Gene × Environment Interactions in Reading Disability and Attention-Deficit/Hyperactivity Disorder

Bruce F. Pennington,
Department of Psychology, University of Denver

Lauren M. McGrath,
Department of Psychology, University of Denver

Jenni Rosenberg,
Department of Psychology, University of Denver

Holly Barnard,
Department of Psychology, University of Denver

Shelley D. Smith,
Molecular Genetics Department, University of Nebraska Medical Center

Hattie B. Munroe,
Molecular Genetics Department, University of Nebraska Medical Center

Erik G. Willcutt,
Department of Psychology, University of Colorado at Boulder

Angela Friend,
Department of Psychology, University of Colorado at Boulder

John C. DeFries, and
Department of Psychology, University of Colorado at Boulder

Richard K. Olson
Department of Psychology, University of Colorado at Boulder

Abstract

This article examines Gene × Environment (G × E) interactions in two comorbid developmental disorders—reading disability (RD) and attention-deficit/hyperactivity disorder (ADHD)—as a window on broader issues on G × E interactions in developmental psychology. The authors first briefly review types of G × E interactions, methods for detecting them, and challenges researchers confront in interpreting such interactions. They then review previous evidence for G × E interactions in RD and ADHD, the directions of which are *opposite* to each other: bioecological for RD and diathesis stress for ADHD. Given these results, the authors formulate and test predictions about G × E interactions that would be expected at the *favorable* end of each symptom dimension (e.g., above-average reading or attention). Consistent with their prediction, the authors found initial evidence for a *resilience* interaction for above-average reading: higher heritability in the presence of lower parental education. However, they did not find a G × E interaction at the favorable end of the ADHD symptom dimension. The authors conclude with implications for future research.

Correspondence concerning this article should be addressed to Bruce F. Pennington, Department of Psychology, University of Denver, 2155 South Race Street, Denver, CO 80208-0001. bpenning@du.edu.

Keywords

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In this article, we review current models of Gene × Environment (G × E) interaction and apply them to two comorbid developmental disorders—reading disability (RD) and attention-deficit/ hyperactivity disorder (ADHD)—and to the favorable ends of their symptom dimensions. These two disorders are good models in which to explore G × E interactions because they are common developmental disorders, with estimates of 5%–10% prevalence in both cases (American Psychiatric Association, 2000; Shaywitz, Shaywitz, Fletcher, & Escobar, 1990), and they both have genetic and environmental components to their etiology. Current behavior genetic analyses estimate the heritability of RD to be about 58% (Pennington & Olson, 2005) and the heritability of ADHD to be about 76% (Faraone et al., 2005). As these estimates show, the influence of genetics in these disorders is quite strong, but the fact that the heritability estimates are not 100% in either disorder leaves room for environmental influences. On the basis of this pattern, it is not too surprising that both disorders show preliminary evidence of G × E interactions.

What is intriguing is that this evidence indicates *opposite* directions for these interactions: RD is more heritable in a favorable environment (a bioecological G × E interaction, which is explained in more detail below), and ADHD is more heritable in a risk environment (the familiar diathesis-stress interaction found in other psychopathologies). This opposite pattern of interactions is important to understand, and we discuss what it may mean. We also test whether this opposite pattern occurs in our large sample of twins selected for RD and ADHD, and then we formulate and test predictions about what direction of interaction should occur at the favorable end of each symptom dimension.

For the purpose of extending G × E interaction models to the favorable end of the phenotypic distribution, it is important that our model disorders, RD and ADHD, have underlying phenotypic liabilities that can be conceptualized on a continuum. Although the disorders are determined by an arbitrary cutoff at the low end of the continuum, there are also individuals who fall at the favorable end of the continuum (e.g., good reading, good attention). As long as the favorable end of the continuum is also heritable, it is reasonable to test for G × E interactions at this end of the distribution. In the case of good reading, previous research has shown that it is similar in heritability to RD (Boada et al., 2002). To our knowledge, similar analyses have not been conducted regarding good attention. We therefore test first for the heritability of good attention before proceeding with our G × E analyses.

In what follows, we first provide an introduction to G × E interactions, highlighting definitional issues and the distinction between G × E interaction and Gene–Environment (G–E) correlations. Then, we provide a brief general review of the two main types of G × E interactions (diathesis stress and bioecological) and extend these two main types of G × E interaction to the favorable extreme of the distribution. Next, we discuss general methodological issues involved in detecting G × E interactions. We then review evidence for bioecological G × E interactions in RD and diathesis-stress interactions in ADHD. Next, we test whether the same pattern is found in our own data. Given that we also find opposite G × E interactions for RD and ADHD, we predict and test what type of G × E interactions should be found at the favorable extreme of the RD and ADHD symptom dimensions. Finally, we conclude by discussing implications for future research.

Introduction to G–E Interplay

G × E interaction refers to the fact that environments can modify the expression of an individual's genetic background, either strengthening or weakening the effect of genes on phenotypes (Rutter, 2006). At the outset, it is important to note that this definition of G × E interaction is quite specific and is distinct from broad notions of the interconnectedness of genetic and environmental factors in development (Gottlieb, 2007; Plomin, DeFries, McClearn, & McGuffin, 2008). Interest in G × E interactions has flourished in recent years. This level of activity indicates a notable paradigm shift in the field of behavioral and psychiatric genetics (e.g., Caspi & Moffitt, 2006; Grigorenko, 2005; Kramer, 2005; Liu, Fallin, & Kao, 2004; Moffitt, Caspi, & Rutter, 2005; Rutter, 2006; Shanahan & Hofer, 2005), although some authors are encouraging caution in the interpretation of G × E findings (e.g., Eaves, 2006). The statistical and methodological difficulties involved in detecting G × E interactions are discussed further below. Throughout this article, we will use the term *G × E interaction* to encompass both behavioral genetic and molecular genetic measures of G, although previous authors have drawn a distinction between Heritability × Environment versus Gene × Environment interactions (e.g., Rutter, Moffitt, & Caspi, 2006).

This distinction is important, as heritability can differ in two environments just because the range of environmental (or genetic) risk or protective factors is different in each environment. If the environmental range is restricted, then heritability will inevitably increase. If the genetic range is restricted, then environmentality will inevitably increase. This is the case because heritability and environmentality are defined as *proportions* of the total phenotypic variance that differences in genes or environments account for, respectively. If one proportion increases, the other must decrease, because they sum to 1.0. So, a Heritability × Environment interaction found with behavioral genetic methods could arise when the frequencies of relevant alleles (i.e., range of genetic differences) are identical across the range of the environmental variable (e.g., parental education), but different levels of that environmental variable provide different ranges of environmental risk (or protective) factors. A bioecological interaction (in which heritability increases as the environment becomes more favorable) is usually thought of in just this way: The range of environmental differences contributing to the outcome is narrower as the environment becomes more favorable; thus, genetic differences account for more phenotypic variance (i.e., higher heritability). Similarly, we could have a null Heritability × Environment interaction, but different alleles could be affecting the outcome in different environments. In contrast, when we find a G × E interaction using molecular methods, we at least know that the effect of a particular allele (i.e., gene variant) on an outcome varies as a function of that environmental variable. But we do not know exactly what it is about the environmental factor that modifies gene expression or how it does it. Both methods of testing for G × E interactions are relevant for developmental science because they help us understand differences in developmental pathways. However, the foregoing makes it clear that interpreting G × E interactions is hardly straightforward, because they can arise for a variety of reasons, especially in the case of Heritability × Environment interactions.

G × E interactions are most easily studied in animal models in which both the genetic background and the environment can be manipulated experimentally. One of the best-known studies of G × E interaction in an animal model was conducted by Cooper and Zubek (1958). In this study, rats bred for a "maze-bright" or "maze-dull" phenotype were placed in "enriched" or "restricted" rearing environments. Results showed that the enriched condition boosted the performance of the maze-dull rats compared with controls, but it did not affect the performance of the maze-bright rats. In contrast, the restricted environment impaired the performance of the maze-bright rats compared with controls, but it did not affect the performance of the maze-dull rats. These results demonstrated that the environment could moderate the impact of genetics on a phenotype, in this case maze learning. Importantly, the pattern of interaction was

quite complex. One could imagine a more simplistic outcome in which environmental risk plus genetic risk could have resulted in multiplicatively worse outcomes. The same could have been true at the positive end of the distribution such that an enriched environment plus favorable genetic background could have resulted in multiplicatively better outcomes. Instead, the pattern of interaction was more complicated, foreshadowing the complexities involved in detecting and interpreting human $G \times E$ interactions.

Another important pattern emerges from this and other animal studies (e.g., Crabbe, Wahlsten, & Dudek, 1999; Valdar et al., 2006). Animal studies that detect a $G \times E$ interaction typically find it in the context of a main effect of genes and a main effect of environment. Without these two main effects, it is quite rare to find a $G \times E$ interaction in animal models (Crabbe et al., 1999; Valdar et al., 2006). In contrast, studies of $G \times E$ interactions in humans have not always found main effects of genes and environment (e.g., Caspi et al., 2002, 2003), leading some investigators to question the validity of the interaction.

As discussed earlier, there is now considerable interest in detecting $G \times E$ interactions in humans through the use of behavioral genetic (e.g., twin studies) or molecular genetic designs (e.g., linkage or association studies). Unfortunately, when the environment cannot be randomly assigned, as in animal experimental studies, a potential complication arises: G–E correlations. The term *G–E correlation* refers to the fact that exposure to environments is often partly genetically determined. In fact, most of the environments that are considered in behavioral research are at least partly determined by genetic factors (Kendler & Baker, 2007; Plomin, 1994; Plomin & Bergeman, 1991; Scarr & McCartney, 1983). For example, many family variables, such as parenting, parent education, and socioeconomic status, have been termed environmental even though these variables are partly under genetic influence (Plomin, 1994). Adoption designs are superior to twin designs in dealing with the problem of G–E correlation, because postnatal E is provided by the adoptive parents and should be uncorrelated with the child's G, unless there is selective placement. Hence, an adoption design allows a clearer test of the main effects of G and E and their interaction than does a traditional twin design.

If there is a positive G–E correlation, meaning that both G and E tend to cause deviations in the same direction from the mean, then G and E are confounded. Therefore, those with a higher genetic risk for a particular outcome also have a higher environmental risk for that outcome, and vice versa. For example, as discussed below, we know there is a genetic main effect on ADHD symptoms (i.e., ADHD is moderately heritable) and that maternal smoking during pregnancy increases the number of ADHD symptoms in offspring (i.e., an environmental main effect). There could also be a $G \times E$ interaction between risk alleles for ADHD and nicotine exposure in utero. But before we could clearly test for such a $G \times E$ interaction in humans, we would need to rule out a positive G–E correlation between risk alleles for ADHD and smoking in the mother. If there were such a positive correlation, then an apparent $G \times E$ interaction could just be a G–E correlation.

The distinction between G–E correlations and $G \times E$ interactions is sometimes a difficult one to understand, especially as both mechanisms are likely to be operating in development. In quantitative genetic theory, G–E correlation and $G \times E$ interaction are defined to be independent sources of phenotypic variance (Plomin, DeFries, & McClearn, 1990), and therefore theoretically a $G \times E$ interaction can occur either in the presence or in the absence of G–E correlation. Of course, practically, it is easier to detect $G \times E$ interaction in the absence of G–E correlation (i.e., in a true experiment in which environments are randomly assigned to genotypes). Conceptually, a $G \times E$ interaction means that there is a nonlinear combination of genetic and environmental effects on the phenotype; in other words, the effect of a given genotype on the phenotype depends on the environment, and vice versa. Thus, a $G \times E$

interaction increases phenotypic variance beyond what is attributable to the main effects of G and E.

There are several mechanisms through which environments can be responsive to genetics, termed passive, evocative, and active G–E correlations (Plomin, DeFries, & Loehlin, 1977; Scarr & McCartney, 1983). We illustrate these three types of G–E correlations using the example of a child with RD and the environments to which the child is exposed. In each case, these positive G–E correlations create a positive feedback loop across development that leads to a more extreme phenotype than the main effects of G and E would produce alone. Passive G–E correlation refers to the fact that parents provide family environments that are partly determined by their own genetic background. Thus, the child with RD may have inherited a genetic propensity for RD from a parent, and this parent may not enjoy reading to his child because of his own weakness in reading, leading to even poorer reading skills in the child. Evocative G–E correlation refers to the fact that individuals evoke certain responses from others on the basis of their genetic background. For example, the child with RD may overtly struggle with reading, leading parents and teachers to suggest alternative activities or to focus on other strengths of the child, thereby reducing the literacy exposure of the child. Finally, active G–E correlation refers to the fact that individuals seek out environments consistent with their own skills. Thus, the child with RD may avoid reading and instead seek out alternative activities, thus creating an environment with reduced literacy activities, resulting in poorer reading skills in the child, even despite an adequate literacy environment in the home. In all three cases, the environments to which the child is being exposed are partly determined by the child's own genetic liabilities, whose effects are accentuated by the correlated environments. There is specific evidence that these kinds of mechanisms are operational in RD (Scarborough, Dobrich, & Hager, 1991) and language development (Gilger, Ho, Whipple, & Spitz, 2001), and such G–E correlations are likely to play a role in many domains of development.

The three mechanisms just discussed were instances of positive G–E correlations, which would increase phenotypic variance. Theoretically, it is also possible for there to be negative G–E correlations (e.g., a child with RD evokes more tutoring help from parents and teachers), which would decrease phenotypic variance. Another difference between G × E interactions and G–E correlations is that G × E interactions only increase phenotypic variance, whereas G–E correlations may increase or decrease it, depending on whether they are positive or negative.

Fortunately, behavioral genetic simulations have shown that G × E interactions can be detected even in the presence of G–E correlations (Purcell, 2002). In most studies, the strategy for dealing with G–E correlations while testing for G × E interactions has been to test for the correlations directly. In this article, we refer to some variables as environmental, such as parent education, although we acknowledge that most environmental variables are under some genetic influence (Plomin & Bergeman, 1991). We refer to these variables as environmental to simplify terminology, but we consider carefully whether our resulting G × E interactions can be explained by G–E correlations. The importance of G–E correlation as a confound is partly dependent on the direction of the G × E interaction that is detected, a subject that is discussed further below in the examination of G × E models.

Types of G × E Interactions

G × E interactions are a complex topic (Grigorenko, 2005), and various forms of interaction are just beginning to be explored (e.g., Kendler & Eaves, 1986; Rutter, 1983; Shanahan & Hofer, 2005). The current G × E models can be distilled down to two theoretical models that make opposite predictions about the direction of the interaction. The diathesis-stress model predicts that a diathesis (genetic vulnerability) coupled with an environmental stress will increase the likelihood of disordered behavior (Rende & Plomin, 1992). In other words, there

is a synergy between genetic and environmental risk factors. In genetic terms, this model predicts that the heritability of the disorder will be higher for individuals in *risk* environments (Rutter et al., 2006). Diathesis-stress models are a cornerstone of the conceptualization of how psychopathologies develop (O'Connor, Caspi, DeFries, & Plomin, 2003). The explanatory power of G × E interactions in the etiology of disordered behavior has been demonstrated in several psychopathologies, including conduct disorder (Cadoret, Yates, Troughton, Woodworth, & Stewart, 1995; Caspi et al., 2002; Rutter et al., 2006) and depression (Caspi et al., 2003; Eley et al., 2004; Silberg, Rutter, Neale, & Eaves, 2001). In both cases, an environmental stress (e.g., maltreatment in conduct disorder; stressful life events, especially loss, in depression) coupled with a genetic risk results in more disordered behavior than would be expected by either factor alone or in additive combination.

Whenever a diathesis-stress interaction is detected, an important confound to consider is G–E correlations. Several studies have been able to rule out a correlation between the genetic and environmental risk factors included in the study either by using an adoption design (e.g., Cadoret et al., 1995) or by testing for them directly and finding that individuals with the genetic risk allele have not been exposed to more environmental stress (Caspi et al., 2002, 2003) than those without the risk allele. However, this direct test does not rule out the possibility that the putative environmental risk is actually due to a separate, unmeasured genetic influence (e.g., harsh parenting may be genetically influenced by genes other than the risk allele). In this case, the diathesis-stress G × E interaction may actually be a Gene × Gene interaction, because the identified risk allele is interacting with other unidentified genetic risk factors that are correlated with the risk environment.

In contrast to the diathesis-stress model, the bioecological model predicts that enriched environments will enable underlying genetic differences to be actualized, whereas risk environments will mask the genetic differences (Bronfenbrenner & Ceci, 1994; Gottesman, 1963). In genetic terms, this model predicts that the heritability of the disorder will be higher in *enriched* environments (Rutter et al., 2006). Although research investigating G × E interactions in psychopathologies has tended to find the diathesis-stress type of G × E interaction, research investigating G × E interactions in RD and other cognitive abilities has tended to find the bioecological form of G × E interactions (Harden, Turkheimer, & Loehlin, 2007; Kremen et al., 2005; Rowe, Jacobson, & van den Oord, 1999; Turkheimer, Haley, Waldron, D'Onofrio, & Gottesman, 2003), with few exceptions (Asbury, Wachs, & Plomin, 2005; van den Oord & Rowe, 1998).

The logic of the bioecological interaction was discussed by Lewontin (1995) through the analogy of genetically variable seeds that are planted in two fields, of which one is rich in nutrients and the other is deprived. In the deprived field, all of the plants will be short because of the environmental adversity. However, in the nutrient-filled field, there will be considerable variability in plant height that is primarily determined by the genetic endowment of the plant. Thus, the environment in which the seed was planted determines how the genetic potential or liability of the plant is expressed—a bioecological G × E interaction.

In the case of bioecological G × E interactions, the potential confound of G–E correlation is less of a problem than in diathesis-stress interactions. In the bioecological case, the interaction is not in the direction that can be explained by a confounding of G and E risk factors, because the genetic risk of the child is being revealed more strongly in a *favorable* environment. The genetic and environmental factors are negatively correlated, in contrast to the diathesis-stress interaction in which the genetic and environmental factors are positively correlated and hence confounded. If the genetic and environmental factors are negatively correlated, then the interaction cannot be explained by a simple G–E correlation. Instead, one has to derive an

explanation for why a child's genetic risk is more strongly expressed when exposed to more favorable environments.

It would be a mistake to consider the diathesis-stress and bioecological models simple opposites of each other, because the nature of the underlying process in each is different (Rutter, 2006). In a diathesis-stress interaction found with molecular methods, we assume that both the diathesis and the stress affect the same specific biological substrate and that the two may be jointly necessary for the phenotype to be observed. (A diathesis-stress interaction found with behavioral genetic methods could arise just because the risk environment provides less variation, thereby increasing heritability relative to the nonrisk environment; thus, it would not necessarily implicate a particular biological substrate.) In contrast, as discussed earlier, a bioecological interaction found with either molecular or behavioral genetic methods can occur just because a variety of environmental risk factors have been reduced in a favorable environment, and therefore the environment will contribute less to individual differences, and genes will contribute more. Unlike in a diathesis-stress interaction, the environmental factor in a bioecological interaction does not necessarily act on the same biological substrate as the genetic risk factors. Instead, it may just allow those genetic risk factors to account for more of the variance in outcome, because environmental risk factors that affect that outcome have been minimized. We next extend the $G \times E$ interaction models to the favorable extreme of the distribution.

Extending G × E Interactions to the Favorable Extreme

Although existing models of $G \times E$ interaction have focused on disorders (the unfavorable extreme of a symptom dimension), it is important to consider the role of $G \times E$ interactions in producing good developmental outcomes (the favorable extreme of a symptom dimension). Some interactions that occur at the favorable extreme of a symptom dimension (e.g., good reading, good attention, and good emotion regulation) are pertinent for understanding resilience. By *resilience* we mean the possibility of a child obtaining a good developmental outcome despite having risk factors that predispose toward a poor outcome. These risk factors could be environmental or genetic. Thus, a resilient child might become a good reader despite growing up in a home environment that did not promote literacy, possibly because the child has favorable gene variants for reading skill. Or a resilient child might become a good reader despite having some risk alleles for poor reading, possibly because of a favorable literacy environment and their own determination. We next consider the theoretical alternatives for $G \times E$ interactions at the favorable extreme of the distribution, given what occurs at the unfavorable extreme, and we later test whether such interactions occur for good reading and good attention.

So what are the conceptual extensions of the diathesis-stress and bioecological models at the favorable end of the distribution? These are illustrated in Figure 1. The key idea in the diathesis-stress model is that to produce an extreme outcome, there must be a synergy between genetic and environmental factors. A diathesis-stress interaction is a negative synergy in that a considerably more negative outcome occurs when both genetic and environmental risk factors are present. In this case, heritability of the deficit (negative outcome) in the proband group is significantly greater in a risk environment than in a nonrisk environment (see also Figure 2B, which illustrates this situation). So a positive synergy (lower right quadrant of Figure 1) would involve an interaction between genetic and environmental *protective* factors. In this case, the heritability of the group with the positive outcome is greater in a protective environment than in a less favorable environment. Although we do not know of documented examples of a positive synergy, we can imagine they occur for extremely favorable outcomes, such as becoming a world-class performer in some field or living past 100 years. For such extreme favorable outcomes, one may need virtually all the favorable alleles, all the favorable

environmental factors, and the synergy or interaction between them. Because research suggests a diathesis-stress G × E interaction for ADHD at the low end of the attention distribution, we expect to find a positive synergy interaction at the high end. In other words, good attention will be more heritable in a favorable environment.

What is the conceptual extension of the bioecological model at the favorable extreme of the distribution? There is an ambiguity here. If the bioecological model predicts that risk environments mask genetic differences at both extremes of the distribution, then the conceptual extension of the bioecological model is redundant with the positive synergy model just described. That is, the heritability of a good outcome would be greater in a protective environment. However, if the key idea in the bioecological model is that genetic variations are more important (heritability of the extreme group is higher) when the range of relevant environmental factors is reduced, then there is a distinct conceptual extension of the bioecological model at the favorable extreme of the distribution. Thus, if a risk environment reduces both the level and the range of environmental factors supporting a good outcome, then the heritability of the good outcome group in a risk environment should be higher than the heritability of the good outcome group in a nonrisk environment. In other words, only genetically resilient children will exhibit the good outcome in a risk environment, whereas genetic variations favoring a good outcome will be less important in a nonrisk environment, which will provide a higher level and more variability of environmental protective factors predisposing toward a good outcome. We call this a *resilience* interaction, because genetic protective factors that predispose toward a good outcome are unmasked in a risk environment. Because evidence suggests that there is a bioecological interaction for RD at the low tail of the reading distribution, we predict there will be a resilience interaction for good reading at the high tail. That is, good reading will be more heritable in a risk environment than in a protective one. We next describe the method used here to test for G × E interactions.

Using the DeFries–Fulker Method to Test for G × E Interactions

Because the method used to test for G × E interactions in this article is the DeFries–Fulker (DF) model, we explain the logic of that model here. This model tests for the etiology of an extreme group in a twin sample, and so it is a powerful approach for selected samples, such as those used in this article (e.g., good and poor reading, good and poor attention). The method allows one to decompose that etiology into main effects of genes (h^2g), shared environment (c^2g), and nonshared environment (e^2g), and to test for interactions (DeFries & Fulker, 1985, 1988). The letter g refers to *group* and makes it clear that these etiological components apply to the extreme group and not to individual differences across the whole distribution.

The DF method capitalizes on the phenomenon of regression to the mean. In this method, at least one member of each twin pair (the proband) is selected to be extreme on the phenotype, and then the regression equation predicts the cotwin's phenotypic score based on the coefficient of genetic relationship between the twins, which is 1.0 for monozygotic (MZ) twin pairs and 0.5, on average, for dizygotic (DZ) twin pairs. The logic is that MZ cotwins will not regress as far back to the population mean as DZ cotwins if the trait is heritable. The DF basic equation is given as

$$C = B_1P + B_2R + K,$$

where C stands for the cotwin's score on the phenotype of interest, P stands for the proband's score on the phenotype of interest, and R stands for the coefficient of genetic relationship (1.0 vs. 0.5). If the beta for the coefficient of genetic relationship (B_2 term) is significant, then there is evidence that being in the proband group is heritable.

Figure 2A illustrates the case in which there is evidence for univariate h^2g because the cotwins of DZ probands regress further back to the population mean than the cotwins of MZ probands (differential regression to the mean). The c^2g and e^2g components may be significant in this case as well.

The DF equation can also incorporate tests of G × E interaction in its extended form, where the new term, E, stands for an environmental variable. Here the product of the environmental variable and the coefficient of genetic relationship tests for the presence of a G × E interaction (B_5 term):

$$C=B_1P+B_2R+B_3E+B_4PE+B_5RE+K.$$

Figures 2B and 2C depict G × E interactions in a simplified form by treating the E factor as binary. In practice, the E variable is often continuous, and the extended DF model tests for interaction across that continuum. As Figures 2B and 2C depict, a G × E interaction in the DF model signifies that differential regression to the mean varies as a function of E. For illustrative purposes, we have depicted the extreme case in which h^2g is zero in one environmental condition and moderate in another, but obviously this is not required. In a diathesis-stress interaction, there is significantly greater differential regression to the mean in the presence of the E risk factor than in its absence (e.g., higher h^2g in unfavorable environments; see Figure 2B). In a bioecological interaction, the opposite is true: greater differential regression to the mean in the absence of the E risk factor than in its presence (e.g., higher h^2g in favorable environments; see Figure 2C). At the favorable extreme of the distribution, a positive synergy interaction would involve greater differential regression to the mean in the presence of an E protective factor. In contrast, a resilience interaction would involve greater differential regression to the mean in the presence of an E risk factor.

The DF method has also been adapted for molecular genetic linkage analyses (Fulker et al., 1991). The logic of the method remains the same, but sibling pairs instead of twin pairs are the sample of interest. Instead of an overall coefficient of genetic relationship (i.e., 1.0 for MZ pairs vs. 0.5 for DZ pairs), the genetic similarity between the siblings is captured by the identity-by-descent (IBD) value of the siblings at a specific genetic locus. Siblings can share both alleles (IBD = 1.0), half their alleles (IBD = 0.5), or none of their alleles (IBD = 0.0) for a specific genetic locus because of the segregation patterns of parental alleles. If this genetic variance significantly predicts the extent of regression to the mean for the cosibling, then there is evidence for linkage. This linkage model can also incorporate additional covariates in its extended form so that G × E interactions can be examined within a linkage framework (Fulker et al., 1991).

In later sections, we use the three illustrations in Figure 2 to explore G × E interactions at the unfavorable and favorable extremes of the distribution.

Complications in Testing for G × E Interactions

We have already alluded to two complications in testing for G × E interactions: G–E correlations and interpretation of G × E in the absence of genetic and environmental main effects. G–E correlations are an important confound to consider in diathesis-stress interactions, but they are less problematic in bioecological interactions. Regarding main effects of genes and environment, it is certainly statistically possible to obtain an interaction without main effects. However, in controlled animal studies, investigators tend to find main effects of both factors when an interaction is detected (e.g., Crabbe et al., 1999; Valdar et al., 2006). Unlike animal studies, human studies of G × E interaction only rarely involve random assignment of environmental risk to different genotypes. Animal studies of G × E interaction provide a gold

standard of what we should expect to find in human studies of $G \times E$ interaction. Unless, quite unexpectedly, $G \times E$ interactions operate differently in humans than in animals, we should be wary of the validity of $G \times E$ interactions in humans in the absence of main effects. We continue our discussion of complications in testing for $G \times E$ interactions by addressing the following issues: biological versus statistical interactions, multiple testing and Type I errors, power and Type II errors, artifactual interactions, and behavioral genetic versus molecular genetic approaches.

The term $G \times E$ interaction carries both biological and statistical implications that are not completely synonymous (Rutter, 2006). In this article, we focus on the statistical detection of $G \times E$ interaction, although we acknowledge that this method captures only a subset of $G \times E$ interactions, those that are multiplicative (Rutter, 1983, 2006). Other biological $G \times E$ interactions may be operational in development but remain undetected with statistical methods, especially if there is no variation in the genetic or environmental risk factors. The disorder phenylketonuria is a good example of a $G \times E$ interaction that would be masked as a genetic main effect in a typical environment. Phenylketonuria results from both a genetic mutation and exposure to phenylalanine, a biological $G \times E$ interaction, but because phenylalanine is a common ingredient in our diets, every individual is exposed to the risk environment unless an intervention is put in place. Because of the ubiquity of the environmental risk factor, this biological $G \times E$ interaction cannot be detected statistically (Rutter, 2006; Rutter & Pickles, 1991). The lesson from this example is that it is important to acknowledge the limitations of the statistical approach to detecting $G \times E$ interactions when considering the full range of possible $G \times E$ interactions.

The issue of multiple testing and Type I error is a large problem in the molecular genetics literature that impacts the $G \times E$ literature. These issues have been discussed extensively in the association literature, where there have been many examples of genetic associations that do not replicate and simulations have documented the potential for false positive results (Sullivan, 2007). With uncertain genetic risk factors, it is difficult to build a case for a $G \times E$ interaction. Rigorous replication of the genetic association is necessary to establish the association itself and to establish which allele is the risk allele. Subsequently, $G \times E$ interactions can be tested with the established risk allele. In these $G \times E$ analyses, issues with multiple testing often become a problem because of the exploratory state of the literature. It is common to test several risk alleles, several environmental factors, and several phenotypes, and it is difficult to make predictions about the expected direction of the interaction because the preexisting literature is sparse. Because the potential for Type I error is large in these exploratory studies, we should rely on strict replication studies that require that the same risk alleles interact with similar environmental risk factors in the same direction of interaction.

Not only is Type I error a problem in $G \times E$ studies, but Type II error and power are also of concern, because interactions require more statistical power to be detected than main effects. Within the framework of the DF method, we computed the sample size of twin pairs needed to detect $G \times E$ interactions that account for 1%, 5%, and 10% of the variance assuming 80% power, a 5% alpha level, and equal numbers of MZ and DZ twin pairs. These variance estimates are reasonable given previous analyses that we have been conducting in our laboratory. Because the DF method is regression based, power can be computed with typical power programs (e.g., G*Power 3; Faul, Erdfelder, Lang, & Buchner, 2007). Given these parameters, the sample sizes needed to detect an interaction that accounts for 1%, 5%, and 10% of the variance are 779 twin pairs, 152 twin pairs, and 73 twin pairs, respectively. Of course, the DF method is based on an extreme group selection; thus, at least one member of each twin pair must qualify for the extreme cutoff. Extremity cutoffs are typically at least one standard deviation below the average, and so sampling must occur below the 16th percentile. On the basis of these sample

size estimates, some of the analyses presented in this article are under-powered. We include them to illustrate the methods and provide directions for future research.

In addition to the problems of Type I and Type II errors, there is a problem of spurious $G \times E$ interactions, which can be detected as a result of different kinds of artifacts in the data, such as scaling artifacts, dichotomization, and selected sampling (Eaves, 2006; Rutter, 2006). These issues were explored in a simulated data set based on an additive model (Eaves, 2006). Analyses of the simulated data detected erroneous $G \times E$ interactions because of the scaling properties or range of the environmental variable in the study. These artifacts are potentially replicable across studies if the same environmental measures are included (Eaves, 2006). Scaling artifacts may be detected by transforming the scale and investigating whether the interaction disappears. Additionally, studies could include several environmental measures of the same construct that have different psychometric properties and look for convergence across measures. The simulations also showed that dichotomizing a continuous phenotype into a diagnosis, for example, resulted in a large percentage of spurious $G \times E$ interactions, suggesting that it is best to use continuous phenotypes as the dependent variable (Eaves, 2006). Finally, the simulations showed that analysis of selected samples without correction for ascertainment resulted in spurious $G \times E$ interactions (Eaves, 2006). In the following analyses, we focus on samples selected for good or poor reading or attention. Although these samples are selected, we are not analyzing them as if they were random. Instead, we are using the DF analysis, which takes advantage of the selected nature of the sample. Thus, we do not believe our analyses are susceptible to spurious $G \times E$ interactions on the basis of selection.

One final issue in the detection of $G \times E$ interaction is the relative costs and benefits of behavioral genetic versus molecular genetic approaches. One weakness in the behavioral genetic approach to $G \times E$ interactions is that it tests for interactions with genetic influences that are inferred rather than directly measured, but the mechanisms underlying the interaction are likely to involve a specific gene or subset of genes rather than all the genes that influence a phenotype. As such, some authors argue that molecular genetic methods are preferable for testing $G \times E$ interactions (Rutter et al., 2006). Ideally, tests of $G \times E$ interaction would involve specific risk alleles (e.g., Caspi et al., 2002, 2003), but in the case of many developmental disorders, these have not yet been determined. In contrast, when taking a molecular genetic approach, the effect size of single-risk alleles may be small, even where there is a $G \times E$ interaction, and therefore such effects may be hard to detect without very large sample sizes.

So we are faced with a methodological dilemma. Behavioral genetic tests of $G \times E$ interaction are potentially more powerful and will detect main effects of G, but they leave the underlying biological mechanisms unknown and may even mask real $G \times E$ interactions involving specific genes. Conversely, $G \times E$ interaction studies using single-candidate genes may have only small effect sizes and not reach significance.

One compromise strategy would be to examine simultaneously several candidate genes that affect the same biological pathway (e.g., dopaminergic transmission in the case of ADHD or neuronal migration in the case of RD), and perhaps several relevant environmental factors as well. In the case of RD, there is evidence that at least some of the candidate genes interact in development (Harold et al., 2006), and so examining their joint effects is biologically plausible. To implement this strategy, one must already have convincing data on which alleles are the risk variants. Then one could compute composite G and E risk scores across candidate genes and risk environments for each subject and test next for G and E main effects and $G \times E$ interactions in one omnibus analysis. If there are significant main effects or an interaction, follow-up analyses with an appropriate correction could be performed to specify which risk alleles and which risk environments are contributing to the overall effect. We next review what is already known about $G \times E$ interactions in RD (and related phenotypes) and ADHD.

Review of G × E Interactions in RD and Related Phenotypes

Previous studies have demonstrated that reading performance and its component processes are highly heritable (Gayan & Olson, 2001) and that environmental factors such as parental education are predictors of child educational outcomes (Walker, Greenwood, Hart, & Carta, 1994). Nevertheless, despite this evidence for genetic and environmental influences on literacy development, G × E interactions have been relatively neglected in reading research. One study of a sample of middle-aged twins found that parent education moderated the heritability of word recognition skills. Results showed that the heritability of word recognition in twins with highly educated parents was higher ($h^2 = .69$) than the heritability in twins with less educated parents ($h^2 = .21$), consistent with the bioecological model of G × E interaction (Kremen et al., 2005).

Similar results were obtained in our Colorado Learning Disabilities Research Center (CLDRC) twin sample. It is important to note that the CLDRC sample is overselected for history of reading problems and that controls are selected for a negative history of reading problems (DeFries et al., 1997). The sample was designed to examine poor reading but was not enriched for probands with good reading (or good attention). Twin pairs are assigned to either a positive school history group if one or both twins have a history of reading problems (Group 1) or a negative school history group if neither twin has a history of reading problems (Group 2); these group assignments are then used in the standardization of measures.

Friend, DeFries, and Olson (in press) investigated whether parental education moderated heritability of group deficits in a weighted composite measure of word recognition, spelling, and reading comprehension. Composite scores were standardized against the Group 2 mean for both groups prior to selection of probands. Probands were selected if they scored at least −1.5 *SD* below the mean on the composite and had a positive history of reading problems. This yielded a sample of probands from Group 1 only. The results from the extended DF regression analysis of twin scores demonstrated that the heritability of word recognition deficits increased significantly with increasing levels of parental education, $t(545) = 3.23$, $p = .001$, $B = 0.215$, which is consistent with the bioecological model of G × E interaction. In other words, if the environment is enriched for literacy development, as we assume it is among better educated parents, deficits in reading are more likely to be driven by genotype.

We also investigated possible G × E interactions in a sample of children with speech sound disorder (SSD) who are at risk for developing RD (Gallagher, Frith, & Snowling, 2000; Pennington & Lefly, 2001; Raitano, Pennington, Tunick, Boada, & Shriberg, 2004). SSD is a developmental disorder characterized by delays in the production of intelligible speech (Shriberg, 2003). In contrast to the previous studies described that used behavioral genetic methods to test for G × E, this study consisted of sibling pairs and used molecular genetic linkage methods, including an extension of the DF method to sibling pair data (Fulker et al., 1991).

Given the comorbidity of SSD and RD, it is not too surprising that SSD has shown linkage to several of the replicated RD linkage peaks (Smith, Pennington, Boada, & Shriberg, 2005; Stein et al., 2004). We tested for G × E at the two SSD–RD linkage peaks with the strongest evidence of linkage to speech phenotypes, 6p22 and 15q21, using continuous measures of the home language–literacy environment. We tested the interactions using composite speech, language, and preliteracy phenotypes. The results showed four significant and trend-level G × E interactions at both the 6p22 and the 15q21 locations across several phenotypes and home environmental measures. All of the interactions with the home environment were consistent with the bioecological model of G × E (McGrath et al., 2007). At this point, these results are preliminary because of the small sample size and exploratory nature of the analyses. Although

these linkage-based methods are a step away from the ideal of using identified risk alleles to test for G × E (e.g., Caspi et al., 2002, 2003), until risk alleles are identified for SSD and RD, these linkage-based methods can be used as a first approximation. For instance, they could be used to develop hypotheses about which combinations of genes and environments are likely to show bioecological or diathesis-stress G × E interactions in different disorders. These hypotheses could be tested more rigorously once the risk alleles for SSD and RD are identified.

When phenotypes beyond speech and literacy are considered, such as other academic and cognitive traits, the results of G × E analyses with measures of the home environment tend to be consistent with the bioecological model (Harden et al., 2007; Rowe et al., 1999; Turkheimer et al., 2003), although there are exceptions (Asbury et al., 2005; van den Oord & Rowe, 1998). A highly influential study of IQ by Turkheimer et al. (2003) found evidence for a bioecological interaction in a sample of twins from diverse socioeconomic backgrounds, including families living near or below the poverty level. Consistent with the bioecological model, results showed that the heritability of IQ in the lower socioeconomic status (SES) sample was near zero ($h^2 = .10$), whereas the heritability in the higher SES sample was much larger ($h^2 = .72$). One caveat to these results is that the sample of twins included a high proportion of children from different ethnic groups. If there were mean differences in IQ between the groups and the ethnic group proportions varied as a function of SES, then the results would be partly attributable to their sample characteristics. It is interesting to note that a recent study partly replicated the results in a more socioeconomically advantaged sample, although the evidence for G × E was less marked (Harden et al., 2007).

Review of G × E Interactions in ADHD

In contrast to RD, there is evidence for diathesis-stress interactions in ADHD. Studies examining G × E in ADHD have generally used a candidate gene approach, in contrast to the behavioral genetic and linkage approaches that have been used in RD and related phenotypes. Notably, most of the earlier literature on environmental influences in ADHD has focused on bioenvironmental risk factors, whereas psychosocial environmental risk factors have been most prominent in RD studies. However, the research is beginning to expand, as illustrated by recent studies in ADHD showing diathesis-stress interactions with psychosocial environmental risk factors such as SES and psychosocial adversity (Lasky-Su et al., 2007; Laucht et al., 2007; Retz et al., 2008; Waldman, 2007). We first discuss the studies using bioenvironmental risk factors and then turn to the study of psychosocial environments in ADHD.

Kahn, Khoury, Nichols, and Lanphear (2003) examined the role of the 10-repeat DAT1 risk allele (DAT1 480bp) and maternal smoking on the manifestation of inattentive, hyperactive-impulsive, and oppositional behaviors. The authors found no main effect of DAT1; however, there was a main effect of smoking on the latter two scales ($p < .05$) and an interaction between prenatal smoke exposure and DAT1 +/+ on the hyperactive-impulsive and oppositional, but not the inattentive, scales ($p < .01$).

Neuman et al. (2007) examined potential interactions between DAT1 and DRD4 polymorphisms and prenatal smoking exposure or prenatal alcohol exposure in the manifestation of ADHD subtypes as defined by the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; *DSM-IV*; American Psychiatric Association, 1994) or population-defined ADHD subtypes. The study demonstrated a main effect of maternal smoking ($p = .006$), but not prenatal alcohol exposure ($p = .34$), on *DSM-IV* ADHD symptoms and showed that children who were exposed to prenatal smoking demonstrated significantly elevated odds ratios (ORs) for developing *DSM-IV* ADHD-C if they had inherited the DAT1 9-repeat risk allele, rather than the 10-repeat allele supported by Kahn et al., 2003 (DAT1 440bp; OR = 2.93,

95% confidence interval [CI] = 1.2–7.1) or the DRD4 7-repeat allele (DRD4*7R; OR = 2.83, 95% CI = 1.1–7.4).

Brookes et al. (2006) introduced a novel genetic association with ADHD by examining main effects and possible interactions between a common DAT1 haplotype (a combination of the 3′ UTR 40-bp VNTR and an intron 8 30-bp VNTR) and maternal smoking or prenatal alcohol exposure. Family-based association tests demonstrated a main effect of genotype on ADHD symptomatology ($p = .003$), and the ORs for transmission of the risk haplotype to offspring differed significantly across alcohol exposure groups ($p = .04$).

A study conducted in Germany by Seeger, Schloss, Schmidt, Ruter-Jungfleisch, and Henn (2004) examined the interaction between the DRD4 7-repeat risk allele and season of birth on co-morbid hyperkinetic disorder (HD; ICD-10 equivalent of ADHD) and conduct disorder (CD). Chi-square analyses demonstrated no main effect for either the risk allele or season of birth, but researchers demonstrated significant ORs for comorbid HD + CD in children with one copy of the DRD4 7-repeat risk allele born in spring and summer (OR = 2.8, $p = .013$) and autumn and winter (OR = −5.4, $p = .002$). An increase in relative risk in one environment (spring and summer) juxtaposed with a decrease in relative risk in another environment (autumn and winter) is suggestive of a crossover interaction between season of birth and DRD4.

Laucht et al. (2007) examined the interaction between the dopamine transporter (DAT1) and psychosocial adversity factors measured by the Rutter Family Adversity Index (Rutter & Quinton, 1977), which assesses 11 adverse family factors, such as low parental education, marital discord, unwanted pregnancy, and poor social support of parents. Results showed no genetic main effect of the 5 DAT1 variants on ADHD symptoms, although there was a significant main effect of psychosocial adversity on inattention and hyperactivity–impulsivity ($p = .012–.003$). There was also a G × E interaction such that individuals who were homozygous for the DAT1 risk allele (10R allele of the 40-bp VNTR) and exposed to higher psychosocial adversity had higher rates of inattention and hyperactivity–impulsivity ($p = .001–.015$). In other words, there was only a DAT1 effect in those individuals exposed to psychosocial adversity.

Retz et al. (2008) investigated the G × E interaction between adverse childhood environments (e.g., financial status of the family, quality of school education, degree of family conflict) and 5-HTTLPR, a serotonin promoter transporter gene polymorphism, on childhood and lifetime persistent ADHD. Results demonstrated associations between the homozygous long (LL) 5-HTTLPR genotype on childhood ADHD and between psychosocial childhood adversity and ADHD. Further, a significant G × E interaction was observed between the gene variants of 5-HTTLPR and negative childhood environments, such that the odds of meeting diagnostic criteria for childhood ADHD increased significantly in individuals who carried at least one small 5-HTTLPR allele (SL or SS genotype) and who were exposed to high levels of childhood psychosocial environmental risk, compared with individuals with the LL genotype (OR = .3, $p = .044$) in similar adverse environments. However, null findings were produced when testing for this G × E interaction on persistent ADHD.

Lasky-Su et al. (2007) tested for G × E interactions involving single-nucleotide polymorphisms (SNPs) in or around brain-derived neurotrophic factor (BDNF) and SES level on ADHD inattentive symptom count. Correlational analyses revealed significant associations between lower SES levels and increased ADHD symptomatology ($r = .10$, $p = .006$ for ADHD diagnosis, and $r = .16$, $p = .0003$, for total number of ADHD symptoms). After the authors employed false discovery rate methods to account for multiple comparisons, three BDNF SNPs (rs1013442, rs1387144, and Vall66Met) showed significant main effects on ADHD inattentive symptom count. Family-based association test interaction analyses demonstrated diathesis-stress-type G

$\times$ E interactions, such that carrying BDNF SNP rs1013442, rs1387144, or Vall66Met significantly increased inattentive symptom counts in lower SES environments.

Waldman (2007) explored the relationship between the dopamine receptor gene, DRD2, and maternal marital stability on child ADHD diagnostic status. Generalized linear modeling analyses demonstrated main effects of maternal marital stability (marital status: OR = 2.36, R^2 = .04; number of marriages: OR = 1.77, R^2 = .04) on child ADHD, such that decreased marital stability was associated with increased ADHD diagnoses. Results also demonstrated significant main effects of child and mother DRD2 genotype status on maternal marital stability (OR = 3.26, R^2 = .03, for mother genotype, and OR = 1.04, R^2 = .01, for child genotype) and for mother DRD2 genotype on child ADHD diagnosis (OR = 2.50, R^2 = .04). Although a main effect was not observed for child DRD2 genotype on ADHD diagnostic status (OR = 1.26, R^2 = .005), after the author controlled for covariates such as main and interactive effects of (child) genotype, results demonstrated a significant interaction between child genotype and maternal marital status on ADHD, showing an increased likelihood of ADHD diagnoses for children homozygous for the risk DRD2 alleles in less stable maternal marital environments (p = .002, R^2 = .06).

Although these studies have provided some evidence in support of molecular G $\times$ E diathesis-stress interactions in the manifestation of ADHD, there continue to be substantial inconsistencies in the literature regarding even the most well associated genetic and environmental risk factors. For example, Langley et al. (2008) tested for G $\times$ E interactions influencing ADHD diagnosis among multiple gene variants associated with ADHD in the literature (DRD4, DAT1, DRD5, and 5-HT) and prenatal smoke exposure, prenatal alcohol exposure, and birth weight. Conditional logistic regression analyses produced null findings for all G $\times$ E interaction tests for ADHD diagnosis. Subsequent analyses focused on G $\times$ E interactions modifying antisocial symptoms related to oppositional defiant disorder and conduct disorder in children diagnosed with ADHD. Despite the null interaction findings related to ADHD diagnosis, linear regression analyses showed evidence of G $\times$ E interactions involving DRD5 and birth weight (p = .0004) and DRD5 and maternal smoking during pregnancy (p = .002) on antisocial behavioral symptoms related to oppositional defiant disorder. Analyses also demonstrated a significant modifying G $\times$ E interaction between DAT1 and birth weight on antisocial symptoms related to conduct disorder (p = .03). However, once covariates such as full-scale IQ, gender, and total number of ADHD symptoms were included in these analyses, none of the modifying G $\times$ E interactions remained significant.

Furthermore, many of the studies investigating ADHD G $\times$ E interactions have notable limitations, among them a narrow scope in the investigation of risk alleles and environmental risk factors. Although all studies claimed a theoretical basis for the selection of their risk alleles or environments (i.e., researchers specified their variables a priori), many of the studies did not correct for multiple comparisons, and there were some failed attempts at specific replications across these studies. Although a lack of replication does not necessarily invalidate initial association findings (Gorroochurn, Hodge, Heiman, Durner, & Greenberg, 2007), it underscores a need for further research in this area.

In view of the mixed results that have been obtained with the candidate gene approach, we attempted to replicate the diathesis-stress G $\times$ E interactions in ADHD using behavioral genetic analyses in our CLDRC twin sample. In addition to the recruitment for children with reading disabilities that was described earlier for the CLDRC sample, there is a separate recruitment for children with attention difficulties. Selecting probands who met diagnostic criteria for *DSM-IV* ADHD—combined type or inattentive (I) type—we employed the extended DF model to investigate G $\times$ E interaction analyses between the ADHD inattentive symptom dimension and parental education. Rather than count symptoms, we asked parents and teachers to rate

each symptom from 0 to 3, and these ratings were summed to yield an inattention score that was normally distributed. This inattention score was standardized against Group 2 (controls), and Z scores were reflected so that a lower Z score meant more inattention. First, preliminary analyses demonstrated that the low end of the ADHD inattentive symptom dimension was heritable in our sample, (188) t= 5.380, p < .001, B = 0.863. Next, bivariate correlation analyses were used to evaluate the association between parental education and child inattentive symptomatology in the current sample. Because significant results were found in the expected direction (r = .235, p < .001), whereby lower parental education was associated with worse child inattention, partial correlations were applied to further test this main effect while we controlled for parent retrospective reports of ADHD (I) symptomatology. A significant main effect of parental education on ADHD (I) remained even after controlling for parental ADHD (I) symptomatology (r = .285, p < .001). To address potential confounds related to G–E correlations in our G × E interaction analyses, we employed linear regression methods to residualize child inattention scores from the parental education environment. G × E results from the extended DF model demonstrated a significant interaction with ADHD (I) and parental education in the diathesis-stress direction, indicating that ADHD was more heritable in the unfavorable parental education environment, (176) t= −2.045, p = .027, B = −0.344. In sum, using behavioral genetics instead of molecular genetics methods, we replicated a diathesis-stress interaction for ADHD and parental education, a psychosocial factor (Laucht et al., 2007; Retz et al., 2008; Waldman, 2007).

Are There G × E Interactions at the Favorable Extreme of the Reading and Attention Distributions?

Given what is already known about G × E interactions for RD and ADHD, what would we predict will occur at the favorable extreme of these two symptom dimensions? Using the possibilities in Figure 1, we predict a resilience interaction will occur at the favorable extreme of the reading dimension and that a positive synergy interaction will occur at the favorable extreme of the attention dimension.

Friend, DeFries, Pennington, and Olson (2008) investigated whether parental education moderates heritability at the high end of word recognition ability in the CLDRC twin sample. Word recognition scores were restandardized against a norming population mean of 100 and a standard deviation of 15 prior to selection of probands. Probands were then selected if they scored above this population mean on word recognition and had no history of reading problems in school. Although probands were above-average readers, they were not selected to be good readers (e.g., more than one standard deviation above the population mean), because more extreme selection led to a much smaller sample size. The results demonstrated that the heritability of above-average word recognition performance *decreased* significantly with increasing levels of parental education, (1013) t= −1.75, one-tailed p = .04, B = −0.173. This suggests that genotype plays a larger role in obtaining a good reading outcome when the environment provides less support for that outcome. In other words, we found evidence for the predicted resilience interaction. Now we turn to G × E interactions at the favorable extreme of the attention dimension.

A preliminary study investigating potential G × E interactions at the high end of the attention distribution (i.e., with a sample of children demonstrating good attention and focus) was conducted within the same CLDRC twin sample. This sample included pairs for whom at least one twin exhibited difficulties in reading or attention and control subjects exhibited no such difficulties. Parents and teachers of recruited participants were asked to complete measures of classroom performance and attention. ADHD inattention symptom dimension ratings of twins were averaged across parents and teachers, yielding a normally distributed score. As in the analyses of word recognition ability and parental education, ADHD inattention mean severity

ratings were age regressed and standardized against the Group 1 mean for both Group 1 and Group 2 twin pairs prior to the selection of probands. Probands were then selected if they scored at least +1 *SD* above the Group 1 mean on ADHD (I) symptomatology ratings (+1 *SD* implies less inattention). This cutoff corresponded to a mean inattention rating of 0.521 (*SD* = 0.497), which is approaching the ceiling of this inattention score.

Before conducting $G \times E$ analyses, we first examined whether the above-average scores in this proband group scores were heritable. DF regression analyses (DeFries & Fulker, 1985, 1988) demonstrated robust univariate group heritability at this end of the distribution, (138) t= 5.043, p < .001, B = 0.990. We also found a significant correlation between parental education and inattention scores (r = .110, p = .038) in the expected direction, which indicated that higher levels of parental education were associated with less inattention. Partial correlations were then used to address potential confounds related to G–E correlations. A main effect of parental education on child attention remained significant when controlling for father retrospective attention ratings (r = .226, p = .033), but this association became insignificant when either mother retrospective attention was partialed out (r = .135, p = .114) or the average of both parents' retrospective attention self-report of attention was controlled (r = .115, p = .189).

An extended DF model was then applied to these high-end probands to test the positive synergy interaction predicted earlier, in which the heritability of less inattention would increase as the favorability of the environment (i.e., parent education) increased. As in our low-end $G \times E$ interaction analyses focusing on a group with high inattention, linear regression methods were used to residualize twin inattention scores from parental education to address the potential G–E correlation confounds owing to nonrandom assignment of twins to environments. Contrary to our positive synergy prediction, results from the extended DF regression model produced null findings for a $G \times E$ interaction for low inattention and parental education, (134) t= .997, p = .321, B = 0.203.

In sum, although we found that both extremes of the inattention dimension are highly heritable and associated with parental education, we did not find the positive synergy interaction we had predicted at the favorable end of the inattention distribution. These results, however, may be due to a threshold effect, whereby once a certain level of low inattention is achieved, an even better score is not functionally meaningful. Nevertheless, we did replicate with behavioral genetic methods the diathesis-stress $G \times E$ interaction for ADHD (I) found by previous researchers using molecular genetic methods (Laucht et al., 2007; Retz et al., 2008; Waldman, 2007), with results suggesting that similar biological mechanisms are operating across methods.

Discussion

In this article, we provided a conceptual framework that encompasses $G \times E$ interactions across the phenotypic distribution. Theoretical models of $G \times E$ interaction have been derived from studies focused on the low end of the phenotypic distribution, and so it is important to extend these models to the high end of the distribution. The etiology of individuals at the high end of the distribution can also teach us about resilience and protective factors that may be important in developmental disorders.

Our discussion focused on two developmental disorders, RD and ADHD. At the low end of the distribution, there is accumulating evidence for bioecological interactions in RD and diathesis-stress interactions in ADHD. At this point, although it is difficult to discern what factors are driving the type of interaction in each disorder because of the inconsistencies in the literature, it seems more likely that the disorder itself and not the environmental risk factors is actually driving these interactions. For example, although studies of $G \times E$ interactions in RD

have focused more on psychosocial environmental factors, whereas studies of G × E interactions in ADHD have focused more on bioenvironmental factors, recent evidence, including our replication of a diathesis-stress-type interaction with ADHD (I) and a psychosocial environmental factor (parental education), suggests that it is the disorder rather than the environmental variable that determines the direction of the G × E interaction. To tease apart the role of the disorder versus the environmental variable in determining the direction of an interaction, future studies should examine both bioenvironmental and psychosocial risk factors in RD and ADHD to determine whether interactions take a different form depending on the environmental variable and use molecular rather than behavioral genetic methods. Moreover, even though parental education has a single measure, it is not a unitary construct but rather the outcome of a multifactorial developmental process and thus has many environmental (and genetic) correlates. So, it is possible that the opposite G × E interactions found for RD and ADHD with parental education may arise because different correlates of parental education are important for each disorder. For instance, family and marital discord may be a more important environmental risk factor for ADHD, whereas family support for language and literacy development may be more important for RD. Just as we have to "unpack" measures of G, we have to unpack measures of E. Additionally, future studies should examine G × E interactions in different developmental disorders to see whether a pattern emerges. Currently, there is a preliminary pattern in which academic and cognitive traits tend to show bioecological interactions and psychopathologies tend to show diathesis-stress interactions.

On the basis of our review of the G × E literature in RD and ADHD, we made predictions regarding the nature of the interactions that could be expected at the high end of the distributions. We predicted resilience interactions for good reading and positive synergy interactions for good attention. We presented new analyses from our CLDRC twin sample that partly supported these predictions. We found evidence for a resilience interaction with parent education at the above-average end of the reading distribution. Although we found null results for a G × E interaction with parental education at the favorable end of the inattention distribution, it is likely that our measure of "good" attention indicated only an absence of attention problems, because it was based on ratings of inattention, not on ratings of good attention. A second limitation of the high-end analyses presented here is that to have an adequate sample size, we had to use cutoffs for proband selection that were not that high. Clearly, more research is needed with larger samples at the high end of the distribution for reading, attention, and other cognitive and socioemotional skills. The conceptual framework that we have advanced in this article may be a useful guide for this research.

Acknowledgments

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Figure 1.
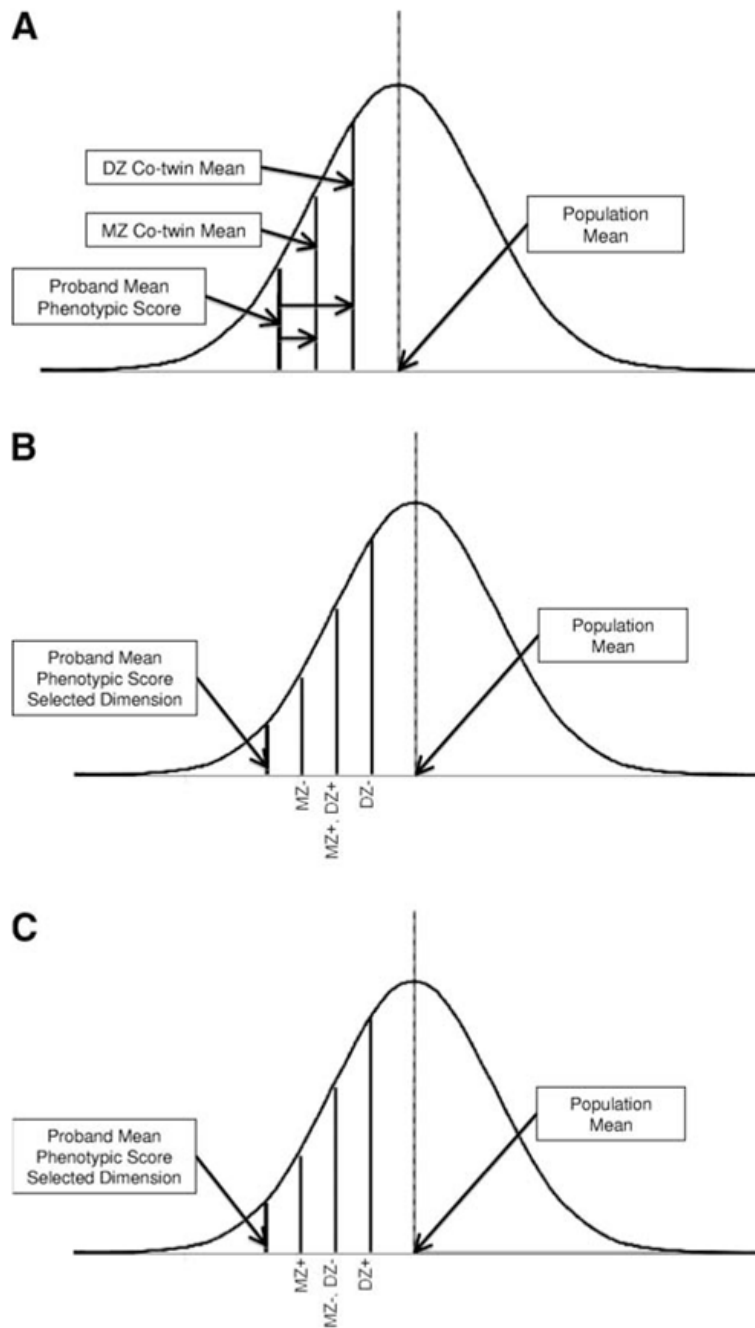Extending Gene × Environment interactions to the favorable extreme of the distribution.

Figure 2.
Testing of main effect of gene (G) and Gene × Environment interactions with the DeFries–Fulker method. In Figures 2B and 2C, MZ−, MZ+, DZ−, and DZ+ refer to cotwin means in different environmental circumstances. Minus sign signifies an unfavorable environment; plus sign signifies a favorable environment.