

# Understanding Comorbidity: A Twin Study of Reading Disability and Attention-Deficit/Hyperactivity Disorder

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**A community sample of twins in which at least one member of each pair exhibited significant reading difficulties (99 monozygotic and 80 dizygotic pairs) or symptoms of attention-deficit/hyperactivity disorder (ADHD; 83 monozygotic and 78 dizygotic pairs) was used to test the etiology of comorbidity between reading disability (RD) and ADHD. Univariate analyses revealed moderate to high heritability for all measures of reading difficulty and ADHD. Subsequent bivariate analyses indicated that the relation between reading difficulties and inattention symptoms is primarily attributable to common genetic influences, whereas bivariate heritability estimates were not significant for hyperactivity-impulsivity and any of the reading measures. Reading difficulties and ADHD symptoms were more highly heritable if the proband met criteria for both disorders versus RD or ADHD alone, suggesting that future molecular genetic analyses of comorbid RD + ADHD may facilitate the identification of susceptibility genes for RD, ADHD, and their comorbidity.** © 2007 Wiley-Liss, Inc.

**KEY WORDS:** reading; ADHD; twins; bivariate; comorbidity

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## INTRODUCTION

Comorbidity is the rule, rather than the exception, for virtually all mental disorders [e.g., Angold et al., 1999]. Over 80% of children with attention-deficit/hyperactivity disorder (ADHD) and 60% of children with reading disability (RD) meet criteria for at least one additional diagnosis [e.g., Faraone et al., 1998; Willcutt and Pennington, 2000a,b], and similar rates of comorbidity have been documented for most other disorders defined in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders [DSM-IV; American

Psychiatric Association, 1994] [e.g., Angold et al., 1999]. The etiology of these comorbidities is largely unknown.

High rates of comorbidity complicate interpretation of both clinical assessments and research studies, and could indicate that the current diagnostic nosology is fundamentally flawed. On the other hand, increasing evidence suggests that RD, ADHD, and most DSM-IV disorders have a complex etiology that involves multiple genetic and environmental risk factors [e.g., Faraone et al., 1999; Fisher and DeFries, 2002], so it is perhaps not surprising that some of these risk factors may increase susceptibility to multiple disorders. Studies of the etiology of comorbidity afford a unique opportunity to determine which risk factors are specific to a disorder and which reflect more general susceptibility. By clarifying the relations between disorders, these methods will help to refine further both the definitions of specific diagnoses and the overarching nosology of disorders. In this paper we describe a series of twin analyses conducted to examine the etiology of comorbidity between RD and ADHD, two of the most common disorders of childhood [e.g., American Psychiatric Association, 1994].

## Competing Explanations for Comorbidity Between RD and ADHD

Before attempting to understand the etiological underpinnings of comorbidity, it is important to first rule out the possibility that the observed comorbidity is an artifact caused by a biased sampling procedure or measurement problem [e.g., Angold et al., 1999]. RD and ADHD co-occur more frequently than expected by chance in both clinic-referred and community samples [e.g., Semrud-Clikeman et al., 1992; Willcutt and Pennington, 2000a], indicating that this comorbidity is not a selection artifact. Because RD is assessed by cognitive tests whereas ADHD is assessed by behavioral ratings, the relation between RD and ADHD cannot be explained by shared method variance, and the defining symptoms of RD and ADHD do not overlap [American Psychiatric Association, 1994].

Numerous competing hypotheses have been proposed to explain non-artifactual comorbidity between disorders [e.g., Neale and Kendler, 1995; Angold et al., 1999], and several of these explanations have received support in at least a subset of studies of RD and ADHD. One initial study found that comorbidity between learning disabilities and ADHD was due to cross-assortment between individuals with ADHD and individuals with a learning disability [Faraone et al., 1993], and a second study suggested that many cases of comorbid RD + ADHD occur because RD leads to a secondary ADHD phenocopy in the absence of the etiological influences typically associated with ADHD [Pennington et al., 1993]. However, neither of these results replicated in subsequent studies [e.g., Doyle et al., 2001; Seidman et al., 2001; Willcutt et al., 2001, 2005; Friedman et al., 2003]. Instead, family and twin studies demonstrate that RD and ADHD are each familial and highly heritable [e.g., Faraone et al., 1993; Willcutt et al., 2000a; Gayán and Olson, 2001; Friedman et al., 2003], and bivariate

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twin analyses suggest that comorbidity between RD and ADHD may be due in part to common genetic influences [e.g., Stevenson et al., 1993; Light et al., 1995; Willcutt et al., 2000b].

### The Present Study

Analyses were conducted in a population-based sample of twins to test the etiology of comorbidity between RD and DSM-IV ADHD. The sample described in this report is completely independent from the sample used for our previous twin analyses of the relation between RD and DSM-III attention deficit disorder [Gilger et al., 1992; Light et al., 1995; Willcutt et al., 2000b]. This study extends previous research in three important ways: (a) probands were selected independently for both RD and DSM-IV ADHD, providing a direct test whether the etiology of comorbidity is the same when probands are selected for each disorder; (b) three measures of DSM-IV ADHD symptoms and three measures of component reading and language skills were analyzed to test if the relation between RD and ADHD differs as a function of these underlying phenotypes; (c) analyses were conducted to test whether the heritability of RD or ADHD was different if the proband had both RD and ADHD versus either disorder alone.

## MATERIALS AND METHODS

### Participants

Participants completed the measures described in this report as part of the Colorado Learning Disabilities Research Center (CLDRC) twin study (study procedures are described in detail by DeFries et al. [1997]). Without regard to reading or ADHD status, twin pairs in 22 Colorado school districts were identified and parents were contacted and invited to participate in the initial screening for the study. Screening procedures were then conducted independently to identify twin pairs in which at least one of the twins met criteria for ADHD and pairs in which at least one of the twins exhibited significant reading difficulties, as well as a comparison sample in which neither twin exhibited ADHD or reading difficulties.

To identify twin pairs in which at least one twin exhibited significant reading difficulties, parental consent was requested to allow study staff to review each twin's academic records. If either member of a twin pair had a positive history of learning difficulties (e.g., low achievement test scores, referral to a tutor, reports by classroom teachers or school psychologists), both members of the pair were invited to participate in the study. Twins then completed a comprehensive battery of reading and language measures, and probands were identified based on the procedure described in the subsequent section.

To identify twins with ADHD, parents and teachers were asked to complete the *Disruptive Behavior Rating Scale* [Barkley and Murphy, 1998] to assess symptoms of DSM-IV ADHD. Twin pairs were included in the overall ADHD sample if either of the twins met symptom criteria for any DSM-IV ADHD subtype based on the diagnostic algorithm described in the DSM-IV field trials for the disruptive behavior disorders [Lahey et al., 1994]. Consistent with other community samples [e.g., Gaub and Carlson, 1997], the majority of the participants with ADHD met criteria for the DSM-IV inattentive type (56.2%) or combined type (36.1%), and only a small subset met criteria for the hyperactive-impulsive type (7.7%). Because too few probands met criteria for the hyperactive-impulsive or combined types to provide sufficient power for separate comparisons between MZ and DZ probands with these subtypes, all three subtypes were analyzed together using the proband selection procedure described in the following section. The pattern of results was similar when probands with the inattentive type were analyzed separately and when all three DSM-IV subtypes were included in the analysis.

Although the overall CLDRC twin sample now includes over 1,500 twin pairs, measures of DSM-IV ADHD were only administered to a subset of the total sample because DSM-IV was not published until 10 years after the study was initiated. Because the goal of this paper is to examine the etiology of comorbidity between RD and DSM-IV ADHD, analyses were restricted to same-sex twin pairs for whom the measure of DSM-IV ADHD was available. The zygosity of each pair was determined based on selected items from the Nichols and Bilbro [1966] questionnaire, and cases with ambiguous zygosity were confirmed by analysis of blood samples. The final sample included 179 same-sex pairs in which at least one twin met proband criteria for RD (99 monozygotic pairs, 80 dizygotic pairs), and 161 same-sex pairs in which at least one twin met criteria for ADHD (83 monozygotic pairs, 78 dizygotic pairs).

### Measures

**Reading.** As part of the larger study each twin completed a battery of measures of reading achievement and component reading and language skills. Three measures from this overall battery were included in the analyses described in this paper. Overall reading ability was assessed by a discriminant function score based on the Peabody Individual Achievement Test [PIAT; Dunn and Markwardt, 1970] Reading Recognition, Reading Comprehension, and Spelling subtests [DeFries, 1985]. A phoneme awareness composite score (comprised of the phoneme transposition, phoneme deletion, and Lindamood auditory conceptualization tasks described by Gayán and Olson [2001]) was included in the analyses because difficulties in the ability to recognize and manipulate the phonemic constituents of speech are regarded by many as the most proximal cause of most cases of RD [e.g., Wagner et al., 1994]. Finally, we analyzed the orthographic choice task [Olson et al., 1994], a measure of the ability to rapidly access the correct orthographic representation of words versus phonological foils (i.e., *rain* vs. *rane*), because previous results from our sample indicated that this task is associated more strongly with ADHD than the other measures in the battery of component reading and language skills [Willcutt et al., 2005].

**ADHD.** Parents and teachers rated each ADHD symptom on the DBRS using a 0–3 scale ranging from *not at all* to *very often*. The mean of the parent and teacher ratings was calculated for each item, and the mean symptom severity score on the 18 DSM-IV ADHD symptoms was used as the total ADHD composite measure. Composite scores based on the DSM-IV inattention and hyperactivity-impulsivity items were also analyzed separately to test if the results differed for the specific ADHD symptom dimensions.

### Data Analysis

**The DeFries–Fulker multiple regression model.** Increasing data suggest that the diagnostic cutpoints for RD and ADHD specified in DSM-IV dichotomize a continuous distribution of underlying liability to each disorder, and that these thresholds are therefore more conventional than natural [e.g., Shaywitz et al., 1992; Willcutt et al., 2000a]. Transformation of a continuous measure such as reading performance or ADHD symptoms into a categorical variable (e.g., RD or ADHD vs. unaffected) results in the loss of important information pertaining to both severity within the disorder and variability in subthreshold symptomatology. In contrast, the multiple regression analysis of selected samples described by DeFries and Fulker [1985], [1988] DF analysis, provides greater statistical power by using information about the entire continuum of scores.

The DF model is based on the differential regression of MZ and DZ cotwin scores toward the population mean when

probands are selected due to an extreme score on a phenotype of interest (e.g., ADHD or RD). Although scores of both MZ and DZ cotwins are expected to regress toward the mean of the unselected population, scores of DZ cotwins should regress further than scores of MZ cotwins to the extent that extreme scores are influenced by genes. After appropriate standardization and transformation of scores, the magnitude of differential regression by zygosity provides a direct estimate of the heritability of the proband group deficit ( $h_g^2$ ; see [DeFries and Fulker, 1985, 1988] for a detailed description of DF analysis).

**Bivariate DF analysis.** A simple generalization allows the univariate DF multiple regression model to be applied to bivariate twin data to test the etiology of comorbidity [e.g., Light et al., 1995]. Rather than comparing the relative similarity of MZ and DZ twins on the same trait, the bivariate model compares the relation between the proband's score on the selected trait and the cotwin's score on a second, unselected trait. For example, if common genetic influences contribute to the association between RD and ADHD, the ADHD score of the cotwins of MZ probands with RD would be expected to regress less toward the ADHD population mean than the ADHD score of DZ cotwins. The bivariate multiple regression model provides an estimate of bivariate  $h_g^2$ , an index of the extent to which the proband deficit on the selected measure is due to genetic influences that are also associated with deficits on the unselected measure. The estimates of univariate and bivariate  $h_g^2$  can then be used to estimate the genetic correlation, a measure of the extent to which the genetic influences on RD and ADHD are common to both disorders (e.g., [Gayán and Olson, 2001]; see note in Table II).

**Testing for a differential etiology in the comorbid group.** The versatility of the DF regression model facilitates a final set of analyses with important implications for comorbidity between RD and ADHD. When probands are selected due to extreme scores on one of the phenotypes of interest (e.g., RD), a set of covariates can be added to the model to test directly if the etiology of reading deficits or ADHD symptoms is significantly different in the group of probands with comorbid RD + ADHD versus the group with RD or ADHD alone (for a detailed description of this extended DF model see [Willcutt et al., 2000a]).

## RESULTS

### Comorbidity of RD and ADHD

Approximately 40% of the individuals who met proband criteria for RD or ADHD also met criteria for the other disorder (94/238 probands with RD, 39.5%; 94/234 probands with ADHD, 40.1%). Phenotypic correlations were significant between all three reading measures and the three ADHD scores ( $P < 0.05$ ). These correlations were low in magnitude for hyperactivity-impulsivity ( $r_{HYP/DISCR} = 0.22$ ,  $r_{HYP/ORTH} = 0.26$ ,  $r_{HYP/PA} = 0.19$ ) and moderate for inattention ( $r_{INATT/DISCR} = 0.41$ ,  $r_{INATT/ORTH} = 0.43$ ,  $r_{INATT/PA} = 0.28$ ) and the total ADHD score ( $r_{ADHD/DISCR} = 0.36$ ,  $r_{ADHD/ORTH} = 0.38$ ,  $r_{ADHD/PA} = 0.25$ ). These results confirm that RD and ADHD are frequently comorbid in this sample, but suggest that the phenotypic relation between RD and ADHD is strongest for symptoms of inattention and weaker for measures of hyperactivity-impulsivity and phoneme awareness.

### Univariate Etiology of RD and ADHD

The basic DF multiple regression model was fitted to data from each measure of reading and ADHD (Table I). To equate the severity of the proband selection threshold for each measure, probands were selected for each analysis based on a cutoff score 1.5 SD below the mean of the comparison sample.

TABLE I. Univariate Heritability of Extreme Reading and ADHD Scores<sup>a</sup>

Measure	Monozygotic pairs			Dizygotic pairs			t	P <sup>c</sup>
	N pairs <sup>b</sup>	Proband M (SD)	Cotwin M (SD)	N pairs <sup>b</sup>	Proband M (SD)	Cotwin M (SD)		
Reading measures								
Discriminant score	99	-2.65 (0.81)	-2.35 (1.05)	80	-2.63 (0.79)	-1.47 (1.25)	-5.15	$4.0 \times 10^{-7}$
Orthographic choice	69	-2.93 (0.78)	-2.35 (1.45)	71	-2.89 (0.72)	-1.44 (1.60)	-2.77	0.003
Phoneme awareness	82	-3.04 (1.16)	-2.66 (1.50)	70	-2.99 (1.18)	-1.74 (1.75)	-3.47	0.0003
ADHD measures								
Total ADHD	80	-3.03 (1.33)	-2.61 (1.68)	77	-3.01 (1.42)	-1.35 (1.86)	-4.99	$8.2 \times 10^{-7}$
Inattention	83	-2.93 (1.10)	-2.60 (1.48)	78	-2.93 (1.23)	-1.33 (1.73)	-5.38	$2.0 \times 10^{-7}$
Hyperactivity-impulsivity	66	-2.95 (1.32)	-2.33 (1.66)	61	-2.91 (1.53)	-1.11 (1.84)	-4.27	$1.7 \times 10^{-5}$

<sup>a</sup>Note: Scores are expressed as standard deviations from the estimated population mean. To simplify interpretation the ADHD scores were multiplied by -1 so that lower scores indicate greater severity on all measures (i.e., deficits on the reading measures and elevations of ADHD symptoms).

<sup>b</sup>Total number of pairs in which at least one twin met the criteria for the proband group.

<sup>c</sup>One-tailed probability.

TABLE II. Genetic Correlations Between Measures of Reading and ADHD<sup>a</sup>

ADHD measure	Reading measure		
	Reading discriminant score	Orthographic choice	Phoneme awareness
Total ADHD	0.63	0.55	0.43
Inattention	0.72	0.71	0.41
Hyperactivity-impulsivity	0.40	0.40	0.37

<sup>a</sup>The genetic correlation is estimated based on the regression coefficients from the univariate and bivariate models:

$$r_g = \sqrt{(\beta_{2(xy)}) * (\beta_{2(yx)}) / (\beta_{2(x)}) * (\beta_{2(y)})}$$

Consequently, the MZ and DZ proband means were well below that cutoff score, falling more than 2.5 SD below the mean of the comparison sample on all variables. For all six variables, the mean score of the MZ cotwins regressed less toward the population mean than the mean score of the DZ cotwins, consistent with what would be expected if genetic influences contribute to each extreme score. Indeed, the multiple regression models revealed that extreme scores on all six measures were moderately to highly heritable ( $h_g^2 = 0.59$ – $0.93$ ; Table I). The heritability estimates for the reading measures are highly similar to results obtained in the overall CLDRC twin sample [e.g., Gayán and Olson, 2001], and the heritabilities of the extreme *DSM-IV* ADHD scores are similar to those obtained for a measure of *DSM-III* attention deficit disorder in an independent subset of our overall sample [Willcutt et al., 2000a].

### Bivariate Analyses

Results of bivariate analyses suggest that deficits on the reading discriminant score and the orthographic choice task are attributable to genetic influences that also lead to elevations of inattention and total ADHD symptoms (Fig. 1). Results were similar whether probands were selected due to extreme scores on the reading measures (Fig. 1A) or due to elevated symptoms of ADHD (Fig. 1B), and the associated genetic correlations suggest that a large proportion of the genetic influences on these reading and ADHD measures are common to both disorders ( $r_g = 0.55$ – $0.70$ ; Table II). In contrast, estimates of bivariate  $h_g^2$  were not significant for hyperactivity-impulsivity and any of the reading measures, and the relations between phoneme awareness and the ADHD measures were weaker and less consistent.

### The Etiology of the Comorbid Group

The final set of analyses assessed the etiology of the comorbid group more directly by testing if the univariate heritability of extreme scores on each measure differed as a function of the presence or absence of the comorbid disorder in the proband. Results indicated that the heritability of deficits on the reading discriminant score and the orthographic choice task were significantly higher if the proband also met criteria for ADHD (Fig. 2). In contrast, the heritability of the phoneme awareness deficit was not influenced by comorbid ADHD. Similar results were obtained when the RD probands were divided into groups with and without elevations of inattention and hyperactivity-impulsivity.

Although the heritability of the three ADHD scores are not significantly different in probands with and without RD, all three comparisons approached significance ( $P < 0.06$ ; Fig. 2). Moreover, the general pattern of results was consistent across the three measures of ADHD and similar to the results when probands were selected for RD; in every case, the heritability of the selected measure was higher if the proband had both RD

and ADHD than if the proband met criteria for the selected disorder alone.

## DISCUSSION

Bivariate twin analyses indicated that the significant comorbidity between RD and ADHD is largely attributable to common genetic influences. Analyses of more specific measures of ADHD and component reading skills suggest that the genetic correlation between RD and ADHD is highest for measures of inattention and orthographic coding and somewhat lower for symptoms of hyperactivity-impulsivity and measures of phoneme awareness. These results suggest that future phenotypic and molecular genetic studies of comorbidity between RD and ADHD should carefully consider the specific measures used to assess each disorder.

The heritability of group deficits on the reading discriminant score and the orthographic choice task were significantly

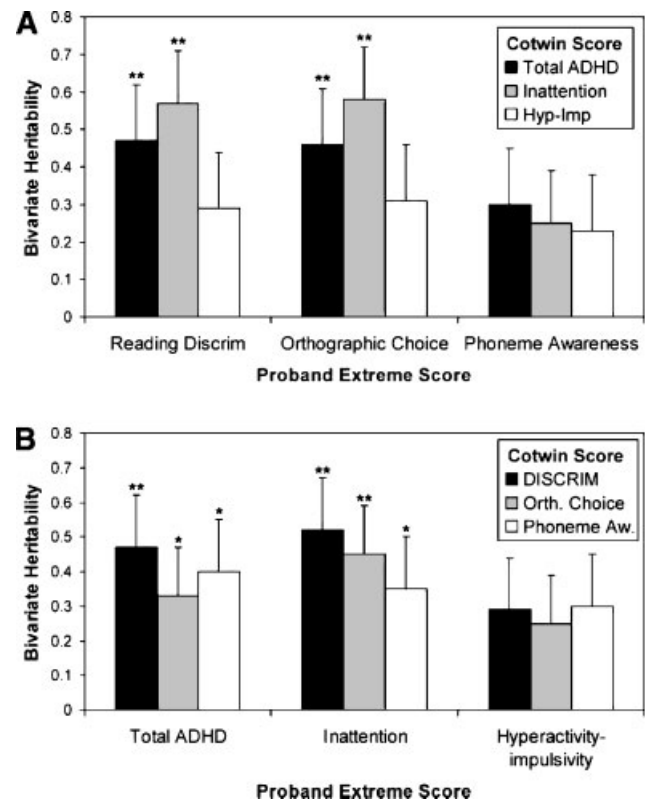


Fig. 1. Bivariate heritability of reading and ADHD. **Panel A:** Probands selected for deficits on each reading measure. **Panel B:** Probands selected due to elevations of ADHD symptoms. Significant bivariate heritability is indicated by (\*\* $P < 0.01$ ) and (\* $P < 0.05$ ).

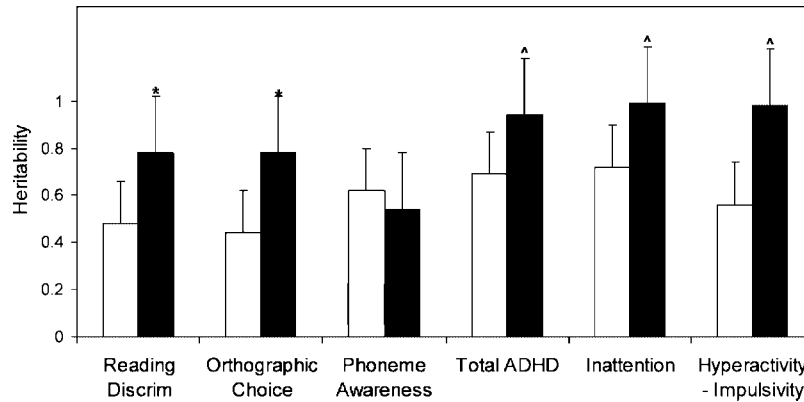


Fig. 2. Univariate heritability of each reading and ADHD score when the proband has both RD and ADHD ■ versus the selected disorder alone □. \* indicates a significant difference between the  $h^2_g$  estimates in the two proband groups ( $P < 0.05$ ), and ^ indicates a trend toward a significant difference ( $P < 0.10$ ).

higher if the proband had comorbid ADHD than if the proband exhibited reading difficulties in the absence of ADHD. Similarly, a statistical trend suggested that ADHD may be more highly heritable in the group with both RD and ADHD than in the group with ADHD alone. Although molecular genetic data will be needed to test definitively which hypothesis best explains comorbidity between RD and ADHD, the higher heritabilities in the group with both RD and ADHD suggest that future molecular genetic analyses of this group may facilitate the identification of genes for RD, ADHD, and their comorbidity [Ogdie et al., 2003].

## CONCLUSIONS

Our findings add to a growing literature that suggests that putatively distinct diagnoses such as RD and ADHD may be due in part to pleiotropic genes that confer risk for more than one disorder.

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