until they can be replicated in other community samples, the finding that the etiology of hyp/imp varies as a function of the number of symptoms of inattention may have important implications for the *DSM-IV* model of ADHD. If this finding can be replicated using a measure of the specific *DSM-IV* ADHD symptoms, this would suggest that the Combined Type and Hyp/Imp Type of ADHD are attributable to different etiological influences. Although such a finding would not provide definitive information regarding the relation between the subtypes, it would provide evidence consistent with the hypothesis that the Hyp/Imp Type and Combined Type may be better conceptualized as separate disorders with largely distinct etiologies.

Interpretation of this finding is complicated by the paucity of empirical data regarding children with specific elevations of hyp/imp in the absence of inattention. Prior to the field trials for *DSM-IV* (Lahey *et al.*, 1994), the Hyp/Imp Type had never been described in previous empirical or clinical literature with the exception of a single cluster analytic study (Bauermeister, 1992). Subsequent studies have suggested that the Hyp/Imp Type is associated with significant elevations of other disruptive symptoms (e.g., Gaub & Carlson, 1997; Faraone, Biederman, Weber, & Russell, 1998; McBurnett *et al.*, 1999; Willcutt, Pennington, Chhabildas, Friedman, & Alexander, 1999), but may be associated with lower levels of functional impairment than the Combined Type on measures of cognitive functioning (Faraone *et al.*, 1998; Lahey *et al.*, 1998; Willcutt *et al.*, 1999), academic achievement (Lahey *et al.*, 1994), and some facets of social functioning (Lahey *et al.*, 1994; Lahey *et al.*, 1998). These differences in the profile of functional impairment associated with the Combined Type and Hyp/Imp Type could be associated with the differences in etiology obtained in the present study, but additional studies with larger samples will be necessary to provide definitive information about the etiology and correlates of the Hyp/Imp subtype and its relation to the other subtypes of *DSM-IV* ADHD.

Limitations and Direction for Future Research

1. The sample utilized in this study was recruited because at least one twin in each pair exhibited evidence of learning difficulties in their school records. Because learning difficulties are significantly associated with ADHD (Fergusson & Horwood, 1992; McGee & Share, 1988; Semrud-Clikeman *et al.*, 1992; Willcutt & Pennington, in press), this method of ascertainment yielded a larger number of twins with ADHD than would be expected in an unselected sample. Although the utilization of a sample enriched for ADHD provided greater statistical power for the behavioral genetic analyses, this could limit the applicability of the current findings to unselected populations. For example, it is possible that the etiology of ADHD differs depending on the presence or absence of comorbid RD. However, a previous study of the etiology of *DSM-III* ADHD in an unselected population yielded heritability estimates similar to those obtained in the present sample (Levy *et al.*, 1997). Moreover, the heritability of ADHD symptoms did not vary significantly as a function of the proband's reading achievement in the present sample. Taken together, these results suggest that ADHD may be highly heritable regardless of comorbidity with RD. Nevertheless, the current findings should be interpreted with caution until they can be replicated in a separate sample of unselected twins.
2. Previous studies of unselected samples have suggested that the high heritability estimates obtained for ADHD may be at least partially attributable to contrast effects (Goodman & Stevenson, 1989; Thapar *et al.*, 1995). Contrast effects occur if parents describe MZ twins as more similar or DZ twins as more distinct based on their knowledge of the twins' zygosity, rather than actual behavioral similarities or differences exhibited by the twins. Two findings in the present sample provide tentative evidence against the hypothesis that the present findings are attributable to contrast effects. First, significant contrast effects are typically reflected in significantly higher means and variances for DZ twins than MZ twins (e.g., Carey, 1986). Therefore, the similarity of the MZ and DZ means and variances for all measures of ADHD argues against this hypothesis. Second, twin correlations between pairs in which the mother reported that she was unsure of the twin's zygosity were compared to correlations between pairs in which the mother reported that she knew the zygosity of her children. MZ twin correlations were similar whether the mother reported that she knew the twins' zygosity ($n = 237; r = .84$ for ADHD, $r = .87$ for hyp/imp, $r = .75$ for inattention) or was unsure of the zygosity of the pair ($n = 90; r = .87$ for ADHD, $r = .79$ for hyp/imp, $r = .84$ for inattention), suggesting that knowledge of the children's zygosity does not influence ratings of MZ twins. Unfortunately, the mothers of only nine DZ pairs reported that they were unsure about their twins' zygosity; therefore, it was not possible to test the hypothesis that parents may exaggerate the difference between DZ twins based on their knowledge of the twins' zygosity (e.g., Simonoff *et al.*, 1998). We are currently collecting reports from both parents and teachers as another method to address this issue.
3. When probands were selected for hyp/imp in the presence of extreme inattention, the heritability estimate for extreme hyp/imp was above the mathematically defined limit of 1.0. Several explanations may explain this finding, including contrast effects or significant nonadditive genetic influences. However, because heritability estimates obtained from the DF method are unconstrained, a heritability estimate slightly above 1.0 may simply reflect the range of sampling error around the true estimate (95% CI $= 0.65 - 1.55$).
4. The version of the DICA utilized in the current study was designed to assess the *DSM-III* symptoms of ADHD. While the factor analysis reported in a previous paper (Willcutt & Pennington, in press) is quite consistent with the findings of one study using the same measure (Sherman *et al.*, 1997) and numerous studies using different measures of ADHD (Bauermeister, 1992; Burns *et al.*, 1997; Conners *et al.*, 1998a, 1998b; Healey *et al.*, 1993; Hudziak *et al.*, 1998; Pelham *et al.*, 1992), the current findings warrant replication with a measure of the specific symptoms of inattention and hyp/imp described in *DSM-IV*.
5. The prevalence of ADHD in the present normal control sample of twins (9.6%) is somewhat higher than the average prevalence of approximately 5%

obtained in previous epidemiological studies using *DSM-III* criteria (see Barkley, 1998 for a summary). The reasons for the higher prevalence in the present sample are unclear, but may have resulted in an ADHD sample that is less extreme than samples ascertained in other studies. Therefore, future studies of larger samples should test if the present findings can be replicated using a more stringent cutoff score for ADHD.

6. Results of previous family studies have suggested that the presence or absence of comorbid psychopathology may represent a marker for different etiological subtypes of ADHD (e.g., Faraone *et al.*, 1991; Sprich-Buckminster *et al.*, 1993). Analyses of the influence of comorbid psychopathology were not possible in the current sample because data were available for only a subset of the participants. Therefore, future studies utilizing larger samples could provide a valuable extension of the current findings by testing directly if the etiology of ADHD differs as a function of comorbid disorders.
7. Finally, although the overall sample utilized for this report is fairly large, the statistical power to detect gender differences in the etiology of ADHD was low. Therefore, future studies utilizing larger samples should continue to test whether ADHD is attributable to different etiological influences in boys and girls.

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