

The Role of Parental Responsiveness in the Development of Co-occurring ADHD and  
Anxiety Symptoms: Interplay of Genotype and Environment

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**Dedication**

This dissertation is dedicated to my husband Ismail, without whom this dissertation would not be possible. I am thankful for always being there for me when the coldest Minnesota days were freezing the tips of our fingers, inspiring me when I did not have the motivation, guiding me when I struggle with graduate student life, encouraging me when I lost hope, and most importantly, being the most amazing dad when mom spent so much time working, away from home.

**Abstract**

Using a novel index of co-occurring psychopathology, this study aims to clarify three research questions: (1) Is co-occurring ADHD-anxiety in school years a continuation of these problems in preschool period? (2) Is parental *unresponsiveness* in the early years of life a risk factor in the development of co-occurring ADHD and anxiety problems in preschool and school age? (3) Does genetic risk moderate the effect of parental *unresponsiveness* on ADHD-anxiety co-occurrence? Participants included 361 families from the Early Growth and Development Study (EGDS), which employs a prospective adoption design. In each family unit, data were collected from the child adopted at birth, the adoptive mother and father, and the biological mother. For the present study, adoptive parent's responsiveness was assessed at child age of 9, 18, and 27 months; biological parent ADHD symptoms were assessed at 56 months; child ADHD and anxiety symptoms were assessed when children are at  $4\frac{1}{2}$  and 6 years of age. Path analyses were conducted for maternal and paternal responsiveness, separately. In both models, ADHD-anxiety co-occurrence at age  $4\frac{1}{2}$  years significantly predicted ADHD-anxiety co-occurrence at 6 years. Neither maternal responsiveness, nor paternal responsiveness had a main effect on child co-occurrence of ADHD-anxiety at  $4\frac{1}{2}$  years. There were significant interactions between genetic risk and maternal/paternal responsiveness in infancy predicting co-occurring ADHD-anxiety problems at  $4\frac{1}{2}$  years. Findings highlight the importance of attending to excessively high parental responsiveness in the context of genetic risk, which is associated with higher co-occurring ADHD and anxiety problems around ages  $4\frac{1}{2}$  and 6.

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## **Chapter 1: The Role of Parental Responsiveness in the Development of Co-occurring ADHD and Anxiety: A Literature Review**

The comorbidity of attention deficit hyperactivity disorder (ADHD) and anxiety has substantial prevalence. It is estimated that one in four cases of ADHD is diagnosed with an anxiety disorder (Deault, 2009). Yet, little is known about children who exhibit this comorbid condition. How does anxiety present in children with ADHD symptoms? Does anxiety precede ADHD, is it an outcome of the child's experience of ADHD problems, or is anxiety a part of ADHD symptomatology? What are the risk factors that lead to this comorbidity? What are the genetic and environmental factors that are associated with comorbid ADHD and anxiety?

While the term “comorbidity” is usually used to refer to the diagnosis of two or more psychiatric disorders, as a temporal concept, “co-occurrence” denotes co-incident or clustering of disorders, problems, symptoms, or scores in the same individual. Thus, it can be argued that comorbidity implies a categorical approach to psychopathology, whereas co-occurrence is more dimensional. This dissertation considers co-occurring of psychopathologies in children in general terms. Throughout the paper, the term comorbidity and co-occurrence are used interchangeably to refer to both coexisting diagnostic classifications and symptoms.

Although the problem of comorbidity is discussed in the developmental psychopathology literature in the general sense, research that examines specific pathways of comorbid psychopathology is still awaiting. This dissertation provides an overview of the ADHD-anxiety comorbidity, and discusses parental influences in relation to this

comorbidity. Specifically, I focus on parental influences on the development of comorbid ADHD and anxiety problems and highlight parental *unresponsiveness* as a potential etiology underlying the co-occurrence of these two conditions. Since parental influences can be transmitted through various mechanisms, including genes (G), environment (E), and most likely the synergistic interactions of the two (GxE), this dissertation aims at examining ways in which parental responsiveness interacts with genetic influences in leading to this comorbidity.

I begin this chapter by defining comorbidity in general and presenting a developmental perspective on the problem of comorbidity. Then, I describe ADHD-anxiety comorbidity including its prevalence, phenomenology, and etiology. Finally, I review and discuss evidence suggesting parental *unresponsiveness* as a potential common etiology for ADHD-anxiety comorbidity.

### **Real or Artifact: A Developmental Perspective on Comorbidity**

While comorbidity is a widely used concept, a number of issues are worth mentioning in its terminology. As a term originated in medicine, comorbidity refers to the existence of two or more simultaneous, independent diseases in the same individual. In the case of mental conditions, comorbidity is very common, rule rather than the exception, because there is no precise distinction between symptoms and disorder (Clark, Watson, & Reynolds, 1995; Wittchen, 1996). Thus, it is widely discussed as a problem with classification and diagnosis of mental disorders.

Although conceptually comorbidity is a condition in which two (or more) disorders coexist simultaneously, empirical work has operationalized it liberally, with

each disorder occurring at varying timing. On one hand, research has operationalized comorbidity as sequential or lifetime where two or more conditions follow a certain order in their presentation (August, Realmuto, Joyce, & Hektner, 1999; Biederman et al., 1996; Moffitt, Harrington, & Caspi, 2007). On a more stringent side, comorbidity has also been seen as concurrent where two conditions are diagnosable at the same time (Gadow & Nolan, 2002; Neuman et al., 2005). Limiting comorbidity to only concurrent occurrences implies a static understanding of comorbidity, whereas from a developmental perspective, comorbidity is seen as a dynamic concept. An accurate assessment of comorbidity requires a longitudinal framework to identify trajectories of co-occurrence of the multiple psychopathologies over time. With these considerations, in this chapter, comorbidity is taken in the broader sense in terms of its timing and both concurrent and sequentially timed co-occurrence of symptoms are conceptualized as comorbidity.

Comorbidity can manifest in two different forms: *homotypic* vs. *heterotypic*. Homotypic comorbidity refers to co-occurrence of similar phenotypes, such as depression and dysthymia, within the same category of disorders. Heterotypic comorbidity on the other hand, refers to co-existence of distinct phenotypes, such as depression and conduct disorder, from different broad classes of disorders (Angold, Costello, & Erkanli, 1999). The distinction between these two forms of comorbidity has its root in the broader framework of developmental psychopathology. In the continuity versus discontinuity debate, developmental scientists coined the term ‘heterotypic continuity’ (Kagan, 1971), which has been widely used by developmental psychopathologists (Rutter & Sroufe, 2000) to argue that although development follows a coherent course, the antecedents of

developmental outcomes can be heterotypic (as well as homotypic), with complex underlying routes to later functioning that can be observed in different forms depending on the specific developmental time point. The focus of this dissertation is on heterotypic comorbidity, as ADHD and anxiety represent distinct phenotypes, from different general classes of psychopathology (i.e., externalizing vs. internalizing broadbands).

In the literature, several issues have been discussed in conceptualizing comorbidity. Perhaps, the fundamental question is whether comorbidity is a real phenomenon or an artifact. Some argue that comorbidity can be seen as a product of methodological issues within the diagnostic classification system or methods of psychological assessment. According to Meehl (1992), the diagnostic classifications are not ‘taxonomic,’ but arbitrary distinctions to be employed for practicality. In the widely used roadmap of mental illness, *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; DSM-5; American Psychiatric Association, 2013), these classifications are overly differentiated resulting in artificial subdivisions of disorders, unclear boundaries between categories, and significant symptom overlap. Also, epidemiological data reveals high comorbidity rates of mental illnesses (Kessler et al., 1996). However, it has been argued that the prevalence rates reported by most of these studies are potentially distorted by unreliability of measures, potential issues with the informants, referral bias (also known as the *Berkson effect*), and reliance on clinical samples that do not provide an accurate estimate of the general population (Angold, Costello, Farmer, Burns, & Erkanli, 1999).

Comorbidity implies that two independent disorders with distinct etiologies are present in the same person. Yet, unlike organic diseases, most mental disorders cannot be traced back to specific etiologies. They are defined according to arbitrary criteria set by various classification systems according to which certain set of symptoms are lumped together or split apart (Angold, Costello, & Erkanli, 1999; Bradshaw, 2001). Thus, a medical model to mental illness cannot account for commonly observed comorbidities. In the literature, it is widely acknowledged that membership in a particular diagnostic category can be polythetic (Krueger & Markon, 2006). In other words, there are multiple ways of meeting criteria for a diagnosis—various combinations of symptoms are possible. Several comorbidity models were suggested in the literature to account for this polythetic nature of psychopathology. Studies searching for underlying latent liability factors giving rise to comorbidity across common forms of psychopathology converged on a specific hierarchical model with two superordinate liabilities: internalizing vs. externalizing psychopathology (Achenbach, 1966; Krueger & Markon, 2006; Krueger, 1999; Vollebergh et al., 2001). Meehl (2001) suggested that latent structures with underlying causal distinctiveness would best explain the comorbidity phenomenon.

It is questionable, however, to what extent broader structures such as ‘internalizing’ can be traced back to a *specific etiology*, which is a precondition for being accepted as a non-arbitrary latent category (a *taxon*). Internalizing and externalizing comorbidity is not uncommon, and overlapping etiologies are possible. Although such models are useful in terms of a more accurate investigation of prevalence, shared etiologies of distinct diagnoses within the latent structure, or improving nosologies of

mental illness, they are limited in accounting for children who present with problems characterizing both internalizing and externalizing liabilities. Most studies in the literature do not account for children with comorbid conditions; they are typically excluded from the sample or studies focus on a single aspect of their problems, which is the topic of interest for the particular study (Jensen, 2003). Rhee and colleagues (2004) suggested that longitudinal designs are crucial to distinguish different causational models of comorbidity. Biometric study designs such as behavior genetics studies (by adding information on the patterns of inherited comorbidities) are also proposed as instrumental in delineating the concept of comorbidity (Simonoff, 2000). Kendler and colleagues (2003), for example, found genetic basis for different liability spectrums and noted that specific disorders in their analysis can be distinguished by genetic factors unique to each condition.

There are theoretical and practical reasons to believe that comorbidity is real—not epiphenomenal. Most mental conditions appear to be multifactorial and there is now considerable evidence from developmental psychopathology research pointing at the presence of common causes in the development of various forms of psychopathology. When ADHD-anxiety comorbidity is considered, theoretical, conceptual, methodological, and substantive reasons can potentially underlie this pattern. However, studies to date have established that ADHD and anxiety comorbidity cannot be explained by mere symptom overlap (Angold, Costello, & Erkanli, 1999). This dissertation focuses on comorbidity of ADHD and anxiety as a real phenomenon, and tackles with the etiological

aspects of comorbid ADHD and anxiety rather than the methodological issues mentioned above.

Developmental psychopathology perspective provides a useful framework to understand comorbidity. It adopts a life span approach that enables the definition of *abnormal* in the context of developmental considerations (e.g., timing) (Sroufe & Rutter, 1984) and integrates the study of maladaptation with normative processes (e.g., development of cognitive control) providing a dynamic understanding of mental illness (Sroufe, 1990). According to this perspective, there are individual patterns of adaptation and maladaptation that place the individual on a pathway towards later psychopathology (Sroufe & Rutter, 1984). Certain risk factors or vulnerabilities (i.e., trauma, poor parenting, poverty etc.) interact with the individual's developmental history in leading to various outcomes. Comorbidity can be framed as a product of individual patterns of adaptation and maladaptation. Thus, from a developmental point of view, potential pathways leading to co-occurring outcomes are an important issue of interest. In this picture, common pathways may result in differential outcomes (*multifinality*), while different pathways have the potential to culminate at the same end product (*equifinality*) (Cicchetti & Rogosch, 1996).

Co-occurrence of different phenotypes can be conceptualized as the manifestation of the same underlying maladaptive pathway or as developmental progressions in which one symptom or disorder contributes to the development of the other. Models of cascades, causal chains, and snowballs have been used to illustrate this form of concurrent or successive comorbidities (Burt, Obradović, Long, & Masten, 2008;

Cicchetti & Cannon, 1999; Cicchetti & Tucker, 1994; Masten et al., 2005). For example, Patterson's *dual failure* model posits that both antisocial behavior and depressed mood in late childhood and adolescence emerges as a developmental progression of a maladaptive pathway. In this model, coercive parent-child interactions lead to early behavior problems (i.e., aggression) that are associated with academic failure and peer rejection in middle childhood. Academic failure and peer rejection, in turn, can lead the way to both depressed mood and commitment to a deviant peer group in late childhood and subsequent delinquency in early adolescence (Patterson & Stoolmiller, 1991).

### **ADHD & Anxiety Co-occurrence**

According to *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; DSM-5; American Psychiatric Association, 2013), ADHD is characterized by three core categories of symptoms (inattention, hyperactivity, and impulsivity) that start early in life and cause significant problems with functioning in the home and the school context placing children at risk for a multitude of adverse outcomes such as social dysfunction, substance abuse, academic underachievement, and delinquency (Barkley et al., 2006). In the DSM-5, anxiety disorders are broadly defined as disorders characterized by excessive fear (i.e., *emotional response to real or perceived imminent threat*), anxiety (i.e., *anticipation of future threat*) and associated disturbances. They include separation anxiety disorder, selective mutism, specific phobia, social phobia, panic disorder, agoraphobia, and generalized anxiety disorder.

Although ADHD is commonly seen as an externalizing difficulty, there are many co-occurring internalizing symptoms associated with ADHD. Children who are at risk for

ADHD are more likely to exhibit internalizing problems as reported by school teachers (Cunningham & Boyle, 2002). This may not be surprising as clinical presentation of individuals with ADHD indicates general struggles with managing a range of emotions including sadness, frustration, anger, or excitement (Nigg, 2013). Important aspects of ADHD symptomatology such as irritability, restlessness, and difficulty concentrating are commonly present in anxiety disorders. However, even after these overlapping symptoms are controlled for, ADHD and anxiety co-occur beyond chance expectations (Bedard & Tannock, 2007; Kessler, Chiu, Demler, & Walters, 2005). Although a substantial proportion of children (25%) with ADHD also present with a co-occurring anxiety condition (Tannock, 2009), little is known about co-occurring ADHD and anxiety symptoms.

The comorbidity of ADHD and internalizing problems including anxiety has been neglected in the literature for several reasons. One possibility is that this group of children is overshadowed by the large number of children who present comorbid externalizing problems in ADHD cases. Also, the lack of emphasis on anxiety in the ADHD literature partly stems from gender differences in prevalence (Deault, 2009): inattention in the context of internalizing problems (common among girls) is less visible compared to inattention in the context of disruptive behavior (common among boys) and remains under-identified. Yet, this comorbidity has paramount importance in the clinical management of the disorder. Research is awaited to understand this comorbidity in order to trace potential developmental pathways leading to its presentation, and to identify targets for effective interventions.

As the two most common psychiatric diagnoses in childhood, ADHD and anxiety disorders co-occur very frequently. In epidemiological studies, child anxiety has been shown to occur at a rate ranging from 6 to 22% (Briggs-Gowan, Horwitz, Schwab-Stone, Leventhal, & Leaf, 2000; Kashani & Orvaschel, 1988; Reinherz, Giaconia, Lefcowitz, Pakiz, & Frost, 1993). This range is between 4 and 12% for ADHD (Brown et al., 2001) although it tends to be higher in studies with smaller samples (Rowland, Lesesne, & Abramowitz, 2002). According to reviews of the literature, in approximately 25% to 30% of ADHD cases, there is a comorbid anxiety diagnosis (Angold, Costello, & Erkanli, 1999; Jensen, Martin, & Cantwell, 1997; March et al., 2000) and among children with anxiety, approximately 15-30% has ADHD (Tannock, 2009). This high prevalence exists even after common symptoms (e.g. restlessness, difficulty concentrating) are controlled for, suggesting that this comorbidity occurs beyond chance expectations (Bedard & Tannock, 2007; Kessler, Chiu, Demler, & Walters, 2005). It is important to note that depending on the specific inclusion criteria, the comorbidity rates vary from one study to another. For example, in the Multimodal Treatment Study of ADHD (MTA), the comorbid anxiety rate was reported as 32% (Jensen et al., 2001); whereas in a study which included specific phobias as comorbid anxiety it was found to be as high as 50% (Bowen, Chavira, Bailey, Stein, & Stein, 2008).

Co-occurrence of child adjustment problems in general pose a serious challenge for interventions (Caron & Rutter, 1991). As anxiety affects the functioning of children with ADHD, it alters the treatment process and outcomes as well (Jensen et al., 2001). Children with comorbid ADHD and anxiety exhibit differential responses to conventional

ADHD treatments. For children with ADHD, methylphenidate (Ritalin, Concerta, Metadate) and guanfacine (Intuniv) have been the two widely used psychopharmacological treatment approaches. Methylphenidate works as a dopamine and norepinephrine reuptake inhibitor, keeping these neurotransmitters in the synapses longer. These drugs work to temporarily resolve the hypo-activation of key brain regions. Thus, they get rid of the symptoms for short periods of time, but do not cure the disorder in the long run. Side effects include nervousness, insomnia, decreased appetite, nausea, abdominal pain, tachycardia, stunted growth, dependence, and abuse among others (Schachar, Tannock, Cunningham, & Corkum, 1997). Guanfacine, on the other hand, enhances attention and behavior regulation via strengthening the prefrontal cortex. It has been used in the treatment of anxiety and tic disorder in addition to ADHD. There is evidence showing that children with the comorbid type do not respond to stimulant treatments as well as those who do not have comorbid anxiety, and side effects of arousal are particularly a problem for them (Bedard & Tannock, 2007; DuPaul, Barkley, & McMurray, 1994). For example, in the MTA study, children with comorbid anxiety benefited from combined approaches where psychopharmacological treatment is combined with behavior therapy (Jensen et al., 2001; March et al., 2000). The evidence that stimulant medications and selective serotonin reuptake inhibitors (SSRI) reduce ADHD symptoms but do not improve anxiety in these children suggests that psychosocial interventions may especially play an important role in this group of children who exhibit the comorbid pattern (Abikoff et al., 2005). Thus, understanding of psychosocial risk processes is crucial to identify targets of intervention.

Parent training has been the most recommended psychosocial treatment for ADHD. However, when ADHD is comorbid with anxiety, treatment has to address a range of clinical issues such as mood and anxiety symptoms, school fears/phobias, self-esteem, social competence, attention difficulties, and hyperactivity. Both the degree of impairment and the developmental sequela of symptoms need to be considered. In the literature, it has been suggested that children with ADHD and comorbid anxiety can potentially benefit from interventions that promote responsive parenting defined as frequent, contingent, and specific positive feedback and those that encourage developmentally appropriate independence and risk taking of the child (Newcorn et al., 2001).

For the most part, the way anxiety presents itself is not different in ADHD cases from non-ADHD cases (Tannock, 2009) but its presence alters the symptom pattern of ADHD (Angold, Costello, & Erkanli, 1999; Newcorn et al., 2001; Pliszka, 1992). There is a considerable amount of research comparing children with ADHD and comorbid anxiety to children with ADHD only. There is evidence that children with ADHD and anxiety are less impulsive (Newcorn et al., 2001; Pliszka, 1992; Tannock, 2009), exhibit impaired working memory and effortful processing (Tannock, Ickowicz, & Schachar, 1995), report more school-related and social difficulties (Biederman, Newcorn, & Sprich, 1991), and experience more stressful life events, parental separation, and divorce (Xenakis & Richters, 1993). There is also evidence that children presenting with this comorbidity have lower self-esteem and higher need for reassurance. In the literature, they are described as “worriers” due to their tendency to be overly worried about their

competence and future events (Tannock, 2009).

In a recent investigation, Bowen and colleagues (2008) examined differences between comorbid ADHD-anxiety and the “pure” forms of ADHD and anxiety using a sample (between the ages of 8-17) representative of pediatric primary care patients. The comorbid pattern was associated with higher attention difficulties, school-related fears, mood disorders, and lower social competence compared to ADHD-only or anxiety-only children. Additionally, this comorbidity was related to more severe symptoms, and more impairment compared to either psychopathology alone. According to parents’ report, the comorbidity group also differed from ADHD only group in terms of age of onset of hyperactivity. The age of onset was reported by parents to be 5.2 ( $SD = 2.3$ ) in the comorbid group while it was reported as 2.2 ( $SD = 1.6$ ) in the ADHD-only group—this was not a large difference but is meaningful given that the range is limited to 7 by the DSM definition of ADHD. In a prior investigation of externalizing and internalizing psychopathology comorbid with ADHD, Connor and colleagues (2003) also found that age of onset of ADHD symptoms differed among comorbidity groups after controlling for several variables that increase risk for ADHD in children and estimated duration of ADHD. Consistent with Bowen et al.’s findings, they found that a later age of onset is correlated with comorbid anxious/depressive symptoms while an early age of onset is correlated with greater child aggression. However, it is also important to consider that in most studies age of onset is defined as the age in which problems are first noticed by parents, and as previously mentioned, externalizing problems might be more readily observed compared to internalizing problems such as anxiety. Internalizing problems

might especially be unnoticed in young children due to their underdeveloped verbal skills. Thus, the findings of a later age of onset for comorbid anxiety with ADHD need to be carefully considered as they might result from underreporting of comorbid internalizing symptoms of young children by parents.

Several trajectories of ADHD comorbidities have been proposed exemplifying *multifinality* in a series of dynamic and nonlinear developmental progressions. These include early hyperactive, impulsive, irritable, defiant, and aggressive characteristics during preschool ages leading to ADHD and ODD comorbidity which later develop into negative outcomes such as CD and juvenile delinquency, or substance use disorders (Beauchaine & Gatzke-Kopp, 2012), combination of severe depression and impulsivity which is associated with high suicide risk (Agosti, Chen, & Levin, 2011), or irritable mood that characterizes disruptive mood dysregulation classification (Leibenluft, 2011). However, there are other possibilities. Children characterized by inattentive, hyperactive, and impulsive behavior in preschool and early elementary years may develop mood and anxiety problems, learning, and achievement problems, which in turn make them relatively socially withdrawn (Nigg, Nikolas, Friderici, Park, & Zucker, 2007). Among this heterogeneous picture of ADHD trajectories, little is known about why some children with ADHD exhibit comorbid anxiety symptoms. Research needs to address the etiology of observed phenotypes of inattention, hyperactivity, impulsivity, and anxiety through studies that account for both genetic and environmental influences.

Tannock (2009) suggested several potential pathways such as attention problems as secondary to anxiety, anxiety symptoms following chronic failure of children with

ADHD, separate etiologies (and treatment responses) of ADHD and anxiety, and a distinct etiology (and treatment response) of the ADHD-anxiety co-occurrence that would suggest a separate disorder by itself. Alternatively, anxiety can moderate or mediate pathways from parental/family influences to ADHD symptoms (Deault, 2009). It is quite possible that there are multiple pathways leading to the presentation of this comorbidity. From a developmental perspective, studying risk factors that are associated with developmental outcomes is crucial to identify developmental pathways. In the literature, there is a considerable gap of research examining risk factors leading to ADHD-anxiety comorbidity. With these considerations, as one of the mechanisms potentially explaining the ADHD-anxiety comorbidity, this dissertation focuses on the “common etiology” model suggesting an underlying common pathway leading to presentation of both conditions.

### **The Role of Parental Responsiveness in the Development of ADHD & Anxiety**

Parenting plays a crucial role in the development of various forms of psychopathology and it is a well-established target for treatment (Wells et al., 2000; Wood, McLeod, Sigman, Hwang, & Chu, 2003; Wood, Piacentini, Southam-Gerow, Chu, & Sigman, 2006). In the literature examining parenting and child ADHD or anxiety, parental responsiveness stands out as a construct that plays a critical role in the development of the symptomatology of both (Carlson, Jacobvitz, & Sroufe, 1995; Chorpita & Barlow, 1998; Keown, 2012; Mash & Johnston, 1982; Pfiffner & McBurnett, 2006a; Roisman & Fraley, 2012). This investigation examines parental *un*responsiveness as one common etiological factor that potentially leads to the comorbid pattern of ADHD

and anxiety. Because most children share both genetic make-up and the environment with their parents, the processes through which parental factors influence children's symptoms can be threefold: genetic, environmental, and most likely the interaction of the two. From a developmental perspective, children who receive *unresponsive* parental care, but do not develop ADHD and anxiety symptoms are also an important issue of interest. In order to account for this group of children, the role of parental responsiveness on child symptoms needs to be considered in the context of genetic risk processes.

**Parental responsiveness.** Recently, there has been surging interest in parental responsiveness as it is thought to play a critical role in promoting children's socio-emotional, cognitive, and communicative development. Especially maternal responsiveness has been consistently found to be a protective factor against maladaptive outcomes (Bornstein & Tamis-LeMonda, 1989; Wakschlag & Hans, 1999). Parental responsiveness can be defined based on several different theoretical orientations and research frameworks including attachment theory (Ainsworth, Blehar, Waters, & Wall, 1978; Sroufe, Fox, & Pancake, 1983), sociocultural approaches (Rogoff, 1990), and the socialization literature (Grusec & Goodnow, 1994; Maccoby & Martin, 1983; Maccoby, 1992). Rather than referring to a single construct, responsiveness has several dimensions such as *nonintrusiveness*, emotional availability, empathic awareness, sensitivity to social cues, predictability, and positive involvement (Martin, 1989). It also involves constructs that have been referred to in the literature as emotional/affective support, contingent and sensitive responding, and *nondirectiveness* (Bornstein & Tamis-LeMonda, 1989; Maccoby & Martin, 1983).

The definition and operationalization of parental responsiveness depends on the particular developmental period of interest, which is predominantly infancy in the responsiveness literature. For example, contingent responding refers to responses that are prompt and contingent on infants' signals (Ainsworth et al., 2014; Sroufe et al., 1983). Emotional/affective support has been defined as warm acceptance of infants' needs and interests through presence of positive affective input (e.g., warmth, smiling) and absence of highly negative behaviors (e.g., harsh voice tone, physical intrusiveness) ultimately communicating the caregiver's interest and acceptance (Darling & Steinberg, 1993; Landry, Smith, & Swank, 2006). Supporting infant's attention foci and providing language input in accordance with developmental needs are also pointed at as core dimensions of parental responsiveness (Landry, Miller-Loncar, Smith, & Swank, 2002).

From an attachment perspective, responsiveness means recognition of infant's cues, accurately interpreting them, and responding to them in appropriate, prompt, and contingent ways (Ainsworth et al., 1978). In other words, to be considered as responsive, the action by the parent in response to the infant's cues needs to be appropriate in its timing, intensity, and quality, meeting the child's developmental needs. According to attachment theory, this kind of parenting contributes to the forming of trust and bond in the parent-child relationship which enables the child to be interested in and willing to explore the environment (Ainsworth et al., 1978; Darling & Steinberg, 1993). For example, in infancy, sensitive and contingent responding to the child's needs, high affection, and positive reinforcement characterizes parental responsiveness. Because the infant finds that their signals are being promptly and sensitively responded to, she

continues to signal and cooperate with the caregiver (Bornstein & Tamis-LeMonda, 1989). Ultimately, this kind of parenting is thought to facilitate the infant's ability to self-regulate through internalization of skills for coping with stressful situations and novelty, laying the foundation for self-regulation and socio-emotional competence in the first few years of life (Kochanska, 1997; Kopp, 1982). In infancy research, intervention studies targeting maternal responsiveness also show that this parenting construct supports attachment security (Bakermans-Kranenburg, van IJzendoorn, & Juffer, 2003), and promotes positive, cognitive and social outcomes in high-risk children such as highly irritable, very low birth weight, or adopted infants (Beckwith, Rodning, & Cohen, 1992; Juffer, Hoksbergen, Riksen-Walraven, & Kohnstamm, 1997).

As an empirical framework, the concept of *interactional synchrony* also supports the premise that parental responsiveness is one of the early foundations of self-regulation (Feldman, 2007). *Interactional synchrony* refers to the parent's successful facilitation of synchronous interactions with the infant (Gianino & Tronick, 1988; Kogan & Carter, 1996; Schore, 2000). Through encouragement of infant's attentiveness and sensitivity to social environment, synchronous interactions with parents allow children to coordinate their behavior in socially appropriate ways. Lack of such synchronous, hence responsive, interactions in the parent-child relationship can involve presence of high parental directiveness or intrusiveness, in which power, accompanied by negative affect, is used to control the child behavior. For several decades using the Still Face Experiment, in which the mother or the father becomes unresponsive to the infant unexpectedly for a brief period of time, researchers has been able to observe the effects of parent's lack of

responsiveness in infants, pointing at the importance of early parental responsiveness in social and emotional development (Adamson & Frick, 2003).

Sroufe (1990) stipulates that responsive parental care plays an important role in the normative development of attention and emotion regulation. In early dyadic interactions, the parent serves as the regulator of arousal by engaging and disengaging the infant's attention in accord with his/her needs. As the infant learns strategies to regulate her own emotions and attention through these interactions, they may constitute the child's templates of attention control and emotion regulation for later development (Fox, Henderson, Marshall, Nichols, & Ghera, 2005). Lack of parental responsive care can contribute to abnormal developmental patterns in these domains (Carlson et al., 1995), potentially leading to co-occurring psychopathologies related to attention and emotion regulation difficulties such as ADHD and anxiety.

In the following sections, above-mentioned constructs conceptualized as different aspects of parental responsiveness in the early years of life are discussed with respect to their linkages with ADHD symptoms, anxiety symptoms, and ADHD-anxiety co-occurrence.

**Parental responsiveness and ADHD symptoms.** In recent years, there has also been a growing interest in parenting factors that predict ADHD symptoms. Studies derived from both clinical and population studies, including longitudinal investigations and treatment research, have demonstrated robust relationships between poor parent-child relationships and children's ADHD symptoms (Deault, 2009). For example, significant associations have been found between poor maternal coping with child behavior, punitive

discipline, disciplinary aggression (i.e., spanking), inconsistent parenting, and childhood hyperactivity (Stormshak, Bierman, McMahon, & Lengua, 2000; Woodward, Taylor, & Dowdney, 1998).

Although the idea that parental responsiveness can be associated with ADHD is relatively new, several dimensions of parental responsiveness discussed above have been found to be associated with ADHD symptoms in the literature (Campbell & Ewing, 1990; Campbell, Shaw, & Gilliom, 2000; Danforth, Anderson, Barkley, & Stokes, 1991; Johnston & Mash, 2001; Mash & Johnston, 1982; Peris & Baker, 2000). Early observational research comparing mother-child interactions of normal versus hyperactive children in middle to upper middle class families suggested that mothers of both younger ( $M$  age = 4.11 years) and older ( $M$  age = 8.4 years) hyperactive children tend to be less responsive to the initiations by their children and initiate fewer interactions with them (Mash & Johnston, 1982). In a longitudinal investigation following 191 children from birth to 11 years, Carlson, Jacobvitz, and Sroufe (1995) found that maternal intrusive care at 6 months and overstimulation at 42 months significantly predicts risk for hyperactivity in middle childhood and distractibility at  $3\frac{1}{2}$  years (distractibility is also found to be a predictor of later hyperactivity in the same investigation). Specifically, mothers' disrupting their infant's ongoing activity and failing to adapt timing and quality of their interactions to the infant's needs, mood, and interests were considered intrusive caregiving. Mothers' physically stimulating contact when not needed or signaled by the child, and psychologically stimulating behavior where the child is in need of modulating his/her arousal (e.g., provoking, teasing) were considered overstimulating caregiving.

Preliminary findings from an earlier investigation also suggested that intrusive maternal care at 6 months and overstimulating maternal care at 42 months are related to ADHD symptoms in kindergartners (Jacobvitz & Sroufe, 1987). These parents can be considered as *excessively responsive* (i.e., intrusive or overstimulating). Rather than being low on responsiveness, they are highly responsive, but in a way that is not appropriate to the developmental needs of their baby.

Similarly, in a clinical sample of children aged 5-11, mostly from Caucasian middle-class background, it was found that in addition to overly negative/inconsistent discipline, lack of warmth and responsiveness was associated with ADHD symptoms (Pfiffner, Mcburnett, Rathouz, & Judice, 2005). However, this finding is confounded with comorbid oppositional defiant disorder (ODD) and conduct disorder (CD). Campbell et al. (2000) argue that co-occurrence of conduct problems with ADHD is an important potential confounding factor to control for in these studies, as they may account for the relationship between psychosocial risk factors and hyperactivity. Based on such considerations, Keown & Woodward (2002) conducted a study examining hyperactivity after controlling for conduct problems and other child and family factors in a community sample of preschool boys (70% White). Lax parenting, maternal and paternal coping, father-child communication, mother-child interactional synchrony were found to be significantly associated with preschool hyperactivity. This study revealed that compared to a group of comparison children and their parents, in the hyperactive group, mother-child interactions tended to be more lacking in shared affect, mutual focus, responsiveness, and connection as indicated by ratings of interactional synchrony during

an observational free play session. More specifically, the poorer interactional synchrony scores in this group indicate that in terms of leading and following an action sequence, their interactions appeared more imbalanced and less coordinated.

While these studies suggest that maternal responsiveness contribute to ADHD in children, the role of father's responsiveness in the development of ADHD remains largely unknown. In the study by Keown & Woodward (2002), as an element of parental responsiveness, the interactional synchrony ratings were only limited to mothers. They examined father-child conversations as an indicator of paternal parenting, and found that father-child conversations were less frequent in the hyperactive group. This finding adds to the existing longitudinal research that supports the link between paternal responsive parenting and children's poor self-regulation (Denham et al., 2000). Thus, paternal responsiveness, in addition to maternal responsiveness needs to be considered as another factor contributing to poorly regulated behavior in children with ADHD. Another prospective longitudinal investigation following a community sample of boys recruited at age 4 (Keown, 2012) examined multi-informant ratings of ADHD symptoms in relation to maternal and paternal predictors. Three aspects of parental responsiveness were observed during interactions of mother-son and father-son dyads: *sensitivity* (tuning in and appropriate responding of the parent to the child's cues, interests, and mood), *intrusiveness* (physical and verbal over-control of the child's play), and *positive regard* (demonstrations of affirmation, warmth, and affection toward the child). The results revealed that low paternal sensitivity and maternal positive regard in early childhood were predictive of higher levels of inattentiveness in school years. Paternal intrusiveness

in preschool age predicted hyperactive-impulsive behavior in middle childhood. Also, in a categorical analysis approach, less maternal warmth predicted later ADHD. Held after controlling for possible effects of ADHD behaviors in early childhood and conduct problems, these predictions highlight the importance of both maternal and paternal responsiveness in relation to ADHD symptomatology.

Overall, several conclusions can be drawn based on the aforementioned studies examining the role of parental responsiveness in children's ADHD symptoms. First, aspects of responsiveness, such as warmth, positive involvement, sensitive and nonintrusive parenting (Kochanska, 1997; Maccoby & Martin, 1983) have been associated with lower presentation of ADHD symptoms. Second, although most of the early work is cross-sectional and conducted around the school age years (7-12), more recent longitudinal evidence indicates a strong link between low responsive parenting in early years of life and ADHD symptoms in preschool and kindergarten (Deault, 2009; Johnston & Mash, 2001). As it is recently becoming more recognized that ADHD symptoms often emerge in early childhood and persist into school years and beyond (DuPaul, McGoey, Eckert, & Vanbrakle, 2001; Pierce, Ewing, & Campbell, 1999; von Stauffenberg & Campbell, 2007), more research is warranted to provide insight on antecedents of ADHD symptoms in early childhood and early-to-middle childhood (4-7), during which, transition to school places new challenges on children's self-regulatory capacities. Predicting preschool children who are at risk for developing ADHD is a key task for early intervention purposes as well (Sonuga-Barke, 2005). Third, the majority of the research has been done on boys, leaving girls' ADHD symptoms largely unattended.

Fourth, despite the call for more research on the role of fathers in the development of child behavior problems (Phares & Compas, 1992), the literature on parental responsiveness and ADHD has been largely confined to maternal responsive parenting. Lastly, early work in this area fails to account for overlapping conduct problems with ADHD symptoms. Thus, in future studies concurrent behavior problems need to be controlled for in statistical analysis in order to see the independent contribution of parental responsiveness on the development of ADHD.

**Parental responsiveness and child anxiety.** Several aspects of parenting have been associated with the development of anxiety in children (Chorpita & Barlow, 1998; Pfiffner & McBurnett, 2006b). Although the constructs that have been employed vary from one study to another, and they are derived from different theoretical orientations, when operationalization is considered, they consistently meet the general definition of parental responsiveness and point at various dimensions of this construct. For example, Chorpita and Barlow (1998) identified two “anxiogenic” parenting styles: overprotectiveness and insufficient sensitivity/responsiveness with regard to child’s communications and behaviors. They define insufficient responding as low positive contingent responsiveness where children are not provided with positive reinforcement synchronized with their behavior in a consistent way and within a general context of acceptance and involvement with them. The opposite of this style would be sensitive, consistent, and contingent caregiving. They argue that parenting that is low on contingent responsiveness, and intrusive or overprotective parenting behaviors deprive the child from experiencing a developmentally appropriate sense of control rendering her

vulnerable to developing subsequent anxiety symptoms. The literature demonstrating an association between overprotective and intrusive parenting and children's high external locus of control support this premise (Carton & Nowicki, 1996).

Some of the other parenting constructs that have been linked with anxiety include disengaged, less warm, withdrawn and excessively controlling parenting in the early years (Roisman & Fraley, 2012), and in observational studies based on both clinical and school-based samples, low parental care/warmth and overprotection (Dumas, LaFreniere, & Serketich, 1995; Moore, Whaley, & Sigman, 2004). From a theoretical perspective, low care or warmth may deprive the child of the most important sources of external validation of a positive self-concept: sense of control, and enjoyment while exploring the environment. Overprotection may signal children that the environment is not predictable and threatening; hence they are in need of being protected. This kind of parenting ultimately prevents mastering of developmental tasks through restriction of activities involving age-appropriate "risk."

Attachment perspective also provides a useful theoretical rationale supporting the link between low responsive caregiving and risk for development of anxiety. Sroufe (1990) provides an example to illustrate this as a process of mother-infant interaction: An overstimulated infant can signal her need to deescalate the interaction (e.g., turning away). By responding appropriately to the infant's subtle cues, the mother facilitates her modulation of arousal. Without such responsive caregiving, the child may fail to internalize skills for negotiating the intensity of interactional exchanges, and may be at risk for subsequent anxiety.

Overall, current state of research on the role of parental responsiveness in the development of child anxiety suggests that parental responsiveness has significant impact on child anxiety. However, it is important to consider that parental responsiveness itself is susceptible to parents' own anxiety. Empirical evidence suggests that anxious parents are more likely to be overprotective, controlling, and low on positive contingent responsiveness (Kashdan et al., 2004; Whaley, Pinto, & Sigman, 1999). Studies with children who have a primary anxiety disorder point at low responsive parental behaviors that indicate parents' own anxiety problems: modeling of anxious behaviors, setting excessively high expectations, and promotion of avoidant solutions to problems (Barrett, Rapee, Dadds, & Ryan, 1996; Dadds, Barrett, Rapee, & Ryan, 1996). Wood and colleagues (2003) also suggest that excessive parental responsiveness, which likely arises from parent's own anxiety, might also constitute risk for child anxiety through sensitizing the child to situations that initially elicited anxious responses and preventing child's further exposure and habituation.

Parental anxiety has been frequently associated with child anxiety relatively to its association with other disorders (Last, Hersen, Kazdin, Orvaschel, & Perrin, 1991). Also, parental anxiety has also been found to strongly predict comorbidity of anxiety with ADHD, even after the association between parental depressive disorders and child comorbid anxiety disorders is controlled (Pfiffner et al., 1999). The link between maternal anxiety and child anxiety seems to be stronger than that of paternal anxiety (Biederman et al., 1991). However, there is also evidence that elements of responsibility such as lack of warmth and autonomy in parenting have effects on child anxiety,

independent of maternal anxiety (Moore et al., 2004). Given that anxiety is heritable (Gross & Hen, 2004), it is important to clarify the role of parental responsiveness independent of genetic influences on anxiety transmitted from parents to a child. To come up with solid empirical evidence clarifying this picture, studies that employ genetically informed designs are needed.

**Parental responsiveness and ADHD-anxiety co-occurrence.** Although research on child anxiety and ADHD has grown independently in the literature of parental responsiveness, the integration of the two suggests that parental responsiveness can indeed be a potential common etiology. Research has shown that a range of parental factors including parental warmth and overprotectiveness are shown to be associated with comorbid anxiety and ADHD (Jarrett & Ollendick, 2008). In a diagnostic sample of children with ADHD, Pfiffner and McBurnett (2006b) examined whether or not there was a unique contribution of parenting on comorbid anxiety when the effects of parental anxiety were accounted for. They compared those with and without comorbid anxiety and found that parental overprotectiveness (possessiveness) and lack of positive parenting, defined as low positive contingent responsiveness, contributed independently to comorbid anxiety with ADHD in children aged 5-11. Greatest risk was inferred when maternal anxiety was present on top of these two maladaptive parenting styles. The authors suggest that these might be the key factors associated with ADHD-anxiety comorbidity.

The study by Pfiffner and McBurnett (2006b) is one of the few empirical investigations examining children presenting with ADHD-anxiety comorbidity in the

context of parental influences. However, the study consisted of children who are already diagnosed with ADHD, most of whom are, as typically seen in the literature, boys (118 boys vs. 25 girls). Thus, the findings are not informative regarding the children who present with symptoms of ADHD but do not meet the diagnostic criteria. Also, the potential gender bias in sampling leaves us with limited information about girls who exhibit comorbid anxiety with ADHD symptoms. The study has additional weaknesses such as using a cross-sectional design and parenting measures that were based on self-report.

Overall, the aforementioned literature review points out the role of several elements of parental responsiveness in the development of ADHD, anxiety, and ADHD-anxiety comorbidity. Specifically, based on what empirical studies suggest so far, parenting that is characterized by less warmth and affection, and low sensitive, positive, and contingent responsiveness seem to be risk factors for the development of both ADHD and anxiety. Constructs that are emphasized in ADHD literature, such as maternal intrusiveness, over-control, overstimulation, directiveness, and asynchronous parent-child interactions, all indicate the opposite of what has been defined as sensitive, positive, contingent responsiveness. In children who are diagnosed with ADHD, overprotectiveness and low responsiveness seem to hold as risks for comorbid anxiety.

**Gene-environment interplay.** Parental responsiveness is a promising venue in unraveling the common cause that drives the development of ADHD-anxiety comorbidity. However, in this line of research, genetic influences on disorders and psychosocial processes in parenting are not differentiated because the majority of the

samples used in these studies come from biologically related families where the totality of parental influences is a package of both genetic and environmental influences. In order to understand how parental responsiveness operates in the development of child comorbidity of anxiety and ADHD, genetically informed studies are needed to account for both genetic and environmental contributions of parental influences.

Genetic influence may stem from passive gene-environment correlations (*rGE*) where associations between parents' (i.e., parental responsiveness) and child's characteristics (i.e., anxiety or ADHD symptoms) occur due to mere sharing of their genotype. With research employing genetically informed designs, the effect of shared genes can be accounted for and alternative explanations can be ruled out regarding the passive *rGE*. Also, increasing evidence suggests that parenting processes interact with genetic influences on a host of child outcomes (Cicchetti & Cannon, 1999; Lifford, Harold, & Thapar, 2009; Natsuaki et al., 2010; Taylor & Kim-Cohen, 2007). These genotype-environment interactions (GxE) contributing to the development of comorbid anxiety with ADHD are another form of genetic influence that needs to be understood in order to delineate the role of parenting as an environmental process in this picture.

When ADHD and anxiety are considered separately, there seems to be a complex picture of parental influences involving both genetic and environmental processes, and considerable influence of child behavior on parenting and parents' overall functioning. It is widely agreed upon that multiple pathways involving a critical role of psychosocial parental influences lead to the development of ADHD-anxiety comorbidity (Wells et al., 2000). While ADHD and anxiety are heritable, the effects of genes seem to depend on the

individual's environment. Several studies from the Early Growth and Development Study (EGDS), the longitudinal adoption study utilized in this dissertation, have demonstrated evidence for GxE in ADHD and anxiety separately. For example, Harold and colleagues (2013) found significant associations between hostile parenting behavior at age 4<sup>1/2</sup> and ADHD symptoms at age 6. They also found that adoptive mothers' ADHD symptoms predict child ADHD symptoms (when passive gene-environment correlations (*r*GE) as an alternative explanation were ruled out). However, they also found evocative effects where biological mothers' ADHD symptoms were related to adoptive mothers' hostile parenting through its relation to early child disrupted behavior at age 4<sup>1/2</sup>. Both maternal hostile parenting and early disruptive child behavior were associated with later child ADHD symptoms in middle childhood (i.e., 6 years), after adoptive mothers' concurrent ADHD symptoms were controlled. In studies examining child anxiety, findings point at the role of supportive caregiving for the development of anxiety when genetic vulnerabilities are present. In a more recent study using a prospective adoption design, Natsuaki and colleagues (2013) found a protective effect of parental emotional and verbal responsiveness at 18 months in children who are at risk for social anxiety at 27 months. Responsive parenting might be particularly effective for children who are genetically liable for anxiety because high contingent responsiveness of parents could help this particular group of children internalize self-control while keeping their levels of anxious arousal low, whereas power-asserting discipline strategies can be counterproductive through exacerbating their fears (Kochanska, Aksan, & Joy, 2007). While these findings reveal the importance of considering the role of parental responsiveness in the context of

genetic risk to understand the development of ADHD and anxiety in children, our knowledge is limited regarding how parental responsiveness and genetic risk for ADHD-anxiety co-occurrence plays a role in creating etiological synergies of co-occurring ADHD and anxiety. The present investigation aims to fill this gap in the literature using a longitudinal adoption study.

### **Summary & Conclusions**

The present investigation aims to examine the case of children who present with co-occurring ADHD and anxiety in relation to parental *unresponsiveness* as an etiology for its development. This group of children has been relatively unattended in the literature despite their substantial prevalence. Developmental psychopathology perspective necessitates identifying specific mechanisms of co-occurring psychopathology in order to achieve a solid understanding of etiology (Cicchetti, 1993; Rutter & Sroufe, 2000). In this dissertation, by reviewing the literature on parental influences in the development of ADHD and anxiety symptoms and paying close attention to a relatively small number of studies on ADHD-anxiety co-occurrence, an attempt was made to identify aspects of parenting that might potentially be related to co-occurring of ADHD and anxiety. Parental responsive care is highlighted as one potential “common etiology” underlying ADHD symptoms co-occurring with anxiety. Based on the current state of the literature in delineating *multifinal* and *equifinal* pathways to ADHD and anxiety outcomes, unresponsive parental care can potentially be an early developmental antecedent of comorbid ADHD and anxiety. Given that not all children who receive low responsive

care develop this comorbid pattern, genetic risk is taken into account as interacting with psychosocial processes.

As noted above, comorbidity is not a matter of methodological nuance, but a profound puzzle of how we conceptualize child psychopathology. Through vigorous attempts at investigating these clinical and developmental issues raised in this chapter, we can improve our understanding of comorbidity in particular and child psychopathology in general.

## Chapter 2: The Current Study

### Utilizing a Longitudinal Adoption Study of Young Children:

The literature reviewed *en masse* indicates that parental *unresponsiveness* in the early years of life is a common etiology linked with both ADHD and anxiety symptoms in children (Keown, 2012; Pfiffner & McBurnett, 2006b; Roisman & Fraley, 2012). Evidence also suggests the linkages between several elements of unresponsive parenting (e.g., low positive contingent responsiveness) and co-occurring ADHD and anxiety (Jarrett & Ollendick, 2008; Pfiffner & McBurnett, 2006b). Despite its substantial prevalence (Deault, 2009), few studies to date have focused on the co-occurrence of ADHD and anxiety problems. Furthermore, among the few that exist, most of the studies on this co-occurrence were based on clinical samples, and employed cross-sectional designs. Clinical samples consisted of mostly school-aged boys, resulting in *referral bias*. Our knowledge on boys and girls who present with co-occurring ADHD and anxiety problems but have not yet been referred for a diagnosis is missing. Also, we have limited insight into how these co-occurring problems develop in early childhood to become more visible in the school context. Although ADHD and anxiety problems tend to be more commonly reported by parents and teachers following children's entrance to the school system, evidence suggests that antecedent problems can be already observed in the preschool period (Pierce et al., 1999; von Stauffenberg & Campbell, 2007). A closer look at the period of transition from early childhood to school years is useful to capture the emergence of this co-occurrence.

Still, not all children who receive *unresponsive parenting* in early years of life develop co-occurring ADHD and anxiety problems. They may develop either ADHD or anxiety, or they may not develop any problems at all. It is more likely that both genes and parenting contribute to the heterogeneity in the development of these psychopathologies in the offspring. However, it is not possible to differentiate parental influences that are environmental (i.e., caregiving) from those that are biological (i.e., shared genotype) in research designs that rely on data from only biological families, where parents share both genes and environment with their offspring. One approach for delineating the mechanism of this heterogeneity is the genotype-environment interaction framework. As pointed out earlier, only with longitudinal studies that employ genetically-informed designs (Rhee et al., 2004; Simonoff, 2000), the interactive effects of environmental predictors (i.e., parenting) and genetic diathesis might be understood and the linkages behind the development of co-occurring presentations of psychopathology could be delineated.

With these considerations in mind, this dissertation employs data from a genetically informed prospective adoption design, the Early Growth and Development Study (EGDS; Leve et al., 2013), to investigate parental *unresponsiveness* as a potential common etiology in the emergence of co-occurring child ADHD and anxiety. The EGDS is ideally suited for the current investigation for the following reasons. First, in the EGDS sample, children were placed in nonrelative adoptive homes within the first weeks of their life; ruling out the possibility of influences due to shared genotype between parents and the child (i.e., passive *rGE*). Second, the EGDS has followed their biological parents and adoptive parents whose information can be used as indicators of genotype and

environmental influences, respectively. Third, the EGDS is based on a community sample of adopted children and their biological and adoptive families, which allowed us to capture children with and without clinical diagnoses of ADHD and/or anxiety. Fourth, child problem behavior was examined around the transition from preschool to school age, which, as noted above, is a missing piece in the literature. Fifth, both mother's and father's responsiveness in infancy were also investigated. Finally, the children's ADHD and anxiety problems were examined in their full spectrum (i.e., continuous measures) using a developmentally sensitive measure of child psychopathology. This is an important point in operationalizing co-occurrence because such a measurement approach enables quantification of co-occurrence on a continuum, without being affected by base rates and clinical cut-offs.

### **A Developmental Perspective: Operationalizing Co-occurrence of Two Psychopathologies**

The key feature of this investigation is how co-occurrence (or comorbidity) is operationalized. In the comorbidity literature, most studies employ an 'all-or-none' method in approaching comorbidity (Hurtig et al., 2007). For example, each child is assigned a diagnosis and data is divided into groups such as: *ADHD-only*, *anxiety-only*, *comorbid, no diagnosis*. Alternatively, a sample of children, all of whom have ADHD diagnosis is taken and the comorbid condition (e.g., anxiety problems) is examined as a dependent variable indexing comorbidity (Jensen et al., 2001). These categorical approaches mask dysfunctioning that is below clinical levels; while from a developmental psychopathology perspective, normative and subclinical levels of

dysfunctioning are as equally important as dysfunctioning that is above clinical levels to understand the development and emergence of problem behavior. Thus, it is crucial to be able to quantify co-occurrence in its full spectrum as an outcome.

Co-occurrence of two psychopathologies can be operationalized according to two dimensions of a bivariate model: *proximity* and *severity*. *Proximity* can be defined as the absolute distance between the subject's scores on two distinct measures (Equation 1). As long as the two conditions are measured along the same scale, proximity reflects the extent to which the levels of two scores go together. *Severity* can be defined as the combined magnitude of scores on the two measures (Equation 2). In other words, severity refers to how much, overall, a particular subject exhibits symptoms of dysfunctions regardless of types of psychopathology.

$$\text{Proximity} = |\text{Psychopathology A} - \text{Psychopathology B}|$$

[Equation 1]

$$\text{Severity} = \text{Psychopathology A} + \text{Psychopathology B}$$

[Equation 2]

In this dissertation, I argue that an accurate quantification of co-occurrence has to incorporate both *severity* and *proximity*. From this perspective, a person who has clinical levels of co-occurrence (i.e., high scores on both Psychopathologies A and B) should be represented as having high proximity and high severity.

The rationale can be demonstrated using the following example of a hypothetical scenario where T scores on two distinct syndrome scales are considered. If only *severity*

is taken as indexing co-occurrence without considering *proximity*, the following scenario (Scenario A) with two cases (90, 30) and (60, 60) would yield the same score:

$$\text{Severity of Case 1} = 90 + 30 = 120$$

$$\text{Severity of Case 2} = 60 + 60 = 120$$

However, if one examines *proximity* between the two psychopathologies, the results reveal a completely different picture. As shown below, the second case (60, 60) would show more similar levels of the two psychopathologies than the first case (90, 30):

$$\text{Proximity of Case 1} = 90 - 30 = 60$$

$$\text{Proximity of Case 2} = 60 - 60 = 0$$

Based on the numbers calculated above, one may conclude that Case 2 represents a person who experience the co-occurrence of the two psychopathologies at the similar magnitude while Case 1 represents a person who displays more symptoms of Psychopathology A than Psychopathology B.

Let's consider Scenario B. In Scenario B, the following two cases have the exact same proximity, but different severity. When *proximity* is taken as the index of comorbidity without considering *severity*, the cases (90, 80) and (40, 30) would produce the same score:

$$\text{Proximity of Case 1} = 90 - 80 = 10$$

$$\text{Proximity of Case 2} = 40 - 30 = 10$$

However, their *severity* is very different:

$$\text{Severity of Case 1} = 90 + 80 = 170$$

$$\text{Severity of Case 2} = 40 + 30 = 70$$

Thus, both *severity* (addition) and *proximity* (subtraction) yield biased indexes of the co-occurrence phenomenon when used solitarily. An accurate quantification of co-occurrence (a rating of the co-occurring of two psychopathologies) should reflect both *severity* and *proximity* dimensions of co-occurrence. For example, among the hypothetical cases above, (90, 80) would be considered as the most *co-occurring*, while (40, 30) would be seen as the case where the least *co-occurring* of these psychopathologies exist.

In this dissertation, a new index, the Co-occurrence Index (CoI) that attempts to include both *proximity* and *severity*, is proposed. The CoI yields a co-occurrence score for each subject reflecting both simultaneous occurring of two behavior problems (i.e., *proximity*) and their combined *severity*.

$$\text{CoI} = (\text{Psychopathology A} * \text{Psychopathology B}) / (\text{Psychopathology A} + \text{Psychopathology B})$$

[Equation 3]

The CoI utilizes multiplication, in addition to addition, as a scaling method that yields a co-product of two conditions (i.e., standardized total scores on ADHD and anxiety subscales). When multiplication (scaling) is divided by addition (adjusting by total severity), the index yields a balanced score of both *severity* and *proximity* components of co-occurrence. The rationale behind this operation is explained via case-by-case examples below.

For simplicity, a hypothetical example is provided on Table 1. In this example, on a 4-point hypothetical scale (1: minimal, 2: mild, 3: moderate, 4: severe) of problems in

Psychopathology A and Psychopathology B, co-product of Psychopathology A and Psychopathology B in a given child yields the matrix presented on Table 1.

Ranging from 1 to 16, scores somewhat reflect the severity for each pair. However, it does not provide a balanced summary when both *severity* and *proximity* of problems are considered. For example, the cases highlighted are problematic because although they have completely different co-occurrence profiles [(1, 4), (4, 1) and (2, 2)], this method yields the same co-product score (4) for all. For the (1, 4) case, Psychopathology A is minimally observed with a score of 1, whereas Psychopathology B is highly severe (scoring 4). The total severity is  $1+4=5$ , whereas absolute distance between the two scores, which indicates *proximity*, is  $|4-1|=3$ . On the other hand, the case (2, 2) has the maximum *proximity* ( $|2-2|=0$ ), as the subject's scores in two psychopathologies are equal to each other. Although their combined *severity* ( $2+2=4$ ) is lower than the (1, 4) case, it has a slightly stronger pattern of co-occurrence than (1, 4) case, where Psychopathology A, which has minimal *severity* (1), could be considered negligible. Thus, an accurate index of comorbidity should reflect both *proximity* and *severity* of two psychopathologies, without sacrificing one for the other. As observed in this matrix above, multiplication of two psychopathologies that are wide apart (low *proximity*) yields an inflated index, when only one of the scores has considerable *severity*. Also, when the distribution of the multiplication index is considered, the range of the scores becomes disproportionately wide.

To illustrate another example, let's consider the two hypothetical cases with T scores on two scales are considered, (50, 50) and (80, 30). While being close in terms of

*severity* ( $50+50=100$  and  $80+30=110$ , respectively), they are very different in terms of *proximity* ( $50-50=0$  and  $80-30=50$ , respectively). However, when multiplication is used (see below for the calculation), the higher score in the second case, 80, inflates the co-product despite the co-occurring psychopathology has low *severity* (30).

$$(50, 50): 50 * 50 = 2500$$

$$(80, 30): 80 * 30 = 2400$$

Thus, multiplication, while being a reasonable scaling for capturing the co-product of two scores, does not accurately balance the degree of *severity* and *proximity*. As the case examples above demonstrate, an over-inflation problem occurs in multiplication when one of the scores is disproportionately high compared to the other. In the index of CoI (see Equation 1), this inflation, however, is adjusted by diving the multiplication product with the actual total *severity*, which is calculated by simple addition of the two scores. As the addition score increases, the inflation in the multiplication term is downwardly modified, and vice versa, correcting for potential bias. In this way, the CoI provides a summary score of both *severity* and *proximity*, which allows comparison of co-occurrence profiles across cases:

The CoI yields a score for each case that reflects minor differences in both *severity* and *proximity* dimensions of bivariate co-occurrence. As long as the co-occurrence profiles of two individuals are not exactly the same, the index does not compute equal scores for them, which was a potential problem when solitary subtraction, addition, or multiplication is used. A brief demonstration based on a hypothetical 4-point scale is illustrated in Table 2; the table lists all possible combinations of pairs in

ascending order of bivariate co-occurrence. As shown in Table 2, the differences between the cases are proportionate to the differences in *severity* and *proximity*, which yields a normal distribution of potential combination possibilities (and of observed data in the current study).

In this study, CoI is used to operationalize the co-occurrence between ADHD and anxiety. The CoI has several advantages over the previous indices of co-occurrence and comorbidity. First, it can be used for symptom counts in both community and clinical samples, as it is not affected by diagnostic cut-offs. It is especially useful for normative samples where two problems are significantly correlated but co-occurrence would have been difficult to detect when base rates for diagnosis are low. The CoI also allows investigation of common etiologies for co-occurring problems without necessarily assuming that the two conditions under study are separate entities. With this approach, one can take scores of any two given psychopathologies and index their co-occurrence for each individual in a sample regardless of the prevalence of Psychopathology *X*, Psychopathology *Y*, and Psychopathology *X&Y*, regardless of whether or not they are significantly correlated in the sample.

### **Research Questions & Hypotheses**

Using a novel index of co-occurrence, CoI, in a longitudinal adoption study, this study aims to clarify the following research questions:

- Is co-occurring ADHD-anxiety in school years a continuation of these problems in preschool period?

- Is parental *unresponsiveness* in the early years of life an etiology for the development of co-occurring ADHD and anxiety problems in preschool- and school-age?
- Does genetic risk moderate the effect of parental *unresponsiveness* on ADHD-anxiety co-occurrence?

The following hypotheses are formed:

**Hypothesis 1: development of co-occurrence.** Consistent with previous research and the principle of continuity in development, co-occurring ADHD-anxiety problems around school age is expected to be preceded by co-occurring ADHD-anxiety problems around preschool.

**Hypothesis 2: the role of parental responsiveness.** Children of adoptive parents who were less responsive in their parenting in infancy are more likely to develop co-occurring ADHD and anxiety problems from preschool to school years than children whose adoptive parents were more responsive in their parenting in infancy.

**Hypothesis 3: genetic moderation.** Children who have genetic risk for co-occurring ADHD-anxiety problems are more susceptible to low responsive parental care compared to children who do not have genetic risk for co-occurring ADHD-anxiety. We tested maternal and paternal responsiveness separately for Hypotheses 2 and 3. The hypothesized path model illustrated in Figure 1 summarizes the hypotheses.

## Chapter 3: Method

### Participants

Participants include 361 families from the Cohort I of the Early Growth and Development Study (EGDS). The EGDS employs a prospective adoption design that has followed the adoptive and biological families involved in adoption since infancy, with an aim at examining how the interplay between genotype and the environment affects children's developmental adjustment, especially in the socio-emotional domain (Leve et al., 2013). In each family unit, data were collected from the child adopted at birth, the adoptive mother and father, and the biological mother. In approximately one-third of the families, biological fathers also participated in the study.

The EGDS Cohort I participants were recruited between 2003 and 2006. The following criteria were used to assess eligibility for recruitment to the study: domestic adoption placement within 3 months postpartum, nonrelative placement, absence of major medical complications (e.g., extensive surgery, extreme prematurity etc.), and parents' ability to understand the English language at the eighth-grade level.

The EGDS sample was drawn from three regions in the United States through 33 adoption agencies in 10 states: the Northwest, Southwest, and Mid-Atlantic. The full spectrum of adoption agencies in the US is reflected in these agencies including public, private, religion-based, and secular agencies. Among them there are agencies that are favoring open adoptions as well as those that are favoring closed adoptions. In general, the demographic characteristics of the EGDS sample indicate that the adoptive parents have a more advantaged socio-economic background than the biological parents, as is

commonly the case in the general population (DeFries et al., 1994). In the current sample, more than half the adoptive families had an average household income that equals to or above \$100,000 (the mode [25%] was \$70,001-\$100,000), whereas 62% of the biological mothers had less than \$15,000. Indeed, the incomes of the adoptive families in the EGDS sample are higher than the US average household income (DeNavas-Walt, Proctor, & Smith, 2014). Additionally, the adoptive parents' education and income levels were higher than the biological families of children in the sample. The majority of the adoptive parents (over 70%) had completed at least a college degree, while 88% of the biological mothers did not have a college degree. Among adoptive mothers, 35.3% had a graduate-level degree, 42.7% had a 4-year college degree, 9.1% had a 2-year college degree, and 9.1% had a high school degree. Among adoptive fathers, 38.1% had a graduate-level degree, 35.5% had a 4-year college degree, 7% had a 2-year college degree, and 15% had a high school degree. Although these sample characteristics are expected when financial demands and the benefits of adoption placements are considered in the process of placement of the child, it can incur a potential bias towards socio-economically advantaged families stemming from potential restriction of the range in the environment (Stoolmiller, 1999). However, systematic investigations of these potential biases have not shown significant effects of range restriction on heritability and environment estimates (McGue et al., 2007). More detailed information on the overall EGDS design is available in Leve et al. (2013).

The current investigation is based on five waves of data from the EGDS. For the present study, adoptive parent's responsiveness was assessed at child age of 9, 18, and 27

months; biological parent ADHD symptoms were assessed at 56 months; child ADHD and anxiety symptoms were assessed when children are at 4<sup>1/2</sup> and 6 years of age. Frequent assessments throughout early childhood were aimed at capturing the developmental processes as they unfold at this time of rapid change.

Fifty-seven percent of the children were male. The mean ages of biological mothers, biological fathers, adoptive mothers, and adoptive fathers at the time of first assessment were 25 ( $SD = 5.9$ ), 26 ( $SD = 7.4$ ), 38 ( $SD = 5.5$ ), 39 ( $SD = 5.8$ ), respectively. More than 90% of the adoptive parents in the sample were Caucasian. The remaining 10% included African American, Hispanic, and other racial backgrounds. Eleven percent of the children were African American, 10% were Hispanic or unknown, 21% were mixed race, and 58% were Caucasian. Seventy-one percent of the biological mothers were Caucasian, 11% were African American, 7% were Hispanic, 6% were American Indian or Alaskan, and 5% were mixed race. Seventy-five percent of biological fathers were Caucasian, 9% were African American, 9% were Hispanic, 5% were mixed race, 2% were unknown. At the time of initial assessment, 92% of adoptive families were heterosexual couples, 5.5% were same-sex parents, 1% were single mothers. Two and six families were indicated as separated or divorced, at 18 and 27 months, respectively. Because we tested separate models for maternal and paternal responsiveness, two-father families ( $n = 12$ ) were included only in father models, whereas two-mother families ( $n = 8$ ) were included only in mother models. Also, single-mother families ( $n = 5$ ) were excluded when examining paternal responsiveness.

## Procedure

The EGDS data was collected via in-person assessments, phone-based interviews, and online assessments. Biological parents' medical records were also collected. As for in-person procedures, the biological parents were assessed for 2.5 hours in their homes or in another convenient location. The assessments for the adoptive families were conducted in their home and included both interviews and observational assessments that took 2.5 hours to complete. A team of trained interviewers administered the interviews with parents via computer-assisted questions. Each parent also completed a set of questionnaires privately to facilitate honest responses. The adoptive families participated in additional tasks in which their behavioral responses were video recorded and observed. The families were compensated for their time in participating the study.

For each family unit, separate teams conducted the interviews for biological parents and adoptive parents. They were completely blind to each other's data. Prior to conducting the assessments with families, interviewers participated in a 2-day group session, administered pilot interviews, and received videotaped feedback as part of their training. All interviews were audio- or video- recorded. A trained evaluator provided feedback to a randomly selected 15% of the interviews to ensure that they adhere to the standardized protocols of the study.

## Measures

**Child ADHD-anxiety Co-occurrence Index.** At age 4.5 and 6, child ADHD and anxiety problems were measured through web-based administrations of Child Behavior Checklist (CBCL) (Achenbach & Rescorla, 2000), a well-established measure of

behavioral and emotional problems of children. The CBCL form used in the current study targeted children between 1 $\frac{1}{2}$  to 5 years of age. At 4 $\frac{1}{2}$ - and 6-year assessments, adoptive parents provided information regarding a range of behavior problems their child exhibited over the past two months. The adoptive mothers and fathers individually rated each child behavior on a 3-point scale ranging from “not true” to “very true.” Higher scores indicated greater problem behavior of the child. Children’s ADHD and anxiety problems were derived from two DSM-oriented subscales of the CBCL: Attention Deficit/Hyperactivity Problems Subscale and Anxiety Problems Subscale. The Attention Deficit/Hyperactivity Problems Subscale consists of 6 items (item #: 5, 6, 8, 16, 36, 59). Anxiety Problems Subscale consists of 10 items (item #: 10, 22, 28, 32, 37, 47, 48, 51, 87, 99). Alphas for the Attention Deficit/Hyperactivity Problems Subscale were 0.81 for the adoptive mothers and 0.86 for the adoptive fathers for the 4 $\frac{1}{2}$ -year assessment; and 0.80 for the adoptive mother and 0.83 for the adoptive father for the 6-year assessment. Alphas for the Anxiety Problems Subscale were 0.72 for adoptive mothers and 0.75 for adoptive fathers at the 4 $\frac{1}{2}$ -year assessment; and 0.71 for both parents at the 6-year assessment.

The ADHD and anxiety scores were significantly correlated at both ages 4 $\frac{1}{2}$  ( $r = .266, p < .001$ ) and 6 ( $r = .376, p < .001$ ). A Fisher’s Z Test to compare the two correlation coefficients yielded no significant difference across two time points ( $z = 1.184, p = .118$  (two tails)). In order to examine co-occurring ADHD and anxiety problems as a single dependent variable, a co-occurrence index is calculated for the 4 $\frac{1}{2}$ - and 6-year assessment separately from the standardized scores of CBCL subscales for

ADHD and anxiety. The rationale for the calculation of the co-occurrence index is explained in more detail in Chapter 2. The two adoptive parents' reports were correlated significantly for both ADHD ( $r_{4,5 \text{ years}} = .432, p < .001$ ;  $r_{6 \text{ years}} = .515, p < .001$ ) and anxiety ( $r_{4,5 \text{ years}} = .495, p < .001$ ;  $r_{6 \text{ years}} = .421, p < .001$ ), therefore they were averaged to indicate the child's respective ADHD or anxiety score for each wave. When one of the parents' reports was not available, only the available parent's report was used. Negative values were eliminated by the addition of a constant (+2) to each mean score. For each child, the multiplication term of the obtained ADHD and anxiety scores was divided by their sum to index co-occurrence, separately for age  $4\frac{1}{2}$  and age 6. The index yielded a normal distribution for the current sample at both times of assessment ( $skewness_{4,5 \text{ years}} = 0.649$ ,  $kurtosis_{4,5 \text{ years}} = 0.752$ ;  $skewness_{6 \text{ years}} = .850$ ,  $kurtosis_{6 \text{ years}} = 1.553$ ).

**Parental responsiveness.** Adoptive mother and father's responsiveness was indexed by The Parental Responsiveness Scale of the infant and toddler version of the HOME (Home Observation for the Measurement of the Environment) Inventory (Caldwell & Bradley, 1984).

The HOME Inventory was originally created as a measure of availability of social, emotional, and cognitive support in the home for children under 3 years of age (Caldwell & Bradley, 1984). The Parental Responsiveness Subscale of the infant and toddler version of HOME Inventory provides interviewer impressions of adoptive parents' responsiveness to the child based on their observation of parent-child interactions during the home-visit. The Responsiveness Scale consisted of 11 items. Examples of the items include: *mother/father responds to the child's vocalizations with*

*verbal or vocal response; when speaking of or to the child, mother/father's voice positive feeling; and mother/father shows some positive emotional response to praise of the child offered by interviewer.* The interviewers rated the rearing parents' emotional and verbal responsiveness during the visit using a "yes/no" response to these items (For adoptive mothers,  $\alpha = .52, .81, .59$ ; for adoptive fathers  $\alpha = .58, .73, .68$  at 9, 18, and 27 months, respectively.)

**Genetic influences on ADHD-Anxiety co-occurrence.** Biological mother and biological father's co-occurring symptoms of ADHD and Anxiety indexed genetic risk, as measured by Barkley's Adult ADHD scale and Beck Anxiety Inventory, respectively. As part of the 56-month assessment, biological parents completed the 18-item Barkley's Adult ADHD Scale (Murphy & Adler, 2004) providing information on their inattention, hyperactivity, and impulsivity symptoms over the past year. The items were based directly on the 18 DSM-IV symptoms of ADHD in the context of adult behavior such as "fidget with hands or feet or squirm in seat." Each item was rated on a 4-point scale ranging from 'never' to 'very often,' where higher scores indicated severer symptoms. The internal consistency of this measure for the total ADHD score was 0.80 for biological mothers and fathers in this sample ( $\alpha = .89$  for biological mothers, and  $\alpha = .84$  for biological fathers).

Biological parents also completed the Beck Anxiety Inventory (Beck & Steer, 1993) at 18 months, a widely used self-report measure of anxiety symptoms with good reliability and validity. Respondents indicate specific symptoms of anxiety, such as numbness or sweating, they experienced over the past week and the degree to which they

feel bothered by these experiences. Items were based on a 4-point scale where a score of 0 (“not at all”) indicated no symptoms and a score of 3 (“severely”) indicated severe symptoms. The alphas were .92 for the biological mothers and .89 for the biological fathers.

Using the aforementioned overall scores on the Barkley’s Adult ADHD Scale at 56 months and Beck Anxiety Inventory for biological mothers at 18 months, a genetic risk index for co-occurring ADHD and anxiety problems was calculated (see Chapter 2 for details). For each scale, biological mother and biological father’s scores were averaged to index a single risk score for ADHD and anxiety, respectively. When one of the parents’ score was not available, only the available parent’s score was used. A constant (2) was added to each score, in order to eliminate negative values in standardized scores. For each child these ADHD-risk score and anxiety-risk scores were multiplied and then divided by their sum, similar to the procedure followed in the calculation of child anxiety-ADHD CoI. The resulting scores yielded a normal distribution for the current sample (*skewness* = 1.445, *kurtosis* = 3.641).

**Covariates.** In the current study, openness in adoption, prenatal risk, adoptive parent anxiety, child aggressive behavior, biological mother’s and adoptive mother’s age at first interview are accounted for as covariates in the statistical analyses.

***Openness in adoption.*** Openness in adoption was entered to the models as a covariate, because interactions between rearing and biological families after the adoption may influence the estimates of genetic effects. Both adoptive mothers and fathers reported on their perception of openness in adoption according to their particular

adoption experience at 54 months. The responses were based on a 7-point scale item that ranges from 1 (“very closed”) to 7 (“very open”). Alphas for adoptive mother are .81 and .84 in response to contact with biological mother and biological father, respectively. Alphas for adoptive fathers are .81 and .82 in response to contact with biological mother and biological father, respectively. Based on high interrater convergence, mean of standardized adoptive mother and adoptive father openness scores was used as the openness index for each subject (Ge et al., 2008).

**Prenatal risk.** Perinatal obstetric complications might potentially confound estimates of environmental and genetic influences (Marceau et al., 2016). With these considerations, such complications are accounted for in the analyses in order to isolate genetic influences from the influences of prenatal context. Utilizing a pregnancy calendar to aid their recall, biological mothers retrospectively reported several complications they experienced during pregnancy (Caspi et al., 1996): teratogens such as maternal psychotropic drug use, fetal exposure to drugs/alcohol, maternal illness or stress, maternal psychopathology, fetal distress; labor and delivery complications such as required interventions, prolonged labor, cord complications; and neonatal complications such as prematurity or low birth weight.

A perinatal risk score was indexed for each participant utilizing the McNeil Sjostrom Scale for Obstetric Complications (McNeil, 1995). Each event reported by the biological mother was rated on a scale ranging from 1 (not harmful or relevant) to 6 (very harmful to offspring) and a total score was derived from the frequency of responses that are greater than 3, reflecting events that involve potential harm to child development.

Higher scores indicate more perinatal risk. Predictive validity of the McNeil Sjostrom Scale for Obstetric Complications was shown in previous studies (Nicodemus et al., 2008).

***Adoptive parent anxiety.*** From a social-learning perspective, when children are exposed to behavioral and emotional responses of their anxious parents, children may learn anxious behaviors through observation and modeling of parental behaviors in everyday experiences (Askew & Field, 2008; Bandura, 1969; Barrett et al., 1996). Thus, adoptive parent anxiety could be a potential confound of children's anxiety problems. Adoptive mothers' and fathers' anxiety were measured by their responses to the Beck Anxiety Inventory (Beck & Steer, 1993) at the 54-month assessment. Adoptive parents were asked to report the degree to which they experience specific symptoms of anxiety (i.e. numbness, sweating) in the past week on a 4-point scale ranging from "not at all" to "severely." Alphas of the anxiety scale were .82 for both adoptive parents.

***Child aggressive behavior.*** As an important potential confound of ADHD symptoms (Campbell et al., 2000), co-occurring child aggressive behavior problems were accounted for in the analyses. The Aggressive Behavior Subscale from the CBCL (Achenbach & Rescorla, 2000) is used to measure aggressive behavior problems at 4<sup>1/2</sup> and 6 years of age. Nineteen items of the Aggressive Behavior Subscale included "destroys things belonging to his or her family or to other children," "gets in many fights," and "physically attacks people." Adoptive mothers and fathers individually rated each aggressive behavior on a 3-point scale ranging from "not true" to "very true." Higher scores indicated greater problem behavior of the child. In order to eliminate the

overlap, scores on common items between ADHD Subscale and Aggressive Behavior Subscale of the CBCL (“can’t stand waiting; wants everything now,” and “demands must be met immediately”) were subtracted from the total raw score in statistical analyses. For the  $4\frac{1}{2}$ -year assessments, the alphas of the scale were .91 for adoptive mothers and .92 for adoptive fathers. For the 6-year assessments, alphas were .90 and .92, for adoptive mother and fathers respectively.

### **Analytical Plan**

Preliminary analysis was conducted using SPSS Version 21.0. First, as a data preparation step, issues pertaining to a) missing data, b) non-normality, c) linearity, and d) independence of observations due to measurement error were considered. Missing data was analyzed as recommended by Schafer and Graham (2002). Second, descriptive statistics was presented. Third, path analyses were performed using Mplus Version 7 (Muthen & Muthen, 1998-2015). Assumptions of path analysis were tested for the study variables in the preliminary analysis. In order to account for missing data and non-normality, a robust maximum likelihood estimator (MLR) was utilized, which provides unbiased estimates in the presence of both violations of normality assumption and missing data. MLR computes standard errors using a sandwich estimator based on a Huber-White algorithm (Muthen & Muthen, 1998-2015).

In each path model, there were two endogenous variables:  $4\frac{1}{2}$  years co-occurrence and 6 years co-occurrence. There were eight exogenous variables, consisting of an environmental predictor (responsive parenting), genetic moderator (co-occurrence risk based on biological mothers’ phenotypes), an interaction term (GxE: co-occurrence

risk x responsive parenting), and five control variables (explained below). In order to account for the cumulative contribution of parental responsiveness throughout infancy and toddlerhood, respective scores for maternal and paternal responsiveness measured at 9, 18, and 27 months were averaged before entering to the path models.

In order to prevent possible multicollinearity and allow accurate interpretation of interactions (Aiken, West, & Reno, 1991; Preacher, Curran, & Bauer, 2006), all predictors were mean centered in Mplus and the interaction terms were created using the mean-centered versions of the predictors. Towards answering the research hypotheses, the main effects of co-occurrence risk and parental responsiveness (Hypothesis 2: the role of responsiveness), as well as their interactions (Hypothesis 3: genetic moderation) were examined when predicting ADHD-anxiety co-occurrence at age 4<sup>1/2</sup>. A stability coefficient was also used to examine 4<sup>1/2</sup> years (preschool) co-occurrence predicting 6 years (school) co-occurrence (Hypothesis 1: developmental continuity). Child aggressive behavior at age 4<sup>1/2</sup>, adoptive mother anxiety and adoptive father anxiety at 4<sup>1/2</sup>, openness in adoption, and obstetric complications were entered as covariates. Based on preliminary findings suggesting correlations with the dependent variables, biological mother's age, and adoptive mother's age at 9 months were also entered as covariates, but subsequently removed from models as they did not improve model fit and did not have significant estimates of path coefficients. To assess model fit, the following measures of fit were reported when available: nonsignificant Chi-square ( $\chi^2$ ), comparative fit index (CFI) values greater than .95, Tucker-Lewis index (TLI) values greater than .90, and root mean square error of approximation (RMSEA) values less than .05 (Hu & Bentler, 1999).

In line with the study hypotheses, maternal responsiveness and paternal responsiveness were examined in separate path models.

Interactions are interpreted according to guidelines recommended by Preacher et al. (2006) and Roisman et al. (2012). Interactions were graphed at low (-1  $SD$ ) and high (+1  $SD$ ) levels of the moderator (genetic risk for co-occurrence), and between -2  $SD$  and +2  $SD$  of the predictor (adoptive parent responsiveness). Unstandardized coefficients were used to calculate simple slopes (Aiken et al., 1991) and regions of significance tests (Preacher et al., 2006) via online tools recommended in the literature (Preacher, Curran, & Bauer, 2003; Fraley, n.d.). The regions of significance, defined as the specific values of the moderator at which the regression of the dependent variable on the focal predictor moves from non-significance to significance, are illustrated in interaction figures.

## Chapter 4: Results

### Data Preparation

Descriptive analysis demonstrated varying percentage of missing data per indicator and per waves of data collection. Overall, variables reported by adoptive fathers had a slightly larger missing data compared to those reported by mothers. For the responsiveness variable, missing cases on mothers' responsiveness ranged between 5% and 12%, and those for fathers' responsiveness ranged between 9% and 16% across 9 through 27 months of data collection. Biological parents' ADHD and anxiety scores at 27 months were missing for 10% of the available cases for biological mothers and 9% of the available cases for biological fathers. Towards indexing genetic risk for co-occurring ADHD and anxiety problems, both parents' information was used whenever available. When one of the parents' score was missing, only the available parent's score was used. CBCL ADHD Subscale, CBCL Anxiety Subscale and CBCL Aggressive Behavior Subscale reported by adoptive fathers were missing for an average of 32% of the cases, and those reported by adoptive mothers were missing for 26% of the cases. When scores were available from both parents' report, their average was used, when one of the parents' report was missing, only the available parent's report was used towards the computation of the Co-occurrence Index (CoI). The CoI was missing for about 20% of the cases at either 4<sup>1/2</sup> or 6 years.

Little's Missing Completely at Random Test (MCAR) showed that the missingness in the data is completely at random (data is not missing with an identifiable pattern) when all variables are considered ( $\chi^2 = 2101.439$ ,  $df = 2046$ ,  $p = .192$ ). Because

missingness was shown as MCAR, utilization of MLR estimator was justified to deal with missing data in statistical analysis [see Blozis et al. (2013) for a discussion of dealing with missing data in multiple informant studies, including EGDS].

### **Descriptive Analysis**

Means and standard deviations for the sample are presented in Table 3. Repeated-Measures Analysis of Variance (ANOVA) with a Greenhouse-Geisser correction determined that maternal responsiveness differed statistically significantly across three waves of measurement in infancy,  $F(1.79, 541) = 5.50, p = .006$ . Based on the results from post hoc tests using the Bonferroni correction, maternal responsiveness did not significantly differ between 9 months ( $M = 10.42, SD = 0.056$ ) and 18 months ( $M = 10.51, SD = 0.075, p = .955$ ), while it was significantly higher at 27 months ( $M = 10.67, SD = 0.047, p < .001$ ) than maternal responsiveness at 9 months. Also, Repeated-Measures ANOVA showed that paternal responsiveness differed statistically significantly across the three waves,  $F(2, 552) = 10.35, p < .001$ . Post hoc tests for paternal responsiveness demonstrated no significant difference between 9 months ( $M = 9.81, SD = 0.087$ ) and 18 months ( $M = 9.95, SD = 0.101, p = .520$ ), while it was significantly higher at 27 months ( $M = 10.29, SD = 0.077, p < .001$ ) compared to paternal responsiveness at 9 months. No significant group differences on the study variables were noted across levels of gender, education, race, and family composition (separate/divorce, single parent, same-sex parents etc.). Additionally, a paired-samples t-test showed that children's CoI scores did not significantly differ between  $4\frac{1}{2}$  years' ( $M = 1.47, SD = 0.35$ ) and 6 years' ( $M = 1.47, SD = 0.35$ ) assessments;  $t(232) = -.001, p = .999$ .

Bivariate correlations among the study variables are presented in Table 4. When associations were examined between outcome variables (i.e., CoI at 4<sup>1/2</sup> years and CoI at 6 years) and demographic data as potential covariates, no significant correlations were noted except biological mother's and adoptive mother's age at the time of adoption. For the substantive hypotheses testing (discussed later), biological mother's age at 9 months was entered as a covariate as it was correlated with co-occurrence at 6 years ( $r = .166, p = .006$ ). Similarly, adoptive mother's age at 9 months was entered as a covariate as it was correlated with co-occurrence at 4<sup>1/2</sup> years ( $r = -.122, p = .046$ ). Income level did not correlate with any of the dependent variables, and therefore was not included as a covariate. No significant associations were noted between biological parents' ADHD or anxiety and measures of adoptive family environment (i.e., responsiveness and anxiety) ruling out potential gene-environment correlations that might complicate estimates of gene-environment interaction.

Descriptive statistics indicated that the dependent variable, child CoI, was normally distributed at both 4<sup>1/2</sup> years and 6 years. Although skewness and kurtosis were within an acceptable range for most of the independent variables [absolute value of skew <2, absolute value of kurtosis <7; see West, Finch, & Curran, (1995)], non-normality issues were noted in parental responsiveness and adoptive father anxiety variables. The HOME Emotional and Verbal Responsiveness Scale was negatively skewed at all three waves for both adoptive mothers (*skewness* = -2.241, -3.943, -3.459, for 9, 18, and 27 months, respectively) and adoptive fathers (*skewness* = -1.674, -2.136, -2.550, for 9, 18, and 27 months, respectively). It was also leptokurtic for adoptive mothers at 18 months

(*kurtosis* = 18.719) and 27 months (*kurtosis* = 14.490). The skewness and kurtosis was a result of high percentage of adoptive parents' scoring high on parental responsiveness across infancy (for example, at 27 months, about 80% of adoptive mothers and 64% of adoptive fathers received the maximum score of 11). This can be expected from adoptive parents during this period, as they are likely to be highly motivated to establish a working relationship with their baby. Anxiety scores for adoptive fathers at 4<sup>1/2</sup> years were also skewed (2.304) and leptokurtic (7.108). In order to deal with the violations of normality, MLR, a robust maximum likelihood estimator, was utilized to produce unbiased estimates (Muthén & Muthén, 1998-2015).

The review of a P-P plot of standardized predicted values regressed on standardized residuals, all independent variables (i.e., parental responsiveness in infancy, genetic risk, child aggressive behavior at age 4<sup>1/2</sup>, adoptive mother anxiety and adoptive father anxiety at 4<sup>1/2</sup>, openness in adoption, obstetric complications, biological mother's age and adoptive mother's age at 9 months) were found to be linearly associated with the dependent variables (4<sup>1/2</sup> years and 6 years child CoI). No heteroscedasticity was observed. Also, the Durbin-Watson test statistic (ranged between 1.6—2 in the current analyses) ruled out the possibility of potential correlated residuals of the study variables. Correlations between the model predictors and collinearity diagnostics for the multiple regressions in the model were also examined to check for potential multicollinearity. None of the predictors were highly correlated with each other ( $r < .4$ ; VIF values  $< 2.3$ ) ruling out the possibility of multicollinearity.

## Path Analysis

The path model for maternal responsiveness yielded good fit,  $\chi^2(30) = 44.30, p = .045$ , CFI = .96, TLI = .98, RMSEA = .037, 90% CI [.006, .050]. Table 5 presents unstandardized path coefficients. Neither adoptive mother responsiveness ( $\beta = .070, p = .100$ ) nor genetic risk ( $\beta = -.055, p = .179$ ) was a significant predictor of co-occurring ADHD-anxiety at  $4\frac{1}{2}$  years. However, Maternal Responsiveness x Genetic Risk interaction was significant ( $\beta = .085, p = .013$ ). The stability coefficient from ADHD-anxiety at  $4\frac{1}{2}$  years predicting ADHD-anxiety at 6 years was also significant ( $\beta = .701, p < .001$ ).<sup>1</sup> The model explained 48% of the variance in co-occurrence at  $4\frac{1}{2}$  years, and 50% of the variance in co-occurrence at 6 years.

The model fit for paternal responsiveness path model was also good,  $\chi^2(29) = 33.44, p = .260$ , CFI = .99, TLI = .99, RMSEA = .021, 90% CI [.000, .048]. Unstandardized path coefficients are presented in Table 5. Co-occurring ADHD-anxiety at  $4\frac{1}{2}$  years was not significantly predicted by adoptive father responsiveness ( $\beta = -.011, p = .822$ ), or genetic risk ( $\beta = -.062, p = .149$ ), but the interaction term for Paternal Responsiveness x Genetic Risk was significant ( $\beta = .102, p = .015$ ). Also, ADHD-anxiety at  $4\frac{1}{2}$  years significantly predicted ADHD-anxiety at 6 years ( $\beta = .702, p < .001$ ). Overall, the model explained 49% and 50% of the variances in co-occurrence at  $4\frac{1}{2}$  years, and 6 years, respectively.

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<sup>1</sup> For both maternal responsiveness and paternal responsiveness path models, these results did not change when biological mother and adoptive parent age were added as control variables, when the correlations among the model predictors (see method section for details) were removed, or when all predictors were allowed to correlate in the model.

To explore the interaction terms, predicted values for co-occurrence at  $4\frac{1}{2}$  years in situations of low and high genetic risk for co-occurrence [at  $+\/-1 SD$  of the mean of the moderator, as recommended by Aiken & West (1991)] were graphed for various (see below) levels of adoptive parent responsiveness as illustrated in Figures 2 and 3 (for maternal and paternal responsiveness models, respectively). Genetic risk for co-occurrence was normally distributed; the region between -1 and +1 SD represented approximately 95% of the sample. Based on scores prior to centering, the mean ( $M = 1.46$ ) score was close to the median (1.40), while the range was [.88, 3.20].  $+1 SD$  of the mean corresponds to the raw score, 1.818, indicating “high risk,” while  $-1 SD$  of the mean corresponds to the raw score, 1.102, indicating “low risk.”

Roisman and colleagues (2012) argue that it is essential to have a consensus across studies on the normative range of the independent variable that is being probed (parental responsiveness in this case). If extrapolated to a wide enough range of the independent variable, all interactions have the potential for eventual crossing over. Thus, depending on what range of interest is plotted (e.g.,  $+\/-1 SD$  vs.  $+\/-2 SD$  from the mean of the focal predictor) the visual inspection of the interaction plot could potentially yield varying interpretations. In order to establish an agreement among researchers on the independent variable’s *range of interest*, they endorse Aiken and West’s (1991) recommendation of probing interactions from -2 to +2 SD of the mean of the focal predictor, because in a normal distribution, this range covers 95% of the sample. In the current study, due to high skewness in adoptive parent responsiveness variables, +2 SD of the mean of adoptive parental responsiveness was outside of the observed range of

scores in the sample. Thus, the range between the 2.5<sup>th</sup> and 97.5<sup>th</sup> percentiles was probed (covering 95% of the total sample).

For maternal responsiveness, the raw scores were 8 and 11 at the 2.5<sup>th</sup> and the 97.5<sup>th</sup> percentiles, respectively. Given the skewed distribution, approximately 90% of the adoptive mothers scored “high” or “very high” (raw scores between 9-11 on a scale of 1 to 11), approximately 8% scored “moderate” (raw scores between 8-9). The number of mothers who scored below 8 was only 5 cases, which did not allow for a real examination of “low responsiveness” in the study. Similarly, for paternal responsiveness, the raw scores were 7 and 11 at the 2.5<sup>th</sup> and the 97.5<sup>th</sup> percentiles, respectively. Based on the distribution, approximately 85% of the adoptive fathers scored “high” or “very high” (raw scores between 9-11), approximately 11% scored “moderate” (raw scores between 8-9). The remaining 4% of the fathers scored between (6-8). This is an important issue when interpreting Figure 2 and Figure 3 because our “moderate” responsiveness groups substantively consisted of “relatively high responsive” parents.

Roisman et al. (2012) also suggest calculating *regions of significance* to examine the values of the moderator for which the association between the independent variable (i.e., focal predictor) and the dependent variable is significant. The test can also be used to examine the values of the focal predictor for which the association between the ‘moderator’ and the dependent variable is significant. The regression of co-occurrence on maternal responsiveness was significant for all values of genetic risk that fall outside the region [-0.999, -0.154] ( $p < .05$ ). In other words, it was significant for values higher than moderate levels of genetic risk (i.e., -0.154, just below the mean of zero; simple slope =

$0.01, SE = 0.007, p = .05$ ). Thus, the regression line representing  $-1 SD$  below the mean of genetic risk ( $-0.358$ ) was not significant (simple slope =  $-0.01, SE = 0.016, p > .05$ ), while the regression line representing  $+1 SD$  above the mean ( $0.358$ ) was significant (simple slope =  $0.08, SE = 0.016, p < .001$ ). The regression of co-occurrence on genetic risk was significant for all values of maternal responsiveness that fall outside the region [- $0.231, 3.266$ ] ( $p < 0.05$ ). When transformed into raw scores, this range corresponds to [10.295, 13.792]. Because 13.792 exceed the observed range of scores (maximum score = 11), it is not shown in Figure 2. As illustrated with the non-shaded area in the figure, the regression of co-occurrence on genetic risk was not significant for extremely high values of maternal responsiveness. In other words, for children who received very high levels of maternal responsiveness, genetic risk did not have an effect on ADHD-anxiety co-occurrence.

Figure 2 shows an interesting pattern of results; when genetic risk is high, the regression of co-occurrence on maternal responsiveness yielded a significant positive slope. These results indicate that for children who were at high genetic risk, higher maternal responsiveness predicted higher co-occurring ADHD-anxiety, and lower maternal responsiveness predicted lower co-occurring ADHD-anxiety. For children, who were at lower genetic risk, maternal responsiveness did not predict co-occurring ADHD-anxiety.

Similar results were obtained when the interaction between father responsiveness and genetic risk was probed. For both components of the interaction term (genetic risk and paternal responsiveness), regions of significance were calculated. For all values of

genetic risk that fall outside the region [0.021, 0.249] ( $p < .05$ ), the regression of co-occurrence on paternal responsiveness was significant. Namely, it was significant for values either lower than moderate levels of genetic risk or higher than moderate levels of genetic risk (i.e., 0.021 and 0.249, around the mean of zero; simple slope at lower bound = -0.001,  $SE = 0.0009$ ,  $p = .05$ , simple slope at upper bound = 0.02,  $SE = 0.0112$ ,  $p = .05$ ). Thus, both regression lines in Figure 3 (representing -1 SD below the mean of genetic risk (-0.358, simple slope = -0.04,  $SE = 0.016$ ,  $p < .01$ ) and +1 SD above the mean of genetic risk (0.358, simple slope = 0.03,  $SE = 0.016$ ,  $p < .01$ ) were significant. The regression of co-occurrence on genetic risk was significant for all values of paternal responsiveness that fall outside the region [-0.308, 4.363] ( $p < .05$ ). This range corresponds to [9.690, 14.361] when transformed into raw scores. As the maximum paternal responsiveness score on the scale was 11, 14.361 exceeds the observed range in the sample and was not graphed. The regression of co-occurrence on genetic risk was significant for values of paternal responsiveness below 9.690, shown by the shaded area in Figure 3. Thus, genetic risk did not have an effect on co-occurrence for children who received very high levels of paternal responsiveness.

Similar to the findings in the maternal responsiveness model, when genetic risk is high, the regression line had a significant positive slope, indicating that higher paternal responsiveness predicted higher co-occurring ADHD-anxiety, and lower paternal responsiveness predicted lower co-occurring ADHD-anxiety (see Figure 3). Differently from what was found in the maternal responsiveness model, however, in the paternal responsiveness model, the negative slope of the regression line when genetic risk is low

was also significant, indicating that higher paternal responsiveness predicted lower co-occurring ADHD-anxiety and lower paternal responsiveness predicted higher ADHD-anxiety.

## Chapter 5: Discussion

To date, no study has examined early parental *unresponsiveness* as an etiology of ADHD-anxiety co-occurrence in the context of genetic risk. This study examined the prospective effects of parental responsiveness during infancy in the development of co-occurring ADHD and anxiety problems at ages 4 $\frac{1}{2}$  and 6 utilizing a genetically informed research design. Developing a novel approach to operationalizing co-occurrence, the current investigation provides evidence that genetic and environmental mechanisms interact in leading to development of co-occurring ADHD and anxiety during the transition from preschool to elementary school. More specifically, the effects of early parental responsiveness on the development of ADHD and anxiety differ depending on the child's genotype.

### Revisiting the Hypotheses

The developmental period examined in this study (ages 4 $\frac{1}{2}$  – 6) is particularly important as transitioning to school poses new challenges on children's capacities for self-regulation. The first hypothesis posited that co-occurring ADHD-anxiety problems reported at age 6 is preceded by co-occurring ADHD-anxiety problems at 4 $\frac{1}{2}$  years. This prediction was supported by the current data analysis. In both maternal responsiveness and paternal responsiveness models, ADHD-anxiety co-occurrence at age 4 $\frac{1}{2}$  years significantly predicted ADHD-anxiety co-occurrence at 6 years. This finding is in line with the increasing evidence that ADHD-related difficulties exhibited in school years are preceded by similar difficulties in early childhood (von Stauffenberg & Campbell, 2007). It also adds to the existing literature demonstrating the continuity of co-occurring ADHD-

anxiety from 4 $\frac{1}{2}$  to 6 years, and points at the importance of understanding the development of these problems at this time of developmental transition.

If co-occurring ADHD-anxiety problems can be observed in early childhood, can etiological roots be identified in the period of infancy? Developmental research has established that parents' sensitive and contingent responsiveness in infancy lays the foundation for the development of aspects of self-regulation in the first few years of life (Gianino & Tronick, 1988; Kochanska, 1997; Kogan & Carter, 1996; Kopp, 1982), including the development of attention and emotion regulation (Sroufe, 1990). Hence, unresponsive parental care in infancy can result in psychopathology related to these developmental domains, including symptoms of inattention and hyperactivity (Carlson et al., 1995). With these considerations, a main effect of parental responsiveness in infancy was hypothesized on children's co-occurring ADHD-anxiety problems at 4 $\frac{1}{2}$  years (the second hypothesis). In the literature, no study has examined parental responsiveness in infancy in relation to ADHD-anxiety co-occurrence, especially in an adoption design in which environmental aspects of parental influence is separated from genetic confounds (i.e., removal of passive *rGE*). The data did not support the second hypothesis. Neither maternal responsiveness, nor paternal responsiveness had a main effect on child co-occurrence of ADHD-anxiety at 4 $\frac{1}{2}$  years. The nonsignificant finding of the main effects of parental responsiveness is perhaps due to our stringent test of parental responsiveness. The majority of previous studies used data from biologically related families, therefore the potential role of genetic transmission is not separated from environmental influences in the parental responsiveness research. Also, potential interactions between parenting

and genotype are not accounted for in these studies. Thus, lack of a main effect of parental responsiveness in infancy needs to be considered in the context of potential genetic influences.

As complementary to the second hypothesis, the third hypothesis predicted a moderating role of genetic risk. In particular, we expected that children who have genetic risk for co-occurring ADHD-anxiety problems are more susceptible to *unresponsive* parental care compared to children who do not have genetic risk for co-occurring ADHD-anxiety. There were significant interactions between genetic risk and maternal responsiveness, and between genetic risk and paternal responsiveness in infancy on co-occurring ADHD-anxiety problems at  $4\frac{1}{2}$  years. Interestingly, however, the interaction effects were not in the predicted direction. The data, instead, yielded a more complex picture.

In the maternal responsiveness model, for children who were at high genetic risk for co-occurring ADHD-anxiety, surprisingly, higher maternal responsiveness in infancy predicted higher co-occurrence of these problems at age  $4\frac{1}{2}$ , whereas lower maternal responsiveness in infancy predicted lower co-occurring problems. For children who were at low genetic risk for co-occurring ADHD-anxiety, this effect was not significant. Similarly, in the paternal responsiveness model, higher paternal responsiveness in infancy predicted higher co-occurrence of ADHD-anxiety problems at age  $4\frac{1}{2}$ , whereas lower paternal responsiveness in infancy predicted lower co-occurring ADHD-anxiety problems for those who were at high genetic risk. This effect of parental responsiveness was significant in the opposite direction for children who were at low genetic risk for co-

occurring ADHD-anxiety. In this group, higher paternal responsiveness in infancy predicted lower co-occurrence of these problems in preschool, whereas lower paternal responsiveness in infancy predicted higher co-occurring problems. Altogether, the picture emerged from the GxE findings suggests that 1) for children whose genetic risk for co-occurrence is low, high parental (specifically paternal) responsiveness predicts lower co-occurrence problems – which is consistent with our prediction--, but 2) for children who inherit high genetic risk for co-occurrence problems, high parental responsiveness in infancy seem to exert adverse effects on later child co-occurring ADHD-anxiety.

Before making a full interpretation of these partially unexpected findings, one needs to consider the context of the distribution of parental responsiveness among adoptive parents in the current study. The adoptive parents' responsiveness was severely negatively skewed. Scores that might be considered as “low responsiveness” were not adequately represented in the sample. Majority of adoptive parents were either highly responsive or moderately responsive in their interactions with the infant, thus what appeared to be “low” responsive parenting in this sample should not be considered “low” substantially; rather it should be considered as “moderately” responsive. Specifically, where the maximum possible score was 11 on the scale, the mode among adoptive parents was 11, while the average was around 10. Ninety percent of adoptive mothers and 85% of adoptive fathers can be considered as either “highly” or “very highly” responsive (scores within the range of 9-11). Approximately 8% of the adoptive mothers and 11% of the adoptive fathers can be considered as “moderately high responsive” (scores between 8-9). In both maternal and paternal responsiveness models, there were only a few mothers

or fathers who scored below “8.” Thus, the sample did not include a sufficient number of cases for a true examination of “low responsiveness” in infancy.

This picture is expected when the study design is considered. First of all, all parents in the sample were adoptive parents who recently underwent their adoption experience. Parental responsiveness was measured across the first 27 months of life, during which adoptive parents welcome the newly adopted infant to the family and work on establishing a bond with her/him. This is a time frame during which adoptive parents are perhaps most motivated and invested in their relationship with their adopted infant in order to make the adoption “work.” Not surprisingly, both adoptive mothers and adoptive fathers likely tried to perform their best to be able to respond to the infants’ needs, cues, and interests, which resulted in higher responsiveness observed in the home environment.

When contextualized for the current sample, the observed scores of responsiveness can be interpreted to range between “moderate,” “high,” and “very high.” Therefore, current findings indicate that for children who were at high genetic risk for co-occurring ADHD-anxiety, very high parental (maternal or paternal) responsiveness in infancy is not adaptive (predicts higher co-occurring ADHD-anxiety at  $4\frac{1}{2}$  years), whereas moderate levels of parental responsiveness in infancy predicted better adaptation (lower co-occurring problems). Perhaps “highly responsive” behavior of adoptive parents in the current sample was “excessively responsive” to the point that it was intrusive for infants who are at high genetic risk.

These findings extend the literature on developmentally inappropriate levels of high parental responsiveness (LeMoyne & Buchanan, 2011; Nelson, 2010; Schiffrian,

Godfrey, Liss, & Erchull, 2015; Segrin, Woszidlo, Givertz, Bauer, & Taylor Murphy, 2012) to the period of infancy by suggesting that children with high genetic risk for ADHD-anxiety co-occurrence do not benefit from extreme levels of parental responsiveness in the first years of life. Although parental responsiveness is generally considered as a positive construct, negative consequences of excessive responsiveness is evident in the literature, especially in the context of the child's certain predispositions. Overly-involved, overprotective, intrusive, and similar parenting behaviors can take off opportunities to practice self-regulation skills from the child in early years of life (Chorpita & Barlow, 1998) and exacerbate anxiety-related behavior (i.e., social withdrawal) in temperamentally inhibited/fearful children (Bayer, Sanson, & Hemphill, 2006; Kiel & Buss, 2011; McShane & Hastings, 2009). In a recent observational study, Kiel and Buss (2012) observed mothers and toddlers in a variety of laboratory tasks and found that protective behavior in low-threat, but not high-threat situations were associated with concurrently observed fearfulness and shy/inhibited behavior (correlates of anxiety) one year later. This association was further strengthened by the mothers' accuracy in anticipating their toddlers' stress in these situations. Parents' protective behavior in low-threat situations can be conceptualized as excessively high responsiveness, which is associated with maladaptive outcomes as shown in the current study. There is also evidence that mothers' intrusiveness in infancy (defined as "the extent to which the mother disrupts the baby's ongoing activity rather than adapting the timing and quality of her interactions and initiations to the baby's state, mood, and current interests") predicts symptoms of ADHD (hyperactivity and distractibility) in

preschool age (Carlson et al., 1995, p. 42). Parents' extreme responsiveness (e.g., over-involvement, intrusiveness, overprotectiveness) could potentially interfere with the early development of autonomy and self-regulation, especially for children who are genetically vulnerable to develop ADHD-anxiety co-occurrence problems. For these children, moderate levels of parental responsiveness can be optimal, as it gives them more freedom to explore on their own, practice self-regulation, and allows the development of autonomy and independent functioning.

Overall, from a classification perspective, these psychopathologies (i.e., ADHD and anxiety) belong to two broader categories: externalizing and internalizing syndromes, respectively. Yet, they commonly present in the same individual posing an example of *heterotypic comorbidity*. The findings from this investigation points at the heterogeneity in the way psychopathology presents in children and the complex interplay of genes and environment in understanding their etiology. Consistent with the developmental principle of *multifinality*, parental *unresponsiveness* is highlighted as a common environmental etiology for co-occurring symptoms of ADHD and anxiety, where genetic risk moderates its influence on the heterogeneity in the symptom manifestation.

### **Strengths**

Developmental psychopathology perspective emphasizes a multiple levels of analysis approach in which understanding the functioning of the organism at one level contributes to the understanding of developmental processes at another level (Cicchetti & Toth, 2009). In most studies on ADHD and anxiety co-occurrence, parental influences at the environmental level are confounded by parental transmission at the genetic level. One

of the major strengths of this investigation is the employment of a multiple levels of analysis approach through utilizing the adoption design. The EGDS study includes information from the phenotypes of biological parents, which represented genetic risk of the respective psychopathologies under study. The study also included information from the adoptive parents, which represented the environmental contribution to the adopted child's development. The interactional effects of these two processes (i.e., genetic and environmental) were examined on the developmental outcomes of co-occurring psychopathologies (i.e., ADHD and anxiety).

The second strength of this dissertation is its novel approach to operationalizing co-occurrence. Unlike previous work, the Co-occurrence Index (CoI) proposed here quantifies co-occurrence by accounting for its two important dimensions simultaneously: *severity* (i.e., regardless of the type of psychopathology, a particular subject's overall level of dysfunction) and *proximity* (i.e., the extent to which two psychopathologies go together). As summarized in Chapter 2, the CoI has many advantages over other methods of measuring co-occurrence and comorbidity. Specifically, it is not affected by base rates, and clinical cut-offs, therefore can be used with any data including normative samples where psychopathology is measured with a continuous scale. The CoI is particularly useful for samples where two conditions significantly covary but co-occurrence is difficult to discover due to low base rates. The CoI does not necessarily assume that the two conditions under study are separate entities, and allows investigation of common etiologies for co-occurrence.

The third strength of the current study is the prospective longitudinal design. Data was collected starting with the time of adoption, and continuing across five waves (birth through 6 years of age) from a normative sample of child, biological family, and adoptive family triads. Most work in the literature on ADHD in general, and ADHD-anxiety co-occurrence in particular, consisted of cross-sectional clinical studies, which do not provide insight on early developmental origins of these co-occurring psychopathologies. The current study provides insight on co-occurring ADHD and anxiety problems in children regardless of clinical referral or diagnosis, and is able to track the developmental antecedents of psychopathology starting from birth. The prospective longitudinal design allowed the examination of parental responsiveness in infancy predicting co-occurring ADHD-anxiety problems later in development. It also allowed capturing these co-occurring problems during an important developmental period (i.e., at 4<sup>1/2</sup> to 6 years), where school transition is a salient developmental task. From a developmental psychopathology perspective, these times of developmental transformation are crucial to understand the transactions between prior adaptations and subsequent environmental challenges (Sroufe & Rutter, 1984).

Another strength is the utilization of information from multiple reporters on child problem behavior. At both 4<sup>1/2</sup> and 6 years, both adoptive mothers and adoptive fathers reported on children's ADHD and anxiety symptoms. Parental responsiveness was measured via interviewer impressions in families' home settings. Compared to self-report measures commonly utilized in the ADHD literature, this study provides a more accurate estimation of parenting in families' natural environment. Also, adoptive parents' anxiety

was controlled in statistical analysis as a potential confound of parental responsiveness (especially excessive responsiveness) and a potential predictor of child anxiety (Wood et al., 2003).

Finally, the examination of paternal responsiveness, in addition to maternal responsiveness, is a major strength of this dissertation. In general, in the literature on parental responsiveness in general, and parental responsiveness in relation to ADHD or anxiety problems in particular, fathers' responsiveness has been largely neglected. Although there is evidence pointing at the important role of paternal responsiveness in the development of ADHD-related problems (Keown, 2012), and the development of child anxiety (Bögels & Phares, 2008), no study to date examined father's responsiveness in infancy in relation to these psychopathologies, and their co-occurrence. This study contributes to the literature by providing insight on the role of paternal responsiveness on the development of ADHD-anxiety co-occurrence utilizing an adoption design.

### **Implications for Intervention**

From a developmental point of view, potential conceptual and empirical concerns emerge with the employment of diagnostic classifications (see Chapter 1). This dissertation aimed at drawing attention to bridging the gap between developmental research and clinical practice for a substantial number of children who present with co-occurring ADHD and anxiety. Thus, clinically relevant child outcomes were utilized while attending to developmental considerations. In most cases, children's ADHD symptoms are readily diagnosed, while co-occurring anxiety symptoms remain

unattended. Moreover, the conventional ADHD treatments could be problematic in terms of their anxiety symptoms (Bedard & Tannock, 2007).

Although parenting interventions have been proven to be useful for children who are diagnosed with ADHD (Newcorn et al., 2001), the parenting context that precedes the development of ADHD problems did not receive as much attention in the literature as the parenting context of anxiety. For children who present with co-occurring ADHD and anxiety problems, treatment needs to involve the parents' responsiveness as a common etiology underlying both psychopathologies. Also, early prevention (i.e., infancy) is an urgent need for children who are at risk for these problems.

The results of the current study reinforce the potential of therapeutic interventions that target parents' understanding of the infant's cues, interests, developmental needs, and capacities in order to respond to the infant in a developmentally appropriate, nonintrusive fashion. Parent-child relationship in infancy is foundational in the development of emerging regulatory capacities, and behavioral and emotional disturbance later in life (Sroufe, 2000). By promoting developmentally and contextually appropriate parental responsiveness in the early years of life, it may be possible to prevent ADHD and anxiety problems before they become more visible in preschool and later in school years. Finally, depending on the child's level of genetic (or other individual-level) risk, over-responsiveness can also be problematic. Interventions need to incorporate this newly emerging phenomenon, and inform parents on the balance between child's need for autonomy versus parental support.

## **Limitations & Directions for Future Research**

The contribution of the presentation and the aforementioned study strength notwithstanding, readers are reminded of a few caveats of the study. First, as the dependent variable in the current study, the CoI consisted of DSM-based CBCL subscales of ADHD and anxiety. When raw scores are considered, the children in the sample were not reported to have very high levels of psychopathology, especially anxiety. Most children in the EGDS sample did not present with symptoms at potentially clinical levels either at age 4<sup>1/2</sup> or 6. This could be a limitation in terms of generalizing these findings to children who have higher levels of co-occurring ADHD and anxiety.

Second, the sample characteristics of the study pose limitations in terms of the generalizability of the findings to high-risk, or more disadvantaged groups of populations. The adoptive families in this sample consisted of mostly White, middle-to-upper-middle class, educated parents. Also, as mentioned before, adoptive parents were likely to be highly motivated in achieving high-quality parenting, especially around the time they adopted the child. These results need to be replicated with more diverse, disadvantaged, and high-risk families where low responsiveness is more frequently observed.

Third, it is important to remind that genetic risk was inferred utilizing data on biological parents' phenotype (ADHD and anxiety symptoms), rather than a direct measure of their genotype (i.e., DNA). When indexing genetic risk, biological parents' self-report of ADHD and anxiety symptoms were not combined with their clinical

evaluation. Also, for two-third of the families whose data from biological fathers were missing, only biological mother's phenotype was used to infer genetic risk.

The fourth limitation is the skewness of the parental responsiveness measure used in this study (i.e., The Parental Responsiveness Subscale of the infant and toddler version of HOME). Most adoptive parents scored very high on responsiveness during infancy. Thus, there was no opportunity to examine the effects of low responsiveness. Also, interviewer ratings measuring parental responsiveness in 2<sup>1/2</sup>-hour interviews on this standardized scale might be limited in documenting the complexities of parent's behavior. Readers are also reminded that the alphas for this scale were not optimal.

An additional limitation is that the computation of the CoI was based on a bivariate model, therefore it cannot account for a co-occurrence whereby three or more psychopathologies co-occur. The CoI index is useful only to operationalize the co-occurrence phenomenon in two psychopathologies. The question of how to account for multimorbidity/multi-occurrence in a research framework needs to be addressed in future studies with multivariate models of psychopathology.

Finally, as implicated in the literature review, the effect of parental responsiveness on the development of the co-occurring psychopathologies of ADHD and anxiety is likely mediated by the child's developing regulatory mechanisms of emotion, attention, and behavior. These mediating mechanisms were not accounted for in the current study. For example, neurocognitive models of anxiety emphasize the regulation of attention to threat via the prefrontal control mechanisms (Bishop, 2009; Eysenck, Derakshan, Santos, & Calvo, 2007; Puliafico & Kendall, 2006), which are also

considered to underlie the executive dysfunctions observed in ADHD (Nigg, 2013).

Future research needs to focus on these mechanisms underlying co-occurring ADHD-anxiety, in order to identify common targets of prevention and intervention.

## **Conclusion**

This dissertation aimed at providing an overview of ADHD-anxiety co-occurrence. A novel approach has been proposed for quantifying bivariate co-occurrence in empirical research. Parental *unresponsiveness* in infancy is examined as a potential common etiology interacting with genetic risk. Findings highlight the importance of attending to excessively high parental responsiveness in the context of genetic risk, which is associated with higher co-occurring ADHD and anxiety problems around ages 4 $\frac{1}{2}$  and 6.

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**Appendix A: Tables**

Table 1. A Hypothetical Example of the Co-Product of Psychopathologies A and B

		Psychopathology A			
		1	2	3	4
Psychopathology B	1	1	2	3	4
	2	2	4	6	8
	3	3	6	9	12
	4	4	8	12	16

Table 2. A Hypothetical Example of the Co-occurrence Index of Psychopathologies A and B

		Psychopathology A			
		1	2	3	4
Psychopathology B	1	0.50	0.66	0.75	0.80
	2	0.66	1.00	1.20	1.33
	3	0.75	1.20	1.50	1.71
	4	0.80	1.33	1.71	2.00

Table 3. Descriptive Statistics of Study Variables

	Maternal Model		Paternal Model	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
TC 6 years Co-occurrence	1.476	0.35	1.474	0.35
TC 4 $\frac{1}{2}$ years Co-occurrence	1.473	0.34	1.469	0.35
AM Responsiveness	10.526	0.75	NA	NA
AF Responsiveness	NA	NA	9.998	1.08
Co-occurrence Genetic Risk	1.461	0.36	1.459	0.36
Obstetric Complications	2.275	1.33	2.279	1.33
Openness in Adoption	2.969	0.95	3.008	0.96
TC 4 $\frac{1}{2}$ years Aggressive Behavior	8.209	4.37	8.086	4.46
AM Anxiety	5.049	4.72	5.063	4.77
AM Anxiety	3.204	4.05	3.238	4.05
AM/AF Age	38.417	5.48	39.109	5.93
BM Age	24.561	5.85	24.582	5.76

Note: AM, adoptive mother; AF adoptive father; BM, biological mother; TC, target child.

\*\* $p < .01$ . \* $p < .05$ .

Table 4. Bivariate Correlations of Study Variables

Variables	1	2	3	4	5	6	7	8	9	10
1. Co-occurrence (6 years)	1									
2. Co-occurrence (4½ years)	.69**	1								
3. AM Responsiveness	.00	.044	1							
4. AF Responsiveness	-.003	-.015	.520**	1						
5. Genetic Risk	-.002	.00	-.002	-.061	1					
6. Obstetric Complications	.086	.049	.025	.030		1				
7. Openness in Adoption	-.081	-.098	-.053	-.012	.053	-.072	1			
8. TC Aggressive Behavior (4½ years)	.528**	.654**	-.036	.012	.093	.008	-.018	1		
9. AM Anxiety	.142*	.167**	.034	.066	-.19**	.026	.059	.137*	1	
10. AF Anxiety	.103	.200**	-.048	-.029	.075		-.017	.123	.150*	1
						.140*				

Note: AM, adoptive mother; AF adoptive father; TC, target child.

\*\* $p < .01$ . \* $p < .05$ .

Table 5. Unstandardized Path Coefficients (*b*) for Final Models: Prospective effects of parental responsiveness in infancy and toddlerhood on co-occurring child ADHD and anxiety problems at age 4 $\frac{1}{2}$  and 6 years.

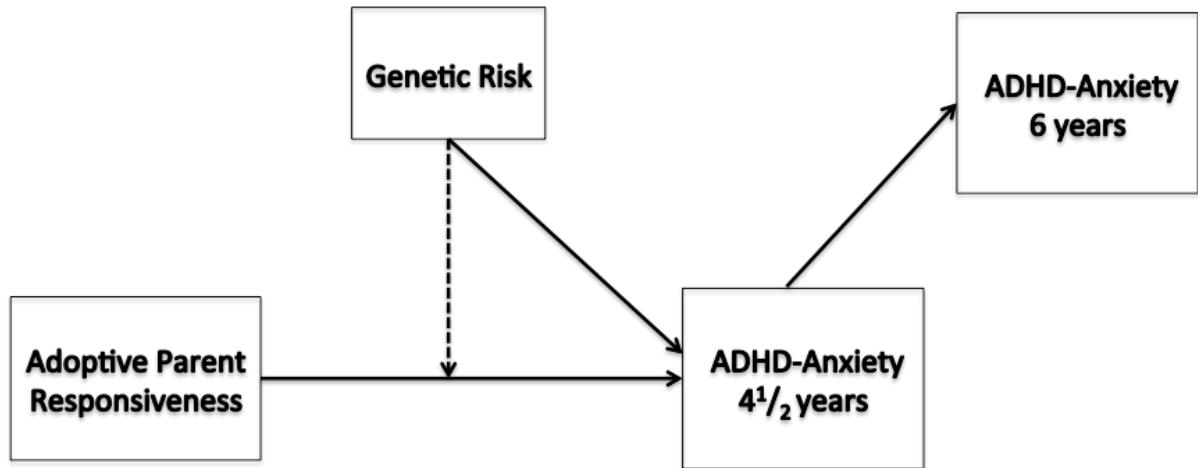
Parameters	Genotype x AM Responsiveness		Genotype x AF Responsiveness	
	<i>b</i>	SE	<i>b</i>	SE
Intercept (Co-occurrence at 6 years)	.412**	.079	.437**	.077
Intercept (Co-occurrence at 4 $\frac{1}{2}$ years)	1.474**	.015	1.473**	.016
Covariates				
Obstetric Complications	.012	.011	.010	.011
Openness in Adoption	-.04	.017	-.037*	.018
TC Aggressive Behavior at 4 $\frac{1}{2}$ years	.049	.004	.051**	.004
AM Anxiety	.005	.003	.004	.003
AF Anxiety	.11*	.004	.010*	.004
Genotype				
Co-occurrence Genetic Risk	-.052	.039	-.060	.042
Environment				
AM Responsiveness	.032	.019	--	--
AF Responsiveness	--	--	-.004	.017
Genotype x Environment				
Genetic Risk x AM Responsiveness	.120*	.044	--	--
Genetic Risk x AF Responsiveness	--	--	.104*	.041
<i>R</i> <sup>2</sup> Co-occurrence at 4 $\frac{1}{2}$ years	.479**	.054	.488**	.053
<i>R</i> <sup>2</sup> Co-occurrence at 6 years	.492**	.062	.493**	.062

Note: AM, adoptive mother; AF adoptive father; TC, target child.

\*\**p* < .01. \**p* < .05.

**Appendix B: Figure**

Figure 1. Hypothesized Model



*Note:* Dashed line represents moderation effect.

Figure 2. Interaction Plot for Genotype Moderation on Maternal Responsiveness

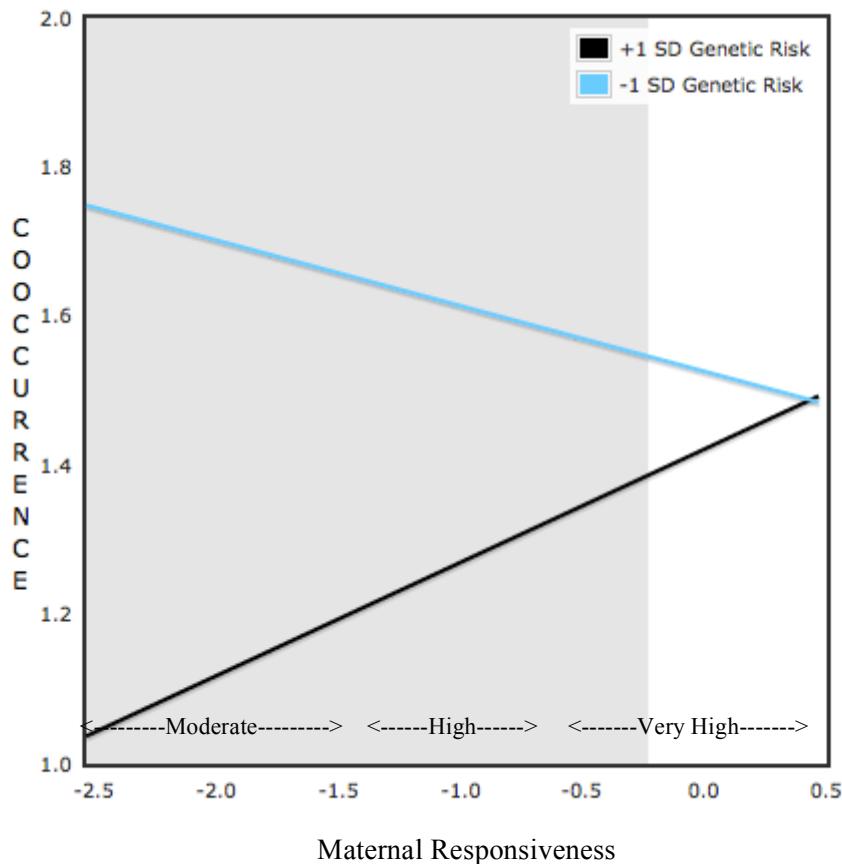
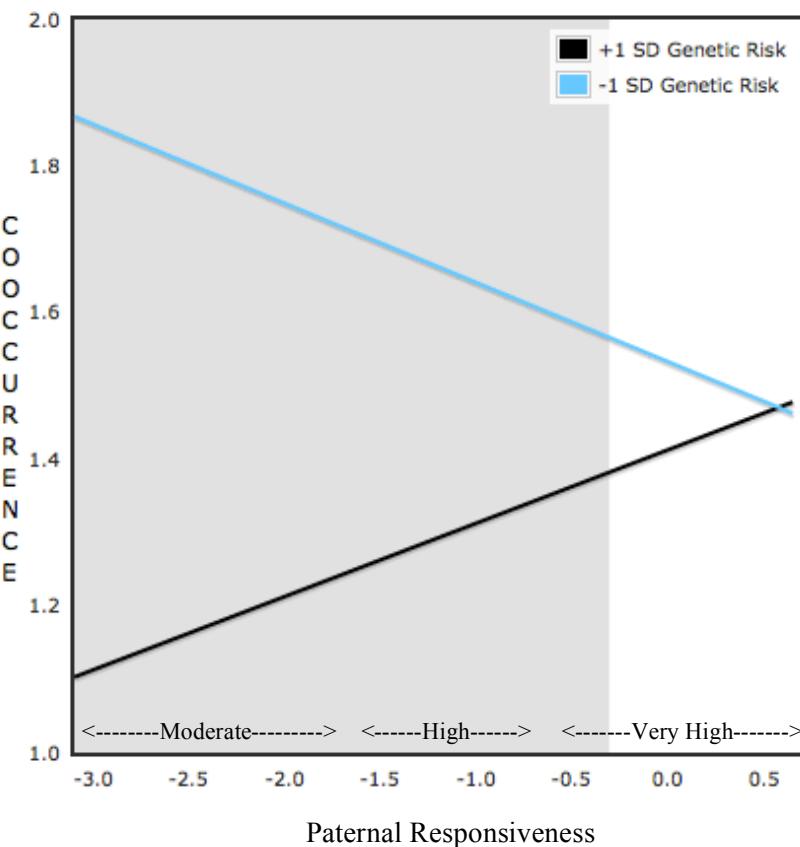


Figure 2. Genetic risk moderates the effect of maternal responsiveness on ADHD-Anxiety co-occurrence at 4 $\frac{1}{2}$  years. Maternal responsiveness scores are centered to the mean. Only the line representing +1 SD of the mean Genetic risk is significant.

Figure 3. Interaction Plot for Genotype Moderation on Maternal Responsiveness



*Figure 3.* Genetic risk moderates the effect of paternal responsiveness on ADHD-Anxiety co-occurrence at 4½ years. Paternal responsiveness scores are centered to the mean. Both lines of Genetic risk (+/-1 SD of the mean) are significant.