Youth Appraisals of Marital Conflict and Genetic Risk for Attention-Deficit Hyperactivity Disorder: Examination of Gene x Environment Interactions Using Behavioral and Molecular Genetic Methodologies

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ABSTRACT

YOUTH APPRAISALS OF MARITAL CONFLCIT AND GENETIC RISK FOR ATTENTION-DEFICIT HYPERACTIVITY DISORDER: EXAMINATION OF GENE X ENVIRONMENT INTERACTIONS USING BEHAVIORAL AND MOLECULAR GENTEIC METHODOLOGIES

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Identifying the specific etiological factors that contribute to the development of attention-deficit hyperactivity disorder (ADHD) holds great promise for future innovations regarding the conceptualization of the disorder as well as prevention and treatment measures. A wealth of evidence has demonstrated that genetic factors make large contributions to ADHD, yet numerous environmental risk factors have also been identified. Uncovering the nature of the exchange processes that are involved in the development of ADHD via investigation of gene x environment interactions (GxE) represents an important step forward in research involving the causal mechanisms of the disorder.

Risk factors related to the family environment may be particularly important for the development of behavioral and emotional regulation capabilities. In particular, conflict in the home has emerged as an important correlate of both symptom severity and impairment for child problems and represents a potential putative environmental risk factor for ADHD.

The current research examined the potential etiological role of children's cognitive appraisals self-blame in relation to their parents' marital conflict in ADHD via tests of GxE effects using two complementary methodologies: behavioral and molecular genetics. However, prior to these tests, the phenotypic relationships among children's appraisals of marital conflict and externalizing behaviors were examined. In Study 1, the unique relationships between

appraisals of self-blame and ADHD symptoms was replicated, indicating that self-blame was related to ADHD symptoms even when oppositional and conduct are controlled.

In Study 2, behavioral genetic methods for testing GxE effects were conducted in a twin sample of 248 twin pairs. Self-blame emerged as a significant moderator of latent genetic and environmental influences on parent rated ADHD symptoms on the Child Behavior Checklist DSM-IV ADHD Scale, such that genetic influences decreased but non-shared environmental influences increased with higher reports of self-blame. In Study 3, tests of GxE effects involving a specific genetic marker, the promoter polymorphism of the serotonin transporter gene (5HTTLPR) were conducted in a completely independent sample of n=304 youth, of whom n=151 had ADHD. That analysis revealed significant interactions, such that increases in teacher-rated DSM-IV ADHD symptoms corresponded with increases in self-blame, but only for individuals with the low and high serotonin-activity genotypes.

Findings from both studies are complementary and suggest that self-blame may indeed have a specific role in the etiology of ADHD via moderating of genetic effects. Results suggest that different exchange processes (i.e., genetic main effects, environmental main effects, GxE interaction effects) may be differentially important for the etiology of ADHD and provide support for an etiological role of self-blame in ADHD. More broadly, these findings offer an innovative approach for understanding the interactional processes between genetic and environmental risk factors and their contributions to ADHD.

Dedicated to my loving parents, Ann and Ron Nikolas, for their invaluable support and encouragement for this and for all of my adventures…

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CHAPTER 1: BACKGROUND AND RATIONALE FOR GXE INVESTIGATION OF ADHD

Attention-deficit hyperactivity disorder (ADHD) is one of the most commonly diagnosed disorders of childhood, affecting approximately 3-5% of school-aged children. Under DSM-IV, ADHD is characterized as a behavioral syndrome that includes two correlated behavioral dimensions: inattention-disorganization and hyperactivity-impulsivity (DSM-IV-TR, APA, 2000). Symptoms of the inattention dimension include difficulties with sustaining attention and listening, forgetfulness, and disorganization while symptoms of hyperactivity include restlessness, fidgeting, and excessive motor activity/ talking. Children with ADHD display these characteristics to an excessive degree that is inappropriate for their age and development and often result in a wide range of impairments across multiple settings (Barkley, 2006). While ADHD is currently classified into three subgroups under DSM-IV (APA, 2000), taxometric work has indicated that the disorder is likely best captured as extremes along these behavioral dimensions as opposed to a discrete category (Haslam et al., 2006). Uncovering the etiological pathways of ADHD has remained a top research priority as discovery of key casual mechanisms for the disorder will likely allow for early intervention and prevention measures as well as the development of more sophisticated treatment approaches.

Etiological Structure of ADHD

Twin and family studies have provided a wealth of converging evidence as to the degree and type of etiological processes involved in the development of ADHD. Family studies of ADHD have demonstrated that risk for the disorder is significantly elevated among family members of ADHD probands, regardless of proband sex and ethnicity (Biederman et al., 1992; Faraone et al., 2000; Samuel et al., 1999). Twin and adoption studies have estimated the genetic

liability for ADHD to be between 70 and 90 percent, indicating that a large portion of the variance between individuals is due to genetic factors (Levy et al., 1997; Nadder et al., 2002; Nikolas & Burt, in press; Sherman, McGue, & Iacono, 1997; Sprich et al., 2000; van den Oord, Boomsma & Verhulst, 1994; Willcutt, Pennington, & DeFries, 2000). Importantly, these high estimates of heritability have been found at both the moderate and extreme ends of the behavioral dimensions of inattention and hyperactivity-impulsivity (Willcutt, Pennington, & DeFries, 2000), indicating genetic effects are strongly influencing the entire range of ADHD behaviors. Further, recent meta-analyses have indicated that genetic factors make strong contributions to the disorder regardless of age, sex, informant, and measurement method. By contrast, contributions from the non-shared environment are small to moderate, and the influence of shared environmental factors is virtually nil (Bergen, Gardner, & Kendler, 2007; Burt, 2009; Nikolas & Burt, in press).

Despite the consistent evidence of moderate to large genetic influences on ADHD, the etiology of the disorder can also be conceptualized within a developmental psychopathology framework as the result of exchanges between multiple risk processes occurring within and across development (Campbell, 2000; Nigg & Nikolas, 2008). While these risk processes will likely include genetic and biological vulnerabilities, many theorists have posited that factors related to the family environment are also particularly influential on the development of ADHD symptoms since the family provides the basic structure and context for the development of behavioral regulation capacities (Campbell, 1994; Campbell et al., 1994; Johnson & Mash, 2001; Sonuga-Barke et al., 2005). That is, a developmental psychopathology model of ADHD would posit that some children may have a chaotic or unresponsive family environment that serves to further enhance genetically-influenced ADHD symptoms to clinically significant levels (Carlson,

Jacobvitz, & Sroufe, 1995). Thus, in addition to genetic influences, components of the family environment may also influencing the development of ADHD behaviors.

In line with this, empirical investigations have also noted many differences among families of children with ADHD compared to families of typically-developing children. First, numerous investigations have found that ADHD children are more likely come from low socioeconomic status homes (Biederman et al., 1995) and are less likely to live in intact families (Johnston & Mash, 2001). Parents of ADHD children have reported higher stress, lower social support, lower parenting and marital satisfaction, and increased marital and parent-child conflict (Biederman et al., 2002; Johnston & Mash, 2001; Lange et al., 2005; Pressman et al., 2006; Whalen & Henker, 1999). Further, parents of ADHD children have been observed to be more negative and demanding and to use less authoritative parenting compared to the parents of control children (Buhrmester et al., 1992; Campbell et al., 1986; DuPaul et al., 2001).

In their seminal review, Johnston and Mash (2001) noted that while there are descriptive differences among families of ADHD children when compared to their non-disordered counterparts, there are multiple mechanisms by which characteristics of the family environment may be related to child behavior. First, characteristics of the family environment may be directly involved in the casual processes that give rise to ADHD (or they might exacerbate or maintain symptoms once they develop). Alternatively, differences in the family environment may be the consequence of having a child with ADHD (i.e., the differences in the family environment are child-driven). In addition, the relationship among family characteristics and child behavior may be the result of shared genes among parents and children.

Overall, the influence of family environment factors on ADHD remains difficult to explain within the context of large and robust genetic effects and small to moderate main

environmental effects. Further, several potential mechanisms have been hypothesized to account for the relationship between the family environment and ADHD. Thus, it appears that examination of the interplay between genetic and family environmental risk processes via gene x environment interactions may be a crucial component to understanding the transactional and ongoing nature of risk and protective factors that may be influencing ADHD.

Theoretical Basis for GxE Effects for ADHD

GxE effects are specifically defined as genetically-modulated individual differences in sensitivity to environmental risk factors, such that specific genetic variants exert effects on a disorder only within particular environmental contexts (Rutter, Moffitt, & Caspi, 2006; Rutter & Silberg, 2002). Recent reviews of theoretical issues regarding gene x environment interplay have noted that the previous view that GxE effects were rare for psychopathology is very likely false because of past failures to specify and measure G and/or E (Rutter, Moffitt, & Caspi, 2006). Importantly, the authors note that these "black box" analyses were, in essence, examining a biologically improbable omnibus interaction between all genes and all environments. Furthermore, as GxE effects involve genetically-influenced sensitivities to specific environmental risks, it has been argued that such sensitivities may only apply to subgroups within the overall population (Rutter & Silberg, 2002). Thus, the importance of specifying and measuring the G and the E is emphasized for current studies of GxE effects for psychiatric disorders.

Rutter and colleagues (2006) also specified conditions under which GxE effects are more likely to influence the etiology of multifactorial disorders. These include (1) the presence of substantial environmental risk factors *but also* substantial heterogeneity as to an individual's vulnerability for developing a particular disorder if exposed to environmental risk, (2) substantial

genetic risk for a disorder operating via indirect risk pathways, and (3) discordance within monozygotic twin pairs. These three conditions are very likely to be applicable to a wide range of illnesses and mental disorders, which nearly all involve multifactorial etiological processes. Even so, determining that these conditions are met for ADHD remains important for understanding the likely mechanisms involved in GxE for ADHD. Below, I consider each condition for ADHD specifically.

With regard to the first condition, namely the existence of environmental risk factors that result in heterogeneous outcomes with respect to ADHD, previous reports have identified numerous candidates. These include exposure to interparental conflict (Wymbs et al., 2008), poor parenting and family dysfunction (Biederman et al., 2002), low parental socioeconomic status (Ornoy, 2003), maternal smoking and alcohol consumption (Banerjee et al., 2007; Knopik et al., 2005; Thapar et al., 2003), and traumatic brain injury (Bloom et al., 2001). For each of these risk factors, there is demonstrated risk for ADHD, yet substantial heterogeneity in terms of overall outcome.

In reference to the second condition (i.e., substantial genetic effects operating via indirect causal pathways), twin and family studies have estimated a large magnitude of genetic effects of all common mental disorders of childhood and adolescence, including ADHD (Bergen, Gardner, & Kendler, 2007; Burt, 2009). Further, endophenotype models for ADHD have posited that genetic influences on ADHD involve changes in neural transmission in key brain regions important for the development of cognitive control, response inhibition, and working memory, which in turn, give rise to the behavioral symptoms of ADHD (Doyle et al., 2005). Initial work examining genotype differences in cognitive performance have shown some positive results (Bellgrove et al., 2005; Cornish et al., 2005; Waldman et al., 2006), suggesting that genetic

effects for ADHD may operate via an indirect causal pathway involving impairments in neural circuitry underlying cognitive control and executive functioning processes.

Lastly, Rutter and colleagues (2006) also specified that GxE effects are more likely to exert risk for a disorder if there is discordance within monozygotic twin pairs. Studies of concordance rates among monozygotic (MZ) twins have demonstrated moderate to high concordance rates (55-75%) among MZ twins using both DSM criteria and empirically-assigned subclasses based on symptom profiles (Neuman et al., 2001; Sherman et al., 1997; Volk et al., 2005). These concordance rates are rather high, and in some cases, appear to be approaching the reliability ceiling. Despite this, important differences have been noted among identical twins discordant for ADHD. First, a recent longitudinal investigation of MZ twin pairs discordant for ADHD found that the affected twin had significantly lower birth weight and delayed physical and motor maturation compared to their unaffected co-twin (Lehn et al., 2007). Secondly, studies of neural anatomy have indicated that the volume of the caudate is significantly smaller in affected twins when compared to their co-twin (Castellanos et al., 2003). Thus, while concordance rates for ADHD among MZ twins appear to be moderate to high, there is some initial evidence suggesting early environmental moderation of genetic risk for ADHD. Further, the discovery of neural differences between discordant MZ twins suggests that environmental factors influencing brain development play a significant role in the etiology of ADHD.

In summary, there is good evidence that both genetic and environmental factors contribute to the development of ADHD (Thapar et al., 2005). Examination of gene-environment interplay thus emerges as one potentially fruitful strategy for understanding associations between ADHD and a variety of environmental risk factors within the context of large genetic effects on the disorder. Furthermore, ADHD appears to meet the conditions set

forth by Rutter and colleagues (2006) for probable GxE effects, namely (1) the presence of environmental risk factors that result in heterogeneous outcomes (e.g., interparental conflict, familial adversity, maternal smoking and alcohol use), (2) substantial genetic effects that likely operate through indirect causal pathways (e.g., via altered effects on neural systems involved in executive functioning and cognitive control), and (3) discordance for ADHD among MZ twin pairs as well as important differences among discordant MZ pairs.

Specification of Genetic and Environmental Risk Factors

As noted, the likelihood of detecting GxE effects increases when G and E contributors are specified and measured (Rutter & Silberg, 2002). Furthermore, Moffitt and colleagues (2005) argued for strategic, hypothesis-driven selection of both genetic and environmental candidates in GxE studies, such that each component is rooted firmly in empirical research. Given this, it is important to specify the genetic and environmental risk factor(s) that may be involved as well as to review why each component may be important in the etiology of ADHD. I will begin with consideration of candidate genes followed by a discussion of candidate environmental factors.

Candidate Gene Selection

In terms of specific genes of influence, it is most likely that several genes, each of small effect, contribute to ADHD (Smalley et al., 2002). In recent years, work examining molecular genetic association with ADHD has grown exponentially, with numerous positive and negative findings. Genes of the dopamine and noradrenergic transmission systems have received much study due to the cognitive and behavioral abnormalities associated with catecholamine dysfunction as well as the influence of psychostimulants such as methylphenidate (the pharmacological treatment of choice for ADHD) on these systems (Spencer et al., 2000). Several

catecholamine candidate gene markers have shown replicated association with ADHD, including the dopamine transporter gene (DAT1), and the dopamine D4 and D5 receptor genes (DRD4, DRD5), (Brookes et al., 2006; Friedel et al., 2007; see Faraone et al., 2005).

These genes remain theoretically important candidates because of their association with cognitive components related to ADHD (e.g., reward processing, cognitive control). However, an integrated theoretical model of the disorder has posited that ADHD reflects deficiencies in both behavioral and emotional regulation capabilities that are underpinned by neural circuitry involved in both reward response as well as emotional processing (Nigg & Casey, 2006). Thus, from this perspective, genes from additional systems, such as the serotonin neurotransmission system, may also be relevant to ADHD.

Genes from the serotonin transmission system have also been hypothesized to play a role in ADHD because of findings demonstrating that altered serotonergic activity is involved in impulse control and aggressive behavior (Coccaro et al., 1989; Evans et al., 2000; Manuck et al., 2002; O'Keane et al., 1992, Retz et al., 2004). In line with this, several markers from multiple genes in the serotonin system have shown association with ADHD in both case-control and family-based analyses (Faraone et al., 2005; Hawi et al., 2002; Kent et al., 2002, Manor et al., 2001). However, the promoter polymorphism of the serotonin transporter gene (5HTTLPR) has emerged as a particularly important candidate in a recent meta-analysis (Gizer, Ficks, & Waldman, 2009). Importantly, the authors also found significant heterogeneity of effects across studies, which suggests the potential for GxE processes (Gizer, Ficks, & Waldman, 2009). In fact, one potential explanation for the inconsistent findings and failures to replicate previous association results is that genetic effects do vary with different levels of environmental risk. In other words, the presence of GxE effects may be influencing the ability to detect the main effects

of generic factors in molecular genetic association studies.

In addition, the serotonin transporter gene itself is expressed in brain regions often implicated in emotion regulation, memory, attention, and motor control (Frankle et al., 2004), areas which are also relevant to ADHD (Nigg & Casey, 2006). Furthermore, the known functionality of 5HTTLPR (i.e., the resultant decrease in transcription efficiency associated with the "short" allele) as well as previous work demonstrating that genetic regulation of serotonin neurotransmission is sensitive to environmental context (Bennet et al., 2002; Manuck et al., 2004) also make it a prime candidate for GxE investigation.

Environmental Candidate Selection

As mentioned earlier, factors related to the family environment are thought to be particularly important for the development and maintenance of ADHD symptoms within a developmental psychopathology framework. In line with this, animal studies have shown that exposure to chronic stress during early development may alter cortical functioning via effects on neurotransmission (Arnsten & Goldman-Rakic, 1998). More specifically, conflict within the family was recently been shown to be a robust predictor of ADHD symptom severity and accounted for 40% of the variance in impairment (Pressman et al., 2006). Thus, stress within the family environment, particularly stress related to conflict, may prove to be a critical environmental moderator of genetic risk for ADHD.

In regard to conflict within the family environment, inter-parental conflict has been found to be a robust predictor of child adjustment and has been associated with ADHD and externalizing behavior problems in numerous studies (Buehler, Lange, & Franck, 2007; Counts et al. 2005; Cummings & Davies, 1994; El-Sheikh & Harger, 2001; Gerard et al., 2005; Grych & Fincham, 1990; Grych et al., 2000; Grych, Harold, & Miles, 2003; Jouriles et al., 2000; Skopp et

al., 2005; Wymbs et al., 2008). Furthermore, studies of inter-parental conflict have demonstrated that conflict is more predictive of child externalizing problems than internalizing problems (Cummings & Davies, 1994), suggesting some specificity of effects on youth behavior and adjustment problems.

Two prominent hypotheses (and not necessarily mutually exclusive) have emerged to explain how inter-parental conflict influences child externalizing problems. First, the exposure hypothesis posits that mere exposure to negative exchanges among parents, regardless of intensity of negative emotions or topic of conflict results in an increase in externalizing behaviors among children (Cummings, Goeke-Morey, & Papp, 2004). This work posits that social learning processes influence how children imitate and carry forward tactics they observe during their parents' marital disputes (Davies et al., 2002). Second, more recent work has also supported emotional-security theorists, who suggest that the topics of marital disputes are differentially related to children's reactions and behaviors, such that conflicts about the child are linked to greater behavioral dysregulation in children (Cummings et al., 2004; Cummings & Davies, 2002; Harold et al.,1997).

In line with the view of emotional-security theorists, Grych and Fincham (1990) convincingly argued that the child's perceptions and appraisals of marital conflict often play a critical determining role as to the effect of marital conflict on youth behavior problems. They advocated strongly for the assessment of inter-parental conflict from the child's perspective as youth reports of inter-parental conflict have been shown to be more predictive of externalizing behavior problems than the parents' own report of their own marital conflict and satisfaction (Cummings, Davies, & Simpson, 1994; Grych, Seid, & Fincham, 1992). The development of the Children's Perception of Interparental Conflict scale (CPIC) provided an important measurement

tool for quantifying youth perception and appraisals of the marital disputes of their parents' (Grych, Seid, & Fincham, 1992). The authors proposed nine subscales reflecting perceptions of conflict frequency, intensity, content, resolution, and triangulation. However, in a recent factor analysis of the CPIC in over 1000 children, four scales reliably emerged, reflecting youth perceptions of conflict frequency and intensity (i.e., properties of conflict), triangulation/stability, self-blame, and perceived threat (Nigg et al., 2009). Moreover, when these CPIC scales were examined together with other family environment variables (SES, familial cohesion, maternal depression), children's appraisals of self-blame in relation to their parents' marital conflict remained a robust predictor of ADHD symptoms (Miller et al., in preparation), indicating that self-blame may be particularly important for ADHD. Importantly, however, the psychometric properties of these newly-identified CPIC scales as well as the specificity of the relationships among the scales and with ADHD and other externalizing behaviors remains to be tested in additional samples.

Overall, the promoter polymorphism of the serotonin transporter gene (5HTTLPR) appears to be a good candidate for GxE effects because of its involvement in emotional regulation processes and expression in key brain regions. Furthermore, inter-parental conflict appears to be relevant for the development of externalizing problems and ADHD. Moreover, there is evidence that this association may be partially dependent on the topic of marital conflict (Cummings et al., 2004), as well as on youth perceptions and cognitive appraisals of their parents' conflict. Given all this, testing for interactions involving 5HTTLPR and cognitive appraisals of self-blame appears to be well-grounded empirically and offers a biologically-plausible mechanisms that may be operating in the etiology of ADHD .

Methodologies for Examination of GxE Effects for ADHD

The next critical consideration for examination of GxE effects in the relationship between youth appraisals of self-blame and ADHD involves the selection of methodologies by which to examine potential differences in genetic effects. While previous work involving twin designs and molecular genetic studies of ADHD have typically involved separate lines of investigation (e.g., quantifying the magnitude of omnibus genetic effects versus examination of association of specific genetic markers, as explained below in detail), the use of the two methodological approaches represents a particularly powerful way to examine possible GxE. Because of scaling effects of both the environmental mediator and the outcome in question, several investigators have warned against potential false-positives in GxE designs (Eaves, 2006; Moffitt et al., 2005; Rutter, Moffitt, & Caspi, 2006). Thus, examination of potential G x self-blame interactions for ADHD using *both* behavioral genetic *and* molecular genetic methodology allows for some protection against false-positive results. Moreover, initial examination of any impact of the environmental risk factor on the latent genetic and environmental variance on a trait using behavioral genetic methodology provides a type of "omnibus" test to determine if GxE effects are likely with a particular environmental moderator. Molecular genetic techniques can then specify *particular* genetic markers that may be relevant to the disorder and examine whether or not association between the genetic marker and the trait changes with different levels of the environmental moderator. The current project will take advantage of the complementary nature of these two GxE methodologies to evaluate whether youth appraisals of self-blame in relation to their parents' marital conflict moderates genetic risk effects for ADHD.

Behavioral Genetic Approaches. Historically, twin studies have focused upon quantifying the degree of genetic, shared, and non-shared environmental influence on a particular disorder. Importantly, however, more recent research has suggested that, contrary to earlier

thinking, these influences are necessarily composed solely of main effects. Instead, they likely contain GxE as well. In particular, Purcell (2002) reasoned that genetic (A) x shared environment (C) interaction loads on A based on the following: shared environmental effects result in similar sibling correlations across different levels of genetic relatedness. Interactions between A and C would thus contribute differentially to sibling similarities with degree of genetic relatedness. Because MZ twins share a greater proportion of their genes than do DZ twins (100% versus 50%), AxC interactions would result in greater MZ than DZ correlations, and would thus load on A term in traditional behavioral genetic modeling. By contrast, because non-shared environmental factors (E) suppress both MZ and DZ twin correlations, AxE interactions would not contribute to similarities in twins, but to variance that is unique across sibling pairs regardless of degree of genetic relatedness. AxE interactions would thus emerge as part of the E term in behavior genetic modeling.

In addition to this important theoretical work, Purcell (2002) also described a methodology for entering a measured environmental variable (M) in a means model, so as to estimate latent genetic and environmental path coefficients as a function of a particular environmental variable. Moreover, Purcell's (2002) model allowed researchers to examine these latent GxE in the presence of a genetic correlation between the moderator and the trait (referred to as a gene-environment correlation, or rGE). This was a crucial analytical advance. If rGE effects are not considered, it becomes impossible to determine if the multiplicative effect in question is due to an actual interaction of the two independent sources of variance (i.e. G and E), or if it stems from an underlying genetic relationship *between* G and E. For example, several studies have reported GxE interactions between genetic factors and stressful life events for symptoms of depression, such that particular genetic markers show greater association with

depression for individuals with higher levels of stressful life events (Caspi., et al., 2003; Laucht et al., 2009; Taylor et al., 2006). Critically, however, recent work has also noted that genetic factors also contribute to the occurrence of stressful life events (see Kendler & Baker, 2007). Given this, it is certainly possible that the genetic factors that influence stressful life events also influence the development of depressive symptoms, and thus what appears to be GxE is in fact rGE "in disguise". In short, rGE can resemble GxE, and thus our ability to account for rGE when examining GxE addresses a major confound in GxE research.

Molecular Genetic Approaches. Over the past 10-15 years, there have been remarkable advances in the area of genomics, which has allowed for direct tests of effects between variations in genetic markers and complex traits, including ADHD. Recent GxE work for ADHD has examined differential relationships between putative environmental risk factors and ADHD across different genotype groups. Several environmental variables have been examined, including parental marital status (Waldman, 2007), prenatal exposure to tobacco and alcohol (Langley et al., 2008; Neuman & Todd, 2007), and low birth-weight (Thapar et al., 2005). In these designs, the presence of a particular allele in combination with increased environmental risk significantly predicted ADHD diagnostic status and symptom severity, an effect that was detected via straightforward moderated regression analyses. Thus, one potentially fruitful model for examining whether youth appraisals of marital conflict moderates genetic risk on ADHD is to directly examine their relationship across different genotype groups.

As mentioned earlier, while catecholamine genes have been frequently examined in molecular genetic association studies of ADHD, the role of genes in the serotonin transmission system have also been posited to influence the development of ADHD as dysregulated serotonergic function has been implicated in impulsive and aggressive behavior in studies of

animals, adults, and children (Coccaro et al., 1989; Evans et al., 2000; Halperin et al., 1994; Halperin et al., 1997; Manuck et al., 2002; Schulz et al., 2002). Moreover, the functional 44-bp promoter polymorphism of the serotonin transporter gene (5HTTLPR) has been associated with ADHD as well as comorbid phenotypes, including persistent aggression and conduct disorder (Kent et al., 2002; Manor et al., 2001; Sakai et al., 2006). 5HTTLPR presents as an ideal candidate for examination of GxE effects for ADHD for several reasons. These include its functionality, its sensitivity to environmental regulation, and its expression in key brain regions often implicated in ADHD.

Outline of Current Studies

The aim of the current set of studies is to investigate the potential etiological role of appraisals of self-blame related to their parents' marital conflict in ADHD. Importantly, the investigation will implement two concurrent lines of investigation. First, I will make use of a behavioral genetic approach in which latent G (and environmental) effects for ADHD are allowed to be moderated by youth reports of self-blame (measured E). In this way, I can determine whether self-blame generally moderates genetic (and environmental) influences on ADHD. Furthermore, while self-blame is likely influenced at least in part by constitutional factors, these analyses will aid in determining whether self-blame influences ADHD at the family-wide level (i.e., via shared environmental factors), at the child-specific level (I.e., via unique environmental factors), or perhaps at both levels. Second, I will make use of a molecular genetic approach to examine potential interactions between a measured G (i.e. 5HTTLPR genotype) and the same measured E (youth appraisals of self-blame). In this way, I hope to identify one of the genes interacting with self-blame in the prediction of ADHD (as indicated in the behavioral genetic GxE study). These complimentary lines of investigation thus allow for a

strong test of GxE effects in ADHD and thereby strengthen the ability to accurately detect any potentially real interactions.

Importantly, however, the phenotypic relationships among the newly-identified scales of the CPIC (see Nigg et al., 2009) as well as their relationships with ADHD and other externalizing behaviors have not been well-examined. Thus, prior to the main tests of GxE effects outlined above, I will first examine relationships among all of the CPIC scales and externalizing disorders in order to accomplish three key goals: (1) to examine the psychometric properties of these scales both in general and across a wide age range, (2) to quantify the strength of relationships among the CPIC scales to determine if higher reports of conflict correspond with higher reports of self-blame, and (3) to determine if relationships among the CPIC scales are specific to ADHD or if they related to externalizing behaviors more generally.

The current project will thus include three studies. Study 1 will involve examination of the phenotypic relationships among scales of the CPIC as well as their relationships with externalizing behaviors within a community-based twin sample. Next, Study 2 will provide the first tests of GxE effects by examining self-blame as a moderator of latent genetic and environmental influences on ADHD. Study 3 will then examine interactions between a specific genetic marker (i.e., 5HTTLPR) and youth appraisals of self-blame within a clinically-diagnosed sample of ADHD cases and non-ADHD control youth. Following presentation of these three empirical studies will be an integrative summary and discussion of findings as well as potential implications for future work involving investigation of GxE effects on ADHD.

CHAPTER 2: PHENOTYPIC RELATIONSHIPS AMONG CPIC FACTORS AND EXTERNALIZING BEHAVIORS

Developmental and family process research has consistently pointed to a robust relationship between marital conflict and child adjustment and behavior problems (Buehler et al., 1997; Grych & Fincham, 2001; Rhoades, 2008). Importantly, prior work has also demonstrated that it is not mere exposure to conflict that contributes to later behavioral problems, as some children exposed to inter-parental conflict do not experience behavioral and adjustment difficulties (Jouriles, Murphy, O'Leary, 1989). Rather, several theorists have agreed that additional proximal processes are responsible for the link between interparental conflict and youth behavior problems (Cummings & Davies, 1994; Grych & Fincham, 1990).

Children's *responses* to interparental conflict are a potential set of proximal processes that likely influence the relationship between conflict exposure and later behavior problems. Children's reactions to marital conflict, including cognitive appraisals, affective regulation, behavioral responses, and physiological reactivity have all been demonstrated to mediate the association between exposure to conflict and resultant internalizing and externalizing problems in children and adolescents (Rhoades, 2008). Of these, cognitive appraisals have emerged as particularly strong predictors of child adjustment and behavior problems (Harold et al., 1997; Grych et al., 2000; Rhoades, 2008). That said, several questions remain regarding relationships among the various components of child response to martial conflict as well as their associations with behavioral phenotypes. These include the relationships between various aspects of conflict severity and youth cognitive appraisals as well as the reliability and validity of the measures of youth appraisals related to martial conflict.

The purpose of the following set of analyses was to examine the phenotypic associations of these various components of child response to marital conflict with child behavior problems. Youth perceptions were assessed via the Children's Perception of Interparental Conflict scale (CPIC; Grych, Seid, & Fincham, 1992), which was designed to specifically tap into youth perception of conflict based on the cognitive-contextual framework hypothesis (Grych & Fincham, 1990). The original CPIC scale was constructed to assess nine different dimensions related to interparental conflict, which included both objective reports on conflict (frequency, intensity) and cognitive appraisals related to conflict (e.g., self-blame, coping efficacy). Despite the potential theoretical relevance of the original nine dimensions of the CPIC, recent factor analytic work (which included data from the sample examined herein) has demonstrated that the item-level data on the CPIC was best represented by four factors (Nigg, Nikolas, Miller, Burt, Klump, & von Eye, 2009), at least in samples like the one being studied here. Analyses primarily focused upon the psychometric properties of the four CPIC scales across the age range, their inter-relationships, and the specificity of their associations with youth behavior problems.

METHOD

Participants

Participants were child and adolescent twin pairs and their primary caregiver who were assessed as part of the Michigan State University Twin Registry (MSUTR), an ongoing project examining genetic and environmental contributions to both internalizing and externalizing psychopathology (Klump & Burt, 2006). Families were recruited through the use of state birth records in collaboration with the Michigan Department of Community Health (MDCH) and the Michigan Bureau of Integration, Information, and Planning Services (MBIIP; for a full description of recruitment procedures for the MSUTR, see Klump & Burt, 2006). 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.

The current sample consisted of 214 child and adolescent monozygotic (MZ) and dizygotic (DZ) twin pairs (total n= 428 twins). This sample was composed of 107 MZ twin pairs (52 male-male, 54 female-female) and 108 DZ twin pairs (59 male-male, 49 female-female) that ranged in age from 5-16 years (*M*=10.5, *SD*=2.6 years). Participating families in the MSUTR were notably representative of individuals living in the mid-Michigan region in terms of racial identification (see Culbert et al., 2008); approximately 88% self-identified as Caucasian, 8% identified as African-American, 3% identified as Latino, and 1% identified as Asian-American.

Perceptions of Marital Conflict

Perceptions and appraisals of marital conflict were assessed with the CPIC (Grych, Seid, & Fincham, 1992). Each twin completed a separate CPIC during the computerized assessment at the MSU laboratory. The 48 CPIC items were rated by participating twins on a three-point scale (1-3: true, sort of true, and false). Because the CPIC was designed to be completed by school-aged children, the questionnaire was read to participating twins with reading levels under 5th grade in order to ensure correct comprehension and completion of the items. Based on exploratory and confirmatory analysis of the 48 items (Nigg et al., 2009), four empirically derived CPIC scale scores were computed. These scales included Conflict Properties, Triangulation/Stability, Self-Blame, and Threat (described below).

Items loading on the Conflict Properties scale (n=11 items, $\alpha = .82$) assessed the perceived frequency and intensity of the observed conflict. Sample items from this scale include "My parents get really mad when they argue" and "My parents hardly ever argue." The

Triangulation/Stability scale (n=13 items, α = .88) required children to report on the extent to which they feel caught in the middle of conflict as well as if their parents' conflict is an entrenched and enduring part of family life. Representative items from this scale include "I feel like I have to take sides when my parents argue" and "Even after my parents argue, they stay mad at each other." The Self-Blame and Threat scales assessed cognitive appraisals regarding inter-parental conflict. Items on the Self-Blame scale (n=9 items, α = .85) assessed the extent to which children blame themselves for conflict they have observed between their parents. Sample items from the CPIC self-blame scale include "My parents usually argue about something that I do"; "It is usually my fault when my parents argue"; and "I am to blame when my parents argue." Lastly, items loading on the Threat scale (n=6 items, α = .84) assessed youth perceptions regarding the negative implications their parents' marital conflict may have for them. Sample items on this scale include "When my parents argue, I worry about what will happen to me" and "I get scared when my parents argue."

Child Externalizing Behaviors and ADHD

Mothers of the twin participants completed the Child Behavior Checklist (CBCL; Achenbach & Rescorla, 2001) to assess child externalizing behaviors. The CBCL is a standardized questionnaire for parents to report the frequency of 118 problem behaviors exhibited by their children during the past six months. Mothers rated how often particular behaviors occurred for each twin using a 3-point Likert scale (0=never true; 1=sometimes/somewhat true; 2=often true). These 118 behaviors were then summed into the 8 empirically-validated syndrome scales and 6 DSM oriented scales. The DSM oriented scales for ADHD, ODD, and CD were selected for analyses as the items most closely map onto DSM-IV criteria for externalizing psychopathology. Note that these scales do not represent clinical

diagnoses of externalizing disorders but rather encompass ratings of these behaviors. The DSM-oriented scales have demonstrated good reliability and validity in terms of predicting clinically significant levels of externalizing disorders (Hudziak et al., 2004). In this sample, internal consistency estimates were adequate for all three scales (ADHD scale α=.88; ODD scale α=.86; CD scale α=.89). While age and sex based norms are available for CBCL scores, raw scale scores were used in the current study, as recommended by the authors for population/community studies to avoid potential age and gender confounds (Achenbach & Rescorla, 2001).

Data Analysis

The current analyses aimed to address three primary questions regarding the properties of the CPIC scale within a community-based twin sample. First, as noted in Nigg et al. (2009), the age-invariance factor analytic model provided some evidence indicating that the CPIC factors may vary in their psychometric properties and relationship across the age-span. This is particularly important for application of the CPIC four-factor solution to this (and any other) large sample that includes a wide age range of children. Thus, internal consistency estimates were examined across the age range of the sample. The sample was divided into four age ranges: 5-7 years (n=66 twins), 8-10 years (n=162 twins), 11-13 years (n=136 twins), and 14-16 years (n=64 twins) and alpha was calculated for each factor at each age range.

Secondly, the analyses set out to examine the inter-relationships among the four CPIC factors within the sample. The particular question guiding these analyses centered on whether or not children reporting higher objective levels of conflict (e.g., frequency) also reported more negative cognitive appraisals of conflict (e.g., higher self-blame and higher perceived threat). Thus, bivariate correlations among the four CPIC scales were examined in order to assess the

nature and strength of the relationships among the scales. These associations were also examined at different age ranges to further test the possibility of age-invariance of the CPIC.

Lastly, the relationships among the four CPIC scales and measures of youth behavior problems (e.g., externalizing behaviors) were examined. Hierarchical linear models (HLM) were used to examine differences in relationships among the four CPIC scales and measures of externalizing behaviors in twins. Hierarchical linear models are an extension of general linear models in which factors are assumed to have a linear relationship with the dependent variable. HLM analyses were selected for use with this sample because the non-independence of the twin data can be accounted for by nesting a level 1 variable (individual twins) within a level 2 variable unit (families). As recommended (Kenny, Kashy, & Cook, 2006), categorical predictors (e.g., gender) were effect coded (1 for males, -1 for females) and continuous variables (e.g., CPIC factors, age) were centered at zero. Models were first run with each of the four CPIC factor scales as predictor variables (ADHD, ODD, and CD scale scores each served as outcome variables). Next, in order to test for specificity of effects, HLM analyses were re-run while controlling for the overlap between the externalizing behaviors (e.g., ODD and CD behaviors were entered as predictors when the ADHD score served as the outcome variable).

RESULTS

Psychometric Properties of CPIC Factors

As noted in the methods section, the internal consistency estimates for each of the four CPIC factors within the overall sample were adequate (Conflict Properties alpha=.82; Triangulation/Stability, alpha=.88; Self-Blame, alpha=.85; Threat, alpha=.84). Examination of internal consistency estimates across the age range of the sample revealed that, in general, all scales demonstrated adequate reliability at all ages (see Table 1). However, the internal

consistency of .66 for Conflict Properties among children ages 5-7 years suggests that even with reading assistance, young children may not be as reliable in answering questions regarding conflict characteristics such as frequency and intensity. Despite this, estimates of internal consistency were adequate in this age range for the other three scales (alphas range from .77-.84). Furthermore (and as expected), reliability estimates generally improved slightly with age, indicating that older youth may be somewhat more reliable reporters of both objective aspects of interparental conflict as well as cognitive appraisals of self-blame and threat.

Inter-relationships among CPIC Factors

Full Sample. Table 2 shows the bivariate correlations among the four CPIC factors. As seen there, the four CPIC scales generally demonstrated moderate to strong and significant relationships with each other. The relationship between Conflict Properties and Triangulation/Stability appears to be especially strong ($r=.59$, $p<.01$), a finding that is not surprising given that both scales are hypothesized to tap more "objective" reports of conflict (e.g., frequency, intensity, stability). The relationship between Conflict Properties and cognitive appraisals of conflict, including Self-Blame ($r=.21$) and Threat ($r=.40$) were significant, but smaller in magnitude. Importantly, inter-scale correlations with Self-Blame in particular appear to be somewhat attenuated (although still significant) when compared to inter-correlations among the rest of the scales (e.g., Self-Blame correlations with other scales range from .21-.36 as compared to .40-.59 across the other scales). Indeed, correlations with Self-Blame were significantly smaller than the inter-correlations among the other scales (Fisher z, all $p < .04$).

Overall, these relationships suggest some commonalities among the four CPIC scales. However, statistical comparisons of the correlations between the scales revealed that the relationships between each of the scales and Self-Blame was significantly weaker than the inter-

relationships among the remaining scales. This pattern of results suggests that while there is overlap among the scales, the frequency, intensity, and stability of marital conflict do not necessarily correspond with self-blame regarding the conflict.

Age. Bivariate correlations were also examined for each age range (e.g., ages 5-7, 8-10, 11-13, 14-16; see Tables 3-6). The overall pattern of relationships remained largely the same for all groups. The relationship between Conflict Properties and Triangulation/Stability was robust across the age range (*r*'s ranged from .41-.77). Furthermore, correlations between Self-Blame and other scales were again somewhat attenuated in both younger and older children (rs range between .03-.35), with the exception of the association with Triangulation/Stability in younger children (r=.57 for children ages 5-7). Examination of differences among the pattern of inter-correlations revealed that the relationship between Conflict-Properties and Self-Blame was significantly weaker than relationships among Conflict Properties and the other two factors for children in the three youngest age ranges (all ps <.05, two tailed). For youth ages 14-16, however, the inter-correlations among all 4 CPIC factors were, for the most part, moderate in nature. In general, however, I would conclude that the overall pattern of inter-relations among the CPIC factor scales appeared to persist across the age range of the sample.

CPIC Factors and Externalizing Behaviors

Full Sample. Next, bivariate correlations were computed to examine relationships between each of the four CPIC factors and parent-reports of child externalizing behavior (i.e., ADHD, ODD, and CD, see Table 2). The four scales demonstrated different patterns of relationships with externalizing behaviors: Conflict Properties was significantly related to all measures of externalizing behaviors (ADHD, ODD, and CD scores), however correlation coefficients were rather small (rs range .10-.17). Triangulation/Stability was also significantly

related to all three measures and correlations were a bit larger in magnitude (rs range from .15-.23). The Self-Blame scale showed the largest correlations of any of the CPIC scales with ADHD, ODD, and CD behaviors (rs range from .16-.28). By contrast, the Threat scale showed no relationship with any of the measures of externalizing behaviors (rs range from -.06 to .04). However, tests of significant differences yielded few significant differences in the strength of the relationships between the CPIC factors and ADHD, ODD, and CD scores. Overall, the correlations generally pointed to significant and positive relationships between the CPIC factors and ADHD, ODD, and CD behaviors (outside of the Threat scale which showed no significant relationship with any of the behavioral measures).

Correlations were further examined across the age range to evaluate whether these relationships were specific to any particular developmental stage (Tables 3-6). As in the overall results, the Threat scale was not significantly related to measures of ADHD and externalizing behaviors at any of the age ranges. Next, the relationship between Conflict Properties and the ADHD score remained modest throughout the age range, whereas the relationships between this scale and ODD and CD each became somewhat stronger in older children (although this effect was primarily driven by the negative associations with CD and ODD behaviors in the youngest cohort). Relationships between the Triangulation/Stability and the ODD and CD scores also significantly increased among older youth (ages 14-16) relative to the younger age groups ($ps<.03$, two tailed). This may be a function of the improved reliability within this age range. In contrast, the relationship between Triangulation/Stability and ADHD did not show significant changes across the age-range. Similarly, the Self-Blame scale showed positive and significant relationships with both ADHD and CD behaviors across all ranges with no significant differences in the strength of the correlations by age. The relationship between Self-Blame and

ODD behaviors showed less of a discernable pattern and was only significant for children ages 5-7 and for those ages 11-13.

CPIC Factors as Predictors of Externalizing Behaviors

Next, HLM analyses were conducted in order to assess the potential specificity of the relationships between the CPIC factors and ADHD, ODD, and CD behaviors (see Table 7). As mentioned earlier, HLM analyses are preferred here in order to account for the non-independence of twin data. All four CPIC scales were entered as predictors and each externalizing measure served as a separate outcome variable. Age and gender were included as covariates. Results revealed that when all scales were entered as predictors, both the Triangulation/Stability (b=.08, p=.02) and Self-Blame (b=.19, p<.001) scales remained significantly related to ADHD behaviors (associations with the other CPIC scales were no longer significant). These same two scales also emerged as significant predictors of ODD behaviors (Triangulation/Stability, b=.06, p=.03; Self-Blame, b=.08, p=.02), and CD behaviors (Triangulation/Stability, b=.10, p=.004; Self-Blame, b=.23, p<.001). Interestingly, the Threat scale demonstrated significant negative relationships with ODD and CD. This is may be due to a suppression effect. Overall, Triangulation/Stability and Self-Blame appeared to show relationships with all measures of externalizing behaviors.

Specificity of Relationships

In order to assess the specificity of the relationships between Triangulation/Stability and Self-Blame with externalizing behavior, the HLM analyses were conducted again (see Table 8). As before, the CPIC factor scales were entered as predictors into the model and the ADHD, ODD, and CD scores again each served as outcome variables. However in these models, the other externalizing behaviors were also entered as predictors in order to parse out the shared

variance among ADHD, ODD, and CD scores. For example, when ADHD behaviors served as the outcome measure, both the ODD and CD scores were entered as predictors.

For ADHD, results revealed that only the Self-Blame scale remained a significant predictor (b=.08, p=.05) after controlling for the overlap with the other externalizing behaviors. None of the CPIC factors remained significant predictors of ODD behaviors after accounting for its overlap with ADHD and CD (all ps >.13). Lastly for CD, Self-Blame and Threat remained significant predictors after the shared variance with ADHD and ODD was accounted for (b=.12, p=.009 and b=-.09, p=.03, respectively).

Such results suggest that while Conflict Properties was moderately correlated with each measure of externalizing psychopathology, it was not a unique predictor of ADHD, ODD, or CD behaviors. The Threat scale was not correlated with any of the externalizing behaviors and was not a significant predictor of any of the externalizing measures, with the exception of CD behaviors. Somewhat surprisingly however, the relationship between Threat and CD behaviors was negative, indicating that higher reports of Threat were corresponded with lower CD scores. There appeared to be a relationship between Triangulation/Stability and externalizing behaviors in general, however, this scale was not specifically related to any one measure of psychopathology. Importantly, the Self-Blame scale was revealed to be a robust predictor of externalizing behaviors in general and ADHD and CD scores in particular.

DISCUSSION

The CPIC was originally developed to examine the child's perspective of interparental conflict as a unique method of measuring the potential impact of marital discord on child behavior problems and adjustment. Recent methodological work by our group has suggested that the measure may be best captured with four factors: Conflict Properties,

Triangulation/Stability, Self-Blame, and Threat (Nigg et al., 2009). Conflict Properties and Triangulation/Stability have been hypothesized to tap into more objective aspects of interparental conflict (e.g., frequency, intensity, and stability), whereas Self-Blame and Threat are posited to measure children's cognitive (and partially emotional) appraisals regarding marital conflict. These cognitive appraisals have emerged as a particularly robust predictor of both internalizing and externalizing problems (Rhoades, 2008) and have been proposed a potential moderator of etiological influences on ADHD.

The purpose of these analyses was to address three primary questions regarding the phenotypic relationships of the CPIC's four factors. First, confirmatory factor analytic models reported by Nigg et al (2009) suggested potential age-invariance of the CPIC scales. Despite this, all four CPIC scales demonstrated adequate internal consistency in the full sample of 5-16 year old twins as well as across four different age ranges (5-7 years, 8-10 years, 11-13 years, 14-16 years). The only notable exception that emerged was the low reliability estimate (α=.66) for the Conflict Properties scale among 5-7 year olds. Overall then, it appeared that youth of all ages in the sample were, in general, reliable reporters on the four CPIC scales.

Secondly, the analyses aimed to examine the relationships among the four CPIC scales in order to determine if higher reports of objective aspects of the conflict (e.g., Conflict Properties) corresponded with more negative cognitive and emotional appraisals of conflict (e.g., higher scores of Self-Blame and/or Threat). Results revealed a general pattern of moderate and positive associations among the 4 CPIC scales that persisted across the age-range. Specifically, the correlation between Conflict Properties and Self-Blame was significantly lower than correlations involving Conflict Properties, Triangulation-Stability, and Threat, a pattern which persisted for each age group. Overall, while the relationship among Conflict Properties and Self-Blame was

positive, the low correlation indicated that the frequency and intensity of interparental conflict do not map directly onto child reports of self-blame regarding the conflicts. In other words, the Self-Blame evidences only a modest association with the level of conflict frequency and intensity.

Lastly, the phenotypic analyses aimed to examine the four CPIC scales as predictors of maternal-report of ADHD, ODD, and CD behaviors. Furthermore, I aimed to examine any potential specificity of the relationships among the four CPIC scales and measures of externalizing behaviors. Results indicated that the Triangulation/Stability and Self-Blame scales significantly predicted ADHD, ODD and CD behaviors. Yet, when the covariance among the externalizing behaviors was taken into account, Self-Blame remained the only significant and unique predictor of both ADHD and CD. None of the CPIC scales appeared to be uniquely related to ODD.

Taken together, these results suggest that cognitive appraisals of self-blame in regard to marital discord are acting as a significant predictor of both ADHD and CD. Furthermore, the level of self-blame appears to be partially independent of the level of overall martial conflict (i.e., the frequency, intensity, or stability of the conflict). These results indicate that self-blame in regard to parents' martial conflict may have a unique relationship with measures of externalizing behavior. However, while these analyses have demonstrated a significant and unique relationship among self-blame and ADHD (as well as CD), additional work is necessary in order to determine the etiological role of self-blame in these behaviors (if any). For example, longitudinal work may be useful in understanding the predictive nature of youth appraisals related to martial conflict and the onset (or maintenance) of externalizing behavior problems. Furthermore, having a child with behavior problems may in fact result in increased marital

conflict. Children may then (perhaps correctly) observe conflict that is related to their behavior, resulting in increased reports of self-blame.

The unique role of self-blame as a predictor of both ADHD and CD behaviors may be somewhat unexpected under social learning theory, which would posit that mere exposure to higher levels of conflict would correspond to higher levels of behavior problems. That said, under the cognitive-contextual framework (Grych & Fincham, 1990), the child's interpretation of the conflict, particularly their role in the conflict, often plays a determining role as to the impact of marital discord on child behavior problems. These results support the latter view and indicate that negative appraisals of self-blame correspond with an increase in inattention and hyperactivity as well as aggressive behaviors.

While the exact mechanisms remain unknown, recent work investigating the LHPA axis (limbic-hypothalamic-pituitary-adrenal axis via cortisol levels), a system believed to be intimately involved in the stress response, have indicated that children's observed distress level, rather than just exposure to conflict, is related to an increase in cortisol (Davies et al., 2008). Further, additional research has indicated that children's internal representations of family relationships mediated the relationship between exposure to conflict and attention problems specifically (Sturge-Apple et al., 2008). Thus, children's cognitions regarding marital conflict may be playing an important etiological role in the development of behavioral and emotional regulatory capacities, both of which are often impaired in youth with externalizing problems such as ADHD and CD. A formal test of a potential etiological role for self-blame in ADHD could thus provide additional insight regarding the role of environmental variables in the causal pathways that underpin the disorder.

CHAPTER 3: THE IMPACT OF YOUTH APPRAISALS OF MARTIAL CONFLCIT ON GENETIC AND ENVIRONMENTAL CONTRIBUTIONS TO ATTENTION-DEFICIT HYPERACTIVITY DISORDER: EXAMINATION OF GXE EFFECTS IN A TWIN SAMPLE

Attention-deficit hyperactivity disorder (ADHD) is one of the most commonly diagnosed psychiatric disorders of childhood, affecting approximately 3-5% of school-aged children. The disorder is characterized by excessive and developmentally inappropriate symptoms of inattention, hyperactivity, and impulsivity that impair functioning across multiple settings and within a variety of domains (Barkley, 2006, Nigg, 2006). While the diagnostic criteria for ADHD continue to evolve, taxometric analyses have revealed that ADHD may be best understood as extremes along a behavioral dimension as opposed to a discrete category (Haslam et al., 2006).

Research involving the etiology of ADHD has provided strong evidence of genetic influence, with heritability estimates ranging between 70-90% (Bergen, Gardner, & Kendler, 2007; Burt, 2009). Importantly, these very high levels of heritability have been found at both the moderate and extreme ends of the behavioral dimensions of inattention and hyperactivity-impulsivity (Willcutt, Pennington, & DeFries, 2000). In contrast to these high estimates of genetic influence, contributions from the environment appear to be much smaller, only accounting for 10-30% of the variance in ADHD (Burt, 2009). Multiple behavioral genetic investigations and meta-analyses have consistently observed no contribution from shared environmental factors (Bergen, Gardner, & Kendler, 2007; Burt, 2009, Nikolas & Burt, in press).

Thus, these environmental influences appear to be exclusively non-shared environmental in origin.

Because the non-shared environment estimate also includes measurement error and its overall contribution to the variance in ADHD is small, it is perhaps not surprising that far less attention has been given to identifying the unique environmental effects that may be operating on ADHD. Even so, there is compelling evidence that non-shared environmental factors are important in the development of the disorder and likely reflect more than measurement error. For example, work examining identical twin pairs discordant for ADHD has revealed important differences between the affected and unaffected siblings. First, a recent longitudinal investigation found that the affected twin had significantly lower birth weight and delayed physical and motor maturation compared to their unaffected co-twin (Lehn et al., 2007). Secondly, studies of neural anatomy have indicated that the volume of the caudate is significantly smaller in affected twins when compared to their co-twin (Castellanos et al., 2003). Thus, while high genetic effects are consistently reported for ADHD, environmental factors also play an important role in the etiology of ADHD.

Developmental research has also demonstrated the importance of environmental factors to the etiology of ADHD (Biederman, Faraone, & Monuteaux, 2003; Johnston & Mash, 2001). Specifically, interparental conflict has been shown to be a robust predictor of child adjustment and behavior problems, including externalizing behaviors (Buehler, Lange, & Franck, 2007; Counts et al. 2005; Cummings & Davies, 1994; El-Sheikh & Harger, 2001; Gerard et al., 2005; Grych & Fincham, 1990; Grych et al., 2000; Grych, Harold, & Miles, 2003; Jouriles et al., 2000; Skopp et al., 2005) and ADHD (Wymbs et al., 2008). One prominent theory for the mechanism underlying this relationship posits that the topics of marital disputes are differentially related to

children's reactions and behaviors, such that conflicts about the child and his/her behavior are linked to greater behavioral dysregulation in the child than are other sources of martial conflict (e.g., financial concerns; Cummings et al., 2004; Cummings et al., 2002; Harold et al., 2004).

Building on this latter line of research, it has also been suggested that youth perceptions and appraisals of marital conflict play a critical determining role as to the effect of marital conflict on youth behavior problems (Grych & Fincham, 1990). From this view, assessing inter-parental conflict from the perspective of the child is critical for determining the actual impact of the conflict on the child's behavior (Grych, Seid, & Fincham, 1992). In line with this, children's distress in relation to their parents' marital conflict, rather than conflict exposure per se, has been associated with an increased stress response in the child (Davies et al., 2008). This view has been further supported by empirical work demonstrating that youth reports of inter-parental conflict are more predictive of their externalizing behavior problems than are the parents' reports of their own marital conflict and satisfaction (Cummings, Davies, & Simpson, 1994; Grych, Seid, & Fincham, 1992).

Recent meta-analytic work has further indicated that specific cognitive appraisals of self-blame and perceived threat made by youth in relation to their parents' marital conflict are robust predictors of child behavior problems (Rhoades, 2008). While these appraisals are also likely influenced by constitutional factors (e.g., temperament), they have been argued to represent a set of proximal process by which family environmental factors exert their influence on child behavior (Grych & Fincham, 1990). Indeed, children's appraisals of self-blame in relation to their parents' marital conflict appear to be a particularly robust predictor of ADHD symptoms (Counts et al., 2005), even after controlling for other family factors such as socioeconomic status, parental psychopathology, and parenting stress. Thus, self-blame appears to be an

important "environmental" factor related to ADHD, yet its potential etiological role in the disorder remains untested.

In sum, both genetic and environmental factors appear to play important roles in the development of ADHD. That said, crucial questions remain regarding how to understand these relationships among family environment variables within the context of large and robust estimates of genetic effects. In particular, how are the relationships between family environment variables and ADHD accounted for in behavioral genetic models that consistently demonstrate large genetic main effects, small non-shared environmental influences, and zero shared environmental effects?

One likely answer involves gene x environment interactions (GxE), in which environmental influences moderate genetic effects on ADHD. Indeed, recent theoretical advances within behavioral genetics (see Purcell, 2002) have shown that the genetic (a^2) and non-shared environmental (e^2) components of variance likely contain not only their respective main effects but also variance due to GxE effects. In particular, Purcell (2002) noted that there are two types of GxE interactions that are captured in the traditional genetic and non-shared environmental variance components, respectively: genetic x shared environment interactions (or AxC) and genetic x non-shared environment interactions (or AxE).

The first type of interaction (i.e., AxC) represents interactions between genetic and shared environmental effects, and is captured in the additive genetic variance term (a^2). Monozygotic (MZ) twins share 100% of their segregating genes, whereas dizygotic (DZ) twins share, on average, 50%. However, all twin pairs (regardless of zygosity) share 100% of the shared environmental factors (indeed, the correlation of shared environmental factors between twins within pairs is set to unity in all biometric twin models). Should these common shared

environmental factors activate genes of risk, they would then do so more for MZ twins as compared to DZ twins (i.e., because MZ twins share 100% of their genes, interactions between A and C would always result in increased MZ correlations, a pattern that would not necessarily hold for DZ correlations). Because genetic influences are inferred by the difference between MZ and DZ correlations, anything that increases the MZ correlation relative to the DZ correlation would "load" on the genetic proportion of variance. Accordingly, AxC interactions would emerge as part of the genetic variance component (a^2) in behavioral genetic models.

By contrast, AxE represents interactions between genetic and non-shared environmental factors, which would be captured in the non-shared environmental variance term. Non-shared environmental factors are necessarily different across twins (i.e., they are shared at 0% in biometric models). Accordingly, if only one MZ twin within a pair is exposed to a given environmental moderator, then only the genes of that twin will be activated. This will increase sibling differences, regardless of zygosity, and would thus emerge as part of the unique environmental variance component (e^2).

Overall, the differential GxE loadings on genetic and non-shared environmental proportions of variance are thus dependent on whether the environmental moderator of interest represents a shared environmental factor (C) that is common across siblings or a non-shared environmental factor (E) that is unique to each sibling. For example, maternal warmth may emerge as a shared environmental factor if both twins in the family experience and are influenced by equal levels of warmth and nurturing from their mother. Should warmth activate genes of risk, it would therefore do so more for MZ twins than DZ twins, and thus load on the genetic proportion of variance. However, should maternal warmth emerge as a non-shared environmental factor (E) that is unique to each sibling (i.e., a mother may be particularly warm

and nurturing to only one of the twins, as described in Caspi et al., 2004), maternal nurturing would then interact only with the genes of one child within the twin pair and load on the non-shared environmental component of variance. Finally, should warmth function as both a C and an E (i.e., maternal warmth may both color the global home environment that surrounds the children and differentially impact each child individually), then moderation of genetic and non-shared environmental effects would be expected.

This biometric framework for understanding GxE has a number of key advantages for studies of GxE (both in general and for ADHD in particular). First, the application of this framework may be particularly relevant for ADHD, for which numerous environmental risk factors have been identified (Banerjee et al., 2007; Nigg, 2006) even though the environmental component of variance in behavioral genetic studies is consistently small to moderate in magnitude. Second, it provides an omnibus test of GxE effects for a particular environmental variable (i.e., children's appraisals of inter-parental conflict), as genetic influences are examined at the latent or composite level of analysis. This advantage stands in contrast to the more specific molecular genetic GxE analyses, which typically examine only one specific polymorphism (Langley et al., 2008; Waldman, 2007) and are thus likely to be explaining only a very small part of the causal chain of polygenic disorders like ADHD. Finally, the biometric framework detailed above would provide critical new information regarding the specific manifestation of any GxE between children's appraisals of inter-parental conflict and ADHD. In other words, if appraisals of self-blame are involved in the etiology of ADHD via GxE effects, the biometric framework would be able to clarify whether interactions occur at the family-level (e.g., AxC interactions) or at the child-specific level (e.g., AxE interactions) or both. While there is an established phenotypic link between self-blame and ADHD, it is unknown whether self-

blame functions as a shared environmental factor (and therefore creates sibling similarity), whether it is operating as a unique environmental factor (resulting in sibling differences), or perhaps both. In other words, application of this methodology to ADHD can help us not only confirm the existence of GxE in ADHD, but also illuminate how environmental variables, such as appraisals of self-blame related to interparental conflict, interact with genetic risk for ADHD. Somewhat surprisingly, however, this type of methodology has yet to be applied to ADHD.

The purpose of the current study was to do just this by examining how youth appraisals of self-blame in relation to their parents' martial conflict influence the magnitude of genetic and environmental contributions to ADHD. Specifically, the current study aimed to examine how the genetic, shared, and non-shared environmental variance components of ADHD shifted as a function of children's report of self-blame. Evidence of significant changes in genetic and environmental contributions to ADHD could provide an omnibus test of GxE effects involving children's appraisals of self-blame and clarify the specific manifestation of these GxE effects.

METHOD

Participants

Participants were child and adolescent twin pairs from the Michigan State University Twin Registry (MSUTR), an ongoing project examining genetic and environmental contributions to both internalizing and externalizing psychopathology (Klump & Burt, 2006). Participants were recruited through the use of state birth records in collaboration with the Michigan Department of Community Health (MDCH) and the Michigan Bureau of Integration, Information, and Planning Services (MBIIP; for a full description of recruitment procedures for the MSUTR, see Klump & Burt, 2006). 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.

The current sample consisted of 246 child and adolescent monozygotic (MZ) and dizygotic (DZ) twin pairs (total n = 492 twins). This sample was composed of 120 MZ twin pairs (55 male-male, 65 female-female) and 126 DZ twin pairs (69 male-male, 57 female-female) that ranged in age from 5-16 years (*M*=10.2, *SD*=2.6 years). Participating families in the MSUTR were representative of individuals living in the mid-Michigan region in terms of racial identification (see Culbert et al., 2008); approximately 88% self-identified as Caucasian, 8% identified as African-American, 3% identified as Latino, and 1% identified as Asian-American.

Zygosity Determination

Zygosity was established using physical similarity questionnaires administered to the twins' primary caregiver (Peeters, Van Gestel, Vlietinck, Derom, & Derom, 1998), as well as a research assistant who independently evaluated the twins on physical similarity indices. Zygosities were then compared between the participant and research assistant reports. Discrepancies were resolved through review of questionnaire data and twin photographs (when available) by one of the MSUTR principal investigators (KLK or SAB) or by DNA markers. On average, the physical similarity questionnaires used by the MSUTR have accuracy rates of 95% or better (Peeters et al., 1998).

ADHD Behaviors

Mothers of the twin participants completed the Child Behavior Checklist (CBCL; Achenbach & Rescorla, 2001) to assess behaviors relating to ADHD. The CBCL is a standardized questionnaire for parents to report the frequency of 118 problem behaviors exhibited by their children during the past six months. Mothers rated how often particular

behaviors occurred for each twin using a 3-point Likert scale (0=never true; 1=sometimes/somewhat true; 2=often true). These 118 behaviors were then summed into the 8 empirically-validated syndrome scales and 6 DSM oriented scales. The 7-item DSM oriented scale for ADHD was selected for analyses since its items have demonstrated adequate predictive power for DSM-IV ADHD (Hudziak et al., 2004). The items included "fails to finish things he/she starts," "can't concentrate or pay attention for long", "can't sit still, restless or hyperactive", "impulsive or acts without thinking", "inattentive or easily distracted", "talks too much,", and "unusually loud". The CBCL has demonstrated good reliability and validity in terms of predicting clinically significant problems related to ADHD and other disorders (Hudziak et al., 2004). In this sample, internal consistency estimates were adequate (α=.88).

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 to avoid potential gender and age bias that can occur with the use of standardized scores in population studies (Achenbach & Rescorla, 2001). Thus, the ADHD measure for each twin was the total raw score added across the seven ADHD items. In order to better approximate normality, the final ADHD scores from the CBCL were log-transformed prior to analysis.

Perceptions of Marital Conflict

Perceptions and appraisals of marital conflict were assessed with the Children's Perception of Marital Conflict scale (CPIC; Grych, Seid, & Fincham, 1992). Each twin completed a separate CPIC during the assessment. The 48 CPIC items were rated by participating twins on a three-point scale (1-3: true, sort of true, and false). Because the CPIC was designed to be completed by school-aged children, the questionnaire was read to participating twins with reading levels under 5th grade in order to ensure correct comprehension

and completion of the items. Based on exploratory and confirmatory analysis of the 48 items (Nigg et al., 2009), four empirically derived CPIC scale scores were computed – the main scale of interest being the self-blame scale. Sample items from the CPIC self-blame scale include "My parents usually argue about something that I do"; "It is usually my fault when my parents argue"; and "I am to blame when my parents argue." Internal consistency measures indicated good reliability for the nine-item CPIC self-blame scale in the full sample (α =.85), as well as across various age groupings (ages 5-7, α =.81; ages 8-10, α =.83; ages 11-13, α =.86; ages 14-16, α =.87).

Because GxE analyses estimate genetic and environmental influences at each level of the moderator, small cell sizes across the range of continuous values (i.e., 9-26) would result in imprecise estimates. Thus, the self-blame scale was trichotomized into low, moderate, and high levels of self-blame, so as to more meaningfully estimate genetic and environmental effects at each broad level of self-blame. The lowest third of the distribution was assigned a score of zero (n=108); the middle third was assigned a score of 1 (n=157), and the highest third was assigned a score of 2 (n=162). This trichotomized self-blame variable was used in all model-fitting analyses.

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 or characteristics (i.e., phenotypes) is partitioned into three components, additive genetic (a^2), shared environment (c^2), and non-shared environment plus measurement error (e^2). The additive genetic component (a^2) is the effect of individual genes summed over loci, and acts to increase twin correlations relative to the amount of genes shared. The shared environment (c^2)

is that part of the environment common to siblings that acts to make them similar to each other. The non-shared environment (e^2) encompasses environmental factors (and measurement error) differentiating twins within a pair. As noted earlier, however, these genetic and environmental estimates are not composed solely of main effects – they also contain GxE effects. Thus, a^2 includes both the main effects of additive genetic factors as well as gene x shared-environment interactions (AxC). The unique environmental variance term (e^2) consists of main effects due to non-shared environmental factors, gene x non-shared environment interactions (AxE), and measurement error.

The question of interest in the current study is whether self-blame in relation to interparental conflict moderates genetic and environmental contributions to ADHD. Whereas GxE is characterized as environmental sensitivity to genetic risk, gene-environment correlation (rGE) represents genetic control of exposure to different environments. For example, a child with ADHD may be more likely to evoke conflict between his or her parents (Whalen & Henker, 1999), and thus be more likely to attribute blame regarding this conflict to him or herself. Thus, a child's genetic proclivities could elicit an "environmental" response that is consistent with his/her genetic make-up (referred to as an evocative rGE). rGE is particularly important for GxE researchers to consider because it can resemble GxE in moderator models (i.e., genetic influences on ADHD could vary across levels of self-blame because the "moderator" is correlated with genetic risk for ADHD). In short, genetic covariation between ADHD and self-blame (i.e., rGE) could resemble GxE if rGE is not simultanesouly considered.

Given this, Purcell (2002) proposed two GxE models: the first model examines GxE regardless of rGE (i.e., the univariate or "straight" GxE model); the second model examines GxE in the presence of rGE. In order to test for GxE effects while also considering the possible

impact of rGE in any GxE that were uncovered, two sets of analyses were conducted. First, the univariate or "straight GxE" model was examined to estimate genetic and environmental influences on ADHD at each level of the moderator. This model provides a test of GxE but does not allow us to consider possible genetic overlap between the moderator and the outcome. Next, the GxE in the presence of rGE model was conducted, thereby allowing us to both confirm the presence of GxE, and evaluate the impact of rGE on these effects. The use of both models thereby allows us to accomplish three critical tasks for examination of GxE effects. These included (1) a test of moderation of the genetic and environmental influences on ADHD by self-blame (GxE), (2) a gauge as to whether rGE effects are present and may be influencing any observed moderation, and most importantly, (3) a method for controlling for rGE while simultaneously re-evaluating GxE effects. It is important to note that the "straight" GxE and the GxE in the presence of rGE models are not nested, and thus their results cannot be statistically compared. However, conceptual comparisons of the results could prove useful for furthering understanding of the issues mentioned above.

The "straight" GxE model 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 age, 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: $Unstandardized\ Variance_{Total} = (a + A_1(self\text{-}blame) + A_2(self\text{-}blame^2))^2 + (c + C_1(self\text{-}blame) + C_2(self\text{-}blame^2))^2 + (e + E_1(self\text{-}blame) + E_2(self\text{-}blame^2))^2$. A series of more restrictive moderator models for each measure were then fit to the data, constraining the moderators for each source of etiological influence to be zero and evaluating the reduction in model fit. As recommended by previous work, the current models

were run a minimum of 5 times using multiple start values to ensure that all the estimates obtained minimized the -2lnL value.

Next, GxE effects were evaluated while accounting for rGE. This GxE in the presence of rGE model is essentially a re-formulation of the standard behavioral genetic bivariate model, such that the moderator is entered twice – as a dependent variable *and* as a moderator variable. Influences on the outcome measure (ADHD) are then partitioned into two sources of genetic influence (as well as from two sources of shared and two sources of non-shared environmental influence): (1) variance *shared* with the moderator, and (2) variance that is *unique* to ADHD (i.e., that residual variance in ADHD that does not overlap with self-blame). The moderator is then allowed to moderate both the genetic and environmental covariance paths between self-blame and ADHD as well as with the genetic and environmental paths unique to ADHD (i.e., that variance remaining in ADHD once the overlap/rGE with self-blame has been partialled out) (Purcell, 2002). Only the latter index "true" GxE (i.e., controlling for rGE).

Because these interaction models effectively involve fitting a separate biometric model for each individual as a function of their self-blame score, they both require the use of Full-Information Maximum-Likelihood raw data techniques (FIML). Mx, a structural-equation modeling program (Neale, 1997), was used to fit models to the transformed raw data. When fitting models to raw data, variances, covariances, and means of those data are freely estimated by minimizing minus twice the log-likelihood (-2lnL). For the "straight" GxE model, the minimized value of -2lnL in the full moderation model is compared with the -2lnL obtained in more restrictive moderator models to yield a likelihood-ratio χ^2 test for the significance of the moderator effects. Non-significant changes in chi-square indicate that the more restrictive model (i.e., that model with fewer parameters and thus more degrees of freedom) provides a better fit to

the data. The chi-square was then converted to the Bayesian Information Criterion (BIC) so as to measure model fit relative to parsimony. The lowest BIC among a series of nested models is considered best. BIC was used to determine the best-fitting model as it is one of the most commonly used indices within the field of behavioral genetics (Markon & Krueger, 2004) and because it weighs parsimony most heavily.

RESULTS

Descriptive Statistics

Sex. Overall levels of ADHD and self-blame and their relationship across sex and age were first examined. Mean levels of ADHD varied significantly across gender, such that boys had higher scores on the CBCL ADHD scale (*M*=3.4, *SD*=3.1) than did girls (*M*=2.9, *SD*=2.8). Boys also had significantly higher scores of self-blame (*M*=12.1, *SD*=3.3) than did girls (*M*=11.0. *SD*=2.7), even after controlling for levels of ADHD behaviors. Despite these mean differences, there was a significant and positive relationship between self-blame scores and ADHD for both boys and girls (boys r=.29, p<.001; girls r=.18, p=.02). Although the relationship appeared somewhat stronger for boys, the difference in the correlations was not statistically significant (Fisher z = 1.29, p=.19 two tailed).

Age. Bivariate correlations revealed a modest association between age and ADHD score (r = -.10, p=.04), such that ADHD behaviors generally decreased with age. In contrast, self-blame was not significantly related to age (r = -.07, p=.17). Importantly, however, the association between self-blame and ADHD remained moderate and significant across the age range of the sample (ages 5-7, r=.29, p<.01; ages 8=10, r=.20, p<.001; ages 11-13, r=.26, p<.001;

ages 14-16, r=.32, p<.001). These correlations were not statistically different from one another (all ps>.25).

Overall then, the associations between self-blame and ADHD behaviors appeared to be robust across both age and sex. It is thus thought to be unlikely that the moderation of ADHD by self-blame would be restricted to a particular age range or to one gender only. That said, however, the current sample size did not offer adequate power for examining latent estimates separately by sex or age. To adjust for potential differences in the moderation analyses, the transformed ADHD score was regressed on age and gender, a very common practice in the field of behavioral genetics (Burt, 2009; McGue & Bouchard, 1984). The residuals were then utilized in the moderation analyses that provided the central test of gene x environment interaction.

Intraclass Correlations

Intraclass correlations for the CBCL ADHD score were first compared across MZ and DZ pairs in order to gauge the relative influence of genetic and environmental influences for ADHD (see Table 9). For the overall sample, the MZ correlation was significantly greater than the DZ correlation. This difference is highly suggestive of genetic influences on ADHD. However, in order to assess potential etiological moderation of ADHD by self-blame, intraclass correlations at various levels of self-blame were also examined. To do so, analyses were restricted to those twin pairs who were concordant for moderator level (i.e., both twins were classified as either low, moderate, or high self-blame). Given this, the sample sizes are small relative to the overall sample. Of note, while this technique was necessary to examine potential moderating effects using intraclass correlations, the twins do <u>*not*</u> have to be concordant on value of the moderator when using structural equation modeling techniques in Mx (and thus the full sample was used for the final analyses).

Results indicate that when both twins reported low levels of self-blame, the MZ-DZ correlation difference, and thus the estimate of genetic influences, was large. As reports of self-blame increased to moderate and high, the DZ correlation dropped moderately, whereas the MZ correlation decreased substantially. The decreasing difference between the MZ and DZ correlations implies that genetic influences may decrease with increasing self-blame. Moreover, the decreasing MZ correlation also implies that non-shared environmental influences increase with increasing levels of self-blame. Such results collectively suggest that self-blame may indeed act to moderate genetic and environmental influences on ADHD.

"Straight" GxE Analyses

Test statistics for the "straight" GxE analyses are reported in Table 10. Results indicate that the linear moderation model best fit the data (as indicated by the non-significant change in χ^2 from the non-linear model, but the significant change in χ^2 as compared to the main effects model, as well as the lowest BIC value). Thus, self-blame appears to be a significant linear moderator of the genetic and environmental contributions to ADHD.

In order to examine the nature of this etiological moderation, we used the estimated paths and moderators from the best-fitting linear model (see Table 11) to calculate and plot the unstandardized genetic, shared, and non-shared environmental variance components at each level of self-blame. Unstandardized parameter estimates are favored here in order to examine the absolute (rather than proportional) shifts in each parameter across each level of the moderator (as recommended by Purcell, 2002). Figure 1 displays the unstandardized estimates of genetic, shared, and environmental variance components for ADHD at different levels of self-blame. As seen there, when self-blame scores are low, genetic influences on ADHD are quite large, with small to moderate contributions from the non-shared environment. Yet, as self-blame scores

increase, the absolute genetic variance appears to decline sharply, whereas the unique environmental variance appears to increase substantially. 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. In other words, increasing levels of self-blame appear to significantly decrease genetic contributions, while also increasing non-shared environmental contributions, to ADHD. Estimates of shared environmental contributions to ADHD were zero at all levels of self-blame.

GxE in the Presence of rGE

We next examined potential GxE effects while simultanesouly considering potential rGE confounds. As a reminder, in this model, the moderator (self-blame) is entered twice so that it can be examined as both a dependent variable *and* as a moderator. Moderation is estimated for the genetic and environmental overlap between self-blame and ADHD (i.e., the covariance paths) as well as for the genetic and environmental contributions to ADHD that do not overlap with those for self-blame. The key estimates of interest in the current study involve the latter (i.e., the unique variance estimates for ADHD as well as the moderation of those unique estimates). Examination of these parameters is crucial for determining if self-blame significantly moderates genetic and environmental influences on ADHD, even after accounting for the presence of possible rGE between self-blame and ADHD. Of note, unlike the former model, the GxE in the presence of rGE model only allows for linear moderation.

The full ACE GxE in the presence of rGE model provided an adequate fit to the data (-2lnL=2109.682, df=831, BIC = -1170.821), as indicated by the negative BIC value. The resultant path estimates and moderators for this model are presented in Table 12. As can be seen there, there was evidence of significant genetic covariance between self-blame and ADHD (.489,

p<.05). Such findings indicate that there is significant genetic overlap between self-blame and ADHD (i.e., rGE) which may be influencing the previously observed "GxE". In order to rule out this possibility, etiological moderation of that variance that is unique to ADHD was next examined (see Figure 2). Importantly, results are generally similar to those reported above. The shared environmental estimates again remained at zero for all levels of self-blame. Examination of the confidence intervals revealed significant contributions from both genetic and non-shared environmental factors to ADHD at low levels of self-blame. Moreover, genetic influences on ADHD decreased as reports of self-blame in relation to parents' martial disputes increased. Critically, however, the effect was clearly more muted than in the prior model (and was no longer significantly greater than zero, as seen by the non-significant A_1 value in Table 4). Most importantly, however, non-shared environmental influences on ADHD still appeared to increase substantially (and significantly so) with increasing levels of self-blame.

The lack of significant change in the estimates of genetic variance for ADHD deserves some additional comment. This difference may be due to differences in the absolute value of genetic variance in ADHD across the two models. As can be seen from Figures 2 and 3, the absolute level of genetic variance within ADHD appears to be smaller after accounting for genetic overlap between ADHD and self-blame (using a visual comparison only, since the two models are not nested and thus cannot be statistically compared). For example, at low levels of self-blame, the unstandardized or absolute genetic variance is .79 in the "straight" GxE model (which does not parse out the covariance between the moderator and the outcome), but only .41 in the model accounting for rGE effects. There thus appears to be some genetic overlap between self-blame and ADHD, a conclusion that is bolstered by the bivariate results reviewed above.

However, even when taking into account this genetic overlap, the moderation on the unique environmental effects for ADHD by self-blame remained significant.

Moreover, as can be seen in Figure 2, the shared environmental path estimates as well as moderation paths of the shared environmental variance unique to ADHD were all estimated to be zero. Thus, the rGE in the presence of GxE model was re-examined, fixing all the shared environmental paths (Cholesky elements as well as common and unique moderation paths) to zero. Fixing these paths resulted in a slight improvement in fit, as indicated by the more negative BIC value (-2lnL = 2119.733, df=836, BIC= -1179.328). Unsurprisingly, the moderation of E remained significant when C was constrained to be zero. However, moderation of the unique genetic variance in ADHD became statistically significant, results that are likely a function of the tightened confidence intervals following the dropping of five paths, especially given the small sample size. In any case, such results indicate that there may be some (albeit small-to-moderate) moderation of genetic effects on ADHD by self-blame even after controlling for rGE.

DISCUSSION

Along with strong estimates of genetic effects for ADHD, prior research has consistently demonstrated that the family environment, particularly children's appraisals of interparental conflict, remain important predictors of ADHD. One potential way of understanding environmental associations within the context of large genetic effects of ADHD may be via GxE effects. The aim of the current study was to investigate the potential etiological role of self-blame related to interparental conflict as a moderator of the genetic, shared, and non-shared environmental influences on ADHD. Two sets of moderator analyses were conducted. First, a "straight" GxE model was conducted that investigated potential moderation of genetic and

environmental influences for ADHD by level of self-blame, but did not consider possible rGE. Results indicated that non-shared environmental influences on ADHD significantly increase with higher levels of self-blame, while genetic influences on ADHD significantly decrease with increasing self-blame. A second moderator model was examined to clarify the role of rGE in the above findings, and in this way, confirm the results. As before, results indicated that the contribution of non-shared environmental factors to ADHD significantly and substantially increased with increasing levels of self-blame. There was also a simultaneous decrease in genetic contributions to the variance in ADHD with increasing levels of self-blame (although only significantly so when shared environmental effects were constrained to be zero). Overall then, these results indicate that non-shared environmental influences on ADHD increase, while genetic influences may decrease somewhat, with increasing levels of child self-blame regarding interparental conflict.

The notion of an environmental risk factor reducing genetic effects on ADHD stands in contrast to previous reports of GxE effects, which have reported increased risk for the disorder within particular environmental contexts (Todd & Neuman, 2007; Waldman et al., 2007). While these lines of research have examined different environmental moderators of genetic risk (e.g. prenatal alcohol and cigarette exposure, parental marital status), the findings have suggested stronger relationships between particular gene variants and ADHD in the high-risk environmental context. By contrast, the current results suggested lower genetic and higher unique environmental effects in the high-risk environmental context (e.g., high levels of self-blame). While it remains unclear what accounts for these discrepancies, one possibility is that this environmental risk factor simply functions differently than other risk factors. This possibility is bolstered by previous work on GxE in personality, which found that for some environmental

risk factors, higher levels of risk may actually attenuate as opposed to enhance genetic influences (Burt, 2008). That is, some environmental risk factors may act as "main effects" for psychopathology even without contributions from genetic factors. This may be particularly true for psychosocial risk factors, like self-blame, which likely reflect the proximal end result of multiple risk processes.

While these results require replication, the current project was strengthened by several factors. First, self-blame regarding interparental conflict was assessed from the child's perspective. This is advantageous both because the child's understanding of marital conflict is more predictive than parental report of marital conflict (as previously discussed), but also because the use of child self-reports for the moderator allowed us to circumvent shared informant variance (since we examined maternal-reports of ADHD). Moreover, because each child reported on his or her own self-blame, the moderator was free to vary across twins, allowing us to examine and control for possible rGE. As noted above, rGE remains a significant confound in GxE research as these effects can resemble GxE. The explicit examination of rGE provides additional assurances that the GxE effects observed here are "real" (or at least not due to rGE). Similar analyses would not be possible if only parent report were used, as it would not vary across twins. This represents an important step forward in behavioral genetic modeling of GxE effects.

Implications

The results of the current study demonstrate that as scores of self-blame increase, the genetic influences on ADHD appear to decrease somewhat. This finding suggests that the large genetic influences previously reported for ADHD may vary, at least somewhat, as a function of the level of environmental risk. One possible explanation for these findings is that genetic

effects are more likely to be expressed as main effects in the absence of environmental challenges (as discussed in Burt, 2008). In other words, genetic factors may make the greatest contribution to ADHD when environmental risk factors, like appraisals of self-blame, are low. This could have particular importance for molecular genetic investigations that are attempting to identify associations between DNA variants and ADHD. Furthermore, future molecular GxE investigations of ADHD may also benefit from examining the strength of association between genetic markers and ADHD in a low-risk environmental context.

Next, these results indicated a substantial increase in the non-shared environmental variance in ADHD with increasingly levels of self-blame, even when controlling for rGE. One possible explanation for this increase in non-shared environmental effects is that it may reflect an overall increase in the importance of unique environmental factors on ADHD. This idea does have some theoretical backing, as prior work examining the development of psychopathology has demonstrated that individual environmental risk factors are not as predictive of child psychopathology as are the aggregate of multiple environmental risk factors (Rutter, 1999). Thus, for ADHD, high levels of one environmental risk factor (cognitive appraisals of self-blame), may signal the presence of other child-specific environmental risk factors exerting main effects on ADHD. For example, youth reporting higher levels of self-blame may also experience greater conflict overall within the family as well as may experience more inconsistent discipline from parents, both of which have been linked to ADHD.

A second possible explanation for the increase in e^2 is that at high levels of self-blame, there are greater contributions from AxE interactions. As illustrated earlier, AxE interactions load on the unique environmental variance component (e^2). Thus, the increase in e^2 with higher levels of self-blame may indicate that there are additional child-specific interactional processes

that are influencing ADHD behaviors. This may make sense, given developmental and family process research demonstrating biological, psychological, and emotional changes in children who report high self-blame and threat in relation to their parents' marital conflict (Rhoades et al., 2008). For example, it may be that with higher levels of self-blame, children have increased problems with behavioral regulation, such that they have difficulties disengaging from the negative cognitive appraisals of blame, leading to greater symptoms of inattention. That is, youth who experience more negative cognitive appraisals may experience more difficulties with cognitive control and set-shifting abilities, which may emerge behaviorally as inattention. Furthermore, these cognitive appraisals may be influencing physiological responses to stress, including increased arousal and cortisol release, which then may result in greater symptoms of hyperactivity and impulsivity. Indeed, recent work has shown elevated stress responses (e.g., cortisol) in youth who presented with high distress levels while witnessing interparental conflict (Davies et al., 2008). While still preliminary, this work does suggest that cognitive appraisals of conflict may indeed influence biological mechanisms underlying ADHD (among other things), systems which should also be influenced by the child's genes. Given this, it may be that high appraisals of self-blame by one twin (but not the other) differentially activate only that particular twin's genes, thereby increasing the non-shared environmental variance within ADHD. Such processes would result in an increase in unique environmental influences on ADHD with higher levels of self-blame, which was in fact observed in the current study.

Limitations

There are some limitations of the current work that are important to note. The sample was underpowered to examine estimates of latent genetic and environmental influences by sex or by age. As a result, effects of sex and age were regressed out of ADHD prior to analysis (a

common practice in the field of behavioral genetics; Burt, 2009; McGue & Bouchard, 1984). Future work should seek to examine potential sex-specific and age-specific effects in a larger sample. Next, the study examined the DSM-oriented ADHD scale on the CBCL rather than DSM-IV symptoms of ADHD. While high scores on DSM ADHD scale have been shown to align with diagnosis of ADHD (Hudziak et al., 2004), the use of the CBCL scale did not allow us to examine ADHD symptom dimensions of inattention-disorganization and hyperactivity-impulsivity separately. Examination of each of the ADHD symptom dimensions as outcomes may be warranted, as work in behavioral genetics, neuroscience, and temperament have demonstrated that there may be important etiological differences between inattention and hyperactivity-impulsivity (Martel & Nigg, 2006; Nikolas & Burt, under review; Sonuga-Barke, 2005).

Lastly, this study relied in part on the GxE in the presence of rGE model advanced by Purcell (2002). The mathematical accuracy of this model has recently been questioned by Rathouz and colleagues (2008), who suggested that a correlated factors model was more appropriate for examining GxE in the presence of high levels of rGE (although this model has yet to be thoroughly tested). At this time, it remains unclear whether small-to-moderate levels of rGE (such as those examined here) also lead to mathematically imprecise GxE estimates (Rathouz, personal communication, July, 2009); future studies are planned to examine this possibility. Regardless, these results are not likely to be a function of any potential problems with the Purcell (2002) rGE model, as the conclusions extended to the univariate or "straight GxE" model results as well (which is not affected by the potential problems noted by Rathouz et al., 2008).

Conclusions

In sum, the data convincingly showed that negative cognitive appraisals (e.g. self-blame) made by children in relation to their parents' marital conflict enhanced non-shared environmental contributions but reduced genetic contributions to ADHD. Such findings not only support additional examinations of family factors as etiological moderators of ADHD, but also highlight the need for an evaluation of self-blame as a moderator of genetic risk in molecular genetic GxE studies of ADHD.

CHAPTER 4: GENE X ENVIRONEMTN INTERACTIONS FOR ADHD: SYNGERGISTIC EFFECT OF 5HTTLPR GENOTYPE AND YOUTH APPRAISALS OF MARITAL CONFLICT

Attention-deficit hyperactivity disorder (ADHD) is one of the most commonly diagnosed disorders or childhood, affecting anywhere between 3-10% of school-aged children. The behavioral symptoms of ADHD likely reflect the interplay of complex developmental processes involving both genetic liability and family environment factors that are believed to shape the gradual, yet staged development of emotional and behavioral regulation during early to middle childhood (Nigg, Hinshaw, & Huang-Pollock, 2006). Whereas the interplay of these processes is emphasized in theoretical work, prior work has often examined the main effects of genetic and environmental influences on ADHD separately. Yet, examination of *interactions* between specific genetic or biological contributors and family risk factors is sorely needed in order to test hypotheses regarding the roles of each in the development of ADHD via behavioral and emotional dysregulation in children.

Examination of gene x environment interactions (GxE) for ADHD provides one potentially fruitful method for testing hypotheses regarding current conceptualizations of the interplay of liability and environmental risk in the development of the disorder. GxE effects may be characterized as genetically-modulated individual differences in sensitivity to environmental risk factors, such that specific genetic variants exert risk for a disorder only in particular environments or after specific environmental exposures have occurred (Rutter & Silberg, 2002). Quantitative behavioral genetic research has consistently shown that genetic contributions to ADHD are moderate to large (Bergen, Gardner, & Kendler, 2007). The association of specific candidate genes with ADHD have been replicated in molecular genetic investigations (Faraone et

al., 2005; Gizer, Ficks, & Waldman, 2009), but effects account for only a small fraction of the heritable component. Importantly, theoretical work has suggested that the genetic and non-shared environmental variance components in traditional behavioral genetic models contain main effects as well as interactions (Purcell, 2002). Further, given that there are also many confirmed environmental risk factors for ADHD (Banerjee, Middleton, & Faraone, 2007; Nigg, 2006), the notion of GxE effects operating for ADHD is a compelling possibility (Pennington et al., 2009). The next steps then involve selection of specific genetic markers and specific family environment risk factors that may likely be operating synergistically in the development of behavioral and emotional regulatory capacities, deficiencies of which are believed to contribute to ADHD symptoms. Because of the hazards of arbitrary selection of variables, selection of the gene and environment variables to study depends heavily on theoretical as well as empirical considerations. Genes are considered first, followed by environments.

Selection of Candidate Gene for GxE in ADHD

Genes of the dopaminergic and noradrenergic neurotransmitter systems have received much attention due to the presumed centrality of the influence of psychostimulants and noradrenergic reuptake inhibitors on these systems (Spencer et al., 2000). However, they have been primarily associated theoretically with ADHD's cognitive and reward-processing elements, rather than emotional dysregulation (Nigg & Casey, 2006). Genes coding for proteins involved in emotional regulation and impulse control systems are needed to test an integrated regulation model of ADHD (Nigg & Casey, 2006; Nigg, Hinshaw, & Huang-Pollock, 2006). A particularly attractive neural system from this perspective is the serotonergic system. It has been hypothesized to play a role in ADHD via its global contribution to externalizing problems such as impulse control and aggressive behavior (Evans et al., 2000; Moffitt et al., 1998).

Furthermore, at the genetic level, the serotonin transporter gene (5HTT) is expressed in brain regions often implicated in emotion regulation, memory, attention, and motor control (Frankle et al., 2004). It is hypothesized that it plays a role in the development of emotional and behavioral regulation and for this reason will be relevant to GxE effects in ADHD.

The functional 44-bp promoter polymorphism of the serotonin transporter gene (5HTTLPR) has been frequently studied for psychiatric conditions as the "short" allelic variant results in reduced transcription efficiency and lower uptake activity (Lesch et al., 1996; Greenberg et al., 1999). In puzzling contrast, the "long" (or "high activity" allele) that has been associated with ADHD in case-control and within-family studies as well as in two meta-analytic investigations (Faraone et al., 2005; Gizer et al., 2009). Yet, Gizer and colleagues (2009) reported substantial heterogeneity in effect sizes across studies in their meta-analysis of main effect association between 5HTTLPR and ADHD.

One potential explanation for the heterogeneity in the mains effects of 5HTTLPR for ADHD is the presence of unmeasured environmental risk factors that may be serving to activate (or attenuate) the genetic association with the disorder. GxE investigations of 5HTTLPR have been encouraged by evidence that the genetic regulation of serotonin neurotransmission is sensitive to environmental context (Bennet et al., 2002; Manuck et al., 2004). In addition, genome-wide investigations of GxE interactions for ADHD found some suggestive evidence of an interaction between parental warmth and a SNP in the serotonin transporter gene ($p=0.008$) (Sonuga-Barke et al., 2008). Thus, 5HTTLPR may be particularly well-suited for investigation of GxE effects for ADHD.

Selection of Environmental Risk Factors for GxE

The only genome-wide association GxE study of ADHD suggested the serotonin transporter may interact with family distress measures (Songa-Barke et al., 2008). This is not surprising given that the development of emotional and behavioral regulation in children is dependent on a range variables related to the family environment. Familial conflict in particular has emerged as particularly good candidate domain, due to its high salience for children and findings that chronic emotional stress during development can alter cortical functioning (Arnsten & Goldman-Rakic, 1998). Family distress or conflict has been assessed in numerous ways over many decades of work. However, recent work consistently has emphasized the role of marital conflict in child adjustment, including ADHD and externalizing behavior problems (Buehler et al., 2007; Counts et al., 2005; Cummings & Davies, 1994; Gerard et al., 2005; Grych & Fincham, 1990; Grych et al., 2000; Jouriles et al., 2000; Skopp et al., 2005; Wymbs et al., 2008). Yet, the mechanism of this relationship is thought to depend on more than mere exposure to marital conflict but also on child liability and construal.

Grych and Fincham (1990) highlighted that the child's appraisals of marital conflict (and not just exposure) often play a determining role as to the effect of marital conflict on youth behavior problems. That is, the frequency of the conflict may not be as important for the development and persistence of attention and behavior problems as the extent to which children blame themselves or feel threatened by their parents' disagreements. In support of this view, youth reports of marital conflict have been shown to be more predictive of behavior problems than the parents' own report of their own marital conflict and satisfaction (Cummings, Davies, & Simpson, 1994; Grych, Seid, & Fincham, 1992). Furthermore, children's observed distress level while witnessing conflict has been especially associated with biological changes, including increased stress response (Davies et al., 2008) and alterations in parasympathetic nervous system

activity (El-Shiekh et al., 2009). Additionally, a recent meta-analysis found that along with physiological and emotional reactivity, cognitive appraisals of self-blame in regard to marital discord emerged as a particularly salient predictor of children's internalizing and externalizing problems (Rhoades, 2008). Thus, construals of self-blame in relation to marital conflict emerges from the literature as a particularly potent experiential moderator that may interplay with genetic liability in child dysregulation, and thus guided the hypothesis about how GxE may influence ADHD in the context of a dysregulation conception.

Additional Considerations: The Role of Serotonin in ADHD

Despite the appeal of 5HTTLPR and self blame as a model micro-system for examining inputs to regulatory problems and ADHD, the role of serotonin in the development of behavioral and emotional regulation in ADHD requires a bit more discussion due to complexities involved in the gene structure itself. First, while the "long" allele has been implicated in risk for ADHD, the "short" or "low-activity" allele of 5HTTLPR has been associated with numerous conditions often comorbid with ADHD including childhood disruptive behavior problems, persistent aggression, and DSM-IV Conduct Disorder (Beitchman et al., 2006; Hallikainen et al., 1999; Sakai et al., 2006). Secondly, studies of peripheral and central serotonergic functioning in children have produced somewhat contradictory results. Both low (Clarke et al., 1999; Flory et al., 2007; Kruesi et al., 1990; Kruesi et al., 1992) and high (Castellanos et al., 1994; Halperin et al., 1994; Stoff et al., 1992) serotonergic functioning have shown relationships with impulsivity and aggression in children with ADHD, whereas studies of animals and adult humans have implicated low serotonergic activity only for these behaviors (Coccaro et al., 1989; Manuck et al., 2002; O'Keane et al., 1992; Retz et al., 2004). Thus, there are surprisingly conflicting findings regarding the direction of association of serotonin activity and ADHD or related

behaviors. This gives pause in terms of the expectation of direction of effects and even the linearity of effects.

A further complexity is the recent discovery of an A>G substitution contained in a subset of the repeat sequences of 5HTTLPR. The A>G substitution has been shown to have functional significance, such that the long allele with the G substitution (Lg) functions similarly to the short allele (i.e., reduced transcription efficiency and decreased expression) (Hu et al., 2005; Kraft et al., 2005; Nakamura et al., 2000). This resultant triallelic model of 5HTTLPR failed to show association with ADHD (Wigg et al., 2006), yet the low functioning alleles (short and Lg) have been associated with conduct problems using case-control and within-family methods (Sakai et al., 2006).

A few potential explanations have been posited to account for these discrepant results. It has been suggested that 5HTTLPR may function differently for ADHD and cognitive impulsivity versus aggressive impulsivity (Oades et al., 2008). Further, differences in etiology of ADHD symptom dimensions of inattention and hyperactivity may be causing disparate results, such that 5HTTLPR may be associated with one symptom dimension but not the other (Nikolas & Burt, in press). Thus, examination of ADHD as a unidimensional construct as well as the two constituent symptom domains of inattention and hyperactivity-impulsivity may aid in clarification of these relationships.

However, another more provocative possibility suggested by the complex mix of prior findings is that both the high and low functioning 5HTTLPR genotypes confer risk for ADHD and related disruptive behaviors. Supporting this notion, the one prior study examining GxE interactions involving 5HTTLPR and ADHD found a main association effect with the more efficient “long” allele of 5HTTLPR (high serotonin transporter activity), yet an interaction with

psychosocial adversity with the low-efficiency "short" allele of 5HTTLPR (Retz et al., 2008). That is, it may be that optimal adjustment occurs at the mid-range of serotonergic transcription, and that at either extreme poor regulatory functioning can occur. This possibility has not been tested for main effects of 5HTTLPR or in studies of GxE effects involving 5HTTLPR.

The aim of the current study was to examine GxE effects for ADHD within the framework of a dysregulatory conception of ADHD, and thus focused specifically on examining a theoretically relevant interaction between the triallelic 5HTTLPR polymorphisms and youth perception of self-blame in relation to marital conflict. Given the mixed literature as to whether high or low serotonin activity would be a risk factor, the hypotheses included both linear models (that either low *or* high serotonin activity genotypes confer sensitivity to the psychosocial risk element) and a non-linear model (both low *and* high serotonin activity genotypes confer sensitivity to environmental risk, whereas moderate levels confer protection).

METHODS

Participants

Participants were 304 children and adolescents ages 6-18 years (M=14.04, SD=2.70, 56.6% male). The sample was recruited using mass mailings to parents in the local school districts, public advertisements, and outreach to local clinics in order to screen as broad of a range of volunteers as possible for the study. A multi-stage screening process was used to identify cases and non-cases meeting research criteria among those who volunteered. At stage 1, rule-outs were evaluated by a telephone screen (physical handicap, non-native English speaking, mental retardation, autistic disorder, and prescription of long-acting psychoactive medications; stimulant use was not a rule out). Families passed through the telephone screen were then invited to complete the stage 2 diagnostic screen. Informed consent was obtained from all participating

parents; children provided written assent. These studies were approved by the local Institutional Review Board[1].

For stage 2, parents and teachers completed normative behavioral rating scales, including (1) the Behavior Assessment Scale for Children (BASC; Reynolds & Kamphaus, 1992) (2) the Conners' (1997) Rating Scale-Revised short form (Conners, 1997), and (3) the DSM-IV ADHD Rating Scale (Du Paul et al., 1998). One parent (in most cases, the mother) completed the Kiddie Schedule for Affective Disorders and Schizophrenia-E (KSADS-E; Puig-Antich & Ryan, 1986) with a trained master's level clinical interviewer.

At stage 3, final eligibility and diagnostic assignment were made using a best-estimate procedure as follows. Data from the KSADS-E and the parent and teacher rating scales, along with interviewer notes and observations and history of medication use, was presented to a diagnostic team consisting of a board-certified child psychiatrist and a licensed child clinical psychologist. Both professionals arrived independently at a clinical decision regarding ADHD subtype and comorbid diagnoses. Agreement rates were acceptable for all diagnoses (all kappas >.89). In all cases of disagreement, consensus was able to be reached upon discussion.

Those youths with subthreshold ADHD (5 symptoms, N=10) or situational ADHD (n=6) were included for analysis of dimensional symptom scores. The final sample consisted of 137 non-ADHD participants, 151 ADHD participants (72 Primarily Inattentive Subtype, 1 Hyperactive-Impulsive Subtype, 78 Combined Subtype), and 16 subthreshold/situational.

Exclusionary Criteria. Youth were excluded if they had mental retardation (based on having a full-scale IQ <75), head injury with a loss of consciousness, a history of seizures as

[1] This study was funded by R01-MH070004 from the National Institutes of Mental Health to K. Friderici & J. Nigg.

ascertained by parent report, autistic or pervasive developmental disorder as reported by the parent, or KSADS-E diagnosis of current major depressive disorder (viewed as rendering ADHD symptom ratings difficult to evaluate), lifetime bipolar disorder, lifetime psychosis, or Tourette's syndrome.

Perception of Marital Conflict

To assess marital conflict, children and adolescents completed the Children's Perception of Marital Conflict scale (CPIC; Grych, Seid, & Fincham, 1992). Youth rated the 48 CPIC items on a three-point scale (1-3: true, sort of true, and false). Recent work has shown that the CPIC yields 4 factors, two of which capture children's appraisals of conflict (Nigg et al., 2009). The nine-item self-blame scale was the focus of analysis here because of previous work demonstrating the importance of the child's construals and appraisals of marital conflict in predicting externalizing behavior problems (Grych & Fincham, 1990). Sample items from the CPIC self-blame scale include "My parents usually argue about something that I do"; "It is usually my fault when my parents argue"; and "I am to blame when my parents argue." Internal consistency reliability for the nine-item self-blame scale was satisfactory (alpha=.83).

DNA Collection and Serotonin Transporter Genotyping

Overview. Buccal DNA samples were requested from all participating children and adolescents and purified using previously used methods (Meulenbelt et al., 1995).

Serotonin Transporter Promoter Polymorphisms. The 44-bp promoter polymorphism of the serotonin transporter gene (5HTTLPR) and the rs25531 A>G polymorphism were genotyped as follows. The "short and long" alleles of the 5HTTLPR were genotyped according to previous methodology [21] with the following modifications to the primer sets (5'-GACTGAGCTGGACAACCACG-3' and 5'-GGTTGCCGCTCTGAATGCCA-3'). Genomic

DNA (40 to 60 ng) was amplified using the *Taq* DNA Polymerase kit (Qiagen Inc., Valencia, CA), standard kit protocol, including 1.5 mM $MgCl_2$, 0.2 mM dNTPs, and 0.7 µM primer. Polymerase chain reaction (PCR) conditions consisted of an initial denaturing step at 95°C for 3 minutes, followed by 35 cycles of: 95°C denaturation for 30 seconds, 63°C annealing for 30 seconds, and an extension at 72°C for 45 seconds, followed by a final extension step of 4 minutes at 72°C. A portion of the amplified DNA was analyzed using a 2% agarose gel to determine the L/S alleles. The remainder of the amplification reaction was digested with *Msp*I endonuclease (New England Biolabs, Ipswich, MA) and examined by 3% agarose gel electrophoresis. The final products were (340, 120, and 64 bp) for (La), (174, 166, 120, and 64 bp) for (Lg), and 484 bp (short).

Based on previous work (Beitchman et al., 2006; Hu et al., 2005) individuals were assigned to the high, intermediate and low activity groups based on their genotypes. Those homozygous for the La allele were classified as "high'' 5HTTLPR activity (n=78). Those with the La/Lg or La/short genotypes were classified as "intermediate" 5HTTLPR activity (n=137). Individuals with Lg/Lg, Lg/short, or short/short genotypes were classified as "low" 5HTTLPR activity (n=89).

ADHD Symptom Outcome Measures

In order to examine effects at all levels of symptomatology and to avoid artifacts associated with examining GxE effects for categorical outcomes (Eaves, 2006), the use dimensional ratings of inattention and hyperactive behaviors were used as the primary outcome measures. The primary dependent measure was teacher-rated symptoms of ADHD for several reasons. First, it enabled complete disaggregation of the sources of data (which could be partially confounded if parent ratings of behavior are used, because parents who are distressed by marital

conflict may also inflate their ratings of child ADHD symptoms). Put another way, teacher ratings of child ADHD behaviors are unlikely to be directly influenced by inter-parental conflict in the home. Teacher reports of attention problems have also been cited as the most robust predictor of life outcomes when controlling for other environmental variables, including single parent status, socially disadvantaged community, parental education, and child IQ as well as disruptive and emotional behavior problems (Breslau et al., 2008; Breslau et al., 2009; Duncan et al., 2007).

To evaluate whether effects were robust to particular measurement approaches, both Teacher ADHD Rating Scale (Du Paul et al., 1998) and teacher report on the Conners' Rating Scale-Revised (Conners et al., 1997) were evaluated. Interactions were first examined for the total DSM-IV ADHD symptom score on the ADHD-Rating Scale (alpha=.88). In a Fisherian strategy (Keppel & Wickens, 2004), if that effect was significant, it was followed by examination of the symptom dimensions of inattention and hyperactivity-impulsivity separately (with p value of .025 as threshold for significance for each dimension in order to adjust for multiple comparisons).

The analyses were then reproduced using the Conners' Rating Scale ADHD Index as the outcome measure in order to provide a within-study replication of any significant findings. In a parallel approach, the Conners' ADHD Index was first examined, and if it was significant then again the Cognitive Problems and Hyperactivity scales were examined separately with the same p value correction as used for the ADHD rating scale (p=.025).

Statistical Analyses

Testing Gene –Environment Interplay for ADHD Symptoms. Prior to examining GxE effects, we first had to examine potential gene-environment correlation effects (rGE). The

presence of an underlying relationship between the genetic and environmental risk factors (e.g., 5HTTLPR and self-blame) can confound any test of GxE, as rGE effects can potentially emerge (falsely) as GxE. Thus, in order to examine this possibility, we first examined differences in reports of self-blame by level of 5HTTLPR genotype. Next, hierarchical linear regression analyses were used to examine potential gene x environment interactions for ADHD. As mentioned earlier, models examined both the linear effects of 5HTTLPR (i.e. that either low *or* high serotonin activity genotypes exert risk) and non-linear effects of 5HTTLPR (i.e. that both low *and* high serotonin activity genotypes exert risk). The interactions (linear x self-blame and non-linear x self-blame) were evaluated using the following orthogonal coding system. For the linear effects, high, intermediate, and low activity 5HTTLPR genotypes were coded as 1, 0, -1 respectively. For non-linear effects, high, intermediate, and low activity 5HTTLPR genotypes were coded -1, 2, -1, respectively.

RESULTS

Sample Characteristics.

Demographic and descriptive statistics of the children with non-intermediate diagnostic status are presented in Table 13. As expected, youth in the ADHD group were rated as having significantly more inattentive and hyperactive symptoms across informants and measurement method. The ADHD group was more predominately male and significantly younger than the non-ADHD group; thus age and gender were covaried in all models. Children in the ADHD group were also less likely to be living in two-parent households and their families had significantly lower annual incomes than the non-ADHD families.

Ethnicity and 5HTTLPR

There were no differences between the ADHD and non-ADHD group in terms of ethnicity. However, ethnic variation is a potentially important variable in genetic studies. Table 14 shows that there were significant differences in the distribution of 5HTTLPR alleles by ethnic group, such that the La and Lg alleles both occurred more frequently in African-American children than non-African-American children, indicating that genotyping the A>G substitution in 5HTTLPR is capturing some important differences among these groups (which is consistent with expectations from the literature, see Hu et al., 2005; Nakamura et al., 2000). Although ethnicity and ADHD were uncorrelated, as a precaution, ethnicity was covaried as follows. Ethnicity was first divided into three codes: (1) Caucasian versus non-Caucasian, (2) African-American versus non-African-American, and (3) Latino versus non-Latino. The three codes were then entered at step 1 of all regression models.

Simple Main Effects of 5HTTLPR on ADHD

Table 13 also includes the 5HTTLPR allele frequencies in the ADHD and non-ADHD groups. There were no significant differences in the distribution of 5HTTLPR alleles among ADHD and control youth (all $p>.25$). There were also no significant main effects of 5HTTLPR genotype when dimensional measures of ADHD were examined (see Table 15). As seen there, 5HTTLPR genotype was unrelated to ADHD and externalizing symptoms (KSADS-E) as well as scores on the ADHD Rating Scale and Conners' Rating Scale.

Test for Gene-Environment Correlation

Before examining interactions, the presence of a relationship between 5HTTLPR genotype and youth appraisals of self-blame was evaluated. There were no significant differences in reports of self-blame across the three genotype groups (p=.22), suggesting an absence of gene-environment correlation between 5HTTLPR genotype and children's report of

self-blame. This is extremely important as the lack of a correlation between this gene and this environmental measure signals that rGE effects are not likely to emerge as spurious interaction findings in the present analyses.

Main Analyses of GxE Interaction Effects

DSM-IV ADHD Symptoms

Total ADHD Score. Hierarchical linear regression analyses revealed a significant main effect of self-blame for ADHD [b=.14, 95% confidence interval .05-.21, p=.002, R^2=.28]. indicating an increase in total ADHD symptoms with higher reports of self-blame. The linear (low activity as risk) and non-linear (low and high activity as risk) main effects of 5HTTLPR genotype were nonsignificant as was the linear x self-blame interaction (all *p*s>.27). However, the non-linear x self-blame interaction was significant [b=.11, 95% confidence interval .01-.1214, p=.019, R^2=.31]. Examination of the simple slopes revealed that there was no relationship between ADHD symptoms and self-blame for those with the intermediate activity genotypes. In contrast, a significant and positive relationship between self-blame and ADHD emerged for those with the high (La/La) and low (Lg/Lg, Lg/short, short/short) activity genotypes (See Figure 3).

ADHD Symptom Dimensions. Next, the ADHD symptom dimensions of inattention and hyperactivity-impulsivity were examined separately. Teacher report of inattention symptoms on the ADHD Rating Scale revealed a significant main effect of self-blame [b=.14, 95% confidence interval .05-.23,p=.004, R^2=.14] and a significant 5HTTLPR non-linear x self-blame interaction [b=.09, 95% confidence interval .01-.14, p=.02, R^2=.17]. All other effects were non-significant (all p>.30). Examination of the simple slopes again revealed a significant positive relationship

between self-blame and inattention symptoms for those with the high (La/La) and low (Lg/Lg, Lg/short, short/short) activity 5HTTLPR genotypes, such that those reporting greater self-blame had increased inattentive symptoms in those genotype groups. There was no relationship between self-blame and inattentive symptoms for those in the intermediate activity 5HTTLPR genotype group (La/Lg, La/short - see Figure 3).

Examination of hyperactivity on the Teacher ADHD Rating Scale also revealed significant main effects of youth appraisals of self-blame [b=.30, 95% confidence interval .03-.57, p=.03, total R^2=.17]. The linear and non-linear main effects of 5HTTLPR genotype were nonsignificant (p>.15) as were the linear 5HTTLPR x self-blame interactions (all p>.26). The non-linear 5HTTLPR x self-blame interaction was just shy of the .025 correction for significance [b=.16, 95% confidence interval .02-.34, p=.03, total R^2=.21]. For completeness this marginal effect was also decomposed. The pattern of results was again the same, such that for those with the high and low functioning 5HTTLPR genotypes, there was a significant positive relationship between self-blame and hyperactivity (See Figure 3). However, for those in the intermediate activity genotype, there was no association of self blame with hyperactivity.

Replication of GxE Effects Using an Alternative Measure (Conners' Rating Scale)

Conners' ADHD Index. In order to check for false-positive results, I next attempted to replicate the non-linear 5HTTLPR x self-blame interactions using a separate but related measure of ADHD symptomatology, beginning with the omnibus Conners ADHD Index. Regression analyses again revealed a significant main effect of self-blame [b=.19, 95% confidence interval .08-.29, p=.003, R^2=.17]. The main effects of 5HTTLPR (both linear and non-linear) were again not significant nor was the linear 5HTTLPR x self-blame interaction (all *p*s>.28).

As before, the non-linear 5HTTLPR x self-blame interaction was significant [b=.17, 95% confidence interval .06-.24, p<.001, R^2=.25]. The pattern of results was again identical, such that scores on the ADHD Index increased with higher levels of self-blame, but only for those with the low and high serotonin activity genotypes (see Figure 2). Given this replication, results were then examined separately for the two ADHD symptom dimensions.

Cognitive Problems and Hyperactivity. The model predicting Cognitive Problems (analog to inattention) on the Teacher Conners' Rating Scale revealed a significant main effect of self-blame [b=.21, 95% confidence interval .09-.32, p<.001, R^2=.07]. There was no main effect of 5HTTLPR genotype group using either the linear (p=.29) or non-linear (p=.54) coding schemes. The linear x self-blame interaction was nonsignificant (*p*=.54). The non-linear x self-blame interaction was also non-significant [b=.07, 95% confidence interval -.01-.14, p=.08, R^2=.08] (see Figure 4).

Regression results for reports of hyperactivity on the Conners' Rating Scale, however, mirrored other results. The main effect of self-blame was again significant [b=.15, 95% confidence interval .05-.26, p=.005, total R^2=.15]. The linear and non-linear main effects of 5HTTLPR genotype were again nonsignificant as were the linear 5HTTLPR x self-blame interactions (all p>.26). As observed with the ADHD Rating Scale, the non-linear 5HTTLPR x self-blame interaction was again significant [b=.15, 95% confidence interval .08-.23, p<.001, total R^2=.20]. Examination of the simple slopes again revealed a similar pattern of results. For youth with the low and high activity serotonin genotypes, there was a significant and positive

relationship between self-blame and hyperactivity. Yet, there was no relationship between self-blame and ADHD for those with the intermediate serotonin activity genotypes (see Figure 4).

DISCUSSION

Prior work has demonstrated the potential relevance of both biological and family environmental factors in the development of emotional and behavioral regulation capabilities. In particular, serotonin genetic risk has been shown to a particularly important biological marker for the development of emotional and behavioral regulation whereas children's appraisals of blame in relation to their parents' martial conflict have been suggested as particularly salient environmental risk factor. The interplay of both biological and family environmental risk factors has been emphasized, and testing for potential GxE interactions provided a test of this hypothesis of interplay.

The results of the current study provide suggestive evidence of GxE effects for ADHD involving 5HTTLPR and youth appraisals of self-blame. Additionally, these analytic methods allowed for a test of a hypothesis previously untested at the genetic level – namely that both high and low serotonergic activity genotypes exert risk for ADHD symptoms. Findings from both the functional serotonin literature as well as from molecular genetic association studies have previously suggested that only one type of serotonergic activity (increased or reduced) is related to ADHD and other externalizing phenotypes, including impulsivity and aggression. These results suggest that perhaps at the genetic level, *both* high and low serotonergic activity genotypes exert risk and that these risk mechanisms are likely modulated by environmental stressors.

The results were strikingly consistent across measures and indicated significant non-linear 5HTTLPR x self-blame interactions for total ADHD symptoms as measured by both the

ADHD Rating Scale and the Conners'. The interactions revealed that youth appraisals of self-blame were significantly related to total ADHD symptoms for children with the low activity (Lg/Lg, Lg/short, short/short) and high activity (La/La) 5HTTLPR genotypes. For those with the intermediate activity genotypes, there was no relation between reports of self-blame and ADHD symptoms. The interactions were significant after including the covariates of age, gender, and ethnicity, and while taking into account potential main effects of 5HTTLPR genotype and youth reports of self-blame.

Analysis of the symptom dimensions revealed a more complex picture. After correcting for multiple comparisons, the non-linear 5HTTLPR x self-blame interaction was significant for inattentive symptoms (on the ADHD Rating Scale). Again, the same pattern of results emerged, such that the relationship between self-blame and inattention was significant only for those youth with the high and low serotonin activity genotypes. However, the attempt to replicate this effect using the Conners' Cognitive Problems scale did not yield a significant interaction. In contrast, the non-linear 5HTTLPR x self-blame interaction was not significant for DSM symptoms of hyperactivity, after correcting for multiple comparisons ($p=.03$). Interestingly, the replication attempt yielded a significant non-linear 5HTTLPR x self-blame interaction for Conners' Hyperactivity. Analysis of the interaction again revealed that for youth with the high and low serotonin activity genotypes, the relationship between self-blame and hyperactivity was positive and significant. Overall, the discrepant pattern of results that emerged in the symptom dimension analysis in combination with the strong results from the overall analysis suggest that the types of gene x environment interactions observed likely extend to ADHD symptoms generally and are not specific to either of the two behavioral dimensions of inattention or hyperactivity.

The overall results are also suggestive of a potential heterozygote advantage, which has been suggested as a potential explanation for some diseases, including mental disorders (Keller & Miller, 2006). Further, these results suggest that the interplay between serotonin activity and the family environment are important for the development of behavioral and emotional regulation capabilities as indicated by the behavioral symptoms of ADHD. Importantly, these results add to recent evidence that serotonin genetic risk as indexed by 5HTTLPR genotype and disruptions in the family environment interact together to predict deficits in behavioral and emotional regulation (Barry et al., 2008; Pauli-Pott et al., 2009).

With regard to the genetic literature for ADHD, these results failed to replicate a main effect of 5HTTLPR genotype with ADHD symptoms that has been previously reported (Kent et al., 2003; Manor et al., 2001; Seeger et al., 2001). Unlike these prior studies, however, the A>G substitution was also genotyped, however, which has been found to have functional significance, such that the "long" allele with the G substitution functions similarly to the "short" allele. Using this triallelic configuration of 5HTTLPR genotype, these results are consistent with those of Wigg and colleagues (2006) who found no main association effect with ADHD.

In regard to the functional serotonin literature, studies have found relationships between both high and low serotonin functioning and impulsivity and aggression ratings in children (Halperin et al., 1994). Results are consistent with the possibility that either extreme of serotonin functioning may exert risk for ADHD. One potential explanation that has been posited is that ADHD children with and without comorbid aggression differ in serotonin functioning. Thus, the discrepant results across studies may be due to the degree to which children have comorbid profiles. I undertook post-hoc analyses in order to examine whether co-occurring oppositional defiant disorder (ODD) symptoms and conduct disorder (CD) symptoms altered the results.

First, there were no significant differences in the distribution of genotype groups among those with ADHD alone and those with ADHD and comorbid ODD/CD (p=.41). Further, all non-linear 5HTTLPR x self-blame interactions remained significant after controlling for ODD and CD symptoms (all *p*s remained <.035), indicating that potential differences in the degree of externalizing comorbidity were not influencing the results.

Given the effects of selective serotonin reuptake inhibitor (SSRI) medications, I also checked whether a history of comorbid depression accounted for the results. When lifetime depression symptoms (as measured on the KSADS-E) were included as a covariate, the non-linear interaction terms remained significant (and resulted in an increase in the unstandardized regression coefficients). This may make sense, given that depression is often associated with only low serotonin activity and the non-linear model posited that both low and high serotonin activity genotypes would show the same relationship between self-blame and ADHD symptoms.

These findings also offer broader implications for genetic association studies of ADHD. These findings, like many of the recently published GxE studies for ADHD, have found that the relation between specific genetic markers and ADHD varies depending on particular environmental influences. These findings, coupled with previous work, suggest that the non-replications of genetic associations may be due in part to differing levels of exposure to various environmental risk factors across samples. While these findings require replication, they do indicate that exposure to stressful environments, such as exposure to inter-parental conflict during childhood and resultant negative cognitive appraisal of that stress (i.e. blaming one's self for the conflict) influences ADHD symptoms.

There are some limitations to this work that are important to note. First, parent DNA was not available for the majority of the sample, thus the use of family-based analyses was not

possible. While unlikely, population stratification effects cannot be ruled out. Second, because the sample is cross-sectional, the longitudinal relationships between appraisals of self-blame and ADHD symptoms cannot be examined. It may be the case that more frequent inter-parental conflict is the result of having a child with more severe ADHD symptoms and that over time, children view themselves (perhaps correctly) as being responsible for their parents' marital problems. As is always the case with single studies of genetic or environmental effects, the current findings may be false-positives. Thus, replication of these results in other samples is necessary.

Yet, the findings are consistent with prior functional work examining the role of serotonin the development of ADHD and several attempts were made to guard against false positive results. These included correction for multiple comparisons as well as replication of findings with an additional teacher-report measure of ADHD symptoms. While only examined one marker was examined, the findings suggest that children's report of self-blame in regard to their parents' marital conflict may represent one potential environmental moderator of the genetic risk for ADHD. These findings may then help inform future genome-wide association studies aiming to examine GxE interactions for ADHD. Moreover, the use of a candidate gene study here provides the opportunity to link and test a particular hypothesis regarding the etiology of ADHD, namely the role of serotonin activity in the etiology of ADHD. By focusing on a particular functional serotonin genetic marker (5HTTLPR), the current GxE study was able to integrate genetic, neurobiological, and psychological theories regarding the processes that underpin the development of behavioral and emotional regulatory abilities, which are often disrupted among individuals with ADHD. If this effect is confirmed, it may justify a more expensive GWAS study of this environmental moderator to identify other genes related to it.

Overall, the current study is among the first to examine relationships between 5HTTLPR and ADHD as well as interaction effects using the triallelic genotype configuration. While replication of these initial findings is certainly needed, these results suggest that both the low- and high-activity 5HTTLPR genotypes increase risk for ADHD symptoms within the context of higher levels of youth self-blame in relation to their parents' marital conflict.

CHAPTER 5: SUMMARY AND DISCUSSION

General Discussion

Within a developmental psychopathology framework, ADHD can be conceptualized as a result of exchanges between multiple genetic and environmental risk processes occurring throughout development (Rutter & Sroufe, 2000). Although behavioral genetic investigations have consistently demonstrated moderate to large genetic influences on ADHD (Bergen, Gardner, & Kendler, 2007; Burt, 2009), multiple environmental risk factors have also been identified for the disorder. Therefore, it appears that one potentially fruitful method for understanding the causal processes that give rise to ADHD involves examination of interplay between genetic and environmental factors. The current series of studies aimed to examine interactions between genetic and environmental risk factors (GxE) for ADHD using both behavioral and molecular genetic approaches.

Youth appraisals of self-blame in regard to their parents' martial conflict were selected as the key environmental variable in tests of GxE effects. As mentioned earlier, these appraisals have been repeatedly linked to measures of internalizing and externalizing behavior (Rhoades, 2008), and have been argued to represent a proximal set of processes by which marital conflict exerts influence on child behavior (Grych & Fincham, 1990). While child appraisals are likely influenced to some degree by genetic/constitutional factors (an intuition that is supported in these data; see Study 2), examination of GxE effects allowed for a direct investigation of the potential etiological role of self-blame in ADHD using two complimentary lines of investigation. Recent review of positive GxE effects in ADHD has been encouraging (Nigg, Nikolas, & Burt, under review), yet the implementation and concurrent examination of both behavioral and molecular

genetic tests of GxE effects for ADHD using the same moderator (e.g., self-blame) could provide confirming support of any positive findings and also aid in understanding the ways in which GxE processes may be operating for ADHD.

While prior work has demonstrated a link between appraisals of self-blame and behavior problems (Rhoades, 2008), recent factor analytic work has reliably identified four factors from the CPIC (Nigg et al., 2009). Yet, the phenotypic relationships among these newly-identified scales as well as their relationships with ADHD and other externalizing disorders have not been well-examined. In order to provide some guiding information regarding relationships among the scales at the phenotypic level, three main sets of analyses were conducted prior to the main tests of GxE effects. These analyses aimed to (1) examine the psychometric properties of these scales across a wide age range, (2) to quantify the strength of relationships among the CPIC scales to determine if higher reports of conflict correspond with higher reports of self-blame, and (3) to determine if relationships among the CPIC scales are specific to ADHD or if they related to externalizing behaviors more generally.

Summary of Results from Study 1. Results of the phenotypic analyses in Study 1 revealed that, in general, the four factors of the CPIC demonstrated adequate internal consistency across the wide age range of the twin sample. Additionally, while all the scales were generally positively correlated with one another, Self-Blame evidenced only a modest association with Conflict Properties. These results indicated that higher levels of frequency and intensity of marital conflict (as reported by the child) do not necessarily correspond with higher levels of self-blame. Lastly, both Self-Blame and Triangulation/Stability appeared to both be positively associated with ADHD and other externalizing behaviors, including ODD and CD. Yet, when

taking into account the covariance among ADHD, ODD, and CD, only Self-Blame remained a significant and unique predictor of both ADHD and CD.

While self-blame might at first seem to be linked more to internalizing behaviors (e.g., depression, anxiety), the results of Study 1 are in line with past work indicating that self-blame shows a generally stronger relationship with externalizing problems in children (Fosco & Grych, 2008; Grych, Harold, & Miles, 2003; Rhoades, 2008). While the mechanisms underlying this relationship remain unknown, some have postulated that children who blame themselves for their parents' conflict may be more likely to act out as a way of re-directing the focus of the conflict back upon themselves, and thereby relieving distress associated with observing conflict (Fosco & Grych, 2008). While more work is needed, particularly longitudinal studies of the relationships between youth appraisals of self-blame and later behavior problems, the results of Study 1 indicate a significant relationship between self-blame and ADHD.

Tests of GxE Effects. Studies 2 and 3 then proceeded to examine self-blame as a potential moderator of genetic (and environmental) influences on ADHD. Study 2 made use of biometric twin models in order to examine moderation of etiological contributors at the latent level, whereas Study 3 examined interactions with a specific candidate marker, the promoter polymorphism of the serotonin transporter gene (5HTTLPR). Results of both studies provided evidence of significant GxE effects for ADHD involving self-blame. Study 2 results indicated significant moderation of latent genetic and environmental influences on ADHD. When levels of self-blame were low, the contribution of genetic factors to ADHD was high, whereas unique environmental influences were low and shared environmental effects were zero. Importantly, as reports of self-blame increased, genetic effects significantly decreased whereas unique environmental contributions increased substantially. A crucial component of the biometric

models implemented in Study 2 is that they allowed for a direct test of genetic overlap between self-blame and ADHD and thus provided a measure of potential confounding effects of gene-environment correlation (rGE). Indeed, the genetic covariance between self-blame and ADHD was significant, indicating that rGE effects may be operating between self-blame and ADHD (i.e., similar genes are contributing to both self-blame and ADHD). Yet, even after controlling for this overlap, significant increases in unique environmental influences for ADHD were still observed with higher levels of self-blame.

Whereas Study 2 examined potential shifts in latent genetic and environmental contributions to ADHD with varying levels of self-blame, Study 3 investigated interactions between 5HTTLPR and self-blame within a clinically-diagnosed sample of ADHD youth. Genes from the dopamine and norephinephrine transmission systems have been more commonly-examined candidates for association with ADHD based on prior work involving the effects of psychostimulants on these systems. However, selection of 5HTTLPR was based upon an integrated theoretical model of ADHD, which postulates that the behavioral symptoms of the disorder are due to deficits in behavioral and emotion regulation abilities, underpinned by frontal-limbic circuitry (Nigg & Casey, 2006). Furthermore, 5HTTLPR has been shown to be a functional polymorphism that is sensitive to environmental context (Lesch et al., 1996; Manuck et al., 2004) and prior meta-analytic work has shown evidence of association with ADHD (Faraone et al., 2005; Gizer, Ficks, & Waldman, 2009).

Importantly, however, the relationship between serotonin functioning and ADHD remains somewhat unclear as both high and low serotonin activity has been associated with impulsive and aggressive behavior in children with ADHD (Castellanos et al., 1993; Halperin et al., 1994, 1997). Thus, tests for GxE effects examined two potential models of association.

These included (1) linear GxE interactions, which presume that only low *or* high serotonergic functioning is associated with ADHD, and (2) non-linear GxE interactions, which presume that both low *and* high serotonergic functioning are associated with the disorder. The latter model is consistent with the notion that optimal functioning may occur at the mid-range of serotonin functioning associated with the heterozygote genotype, a phenomenon called heterozygote advantage, which has been noted for other disease models.

Results of Study 3 indicated significant non-linear 5HTTLPR x self-blame interactions predicting teacher reports of total ADHD symptoms. That is, for youth with the low functioning and high activity 5HTTLPR genotypes, there was a significant and positive relationship between self-blame and ADHD symptoms. Yet, for those with the intermediate functioning 5HTTLPR genotype, there was no relationship between self-blame and ADHD symptoms. Of note, findings for total ADHD symptoms were observed for two separate measures of ADHD symptomatology. These included a DSM-based measure, the ADHD Rating Scale, as well as the Conners' Rating Scale. Findings also remained significant after controlling for gender, age, and ethnicity, as well as the main effects of 5HTTLPR and self-blame. Furthermore, interactions remained significant after controlling for potential confounds of comorbid psychopathology, including ODD, CD, and major depressive disorder.

The use of ratings of ADHD symptoms in Study 3 also allowed for separate examination of the inattention and hyperactivity symptom dimensions. Meta-analytic work has indicated that the genetic etiology of the two symptom dimensions may differ (Nikolas & Burt, in press). Examination across two separate measures of each dimension however did not reveal a consistent pattern of association. Significant interactions were observed for inattention and hyperactivity symptoms on the ADHD Rating Scale, although the interaction predicting

hyperactivity did not survive correction for multiple tests. Conversely, the interaction predicting Cognitive Problems (e.g., Inattention) on the Conners' Rating Scale was not significant, whereas the interaction predicting Hyperactivity remained significant after correction. Thus, the interactions appear to generalize to the combined symptom dimensions of inattention and hyperactivity, indicating that 5HTTLPR may represent a general genetic risk factor for ADHD.

Integration of GxE Results

Studies 2 and 3 both provided evidence of significant GxE effects on ADHD utilizing two complimentary methodologies across two different samples (community-based twin sample and clinically-diagnosed ADHD sample). Positive findings from both studies thus provide good initial evidence that self-blame may have an important etiological role in ADHD. However, integration of the results from each line of inquiry remains necessary for understanding how GxE processes may be operating more generally for the disorder.

Study 2 indicated that genetic influences on ADHD were highest at low levels of self-blame. In other words, reports of higher levels of self-blame may be reducing genetic effects for the disorder. At first, this may appear to stand in contrast to Study 3, which demonstrated a positive association between self-blame and ADHD for those with low and high activity 5HTTLPR genotypes. Importantly, however, results from Study 2 indicate that while genetic influences on ADHD decline with increases in self-blame, they were still significantly greater than zero at the highest levels of self-blame. That is, while overall genetic influences decreased with higher self-blame, there were still significant genetic contributions to ADHD within this high risk environmental context. Thus, while genetic influences may be smaller in magnitude at higher levels of self-blame, 5HTTLPR may be one of the genetic factors that exert influence on ADHD within the context of high levels of environmental risk.

While a decline in genetic influences on ADHD was observed with higher levels of self-blame, the increase in unique environmental contributions to ADHD was substantial and independent of rGE effects. This increase in e^2 may reflect an increase in contributions from the main effects of child-specific environmental risk factors. That is, reports of self-blame may signal the presence of other child-specific environmental risk factors exerting main effects on ADHD. Additionally, the observed increase in unique environmental contributors to ADHD may also reflect an increase in contributions from gene x non-shared, or AxE interactions, which have been shown to contribute to the non-shared environmental variance in behavioral genetic models (Purcell, 2002). Increases in self-blame may be signaling the presence of other child-specific environmental risk processes (e.g., family conflict, parental discipline), which are then, in turn, also interacting with genetic influences on ADHD. That is, the high-risk environmental context associated with higher reports of self-blame may reflect increases in the contribution from exchanges between genetic and child-specific environmental factors. In other words, high levels of self-blame may serve to signal the presence of multiple AxE interactions that contribute to ADHD. Indeed, Study 2 revealed that self-blame, while partially influenced by genetic factors (a^2=23%), was primarily influenced by child-specific environmental risk factors (e^2=77%). Thus, the interactions observed in Study 3 between 5HTTLPR genotype and self-blame may be characterized as AxE interactions, which would then correspond with the increase in E observed with higher levels of self-blame in Study 2.

Implications

Understanding the Genetic Etiology of ADHD. Previous work examining GxE interactions for ADHD has primarily relied on molecular genetic approaches, which have examined the statistical interactions between specific DNA polymorphisms and environmental

risk factors that have been previously associated with ADHD (e.g., DAT1 VNTR genotype and prenatal cigarette exposure). Yet, findings of positive GxE effects on ADHD involving self-blame in the current project emerged using both behavioral genetic methodology, which examined shifts in latent genetic and environmental contributions to the disorder, as well as with molecular genetic approaches. Thus, both approaches provide complimentary lines of evidence suggesting that self-blame may indeed play an etiological role in ADHD. This work thus extends beyond prior reports of correlational relationships between self-blame and child behavior problems and provides some initial evidence that self-blame may serve to moderate genetic influences on ADHD.

Findings from the current project are in line with a recent review of initial work examining GxE effects on ADHD, which has indicated mostly consistent moderating effects of post-natal environmental risk factors on genetic risk for ADHD (Nigg, Nikolas, & Burt, under review). This stands in contrast to GxE studies examining pre-or perinatal risk factors, such as prenatal cigarette and alcohol exposure and low birth weight, which have shown less consistent positive findings. In particular, variables relating to the family context, including parental discipline, parental education, marital stability, and psychosocial adversity (conceptualized broadly via measures of family stress, SES, and parental psychopathology) appear to moderate the association between a variety of candidate genes and ADHD. Results from the current set of studies provide additional evidence of the importance of the family environment for shaping the development of behavioral and emotional regulation capabilities in children (Nigg, Hinshaw, & Huang-Pollock, 2006). Further, this work, combined with previous reports, indicates that the quality of the family environment may in fact play an important role in shaping the genetic etiology of ADHD by moderating the influence of a variety of candidate genes. Thus, the family

environment may effectively turn "on and off" the association between candidate genes from the catecholamine and serotonin neurotransmission systems and ADHD as children develop.

Additionally, the emergence of positive GxE effects in both Studies 2 and 3 may have crucial implications for future work aiming to identify the numerous genetic markers that are likely involved in the etiology of ADHD. First, positive GxE effects indicate differential association between candidate genes and ADHD at various levels of environmental risk. That said, the presence of GxE effects may be partially responsible for the numerous non-replications in ADHD molecular genetic research (as well as for other phenotypes). Therefore, the search for genetic factors operating for ADHD may be improved by considering the heterogeneity of the environment, particularly the family environment, in order to obtain a clearer signal of association. Understanding the ways in which particular genetic risk factors operate may thus be enhanced by examination of association among probands that have common environmental characteristics (in addition to a more homogenous phenotype as suggested by Todd et al., 2001).

Enhanced Versus Reduced Genetic Influences on ADHD. The results of Study 2 suggest that genetic effects for ADHD may be attenuated as opposed to enhanced within the high-risk environmental context, which stands in contrast to previous GxE work for ADHD. While this phenomenon of reduced genetic influence within a risk environment has been observed for other phenotypes, including IQ, personality, and reading disorder (Burt, 2008; Pennington et al., 2009; Turkheimer et al., 2003), the notion of reduced genetic expression within a high-risk environment has not been advanced for ADHD. It may be the case that certain types of environments "override" genetic influences for ADHD. That is, perhaps certain family environments serve to enhance ADHD symptoms for a wide-range of genetic vulnerabilities, causing the environment to appear to exert a type of "main effect." Alternatively, an increase in

the variance due to the non-shared environment may also be due to additional AxE interactional processes which are subsumed in the variance due to this 'main environmental effect.' Thus, while the models may suggest different processes at first (i.e., enhanced versus attenuated genetic risk in the high-risk environment), consideration of the impact of AxE interactions may serve to integrate the two process models.

Pennington and colleagues (2009) described these processes as bioecological GxE effects and diathesis-stress GxE effects. They argue that for some disorders, the high-risk environment "turns on" genetic influences, which would be consistent with the traditional diathesis-stress framework of the development of psychopathology. In contrast, the bioecological model of GxE effects posits that genetic influences express their wide range of influence with the low-risk environmental context. Increases in environmental risk thus serve to depress genetic influences. Importantly, the authors argue that disorders may be defined by one type of process and suggest that GxE effects for ADHD are operating via a diathesis-stress process, whereas GxE effects for reading disorder are operating via a bioecological process.

While Pennington et al. (2009) initial analyses support this type of model (i.e., a specific GxE process for each disorder), they also examined only one type of moderator (e.g., parental education). Results from the current study suggest that different environmental moderators (as opposed to overall disorders) may operate via both diathesis-stress and bioecological processes. In other words, it may be the case that some environmental risk factors serve to activate some genetic effects (and reduce others) and other environmental risk factors may serve to reduce some genetic influences (but enhance others). While this idea is only a hypothesis and remains to be tested, it allows for the possibility that different environmental risk factors may operate differentially over time, either serving to enhance or reduce genetic influence for ADHD.

Furthermore, it allows for the possibility of interactional processes with the environment both when overall estimates of genetic influence are high (e.g., a^2 contains variance due to genetic main effects and due to AxC interactions), as well as when genetic influences are lower and unique environmental effects are high (e.g., e^2 contains variance due to non-shared environmental main effects and AxE interactions). Importantly however, these ideas remain speculative and further examination of latent G x measured E interactions will be crucial for gaining a greater understanding as to the type of interactional processes that are occurring for ADHD as well as for other types of psychopathology.

Appraisals of the Environment as an Etiological Mechanism. The current projects provided some evidence suggesting a role for appraisals of self-blame in the causal processes that give rise to ADHD. These findings add support to Grych and Fincham's (1990) argument for the cognitive-contextual framework, which posits that children's understanding of conflict and the ways in which they attribute meaning to those experiences are what determines the impact of conflict on behavior. That is, the objective presence of conflict does not seem to be as important to the etiology of behavior problems as is the interpretation and attribution of the conflict. Results of the current study indicated that while appraisals of self-blame were partially influenced by genetic factors, the remaining variance was due to non-shared environmental factors. In other words, appraisals of self-blame appear to be a child-specific as opposed to a family-wide environmental risk factor that serves to create differences among siblings, even when they are likely exposed to similar environmental contexts.

Similar findings have also emerged for different types of "environmental" processes, such as stressful life events. Caspi and colleagues (2003) influential GxE investigation found that genetic risk for depression was enhanced by the presence of multiple stressful life events.

Yet, further examination of these events determined that, like self-blame, they are partially influenced by genetic factors (Kendler & Baker, 2007). That is, stressful life events are not random but tend to occur more commonly in people that are already genetically vulnerable for developing depression (Kendler et al., 1995; Jaffee & Price, 2007; Silberg et al., 1999). Recent work has also indicated that the number of events may not be as important for understanding the potential etiological role as is the perception of distress associated with the events (Monroe & Reid, 2008). Thus, appraisals of the situation (e.g., how stressful is the event, how much does one blame themselves for their parents' marital conflict) may be the key mechanisms by which environmental contexts exert their risk on the etiology of psychopathology (e.g., by serving to turn genetic risk on and off). Furthermore, these processes may serve as an entry point for interventions. Cognitive-behavioral interventions that may serve to reduce the negative attributions and resultant negative affect (e.g, via cognitive restructuring) associated with these risk factors may aid in serving to reduce genetic vulnerability for the development and perhaps the maintenance of psychopathology.

Limitations

There are some limitations to the current work that are important to note. First, both samples were cross-sectional and thus the longitudinal relationships between conflict, appraisals of self-blame, and ADHD behaviors could not be determined. Secondly, the size of the twin sample did not permit the examination of separate estimates by sex or by age. As prior work indicates that ADHD behaviors vary in both mean levels and variance by sex and by age, these will be important considerations in future GxE studies of ADHD. Furthermore, the twin sample relied on the CBCL and thus separate examination of moderation for inattention and hyperactivity was not possible. Future work investigating GxE effects for each of the symptom

dimensions will likely be valuable for considering what risk processes are common to both as to which processes may be unique to either inattention or hyperactivity.

The molecular genetic GxE study relied on case-control data from a single marker (5HTTLPR). While results were robust to measure and survived correction for multiple tests, the chance of false positive data in molecular studies remains high, as each marker likely only accounts for a small proportion of the variance in ADHD. However, steps were taken to guard against false positive results including the use of two dimensional measures for replication effects as well as correction for multiple tests. Additionally, because the data were case-control, population stratification effects, while unlikely, cannot be fully ruled out.

Overall Conclusion

Overall, the current project replicated prior work demonstrating a significant link between appraisals of self-blame and ADHD. Yet, examination of GxE effects using both behavioral and molecular genetic approaches took this link one step further by investigating a potential etiological role of self-blame in ADHD. The results indicated that self-blame may moderate genetic influences on ADHD. Examination of GxE effects using a behavioral genetics approach indicated a substantial increase in non-shared environmental influences on ADHD with increases in self-blame, a finding that remained when accounting for potential gene-environment correlation. Furthermore, investigation of specific interactions involving 5HTTLPR and self-blame revealed that self-blame and ADHD were only significantly related for individuals with low and high 5HTTLPR activity genotypes. Both GxE investigations taken together suggest an increase in the potential importance of genetic x non-shared (or AxE) interactional processes on ADHD within a high-risk environmental context. These results are also consistent with a developmental psychopathology conceptualization of the etiology of ADHD and point to the

potential utility of future investigations of the exchanges between genetic and environmental risk processes in order to understand the mechanisms that give rise to psychopathology.

APPENDICES: TABLES AND FIGURES

Table 1. Internal Consistency Estimates of Four CPIC Factors across the Age Range.

Scale	Overall α	5-7	8-10	11-13	14-16
Conflict Properties	.82	.66	.79	.88	.90
Triangulation/Stability	.88	.84	.87	.87	.91
Self-Blame	.85	.81	.83	.86	.87
Threat	.84	.77	.80	.87	.85

Note. Conflict Properties scale (n=11 items); Triangulation/Stability scale (n=13 items); Self-Blame scale (n=9 items); Threat scale (n=6 items).

Table 2. Bivariate Correlations among CPIC Factors and Externalizing Behaviors – Full Sample

	CP	TS	SB	TH	ADHD	ODD	CD
CP	1.0						
TS	.59**	1.0					
SB	.21**	.36**	1.0				
TH	.40**	.47**	.16*	1.0			
ADHD	.17**	.23**	.25**	.04	1.0		
ODD	.10*	.15**	.16**	-.04	.51**	1.0	
CD	.10*	.19**	.28**	-.06	.54**	.69**	1.0

Note. CP=Conflict Properties, Triangulation/Stability, SB=Self-Blame, TH=Threat, ADHD=DSM oriented CBCL raw score, ODD=DSM oriented CBCL raw score, CD=DSM oriented CBCL raw score.
* $p<.05$, ** $p<.01$

Table 3. Bivariate Correlations among CPIC Factors and Externalizing Behaviors – Ages 5-7 (n=33 twin pairs).

	CP	TS	SB	TH	ADHD	ODD	CD
CP	1.0						
TS	.41**	1.0					
SB	.03	.57**	1.0				
TH	.45**	.48**	.16*	1.0			
ADHD	.09	.29**	.29**	- .04	1.0		
ODD	-.28*	.05	.25**	-.21	.50**	1.0	
CD	-.33 *	.06	.32**	-.13	.42**	.74**	1.0

Note. CP=Conflict Properties, Triangulation/Stability, SB=Self-Blame, TH=Threat, ADHD=DSM oriented CBCL raw score, ODD=DSM oriented CBCL raw score, CD=DSM oriented CBCL raw score.
* $p<.05$, ** $p<.01$

Table 4. Bivariate Correlations among CPIC Factors and Externalizing Behaviors – Ages 8-10 (n=81 twin pairs).

	CP	TS	SB	TH	ADHD	ODD	CD
CP	1.0						
TS	.61**	1.0					
SB	.27**	.32**	1.0				
TH	.34**	.41**	.21**	1.0			
ADHD	.18*	.13	.20**	.08	1.0		
ODD	.17*	.12	.08	.04	.46**	1.0	
CD	.13	.07	.20**	-.08	.57**	.65**	1.0

Note. CP=Conflict Properties, Triangulation/Stability, SB=Self-Blame, TH=Threat, ADHD=DSM oriented CBCL raw score, ODD=DSM oriented CBCL raw score, CD=DSM oriented CBCL raw score.
* $p<.05$, ** $p<.01$

Table 5. Bivariate Correlations among CPIC Factors and Externalizing Behaviors – Ages 11-13 (n=68 twin pairs).

	CP	TS	SB	TH	ADHD	ODD	CD
CP	1.0						
TS	.77**	1.0					
SB	.21*	.23**	1.0				
TH	.52**	.59**	.14	1.0			
ADHD	.16	.23*	.26**	.03	1.0		
ODD	.17*	.17*	.29**	.01	.50**	1.0	
CD	.22*	.25*	.33**	.06	.51**	.64**	1.0

Note. CP=Conflict Properties, Triangulation/Stability, SB=Self-Blame, TH=Threat, ADHD=DSM oriented CBCL raw score, ODD=DSM oriented CBCL raw score, CD=DSM oriented CBCL raw score.
* $p<.05$, ** $p<.01$

Table 6. Bivariate Correlations among CPIC Factors and Externalizing Behaviors – Ages 14-16 (n=32 twin pairs).

	CP	TS	SB	TH	ADHD	ODD	CD
CP	1.0						
TS	.47**	1.0					
SB	.30*	.35**	1.0				
TH	.23	.31*	.12	1.0			
ADHD	.25*	.33**	.32**	- .16	1.0		
ODD	.16	.32**	.08	- .12	.69**	1.0	
CD	.24	.47**	.27*	-.09	.73**	.82**	1.0

Note. CP=Conflict Properties, Triangulation/Stability, SB=Self-Blame, TH=Threat, ADHD=DSM oriented CBCL raw score, ODD=DSM oriented CBCL raw score, CD=DSM oriented CBCL raw score.
* $p<.05$, ** $p<.01$

Table 7. Hierarchical linear models examining CPIC factors as predictors of ADHD, ODD, and CD behaviors among 5-17 year old twins.

Scale	*Estimate*	*Std Error*	*t*	*p*
Outcome: ADHD Scale				
Conflict Properties	.05	.04	1.4	.16
Triangulation/Stability	.08	.03	2.4	.02*
Self-Blame	.19	.05	3.8	<.001*
Threat	-.10	.06	-1.8	.073
Outcome: ODD Scale				
Conflict Properties	.02	.02	.88	.38
Triangulation/Stability	.06	.02	2.3	.03*
Self-Blame	.08	.03	2.4	.02*
Threat	-.12	.04	-2.7	.007*
Outcome: CD Scale				
Conflict Properties	.01	.03	.32	.75
Triangulation/Stability	.10	.03	2.9	.004*
Self-Blame	.23	.05	4.9	<.001*
Threat	-.20	.06	-3.5	.001*

Note. Age and gender covaried in all models. * indicates significance at $p<.05$.

Table 8. Hierarchical linear models examining CPIC factors as predictors of ADHD, ODD, and CD behaviors among 5-17 year old twins: Specificity of relationships.

Scale	***Estimate***	***Std Error***	***t***	***p***
Outcome: ADHD Scale				
Conflict Properties	.04	.03	1.4	.17
Triangulation/Stability	.03	.03	.89	.37
Self-Blame	.08	.04	1.9	.05*
Threat	-.02	.05	-.17	.72
ODD	.38	.08	4.8	<.001*
CD	.32	.06	5.6	<.001*
Outcome: ODD Scale				
Conflict Properties	.02	.04	.51	.61
Triangulation/Stability	.01	.05	.16	.88
Self-Blame	-.06	.03	-1.5	.13
Threat	-.01	.04	-.28	.78
ADHD	.20	.04	4.8	<.001*
CD	.60	.04	14.1	<.001*
Outcome: CD Scale				
Conflict Properties	-.02	.04	.61	.54
Triangulation/Stability	.07	.04	1.6	.11
Self-Blame	.12	.04	3.2	.001*
Threat	-.09	.04	-2.2	.03*
ADHD	.22	.04	5.6	<.001*
ODD	.54	.04	14.2	<.001*

Note. Age and gender covaried in all models. * indicates significance at $p<.05$.

Table 9. Twin Intraclass Correlations for Mother-Rated CBCL ADHD Score: Overall and by level of CPIC Self-Blame.

	MZ	DZ
ADHD Score	.55**	.15*
CPIC Self-Blame: LOW (N=66)	.80**	.21*
CPIC Self-Blame: MODERATE (N=24)	.52*	.04
CPIC Self-Blame: HIGH (N=36)	.10	.01

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

Table 10. Fit statistics for nested "straight" GxE models.

	-2lnL	df	$\Delta\chi^2$	Δdf	p	BIC
Non-Linear Model	1143.019	413	NA	NA	NA	-534.626
Linear Model	**1143.604**	**416**	**.585**	**3**	**.90**	**-550.374**
Main Effects Model	1154.187	419	10.58	3	.014	-542.368

Note. In the main effects model, genetic, shared, and non-shared environmental parameter estimates do *not* vary by self-blame. In the linear model, genetic and environmental parameter estimates vary linearly. In the non-linear model, parameter estimates vary linearly and quadratically. Each model is compared with the preceding model when calculating the change in χ^2 and degrees of freedom. Non-significant changes in chi-square indicate that the more restrictive model (i.e., that model with fewer estimated parameters and therefore more degrees of freedom) provides a better fit to the data. Lower or more negative values of BIC also indicate the best-fitting model. By these criteria, the linear moderation model fit the data best.

Table 11.Unstandardized path and moderator estimates in the best-fitting "Straight" GxE model.

PATHS			**LINEAR**			**QUADRATIC**		
a	c	e	A_1	C_1	E_1	A_2	C_2	E_2
ADHD								
.890*	.000	.468*	-.188*	.000	.184*	----	----	----
(.634, 1.07)	(-.546, .546)	(.323, .673)	(-.369, -.013)	(-.354, .354)	(.043, .301)			

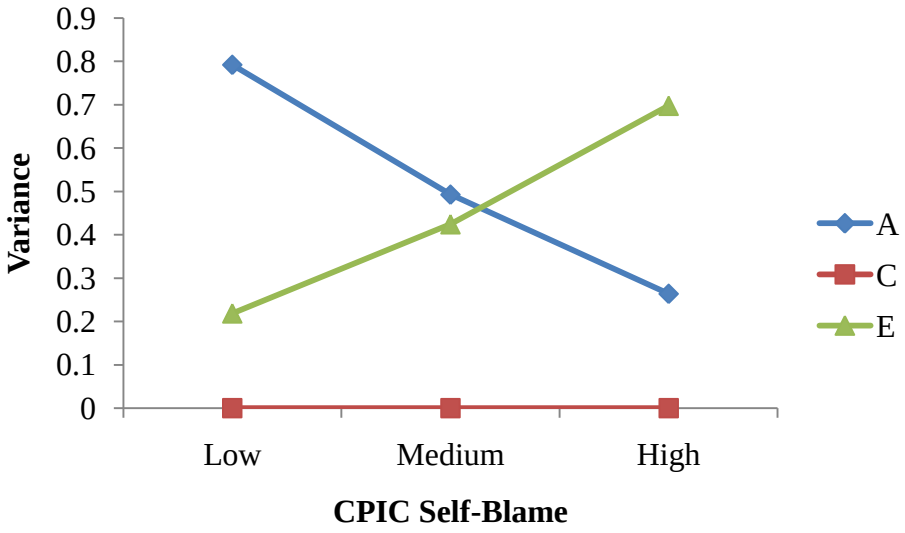
Note. Paths and moderators are presented; their 95% confidence intervals are presented below them in brackets. A, C, and E (both upper and lower case) represent genetic, shared, and non-shared environmental parameters, respectively. In the left portion of the table, the path estimates (i.e., a, c, and e) are presented. Because self-blame was divided into tertiles and those with scores within the lowest third of the distribution were coded as zero, these estimates function as intercepts. Accordingly, the genetic and environmental variance components at low levels of self-blame can be obtained simply by squaring these path estimates. At each subsequent level of self-blame, significant linear (i.e., A_1, C_1, E_1) moderators were added to these genetic and environmental paths using the following equation: $Unstandardized\ Variance_{Total} = (a + A_1(self\text{-}blame) + A_2(self\text{-}blame^2))^2 + (c + C_1(self\text{-}blame) + C_2(self\text{-}blame^2))^2 + (e + E_1(self\text{-}blame) + E_2(self\text{-}blame^2))^2$. The variance component estimates calculated this way are presented in Figure 1. The quadratic moderation terms (e.g., A_2, C_2, E_2) are not included as the linear model provided the best fit to the data (and are thus zero in the above equation). * indicates that the estimate is statistically significant at $p<.05$.

Table 12.Unstandardized path and moderator estimates for the GxE in the presence of rGE model.

PATHS			**LINEAR MODERATION**		
a	c	e	A_1	C_1	E_1
Covariance (or overlap) between ADHD and self-blame					
.489*****	.325	.014	.003	-.243	.101
(.024, .798)	(-.715, .715)	(-.230, .205)	(-.289, .353)	(-.451, .451)	(.-.067, .273)
Variance unique to ADHD					
.636*	.000	.426*	-.115	.000	.200*
(.287, .886)	(-.663, .663)	(.303, .598)	(-.347, .347)	(-.335, .335)	(.079, .303)

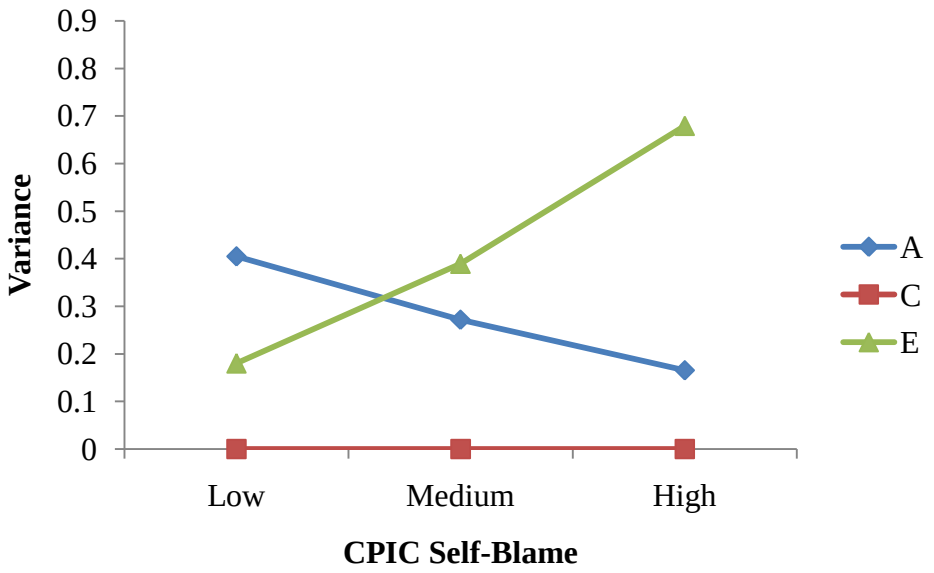
Note. Paths and moderators are presented; their 95% confidence intervals are presented below them in brackets. A, C, and E (both upper and lower case) represent genetic, shared, and non-shared environmental parameters, respectively. In the left portion of the table, the path estimates (i.e., a, c, and e) are presented. Because self-blame was divided into tertiles and those with scores within the lowest third of the distribution were coded as zero, these estimates function as intercepts. Accordingly, the genetic and environmental variance components at low levels of self-blame can be obtained simply by squaring these path estimates. At each subsequent level of self-blame, significant linear (i.e., A_1, C_1, E_1) moderators are added to these genetic and environmental paths using the following equation: $Unstandardized\ Variance_{Total} = (a + A_1(self\text{-}blame) + A_2(self\text{-}blame^2))^2 + (c + C_1(self\text{-}blame) + C_2(self\text{-}blame^2))^2 + (e + E_1(self\text{-}blame) + E_2(self\text{-}blame^2))^2$. The variance component estimates calculated this way are presented in Figure 2. * indicates that the estimate is statistically significant at $p<.05$.

Figure 1. Unstandardized Genetic (A), Shared Environmental (C), and Non-Shared Environmental Variance Contributions to ADHD by Level of Self-Blame: "Straight" GxE Model.



Note. Moderation analyses revealed that the increase in unique environmental contributions to the variance in ADHD (E) was significant. In addition, the decrease in genetic contributions to ADHD with increasing levels of self-blame was also significant.
For interpretation of the references to color in this and all other figures, the reader is referred to the electronic version of this dissertation.

Figure 2. Unstandardized Genetic (A), Shared Environmental (C), and Non-Shared Environmental Variance Contributions to ADHD by Level of Self-Blame: GxE in the Presence of rGE Model.



Note. Moderation analyses revealed that the increase in unique environmental contributions to the variance in ADHD (E) was significant. The decrease in genetic contributions to ADHD with increasing levels of self-blame was only significant when all shared environmental paths (C) were constrained to be zero.

Table 13. Demographics and Descriptive Statistics for ADHD Cases and non-ADHD Controls.

	Control (N=137)	ADHD (N=151)	p
% Male	48.2	64.2	.006
% Caucasian	74.5	78.1	.46
% African American	14.6	11.3	.40
% Latino	6.6	3.3	.20
% Other	4.4	7.3	.30
Age (SD)	14.7 (2.4)	13.5 (2.8)	<.001
% Two Parent Households	74.1	62.2	.03
Yearly Household Income (SD)[+]	74 (36)	63 (36)	.02
KSAD Diagnostics			
Inattentive Symptoms (SD)	1.2 (2.0)	7.3 (1.8)	<.001
Hyperactive Symptoms (SD)	.57 (1.1)	4.1 (3.2)	<.001
% ODD	8.8	27.2	<.001
% CD	1.5	9.9	.002
% MDD	10.2	21.9	.008
Conners' Teacher Report			
Cognitive Problems T Score	51.8 (12.3)	61.7 (14.6)	<.001
Hyperactivity T score	49.8 (9.3)	60.3 (11.8)	<.001
ADHD Rating Scale – Teacher Report			
Inattentive Symptoms	.62 (1.7)	4.0 (3.2)	<.001
Hyperactive Symptoms	.32 (.10)	2.1 (2.8)	<.001
5HTTLPR Genotype			
% High Activity (La/La)	.28	.25	.53
% Moderate Activity (La/Lg, La/s)	.42	.46	.49
% Low Activity (Lg/Lg, Lg/s, or s/s)	.30	.29	.88

Note. SD=standard deviation; ODD=Oppositional Defiant Disorder; CD=Conduct Disorder; MDD=Major Depressive Disorder-Lifetime. KSADS-E Diagnostics based upon parent report.
+ Income in thousands of dollars.

Table 14. 5HTTLPR Allele Frequencies and Genotypes by Self-Reported Ethnic Group.

	La	Lg	Short
Caucasian (N=229)	.49	.06	.45
African-American (N=42)*	.61	.19	.20
Latino (N=15)	.33	.07	.60
Other (n=18)	.28	.17	.55
Total	*.48*	*.09*	*.43*

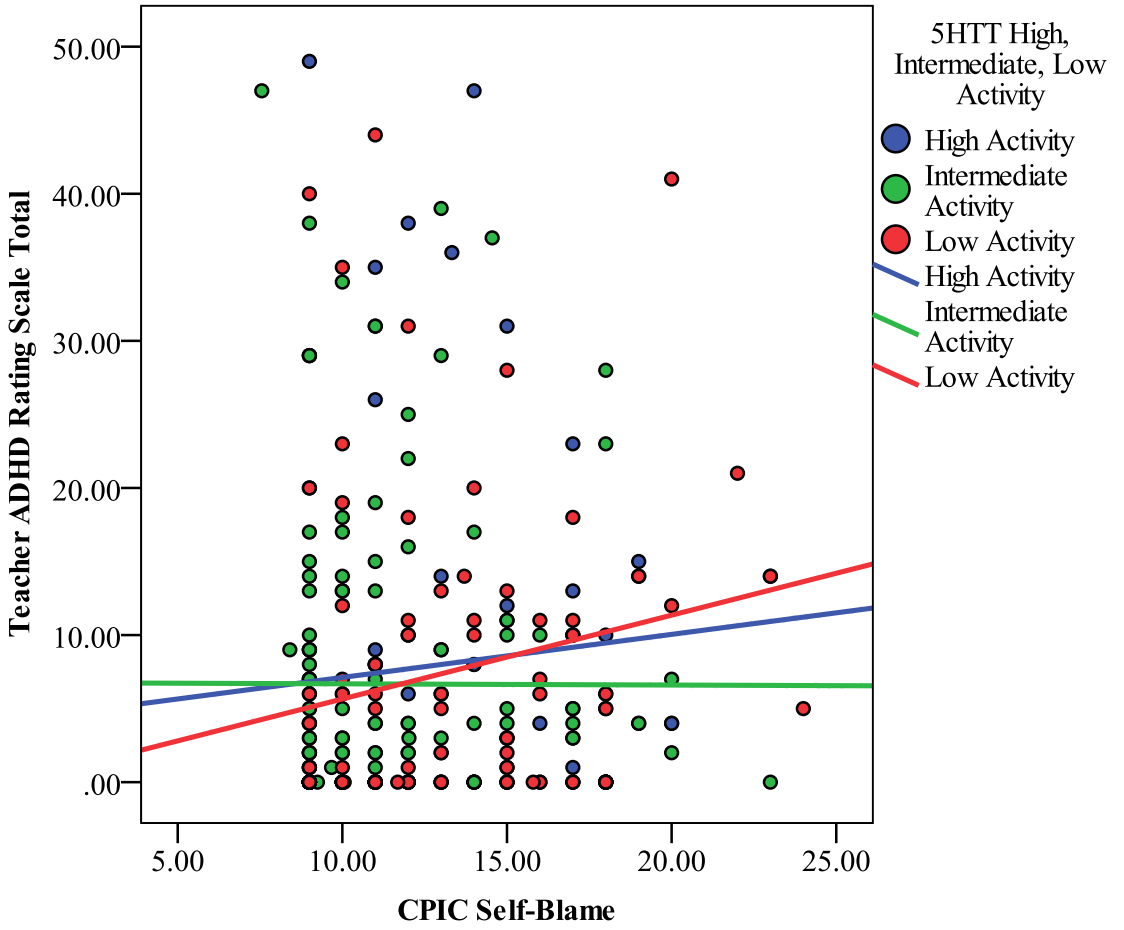
Note. *La and Lg allele frequency significantly greater in African-American participants compared to non-African American participants, (La, p=.048; Lg, p=.007).

Table 15. ADHD and Externalizing Symptoms: Main Effect Tests of High, Moderate and Low Activity 5HTTLPR Genotypes.

	High (La/La)	Moderate (La/Lg, La/s)	Low (Lg/Lg, Lg/s, s/s)	p	p^e	p^{eas}
N	78	137	89			
KSAD Diagnostics						
Inattentive Symptoms	5.5 (3.5)	6.0 (3.2)	5.5 (3.7)	.49	.51	.22
Hyperactive Symptoms	3.7 (3.3)	3.8 (3.3)	4.2 (3.3)	.60	.47	.52
ODD Symptoms	1.7 (2.3)	1.6 (2.2)	1.8 (2.4)	.81	.80	.83
CD Symptoms	.33 (.65)	.57 (1.3)	.30 (.87)	.10	.09	.09
Conners' Teacher Report						
Cognitive	3.0 (3.5)	3.4 (4.0)	3.8 (4.7)	.47	.45	.44
Hyperactivity	4.3 (4.8)	3.6 (3.8)	3.1 (3.8)	.20	.24	.13
ADHD Rating Scale Teacher Report						
Inattention	4.6 (6.7)	4.3 (6.1)	4.9 (6.5)	.95	.96	.93
Hyperactivity	3.1 (5.9)	2.4 (4.5)	2.3 (4.6)	.49	.65	.46

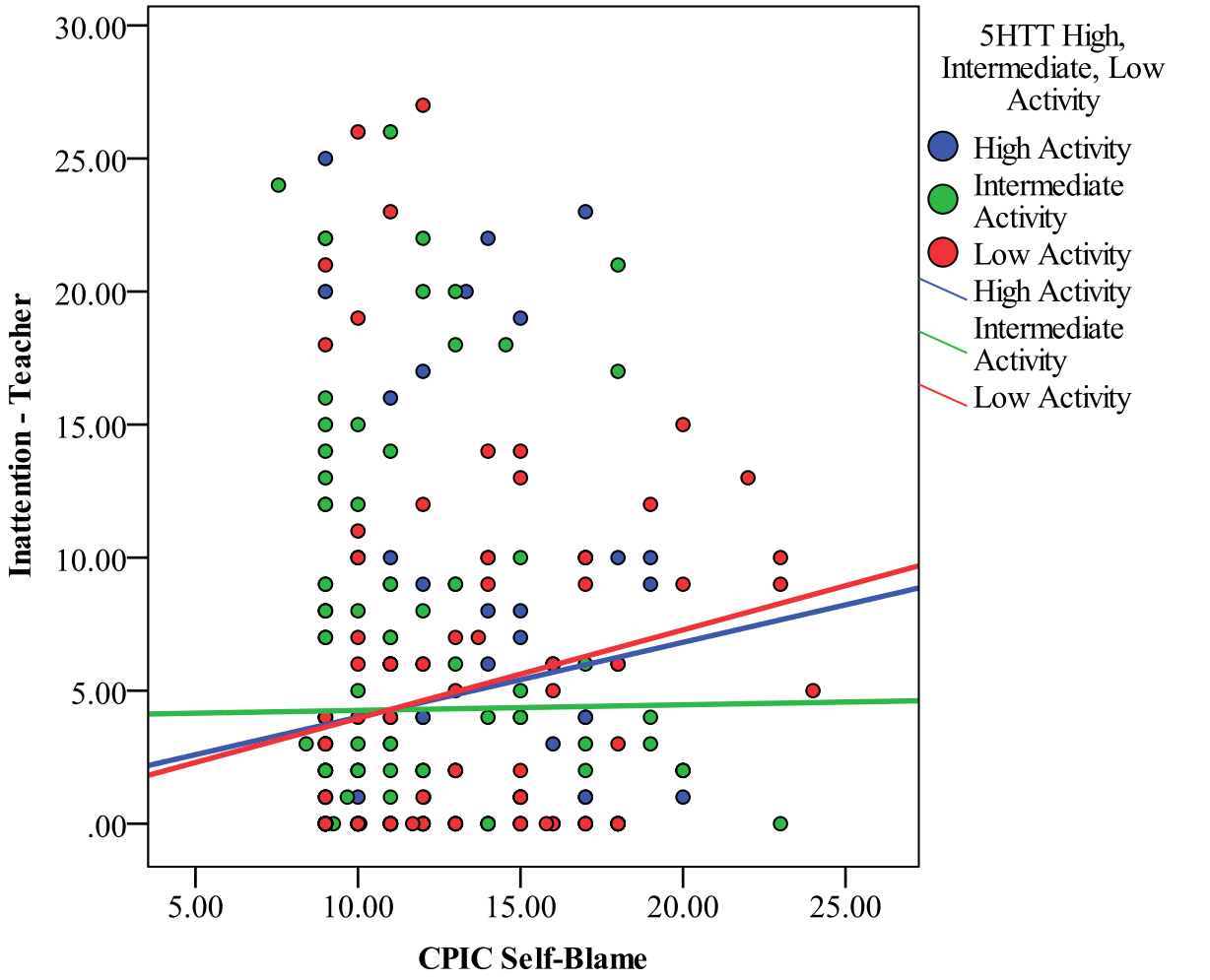
p^e = ethnicity corrected p value, p^{eas} = ethnicity age, and sex corrected p value. Inattentive, Hyperactive, ODD, and CD symptoms are parent report on the KSADS-E. Conners' Scores and ADHD Rating Scale scores are raw total scores on each measure (higher scores signify symptoms/problems).

Figure 3. Relationship between CPIC Self-Blame and ADHD Rating Scale Total Symptoms Score (Teacher Report) by 5HTTLPR Genotype Group.



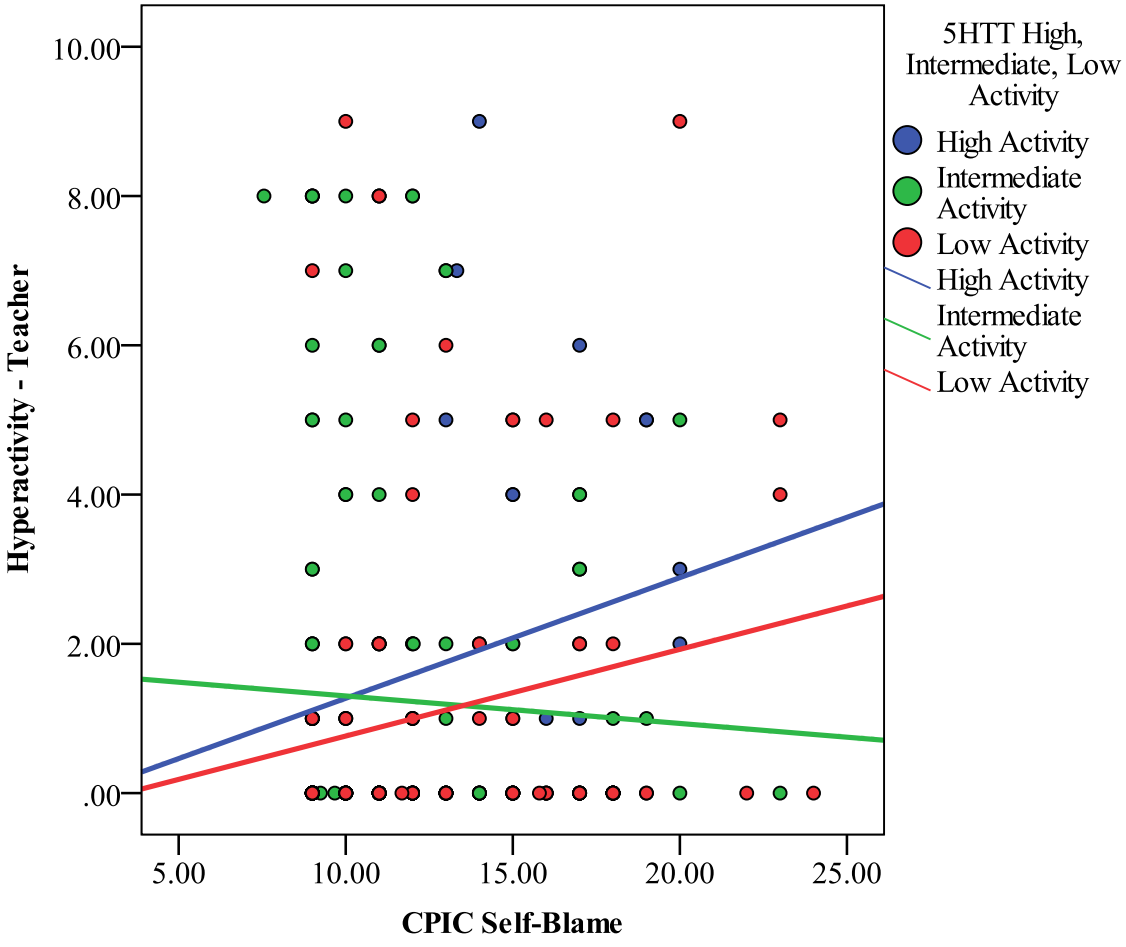
Note. Scatter plot data and best-fitting regression line are color-coded by genotype group. ADHD Rating Scale Total Symptom score is total raw score on likert scale (0-3) for all18 DSM-IV ADHD items.

Figure 4. Relationship between CPIC Self-Blame and ADHD Rating Scale Inattention Symptom Scores (Teacher Report) by 5HTTLPR Genotype Group.



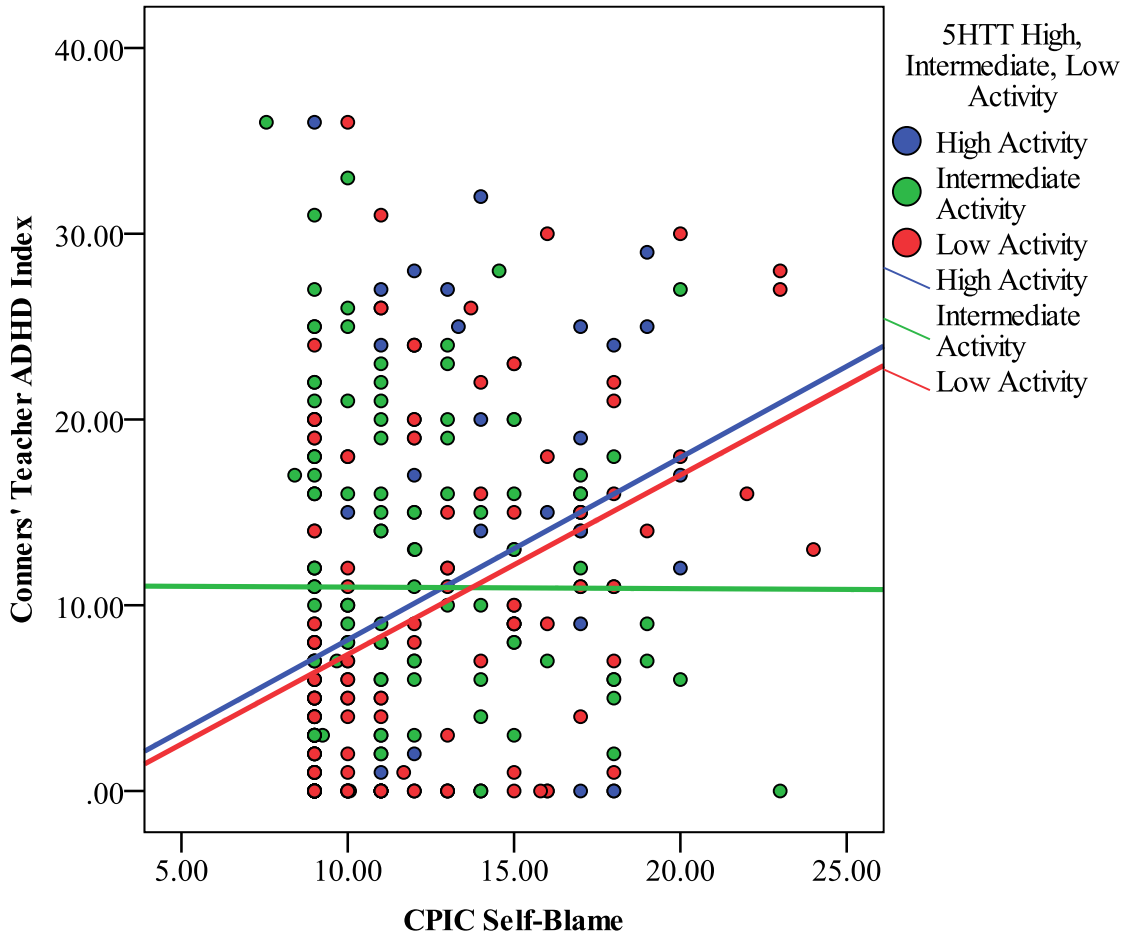
Note. Scatter plot data and best-fitting regression line are color-coded by genotype group. ADHD Rating Scale symptom dimension scores are the total raw scores on likert scale (0-3) for the 9 inattention symptoms and 9 hyperactive-impulsive symptoms, respectively.

Figure 5. Relationship between CPIC Self-Blame and ADHD Rating Scale Hyperactivity Symptom Scores (Teacher Report) by 5HTTLPR Genotype Group.



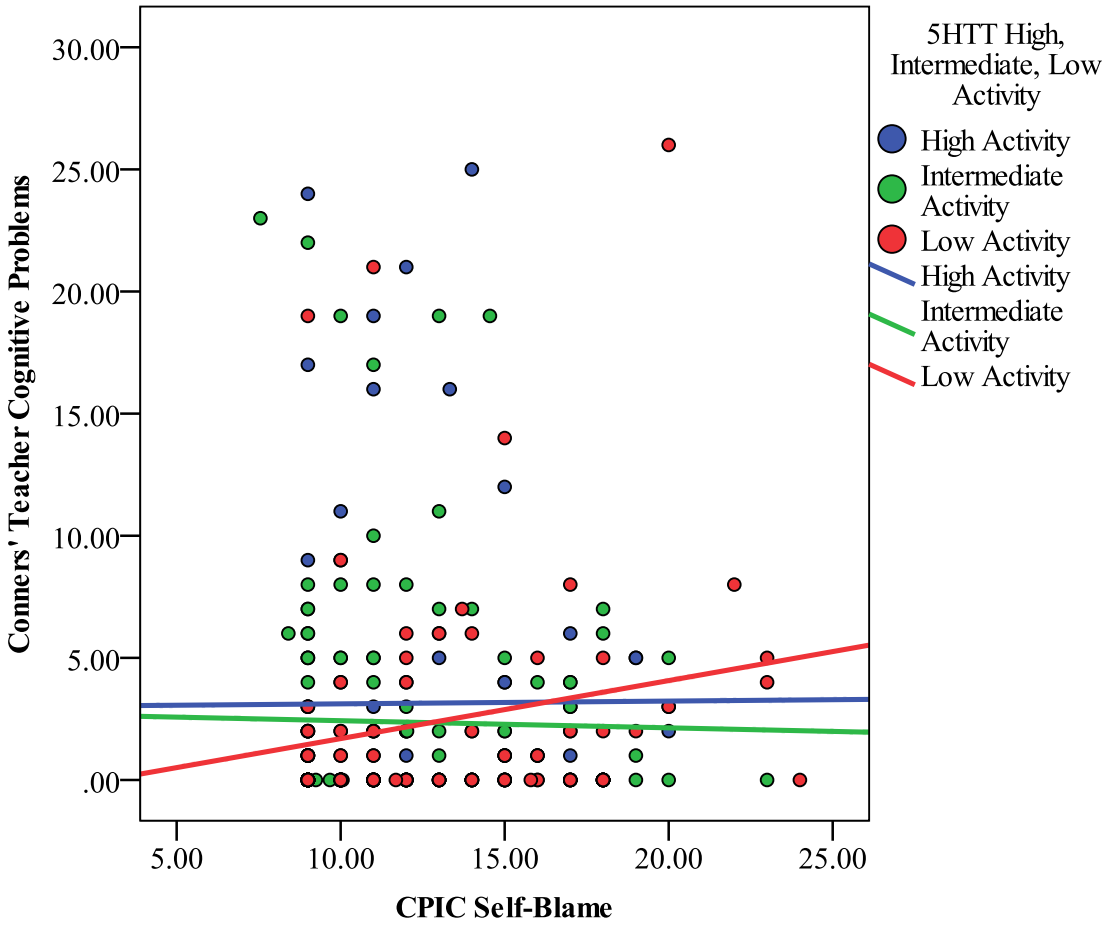
Note. Scatter plot data and best-fitting regression line are color-coded by genotype group. ADHD Rating Scale symptom dimension scores are the total raw scores on likert scale (0-3) for the 9 inattention symptoms and 9 hyperactive-impulsive symptoms, respectively.

Figure 6. Relationship Between CPIC Self-Blame and Conners' ADHD Index (Teacher Report) by Genotype Group.



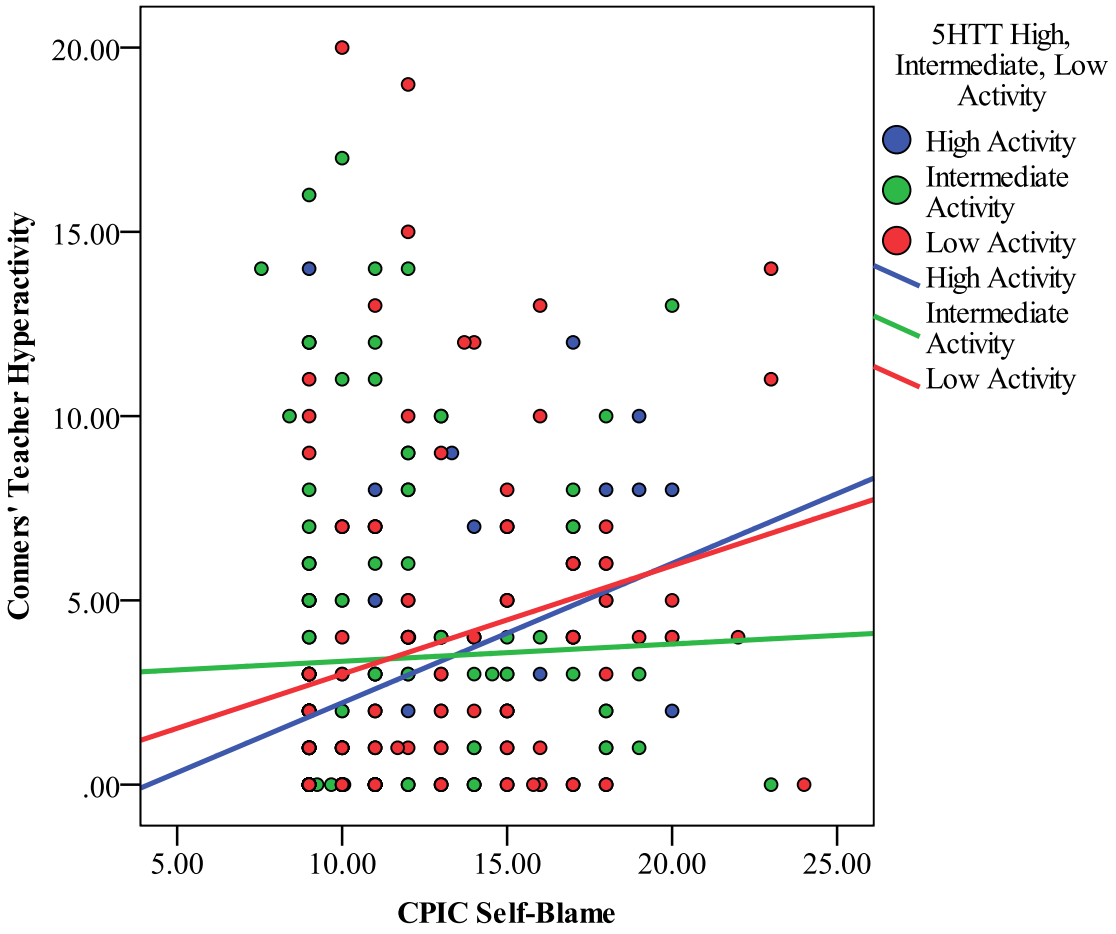
Note. Scatter plot data and best-fitting regression line are color-coded by genotype group. ADHD Rating Scale Total Symptom score is total raw score on likert scale (0-3) for ADHD Index items.

Figure 7. Relationship Between CPIC Self-Blame and Conners' Cognitive Problems (Teacher Report) by Genotype Group.



Note. Scatter plot data and best-fitting regression line are color-coded by genotype group. ADHD Rating Scale Total Symptom score is total raw score on likert scale (0-3) for ADHD Index items.

Figure 8. Relationship Between CPIC Self-Blame and Conners' Hyperactivity (Teacher Report) by Genotype Group.



Note. Scatter plot data and best-fitting regression line are color-coded by genotype group. ADHD Rating Scale Total Symptom score is total raw score on likert scale (0-3) for ADHD Index items.

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