

8-9-2014

ANTENATAL ANXIETY PREDICTING CHILD OUTCOMES IN FRAGILE X SYNDROME

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ANTENATAL ANXIETY PREDICTING CHILD OUTCOMES IN FRAGILE X
SYNDROME

by

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Submitted in Partial Fulfillment of the Requirements

For the Degree of Doctor of Philosophy in

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2014

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DEDICATION

To my parents, my younger brother, and my grandparents. Your confidence in me has always been my most powerful form of motivation. I am forever grateful for your unwavering love and support.

ACKNOWLEDGEMENTS

This dissertation would not have been possible without the assistance of my committee members. I sincerely appreciate the help and guidance that each of you provided me throughout this process. I would also like to thank the Neurodevelopmental Disorders Research Lab at the University of South Carolina. Working as a member of this team throughout my graduate career has been an invaluable learning experience. Finally, I would like to acknowledge my wonderful roommate for her frequent encouragement and priceless friendship.

ABSTRACT

A relationship between maternal anxiety during pregnancy, known as antenatal anxiety, and negative child outcomes has been consistently shown in the literature. Children of mothers who experienced antenatal anxiety have higher rates of physical, behavioral, cognitive, and emotional deficits compared to children whose mothers did not experience clinical levels of anxiety during pregnancy. To date, research on antenatal anxiety and child outcomes is almost exclusively limited to non-clinical populations. Therefore, little is known about the relationship between maternal anxiety during pregnancy and suboptimal cognitive and behavioral development in children with disabilities. Families with fragile X syndrome (FXS) are a unique population with which to examine these relationships, as children with the full mutation have higher rates of problem behavior and cognitive deficits compared to typical children and mothers with the pre- and full-mutation are at an increased risk for developing psychopathology. The current study examines the relationship between maternal antenatal anxiety and child outcomes, specifically problem behavior, autistic symptoms, and HPA axis functioning in children with the full mutation. Results suggested that maternal antenatal anxiety significantly predicted child anxiety/depression. Current maternal anxiety was also predicative of child internalizing behaviors and attention problems. Implications of findings, limitations, and directions for future research are discussed.

TABLE OF CONTENTS

DEDICATION.....	iii
ACKNOWLEDGEMENTS.....	iv
ABSTRACT.....	v
LIST OF TABLES.....	vii
CHAPTER I INTRODUCTION.....	1
CHAPTER II METHOD	17
CHAPTER III RESULTS	31
CHAPTER IV DISCUSSION	39
REFERENCES	53

LIST OF TABLES

Table 2.1. Demographics of maternal sample with the FMR1 premutation.....	25
Table 2.2. Descriptive statistics of child problem behavior scores.....	26
Table 2.3. Descriptive statistics of autism symptom severity scores.....	27
Table 2.4. Descriptive statistics of cortisol scores.....	28
Table 2.5. Descriptive statistics of adaptive behavior scores.....	29
Table 2.6. Correlation Matrix.....	30
Table 3.7. Effects of regression model parameters predicting child problem behavior scores.....	36
Table 3.8. Effects of regression model parameters predicting autism symptom severity.	37
Table 3.9. Effects of regression model parameters predicting child salivary cortisol from antenatal anxiety.....	38

CHAPTER I

INTRODUCTION

The prenatal period is a critical time for development and vulnerability, as evidenced by research examining the influence of teratogenic agents on fetal growth. Teratogens such as viruses, alcohol, and drugs are related to undesirable outcomes in offspring that may be evident at birth or emerge later in life. Of recent interest in the literature is the role of maternal anxiety during pregnancy, also known as antenatal anxiety, in predicting negative child outcomes. Antenatal psychological stress, including anxiety, has been consistently shown to be related to physical, behavioral, and cognitive deficits in children (Beversdorf et al., 2005; Felice, Saliba, Grech, Cox, & Calleja, 2007; Giardinelli et al., 2012; Wadhwa, Sandman, Porto, Dunkel-Schetter, & Garite, 1993). Research on antenatal anxiety and deleterious child outcomes is almost exclusively limited to non-clinical populations. Subsequently, little is known about the relationship between clinical levels of maternal anxiety during pregnancy and suboptimal cognitive and behavioral development in children with disabilities. Although a few studies have looked at these relationships in autism (Beversdorf et al., 2005; Ward, 1990), no research has been conducted in populations with fragile X syndrome (FXS). Families with FXS provide a unique population with which to examine these associations, as children with the full mutation may have a distinct vulnerability for negative outcomes due to their genetic disorder. Further, mothers with the pre- and full-mutation are at an increased risk

of developing psychopathology. When examining the development of negative outcomes in children with FXS, it is important to consider the interaction between the child's environment, both pre- and postnatal, and their individual characteristics. As proposed by Sameroff's transactional theory (Sameroff, 1975), the continuously dynamic process between the child and their environment plays a critical role in development. While a child may have a genetic predisposition for certain behaviors, the interaction between those genes and the child's environment shape how the child develops. The goal of this study is to examine the influence of the child's prenatal environment, as measured by maternal antenatal anxiety, on postnatal child outcomes (i.e., child problem behavior, autism symptom severity, and salivary cortisol) in children with FXS, while taking into account additional variables that influence child development such as current maternal anxiety.

Antenatal Stress in Non-Clinical Populations

Underlying mechanisms. Maternal antenatal anxiety has been proposed to affect children through a variety of mechanisms including exogenous variables and fetal programming (Gitau, Fisk, Teixeira, Cameron, & Glover, 2001; Talge, Neal, & Glover, 2007). Exogenous, third party variables include maternal caregiving style, demographics, drug and alcohol use, and diet. Literature on maternal diets in animals suggested that mothers on a low protein diet during pregnancy had offspring with higher blood pressure and affected heart rate (Brawley, Poston, & Hanson, 2003; Langley & Jackson, 1994; Petry, Ozanne, Wang, & Hales, 1997). Fetal programming also influences the interaction between maternal antenatal anxiety and child outcomes. With fetal programming, the maternal anxiety experienced during pregnancy ultimately alters the developing

physiological system of the fetus (Talge, Neal, & Glover, 2007). Environmental influences are not the only mechanisms proposed to affect fetal development as research has also explored endogenous variables. There are a number of studies on the underlying physiological mechanisms of suboptimal child outcomes due to exposure to mothers experiencing antenatal anxiety. Two primary hypotheses have emerged to explain these relationships: the hypothalamic-pituitary-adrenal (HPA) axis hypothesis and the sympathetic nervous system hypothesis.

The HPA axis is attributed to regulating and reflecting physiological arousal associated with social and emotional functioning and stress. The HPA system allows individuals to adapt to changes in their environment by aiding in the body's return to homeostasis after the experience of stressful stimuli. When the body experiences stress, the hypothalamus is triggered and hormones are secreted that lead to the production of adrenocorticotrophic hormone or ACTH. ACTH is responsible for the production of cortisol, a glucocorticoid hormone, from the adrenal cortex. Subsequently, a common measurement of the HPA system that is related to social and emotional functioning is salivary cortisol. High levels of salivary cortisol are correlated with increased experienced stress, and research has suggested that high and low baseline cortisol levels are indicative of suboptimal outcomes. The relationship between maternal and fetus cortisol is evident during pregnancy, as there is support for similar cortisol values in mother and child due to the passing of metabolized cortisol through the placenta (Gitau et al., 2001). Although the transmission of some cortisol is normal, higher doses may cause changes in fetal development that have been associated with negative emotions and

withdrawal reactions in newborns (Davidson, 1998; Dawson, Klinger, & Panagiotides, 1992).

In addition to the HPA axis hypothesis, the literature provides support for other physiological mechanisms that may allow for insight into the relationship between antenatal stress and negative child outcomes (Monk, Myers, Sloan, Ellman, & Fifer, 2003). One mechanism associated with the sympathetic nervous system is noradrenaline. This hormone is produced in the mother when she experiences stress or anxiety and may cause contractions in the uterus or reduce uterine blood flow (Talge, Neal, & Glover, 2007) , which, subsequently, negatively affects fetal outcomes.

Measurement. While few studies have specifically examined antenatal anxiety, the majority of literature exploring the relationship between negative maternal emotional and/or psychological characteristics during pregnancy and child outcomes has focused on the broader topic of psychological stress. Antenatal psychological stress is commonly measured by the presence of maternal psychopathology (i.e., anxiety and/or mood disorders), exposure to a traumatic experience, or maternal self- reported stress (i.e. life events, daily hassles, perceived stress, or pregnancy related stress). Ratings on self-report measures are frequently used to determine criteria for maternal psychopathology and only two known studies have used clinical interviews as a diagnostic measure for maternal anxiety or mood disorder during pregnancy (Felice et al., 2007; Giardinelli et al., 2012). These studies, however, only explored prevalence of maternal antenatal psychopathology as opposed to the relationship with child outcomes. Antenatal psychological stress has been measured throughout pregnancy, although the majority of mothers were questioned between 10 and 32 weeks gestation. A few studies have also used retrospective

screenings as a measure of maternal psychological stress (Beversdorf et al., 2005; Ward, 1990). There is debate in the literature, however, regarding the stage of fetal development that is most sensitive to maternal psychological stress. Collectively, studies on indicate there are critical periods throughout pregnancy in which maternal psychological stress can be harmful to the fetus including 12-22 weeks (Huizink, Robles de Medina, Mulder, Visser, & Buitelaar, 2003; O'Connor, Heron, Golding, Beveridge, & Glover, 2002; Field et al., 2003; Van den Bergh et al., 2005), 25 – 28 weeks (Beversdorf et al., 2005), 28 – 30 weeks (Wadhwa, Sandman, Porto, Dunkel-Schetter, & Garite 1993), and 32 weeks (O'Connor et al., 2002). There is little agreement in the literature about how much maternal psychological stress is necessary for sustainable, negative developmental effects, as similar outcomes have been found in children of mothers with reportedly low levels of experienced stress when compared to mothers who reported high levels of stress.

Of particular relevance to the current study is the impact of maternal antenatal psychopathology, specifically clinical levels of anxiety, on child development. One consistent finding in the literature is a more robust relationship between antenatal anxiety and adverse child outcomes when compared to maternal depression, during pregnancy (Field et al., 2003; Glover, O'Connor, Heron, & Golding, 2004; O'Connor et al., 2002). For example, Glover and colleagues (2004) found that it was maternal antenatal anxiety, and not depression, that predicted mixed-handedness in children. An additional study found that mothers who experienced high levels of anxiety during pregnancy had preschool children with increased risk of emotional problems when compared to children of mothers who experienced depression (Barker, Jaffee, Uher, & Maughan, 2011).

A variety of covariates have emerged in the literature examining antenatal anxiety and child outcomes including maternal demographic variables and postnatal psychopathology. In reference to demographic variables, Copper and colleagues (1996) found low education (i.e. < 13 years) and marital status were associated with maternal anxiety and depression during pregnancy. Maternal age, ethnicity, and education level are also related to child outcomes including hyperactivity/inattention, emotional symptoms, and preterm births (Brett, Strogatz, & Savitz, 1997; Loomans et al., 2011). In addition to demographic variables, postnatal maternal psychopathology has been found to be predictive of child outcomes; however, the majority of studies continued to find a relationship between antenatal anxiety and child variables even after controlling for current maternal psychopathology (Brouwers, van Baar, & Pop, 2001; O'Connor et al., 2002; Van den Bergh & Marcoen, 2004; Van den Bergh et al., 2005). For example, Loomans and colleagues (2011) found maternal current emotional distress, as measured by scores on a depression, anxiety, and stress questionnaire, to be related to inattention and emotional symptoms in 5-year-old children. Once controlling for current maternal distress and a number of other covariates, antenatal anxiety was still predictive of child emotional problems and inattention in both male and female children. It is critical to control for current maternal psychopathology due to the bi-directional nature of the maternal-child interaction and the influence this interaction can have on child development (Sameroff, 1975). Once controlling for this relationship, research can attempt to more clearly elucidate the relationship between maternal anxiety during pregnancy and the later development of negative outcomes in the child.

Ultimately, antenatal psychological stress, including clinical levels of anxiety, has consistently shown a relationship with children's physical, behavioral, and cognitive development, notwithstanding the use of different methods for measuring maternal variables across studies. These relationships, however, have been sparsely examined in populations with disabilities and have never been explored in individuals with genetic disorders such as FXS.

Child Outcomes. The effects of antenatal psychological stress, including anxiety, are often seen as early as birth with children exhibiting smaller head circumference, lower birth weights, and earlier deliveries (Lou et al., 1994). Outcomes related to antenatal psychological stress persist further into the postnatal life, with the majority of research on suboptimal development in infancy and early childhood. The areas most strongly associated with suboptimal development due to exposure to antenatal psychological stress are child cognitive and social-emotional functioning. In studies on children's cognitive abilities, scores on the Bayley Mental Developmental Index (MDI) in infants and toddlers are most commonly used to predict outcomes. Across studies, maternal psychological stress, including anxiety, was related to decreased MDI scores in children aged 8 months (Huizink, Robles de Medina, Mulder, Visser, & Buitelaar, 2003), 18 months (Bergman, Sarkar, O'Connor, Modi, & Glover (unpublished), and 2 years of age (Laplante et al., 2004). An additional study examined school performance in 6-year-old children and showed that increased maternal antenatal psychological stress was related to lower grades in school (Niederhofer & Reiter, 2004) suggesting that antenatal stress is associated with deficits in broader cognitive development in children. In regards

to social-emotional functioning, antenatal psychological stress has been predictive of child behavior problems (Brouwers et al., 2001; Field et al., 2002).

Specific to antenatal anxiety, a relationship was found in a sample of 5-year-old children suggesting that those with mothers who experienced antenatal anxiety had higher rates of overall problem behavior and less pro-social behavior after controlling for maternal age, ethnicity, education level, current maternal distress, and self-reported history of psychopathology (Loomans et al., 2011). Gender and age effects have also been suggested in the literature with males showing greater behavioral problems than females at 4 years of age (O'Connor et al., 2002; Van den Bergh and Marcoen, 2004); however, O'Connor and colleagues (2002) showed that both males and females were equally affected by antenatal anxiety at age 7.

More specific behavioral outcomes due to antenatal anxiety such as increased self-reported child anxiety have also been reported even after controlling for maternal postnatal anxiety and SES (Van den Bergh & Marcoen, 2004). In a review of the literature by Talge and colleagues (2007), the authors examined the strength of these effects and suggested that, among studies, the magnitude of these findings were collectively considerable with antenatal anxiety accounting for around 15% of the variance in child behavioral problems (i.e. ADHD, anxiety or depression, or conduct disorder). The most robust relationship between antenatal anxiety and child behavior, however, has been on deficits in attention with a number of studies supporting this relationship in children ranging in age from four to fifteen (O'Connor et al., 2002; Van den Bergh et al., 2005). More specifically, one study found that maternal antenatal

anxiety was responsible for 22% of the variance in ADHD symptoms in children between the ages of eight and nine (Van den Bergh & Marcoen, 2004).

HPA-Axis Functioning. As discussed, the HPA axis is one potential mechanism by which antenatal stress influences child outcomes. The HPA axis is known as the body's stress system and is commonly measured by salivary cortisol with higher cortisol scores indicative of increased stress. In animal research, rats that were exposed to stressors during pregnancy were more likely to have offspring with increased basal activity of the HPA axis and more powerful and extended HPA responses during a stress paradigm (Weinstock, Matlina, Maor, Rosen, & McEwen, 1992). Postnatal behavioral outcomes such as increased emotionality in the offspring were also discovered in this population (Weinstock et al., 1992). An additional study on prenatally stressed rats found that maternal stress exposure was predictive of anxious behavioral responses related to HPA axis functioning in offspring including increased escape behaviors when the rats were exposed to novel stimuli (Vallee et al., 1997). Ultimately, findings in animal research provide support for hyper arousal in prenatally stressed offspring.

Investigators focusing on HPA axis dysregulation in children of mothers who experienced anxiety during pregnancy have shown similar results with increased levels of child salivary cortisol in children associated with the presence of maternal antenatal anxiety. A study of diurnal cortisol, an indicator of HPA-axis functioning, in 10-year-old children suggested that antenatal anxiety in late pregnancy predicted child awakening cortisol levels. This relationship continued to remain once the authors controlled for maternal postnatal anxiety and depression (O'Connor et al., 2005). These findings have extended into research on children in later adolescence (14–15 years old) as Van den

Bergh and colleagues (2008) showed that mothers who were experiencing anxiety between 12 and 22 weeks of gestation had adolescents with a higher, flattened daily cortisol profile. A flattened cortisol profile was also found to be associated with depression in the post-pubertal daughters of mothers who had experienced stress during pregnancy.

Antenatal Anxiety in Populations with Disabilities

The effects of antenatal anxiety on child outcomes in populations with disabilities are, for the most part, unknown. What has been published in this area, however, has focused predominately on antenatal psychological stress and autism outcomes. One study by Beversdorf and colleagues (2005) suggested that maternal prenatal stress, as measured by stressful life events, was associated with an increased risk for autism. Mothers of children with autism had a higher rate of antenatal life stressors, particularly between 21 and 32 weeks gestation, compared to mothers of children with Down syndrome and controls. Additionally, the authors found that children with autism who experienced antenatal stress in utero during this time frame had increased deficits in language suggesting a relationship between antenatal stress and autism symptom severity. Ward (1990) also conducted a retrospective study on autism and prenatal exposure to family stress in addition to psychiatric problems and showed that 32% of mothers of children with autism experienced family discord while pregnant with their child with autism as opposed to 3% of mothers of typically developing children.

Stress experienced due to exposure to a natural disaster may also be related to increased risk for autism as Kinney and colleagues (2008) found that the prevalence of autism increased significantly in a cohort of mothers who experienced the severe

exposure to storms while pregnant. The risk for developing autism was greatest in children who were prenatally exposed to storms during the middle and end of gestation. As discussed, atypical laterality in the child's brain also relates to maternal stress during pregnancy. Although not unique to populations with disabilities, atypical laterality has been observed in children with schizophrenia, attention problems, learning disabilities and autism (Glover et al., 2004).

In contrast to retrospective studies, Ronald and colleagues (2011) assessed the relationship between maternal reported stress during pregnancy, as measured by the experience of stressful life events, and the later development of autistic symptoms in two-year-old males and females. Results suggested that, in males alone, antenatal stress exposure predicted autistic traits in toddlers after controlling for ADHD and additional confounding variables (Ronald, Pennell, & Whitehouse, 2011). To date, however, no studies have examined the role of maternal antenatal anxiety in the development of autistic characteristics in children.

Fragile X Syndrome

Affecting approximately 1 in 4,000 males, the full mutation (>200 CGG repeats), also known as FXS, involves FMR1 gene dysfunction (Crawford et al., 1999) and is the leading known genetic cause of heritable intellectual disability and autism. The full mutation is associated with delays in development (Bailey, Hatton, & Skinner, 1998; Bailey, Raspa, Bishop, & Holiday, 2009), speech abnormalities (Belser & Sudhalter, 2001), behavioral problems (Sarimski, 2010), anxiety (Woodcock, Oliver, & Humphreys, 2009), deficits in adaptive skills (Sarimski, 2010), and social abnormalities (Hall, Lightbody, Huffman, Lazzeroni, & Reiss, 2009; Roberts et al., 2009b). Up to 90% of

individuals with the full mutation exhibit at least one autism symptom (Hagerman & Hagerman, 2002) and between 25 and 60% of children with the full mutation meet diagnostic criteria for autism (Bailey, Hatton, & Skinner, 1998; Turk & Graham, 1997). Due to the X-linked nature of the disorder, males typically express more severe deficits than females; however, development across females is highly variable (Bailey et al., 2009). As opposed to the full mutation, carriers with CGG repeats ranging from 55-199 are considered to have the FMR1 premutation. As many as 1:110 females in the general population are affected with the FMR1 premutation.

Transmission patterns in FXS are well established with mother carriers, both with the full mutation and FMR1 premutation, having a 50% chance of passing the FMR1 gene onto their offspring. Due to the disorder being X-linked, a male carrier has an 100% chance of passing the gene on to his daughters and a 0% chance of passing it to his sons; however, the majority of males with the full mutation do not reproduce (Sherman, 1995). Expansion to the full mutation in the child is associated with CGG repeat length and research has found that the number of repeats is often higher in offspring compared to parents (Fu et al., 1991). Research has also suggested that the risk of expansion from the FMR1 premutation to the full mutation in the offspring is greater if passed through the female carrier and dependent on maternal CGG repeat length. This is in contrast to a male carrier whose risk of expansion of the gene in his offspring is exceptionally small (Sherman, 1995).

Maternal FMR1 Premutation. Unique health problems have been found to be associated with the FMR1 premutation including fragile X-associated tremor/ataxia syndrome (Tassone & Hagerman, 2012) primary ovarian insufficiency (Allen et al.,

2007), and increased rates of stress, depression, and anxiety (Bailey, Sideris, Roberts, & Hatton, 2008; Roberts et al., 2009a; Seltzer et al., 2011). Studies on mothers with the FMR1 premutation report 57% meet DSM-IV diagnostic criteria for a mood or anxiety disorder (Roberts et al., 2009a). The majority of research on females with the FMR1 premutation has been on mothers of children with the full mutation and suggests that child problem behavior and poor social support are associated with elevated parenting stress and comprised quality of life in this population (Wheeler, Skinner, & Bailey, 2008). Investigators interested in exploring additional maternal characteristics associated with increased psychopathology in women with the FMR1 premutation found an association with negative life events, marital status, and genetic markers (Hartley et al., 2012; Roberts et al., 2009; Seltzer et al., 2011). Specific to genetic markers, midsize CGG repeat length (90-105 CGG repeats) combined with the experience of an increased number of negative life events was predictive of higher rates of mood and anxiety symptoms and blunted morning cortisol values in mothers with the premutation (Seltzer et al., 2011).

Child Outcomes. Early in childhood, the full mutation has been associated with autism, emotional and behavioral problems, and abnormal arousal regulation. Research on autism in children with the full mutation suggest the prevalence approaches 50% when using autism diagnostic criteria that includes pervasive developmental disorder not otherwise specified (Demark, Feldman, & Holden, 2003; Kaufmann et al., 2004; Philofsky et al., 2004). When examining within-syndrome differences, children with the full mutation and comorbid autism display profiles analogous to individuals with idiopathic autism compared to those with the full mutation (Demark et. al., 2003; Lewis

et al., 2006). The largest difference between the two groups has been found in the communication domain (Kaufmann et al., 2004; McDuffie et al., 2010) and the restricted interests/repetitive behaviors domain (McDuffie et al., 2010).

Behavioral symptoms of the full mutation include increased rates of internalizing disorders (e.g., anxiety) and attention difficulties. Research has found that as many as 63% of boys with the full mutation meet criteria for an internalizing disorder (von Gontard et al., 2002) and 86% of males and 77% of females meet diagnostic criteria for an anxiety disorder (Cordeiro, Ballinger, Hagerman, & Hessler, 2011). In addition to high rates of anxiety, attention deficits are characteristic of the full mutation in infants and children (Cornish, Scerif, & Karmiloff-Smith, 2007; Scerif et al., 2012) with notable difficulties in visual attention (Cornish, Scerif, & Karmiloff-Smith, 2007; Hooper et al., 2008) and executive functioning (Munir, Cornish, & Wilding, 2000).

With respect to HPA functioning in individuals with the full mutation, research has suggested a range of abnormalities including early onset puberty (Moore, Chudley, & Winter, 1990), anomalies in prepubertal growth (Loesch, Huggins, & Hoang, 1995), and elevated melatonin production (Gould et al., 2000). When cortisol is examined in relation to behavioral characteristics, investigators suggest that children with FXS who had deficits in social behavior, particularly increased gaze aversion and fidgeting behavior, were more likely to have reductions in cortisol scores (Hall, DeBernadis, & Reiss, 2006; Hessler, Glaser, Dyer-Friedman, & Reiss, 2006). Blunted cortisol change scores were also found to be associated with higher levels of autism symptom severity in males with FXS and autism (Roberts et al., 2009b).

Present Study

There is consistent evidence of a relationship between maternal antenatal psychological stress, including anxiety, and negative child outcomes in non-clinical populations; however, research on these associations is limited in its understanding of the role of vulnerability factors such as genetics and developmental disabilities. Families with FXS provide a unique population with which to examine these relationships, as children with the full mutation can be proposed to have a double vulnerability due to their genetic disorder and the increased rates of psychopathology in mothers with the pre- and full-mutation. Further, children with the full mutation display a range of behaviors that have been found to be related to antenatal anxiety in non-clinical populations so it is of particular interest whether antenatal anxiety is predictive of any of these behaviors in children with the full mutation. The current study examines the following research questions:

1. What is the relationship between antenatal anxiety and problem behavior (i.e., internalizing, anxiety/depression, and inattention) in children with the full mutation?
2. Is there a relationship between antenatal anxiety and HPA axis functioning in children with the full mutation?
3. What affect, if any, does maternal antenatal anxiety have on autism symptom severity in children with the full mutation?

Based on previous literature on antenatal anxiety in typical developing populations, it is hypothesized that children of mothers who experienced antenatal stress will have higher rates of behavior problems, particularly in the domains of internalizing behaviors, anxiety/depression, and inattention. These children are also expected to have atypical HPA axis functioning as measured by salivary cortisol. Finally, based on the

autism literature, we predict higher rates of autism symptom severity in children who experienced antenatal anxiety.

CHAPTER II

METHOD

The present study included data from a longitudinal study on families of children with FXS. A sample of families were recruited nationally for the study through FXS support groups, ongoing studies, advertising and networking at conventions, parent list serves, and the Neurodevelopmental Disorders Research Center's Autism Research Registry at the University of North Carolina – Chapel Hill. Inclusion criteria included having at least one child with the full mutation and a maternal diagnosis of pre- or full mutation.

Subjects

Data on 108 mothers aged 20 – 49 years ($M = 36.40$) were available for this study. Eleven mothers had the full mutation and 93 mothers had the FMR1 premutation. Data on mutation status were missing for four mothers. This study focused on women with the FMR1 premutation ($N = 93$) because previous literature has suggested vulnerabilities for psychopathology in this population (Hessl et al., 2005; Lachiewicz, Dawson, Spiridigliozzi, & McConkie-Rosell, 2006); Roberts et al., 2009a); however, secondary analyses were run including those with the full mutation. Mothers without mutation status were dropped from analyses. The average IQ for the FMR1 premutation group was 107.64 (range 73 – 132). See Table 2.1 for descriptive statistics of the FMR1 premutation sample. Child participants included 79 males between the ages of 11 and 178 months (M

= 72.94; *SD* = 52.22) and 14 females ages 11 to 179 months (*M* = 57.21; *SD* = 54.40). All children had the full mutation.

Measures

Primary Variables

Given our research questions, the primary independent variable across all models was maternal antenatal anxiety. The primary dependent variables represented a range of child outcomes including problem behavior (internalizing, anxiety/depression, attention), autism symptom severity, and salivary cortisol (baseline, reactivity, regulation).

Maternal Antenatal Anxiety and Depression. For the current study, maternal mood and anxiety disorders were assessed using the Structured Clinical Interview for DSM Disorders (SCID-I). The SCID is a semi-structured interview developed to assess DSM-IV Axis I diagnoses with test-retest reliabilities ranging from .35 to .78 (First et al., 2002; SCID). Prior to administering the SCID, assessors underwent extensive training and were required to have a SCID interview observed by a psychiatry research interviewer. Once trained, assessors administered the SCID to the mothers in person.

In order to meet criteria for a mood or anxiety disorder, mothers had to endorse a set of symptoms within a diagnostic hierarchy directly derived from DSM-IV criteria for one or more of the following mood or anxiety disorders: major depression, panic disorder, panic disorder with or without agoraphobia, social phobia, specific phobia, obsessive compulsive disorder, post traumatic stress disorder, generalized anxiety disorder. Examiners also requested onset and offset dates for each episode of psychopathology. Antenatal anxiety was defined as meeting diagnostic criteria for any anxiety disorder at any time during pregnancy. The majority of mothers with antenatal

anxiety met criteria for an anxiety disorder during their whole pregnancy. Audio recordings of the interviews were reviewed following the assessments to ensure correct scoring. A consulting research psychiatrist also verified any identified or questionable diagnoses. Twenty percent ($n = 19$) of mothers with the FMR1 premutation met criteria for antenatal anxiety. Current occurrence of an anxiety/mood disorder was also calculated for this study. Current anxiety was defined by the mother meeting full criteria for a major depressive episode and/or criteria for any anxiety disorder within 30 days of the interview. Thirty mothers with the FMR1 premutation met criteria for current anxiety disorder and two of these mothers also met for current mood disorder. For the current study, a categorical score of present or not present antenatal anxiety was the dependent variable and a categorical score on current maternal anxiety was included as a covariate.

Child Problem Behavior: Internalizing Symptoms, Anxiety/Depression, and Inattention. Problem behaviors were assessed using The Child Behavior Checklist (Achenbach, 1991), a parent-report measure with a standardized procedure for assessing behavioral and emotional difficulties in children. Items on the CBCL are rated as not true (0), somewhat or sometimes true (1), or very true or often true (2). The CBCL is often used in research on children with disabilities and has been proven to be a reliable and valid measure of child problem behavior with children with the full mutation (see Bailey, Sideris, Roberts, & Hatton, 2008). For the current study, raw scores on the internalizing, anxiety/depression, and attention domains were converted to T-scores and included as a continuous dependent variable to determine what child emotional and behavioral outcomes were related to antenatal anxiety; see Table 2.2 for descriptive statistics of child problem behavior scores. Two separate CBCL checklists were used, as one form is

designed for children 1.5- 5 years and the second form is for children 6-18 years. For younger children, the internalizing domain was comprised of scores on anxious/depressed, somatic complaints, withdrawn/depressed, and emotionally reactive domains. The checklist for children between the ages of 6 and 18 years of age combined scores on anxious/depressed, somatic complaints, and the withdrawn/depressed domains to calculate internalizing scores. Internalizing T-scores between 60 and 63 are in the borderline range and scores above 63 are in the clinically significant range at the 90th percentile. For anxiety/depression and attention scores, T-scores between 67-70 are considered to be at-risk and T-scores above 70 are clinically significant. For the current study, 9 children scored at-risk in the internalizing domain, 6 in the anxious/depressed domain, and 18 in the attention domain. Seventeen children scored in the clinically significant range for Internalizing behaviors and 17 also scored clinically significant for attention behaviors. No children were in the clinically significant range for anxiety.

Child Autism Symptom Severity. The Childhood Autism Rating Scale (CARS) was used to measure autistic behavior. The CARS is a 15-item examiner rating scale that represents a range of behaviors related to autism including communication, anxiousness, imitation, and relating to people. Each item is scored on a likert scale from 1 (within normal limits) to 4 (severely abnormal). Scores on the individual items are tallied and an overall score above 30 is indicative of mild to severe autistic symptoms. Two examiners completed the CARS via consensus using standardized guidelines following each assessment. The CARS is frequently used as a reliable and valid measure of autism symptom severity in the FXS literature (Hatton et al., 2002, Shanahan, Roberts, Hatton, Reznick, & Goldsmith, 2008; Sullivan et al., 2006). For the current study, the overall

score on the CARS was included as a continuous dependent variable to determine the relationship between autism symptom severity and antenatal stress. Twenty-three children scored above 30 in the mild to severe autistic range; refer to Table 2.3 for descriptive statistics of CARS scores.

Child Salivary Cortisol. Child cortisol, a marker of the HPA system, was collected at two time points during each assessment by cotton salivettes. Cortisol is a common, reliable measurement of HPA-axis dysfunction in children with the full mutation (Hessl, Glaser, Dyer-Friedman, & Reiss, 2006; Roberts et al., 2009b). To collect the salivary cortisol, children were asked to chew on cotton salivettes for one to two minutes. It was also requested that the mothers have their children refrain from drinking dairy products or anything acidic for at least one hour prior to the saliva collection to avoid contamination of the sample. The first cortisol sample was collected within 15 minutes of the examiners' arrival at the family's home (baseline) and the second collection occurred at the end of the assessment (reactant). The average time between collections was three and a half hours. A cortisol change score was calculated by subtracting the initial baseline cortisol score from the reactant score and then recording the absolute value. The change score provides a measure of the child's physiological response to the assessment process and is indicative of HPA regulation. Thirty-two children had baseline data and all but five of these children had reactant and change cortisol data. Missing cortisol data were due to failure to collect the sample during the assessment and errors in saliva collection. Once collected, the Salimetrics' Salivary Cortisol Enzyme Immunoassay kit (EIA) was used to process the salivettes and amounts were reported in micrograms/deciliter. For the current study, baseline, reactant, and

change cortisol scores were included as a continuous dependent variable to examine the influence of maternal antenatal stress on child HPA functioning. See Table 2.4 for descriptive statistics of cortisol scores.

Potential Covariates

Child Adaptive Behavior. Children’s adaptive functioning abilities and overall status were assessed using the Vineland Adaptive Behavior Scales (VABS), Interview Edition (Sparrow, Balla, & Cicchetti, 1984). Trained examiners administered the VABS to mothers in a semi-structured interview format. Investigators interested in examining adaptive functioning in children with disabilities, including FXS, frequently use the VABS (see Bailey, Sideris, Roberts, & Hatton, 2008). The total age equivalent score was used for the present study; refer to Table 2.5 for descriptive statistics of adaptive behavior scores.

Maternal Demographic Variables. Mothers provided information on their ethnicity, age, education level, income, and marital status. Mothers were also administered the Vocabulary and Matrix Reasoning subtests of The Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999) to obtain a two-subtest full-scale IQ score.

Statistical Procedures

Seven multiple regression models were constructed to test whether or not antenatal anxiety predicted child problem behavior, autism symptom severity, and salivary cortisol levels. The models were represented by the following formula:

$$\hat{Y} = A + \dots + B_k X_k + B_{AA} AA$$

Where \hat{Y} was the dependent variable of interest, A was the Y intercept, X s represented the covariates, B s were the coefficients assigned to the variables, and AA referred to antenatal anxiety. Analyses were performed using the IBM SPSS software.

Prior to the regression analyses, assumptions of the data were examined including normality, linearity, and homoscedasticity of residuals. To examine normality and homoscedasticity, visual examinations of histograms were conducted. Linearity was also assessed through an examination of bivariate scatterplots. The variables that violated assumptions were transformed using appropriate transformation methods. Outliers within the data were also identified prior to the major analyses. Box plots were used to examine univariate outliers. Multivariate outliers were assessed using Mahalanobis distance with criteria of $p < .001$ and no outliers were detected. Regression results were reported with the original data; however, differences across the two models are discussed below, if necessary.

Following the evaluation of the assumptions, Pearson correlations were conducted to assess the degree of relationship between antenatal anxiety, the dependent variables, and the following potential covariates: current anxiety; maternal age, IQ, race; and child adaptive functioning. Any significant correlations among variables were examined for their inclusion in the models. Multicollinearity was determined by a correlation of $> .90$ as suggested by Tabachnick and Fidell (2007).

Once the above steps were complete, seven separate regression analyses were conducted. As stated, each regression model included maternal antenatal anxiety in addition to the identified covariates for the dependent variable of interest. The proportion of variance accounted for by maternal antenatal anxiety and the covariates were

examined and reported. Follow up analyses were run including mothers with the full mutation and the significance of the overall models did not change. As a follow-up, Bonferroni correction was applied to adjust for multiple comparisons at the significance level of $p < .007$. The purpose of the correction was to reduce inflation in Type I error resulting from the analysis of seven separate regression models. Results before and after the Bonferroni correction are discussed.

Table 2.1. Demographics of maternal sample with the FMR1 premutation.

	<i>N</i>	<i>%</i>
Race/ethnicity		
White	72	77
African American	17	18
Latino	2	2
Other	2	2
Marital status		
Married	79	73
Divorced	14	13
Separated	2	2
Single, never married	8	7
Engaged	1	1
Education		
Less than high school	3	3
High school and additional training	14	15
Some college	20	21
Associates degree	12	13
College degree	19	20
Some post college	9	10
Masters degree	15	16
Professional or advanced degree	1	1
SES		
Lower	21	22
Middle/Upper	72	77

Table 2.2. Descriptive statistics of child problem behavior scores

	Measure	<i>N</i>	<i>M</i>	<i>SD</i>	Min	Max
	Internalizing	89	55.13	9.70	33	80
CBCL	Anxiety/Depression	89	54.92	5.98	50	70
	Attention	89	62.98	8.34	50	83

Table 2.3. Descriptive statistics of autism symptom severity scores

Measure	<i>N</i>	<i>M</i>	<i>SD</i>	Min	Max
CARS	90	26.49	6.37	15.5	47.5

Table 2.4. Descriptive statistics of cortisol scores

	Measure	<i>N</i>	<i>M</i>	<i>SD</i>	Min	Max
Cortisol	Baseline	26	.30	.38	.07	1.79
	Reactant	22	.24	.36	.04	1.63
	Regulation	22	.14	.22	.00	1.00

Table 2.5. Descriptive statistics of adaptive behavior scores

Measure	<i>N</i>	<i>M</i>	<i>SD</i>	Min	Max
Vineland	73	29.05	23.07	8.0	129.0

Table 2.6 Correlation Matrix

Variables	1	2	3	4	8	9	10	11	12	13	14
1. Internalizing Scores											
2. Attention Scores	.59**										
3. Anxiety Scores	.74**	.33**									
4. CARS Scores	.27*	.33*	.03								
5. Antenatal Anxiety	.35**	.16	.32**	.00							
6. Maternal IQ	.37**	.16	.33**	.01	.20						
7. Current anxiety or depression	.40*	.26*	.23*	-.01	.67**	.20					
8. Maternal Age	-.02	.16	.09	.04	-.03	.15	.07				
9. Child Age	.02	.25*	.13	.01	.14	-1.92	.18	.56**			
10. Adaptive Behavior	.07	.20	.17	-.24*	.27*	.00	.27*	.44**	.77**		
11. Child Gender	-.01	-.20	.19	-.34**	.10	.07	.01	-.06	-.11	.28*	

CHAPTER III

RESULTS

Preliminary analyses

As noted, assumptions were examined and led to the transformation of multiple variables to reduce skewness and improve the normality and homoscedasticity of residuals. The baseline and reactant cortisol data were positively skewed and, subsequently, log₁₀ transformed prior to the primary analyses. This transformation is commonly used in cortisol analyses, as the data are often skewed (Gunnar & Vazquez, 2001; Hessler et al., 2002; Roberts et al., 2009b). The total age equivalent scores for adaptive behavior were positively skewed and log₁₀ transformed. T-scores for the attention domain on the CBCL were also skewed; however, they remained skewed following a transformation of the data so the original data were included in this study. All other variables were normally distributed and did not require transformations.

Multivariate outliers and collinearity were assessed for each regression model. There were no instances of multicollinearity among variables or outliers within the models.

Pearson correlations were run to determine if correlations were present between maternal antenatal anxiety, the covariates identified in the literature (current anxiety and depression; maternal age, IQ, race; child adaptive functioning; child age; and child gender), and the child related dependent variables (internalizing scores, anxiety scores,

attention scores, autism symptom severity, baseline cortisol, reactant cortisol, and regulation cortisol). Table 3.6 displays the results of the correlation matrix.

As seen in Table 3.6, child internalizing scores were significantly correlated with maternal antenatal anxiety, maternal IQ, and current maternal anxiety. Child anxiety/depression scores were correlated with maternal antenatal anxiety, maternal IQ and current maternal anxiety. Child attention scores were related to child age and current maternal anxiety or depression. Autism symptom severity scores were correlated with child gender and adaptive behavior. No variables were correlated with baseline cortisol, reactant cortisol, or regulation cortisol scores. Significant relationships ($p < .05$) demonstrated by these correlations were included in the models.

Primary analyses

The research question in this study addressed the relationship between antenatal anxiety and child outcomes, specifically problem behavior, autistic symptoms, and HPA axis functioning in children with the full mutation. Seven regression models were used to test the hypotheses. The first three regression models dealt with child problem behavior, one dealt with autism symptoms severity, and the last three reflected child cortisol analyses.

Child Problem Behavior

Child Internalizing Scores. The first multiple regression equation predicted child internalizing scores from maternal antenatal anxiety and included maternal IQ and child age as covariates. The full model including all variables predicting internalizing scores was statistically significant, $F(3, 77) = 19.440, p = .000, R^2 = .269$. Specific to the variable of interest, antenatal anxiety was not found to significantly predict child-

internalizing scores. Maternal IQ and current maternal anxiety were significant predictors of child internalizing behaviors. These results suggest that mothers with current anxiety and mothers with higher IQs had children with elevated internalizing scores. When this analysis was adjusted for multiple comparisons using Bonferroni, the overall model remained significant; however, current maternal anxiety was no longer a significant predictor. See Table 3.7 for estimates of the parameters predicting internalizing scores.

Child Anxiety/Depression Scores. The second regression equation included child anxiety/depression scores predicted by maternal antenatal anxiety. Maternal IQ and current anxiety were included as covariates. The model including all predictors was significant, $F(3, 77) = 6.314, p = .001, R^2 = .197$. Antenatal anxiety approached significance ($p = .056$) in the prediction of child anxiety scores; however, when current maternal psychopathology was removed from the regression analyses in an attempt to find a model with the best fit, the prediction of child anxiety/depression was strengthened, $F(2, 79) = 9.771, p = .000, R^2 = .198$. These findings suggest that children of mothers who experienced antenatal anxiety have higher anxiety scores. Higher maternal IQ scores were also predictive of more severe child anxiety scores. Current maternal anxiety was not found to significantly predict child anxiety/depression. No differences in significance were found following the adjustment for multiple comparisons, see Table 3.7.

Child Attention Scores. The third multiple regression equation predicting child attention scores included antenatal anxiety as the variable of interest and child age and current maternal anxiety as covariates. The results indicated an overall model that was statistically significant $F(3, 86) = 3.958, p = .011, R^2 = .125$; however, antenatal anxiety

did not significantly predict attention problems. The results suggest that older children and children whose mothers met criteria for current anxiety had elevated attention problems. Following the adjustment for multiple comparisons using a Bonferroni correction, the overall model was no longer significant and current maternal anxiety and child age were no longer significant predictors of child attention problems. Refer to Table 3.7 for estimates of the parameters.

Child Autism Symptom Severity

In the regression model predicting autistic symptoms from maternal antenatal anxiety, child gender and adaptive behavior were included as covariates. Regression results indicated a significant effect for the overall model, $F(3, 66) = 5.021, p = .003, R^2 = .186$. Maternal antenatal anxiety failed to independently predict child autistic symptom severity. Child gender did, however, significantly predict child autism symptom severity in that males had higher autism severity scores. No differences were found in the results once controlling for multiple comparisons; see Table 3.8. As a follow-up analysis, CARS scores were categorized by above and below the clinical cutoff score of 30 and the regression model was reran to determine if antenatal anxiety was predictive of a categorical, as opposed to continuous, measurement of an autism diagnosis. Results indicated that antenatal anxiety still failed to predict CARS scores even when categorized.

Child Salivary Cortisol

To examine the relationship between child salivary cortisol and maternal antenatal anxiety, three separate regression models were constructed. As discussed, there were no identified covariates for baseline, reactant, or regulation cortisol. The results for the three

equations were non-significant. Refer to Table 3.9 for estimates of the parameters predicting child salivary cortisol.

Table 3.7. Effects of regression model parameters predicting child problem behavior scores

	Effect	Estimate	SE	<i>t</i>	<i>p</i>
Internalizing Scores	<i>Intercept</i>	28.51	8.14	3.50	.001**
	<i>Maternal antenatal anxiety</i>	3.637	3.281	1.109	.270
	<i>Maternal IQ</i>	.227	.076	2.987	.004**
	<i>Maternal current anxiety</i>	5.551	2.787	1.992	.05*
Anxiety/Depression Scores	<i>Intercept</i>	39.27	5.30	7.41	.000**
	<i>Maternal antenatal anxiety</i>	4.584	1.615	2.839	.006**
	<i>Maternal IQ</i>	.140	.049	2.828	.006**
Attention Scores	<i>Intercept</i>	59.28	1.50	39.58	.00**
	<i>Maternal antenatal anxiety</i>	-1.185	2.848	-.416	.679
	<i>Maternal current anxiety</i>	4.793	2.431	1.971	.05*
	<i>Child age</i>	.036	.017	2.103	.04*

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

Table 3.8. Effects of regression model parameters predicting autism symptom severity

	Effect	Estimate	SE	<i>t</i>	<i>p</i>
	<i>Intercept</i>	31.289	3.348	9.345	.000**
CARS scores	<i>Antenatal Anxiety</i>	.759	1.620	.469	.641
	<i>Adaptive Behavior</i>	-3.121	2.483	-1.257	.213
	<i>Child Gender</i>	-6.501	1.927	-3.374	.001**

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

Table 3.9. Effects of regression model parameters predicting child salivary cortisol from antenatal anxiety

	Estimate	SE	<i>t</i>	<i>p</i>
Baseline Cortisol	.055	.159	.349	.730
Reactant Cortisol	.152	.170	.896	.382
Regulation Cortisol	.047	.112	.424	.677

CHAPTER IV

DISCUSSION

The current study examined the relationship between antenatal anxiety in mothers with the FMR1 premutation and child outcomes, specifically problem behavior, autistic symptoms, and HPA axis functioning, in children with the full mutation. Findings suggest that the overall models predicting child problem behavior and autism symptom severity were significant, with maternal antenatal anxiety emerging as a significant predictor of child anxiety/depression. Antenatal anxiety was not found to independently predict child internalizing behaviors, inattention, autism symptoms severity, or child salivary cortisol levels. However, current maternal anxiety was predicative of child internalizing behaviors and attention problems. Unfortunately, these relationships did not remain once correcting for multiple comparisons.

The findings of the current study may be best understood in the context of Sameroff's transactional theory (Sameroff, 1975), which states that the development of a child is the result of continuous interactions between the child and the environment. In children with the full mutation, it appears that the prenatal environment, in combination with the child's genetic predisposition, influences the development of anxiety/depressive behaviors. These behaviors, in turn, influence the child's postnatal environment and subsequent interactions with the family system, which then affect the child's development. Therefore, vulnerability for problem behavior that may emerge as early as utero can have a significant impact on a child's developmental trajectory.

Child Problem Behavior

Child Internalizing Behaviors. Although maternal anxiety during pregnancy was correlated with child internalizing behaviors in the primary analyses, this relationship did not remain when antenatal anxiety, along with maternal IQ and current anxiety were included in the regression model and analyzed. These findings are in contrast to previous literature in nonclinical populations suggesting that the presence of antenatal anxiety leads to an increase in child internalizing difficulties (Barker, Jaffee, Uher, & Maughan, 2011) even after controlling for postnatal psychopathology and risks during pregnancy such as low SES, teen pregnancy, and substance use. As suggested in previous research, children's anxiety/depression scores may drive the relationship between antenatal anxiety and internalizing behaviors, in part. The finding in the current study that antenatal anxiety significantly predicted child anxiety/depression scores provide support for these claims; however, additional research is needed to determine the relationship between antenatal anxiety and other measures of child internalizing behaviors to gain a more accurate understanding of this relationship.

The results of the current study suggested that higher maternal IQs were indicative of increased rates of child internalizing behaviors. Similar research on boys with the full mutation aged 4 to 12 years old found that mothers with college degrees reported higher levels of overall problem behavior in their sons (Hatton et al., 2002). Although maternal education level was not a variable included in the analyses for this study, it was significantly correlated with maternal education in this sample. Previous literature suggested that the relationship between increased child problem behaviors and mothers with higher education levels may be due to the ease in which highly educated

mothers identify discrepancies between their level of functioning and their child's. Another possibility is that children with increased problem behavior are more commonly found in families with mothers who have a college degree or higher (Hatton et al., 2002). Contrary findings have also been suggested in the FXS literature. A study on preschool children with the full mutation found higher levels of maternal education to be related to a more positive maternal interactional style and higher scores on a composite of child development (Sterling, Brady, Warren, Fleming, & Marquis, 2006). Research on nonclinical populations have had similar findings, as a study on 505 kindergarten children from Israel found a negative correlation between maternal education level and child problem behavior on the CBCL (Auerbach, Lerner, Barasch, & Palti, 1992).

Finally, child-internalizing behaviors was also predicted by current maternal anxiety; however, this relationship did not remain once correcting for multiple comparisons. These results are partially consistent with previous literature, as the presence of lifetime occurrence of an anxiety disorder in mothers with the FMR1 premutation was positively associated with child problem behavior (Roberts et al., 2009a). The previous research, however, used the Total Score from the CBCL as a measure of child problem behavior as opposed to examining specific indices. Additionally, the previous research examined lifetime anxiety, which was defined as meeting criteria for an anxiety disorder at any time, including at the time of the interview. Subsequently, the previous study included mothers who met for current anxiety disorder and those with a history of at least one anxiety disorder (Roberts et al., 2009a). The current study provides a more detailed look at the problem behaviors in children with the full mutation and their relationship with maternal psychopathology by exploring problem

behaviors that are most closely related to current, as opposed to lifetime, psychopathology in mothers with the FMR1 premutation.

Child Anxiety/Depressive Behaviors. Children whose mothers met criteria for an anxiety disorder during pregnancy scored significantly higher on anxiety/depression symptoms compared to children of mothers who did not meet clinical criteria for an anxiety disorder while pregnant. This finding is in agreement with previous literature that has suggested a relationship between antenatal anxiety and internalizing behaviors, driven by a robust relationship between antenatal anxiety and child anxiety in particular (Barker et al., 2011). Although higher anxiety/depression scores were found in the current study, it should be noted that only six children in the study scored in the “at-risk” range in this domain on the CBCL and none scored in the clinically significant range. Therefore, although children with the full mutation of mothers who experienced anxiety during pregnancy score higher on anxiety/depressive symptoms, these symptoms may not be significant enough to impair their daily functioning.

A conclusion regarding the mechanisms of this relationship in fragile X populations is beyond the scope of this study; however, previous literature in nonclinical populations has suggested that the associations between the variables may be due to key influences including fetal programming and inherited factors. In regards to fetal programming, researchers have suggested that intrauterine environmental mechanisms may affect set points of physiological systems in the body, including those affecting the body’s ability to maintain homeostasis. If this is the case, fetal programming, which claims that antenatal anxiety interferes with the developing physiological system of the fetus, may explain why maternal antenatal anxiety is predictive of increases in

experienced anxiety/depression in children with the full mutation. Specifically, mothers with the FMR1 premutation who experienced clinical levels of anxiety while pregnant may alter their child's physiological systems in utero making them more prone to anxious/depressive behaviors during childhood. Future research is needed to determine if inherited factors, fetal programming, or a combination of the two influences the later development of anxiety/depressive behaviors in children with the full mutation who had mothers that met criteria for an anxiety disorder during their pregnancy.

Child Attention Problems. Interestingly, antenatal anxiety did not significantly predict attention scores. These results are in contrast to some of the most robust findings in the literature on nonclinical populations which have found that antenatal anxiety predicts attention deficits in children ages four to fourteen (O'Connor et al., 2002; Van den Bergh & Marcoen, 2004; Van den Bergh et al., 2005). Higher attention scores reflect the child's ability to sit still and concentrate, in addition to how often they are clumsy, shift between activities, and wander. The failure to find similar effects may be due to differentiations in ages across samples, as there was an age range between a 11 months and 14 years, 9 months in the current study. The inclusion of younger children may be partially responsible for our differing findings, as the majority of children in this study were under the age of four and child age and attention scores are positively related. Such a relationship implies that higher attention scores are found in older children. Because previous studies had older populations, they may have found an effect due to higher attention scores. The differences in findings may also be due to different mechanisms underlying ADHD symptoms in children with the full mutation compared to children without genetic disorders. For example, a pattern of over-responsiveness to sensory

stimulation is common in children with the full mutation (Baranek et al., 2002; Rogers, Hepburn, & Wehner, 2003) and these behaviors have been found to be related to physiological mechanisms such as reduced vagal tone (Roberts et al., 2006). Such research poses the argument that the ADHD behaviors in individuals with the full mutation are solely features of the genetic syndrome rather than an independent diagnosis (Reynolds & Lane, 2008). This would be in contrast to nonclinical populations whose attention problems would be indicative of an individual diagnosis.

Although current anxiety or depression did not significantly predict children's rate of anxious/depressive behaviors, it approached significance in the prediction of higher ratings on attention problems. As discussed with internalizing behaviors, these findings may provide deeper understanding into a previously identified relationship between lifetime occurrence of anxiety disorders in mothers with the FMR1 premutation and child problem behavior (Roberts et al., 2009a). The results, however, did not remain once controlling for multiple comparisons so more research is needed on the relationship between current maternal anxiety and attention problems in children with the full mutation.

Child Autism Symptom Severity

Inconsistent with prior research, antenatal anxiety was not found to predict autistic symptom severity. In previous literature, maternal stress was most frequently measured retrospectively by maternal report of negative life events that occurred during pregnancy (Beversdorf et al., 2005; Ward et al., 1990). This is in contrast to the current study, which measured diagnostic criteria for an anxiety disorder through a clinical interview, a higher threshold for antenatal stress/anxiety. The failure to find similar

results may suggest that negative life events (e.g., divorce, separation, death of a loved one, loss of job, etc.), as opposed to maternal antenatal anxiety, are a stronger predictor of autism symptom severity in the child.

Autistic symptoms were also measured through the CARS in the current study, a clinician report of symptom severity that provides scores on a continuum. This method of measurement differs from previous literature, which used DSM-IV diagnostic criteria to determine inclusion (Beversdorf et al., 2005). It may be that antenatal anxiety is a stronger predictor of an autism diagnosis, as opposed to a range of scores on an autism symptom severity rating scale; however, when the CARS data were categorized by above and below the clinical cutoff score and reran, results remained the same. The CARS has been shown to be a valid measure of an autism diagnosis, as it has significant agreement with diagnostic criteria determined by the ADI-R (Pilowsky et al., 1998; Saemundsen et al., 2003) and the ADOS-G (Ventola et al., 2006). Therefore, failure to find a relationship between antenatal anxiety and CARS scores may provide support that antenatal anxiety is not predictive of autism in children with the full mutation, although additional research is needed before definitive conclusions can be drawn.

Child Salivary Cortisol

This study found no evidence of a relationship between antenatal anxiety in mothers with the FMR1 premutation and salivary cortisol, an objective measure of stress and HPA-axis dysfunction. While it may be true that a relationship between antenatal anxiety and child cortisol does not exist in FXS, the inability to find a relationship may also be due to other factors. For example, saliva was only collected at two time points during the assessment as opposed to measuring diurnal cortisol profiles. Previous

literature found support for atypical awakening cortisol levels (O'Connor et al., 2005) and a higher, flattened daily cortisol profile (Huot et al., 2004) in children of mothers who experienced psychopathology during pregnancy, neither of which were measured in this study. It is also important to note that the research measuring baseline cortisol and HPA reactivity to stress paradigms, similar to the current study, which found relationships with antenatal anxiety were conducted with rats exposed to stress in utero (Weinstock et al., 1992). No known studies have measured cortisol similar to the current study in children from nonclinical populations or in those with the full mutation in order to explore the relationship with antenatal anxiety.

Limitations

Despite the relatively large sample size compared to other research on fragile x syndrome, our results must be interpreted in the context of multiple limitations. First, child salivary cortisol was only assessed at two time points during the assessment. While assessments were generally conducted in the morning, it was not possible to collect all saliva samples at the same time during the day. Variations in the times that the data were collected may help explain the failure to find a relationship between antenatal anxiety and child salivary cortisol. Future research should consider assessing diurnal cortisol in children with the full mutation in order to gain a more comprehensive understanding of the relationship between antenatal anxiety and HPA-axis functioning in fragile X syndrome. A second minor limitation of the study was the use of the CARS as a measure of autism symptom severity as opposed to gold standard measures such as the ADOS or ADI-R. It is important to note, however, that the CARS has significant agreement with

both the ADOS and ADI-R so its inclusion should not be considered a major flaw of the study.

Also, a structured clinical interview was used to assess antenatal anxiety, which may be a limitation given its categorical as opposed to dimensional approach. The categorical scores of the SCID utilizes a higher threshold for determining maternal anxiety; however, our study was limited by the inability to use continuous scores on anxiety to predict our dependent variables. In contrast to previous studies that commonly assessed anxiety during pregnancy, our study utilized retrospective self-report of anxiety and determined whether or not mothers met diagnostic criteria for an anxiety disorders based off DSM-IV standards. It may be argued that mothers with older children had a more difficult time recalling their experienced anxiety during pregnancy; however, latency of report since the child's birth, as measured by child age, was not correlated with antenatal anxiety, providing support for the use of the SCID.

It is also important to consider the unique position of mothers of children with the full mutation in regards to their potential knowledge during pregnancy of their likelihood of having a child with a disability. It is unknown how many mothers in this sample had knowledge that they were carriers during their pregnancy, either because they had at least one child with the full mutation or because of family history, as this could potentially affect their experienced anxiety. It should be noted that Roberts et al. (2009) found an association between a diagnosis of an anxiety disorder in women with the FMR1 premutation and the number of children they had with the full mutation suggesting that pregnant women with at least one child diagnosed with the full mutation may be at

an increased risk for meeting diagnostic criteria for an anxiety disorder during pregnancy as opposed to mothers who do not already have a child with the full mutation.

Finally, the current study did not include any comparison groups, restricting our interpretation to mothers with the FMR1 premutation and their children with the full mutation.

Summary and Implications

The results of this study provide support for a relationship between antenatal anxiety in mothers with the FMR1 premutation and anxious/depressive behaviors in children with the full mutation. These findings align with previous evidence that antenatal anxiety leads to suboptimal child outcomes, specifically increased rates of anxiety and depression, even after controlling for current anxiety in mothers with the FMR1 premutation. Research has shown that around 86% of males and 77% of females with the full mutation between the ages of 5 and 33 years meet criteria for an anxiety disorder, with certain types of disorders being more common in adults (Cordeiro et al., 2011). The ability to identify early indicators of anxiety/depression in children with the full mutation is critical, as anxiety is present at such high rates in FXS. The current finding on the relationship between maternal antenatal anxiety and increased rates of anxiety/depression in children with the full mutation provide key support for prevention work aimed at reducing maternal anxiety prior to pregnancy which may subsequently reduce anxiety in children, a critical feature of individuals with the full mutation. Additionally, children with the full mutation who had mothers that experienced anxiety during pregnancy may need extra supports as they are at an increased risk for developing higher rates of anxiety/depression in early childhood. These behaviors in early childhood could lead to strains on the

maternal-child relationship and, subsequently, negatively affect parenting behaviors. This bidirectional relationship between the child and the child's environment is critical for development (Sameroff, 1975). Previous research on children with the full mutation has shown the importance of maternal responsiveness in promoting children's positive development (Warren and Brady, 2007) so it is critical to intervene as early as possible on children's problem behavior in order to improve the child's quality of life, the family's quality of life, and the parent-child relationship.

Another important finding of this study is the relationship between internalizing behaviors and attention problems in children with the full mutation and current anxiety in mothers with the FMR1 premutation. Previous research has examined the relationship between general child problem behavior and lifetime maternal psychopathology (Roberts, 2009a); however, no studies to date have targeted the relationship between current maternal anxiety and specific child problem behavior in this population. Our results may be best understood in the context of Sameroff's transactional theory (Sameroff, 1975), which emphasizes the critical influence of the bidirectional relationship between the child and his or her environment on development. High rates of problem behavior in children with the full mutation are influenced by genetics in addition to the child's environment. In regards to the uniqueness of the FXS population, mothers with the FMR1 premutation, particularly those with multiple children with the full mutation, are at an increased risk for the development of an anxiety disorder. Our results suggest that maternal antenatal anxiety likely influences the child's prenatal environment, which, in turn, affects the development of anxiety/depressive behavior in children with the full mutation. As in non-clinical populations, developmental anomalies in children with the full mutation were

identified as early as the first year of life. These behaviors, in turn, influence the child's postnatal environment and subsequent interactions with the family system, which can further impact the child's development. This is evident through our findings of a relationship between child anxiety/depressive behaviors and antenatal anxiety into early adolescence. It is also important to consider the environment that the child may be entering and how this can affect the maternal-child interaction, as the number of children with the full mutation in the home is predictive of a clinical diagnosis of an anxiety disorder in mothers with the FMR1 premutation (Roberts et al., 2009).

The relationship between current maternal anxiety and child internalizing behaviors and attention problems represented in this study underscores the importance of intervening on maternal psychopathology in addition to implementing interventions to decrease internalizing symptoms and improve attention problems in children with the full mutation in an effort to enhance the quality of life of both mothers and children within a vulnerable population. A study on families affected by the full mutation reported findings in support of interventions targeting the improvement of maternal responsiveness (Warren & Brady, 2007). Similar research has found that training programs lead to positive developmental outcomes in children in addition to decreased maternal stress and physiological arousal in parents of children with disabilities (Warren & Brady, 2007). Such interventions can improve the maternal-child interaction and, subsequently, enhance child development in the fragile X population. The results of this study advocate for a family systems approach to decreasing maternal symptoms of psychopathology in mothers with the FMR1 premutation while simultaneously working with the children to

effectively manage their internalizing behaviors and attention problems through the implementation of interventions that take both a family and an individualized focus.

Ultimately, the current findings are of importance because they are the first to suggest a relationship between antenatal anxiety and negative child outcomes in male and female children with fragile X syndrome. Further, in comparison to previous literature, this study takes a more detailed approach in the examination of the relationship between current maternal anxiety and child problem behavior. These results are critical because children with the full mutation may have a double vulnerability for negative outcomes due to their genetic disorder and the increased rates of psychopathology in mothers with the FMR1 premutation.

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