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Gene by environment interactions influencing reading disability (RD) and the inattentive symptom dimension of attention deficit/hyperactivity disorder (ADHD)

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Abstract

Background—RD and ADHD are comorbid and genetically correlated, especially the inattentive dimension of ADHD (ADHD-I). However, previous research indicates that RD and ADHD enter into opposite gene by environment (GxE) interactions.

Methods—This study used behavioral genetic methods to replicate these opposite GxE interactions in a sample of same-sex MZ and DZ twin pairs from the Colorado Learning Disabilities Research Center (CLDRC; DeFries et al., 1997) and to test a genetic hypothesis for why these opposite interactions occur.

Results—We replicated opposite GxE interactions for RD (bioecological) and ADHD-I (diathesis-stress) with parental education in the same sample of participants. The genetic hypothesis for this opposite pattern of interactions is that only genes specific to each disorder enter into these opposite interactions, not the shared genes underlying their comorbidity. To test this hypothesis, we used single models with an exploratory three-way interaction, in which the GxE interactions for each disorder were moderated by comorbidity. Neither three-way interaction was significant. The heritability of RD did not vary as a function of parental education and ADHD-I. Similarly, the heritability of ADHD-I did not vary as a function of parental education and RD.

Conclusions—We documented opposite GxE interactions in RD and ADHD-I in the same overall twin sample, but the explanation for this apparent paradox remains unclear. Examining specific genes and more specific environmental factors may help resolve the paradox.

Keywords

gene; environment; interactions; reading disability; attention deficit/hyperactivity disorder; bioecological; diathesis-stress

Background

Reading disability (RD) is a common neurodevelopmental disorder with defining symptoms including deficits in accurate and fluent word recognition (International Dyslexia Association Board of Directors [IDA], 2002). Numerous studies have substantiated the familiarity of RD (e.g., Gilger, Borecki, and DeFries, 1991), and modern twin studies have confirmed the substantial genetic etiology of this disorder (e.g., DeFries and Gillis, 1993). Attention deficit/hyperactivity disorder (ADHD) is also a common familial and heritable neurodevelopmental disorder (e.g., American Psychiatric Association, 1994, 2000) with defining symptoms categorized into three subtypes: primarily inattentive, primarily hyperactive/impulsive, and combined (both inattentive and hyperactive/impulsive) symptomatology.

Importantly, research suggests etiologic differences between the inattentive and hyperactive/impulsive symptom dimensions (e.g., Willcutt et al., 2007; Nikolas and Burt, 2010; Nigg, Nikolas, and Burt, 2010). RD and ADHD co-occur in approximately 15–40% of cases in epidemiological samples and their comorbidity is more pronounced for the inattentive symptom dimension of ADHD than the hyperactive/impulsive symptom dimension (e.g., Gilger, Pennington, and DeFries, 1992). The best supported hypothesis for the comorbidity between RD and ADHD is that they partially share genetic risk factors, again with the genetic correlation being stronger between RD and inattention (e.g., Gayán et al., 2005, Nigg, Nikolas, and Burt, 2010). In addition to shared genes, there is some evidence for genes specific to each disorder (e.g., Gayán et al., 2005). More specifically, a number of dopamine receptor gene polymorphisms, such as DAT1, DRD4, and DRD5, have been identified as ADHD candidate genes (e.g., Lasky-Su et al., 2007). In contrast, linkage and association studies suggest that the majority of identified RD candidate genes (ROBO1, DCD2, KIAA0319) are related to neuronal migration (e.g., Taipale et al., 2003) but much more work is needed to establish which candidate genes are shared and which are specific to RD or ADHD.

Nonetheless, previous research suggests that the two disorders enter into opposite types of GxE interactions, bioecological for RD and diathesis-stress for ADHD. In a bioecological interaction, risk genes will have stronger effects in a uniformly protective environment than in environments varying in risk simply because there is less variance in the protective environment than in the risk environments (Gottesman, 1963; Turkheimer and Gottesman, 1991; Bronfenbrenner and Ceci, 1994). Such interactions with parental education have been found for reading in adult twins (Kremen, et al., 2005), in school-age twins selected for RD in the CLDRC twin sample utilized in the current study (Friend, DeFries, and Olson, 2008), for pre-literacy and language phenotypes in speech sound disorder (SSD; McGrath, Smith, and Pennington, 2006), and for IQ (Turkheimer, Haley, Waldron, D'Onofrio, and Gottesman, 2003).

In contrast, in a diathesis-stress interaction (Rende and Plomin, 1992), risk genes have multiplicatively stronger effects in a risk environment. Several studies of ADHD have found diathesis-stress interactions between risk alleles for ADHD and psychosocial risk environments. For example, a recent meta-analysis by Nigg, Nikolas, and Burt (2010) replicated findings indicating a diathesis-stress GxE interaction for ADHD risk alleles, primarily for DAT1 and 5-HTT, and psychosocial risk environments (e.g., SES, family adversity), particularly for the inattentive symptom dimension. On the other hand, inconsistent GxE interaction results were demonstrated when considering ADHD risk alleles and bioenvironmental risk environments (e.g., pre- and peri- natal risk variables, such as prenatal smoke or alcohol exposure). In addition, such GxE interactions involving bioenvironmental risk environments generally failed to replicate in the literature. Further,

some literature suggests that bioenvironmental risk factors may influence the manifestation of the hyperactive/impulsive symptoms of ADHD, whereas psychosocial risk factors have a greater influence on the inattentive symptom dimension of ADHD (Nigg, Nikolas, and Burt, 2010).

Although the aforementioned results indicating a diathesis-stress GxE interaction involving the inattentive symptom dimension of ADHD (ADHD-I) and psychosocial environmental variables seem promising, extension of this research using a behavioral genetics framework is necessary, as studies examining GxE interactions in ADHD have generally used molecular genetics methods. Although taking a molecular genetics approach confers the benefit of directly measuring the genetic contribution of a risk allele(s) (e.g., Caspi et al., 2002, 2003), behavioral genetics tests potentially provide more power to detect genetic main effects (Pennington et al., 2009).

Pennington et al. (2009) employed behavioral genetics methods to test for GxE interactions influencing RD or ADHD-I and parental education in subsamples from the CLDRC twin study. Consistent with the molecular genetics literature, results indicated a significant bioecological GxE interaction for RD and a significant diathesis-stress GxE interaction for ADHD-I. Of note, Pennington et al. (2009) used a weighted composite of word recognition, spelling, and reading comprehension measures as the reading phenotypic variable. In contrast, the current study employed a reading composite composed only of single word reading measures, because RD is defined as a deficit in the accuracy and fluency of reading single words (IDA, 2002). So, it was important to test if the bioecological interaction for RD with parent education would be found with a purer measure of RD.

The current study aims to extend Pennington et al.'s (2009) findings in order to better understand the etiologies of RD and ADHD-I, as the opposite pattern of GxE interactions for both disorders has not been demonstrated in the same overall sample using the same methodology. Only those participants whose reading, attention, and parental education data were available were included in the current study analyses in order to ensure that both the reading and attention scores were standardized against the same group of control participants. Although the participants included in the Pennington et al. (2009) study were subsamples of the CLDRC twin study, the RD and ADHD analyses included overlapping but not identical groups of participants. A third and key difference between the Pennington et al (2009) study and the current study is that the current study takes the next step and tests why these opposite interactions are occurring. We elaborate a genetic hypothesis for these opposite interactions, which posits that genes specific to each disorder are entering into the opposite interactions, not those genes that they share.

Returning to the issue of why testing these opposite interactions in the same overall sample is prudent, Risch and colleagues (2009) highlight the importance of using the same study design, sample, and methodology to accurately compare findings across studies, as non-replication of findings in the literature may stem from differences in such study parameters. Investigating whether RD and ADHD-I demonstrate opposite types of GxE interactions within the same overall sample addresses some of these potential confounds. Furthermore, it is important to distinguish heritability $\times$ environment interactions (behavioral genetics) from gene $\times$ environment interactions (molecular genetics) when comparing GxE interaction findings across studies (e.g., Rutter, Moffit, and Caspi, 2006). The aforementioned "paradox" only exists if opposite types of GxE interactions influencing RD and ADHD-I are found within the same method. One goal of this study is to evaluate whether this is the case using behavioral genetics methods. Therefore, we use the term, *GxE interaction*, when referring to our analyses to imply a heritability $\times$ environment interaction.

Moreover, additional methodological issues must be considered when studying GxE interactions, such as the potential confound for gene-environment (G-E) correlation. Many GxE studies have not addressed the potential confound of G-E correlation (e.g., Kendler and Baker, 2007; Plomin, 1994; Scarr and McCartney, 1983). If genetic risk factors occur more frequently in risk environments, then we cannot clearly distinguish main effects from interaction effects. Our study attempts to clarify the GxE interaction literature for ADHD and RD by directly addressing issues related to G-E correlation.

One of the principle aims of the current study was to test whether opposite GxE interactions with parental education would be found for RD and ADHD-I within the same overall sample of MZ and DZ same-sex twin pairs, while also controlling for G-E correlations. Additionally, if the seemingly paradoxical opposite GxE interactions were found, our next goal was to attempt to resolve the paradox by testing whether the shared or non-shared genes were involved in these opposite interactions. To summarize, the current study tested two hypotheses: 1) That opposite GxE interactions would be found for RD and ADHD-I with parental education in the same sample using behavioral genetic (BG) methods; and 2) That the non-shared genes between RD and ADHD-I are responsible for the opposite GxE interactions.

Methods

Participants

The current study was part of the ongoing Colorado Learning Disabilities Research Center (CLDRC) study of the etiology of learning disabilities, ADHD, and other related disorders (e.g. DeFries et al., 1997). Participants were recruited from 22 school districts in the Front Range area. Parents of all twins between the ages of 8 and 18 in these districts were contacted and invited to participate in the study. After initial parental consent was obtained, two parallel recruitment processes were conducted independently to identify twin pairs in which at least one of the twins met criteria for either ADHD or RD.

Only MZ and DZ same-sex twin pairs selected from the aforementioned overall sample were included in this study. To identify twin pairs in which at least one twin met criteria for significant reading or attentional difficulties, parental consent was requested to allow study staff to review each twin's academic record. If either member of the twin pair had a positive history of reading difficulties (e.g., low achievement test scores) or ADHD, both twins were invited to participate in the study. Twin pairs in which neither twin met criteria for reading difficulties or ADHD were included in a comparison sample. Exclusion criteria and study parameters have been described previously (DeFries et al., 1997).

Measures

Reading—Reading ability in the current study was assessed using a word recognition composite that was created using two relevant reading measures: the PIAT Word Recognition (PWR) subtest (Dunn and Markwardt, 1970), an untimed single word reading test, and the Timed Word Recognition (TWR) subtest (Olson, Wise, Conners, Rack, and Fulker, 1989; Olson, Forsberg, Wise, and Rack, 1994), a single-word reading test, which implements a time limit. PWR and TWR scores were age-regressed and subsequently standardized to the recruited control group. PWR and TWR scores were then averaged within participants in order to create the reading composite. Probands who met criteria for RD in the current study were defined as those whose word recognition composite scores fell below 1.5 standard deviations from the control mean.

ADHD—Parents and teachers were asked to complete the Attention Deficit Hyperactivity Rating Scale –IV (ADHDRS-IV; DuPaul, Anastopoulos, & Reid, 1998) to assess symptoms of DSM-IV ADHD. Affection status was defined by DSM-IV ADHD criteria (i.e., six or more symptoms of inattention, hyperactivity/impulsivity, or both) rated by either a parent or teacher. Once probands were defined by affection status (i.e., a “diagnosis” of ADHD based on parent or teacher ratings), participants were further classified into the three ADHD subtypes: ADHD- primarily inattentive, ADHD- primarily hyperactive/impulsive, and ADHD- combined. To create ADHD composites, the mean severity of score ratings for each symptom dimension was calculated, using data from all available raters for each child (e.g., mother, father, teacher). Mean severity scores for all three symptom dimensions were then standardized and age-regressed based on the recruited controls.

Since research has shown that the ADHD-primarily hyperactive/impulsive subtype has a different etiology than the ADHD-primarily inattentive subtype (Willcutt et al., 2007; Nikolas and Burt, 2010), preliminary univariate and bivariate (with RD) heritability analyses were assessed to see whether the ADHD-hyperactive/impulsive subtype demonstrated these characteristic differences within the current sample. Analyses indicated that the ADHD-hyperactive/impulsive symptom dimension did not show significant bivariate heritability with RD, whereas the ADHD-inattentive and ADHD-combined symptom dimensions did. Therefore, based on exploratory and confirmatory factor analyses previously applied to the ADHDRS-IV scores from the CLDRC sample (McGrath et al., 2011), the final group of ADHD probands was created by combining only those probands who met criteria for the ADHD-primarily inattentive and ADHD-combined subtypes, and only symptoms of inattention (ADHD-I) were included in the analyses. In other words, the aforementioned paradox centers on the idea that RD and ADHD share genes but yet enter into different types of GxE interactions. Therefore, the hyperactive/impulsive symptom dimension was not included in the GxE analyses since this symptom dimension did not have a genetic correlation with RD. Of note, previous research indicates that the ADHD-primarily inattentive and ADHD-combined subtype probands have similar profiles of neuropsychological impairments (e.g., Chhabildas, Pennington, and Willcutt, 2001). Therefore, there was no reason to suspect that the ADHD-combined subtype probands and the ADHD-primarily inattentive subtype probands would produce different GxE interaction results.

In cases where both twin pairs qualified as “extreme” on a particular phenotype, both twins were selected as probands in the analyses. Correction for double-entry of concordant twin pairs is addressed below. Zygosity of the twin pairs was determined based on selected items from the Nichols and Bilbro (1966) questionnaire. In ambiguous cases, zygosity was determined based on blood sample analyses.

Parental Level of Education—Parental level of education is often used as a proxy for SES (Smith, Brooks-Gunn, and Klebanov, 1997). Maternal and paternal level of education was obtained by self-report. A variable for mean years of parental education was computed if both maternal and paternal education data was provided. In cases where only maternal or paternal education was provided, only that parent’s data was included in analyses.

Retrospective Reports of Parent Reading and Attention—Both parents completed the Adult Reading History Questionnaire (RHQ; Lefly and Pennington, 2000), which includes Likert-scale items asking them to recall and assess their attitude toward and experiences with reading and academics as children. Parents also completed the Retrospective ADHD Interview for Parents (MSRADD for Mothers, FSRADD for Fathers). Parents provided information regarding their experiences of inattention and hyperactivity/impulsivity as children before the age of 12.

DeFries-Fulker (DF) Method

Univariate and Bivariate Heritability—The DF (DeFries and Fulker, 1985; DeFries and Fulker, 1988) method for analyzing twin pairs on extreme traits was used to replicate previous findings of univariate heritability for RD and ADHD-I (e.g. DeFries and Alarcón, 1996). Using this method, at least one member of a twin pair was chosen for an extreme trait (i.e., symptoms of RD or ADHD-I). The DF method capitalizes on the phenomenon of differential regression to the mean. The logic is based on the idea that monozygotic (MZ) twins share 100% of their segregating genes, whereas dizygotic (DZ) twins share only 50%, on average. Given an underlying genetic liability, a cotwin that shares 100% of his segregating genes (MZ) will not regress as far to the population mean compared to a cotwin who only shares on average 50% of his segregating genes (DZ), on average (See Figure 1). The main advantage of the DF method is that it is designed for selected samples and has more power than a traditional concordance analysis (Fulker et al., 1991). This property makes the DF method ideal for investigating the etiology of individual and comorbid disorders because, by definition, the individual with the disorder is extreme on a phenotype. When both twins in a twin pair met proband criteria, the standard errors of the regression coefficient were corrected prior to significance tests to account for inflated sample size (e.g., Thompson and Thompson, 1986).

Univariate heritability analyses for RD and ADHD-I were conducted. MZ proband and cotwin scores were divided by the MZ proband mean and DZ proband and cotwin scores were divided by the DZ proband mean. This step ensured that MZ and DZ probands were equally divergent from the control mean prior to the regression analysis, and it re-scaled the final variables so that cotwin scores were regressing from probands' means of 1.0. The regression model is as follows:

$$C = B_1P + B_2r + K \quad \text{Eq. 1}$$

In this case, C represents the expected cotwin score, P is the proband score, r is the coefficient of relationship ($r=1$ for MZ twins, $r=.5$ for DZ twins), and K is the regression constant. The B_1 coefficient in this equation represents the partial regression of the cotwin's score on the proband score, and provides a measure of twin similarity (i.e., familiarity) across zygosity. The variable of most interest for the purposes of this study, however, is the B_2 coefficient, which represents the partial regression of the cotwin's score on the coefficient of relationship, and provides a direct measure of the extent to which extreme scores on the selected dimension are due to genetic influences (h^2_g).

The t -values provided by this multiple regression analysis are an overestimate due to the double-entry of concordant pairs. In order to obtain the correct values, the following correction was performed (for detailed procedure see Stevenson, Pennington, Gilger, DeFries, and Gillis, 1993):

$$\text{Correction Factor} = \sqrt{((N_d - N_p) / (N_s - N_p))} \quad \text{Eq. 2}$$

Where N_d is the number of probands using double entry, N_s is the number of probands using single entry, and N_p is the number of parameters.

$$\text{Corrected Standard Error} = \text{Obtained Standard Error} \times \text{Correction Factor} \quad \text{Eq. 3}$$

$$\text{Corrected } t - \text{value} = B_2 / \text{Corrected Standard Error}$$

Eq. 4

Bivariate heritability analyses were also conducted, using similar methods. Bivariate heritability estimates were obtained by selecting RD probands to predict cotwin inattention and vice versa. For example, if selecting RD probands, P represents the proband reading score, and C represents the cotwin inattention score. Similarly, if selecting ADHD probands, P represents the proband inattention score, and C represents the cotwin reading score.

Extending the DF regression model described above, GxE interactions were assessed for RD and ADHD-I (Fulker et al., 1991). Within this step, we attempted to replicate and extend previous univariate GxE findings affecting reading and attention. An extended form of the DF regression model can incorporate a GxE interaction term (terms added to Eq. 1 are in bold).

$$C = B_1P + B_2r + \mathbf{B_3e} + \mathbf{B_4P^*e} + \mathbf{B_5r^*e} + K$$

Eq. 5

C represents the cotwin's phenotypic score. P represents the proband's phenotypic score, and r is the coefficient of relationship. The term, "e" represents the pair-specific environment (i.e. parental education). The beta weight of interest in this equation is B₅, which tests for the significance of the GxE interaction. A bioecological interaction will be indicated if heritability is significantly higher in the favorable environment than the unfavorable environment, whereas higher heritability in the unfavorable environment would indicate a diathesis-stress interaction.

Results

Replication of Univariate and Bivariate Heritability Findings

Univariate heritability estimates were significant for RD (N=283, $h^2_g = .593$, $p < .001$) and ADHD-I (N=171, $h^2_g = .874$, $p < .001$), and were similar to previous results reported in this sample (e.g., Willcutt et al., 2007). Similarly, bivariate heritability of reading and inattention was significant whether probands were selected for RD (N=283, $h^2_g = .447$, $p = .013$) or inattention (N=171, $h^2_g = .352$, $p = .009$).

As expected, parental education was correlated with child reading ($r = .308$, $p < .001$), so we next partialled maternal and paternal retrospective self-reports of reading difficulties from this relation to control for the well-established familiarity of reading skill (Table 1), and found a significant relation remained. Parent education was also related to child ADHD-I ($r = .149$, $p = .003$) even after controlling for retrospective parent attentional difficulties (Table 2). These results are consistent with a potential environmental main effect of parental education on RD and ADHD-I, but do not prove that this relation is environmental.

Replication and Extension of Univariate GxE Interactions for RD and ADHD

Replicating methods implemented by Friend et al. (2008), parent education data was residualized by proband reading scores using linear regression in order to address the confound of a potential G-E correlation. GxE analyses showed a significant positive interaction in the bioecological direction, whereby RD was more heritable when parents completed more years of education (See Table 3). Applying a median split to the residualized parental education variable (to make the variable categorical), the univariate

heritability of RD was investigated in the “low” and “high” parental education environments to illustrate the direction of the interaction.

To test for a GxE interaction in ADHD-I, similar regression procedures were implemented to address the potential confound of a G-E correlation. There was a significant GxE negative interaction (hence, in the diathesis-stress direction), indicating that ADHD-I was more heritable when parents completed fewer years of education (See Table 4).

Since the predicted opposite GxE interactions were found in this sample, supporting the apparent paradox documented in the literature and found in Pennington et al. (2009), we next tested the hypothesis that non-shared genes account for this pattern of interactions by repeating the GxE analyses with three subtypes of probands: RD-only, ADHD-I-only, and RD+ADHD-I. We expected to find stronger GxE interaction results in the RD-only and ADHD-I-only groups compared to the comorbid group because the former two “only” groups should have more of the non-shared genes hypothesized to drive the opposite GxE interactions.

Results initially seemed to indicate that the bioecological interaction in the RD-only probands was slightly stronger than our original interaction (See Table 5), and the diathesis-stress interaction in the ADHD-I-only probands was stronger than our original interaction (See Table 6), whereas the GxE interaction was not significant in the comorbid probands for either RD or ADHD-I (See Tables 7 and 8). However, upon further investigation, it was not the case that interactions for the “pure” proband groups were significantly stronger than the GxE interactions observed with the comorbid probands. If the interactions with the “pure” proband groups were stronger than those in the comorbid probands, we would expect that when the interactions were broken down by median splits into “high” and “low” parental education environments, the magnitude of the differences in the heritability estimates (e.g., the difference between the heritability of RD in the high parental education environment and the heritability of RD in the low parental education environment) would be significantly greater in the pure proband groups compared to the comorbid twins. This pattern, however, was not as clear as we anticipated.

Since the evidence for the genetic hypothesis was less clear than one would expect, we performed exploratory analyses to directly test for the implied three-way interaction among RD, ADHD-I, and parental education. The three-way interaction equation is as follows:

$$C = B_1P + B_2r + B_3e + \mathbf{B_4Inatt.} + B_5P^*e + \mathbf{B_6P^*Inatt.} + B_7r^*e + \mathbf{B_8r^*Inatt.} + B_9Inatt.^*e + \mathbf{B_{10}r^*e^*Inatt.} + K$$

Eq. 6

C represents the cotwin’s phenotypic score (i.e., RD in the example above). P represents the proband’s phenotypic score (i.e., RD in the example above), r is the coefficient of relationship, e is the environmental term, parental education, and Inatt. is the proband measure of the other phenotypic dimension. The equation has added terms (in bold) relative to Eq. 5 for an ADHD-I main effect, three new two-way interactions, and the three-way interaction of interest, whose beta weight is B_{10} . If this term is significant, it means the GxE interaction for RD (in the above example) changes as a function of proband ADHD-I (i.e., comorbidity). There were null results for both three-way interaction tests. So, our results did not support the genetic hypothesis for the opposite pattern of GxE interactions.

Discussion

The primary goals of this study were 1) to replicate opposite GxE interactions with parental education in RD and ADHD-I within the same subsample of CLDRC twin pairs, using a more appropriate measure of RD, and controlling for the potential confounds of G-E correlations, and 2) to test whether non-shared genes were involved in the opposite interactions. Extending the current literature, we found these opposite interactions in the same overall sample using BG methods.

Since significant opposite GxE interactions were found with parental education for RD and ADHD-I using the same sample of twins, we hypothesized that only genes specific to each disorder were involved in these opposite interactions, not those contributing to their genetic correlation. Although results were in the predicted direction when probands were split into the “pure” and comorbid groups, the exploratory three-way interaction tests demonstrated that the GxE interactions in the “pure” groups were not significantly stronger than the comorbid group. The 3-way interaction analyses produced null results for both three-way interaction tests, providing evidence that does not support the genetic hypothesis. It is possible that these findings are due to insufficient power using the three-way interaction test (Risch et al., 2009).

These findings highlight the importance of further investigation into this paradox. For instance, it is possible that the opposite GxE interactions are due to non-shared proximal environmental variables instead of non-shared genes. Parent education is correlated with both home and school literacy practices (important for RD; e.g., Phillips and Lonigan, 2005) and psychosocial adversity factors demonstrated to play a role in the manifestation of ADHD-I (e.g., Nigg, Nikolas, and Burt, 2010). These different proximal environmental factors are both nested under the broad environmental variable, parental education. So, it would be important to directly test this non-shared proximal environment hypothesis in future studies, as well as to use molecular methods to directly test the genetic hypothesis.

Conclusions

Taken together, this study supports three main conclusions: 1) opposite GxE interactions are robust in RD and ADHD-I, using BG methods in the same overall sample with a purer measure of RD, even when G-E correlation is controlled; 2) significant main effects of parent education on both child RD and ADHD-I remain after controlling for the relation between parent education and parent history of reading and attentional difficulties; and 3) it remains unclear whether the opposite GxE interactions in RD and ADHD-I with parental education are due to non-shared genes, non-shared proximal environments, or some combination of the two.

Limitations and Future Directions

Power analyses indicated that power was adequate to test for the primary GxE interactions between parental education and RD and ADHD-I, and these interactions were robust in all analyses. In contrast, power was lower to detect the exploratory three-way interaction when probands were split into groups with comorbid RD and ADHD-I and each disorder alone. Additionally, the participants in this study were volunteers recruited from mainly suburban Denver populations, and the sample may therefore have included a restricted range of parental education in comparison to the overall population. Finally, due to the nature of a BG design, we cannot distinguish a GxE interaction from that of a GxG, ExE, or a three-way interaction.

Given these limitations, it will be important for future studies to ensure an adequate range of environmental variables and populations studied, as a restricted range can greatly vary GxE results. Further, in order to tease apart the influences of GxE, GxG, and ExE interactions, employing a molecular framework to extend this research would be beneficial. A follow-up study using both molecular genetics methods and measures of proximal environments would provide a useful extension of the current study.

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Abbreviations

RD	reading disability
ADHD	attention deficit/hyperactivity disorder
ADHD-I	Inattentive symptom dimension of ADHD
MZ	monozygotic
DZ	dizygotic

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Main Points

- RD and ADHD are two of the most common disorders of childhood, and they frequently co-occur.
- Shared genes largely explain their co-occurrence but the environments that influence each disorder appear to differ.
- Interestingly, RD and ADHD enter into opposite GxE interactions with parental education in previous research, and we replicated that result in the same overall sample.
- A genetic hypothesis for this opposite pattern of interactions, positing that the genes specific to each disorder enter into opposite interactions, was not supported in the current study.
- Therefore, different aspects of the environment that are correlated with parental education may produce the opposite interactions (e.g., home literacy practices for RD and disorganized parenting for ADHD).

Figure 1.
Univariate heritability. Testing for main effects of G.

Table 1

Main Effects of E: Parental Education on Child Reading

	N	Pearson's r	(2-tailed) p
Bivariate Correlation Word Recognition Composite and Parental Education	408	.308	<.001 *
Partial Correlation controlling for MRHQ	346	.254	<.001 *
Partial Correlation controlling for FRHQ	324	.250	<.001 *
Partial Correlation controlling for the mean of both parents' RHQ	147	.169	<.001 *

* denotes significant main effect detected

Table 2

Main Effects of E: Parental Education on Child Inattention Symptomatology

	N	Pearson's r	(2-tailed) p
Bivariate Correlation Inattention Symptomatology and Parental Education	408	.149	.003 [*]
Partial Correlation controlling for mother retrospective symptoms of ADHD	205	.202	.003 [*]
Partial Correlation controlling for father retrospective symptoms of ADHD	157	.186	.019 [*]
Partial Correlation controlling for the mean of both parents' retrospective symptoms of ADHD	216	.181	.007 [*]

* denotes significant main effect detected

Table 3

Univariate GxE Interaction RD and Parental Education

	N Probands (Double Entered)	B	SE	t	p
Univariate GxE Interaction RD and Parental Education	283 (178)	.249	.103	2.41	.008
h^2_g RD in "High" Parental Ed. E	142 (81)	.736	.164	4.49	<.001
h^2_g RD in "Low" Parental Ed. E	141 (97)	.459	.153	3.01	.002

Table 4

Univariate GxE Interaction ADHD-I and Parental Education

	N Probands (Double Entered)	B	SE	t	p
Univariate GxE Interaction ADHD-I and Parental Education	171 (74)	-.345	.171	-2.01	.023
h^2_g ADHD-I in "High" Parental Ed. E	86 (30)	.557	.249	2.24	.014
h^2_g ADHD-I in "Low" Parental Ed. E	85 (44)	1.16	.206	5.62	<.001

Table 5

Univariate GxE Interaction RD and Parental Education in RD-Only Twins

	N Probands (Double Entered)	B	SE	t	p
Univariate GxE Interaction RD and Parental Education	197 (121)	.266	.117	2.28	.012
h^2_g RD in "High" Parental Ed. E	98 (52)	.782	.186	4.20	<.001
h^2_g RD in "Low" Parental Ed. E	99 (69)	.503	.190	2.64	.005

Table 6

Univariate GxE Interaction ADHD and Parental Education in ADHD-Only Twins

	N Probands (Double Entered)	B	SE	t	p
Univariate GxE Interaction ADHD-I and Parental Education	85 (32)	-.403	.206	-1.80	.038
h^2_g ADHD-I in "High" Parental Ed. E	42 (12)	.512	.366	1.34	.085
h^2_g ADHD-I in "Low" Parental Ed. E	43 (20)	1.19	.288	4.13	<.001

Table 7
Univariate GxE Interaction RD and Parental Education in Comorbid Twins

	N Probands (Double Entered)	B	SE	t	p
Univariate GxE Interaction RD and Parental Education	86 (57)	.206	.229	.898	.186
h ² _g RD in "High" Parental Ed. E	43 (27)	.697	.327	2.13	.020
h ² _g RD in "Low" Parental Ed. E	43 (30)	.292	.250	1.17	0.130

Table 8

Univariate GxE Interaction ADHD and Parental Education in Comorbid Twins

	N Probands (Double Entered)	B	SE	t	p
Univariate GxE Interaction ADHD-I and Parental Education	86 (42)	-.335	.277	-1.21	.115
h^2_g ADHD-I in "High" Parental Ed. E	43 (17)	.786	.352	2.23	.016
h^2_g ADHD-I in "Low" Parental Ed. E	43 (25)	.883	.294	3.00	.002