

# ■ No Clear Genetic Influences on the Association Between Dyslexia and Anxiety in a Population-based Sample of Female Twins

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Individuals with dyslexia are at an increased risk for anxiety disorders (e.g. generalized anxiety disorder, stress disorders, panic disorder). The extent to which this association is mediated by genetic and/or environmental influences is unclear. The current study explored the relationship between these two phenotypes using a large population-based twin sample. In total, 940 monozygotic and 903 dizygotic female twin pairs were included in the analyses. The presence of dyslexia and anxiety was determined by self-report of diagnosis by a health professional. Tetrachoric correlations confirmed an association between the two phenotypes, but suggested that there was no evidence for shared genetic risks. Bivariate twin modelling corroborated this finding and indicated the relationship between dyslexia and anxiety is mediated by shared environmental factors. Future research should seek to identifying the environmental factors that increase the vulnerability of individuals with dyslexia to emotional problems should be a priority for future research. Copyright © 2008 John Wiley & Sons, Ltd.

**Keywords:** dyslexia; anxiety; twin study; co-morbidity

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## INTRODUCTION

**R**eading disability carries an increased risk for a number of other psychiatric disorders. Although externalizing disorders such as attention deficit hyperactivity disorder (ADHD) are the most frequently observed co-morbidities (Carroll, Maughan, Goodman, & Meltzer, 2005; Willcutt & Pennington, 2000), findings have also indicated an elevated risk for internalizing problems (Maughan & Carroll, 2006). Anxiety disorder,<sup>†</sup> in particular, is found at greater than expected levels in reading disabled samples. For example, a recent UK epidemiological study (Carroll *et al.*, 2005) found that 9.9% of children with specific reading and/or spelling disability had a co-morbid anxiety disorder, a significantly greater prevalence than those without literacy difficulties (3.9%). Females with reading disability appear to be at particular risk for these internalizing problems (Willcutt & Pennington, 2000).

There is now clear evidence that many developmental and psychiatric disorders involve a strong genetic component (Rutter, Silberg, O'Connor, & Simonoff, 1999). The association between reading disability and psychiatric disorders such as ADHD and anxiety has prompted queries as to whether there may be shared genetic risks. Using a twin design, Willcutt, Pennington, and DeFries (2000) demonstrated significant bivariate heritability between reading disability and ADHD. Considerably less research has investigated whether there are shared genetic effects with internalizing problems. Willcutt and Pennington (2000) found that children with reading disability demonstrated significantly greater internalizing symptoms than their non-disordered co-twins, and concluded that these problems are unlikely to run in families. However, due to limited statistical power, this study was unable to capitalize upon the genetically informative data inherent in the twin design in order to draw more firm conclusions. Another possibility is that the association between reading disability and internalizing problems is due to environmental effects. For example, poor reading ability is known to exacerbate school- or work-related stressors as well as increase the likelihood of bullying (Riddick, Sterling, Farmer, & Morgan, 1999)—both of which may prompt feelings of anxiety (Bond, Carlin, Thomas, Rubin, & Patton, 2001).

The current study sought to explore the relationship between the genetic and environmental risk factors for dyslexia and anxiety, using data from a large volunteer UK twin registry (see [www.twinsuk.ac.uk](http://www.twinsuk.ac.uk)).

## METHODS

### Participants

Twin pairs were recruited from the St Thomas' Adult Twin Registry (Spector & Williams, 2006). The twins in this registry have been found to be broadly representative of the general population in the UK (Andrew *et al.*, 2001).

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<sup>†</sup>DSM-IV (American Psychiatric Association, 1994) lists seven broad types of anxiety disorder including generalized anxiety disorder, stress disorders, panic disorder and specific phobias. In the current study, these subtypes are subsumed under the umbrella term 'anxiety disorder'.

Considerably more comprehensive data were available for female twin pairs, leading us to omit male participants from analyses. Zygosity was determined through a standardized questionnaire and was confirmed when necessary by DNA genotyping. The 903 dizygotic (DZ) twin pairs ( $M$  age = 54.13 years;  $SD$  = 11.82) were slightly older than the 940 monozygotic (MZ) twin pairs ( $M$  age = 52.37 years;  $SD$  = 13.95), which was highly significant in this large sample  $t(1848) = 2.92, p < 0.001$ .

### **Questionnaire Measure**

A postal self-administered questionnaire was sent to participants. Data were collected on 16 different areas of participants' general health including cardiology, immunology, dermatology and rheumatology. Data analysed in the current study came from the neurology and psychiatry section, where participants were asked whether they had ever been told by a doctor or other health professional that they had dyslexia. Participants were also asked the age at which they received any diagnosis. Similar questions were asked about anxiety disorder.

A considerable proportion of participants in the current sample (31.7% of MZ twins and 69.52% of DZ twins) had completed the General Health Questionnaire-28 (GHQ; Goldberg, 1992) in a previous wave of data collection (roughly 2 years previous). The GHQ is a self-report questionnaire that asks about recent history of non-psychotic psychiatric disorders. One of the four GHQ subscales asks about symptoms commonly associated with anxiety disorder (subscale B).

### **Statistical Analysis**

The rationale of the twin design is as follows: whereas MZ and DZ twins differ in their genetic similarity (i.e. MZ twins have identical genotypes, while DZ twins have, on average, 50% of their genes in common), the environment is shared to a similar extent between the two twin types. Greater similarity between MZ than DZ pairs would indicate that a trait is under genetic influence. In the bivariate case (i.e. dyslexia and anxiety), the focus is on the association between the two phenotypes across a twin-pair. A higher cross-trait cross-twin correlation in MZ than DZ twins indicates that the two traits may have some shared genetic effects.

Tetrachoric correlations were calculated from the dichotomous data using a liability threshold model. This model assumes that the liability for a certain trait (i.e. dyslexia or anxiety) is normally or approximately normally distributed in a population, and only those above a certain threshold of liability will display that trait. Genetic models were then fitted to these data with the structural equation modelling programme *Mx* (Neale, Boker, Xie, & Maes, 2002). A bivariate Cholesky Decomposition model was used to estimate the components of phenotypic variance and covariance due to additive genetic (A), shared environmental (C) and non-shared environmental (E) effects. Reduced models, constructed by removing shared parameters, were then compared with the full model for goodness of fit by using a likelihood ratio chi-square test. A significant chi-square indicated a significant degradation of fit. The best fitting model was selected based upon the principle of parsimony, where models with fewer

parameters are preferred provided they do not provide a significantly worse fit. Parsimony was indexed by Akaike's Information Criterion (AIC), with the lowest AIC indicating the optimal combination of explanatory power and parsimony. (For more information on this procedure, see Purcell, 2001.)

## RESULTS

### Sample Characteristics

Table 1 shows the frequency of dyslexia and anxiety diagnoses in the current sample. The number of individuals who reported a history of dyslexia, with or without anxiety, was 2.35%. Anxiety disorder was much more common, being reported by 14.51% of the sample. The low prevalence of the two phenotypes of interest gave this study modest statistical power.

Information regarding age of diagnosis was missing for 5 participants with dyslexia and 40 participants with anxiety, including 4 participants who had a comorbid diagnosis. The mean age of diagnosis for dyslexia was 26.83 years ( $SD = 15.47$ , median = 25, range: 5–58) compared with 36.11 years for anxiety ( $SD = 13$ , median = 36, range: 7–70). Diagnoses of dyslexia were made between the years 1934 and 2005 (median = 1989) and diagnoses of anxiety were made between the years 1945 and 2006 (median = 1993).

We then examined the mean age of diagnosis for those with a diagnosis of both dyslexia and anxiety disorder and for whom these data were available ( $n = 17$ ). A paired  $t$ -test found no difference between the age of diagnosis for dyslexia ( $M = 30.47$ ,  $SD = 14.49$ , median = 33) and for anxiety ( $M = 35$ ,  $SD = 12.14$ , median = 32),  $t(16) = 1$ ,  $p = 0.32$ , Cohen's  $d = 0.34$ . Nine of the 17 participants received a diagnosis of dyslexia prior to a diagnosis of anxiety disorder, while the reverse was true for eight participants.

As highlighted previously, 31.7% of MZ twins and 69.52% of DZ twins had previously completed the GHQ. To examine the validity of the dichotomous measure of anxiety disorder used in the current study, we compared scores on the anxiety subscale of the GHQ between those who did ( $n = 257$ ) and did not ( $n = 1591$ ) report a history of anxiety disorder. An independent  $t$ -test confirmed that individuals who reported a history of anxiety disorder scored significantly higher (greater impairment) on the anxiety subscale ( $M = 6.67$   $SD = 4.73$ ) than the those who completed the GHQ but did not report a history of anxiety disorder ( $M = 4.09$   $SD = 3.73$ ),  $t(309.54) = 8.31$ ,  $p < 0.001$ , Cohen's  $d = 0.55$ .

Table 1. The number of participants who had a self-reported physician diagnosis of dyslexia and/or anxiety disorder

	Anxiety	
	No	Yes
Dyslexia		
No	3097	516
Yes	66	21

Table 2. Tetrachoric correlations (95% confidence intervals) for monozygotic (MZ) and dizygotic twins (DZ)

	MZ twins	DZ twins
Within-twin pair		
Dyslexia	0.73 (0.7–0.77)	0.43 (0.38–0.49)
Anxiety	0.44 (0.39–0.5)	0.31 (0.26–0.38)
Within twin		
Dyslexia and anxiety	0.23 (0.19–0.28)	0.10 (0.05–0.15)
Cross-twin cross-trait correlations		
Dyslexia and anxiety	0.11 (0.07–0.16)	0.18 (0.14–0.23)

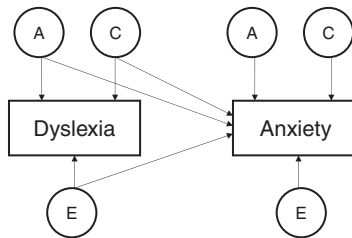


Figure 1. The full Cholesky Decomposition model, specifying specific and shared additive genetic (A), common environmental (C) and unique environmental (E) effects.

### Biometric Genetic Models

Table 2 shows the tetrachoric matrices for dyslexia and anxiety in MZ and DZ twins. The within-twin correlations for each disorder were higher in MZ than DZ twins but not greater than double, suggesting influence of additive genetic effects and shared environmental effects to individual differences. The within-twin phenotypic correlations (i.e. between the two traits) indicate that dyslexia is associated with anxiety, although the magnitude of these correlations was small. The cross-twin cross-trait correlation for MZ twins was similar to that of DZ twins (i.e. overlapping 95% confidence intervals), suggesting that the association between dyslexia and anxiety is not explained by genetic influences.

### Bivariate Genetic Analysis

A bivariate model of dyslexia and anxiety was specified that included shared and specific additive genetic, common and unique environmental components (see Figure 1). Reduced models were then tested against this full model by removing shared factors. Table 3 shows the model fitting results. The best fitting model included shared common environmental influences for dyslexia and anxiety as well as specific additive genetic, common and unique environmental effects for each phenotype (bolded in Table 3). This model with standardized pathway coefficients is shown in Figure 2. Unique additive genetic effects accounted for 60% of the variance in dyslexia and 24% of the variance in anxiety disorder. The shared environmental correlation between dyslexia and anxiety, calculated as  $(0.08) \cdot (0.19) / \sqrt{((0.08^2) \cdot (0.19^2 + 0.45^2))}$ , was 0.39. Thus, shared environmental

Table 3. Bivariate genetic model fitting for dyslexia and anxiety

Common factors	Dyslexia			Anxiety			Common			Fit statistics			
	$a^2$	$c^2$	$e^2$	$a^2$	$c^2$	$e^2$	$a^2$	$c^2$	$e^2$	df	$\chi^2$	p	AIC
ACE	0.53 (0.01–0.85)	0.2 (0–0.61)	0.27 (0.12–0.5)	0.21 (0–0.5)	0 (0–0.38)	0.55 (0.41–0.68)	0.01 (0–0.39)	0.21 (0–0.44)	0.01 (0–0.13)	–	–	–	–
CE	0.62 (0.02–0.83)	0.11 (0–0.59)	0.26 (0.12–0.48)	0.25 (0–0.50)	0 (0–0.37)	0.56 (0.43–0.68)	–	0.19 (0–0.38)	0 (0–0.09)	1	0.27	0.6	–1.73
AE	0.69 (0.06–0.88)	0.05 (0–0.56)	0.26 (0.12–0.49)	0.05 (0–0.56)	0.17 (0–0.42)	0.56 (0.43–0.68)	0.04 (0–0.39)	–	0 (0–0.09)	1	2.15	0.14	0.15
AC	0.56 (0–0.85)	0.17 (0–0.61)	0.27 (0.12–0.5)	0.23 (0–0.5)	0 (0–0.39)	0.56 (0.45–0.68)	0 (0–0.37)	0.21 (0–0.45)	–	1	0.31	0.58	–1.7
A	0.69 (0.06–0.88)	0.05 (0–0.56)	0.26 (0.12–0.49)	0.24 (0–0.52)	0.17 (0–0.42)	0.56 (0.44–0.68)	0.04 (0–0.37)	–	–	2	2.16	0.34	–1.84
<b>C</b>	<b>0.6</b> <b>(0.01–0.81)</b>	<b>0.13</b> <b>(0.01–0.6)</b>	<b>0.26</b> <b>(0.12–0.49)</b>	<b>0.24</b> <b>(0–0.49)</b>	<b>0</b> <b>(0–0.37)</b>	<b>0.56</b> <b>(0.45–0.68)</b>	–	<b>0.19</b> <b>(0.01–0.44)</b>	–	<b>2</b>	<b>0.39</b>	<b>0.82</b>	<b>–3.61</b>
E	0.68 (0.05–0.87)	0.05 (0–0.55)	0.27 (0.13–0.5)	0.27 (0–0.55)	0.16 (0–0.43)	0.52 (0.37–0.66)	–	–	0.04 (0–0.17)	2	5.89	0.05	1.89

The values represent the proportion of variance accounted for by the specific and common factors (95% confidence intervals are in parentheses). The accepted model is bolded.

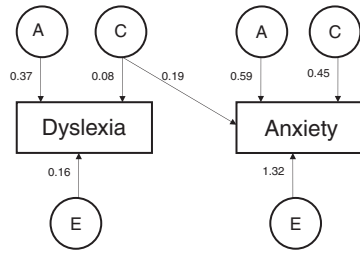


Figure 2. Path model depicting the shared environmental effects that are common to dyslexia and anxiety. The figure also shows the additive genetic, shared environmental and non-shared environmental effects that are unique to each phenotype.

effects, which are correlated at 0.39, account for all of the covariation between dyslexia and anxiety.

In the current sample, the DZ twins were significantly older than the MZ twins. To examine whether age differences had an effect on the findings, we reran the analyses presented above after homogenizing the samples by excluding twin pairs at the older end of the DZ distribution i.e. over the age of 70 years (MZ twin pairs:  $n = 940$ ; 52.37 years;  $SD = 13.95$ ; DZ:  $n = 845$ ;  $M = 52.8$  years;  $SD = 11$ ,  $p = 0.48$ ). Among the DZ cases omitted from these analyses, two had received a diagnosis of anxiety disorder and a separate case had received a diagnosis of dyslexia. The analyses revealed highly similar findings with the best fitting model including specific A, C and E for each phenotype along with a shared common environmental pathway (correlation = 0.4).

## DISCUSSION

The present study utilized a twin methodology to investigate the relative contribution of genetic and environmental effects on the association between dyslexia and anxiety. In accordance with previous studies, dyslexia was found to be moderately heritable (deFries & Alarcón, 1996), while anxiety showed a smaller degree of heritability (Hettema, Neale, & Kendler, 2001). Tetrachoric correlations replicated previous findings of an association between dyslexia and anxiety disorder, but suggested this was independent of genetic effects. Bivariate genetic analyses confirmed this finding and indicated that the covariance between dyslexia and anxiety reflects environmentally mediated influences that are common to both members of a twin pair.

Existing research allows us to speculate on the environmental factors that may underlie the relationship between dyslexia and anxiety disorder. One possibility is that negative academic and/or social experiences mediate the association between dyslexia and anxiety (Riddick *et al.*, 1999), and that this also impacts upon the unaffected co-twin. Twins are known to share much of their friendships (Thorpe & Gardner, 2006); thus, any victimization, bullying or social isolation of one twin is unlikely to happen to the exclusion of the second twin. Other environmental influences such as nutrition and lower socio-economic status have also been implicated in dyslexia (Phillips & Lonigan, 2005) and anxiety disorder (Gennetian & Miller, 2002) and may explain the covariation between the two traits. It is also possible that there is a reciprocal causal relationship between dyslexia and anxiety, where the combination of reading difficulties and a propensity to anxiety may lead to an anxious avoidance of reading, thereby

exacerbating the underlying reading impairment. Other mechanisms such as social anxiety (i.e. difficulty reading in front of others) or generalized low self-esteem may have a similar reciprocal association with reading development. Finally, it is necessary to consider the possibility that the association between the two disorders does not involve a causal relationship, but rather is indicative of other factors that may run in families, such as a willingness to seek out health services (and therefore procure a diagnosis).

Although the current study is strengthened by the use of genetically informative data, the assessment of each disorder was limited, relying on self-report of diagnosis by a health professional. The rate of dyslexia in our sample (2.35%) is lower than current prevalence estimates (5%; Shaywitz, Shaywitz, Fletcher, & Escobar, 1990). It is possible that the questionnaire-based methodology used by this study deterred individuals with dyslexia from participating. Note, however, that the prevalence rate of dyslexia in the current sample is in keeping with the rate for clinically referred cases of dyslexia (3.2%, for females; Shaywitz, Shaywitz, Fletcher, & Escobar, 1990), which is how the current sample was identified (as opposed to being identified via research). We would also caution that the results of this study are restricted to adult women. Dyslexia is more prevalent in males than females (Rutter *et al.*, 2004), while the reverse is true for anxiety (Kessler *et al.*, 1994). It is possible that different genetic and environmental influences may be at play both within and between traits for males and females. For example, there is some evidence for gender-specific genetic influences upon risk for dyslexia (Knopnik, Alacron, & DeFries, 1998) and anxiety (Jang, Stein, Taylor, & Livesley, 1999). This notwithstanding, Willcutt and Pennington (2000) found that females with reading disability are at greater risk for anxiety disorder than males, and the current study suggests that this association is independent of genetic effects. Finally, it is important to note that although the overall sample was large, the number of individuals who had received a diagnosis of either disorder was relatively small, giving this study low statistical power (Neale, Eaves, & Kendler, 1995). Twin samples that contain a greater number of affected individuals would facilitate more complex bivariate genetic analyses and provide complementary data to those presented here. Future studies can build upon this research by broadening the sample characteristics as well as by clarifying the environmental factors that impact upon the emotional well being of individuals with dyslexia.

## ACKNOWLEDGEMENTS

The authors would like to thank Dorothy Bishop, Jennifer Lau and Angelica Ronald for their statistical advice, Emma Whitehouse for her comments on previous version of this manuscript and the participants for taking part in this research.

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