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Parental Involvement Moderates Etiological Influences on Attention-Deficit Hyperactivity Disorder (ADHD) Behaviors in Child Twins

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Abstract

Although few would now contest the presence of gene x environment (GxE) effects in the development of child psychopathology, it remains unclear how these effects manifest themselves. Alternative GxE models have been proposed (i.e., diathesis-stress, differential susceptibility, bio-ecological), each of which has notably different implications for etiology. Child twin studies present a powerful tool for discriminating between these models. The current study examined whether and how parental involvement moderated etiological influences on ADHD within 500 twin pairs aged 6–11 years. Results indicated moderation of genetic and non-shared environmental contributions to ADHD by parental involvement, and moreover, suggested both differential susceptibility and bio-ecological models of GxE. Results highlight the utility of child twin samples in testing different manifestations of GxE effects.

Attention-deficit hyperactivity disorder (ADHD) is a common and costly neurodevelopmental disorder characterized by excessive and developmentally inappropriate symptoms of inattention-disorganization and hyperactivity-impulsivity (American Psychiatric Association, 2013). Past behavioral genetic work has convincingly shown that genetic factors make moderate to large contributions to the etiology of ADHD symptoms (Nikolas & Burt, 2010), including at both the moderate and extreme ends of the behavioral dimensions of inattention and hyperactivity-impulsivity (Willcutt, Pennington, & DeFries, 2000) and over the course of development (Chang et al., 2013). However, molecular genetic studies have only uncovered a relatively small number of relevant genetic variants (both common and rare in the population) that may be directly involved in the etiology of ADHD (Yang et al., 2013). This mismatch between the estimates of genetic influence derived from behavioral genetics research (or heritability estimates, which consistently converge at around 70% for ADHD) and the small effect sizes derived from large-scale, whole-genome association studies (genome-wide association markers accounting for approximately 1–3 % of the variance in ADHD) has led to renewed interest in the role of gene-environment interplay processes as causal processes underlying ADHD (Nigg, 2012).

Importantly, much of this renewed interest in gene-environment interplay can be directly traced to Bronfenbrenner's bioecological framework for understanding the impact of these exchange processes in human development. In his seminal theory (see Bronfenbrenner &

Ceci, 1994), bidirectional influences between an individual child's development and his/her surrounding environment are emphasized. Bronfenbrenner's theory acknowledged the relevance of genetic and biological processes, but noted that it is the reciprocal interchanges between these factors and the larger environmental context that shape psychological function. Bronfenbrenner noted that these transactional mechanisms begin early in development and most importantly, rely on assessment of proximal processes, as these are the mechanisms through which genetic influences on psychological functioning are actualized. The synergistic nature of these processes has fueled much of the recent interest in the interactive effects of genetic and environmental influences on child psychopathology.

Gene x environment interaction effects (GxE) can be defined as genetically-modulated sensitivity to environmental factors, such that the impact of the environment may vary depending on an individual's genetic make-up. Broadly speaking, the environment may then serve to "activate" or "attenuate" the specific genetic and biological mechanisms underlying ADHD. In addition to clarifying the role of genetic contributions to the disorder, identification of GxE effects may also aid in clarifying the types of environmental processes that contribute to the development and/or maintenance of ADHD symptomatology over time. A recent review of the initial empirical GxE studies for ADHD indicated overall small to moderate effects, but that more positive findings emerged for interactions involving family environmental and contextual factors compared with pre- and perinatal risk factors (see Nigg, Nikolas, & Burt, 2010).

Focusing on family processes as moderators of genetic influences on ADHD thus appears to be a particularly fruitful approach for illuminating the origins of ADHD. Indeed, initial tests of genetic-by-family environment effects for ADHD have been uniformly positive (see Martel et al., 2011; Nikolas et al., 2010). Past work has shown that parenting and familial context serves to play a crucial role in shaping behavioral and emotion regulation for youth with ADHD (Nigg, Hinshaw, & Huang-Pollock, 2006). Thus, the family environment may shape the developmental trajectory of genetically-influenced dysfunction in neural circuitry underlying self-regulation, leading to the onset and maintenance or decline of ADHD behaviors across development. This has been echoed in the empirical GxE work - for example, the effects of child perceptions of inter-parental conflict on teacher reports of ADHD symptoms were moderated by serotonin promoter polymorphism genotype (Nikolas et al., 2010). Additionally, dopamine D4 receptor genotype moderated the impact of parental inconsistent discipline on ADHD symptoms (Martel et al., 2011).

Critically, however, all of these studies have focused solely on environmental *risk* factors, with little-to-no consideration of moderation by *protective or enhanced* environmental experiences. This omission from the literature is curious, given that the latter has also been highlighted as critically important for understanding the mechanisms by which genes and environments exude risk for psychopathology in childhood (Bakermans-Kranenburg & van Ijzendoorn, 2007; Belsky & Pluess, 2009). Moreover, the lack of positive parenting (i.e., warmth, involvement) has been directly associated with subsequent development of externalizing behaviors (Boeldt et al., 2012) and ADHD (Ellis & Nigg, 2009; Rogers et al., 2009). Similarly, the presence of high levels of warmth and involvement may serve to attenuate ADHD-related impairments (Deult, 2010). Examinations of positive parenting as a

moderator of genetic influences may thus be of critical importance for understanding the etiology of ADHD (see Boeldt et al., 2012).

Types of GxE Effects

As noted in recent years, GxE effects can take many forms (Belsky & Pluess, 2009; Burt, 2011). To date, however, the most commonly examined and widely accepted model of GxE influences on child psychopathology is the diathesis-stress model. Within this framework, genes and environments exert risk synergistically, such that individuals possess an inherent “vulnerability” (indexed by higher genetic liability or more “risk alleles”) to psychopathology that emerges within the context of increased environmental stressors. Put differently, genetic influences on individual differences in psychopathology will be greatest within the context of riskier environments. By contrast, in neutral or enriching environmental contexts, both vulnerable and resilient individuals (i.e., those with low genetic liability or fewer “risk alleles”) will exhibit equivalent low (or absent) levels of psychopathology.

Although the diathesis-stress model of GxE effects has been most often examined empirically for ADHD (as well as for other traits), additional frameworks for understanding GxE processes have been advanced. Belsky and Pluess (2009) argue that based upon evolutionary theory, individuals will also be more or less *susceptible* to environmental influences based upon their genetic make-up. That is, it is hypothesized that some individuals are both more vulnerable to environmental stressors or risks, as well as disproportionately influenced by the beneficial effects of positive and enriching environments. Under this framework, some genes may not confer risk for psychopathology directly per se, but instead influence vulnerability to environmental exposures, both positive and negative. Like the diathesis-stress model, the differential susceptibility model would predict that genetic influences on individual differences in psychopathology will be high within the context of riskier environments. Yet, this model would also predict a high degree of genetic influence on individual differences in psychopathology within in the context of enriching and supportive environments.

Few studies of molecular GxE effects have specifically focused on examining differential susceptibility models of gene-environment interaction, although reanalysis of prior published studies revealed some potential for this type of GxE effect for ADHD (Belsky & Pluess, 2009). Furthermore, GxE work thus far has almost exclusively examined the impact of genetic risk in combination with putative environmental risk factors (in line with the diathesis-stress model), but not within the context of environmental protection or enrichment. As an exception, Lahey and colleagues (2012) reported positive GxE effects involving the dopamine transporter gene and positive parenting (as well as negative parenting) in predicting the development of conduct problems within a longitudinal sample of ADHD youth. These results indicate that future work examining GxE effects involving positive and enriching environments is needed in order to more fully evaluate differential susceptibility mechanisms.

The final GxE model, the bio-ecological model (Pennington et al., 2009) focuses more on environmental moderation than on genetic moderation per se. In this model, adverse environmental factors are hypothesized to shape the development of the disorder regardless of the child's genetic risk for that condition. Genetic influences on the condition, by contrast, are thought to be more influential in the *absence* of adversity. That is, environmental sources of variance are strongest in the presence of environmental risk, whereas genetic influences are most prominent in the absence of environmental risk. Past child twin work has provided some initial support for this model of GxE effects for ADHD (Nikolas, Klump, & Burt, 2012), however other child twin work has not (Pennington et al., 2009; Rosenberg et al., 2012). The emergence of significant moderation of environmental contributions to ADHD across different levels of enriching environments, such that environmental influences on ADHD are highest at *lowest* levels of enrichment, could provide additional support for a bio-ecological model of GxE effects (albeit indirect, as it may not be the case that low levels of support are necessarily deleterious).

Utility of Twin Designs for Distinguishing among the Various Models of GxE

Bronfenbrenner's bioecological framework highlighted the potential utility of twin designs in exploring the systematic variation in heritability of child traits or behaviors as a joint function of both proximal processes as well as the environments in which these processes take place. Bronfenbrenner and Ceci (1994) argued that future research should employ designs that included methods to measure heritability as well as the proximal processes that may influence systematic changes in genetic influences on child behavior. Recent theoretical work in behavior genetics has done just this and expanded the traditional biometric framework to account for GxE effects – thus, child twin samples can provide a complementary approach for investigating these processes (Purcell, 2002). Within these models, the genetic (A) and non-shared environmental (E) variance components contain not only their respective main effects but also variance due to GxE effects. Because child twin designs can examine moderation of trait variances at the latent level, they can provide a powerful method for detecting GxE effects as well as for systematically distinguishing the diathesis-stress, differential susceptibility, and bio-ecological models. Additionally, child twin designs allow for concurrent examination of moderation on genetic, shared, and non-shared environmental influences, which is particularly important for detecting bio-ecological GxE effects.

Analysis of moderation of genetic and environmental contributions to ADHD at different levels of positive parenting can first allow for evaluation of the various models of GxE. Should GxE effects involving positive parenting follow a diathesis-stress model, genetic influences on ADHD would be expected to be *highest* within the context of *highest environmental adversity*. Because the current study is focused on environmental enrichment (the absence of which is not necessarily a direct measure of adversity), we would expect the *relative* genetic contributions in the current study to be *highest at low levels of positive parenting*, should diathesis-stress GxE effects be operating. However, should GxE effects be operating via differential susceptibility mechanisms, we would expect genetic influences on

individual differences in ADHD behaviors to be *highest* at the *most beneficial levels* of positive parenting and also at the *most adverse levels* of negative parenting. Again, given the focus of the current study on measures of environmental enrichment, a test of the second condition for differential susceptibility (i.e., high genetic influences at most adverse levels of negative parenting) is not possible without a bipolar measure of positive parenting (or by using two measures, one of positive parenting and one of negative parenting). Thus, partial support for differential susceptibility would be found if the *relative* genetic contributions to ADHD are *highest* at the *high levels of positive parenting*.

Importantly, however, high contributions from genetic factors at high levels of positive parenting would not specifically point toward differential susceptibility mechanisms, as this scenario would also be predicted by bio-ecological models of GxE effects. Thus, findings of large genetic contributions to ADHD at high levels of positive parenting would then signal *either* differential susceptibility *or* bio-ecological mechanisms of GxE. Further, changes in *environmental contributions* to ADHD at different levels of positive parenting, such that environmental influences are *largest* in the context of *higher risk* environments (i.e., low levels of positive parenting) would provide evidence of a bio-ecological model of GxE effects. By contrast, support for the diathesis-stress model of GxE effects would require relatively small environmental influences (but large genetic influences) at high levels of environmental risk.

The goal of the current study was to examine positive parenting, namely parental involvement, as a moderator of genetic and environmental influences on ADHD behaviors using a sample of child twins. Results can then provide concurrent tests for various models of GxE effects for ADHD (diathesis-stress, differential susceptibility, bio-ecological) as well as aid in clarifying the potential etiological role of parental involvement in ADHD.

METHOD

Participants

The Michigan State University Twin Registry (MSUTR) includes several independent twin projects (Burt & Klump, 2013). The 500 twin pairs (50.2% monozygotic) included in the current study were assessed as part of the Twin Study of Behavioral and Emotional Development in Children (TBED-C) within the MSUTR. Families were recruited via State of Michigan birth records in collaboration with the Michigan Department of Community Health (MDCH). The MDCH manages birth records and can identify all twins born in Michigan. Birth records are confidential in Michigan; thus, recruitment procedures were designed to ensure anonymity of families until they indicated an interest in participating. Once twins were identified, MDCH then made use of the Michigan Bureau of Integration, Information, and Planning Services database to locate current addresses through parent drivers' license information. MDCH then mailed pre-made recruitment packets to parents. A reply postcard was included for parents to indicate their interest in participating. Interested families were then contacted directly by project staff. Parents who did not respond to the first mailing were sent additional mailings approximately one month apart until either a reply was received or up to four letters had been mailed. The final letter is sent via certified mail, a highly effective way of reaching non-responding families.

This recruitment strategy yielded an overall response rate of 62%, which is similar to or better than those of other twin registries that use anonymous recruitment mailings (Baker, Barton, & Raine, 2002; Hay, McStephen, Levy, & Pearsall-Jones, 2002). The final sample was broadly representative of the area population and of recruited families more specifically (as assessed via a brief questionnaire screen administered to 70% of non-participating families, see Burt & Klump, 2013). Endorsement of ethnic group membership by participating families was comparable to area inhabitants (e.g., Caucasian: 86.4% and 85.5%, African-American: 5.4% and 6.3% for the participating families and the local census, respectively). Similarly, 14.0% of families in our sample lived at or below federal poverty guidelines, as compared to 14.8% across the state of Michigan. Participating twins did not differ from non-participating twins in their average levels of conduct problems, emotional symptoms, and hyperactivity (as assessed via the Strength and Difficulties Questionnaire (Goodman & Scott, 1999; Cohen's d standardized effect sizes = $-.047$, $.010$, and $-.076$, respectively; all $p > .29$). Participating families also did not differ from non-participating families (all $p > .16$) in paternal felony convictions ($d = -.01$), paternal years of education ($d = .00$), proportion of Caucasian twins ($d = .01$), rate of single parent homes ($d = -.09$), proportion of dizygotic twins ($d = -.08$), maternal or paternal age at assessment (both $d < .10$), use of fertility medications to conceive the twins ($d = -.05$), number of twin siblings ($d = -.10$), or maternal and paternal alcohol problems ($d = .05$ and $.03$, respectively). However, participating mothers reported slightly more years of education ($d = .17$; $p = .02$) and a slightly lower rate of felony convictions ($d = -.20$; $p = .03$) than did non-participating mothers. A trend was also observed for family income, although income was slightly lower in participating as compared to non-participating families ($d = -.13$, $p = .06$). For a full description of recruitment procedures for the MSUTR, see Burt and Klump (2013).

The current sample consisted of 500 child monozygotic (MZ) and dizygotic (DZ) child twin pairs (total $n = 1,000$ twins). Twins ranged in age from 6–10 years ($M=8.3$, $SD=1.4$ years), although a few pairs ($n=14$) had turned 11 by the time they completed their assessment. Parents gave informed consent for both themselves and their children and children provided informed assent. All research protocol was approved by the Michigan State University Institutional Review Board.

Zygosity Determination

The current sample was composed of 251 MZ twin pairs (47.0% female) and 249 DZ twin pairs (49.0% female). Zygosity was established using physical similarity questionnaires administered to the twins' primary caregiver (Peeters, Van Gestel, Vlietinck, Derom, & Derom, 1998). On average, the physical similarity questionnaires used by the MSUTR have accuracy rates of 95% or better when compared to other methods (Peeters et al., 1998). Because of their high validity in assigning zygosity and their low-cost and ease of administration to large samples, physical similarities questionnaires, like the one used in the current study, are one of the most common methods for determining zygosity within the field of behavioral genetics (Iacono et al., 1999; Levy et al., 1997; Lichtenstein et al., 2002; Rietveld et al., 2000).

ADHD Behaviors

Parents of the twin participants completed the Child Behavior Checklist (CBCL; Achenbach & Rescorla, 2001) to assess behaviors relating to ADHD. Each parent rated how often particular behaviors occurred during the past six months in each twin using a 3-point Likert scale (0=never true; 1=sometimes/somewhat true; 2=often true). The 7-item DSM-oriented scale for ADHD was selected for our analyses since its items were chosen to closely map onto DSM-IV and DSM-5 criteria for ADHD. Sample items include “fails to finish things s/he starts,” “can’t sit still, restless or hyperactive”, and “impulsive or acts without thinking”. The CBCL has demonstrated good reliability and validity (Achenbach & Rescorla, 2001). Additionally, receiver-operator characteristic analyses have shown the CBCL to be a robust predictor of clinically-diagnosed ADHD (Hudziak et al., 2004). Youth did not undergo a formal diagnostic procedure for ADHD, and we included all youth with scores across the behavioral dimension, given past taxometric work supporting the dimensionality of ADHD (Marcus & Barry, 2011) and the high degree of genetic influence across the spectrum of ADHD behaviors (Willcutt, Pennington, & DeFries, 2000). Internal consistency estimates in the current sample were adequate ($\alpha=.88$ for mothers, and $\alpha=.87$ for fathers, respectively). Cross-informant agreement for mothers and fathers was moderate ($r=.58, p<.001$) so a final composite was computed by averaging mother and father report, as done in previous work (Burt & Klump, 2014; Burt et al., 2012). All twins ($n=1000$) had report from at least one parent. When report from only one parent was available ($n=142$), this was used for analyses.

While age and sex based norms are available for CBCL scores, the raw scores for the DSM-ADHD scale were used in the current study, as recommended by the manual (Achenbach & Rescorla, 2001). Thus, the ADHD measure for each twin was the total raw score added across the seven ADHD items (score range 0–14). The ADHD raw score was log-transformed prior to analysis in order to better approximate normality (skew following transformation = $-.13$), as skewness may result in distorted estimates of moderation in the GxE analyses (Purcell, 2002). Additionally, because the current sample was underpowered to examine estimates separately by age and sex, the ADHD scale was regressed on age and sex prior to analyses. The final score (with age and sex covaried) was then used in all model-fitting analyses (McGue & Bouchard, 1984).

Parental Involvement

Parental involvement was assessed via informant-reports obtained via the Parenting Environment Questionnaire (PEQ, Elkins et al., 1997). The PEQ was developed by the Minnesota Twin Family Study to assess mother, father, and twin reports of each twin's relationship with each parent, making it possible to determine how each family member perceives his/her relationship with other family members. The PEQ assess multiple domains of each twin-parent relationship, including conflict, involvement, regard, and structure, and has been frequently used to assess parenting and family functioning in past twin studies (see Burt et al., 2007). The 12 involvement items were rated on a 4-point scale (from definitely true to definitely false). Mothers and fathers each completed a separate set of ratings for each of their twins. Each twin also completed two sets of ratings on the same items, one pertaining to the relationship with his/her mother, and one pertaining to the relationship with

his/her father. To ensure adequate comprehension of the items, the PEQ was read to twins with reading levels under 5th grade (assessed via brief screen, Torgesen et al., 2009). Internal consistencies for all informant-reports were adequate ($\alpha=.72$ for twin report of maternal involvement, $\alpha=.79$ for twin report of paternal involvement, $\alpha=.81$ for maternal report, $\alpha=.80$ for paternal report). Given the high level of correlation between twin ratings of each parent ($r=.68, p<.001$) and between parental ratings of their respective relationships with a given child (r s ranging from .77–.86, $p<.001$), we conducted our primary analyses using a composite of parental involvement, in which twin and parent informant-reports were averaged. Nearly all twins had reports of involvement from at least one informant ($n=999$). We then conducted secondary analyses separately by informant type (parental ratings of involvement and twin ratings of involvement) to evaluate the consistency of results across informants. Parent-report was available for $n=997$ twins and twin-report was available for $n=987$ twins.

Several data preparation steps were necessary to complete the analyses (Purcell, 2002). Data were first floored to zero by subtracting 12 from all scores. A continuous moderator (parental involvement) with a range of scores from 0–1 was then computed by dividing all scores by 36. This process was repeated for the informant-specific ratings.

Data Analyses

Behavioral genetic analyses make use of the difference in the proportion of genes shared between reared-together siblings. Utilizing these differences, the variance within observed behaviors is partitioned into three components: additive genetic, shared environment, and non-shared environment plus measurement error. The additive genetic component (A) includes the effect of individual genes summed over loci and as well as any effects due to interactions between additive genetic factors and shared environmental factors (i.e., those effects that increase twin similarity relative to the amount of genes shared). The shared environment (C) is that part of the environment common to siblings that serves to increase sibling similarity regardless of the proportion of genes shared. The non-shared environment (E) encompasses environmental factors (and measurement error) differentiating twins within a pair, as well as any interactions between additive genetic and unique environmental influences (i.e., those effects that decrease twin correlations regardless of genetic relatedness).

GxE Models—Biometric GxE models (Purcell, 2002; van der Sluis, Posthuma, & Dolan, 2012) were fitted to the data in order to determine the extent to which genetic and environmental contributions to ADHD varied across different levels of parental involvement. The original biometric GxE model developed by Purcell (2002) has recently been reformulated (van der Sluis, Posthuma, & Dolan, 2012) to account for potential estimation problems that can arise when the moderator (involvement) and the outcome (ADHD) are correlated and when the moderator (involvement) is correlated within twins. To address this issue, the moderator values of twin 1 and twin 2 are simultaneously entered into a means model of ADHD (see van der Sluis et al., 2012). Moderation is then modeled only on the residual ADHD variance (i.e., that which does not overlap with either twins' reported levels of involvement). This 'extended' univariate GxE model is presented in Figure 1a.

Importantly, the confounding role of gene-environment correlation must also be addressed in the modeling process. Gene-environment correlation effects (rGE) can resemble GxE in moderator models. That is, false GxE effects may be spuriously detected that are actually due to common genes shared among parents and children in the same family. For example, a child with ADHD might exhibit more disorganized, hyperactive, and impulsive behavior, making him/her more difficult to parent, and resulting in lower levels of parental supervision, warmth, and involvement (Wymbs et al., 2008). Thus, the genetic influences associated with ADHD may be correlated with levels of involvement. Another example of this confound may occur if genetic influences on child ADHD (transmitted from parent to child) also influence levels of parental involvement. This type of rGE effect would emerge as shared environmental influences on the covariance between involvement and ADHD in a child twin design (Neiderhiser et al., 2007). Thus, a child's genetic proclivities could elicit or be directly correlated with an environmental response from parents that is consistent with his/her genetic make-up (Klahr & Burt, 2014; Scarr & McCartney, 1983).

In order to determine whether rGE effects were operating, we first conducted the bivariate GxE model (see Figure 1b). This model is based on the bivariate biometric ACE model and examined (1) the magnitude of any potential etiological overlap between parental involvement and ADHD (indexed via significant covariance pathways between involvement and ADHD), and (2) whether or not these covariance pathways between involvement and ADHD were also moderated by involvement (as recommended by van der Sluis et al., 2012). In this model, the moderator (involvement) is entered twice (once as a variable in the bivariate model and once as a moderator of the covariance pathways, see Figure 1b). Findings indicated no significant genetic or shared environmental overlap between parental involvement and ADHD. Further, results indicated no significant moderation of the genetic or environmental covariance terms (e.g., covariance pathways between involvement and ADHD) and only the terms specific to ADHD). For simplicity, results of the full bivariate model are not presented as the model did not indicate any significant moderation of covariance pathways. Path estimates and moderator values from the bivariate model are available from the first author. We therefore elected to proceed with the extended univariate GxE model described above to evaluate parental involvement as a moderator of etiological influences on ADHD (van der Sluis, Posthuma, & Dorlan, 2012). Importantly, this model examines moderation of variance unique to ADHD, thus providing control of rGE confounds.

The extended univariate GxE model actually encompasses three nested moderator models. The first and least restrictive model allows for both linear and non-linear moderation of the genetic, shared, and non-shared environmental contributions (i.e., a, c, e) to ADHD. At each level of parental involvement, linear (i.e., A_1 , C_1 , E_1) and non-linear (i.e., A_2 , C_2 , E_2) moderators are added to these genetic and environmental paths using the following equation: $Unstandardized\ Variance_{Total} = (a + A_1(involvement) + A_2(involvement^2))^2 + (c + C_1(involvement) + C_2(involvement^2))^2 + (e + E_1(involvement) + E_2(involvement^2))^2$. We then fitted a series of more restrictive moderator models, constraining the moderators for each source of etiological influence to be zero and evaluating the reduction in model fit. As recommended, the current models were run a minimum of 5 times using multiple start

values to ensure that all the estimates obtained minimized the $-2\ln L$ value (Purcell, 2002; van der Sluis et al., 2012).

Mx (Neale et al., 2003) was used to fit models to the transformed raw data. Because these interaction models effectively involve fitting a separate biometric model for each individual as a function of their parental involvement score, they require the use of Full-Information Maximum-Likelihood raw data techniques (FIML). FIML raw data techniques produce less biased and more consistent estimates than do other techniques, such as pairwise or listwise deletion (Little & Rubin, 1987). FIML assumes that the data are missing at random and are thus ignorable. Consistent with this assumption, missing data was generally low for this sample (less than 3.8%). Moreover, missingness (data coded as present versus absent for the ADHD and parental involvement scores) was unrelated to family constellation, age of twins, age of mother, parental education, or parental income (all $ps > .47$).

When fitting models to raw data, variances, covariances, and means of those data are first freely estimated by minimizing minus twice the log-likelihood ($-2\ln L$). The minimized value of $-2\ln L$ is then compared with the $-2\ln L$ obtained in more restrictive moderator models to yield a likelihood-ratio χ^2 test for the significance of the moderator effects. Model fit was evaluated using four information-theoretic indices that balance overall fit ($-2\ln L$) with model parsimony. These included the Akaike's Information Criterion (AIC; Akaike, 1987), the Bayesian Information Criterion (BIC; Raftery, 1995), the sample size-adjusted BIC (SABIC; Sclove, 1987), and the deviance information criterion (DIC; Spiegelhalter et al., 2002). The lowest or most negative AIC, BIC, SABIC, and DIC among a series of nested models was considered best. Because fit indices do not always agree (as they place different values on parsimony among other model characteristics and may be relatively close in magnitude), we concluded that the best-fitting model should yield lower or more negative values for at least three of the four fit indices (Burt & Klump, 2013; Burt, & Klump, in press; Hicks et al., 2009).

RESULTS

Intraclass Correlations

Intraclass correlations were first compared across MZ and DZ pairs in order to preliminary gauge the relative influence of genetic and environmental influences on ADHD (see Table 1). For the overall sample, the MZ correlation was significantly greater than the DZ correlation and therefore highly suggestive of genetic influences on ADHD. Intraclass correlations for parental involvement were moderate and similar for both MZ and DZ twins, suggesting that shared environmental influences are largely contributing to this measure. Consistent with past work, univariate ACE models estimated high genetic and moderate non-shared environmental effects on ADHD, and moderate shared and non-shared environmental effects on parental involvement. Preliminary assessment of the potential moderating role of parental involvement on etiological influences on ADHD was conducted via examination of the ADHD intraclass correlations at different levels of parental involvement. To do so, we restricted analyses to those twin pairs who were concordant for moderator level; the sample sizes are thus small relative to the overall sample. Of note, while twins are required to be concordant on the moderator to examine potential etiological moderation using intraclass

correlations, twins do not have to be concordant on the value of the moderator when using structural equation modeling techniques in Mx (and thus the full sample was used for all biometric models described below).

Results indicated that when both twins reported low levels of parental involvement, both the MZ and DZ correlations were reduced, suggesting low levels of genetic influences. As reports of parental involvement increased, both the MZ and DZ correlations increased, however, the MZ correlation appeared to increase more substantially. The increasing difference between the MZ and DZ correlations implies that genetic influences may increase as parental involvement increases. Moreover, the low MZ correlations at low-levels of involvement implies that non-shared environmental influences may be higher when involvement is low, but decrease with increasing levels of parental involvement. Collectively, these results suggest that parental involvement may indeed moderate genetic and environmental influences on ADHD.

GxE Analyses

Test statistics for the involvement composite GxE analyses are reported in Table 2. As can be seen there, the best-fitting model included linear moderation of the A (genetic) and E (non-shared environmental) variance components. Notably, the fit indices for three of the models (linear A moderation only, linear E moderation only, and linear A and E moderation only) were quite similar in magnitude; however, the linear A and E moderation model fit appeared to fit best across all four relative fit indices. Next, we used the estimated paths and moderators from the best-fitting model (see Table 3) to calculate and plot the unstandardized genetic, shared, and non-shared environmental variance components at different values of parental involvement. We elected to present unstandardized parameter estimates in order to examine absolute (rather than proportional) shifts in each parameter across each level of the moderator (as recommended by Purcell, 2002). Figure 2 displays the unstandardized estimates of genetic, shared, and non-shared environmental variance components for ADHD at different levels of parental involvement ranging from low (0) to high (1). As seen there, when parental involvement is low, unique environmental influences on ADHD are large, with moderate genetic contributions. As levels of parental involvement increased, however, genetic contributions to ADHD increased whereas the unique environmental variance decreased. Moreover, as indicated by moderator estimates whose confidence intervals do not overlap with zero (see Table 3), both the increase in non-shared environmental factors and the decrease in genetic factors were statistically significant.

Secondary Checks by Informant—To confirm that our results persisted across various informant-reports of parental involvement, we conducted follow-up GxE analyses using (1) parent reports of involvement and (2) twin reports of involvement. The latter represented a particularly important confirmation, as the examination of twin reports of involvement circumvents issues of shared informant effects (given that ADHD was assessed via parental informant-reports). For both types of informants, the models specifying linear A and linear E moderation fit best (see Table 4). The estimated paths from these best-fitting models are presented in Table 3. As with the informant composite ratings, we used these path estimates to calculate and plot the unstandardized genetic, shared, and non-shared environmental

variance components at different values of parental involvement. Results are presented in Figure 3. As can be seen there, the results for both parent report and twin report are markedly similar to those for the composite collapsed across informant. Therefore, it appears that the pattern of significant moderation of both genetic and non-shared environmental contributions by parental involvement is consistent across informant.

DISCUSSION

Twenty years ago, Bronfenbrenner and Ceci (1994) highlighted the potential utility of twin designs for understanding the ways in which proximal processes may shape the degree to which genetic and biological factors influence psychological development in children. That utility was demonstrated in the current study via examination of parental involvement as a moderator of etiological contributions to ADHD during middle childhood. While past work examining GxE effects for ADHD has almost solely focused on environmental risk indicators, changes in the estimates of genetic and environmental influences on ADHD at varying levels of a positive or enriching environments (i.e., parental involvement) could signal the potential presence of other forms of GxE as well. This is precisely what the current study revealed. Overall, parental involvement significantly moderated genetic and non-shared environmental contributions to ADHD symptomatology. Specifically, non-shared environmental contributions to ADHD were highest when parental involvement was low and decreased as involvement with parents increased. By contrast, genetic influences on ADHD increased at higher levels of parental involvement, but were low when parental involvement was also low.

Additionally, we conducted secondary analyses to evaluate the consistency of results across parent-only and twin-only reports of parental involvement. The pattern of results was strikingly similar to the primary analyses when examining parent-only report and twin-only report. In both cases, genetic effects on ADHD increased with higher reports of parental involvement, whereas non-shared environmental effects, while high at low levels of involvement, decreased with reports of increased involvement. Although past work has indicated potential differences regarding the impact of maternal versus paternal involvement on child behavior (Hoeve et al., 2009; Winsler, Madigan, & Aquilino, 2005; Wood & Repetti, 2004), reports of maternal and paternal involvement were highly correlated in the current sample (r s ranging from .58–.61, $p < .01$), suggesting that in this age range, there may not be much differentiation in terms of involvement across mothers and fathers. Exploratory GxE models were conducted separately for maternal and paternal involvement, which revealed a largely similar pattern of findings as those collapsed across parent. Notably however, changes in genetic and non-shared environmental contributions in ADHD at different levels of paternal involvement appeared to be non-linear in nature. Parent-specific effects may be particularly relevant later in development (i.e., adolescence, Hoeve et al., 2009) or may be more detectable using observational measures of parenting. Future research should examine these possibilities.

Importantly, while much of past molecular genetic work has operated under the assumption of a diathesis-stress model of GxE effects for ADHD, our analyses of GxE effects among child twins revealed little support for diathesis-stress GxE interaction effects involving the

absence of positive or enriching environments for ADHD. Importantly, however, moderation of genetic influences under diathesis-stress GxE models would likely be more robustly assessed using measures of environmental risk (i.e., poor parenting). Even so, the current findings regarding high genetic influences at high levels of parental involvement support the presence of *either* differential susceptibility *or* bio-ecological GxE mechanisms operating for ADHD. Additionally, the presence of non-shared environmental moderation, such that these unique environmental effects were highest at *low* levels of involvement provides additional support for the bio-ecological model of GxE effects.

Our findings of two converging lines of support for the bio-ecological model of GxE effects are in line with prior GxE twin work. Using a portion of this sample, we found that genetic influences on ADHD were highest within the context of the low risk environment (i.e., low self-blame in relation to inter-parental conflict, Nikolas, Klump, & Burt, 2012). Further, evidence of bio-ecological GxE effects has also been recently documented in work examining parent-child conflict as a moderator of etiological influences on conduct problems (Burt & Klump, in press). However, other work investigating GxE effects for ADHD using a child twin sample have provided support for a diathesis-stress model (Pennington et al., 2009). Methodological differences (i.e., age range of twins, assessment of ADHD, statistical models of GxE effects) may underlie differences across these studies, including ways of quantifying and controlling for gene-environment correlation. Yet more work examining additional environmental indicators of risk and protection is needed to determine (1) how the magnitude of genetic and environmental influences on ADHD changes across different contextual factors, and (2) any additional factors (e.g., age, developmental status, sex) that may also shape these associations.

Implications

As mentioned previously, twin and adoption work examining etiological influences on ADHD has consistently estimated main shared environmental effects for the disorder at zero (Burt, 2009; Burt et al., 2012; Chang et al., 2013; Nikolas & Burt, 2010). However, this does not mean that shared environmental factors (such as parental involvement, which was found to be largely shared environmental in origin, $C=58\%$ of the variance) are unrelated or unimportant for understanding the etiology and/or developmental continuation of the disorder. Evidence of significant increases in additive genetic variance (A), as was found in the current study, indicates that contributions from the main effects of genes are increasing at higher levels of parental involvement as are contributions from GxE effects involving additive genetic and shared environmental factors (termed AxC effects). That is, it may be the case that within more positive and enriching environments, genetic risk for ADHD becomes even more relevant in shaping individual differences in behavior (Purcell, 2002). This pattern of results is similar to those described in the seminal work of Turkheimer and colleagues (2003), which demonstrated increased genetic influences on IQ within more enriching environmental contexts. Shared environmental effects may be particularly relevant within this age range, as past work has shown that these factors tend to decrease with age (as genetic factors increase – see Bergen, Gardner, & Kendler, 2007). Furthermore, findings are consistent with hypothesis of Kan and colleagues (2013), who argue that increased genetic influence on “culture-loaded” subtests of intelligence (relative to “culture-reduced” subtests)

likely reflects the notion that environmental factors, particularly advantageous environments, may serve to promote genetic contributions to individual differences. In line with work in IQ, we have also found a similar impact of positive parental environments (e.g., involvement) on the genetic contributions to ADHD. Given the consistency of such findings across outcomes, it may also be the case that genetic influences on individual differences in ADHD are highest in other enriching environments as well, particularly the classroom. For example, Taylor et al. (2010) demonstrated that higher teacher quality was associated with an increase in genetic influences on early reading. It is important to note that enriched environments may increase genetic contributions to *variability* in behaviors or traits, while also enhancing or attenuating effects on *mean levels* of adaptive and maladaptive behavior. Future empirical work is needed to determine if our findings regarding parental involvement extend to other enriching environments as well (such as supportive classroom environments) as well as to other behavioral outcomes, both adaptive and maladaptive.

Similarly, in the absence of positive environments (i.e., low parental involvement), unique environmental influences on ADHD were moderate to large, indicating that it is possible that additional non-shared environmental risk factors may emerge within these contexts that also influence the development of ADHD (Rutter, 1999). Additionally, it is important to note that high levels of involvement may not necessarily be positive or enriching (e.g., over-involvement may have negative effects on adaptation later in development). Taken together, these analyses further support the notion that (1) the environment is crucial for understanding the etiology of ADHD, and (2) examination of GxE effects for ADHD can aid in identifying the specific genetic variants that exude risk, but also the ways in which environmental risk and protective factors modify the impact of genes.

Importantly, genetic influences were different from zero at all levels of involvement, indicating that genes continue to play a role in the etiology of ADHD across a variety of contexts. Thus, future molecular genetic studies that implement genome-wide and sequencing methods remain critical for identifying the specific variants that contribute to the onset of inattention and hyperactivity in childhood. Recent work in this area (which now includes tens of thousands of ADHD probands and controls) has indicated that while the heritability estimates from twin studies are consistently large, heritability based solely on the contribution of single nucleotide polymorphisms (SNPs – the markers examined in genome-wide association studies) is likely substantially lower (estimated at .42, see Yang et al., 2013). Thus, the remaining genetic variance unaccounted for by SNPs could possibly represent GxE effects. This possibility clearly warrants continued examination of gene-environment interplay in ADHD.

Lastly, the current study found evidence of significant moderation of etiological influences on ADHD across differing levels of parental involvement, providing some complementary evidence that differential susceptibility effects may be occurring for ADHD (Belsky & Pluess, 2009). That is, it may be the case that some genes may directly influence the pathophysiology implicated in the disorder (i.e., neurite outgrowth, calcium sub-channels, dopamine neurotransmission, see Neale et al., 2010), whereas other genetic effects may influence vulnerability to environmental influences more generally (i.e., genes influencing

neural systems underlying emotional reactivity and regulation via HPA axis development, connectivity between frontal and medial temporal lobe structures). Future molecular genetics work investigating causal processes underlying ADHD may benefit from testing both diathesis-stress and differential susceptibility frameworks when interpreting GxE effects. Furthermore, the current findings also support continued exploration of the role of non-shared environmental factors in shaping the trajectory of ADHD behaviors. Importantly, recent GxE work in temperament and child psychopathology has begun to consider ways in which parsing diathesis-stress from differential susceptibility models (see Kochanska et al., 2011). Additional methodological contributions, such as those by Roisman and colleagues (2012), may also be beneficial for maintaining consistency in the quantification of diathesis-stress and differential susceptibility GxE effects. As molecular work proceeds, the current study indicates behavioral genetic tests of GxE can also provide important and unique contributions for evaluating the etiological role of a variety of environmental and contextual factors at an omnibus level. Such approaches will remain important for narrowing in on the types of environmental factors that may be most relevant to the etiology and maintenance of ADHD across development.

Limitations

There are some limitations to the current work that are important to note. First, the current sample was underpowered for examining GxE effects separately by sex and age. Given that the age range of our sample (6–11 years) was more narrow compared to other twin studies, we feel assured that the current results likely generalize to middle-childhood specifically. However, given the sex difference in prevalence of ADHD, future examination of sex differences in etiological mechanisms, including GxE effects, remains important. Additionally, future analyses of these effects within a larger sample of twins that utilize alternative measurement methods (e.g., observational measures of parenting, neurocognitive measures of attention, inhibition, and working memory) may also be better distinguish different sources of moderation (linear A only, linear E only, and linear A and E only), as the fit indices for these 3 models were quite close in magnitude. Secondly, we examined ADHD behaviors dimensionally and did not over sample for clinically diagnosed or affected youth (7.1% of twins had T-scores ≥ 65 on the DSM ADHD problems scale, defined as the clinical range, similar to the general population). Thus, analyses within twins selected for clinically-significant levels of ADHD problems may be beneficial. Additional work may also examine specificity of effects of inattention and hyperactivity-impulsivity separately, as these related but distinct dimensions will likely provide additional clues regarding the heterogeneity of etiological mechanisms in ADHD (Willcutt et al., 2012). Mean levels of parental involvement were also moderate to high for this sample. Examination of effects within higher-risk samples may be particularly important for understanding the ways in which genetic influences on ADHD may be influenced both by proximal processes and larger environmental contexts (Bronfenbrenner & Ceci, 1994). Furthermore, our study, like all behavioral genetic investigations, relies on the Equal Environments Assumption, which posits that identical twins reared together are no more likely to share environments than are fraternal twins reared together. This assumption has been examined and validated for numerous phenotypes (Plomin et al., 2008), including ADHD (Cronk et al., 2002), and has been recently investigated using “misclassified twins” in order to gauge the potential impact

of gene-environment covariance on the Equal Environments Assumption (Conley et al., 2013). Even so, the Equal Environments Assumption remains an assumption and thus a potential limitation to our findings.

Conclusion

Overall, results from the current study indicated that parental involvement moderated etiological influences on ADHD. Findings provide some converging support for potential differential susceptibility and bio-ecological GxE mechanisms in ADHD as well as the importance of considering the impact of enriching environments on the developmental progression of the ADHD symptomatology.

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a. Extended Univariate GxE Model

b. Extended Bivariate GxE Model

Figure 1.

The extended univariate and bivariate gene x environment interaction models.

Note. For ease of presentation, co-twin paths and variables are not presented (although they are estimated in models). In 1a, the variance decomposition of ADHD behaviors is modeled as a function of parental involvement (the moderator M). rGE is controlled as the involvement values of both twins are entered in a means model of ADHD behaviors. Linear moderation was then modeled on the residual ADHD variance (that which does not overlap with involvement) separately for each component of variance (e.g., $\beta_X M$, $\beta_Y M$, $\beta_Z M$, a , c , and e paths respectively). Non-linear moderators are not shown but were also examined. In 1b, the moderator is entered twice – once as a variable that is allowed to correlate with the

outcome (ADHD) and once as the moderator of (1) variance common to involvement and ADHD and on (2) the unique variance in ADHD. a_C represents genetic variance common to involvement and ADHD whereas a_U represents variance unique to ADHD. Interactions with the moderator (e.g., $\beta_{ac}M$) are added to these common and unique genetic influences (and similar interactions are modeled for the shared and non-shared paths). Only the unique paths index “true” GxE effects in this model.

Figure 2.

Unstandardized genetic (A), shared environmental (C), and non-shared environmental (E) variance contributions to ADHD by level of parental involvement – informant composite.

Note. Moderation analyses revealed that the increase in genetic contributions to the variance in ADHD (A) was significant. In addition, the decrease in non-shared environmental contributions to ADHD (E) with increasing levels of parental involvement was also significant.

a. Parent Report

b. Twin Report

Figure 3.

Unstandardized genetic (A), shared environmental (C), and non-shared environmental (E) variance contributions to ADHD by level of parental involvement – parent and twin report. *Note.* Moderation analyses revealed that the increase in genetic contributions to the variance in ADHD (A) was significant. In addition, the decrease in non-shared environmental contributions to ADHD (E) with increasing levels of parental involvement was also significant.

Table 1

Twin intraclass correlations for parent-rated CBCL ADHD score and parental involvement: Overall and by level of parental involvement.

Overall	MZ	DZ	A	C	E
Mean ADHD Score (SD)	4.3 (2.9)	4.5 (2.9)	--	--	--
Mean Parental Involvement (SD)	39.7 (3.5)	40.6 (3.5)	--	--	--
CBCL DSM ADHD Score	.60**	.28**	69.5*	0	30.5*
Parental Involvement Composite	.55**	.46**	9.8	58.3*	31.9*

ADHD Intraclass Correlation by Level of Parental Involvement Composite Score	
	DZ
Parental Involvement: Lowest 3 rd (n=164)	.15*
Parental Involvement: Middle 3 rd (n=165)	.47**
Parental Involvement: Highest 3 rd (n=164)	.73**

Note.
* $p<.05$,
** $p<.01$.

Overall intraclass correlations and univariate genetic, shared, and non-shared environmental variance estimates are presented in the top portion of the table. The bottom portion of the table includes twin intraclass correlations for ADHD at different levels of parental involvement. Here, we present correlations for twins at the lowest, middle, and highest third of the continuous moderator score. Although correlations are presented in three groups here, a continuous measure of parental involvement was used as a moderator of genetic and environmental influences on ADHD in all biometric GxE models.

Table 2

Univariate GxE model fit statistics – Parental involvement informant composite.

Moderation Model	-2lnL	df	AIC	BIC	SSA-BIC	DIC
Linear and Non Linear ACE	4009.51	1483	1037.51	-2906.04	-551.49	-1543.25
Linear ACE	4010.17	1486	1034.17	-2919.26	-556.77	-1551.88
Linear A moderation only	4008.40	1488	1032.40	-2920.14	-557.66	-1552.66
Linear C moderation only	4017.17	1488	1036.17	-2909.26	-546.77	-1541.88
Linear E moderation only	4006.02	1488	1030.02	-2921.33	-558.84	-1553.95
Linear A and E moderation only	4003.97	1487	1029.97	-2922.05	-559.15	-1554.59
No moderation	4025.43	1489	1047.43	-2901.94	-550.86	-1539.64

Note. Best-fitting model is in bold. -2lnL=minus twice the log-likelihood value, df=degrees of freedom, AIC=Akaike Information Criterion, BIC=Bayesian Information Criterion, SSA-BIC=sample-size adjusted Bayesian Information Criterion, DIC=Deviance Information Criterion.

Table 3

Unstandardized path and moderator estimates in the best-fitting Univariate GxE model.

a	PATHS		LINEAR MODERATOR PATHS			NON-LINEAR MODERATOR PATHS		
	c	e	A ₁	C ₁	E ₁	A ₂	C ₂	E ₂
<i>Parental Involvement Informant Composite– Full ACE Moderator Model</i>								
.387*	.002	.802*	.306*	-.008	-.426*	----	----	----
(.05, .48)	(-.26, .26)	(.67, .90)	(.09, .47)	(-.63, .63)	(-.68, -.28)			
<i>Parental Involvement Informant Composite– Best-Fitting Model (Linear A and E Moderation Only)</i>								
.346*	.002	.778*	.352*	----	-.439*	----	----	----
(.07, .50)	(-.60, .58)	(.66, .92)	(.10, .48)	----	(-.59, -.35)			
<i>Parental Involvement (Parent Report) – Best-Fitting Model (Linear A and E Moderation Only)</i>								
.399*	.008	.787*	.320*	----	-.414*	----	----	----
(.09, .53)	(-.71, .55)	(.64, .89)	(.11, .46)	----	(-.57, -.30)			
<i>Parental Involvement (Twin Report) – Best-Fitting Model (Linear A and E Moderation Only)</i>								
.338*	.006	.796*	.354*	----	-.409*	----	----	----
(.08, .48)	(-.77, .62)	(.61, .88)	(.13, .48)	----	(-.55, -.29)			

Note. Paths and moderators are presented; their 95% confidence intervals are presented below them in brackets.).

* indicates that the estimate is statistically significant at p<.05. A, C, and E (both upper and lower case) represent genetic, shared, and non-shared environmental parameters, respectively.

Table 4

Univariate GxE model fit statistics – parental involvement by informant.

Moderation Model	-2lnL	df	AIC	BIC	SSA-BIC	DIC
<i>Parent Report</i>						
Linear and Non Linear ACE	4009.61	1477	1055.61	-2880.17	-535.15	-1522.90
Linear ACE	4010.04	1480	1050.04	-2889.98	-540.10	-1529.85
Linear A moderation only	4010.50	1482	1048.50	-2892.95	-541.59	-1532.59
Linear C moderation only	4018.42	1482	1056.42	-2876.30	-523.35	-1514.44
Linear E moderation only	4011.21	1482	1047.21	-2895.91	-542.95	-1534.04
Linear A and E moderation only	4010.97	1481	1046.97	-2896.03	-543.07	-1534.16
No moderation	4021.25	1483	1065.25	-2879.20	-534.66	-1516.41
<i>Twin Report</i>						
Linear and Non Linear ACE	3931.90	1461	1009.90	-2858.23	-538.64	-1515.66
Linear ACE	3934.43	1464	1006.43	-2866.87	-542.51	-1521.54
Linear A moderation only	3937.07	1466	1005.07	-2872.16	-544.63	-1524.99
Linear C moderation only	3949.51	1466	1017.51	-2860.93	-533.40	-1513.77
Linear E moderation only	3938.66	1466	1006.66	-2871.36	-543.83	-1524.20
Linear A and E moderation only	3935.02	1465	1005.02	-2873.88	-544.94	-1523.64
No moderation	3948.39	1467	1014.39	-2859.80	-540.68	-1511.72

Note. Best-fitting models for parent report and twin report are in bold-2lnL=minus twice the log-likelihood value, df=degrees of freedom, AIC=Akaike Information Criterion, BIC=Bayesian Information Criterion, SSA-BIC=sample-size adjusted Bayesian Information Criterion, DIC=Deviance Information Criterion.