MOOD, ANXIETY, AND STRESS IN MOTHERS OF CHILDREN WITH FRAGILE X SYNDROME, AUTISM, AND FRAGILE X SYNDROME AND AUTISM

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ABSTRACT

JEAN BOSWELL MANKOWSKI: Mood, Anxiety, and Stress in Mothers of Children with Fragile X Syndrome, Autism, and Fragile X Syndrome and Autism
(Under the direction of Deborah Hatton and Rune Simeonsson)

Research has shown elevated mood, anxiety, and stress in mothers of children with developmental disabilities. These findings remain ambiguous due to inconsistencies in the definitions and groupings of maternal disorders, measurement instruments used, and inadequate samples. The behavioral overlap between these disorders permits examination of the association between the autistic and/or problem behavior of children and maternal mood, anxiety, and stress. This study examines the frequency and predictors of mood, anxiety, and stress in mothers of three groups: children with FXS, children with FXS/autism, and children with autism. Lifetime and current mood and anxiety disorders and current levels of stress were assessed in 56 mothers of children with the full mutation of FXS, 19 mothers of children with the full mutation of FXS and autism, and 38 mothers of children with autism.

Mothers of children with autism reported increased rates of generalized anxiety disorder (GAD) compared to mothers of children with FXS or FXS/autism. A greater proportion of mothers of children with autism reported experiencing two or more mood or anxiety disorders over their lifetime than mothers of children with FXS. Child problem behavior predicted maternal mood, anxiety, and stress across all groups. Autistic symptomatology of the child predicted maternal stress. In the majority of mothers, the initial

onset of a reported mood or anxiety disorder was prior to the birth of the child, suggesting that childrearing burden cannot fully explain mood and/or anxiety in these mothers.

The environmental and/or genetic contributions related to increased rates of GAD in mothers of children with autism compared to mothers of children with FXS should be examined further. Future studies should compare frequency of mood and anxiety in mothers of these groups to population estimates. Intervention and support services for mothers of children with FXS and autism should focus on reducing maternal stress by assisting them to manage the autistic and/or problem behavior of the child.

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ABBREVIATIONS

ABC	Adaptive Behavior Composite
ASD	Autism Spectrum Disorders
CARS	Child Autism Rating Scale
CBCL	Child Behavior Checklist
CFXP	Carolina Fragile X Project
DD	Developmental Disability
FMRP	Fragile X Mental Retardation Protein
FMR1	Fragile X Mental Retardation Gene
FXS	Fragile X Syndrome
FXS/Autism	Fragile X Syndrome and Autism
MDD	Major Depressive Disorder
OCD	Obsessive Compulsive Disorder
PSI	Parent Stress Index
SS	Standard Score
VABS	Vineland Adaptative Behavior Scale
WASI	Wechsler Abbreviated Scale of Intelligence

CHAPTER 1

INTRODUCTION

The diagnosis of a developmental disability in a child can elicit various emotional and behavioral responses in parents and across family systems. A parent's reaction to learning of a child's disability may range from feelings of loss that necessitate psychological adjustment, to positive feelings believing that the child is a gift from God, to realizing that the child gave family members a new perspective or heightened the family's functioning. Family members can respond in many diverse ways to having a child with a disability in the home, ranging from adaptation to maladaptation, and the impact can vary depending on the characteristics of the child and family environment as he or she develops through the stages of life. Family systems theory affirms that family members exist within a circular coordination of causal relations within or between the system and subsystems that can be changed by forces either inside the system or in the environment (Grych, 2002). The heightened demands of childcare, questions concerning the child's development and progression, and the physical and emotional fatigue of regular care for an individual with a disability are long-standing challenges that can have potentially negative impacts on individuals within the family system.

Undoubtedly, both mothers and fathers play a significant role in a child's life. In our society, however, mothers arguably remain the primary caregiver and therefore assume much of the responsibility for a child's daily care. As a result, characteristics of both mother and

child can profoundly influence one another. Mothers of children with developmental disabilities have shown elevated rates of depression, anxiety, and stress (Dunn, Burbine, Bowers, Tantleff-Dunn, 2001; Franke et al., 1998; Singer, 2006). The etiology of children's disability and their level of problematic behavior have proved important factors in parental stress and adaptation (Abbeduto et al., 2004; Dunn et al., 2001; Hodapp, Dykens, & Mashino, 1997; Hodapp, Fiddler, & Smith, 1998; Johnston et al., 2003). In fact, increased child problem behavior has been linked to higher levels of depression and stress in mothers (Abbeduto et al., 2004; Hastings et al., 2005). Baker and colleagues found parenting stress and child behavior interact with each other to cause each to worsen over time (Baker et al., 2003). The chronicity, nature, and direction of the association between child variables and maternal mood, anxiety, and stress need further exploration to inform intervention and support services for these families with heightened maternal and child needs.

Exploring this association may have particular importance in families with a child with FXS (fragile X syndrome), as the full mutation of this X-linked disorder is inherited from mothers whose FXS carrier status has been tentatively associated with physical, behavioral, and psychiatric characteristics (Franke et al., 1998; Sobesky et al., 1996; Mazzoco, 2000), and whose children demonstrate phenotypic behaviors related to the genetic syndrome. In particular, these mothers may be at heightened risk for difficulties associated with child characteristics. The impact of various child characteristics can be explained using a comparison group of children with autism, as a developmental and behavioral overlap exists between these disorders, with 15-35% of individuals with FXS meeting the behaviorally defined criteria for autism (Dykens & Volkmar, 1997).

FXS and autism are developmental disorders that can have significant impacts on the family because children with both conditions have deficits in sociability, and many display maladaptive behavior, a characteristic that has been linked to parental psychological well being (Hodapp et al., 1997; Hodapp et al., 1998). In addition, families of children with FXS and families of children with autism often have the added stress and uncertainty caused by not having a definitive diagnosis until several years after the birth of the child. FXS and autism have very different heritable components (described in detail later), nevertheless, families of children with either disorder have an increased risk for more than one individual in the family with neuropsychological deficits or complications.

FXS and autism are distinct disorders that share some behavioral symptoms, neurological irregularities, functioning expressed within a range, and differential patterns of gender risk (Feinstein & Reiss, 1998). Autism is a clinical diagnosis based on a cluster of behavioral symptoms, while FXS is diagnosed through genetic testing. Three groups which share overlapping features exist: children with FXS only, children with autism only, and children with both FXS and autism (FXS/autism). Therefore one can begin to tease apart the effects of the child behavior and study how children with either or both disorders challenge or exacerbate mood, anxiety, or stress in mothers.

This study compares the frequency of mood, anxiety, and stress across groups of mothers with FXS, FXS/autism, and autism and examines the impact of child autistic and problem behavior on maternal mood, anxiety, and stress.

CHAPTER 2

Literature Review

Adaptation to Disability

There is no doubt that raising a child with any disability can be very demanding and bring about challenges not faced by parents raising typically developing children. Family systems theory recognizes the bi-directional process of socialization, wherein children are both influenced by and shape parental behavior (Belsky, 1984). Early researchers found differences between families with a child affected by a disability and typical families (Harris, 1984). Greater stress was correlated with being a parent or sibling of a child with a disability. Mothers were more likely than fathers to experience guilt, physical symptoms, tension, and uncertainty about their parenting abilities as well as to encounter more problems with personal freedom, mood, and sensitivity about their child's fit into the community. Although many changes have occurred within the gender roles of families, mothers continue to have a primary role in responsibility for children, and thus can be subject to more of the stress and challenges inherent in raising a child with a disability. The extent of those challenges, whether they are physical, emotional, and/or behavioral obstacles, will vary across disabilities, and thus the reactions of mothers will likely vary, too. In fact, researchers have shown that the nature of the child's disability can affect the type of challenges families face and how families cope with these challenges (von Gontard et al., 2002; Walker, Van Slyke, & Newbrough, 1992).

A recent meta-analysis of comparative studies of depressive symptoms in mothers of children with and without developmental disabilities found that mothers of children with disabilities are at elevated risk of depressive symptoms compared to mothers of nondisabled children (Singer, 2006). Measuring the reactions of mothers can become complicated when the child's disability is of a genetic origin, like FXS and autism. Whether or not the increased psychosocial burden of the child with a disability causes maternal depression, anxiety, or elevated levels of stress, or whether these behaviors result from the maternal expression of the syndrome-causing-gene, has been of interest to researchers for many years.

Disorders Overview

Fragile X Syndrome

FXS, the most common inherited form of intellectual disability, results from a mutation in a single gene that is transmitted from one generation to the next. The cognitive, behavioral, and physical phenotype of FXS varies with gender, with males more severely affected because of the X-linked inheritance of the mutation. FXS results from a mutation on the fragile X mental retardation gene (FMR1) on the long arm of the X chromosome. This mutation causes a reduction of the FMR1 protein (FMRP) leading to dysregulation of multiple genes resulting in the phenotype expressed in individuals with FXS.

Males with full mutation typically demonstrate cognitive impairments, social difficulties, communication delays, attention problems, and characteristic physical (i.e., long face, large prominent ears, high-arched palate, hyperextensible joints, and macroorchidism if post-pubertal) and behavioral (e.g., hypersensitivity to sensory stimuli, eye gaze aversion, tactile defensiveness, hand flapping, perseverative speech) features from a young age. Males with FXS are often shy and less sociable than individuals their age (Kerby & Dawson, 1994)

and may show excessive social anxiety (Hagerman, Jackson, Levitas, Rimland, & Braden, 1986). A significant number of males with FXS exhibit autistic-like behaviors and meet the diagnostic criteria for autism (Cohen, 1995; Kau et. al., 2004; Rogers, Wehner, & Hagerman 2001).

Autism

Autism, a pervasive developmental disorder (PDD), is a behavioral syndrome characterized by deficits in social reciprocity, communication, and a restricted repertoire of activity and interests (American Psychiatric Association, 1994). Manifestations of the disorder vary greatly depending on the developmental level and age of the individual. It is estimated that as many as 10 per 10,000 individuals are affected with autistic disorder (Fombonne, 2003). Approximately 75% of children with autism have significant intellectual disabilities, and their profile of cognitive skills is usually uneven (American Psychiatric Association, 1994). The wide range of behavioral symptoms often seen in individuals with autism includes aggressiveness, self-injurious behavior, hyperactivity, impulsivity, attentional difficulties, difficulty with sensory stimuli, and abnormalities in mood or affect. Individuals with autism may lack interest in relationships or friendships with others, prefer solitary activities, or fail to understand the emotions or needs of others. As a result, parents of children with autism may feel isolated and/or emotionally distanced from their child.

Fragile X syndrome and autism

Before the elucidation of the fragile X gene, Brown et al. (1982) suggested that a considerable number of the cases of autism may originate in FXS. Thus, early studies that investigated the association between FXS and autism focused on the rates of co-morbidity of the two disorders. Using meta-analysis to analyze the percentage of individuals with autism

who have FXS, investigators reported a FXS prevalence of approximately 5% (Fisch, 1992). Recent studies have found the prevalence of autism and/or autistic behavior within the FXS population to range from 15% to 35% (Bailey, Hatton, & Skinner, 1998; Cohen, 1995; Dykens & Volkmar, 1997; Hatton et al., 2006; Kau et. al., 2004; Rogers et. al., 2001).

Reiss and Freund (1990) analyzed specific behaviors characteristic of autism that were manifested in males with FXS and concluded that some of the autistic-like behavior seen in individuals with FXS were a subset of behaviors that differed from the behavior seen in individuals with autism. They reported that the major reciprocal social impairment in interactions with caregivers typically seen in individuals with autism was not seen in individuals with FXS. They acknowledged that individuals with FXS seemed to have considerable difficulty interacting with peers, unlike individuals with autism who typically have pervasive social difficulties with all others. However, using the Childhood Autism Rating Scale (CARS; Schopler, Reichler, & Renner, 1988), Bailey, Mesibov, et al. (1998) did not find significantly different profiles of autistic behavior between boys with FXS and autism (FXS/autism) and boys with autism and no FXS. Lewis, Abbeduto, Murphy, Richmond, Giles, Bruno, and Schroeder (2006) recently found that children with FXS/autism demonstrated more impairment in receptive language and theory of mind than children with FXS alone, even when controlling for their lower IQs.

Many researchers have reported that males with FXS/autism have lower IQ scores (Cohen, 1995; Hagerman et al., 1986; Kau et al., 2004; Lewis, Abbeduto, Murphy, Richmond, Giles, Bruno, & Schroeder, 2006; Turk & Graham, 1997) and/or lower developmental levels (Bailey, Hatton, Mesibov, Ament, & Skinner, 2000; Bailey, Hatton, Skinner, & Mesibov, 2001; Roberts, Mirrett, & Burchinal, 2001; Rogers et al., 2001) than

individuals who have FXS without autism. Reiss and colleagues, however, did not find associations between IQ and autistic behavior in the males with FXS in their sample (Reiss & Freund, 1990; Reiss & Freund, 1992). It remains to be determined whether these disparate findings exist as a result of differences in samples, or because of differences in the various measures of IQ, developmental level, or autistic behavior used.

Two studies have found that autistic behavior in individuals with FXS is associated with increased problem behaviors (Hatton et al., 2002; Kau et al., 2004). Hatton and colleagues found that autistic behavior as, measured by the CARS, was related to more problem behavior, as measured by the Child Behavior Checklist (CBCL; Achenbach, 1991). Kau and colleagues (2004) found that boys with FXS who met the behavioral criteria for autism, based on the Autism Diagnostic Interview-Revised (ADI-R), demonstrated more problem behaviors. In particular, children with FXS/autism showed more withdrawn behavior and more problems with attention (Kau et al., 2004).

In a longitudinal study of adaptive behavior, Hatton et al. (2003) found that children with FXS/autism had lower and flatter developmental trajectories in adaptive behavior. Similar results have been reported in cross-sectional studies of adaptive behavior in which children with FXS/autism score lower on measures of adaptive behavior than children with FXS without autism (Cohen, 1995; Kau et al., 2004; Rogers et al., 2001; Turk & Graham, 1997). In fact, Rogers et al. (2001) plotted the adaptive behavior composite scores in order to compare profiles across four groups of children: (1) children with autism, (2) children with FXS/autism, (3) children with FXS without autism, and (4) children who had developmental delay (DD) other than FXS or autism. Two similar groups emerged. The children with FXS/autism had scores comparable to the children with autism, while the children with FXS

without autism had scores comparable to the children in the DD group. Additionally, the group consisting of the children with FXS without autism and the children with DD had a more even developmental profile, while the other groups (autism and FXS/autism) had a lower developmental level overall, but demonstrated similar uneven profiles of higher motor and daily living domains with more delayed social and communication skills. Bailey et al. (2000) reported similar findings that children with FXS/autism demonstrated lower developmental outcomes.

Whether autistic behavior changes over time in individuals with FXS is inconclusive. Several early researchers reported that young children with FXS may exhibit more autistic-like symptoms than older children with FXS (Borghgraef, Fryns, Dielkens, Pyck, & Van Den Berghe, 1987; Hagerman et al., 1986; Reiss & Freund, 1992), but more recent studies typically have not (Bailey, Mesibov, et al., 1998; Cohen, 1995). In the only longitudinal study of autistic behavior, Hatton and colleagues (2006) reported slow, yet significant, increases in autistic behavior over time.

Autism Phenotype

The Genetics of Autism

Considerable evidence suggests that hereditary factors have a significant role in the etiology of autism. The prevalence of autism in siblings of individuals with autism is 50 times greater than the prevalence in the general population (Rutter, 1967). Monozygotic twins (MZ) show a much greater concordance for autism than dizygotic twins (DZ) (Bailey et al, 1995; Folstein & Rutter, 1977). Twin studies have suggested autism is under a high degree of genetic control and is rooted in the involvement of multiple genetic loci (Bailey et al., 1995). Folstein and Rutter (1997) completed a seminal study that suggested a broad

autism phenotype. They found the concordance for autism in MZ and DZ twins was 36% and 0% respectively. Yet when they looked at the concordance of a more broadly defined phenotype, the percentage in MZ and DZ twins was 82% and 10% respectively. Thus, investigators postulated that a milder form of autism, or a *broad autism phenotype*, might be inherited in families (Piven, 2001).

Broad Autism Phenotype

Defining the broad autism phenotype has not been confined to autism or PDD diagnoses, but to a collection of subtle abnormalities found in relatives of individuals with autism. Many of the behavioral, cognitive, and personality characteristics are considered similar, but expressed to a lesser degree, than the defining characteristics of autism. These abnormalities include social and communication impairments (Piven et al., 1997c), stereotypic behaviors (Bolton et al., 1994; Piven & Palmer, 1997a; Piven, Palmer, Jacobi, Childress, & Arndt, 1997b; Piven et al., 1997c), social abnormalities (Bailey, Mesibov, et al., 1998), cognitive impairments (August, Stewart, & Tsai, 1981; Piven et al., 1989; Piven & Palmer, 1997a), and specific autistic-spectrum-like personality characteristics (Narayan, Moyes & Wolff, 1990; Piven et al., 1994; Piven et al., 1997c; Wing & Potter, 1981; Wolff, Narayan, & Moyes, 1988). Compelling evidence for the broad autism phenotype exists in studies of siblings where increased rates of cognitive impairment (e.g., language deficits, learning disabilities; August et al., 1981), lesser variants of autism (Bolton et al., 1994), and neuropsychiatric disorders (Piven et al., 1989) have been found in the siblings of individuals with autism.

Some have postulated that psychiatric disorders may be within the broad autism phenotype given the greater incidences of affective disorders (Delong & Dwyer, 1988; Piven

et al., 1989, Piven et al., 1991; Smalley, McCracken, & Tanguay, 1995), anxiety disorders (Piven et al., 1991; Smalley et al., 1995), and particular personality traits (Narayan et al., 1990; Piven et al., 1994; Piven et al., 1997c; Wolff et al., 1988) found in families of individuals with autism.

Psychopathology. Regarding psychiatric disorders within the broad autism phenotype, literature suggests higher rates of several disorders within relatives of individuals with autism. Unfortunately, these researchers did not report incidence rates on mothers only. Thus, the following review of psychopathology will include findings of first degree (parents and siblings) and second degree relatives of individuals with autism.

In a comparison study of 81 parents of children with autism (without FXS) to 18 parents of children with Down syndrome, the lifetime frequency of anxiety disorders was found to be significantly higher in parents of children with autism (Piven et al., 1991). While the rate of recurrent major depressive disorder in parents of individuals with autism was 16%, threefold that of the 6% rate in parents of individuals with Down syndrome, it did not reach significance.

Smalley and colleagues (1995) investigated the occurrence of affective and/or anxiety disorders among relatives of individuals with autism. In the 36 families with a child with autism, 64% had a first-degree relative (parent or sibling) diagnosed with major depressive disorder and 39% had a first-degree relative diagnosed with social phobia. These rates are quite high when they are compared to 19% and 5% respectively in families of children with a genetic condition but no autism. Of the 64% of the first-degree relatives with major depressive disorder, 30.6% were parents—much like the 27.2% of major depressive disorder

(MDD) found by Piven and colleagues (1991). Of note, Smalley et al. (1995) did not find elevated rates of bipolar disorder as was found by Delong and Dwyer (1988).

Micali, Chakrabarti, and Fombonne (2004) examined the broad autism phenotype in relatives of children with autism and less severe PDDs compared to a group of children with developmental disabilities other than autism. Depression and anxiety were significantly more prevalent in mothers of children with PDD. In addition, children with PDD had significantly more first-degree relatives with anxiety or PDD and second-degree relatives with obsessive compulsive disorder (OCD) than found in the control group.

Onset of psychopathology. Interestingly, the broad autism phenotype literature has compelling findings against the hypothesis that the psychosocial burden of parenting a child with autism exclusively predicts psychiatric morbidity. For example, Piven et al. (1991) reported that 63% of the parents of children with autism who reported anxiety disorder and 77% who reported major depressive disorder had experienced at least one episode prior to the birth of their affected child. In the study by Smalley et al. (1995), 64% of the parents with a history of major depression, and all of the parents who met for social phobia, had experienced the first episode of their mood disorder prior the birth of the affected child. Moreover, Micali et al. (2004) reported that 83.3% of the mothers of children with depressive disorders experienced onset prior to the birth of their child with PDD.

As shown above, compelling evidence exists to indicate that a broad autism phenotype exists within the families of individuals with autism. In many ways, the broad autism phenotype has similarities to the expression of FXS in females. In order to compare mothers of children with FXS to mothers of children with autism, one must first understand

how FXS manifests behaviorally, emotionally, and cognitively in females with the FMR1 mutation.

Interestingly, none of the family or parent studies of autism used a control group of families where the target child had FXS. However, in the review to follow, it is apparent that many of the maternal psychiatric studies within the FXS literature used mothers of children with autism as their control group. While such findings have suggested higher rates of depression and anxiety in mothers of children with autism, it has not been incorporated into the broad autism phenotype literature. Thus, the broad autism phenotype literature does not include some critical evidence in support of this phenotype in mothers of children with autism.

Females with Fragile X Syndrome

Genetics of FXS

The fragile X gene, FMR1, contains a trinucleotide (CGG) repeat in the promoter region that is mutated in individuals affected by FXS (Verkerk et al., 1991). Individuals without FXS have between 6-45 repeat units, and the CGG repeat number remains constant over generations. Conversely, individuals with a fragile X mutation have a greater number of CGG repeats, and the repeat number is unstable and tends to increase as the gene is passed to the next generation. There is a "gray zone" between 45 and 54 repeats that is associated with minor instability from generation to generation (Hagerman, 2006). Researchers advanced a categorical classification of FXS status based on the molecular characteristics and associated clinical affectedness (Reiss, Freund, Abrahams, Boehm, & Kazazian, 1993). Individuals who are classified as having the premutation show an increase of 55-200 repeat units. For those with a premutation, like those without FXS, an adjacent CpG island is unmethylated.

Females with the premutation typically have normal IQ scores and approximately 21% have premature ovarian failure (Hagerman, 2006). The prevalence of the premutation in the general population is approximately 1 in every 259 females (Hagerman, 2006). Individuals who are classified as full mutation have more than 200 CGG repeats, and the full mutation is associated with methylation of the adjacent CpG island and presumed inactivation of the FMR-1 gene. Thus, the full mutation presents with the hypermethylation of the FMR-1 gene, which impedes protein production from FMR-1 (Pieretti et al, 1991). It is this lack of FMR-1 protein (FMRP) that is thought to cause the physical, emotional, neurological, and cognitive symptoms of FXS. There is an estimated prevalence rate of 1:4,000 males and 1:8,000 females with the full mutation of this disorder (Mazzocco, 2000).

Women with full mutation FXS are affected differently than males with the full mutation. Women have two X chromosomes, but typically one carries the mutation. In females, one X chromosome is randomly inactivated to prevent overproduction of proteins coded by X chromosome genes. Consequently, they can produce some FMRP. Because of random X inactivation, individual females with the full mutation vary in the proportion of normal X chromosomes that are active, determining the amount of FMRP produced. Thus, the percentage of cells with the genetic mutation varies across individuals. The activation ratio, or percentage of cells with the normal FMR-1 gene on the active X chromosome, influences the amount of FMR, resulting in a broader range of cognitive, emotional, and physical symptoms of FXS in women than in men with the full mutation. Recently, researchers have documented an abnormal elevation of FMR1 mRNA in individuals with the premutation of FXS, and have suggested a pathogenic gene-brain behavior mechanism (Hessl et al., 2005).

Cognitive Performance

Researchers have found cognitive and neuropsychological differences between women carrying the full mutation and premutation of the fragile X gene. The majority of females with the premutation demonstrate IQs within the average range (Bennetto, Pennington, Porter, Taylor, & Hagerman, 2001; Johnston et al., 2001; Mazzocco, Pennington, & Hagerman, 1993; Meyers, Mazzocco, Maddalena, & Reiss, 2001; Reiss et al., 1993). Some researchers have reported a relation between IQ and the number of CGG repeats (Abrams et al.,1994; Block et. al., 2000, Thompson et al., 1994) while others have not (Allingham-Hawkins et al., 1998; Bennetto et al., 2001; Franke et al., 1998; Franke et al., 1999; Johnston et al., 2001; Taylor et al., 1994). Regardless of their IQ scores, the fragile X gene in many women may lead to psychiatric morbidity.

Psychopathology

In a seminal study by Reiss and colleagues (Reiss, Hagerman, Vinogradov, Abrams, & King, 1988), psychiatric morbidity in 35 mothers of children with FXS was compared to that in a well matched control group of 24 mothers of developmentally delayed and behaviorally dysfunctional children. Mothers were administered a modified version of a structured interview to assess lifetime history of affective disorders. While 40% of the mothers of children with FXS met diagnostic criteria for recurrent depression, compared to 17% of controls, this difference failed to reach significance. This study was limited in that it occurred prior to the advent of molecular subtyping; thus, mothers with premutation and full mutation of FXS were grouped together.

Later, Reiss and other colleagues (1993) studied neurobehavioral effects of 34 mothers of children with FXS who were premutation carriers compared to 41 well-matched

mothers of children with developmental disabilities other than FXS. No meaningful differences were shown to exist among the psychiatric diagnoses, psychiatric symptoms, or self-rated personality profile of the two groups. However, very high rates for lifetime of major depression were found in both the FXS premutation mothers (44%) and control mothers (47.5%). In community samples, the lifetime risk for MDD has varied from 10% to 25% for women (American Psychiatric Association, 1994). Most of the mothers in Reiss et al.'s study related their problems with depression to their first becoming aware of their child's disability and/or the stress related to parenting the child. Thus, Reiss concluded that parenting a developmentally disabled child had a significant impact on maternal psychological health. Although these mothers attributed their depression to the diagnosis and stress of childrearing, researchers did not examine child characteristics and diagnosis dates to delineate whether the timeline of maternal depression was associated with such factors.

Thompson et al. (1994) found a history of MDD in 71% of a sample of 12 premutation and 5 full mutation mothers of children with FXS. In a follow-up study using much of the same sample, Thompson, Rogeness, McClure, Clayton, and Johnson (1996) assessed depression in 18 mothers of children with FXS (5 full mutation and 14 premutation) compared to 19 mothers of children with Down syndrome or spina bifida. Women with FXS continued to demonstrate a significantly higher frequency of lifetime major depressive disorder (78%) than the control group (37%). While the mothers of children with FXS demonstrated a much greater frequency of MDD than found by Reiss and colleagues (1993), the comparison groups of mothers of children with disabilities had similar frequency rates.

Franke et al. (1996) investigated the psychological phenotype in four groups: 1) 6 full mutation mothers of children with FXS, 2) 29 premutation mothers of children with FXS, 3)

30 unrelated mothers of typically developing children, and 4) 17 unrelated mothers of non-FXS children with mental retardation and autism. Mothers of children with autism had the highest frequency of affective disorders (58.8%) which was comparable to the high incidence in mothers with premutation fragile X (45%), both of which were significantly greater than the frequency shown in the mothers with typically developing children (13.3%). Of note, the group of mothers with premutation fragile X met diagnoses for anxiety disorders three times more frequently than mothers of children with autism or typical development. In fact, 10% of premutation carriers with FXS met diagnostic criteria for social phobia. They also reported more relatives with affective disorders than the other two groups, with mothers of children with FXS reporting 20%, with mothers of children with autism reporting 11.7%, and with mothers of children developing typically reporting 3.3% of their relatives had affective disorders. An unexpected, but significant finding from this study revealed that the age of onset of psychiatric morbidity in the groups of mothers of children with autism and mothers of children with FXS was much earlier than the age at which the child's diagnosis was made. Thus, Franke et al. (1996) concluded that the mother's guilt and psychosocial burden is not fully responsible for the higher rate of affective disorders in mothers of children with FXS and autism.

In order to control for the psychosocial stress of raising children with FXS, Franke et al. (1996) compared premutation mothers of children with FXS to premutation women without children affected with FXS. Mothers with the premutation more often reported a major depressive episode than their premutation siblings without affected children of their own. Additionally, premutation mothers of children with FXS reported more major depression than the group of siblings with a normal number of CGG repeats.

After the influential findings from the initial study, Franke et al. (1998) designed a more comprehensive study with a larger sample and an additional control group. This study had five participant groups including: 1) 13 full mutation mothers of children with FXS, 2) 61 premutation mothers of children with FXS, 3) 17 premutation women who did not have a child with mental retardation (MR) but were siblings of the FXS carriers in group one or two, 4) 18 women with a normal FMR1 gene who were siblings of individuals with FM or premutation and do not have a child with MR, and 5) 39 mothers of children with non-FXS autism. They found that 41% of the mothers with the premutation reported a history of anxiety disorders, a greater frequency of overall anxiety disorder diagnoses than both the mothers of children with autism and the women with a premutation who did not have any affected children. Interestingly, among individual anxiety disorders, the mothers with the premutation only differed significantly from the mothers of children with autism on frequency of social phobia, with 18% of premutation mothers of children with FXS, and only 4.8% of the mothers of children with autism meeting criteria. Women with the premutation and a child with FXS did not differ significantly in frequency of social phobia from their siblings with the premutation and no children with FXS. Although none of the individuals in the FXS groups (including adult siblings with no mutation) met diagnostic criteria for OCD, 9.5% of the mothers of children with autism endorsed OCD.

Researchers have speculated that CGG repeat size is correlated with psychiatric difficulties, yet studies examining this association have reported dissimilar results. Franke et al. (1996) reported a trend of carriers of FXS who did not report psychiatric disorders having larger CGG repeats. Franke et al.'s follow-up study (1998) reported a trend of higher frequencies of lifetime depression in female premutation carriers than female full mutation

carriers. Yet, no evidence of a correlation between CGG repeat size and depression was found. Johnston and colleagues (2001) examined the association between CGG repeat size and self report of psychological symptoms in 85 women with the premutation. They created a dichotomous variable of small CGG repeats less than 100 (n = 66) and large CGG repeats equal to or greater than 100 (n = 19) and found significant differences between groups for the dimensions of interpersonal sensitivity and depression, such that women with a larger number of CGG repeats scored significantly higher on both subscales. Thus, they concluded that females in the upper premutation range may have greater susceptibility to psychological difficulties than those in the lower range.

In a recent study, Hessel and colleagues (2005) found that elevated FMR1 mRNA, but not CGG repeat size, was significantly associated with increased psychological symptoms (e.g., obsessive-compulsive symptoms) in premutation men. They did not find an association among CGG repeat size, FMR-1 mRNA, or FMRP and greater psychological symptoms across the entire sample of premutation women. However, when they grouped the sample into women with an activation ratio of less than .5 (more than half their cells with the premutation X active) and greater than .5, they found elevated FMR1 mRNA was significantly associated with more anxiety. Thus, researchers have postulated that emotional problems in individuals with the premutation may be related to a toxic mRNA effect (Hagerman , 2006).

Limitations in previous FXS psychopathology research. While numerous studies have assessed mood disorders in female carriers of the fragile X gene in the last decade, such findings have been inconsistent, with lifetime incidence rates of major depressive disorder ranging between 38%-78% in female carriers (Franke et al., 1998; Thompson et al., 1996).

These inconsistencies have resulted from considerable variations in samples and instrumentation. Samples have varied by size, inclusion of a control group or groups, whether premutation and full mutation carriers were both included and/or analyzed separately, and by participants' parental status. Instrumentation has varied from self-report rating scales to semi-structured psychiatric interviews, whether criteria included current or past symptomatology, and whether triggers for symptoms and/or age of onset were considered.

In terms of measurement, some researchers examined current symptomatology, while others have examined past depressive symptomatology. Using self-report rating scales, 24% of a sample of premutation carriers displayed current symptoms of depression (Johnson et al., 2001). In contrast, researchers using structured psychiatric interviews reported that 41-44% of premutation carriers had at least 1 major depressive episode in their lifetime (Franke et al., 1998; Reiss et al., 1993; Sobesky, Pennington, Porter, Hull, & Hagerman, 1994). Studies that did not differentiate between premutation and full mutation carriers showed even more pronounced differences between current self-report ratings (18%) of depressive symptoms (Abbeduto et al., 2004) and lifetime rates (78%) of depression based on a psychiatric interview (Thompson et al., 1996).

While Abbeduto and colleagues (2004) found higher levels of current depressive symptoms in mothers of children with autism (33%; $n = 174$), than in mothers of children with Down syndrome (10.3%; $n = 39$), the level of symptoms in mothers of children with FXS (18%; $n = 22$) did not statistically differ from that found in the other two groups. While the small sample sizes in this study could account for the lack of statistical significance, it should also be noted that the authors excluded children with FXS who also met behavioral criteria for autism. Because a 15-25% (Dykens & Volkmar, 1997) prevalence rate of autism

has been reported in FXS, and children with FXS/autism demonstrate lower cognitive and adaptive abilities and more problem behavior than individuals with FXS only, Abbeduto's study may have potentially excluded a subset of very challenging children with FXS.

Gene-Environment Interaction

From the literature reviewed, one could postulate that the seemingly high frequency of depression and anxiety found in mothers of children with FXS could result from an interaction of their genetic status and environmental factors such as the psychosocial challenges inherent in raising a child with FXS. It is possible that the mother's genes give her a predisposition or vulnerability for psychiatric difficulties, and the increased challenges presented by her child then amplify the likelihood of mood or anxiety disorders and/or higher levels of stress. Because the genetic status of mothers with autism is still unknown, a gene-environment interaction could be responsible for the high incidence of mood and anxiety disorders seen in mothers of children with autism as well. From a review of the literature on mothers, the gene-environment interaction seems likely given two of the findings of Franke et al. (1998): (a) the frequency of depressive disorders shown in premutation women without children was less than the frequency shown in the premutation women who were raising a child with FXS, and (b) most mothers of children with autism and mothers of children with FXS demonstrated onset of depression before the birth of their affected offspring. Unfortunately, many researchers propose that the psychosocial burden of children with FXS or autism affects maternal well-being without considering how differences within the children shape such maternal outcomes. Do differences in the characteristics or the etiology of these children account for differences in maternal mood, anxiety, and stress?

Child Influences on Maternal Outcomes

Parenting Children With Autism

Research on parenting stress has shown that parents of children with autism demonstrate elevated levels of anxiety and symptoms of depression compared to the typical population, while the most common source of this stress was noted to be their child's difficult behavior (Sharpley, Bitsika, & Efremidis, 1997). Moreover, a high majority of these parents reported sometimes feeling stretched beyond their limits. Several studies have found child autistic symptoms and/or child problem behavior to predict of parental stress (Hastings et al., 2005; Hastings & Brown, 2002; Kasari & Sigman, 1997; Koegel et al., 1992).

Caregivers of children with PDD reported higher levels of persistent distress and depression than caregivers of typical children and caregivers of children with Down syndrome. The parents reported two contributing factors of their distress: (a) the difficult characteristics of the child, and (b) the difficult interactions with the child (Fisman, Wolf, Ellison, & Freeman, 2000).

Noh, Dumas, Wolf, and Fisman (1989) compared the levels of perceived stress on several dimensions of parenting in parents of children with conduct disorder, autism, and Down syndrome using the Parenting Stress Index (PSI; Abidin, 1983). In doing so, they also wanted to address whether or not the level of stress was of a clinical significance that could justify preventative or clinical interventions. On the Parent Domain, they found that mothers of children with disabilities had more difficulties than mothers of typical children with respect to both depression and sense of competence in their parenting role. They also reported that these mothers felt more isolated and restricted by the demands of childcare. On the Child Domain, mothers of the children with autism reported substantial difficulties

dealing with child characteristics such as adaptability, acceptability, demandingness, and distractibility. Depression was related to maternal perception of stress. On the Parent Domain, mothers of children with autism were between three to eight times more likely to be at risk for clinical levels of stress than mothers of typically developing children. On the Child Domain, mothers of children with autism were six times more likely to be at risk for clinically significant levels than parents of typical children. Stress reported on the Child Domain is a fundamental reflection of the child characteristics.

Overall, evidence has shown that having a child with autism can cause considerable stress for mothers, with most of the stress being accounted for by child characteristics which make it difficult to parent. Nevertheless, questions remain regarding how much of this stress is accounted for by the variance in the child's behavior and/or intellectual ability. To understand the experience of families and provide appropriate supports and interventions, increased knowledge of how autistic and problem behavior affect maternal stress in needed.

Parenting Children With FXS

Several studies have found elevated levels of parenting stress in mothers of children with FXS when compared to normative scores on the Parenting Stress Index (Johnston et al, 2003; McCarthy, Cuskelly, van Kraayenoord, & Cohen, 2005; Sarimski, 1997). Wheeler, Hatton, Reichardt, and Bailey (in press) reported that maternal stress was related to children's problem behavior. Johnston and colleagues (2003) also found child behavior problems, but not child age or intelligence, were significantly associated with overall parenting stress. Contrary to this finding, McCarthy and colleagues (2005) did not find behavioral problems predicted psychological stress in their sample of 40 mothers of children with FXS.

The only group of researchers that included a group of children with FXS and a group with FXS/autism did not measure parenting stress. However, they reported that the child's diagnosis of autism was not related to general dimensions of maternal psychological well-being, including depressive symptoms, life satisfaction, and coping style (Lewis, Abbeduto, Murphy, Richmond, Giles, Bruno, Schroeder, Anderson et al., 2006).

In a recent study by Hall, Burns, and Reiss (2007), child problem behavior was reported to have strong direct effects on maternal distress. Interestingly, maternal distress appeared to be equally influenced by the behavior problems of children with FXS as of their unaffected siblings. A further look at the impact of maternal distress on the family, suggested that increased maternal distress did not appear to have any effects on the dysfunctional behaviors of the child.

Comparing the Influence of Autism Versus FXS

One study has compared child behavior and maternal outcomes between mothers of children with FXS and autism. Abbeduto and colleagues (2004) examined how particular characteristics of children with FXS, autism, and Down syndrome predicted maternal well-being using the Autism Behavior Checklist (ABC; Krug, Arick, & Almond, 1980) as a measure of problem behavior in children and the Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977) as a measure of current depressive symptoms in mothers. As previously mentioned, their FXS sample did not include children with FXS/autism. Thirty-three percent of the mothers of children with autism were over the clinical cut-off for current depression, as were 18.2 % of the mothers of children with FXS and 10.3% of the mothers of children with Down syndrome. Yet, the depression frequency in mothers of children with FXS did not significantly differ from that in the other two groups.

Overall, results suggested that mothers tended to be more depressed if there was lower family income, other children in the family with disabilities, if the target child had a greater number of behavior symptoms, and if the mother reported less use of problem-focused and greater use of emotion-focused coping. However, the strongest and most consistent predictor of maternal outcomes was the extent and severity of the behavioral symptoms as measured by the ABC.

Limitations to existing comparative literature. While the findings of Abbeduto et al. (2004) are important because they suggest behavior problems in children with FXS and autism can affect parental psychological well-being, there were several limitations of their study. First, their measure of problem behavior only measured autistic behavior. While many children with FXS demonstrate autistic behaviors, they have other difficult behaviors that may be as, or more, challenging to parents. In addition, measuring only autistic behavior confounds the findings, as the children with autism naturally have higher scores. In addition, the removal of the children with FXS/autism possibly narrows the range of children with FXS. Because children with FXS/autism are lower functioning overall, they may demonstrate more difficulty with non-communicative and/or aggressive behavior. If child behavior predicts depressive symptoms in mothers, this exclusion of children who have FXS/autism may explain Abbeduto et al.'s lower frequency of depressive symptoms seen in mothers of children with FXS than in other studies (Franke et al., 1996; Franke et al., 1998; Reiss et al., 1988; Reiss et al., 1993; Thompson et al., 1996). In addition, Addeduto et al. only investigated current depressive symptoms while examining past psychopathology can provide valuable data to determine if the psychosocial burden of the child may have triggered the psychiatric condition. As noted earlier, genetic status of mothers of children with FXS

was unknown in this study, thus, it included mothers with both the full mutation and premutation of the FXS gene. A study that measures a broader range of children's behavior, includes a broader range and history of maternal psychiatric features, does not exclude children with FXS/autism, and has the ability to consider the genetic status of mothers is important to further clarify these findings. Including a group of children with FXS/autism may also help delineate differences between mothers of children with autism and mothers of children with FXS.

Summary

Research has shown that children with developmental disabilities, such as FXS and autism, present a distinctive pattern of behavioral characteristics that both positively and negatively influence their family environment. Researchers have begun to examine differences in parental functioning across etiological groups (Abbeduto et al., 2004). Still, whether unique variations in the expression of underlying disabilities impact mothers differently is not well understood. Because individuals with FXS and individuals with FXS/autism differ not only in the presence of an autism diagnosis, but also in the severity of their cognitive, behavioral, and language deficits, it is likely that they present different challenges to their mothers.

Although mood, anxiety, and stress in mothers of children with FXS or autism have been studied before, no research to date included a third group of children with FXS who also meet criteria for autism in order to delineate the impact of autistic characteristics on maternal outcomes in FXS. Additionally, the literature suggests that both mothers of children with FXS and mothers of children with autism appear to face specific challenges in their

relationships with their children, possibly related to being a carrier of FXS or having the broad autism phenotype.

The main goal of this study was to better examine maternal mood, anxiety, and stress in mothers of children grouped on the basis of differences in the expression of their child's developmental disability. In this study, children with FXS were grouped by the severity of their autistic symptoms and whether or not they had FXS. The study is based on the overall hypothesis that maternal mood, anxiety, and stress level are influenced by a combination of child problem behavior, child autistic behavior, and maternal genetics.

This comparative research permits an examination of the extent that child and maternal characteristics and outcomes differ as a result of the child's disability. An examination of such similarities and differences will increase our understanding of how characteristics of FXS and/or autism impact outcomes.

This goal is accomplished in several ways. First, the lifetime and current mental health status of mothers of children from the three groups will be described and compared. Second, the association between child characteristics (problem behavior and autistic behavior) and maternal characteristics such as mood, anxiety, and stress will be explored. A detailed description of the research questions guiding this study are provided in the following chapter.

CHAPTER 3

Methods

This study examined mood, anxiety, and stress in three groups: a) mothers of children with FXS, b) mothers of children with FXS/autism, and c) mothers of children with autism, by investigating differences in the frequency of diagnoses from a semi-structured clinical interview and in responses to a self-report stress rating scale. Four research questions and associated hypotheses are addressed:

1) What is the frequency of current and lifetime mood and anxiety disorders within and across diagnostic classes in mothers grouped on the basis of their child's diagnosis of FXS, FXS/autism, and autism?

Mothers of children with FXS/autism will experience a greater frequency and number of mood and anxiety disorders.

2) If a maternal mood or anxiety disorder has been identified was the age at first onset before the birth of the target child with FXS, FXS/autism, or autism? Is this different across groups?

More than half of all mothers that have a diagnosed mood or anxiety disorder will experience the onset prior to the birth of their child with FXS and/or autism.

3) Does child problem behavior predict maternal mood, anxiety, or stress? Is this prediction different across the three groups?

Problem behavior will not predict maternal mood or anxiety disorders measured at the diagnostic level. Higher levels of child problem behavior will predict significantly increased stress in mothers.

4) Regardless of the child's diagnostic group do ratings of autistic behavior predict maternal stress?

Mothers of children with higher levels of autistic behavior will report significantly increased levels of stress.

Participants

The participants in this study were 56 mothers and their male child with FXS, 19 mothers and their male child with FXS/autism, and 42 mothers and their male child with autism. Only biological mothers and their children were recruited for this study. All children were males between the ages of 11 months and 175 months.

Children with FXS

The data from the 75 mothers and their children with FXS (including those with autism) were gathered by the ongoing University of North Carolina at Chapel Hill (UNC-CH) study *Family Adaptation to Fragile X Syndrome*. These participants were recruited through three main sources: (1) currently funded projects at UNC-CH that had an enrolled sample of children with FXS; (2) a group of recent pilot studies at the University of Kansas; and (3) the FX Subject Registry Core of the UNC Neurodevelopmental Disorders Research Center. A review of maternal and child DNA reports established that all 75 of these mothers have the premutation of FXS, while all of their sons have full mutation FXS.

The 75 children with FXS syndrome were grouped depending on whether their total CARS score was above or below the autism cut-off. Out of the 75 children with FXS, 19

(25%) children were placed into the FXS/autism group, while the remaining 56 (75%) children comprise the FXS only group. The percentage (25%) of the children in this sample with FXS who also met behavioral criteria for autism is similar to that typically found in the FXS population (Bailey, Hatton, et al., 1998; Cohen, 1995; Hatton et al., 2006; Kau et. al., 2004; Rogers et. al., 2001).

Children with Autism

Forty-two mothers and their children with autism were recruited through three primary sources: (1) the Autism Society of North Carolina's parent listserv; (2) the Autism Subject Registry Core of the UNC Neurodevelopmental Disorders Research Center; (3) existing studies at UNC (two ongoing studies of children with autism). Autism status of each child was determined in one of two ways: (1) protocols that measured autism symptomatology were gathered from collaborating studies; (2) diagnostic evaluation reports were gathered and reviewed. If the child had participated in one of the ongoing UNC studies, consent for exchange of information between projects was obtained from the family. Subsequently, the results of the completed autism specific measures (ADOS and ADI-R) were procured from the other studies and reviewed for positive autism diagnosis. Five study participants had their diagnoses verified through this method. For the other 37 participants, diagnostic reports and/or exchange of information consents for their diagnostic agency were requested from the families. Two families never supplied a report or signed consent. Thus, their data were dropped from analysis. Diagnostic and/or follow-up reports for the other 35 individuals were obtained and reviewed. From review of diagnostic reports, two individuals were diagnosed with PDD and subsequently dropped from analysis. The remaining 33 individuals had diagnostic evaluations documenting autism from medical doctors (3),

licensed psychologists (26), and licensed school psychological associates (4). In addition, all received scores of 30 or above on the CARS administered as part of this study. An examination of records and discussion of genetic family markers (family history of MR or known diagnosis of FXS) of each child with autism were conducted to ensure that none of the children also had a diagnosis of fragile X syndrome. Thus, out of the 42 participants, 38 were included in the analyses (4 excluded due to undocumented autism status).

Selection

Extensive sociodemographic information was gathered from all families. While it was difficult to ensure similar groups during the data collection phase, this investigator attempted to assess all families of individuals suspected of having autism. After data collection, if the individual did not meet study established autism criteria, he was excluded from the analysis.

Based on the predetermined selection criteria, the three groups were similar (in order of importance) on gender (male); child chronological age (+/- 2 years); child developmental quotient (+/- .5 standard deviations in standard score); proportion of children not European American (+/- 10% of group); maternal age (+/- 5 years); maternal IQ (+/- .5 standard deviations in standard score); family socio-economic status (+/- $10K); maternal education (+/- 2 years). Statistical analyses based on group means were completed and are described in the results section.

Instrumentation

Data collection involved the use of a structured clinical interview, standardized instruments, and parental questionnaires.

Maternal Measures

Structured Clinical Interview for the DSM-IV-I: *Non-patient Edition* (SCID-I/NP; First, Spitzer, Gibbon, & Williams, 2002; First, Spitzer, Gibbon, & Williams, 1997). The SCID-I/NP is a semi-structured diagnostic interview that was used to diagnosis all mothers for depression and anxiety. The SCID-I/NP systematically evaluates current and past psychiatric symptomatology for DSM-IV psychotic, mood, substance use, anxiety, somatoform, post traumatic stress disorder, eating, and personality disorders. For this study, only the mood and anxiety disorder modules were administered. This investigator was trained in the administration of the SCID and administered the SCID-I/NP to each mother. A typical SCID-I/NP administration required 45 minutes of the mother's time.

Demographic information. Demographic information was gathered from each mother using a general information form. This form recorded information about the mother's ethnic background, age, age at child's birth, marital status, and education. This form also recorded information about the child's age, FXS or autism diagnosis dates, ethnic identity, and family income. Additionally, this form recorded information regarding other children in the family (i.e., age, diagnosis of disability).

Wechsler Abbreviated Scale of Intelligence (WASI; Psychological Corporation, 1999). The WASI was used to provide an estimate of the cognitive functioning of the mothers. The WASI, which is appropriate for individuals between age 6 and 89, consists of four subtests (Vocabulary, Similarities, Block Design, and Matrix Reasoning) that produce a standard full-scale IQ score (FSIQ), as well as Verbal and Performance IQ standard scores (VIQ and PIQ). An estimate of general intellectual ability can be obtained from the two-subtest form, which can be given in about 15-30 minutes. This form includes Vocabulary and

Matrix Reasoning and provides only the FSIQ score. Evidence shows that WASI FSIQ produces scores consistent with the longer more widely used IQ batteries in the Wechsler series. The reliability coefficients for the adult FSIQ-4 was .98, for the adult FSIQ-2 was .96, and for the subtests ranged from .92 to .94 (Psychological Corporation, 1999).

Parenting Stress Index Short Form (PSI; Abidin, 1983). The PSI was used to assess the magnitude of stress in the parent-child system. The PSI Short Form is a self-scoring questionnaire made up of 36-items, which yields three factor scores (Parental Distress, Parent-Child Dysfunctional Interaction, and Difficult Child) and a Total Stress score. The parent rates each item using a Likert scale ranged from 1 (Strongly agree) to 5 (Strongly Disagree). The higher scores indicate a greater magnitude of stress. The PSI Short Form is derived from a longer 101-item PSI. This questionnaire, which typically requires 15 minutes for completion, was completed by the mother of each child. According to the PSI manual, parents whose scores are clinically significant are candidates for referral to professional services.

Child Measures

Child Behavior Checklist for ages 1 ½ to 5 years (CBCL 1½ to 5; Achenbach, 1991; Achenbach & Rescorla, 2000). The CBCL 1 ½ to 5 was collected for all the children between 1 ½ and 5 years to assess the child's competencies and behavioral/emotional problems based on child's activities, social relations, and school performance. The CBCL 1½ to 5 is a 99-item standardized questionnaire in which parents or caregivers rate statements describing child behaviors on a three-point scale from 0 (not true) to 2 (very true or often). The CBCL 1½ to 5 produces scores on the following factors: Anxious/Depressed, Somatic Complaints, Withdrawn, Emotionally Reactive, Attention Problems, Aggressive Behavior, and Sleep

Problems. These factors contribute to three broad scales: Internalizing, Externalizing, and Total Problems. Internal consistency for the CBCL Total Problems score was reported at .76 with a range from .53 on the Withdrawn subscale to .64 on the Anxious/Depressed subscale. Test-retest reliability for the Total Problem score was .90 with a range on subscales from .68 on the Anxious/Depressed subscale to .92 on the Sleep Problems subscale. This questionnaire, which was completed by all mothers with children within the proper age range, typically required 20 minutes for completion.

Child Behavior Checklist for ages 6-18 years (CBCL 6-18; Achenbach, 2001; Achenbach & Rescorla, 2001). The CBCL 6-18 was collected for all children older than six years of age to broadly assess child competencies and maladaptive functioning based on child's activities throughout multiple settings. The CBCL for ages 6-18 years is a 113-item standardized questionnaire in which parents describe their child's behavior on a three-point scale from 0 (not true) to 2 (very true or often true). The CBCL produces scores for the child's competencies in the following areas: Activities, Social, and School. Additionally, it produces scores for the three broad scales of Internalizing, Externalizing, and Total Problems which are made up of the following factors that also score: Anxious/Depressed, Withdrawn/Depressed, Somatic Complaints, Social Problems, Thought Problems, Attention Problems, Rule-Breaking Behavior, and Aggressive Behavior. Test-restest reliability for the Total Problem scale is .94 with a range on subscales from .82 on Anxious/Depressed to .92 on Somatic Complaints, Attention Problems, and Externalizing Behavior. Internal consistency for the CBCL for ages 6-18 years was a .81 for Total Problems, ranging from a .64 for Somatic Complaints to a .82 for Aggressive Behavior. This questionnaire, which was

completed by all mothers with children within the proper age range, typically required 20 minutes for completion.

Childhood Autism Rating Scale (CARS; Schopler et al., 1988). The CARS was used to provide a rating of autistic characteristics in the boys with FXS and the boys with autism. The CARS is a 15-item measure in which a professional rates the child in each of the 15 areas using a score from 1 (within normal limits for age or skill level) to 4 (severely abnormal for age or skill level). The CARS includes the following areas: Relating to People; Imitation; Emotional Response; Body Use; Object Use; Adaptation to Change; Visual Response; Listening Response; Taste, Smell, and Touch Responses; Fear and Nervousness; Verbal Communication; Nonverbal Communication; Activity Level; Intellectual Response; and General Impression of Autism. The CARS has good internal consistency (.94) and test-retest stability over a one-year period (.88). Inter-rater reliability, which is crucial in a behavioral observation measure, is reported at (.71) by the CARS manual. The CARS was completed after this investigator observed the child in enough contexts to be able to rate all 15 items. Parental report was used if questions remained. The item scores were added to create a total score, which is often used as a continuum of autistic behavior. In addition, the child's total score on the CARS can be interpreted as nonautistic (15-29.5), mildly or moderately autistic (30-36.5), and severely autistic (37 or higher). As detailed above, CARS scores were used to define the FXS group (n = 75) into two: those with FXS only (scores < 30; n = 56) and those with FXS/autism (scores ≥ 30; n = 19). In addition, the CARS was used to as a clinical confirmation of autism in boys with autism only.

Vineland Adaptive Behavior Scales-Interview Edition: Survey Form (VABS; Sparrow, Balla, & Cicchetti, 1984). The VABS is a semi-structured interview conducted with

a parent or guardian to measure the adaptive behavior skills of an individual. The VABS focuses on four sub domains of adaptive behavior: communication, daily living skills, socialization, and motor skills. A standard score is then produced to determine their adaptive level and age equivalence. The survey form of the VABS has good internal consistency with split half means for the domains ranging from .83 to .90 and a .94 for the Adaptive Behavior Composite (ABC). Test-retest reliability ranges from .81 to .86 for the domains and is .88 for the ABC. Interrater reliability range from .62 to .78 for the domains and is .74 for the ABC.

Procedures

Recruitment

As mentioned above, data on the mothers of children with FXS and their children were gathered by the *Family Adaptation to Fragile X Syndrome* UNC-CH study. Following IRB approval, mothers of children with autism were recruited. First, parents of children already enrolled in other UNC-CH studies were contacted via letters, postcards, or hand-outs and asked to participate in this mother-child study. If interested, they completed and returned a pre-paid postcard. Second, a brief explanation of the study along with contact information for this investigator was posted on the parent listserv maintained by the Autism Society of North Carolina. Mothers interested in participating were asked to email or call the investigator. Additionally, mother-child dyads that met criteria for this study and were registered in the Autism Subject Registry Core of the UNC Neurodevelopmental Disorders Research Center were mailed a letter with an enclosed postcard to return if interested in learning about or participating in this study. Follow-up phone calls were made to mothers who specified interest in the study. The mothers were given a more detailed description of

the measures, rationale for the measures, and the time/commitment involved in study participation.

General Assessment Procedures

Once verbal consent was obtained, a visit with mother, or mother and child, was scheduled. Prior to the scheduled visit, a packet that included the written consent form, demographic form, and maternal and child questionnaires was mailed to the mother. The mother-child dyads who participated in one of the other UNC-CH studies had already been administered some of measures used for this study. If the date of administration of any measure was within six months of the scheduled visit, the measure was not repeated.

Attempts were made to schedule visits in the family's home in order to provide a comfortable environment for both the mother and child and to be consistent with the procedures of the *Family Adaptation to Fragile X Syndrome* study. In addition, attempts were made to avoid outside interference (i.e., siblings, transition times) during test/interview administration. One mother felt that her son would be more likely to participate outside of the home environment. Thus, the mother-child dyad was assessed and interviewed at The FPG Child Development Institute. Other than that one exception, assessments were completed in the family's home. At the beginning of each scheduled visit with the mother or mother/child dyad, this investigator spent several minutes with the participants, during which a description of the visit's procedures was given, questions were encouraged, and rapport was established. At this time written informed consent was obtained. Subsequently, the researcher collected the completed packet of information mailed to the mother and ensured all items were complete. If the mother did not complete the packet prior to the visit, she was given a stamped addressed envelope in which she could return the information. During the visit, this

investigator administered the WASI, Vineland, and the SCID-I/NP to the mother. The SCID-I/NP was audio recorded

Collection of the Childhood Autism Rating Scale

Within the *Family Adaptation to Fragile X Syndrome* study, the collection of the CARS on children with fragile X syndrome varies slightly depending on the age of the child. Children under the age of 68 months are given the Mullen Scales of Early Learning (Mullen, 1995) and a battery of temperament and maternal interaction tasks over the course of a two-day, 6-8 hour assessment in their home. The CARS is completed based on the observations of the assessor and parental report. Children with fragile X syndrome between the age of 68 months and 14 years do not receive such a lengthy battery of tasks. Instead, they are given the Brief IQ index (four subtests which take approximately 30 minutes to complete) from the Leiter International Performance Scale-Revised (Leiter-R; Roid & Miller, 1997) and observed in interaction with their mother. This home visit typically lasts between 3-4 hours. The assessor completes a CARS based on their assessment, observations, and parental report.

Thus, for the children with autism, an assessment situation similar to that completed with the children with fragile X syndrome was simulated. They were assessed in the home during a period that lasted from 3-5 hours. This investigator observed a routine mother-child interaction such as snack time. With younger children a free play period between the mother and her child was observed. This investigator also engaged the child with autism in play for a 10-15 minute period. In addition, the Mullen was completed with children under 68 months and the Leiter-R Brief IQ with children between 68 and 144 months. The CARS was completed after the assessment based on the observations of this investigator and parental

report. The visits occupied between three and five hours of the family's time. Each family was given $25.00 for their participation.

Determination of Mood and Anxiety Disorders

After completion of the assessment, every SCID-I/NP was reviewed by the investigator, who also reviewed those administered in the *Family Adaptation to Fragile X Syndrome* study. When necessary, follow-up phone calls were made by this investigator to the maternal participants to clarify answers and/or diagnoses. In addition, all cases with positive or questionable diagnoses of any mood or anxiety disorder were verbally presented to and reviewed by the *Family Adaptation to Fragile X Syndrome* project's consulting psychiatrist.

In order to augment the prospect of identifying differences among the three participant groups in the rate of low-frequency diagnoses, two categorical variables were constructed from pragmatic clusters of the DSM-IV diagnoses (Table 1): (1) a mood disorder category consisting of any diagnosis of major depression, minor depression, dysthymia, or bipolar disorder, (2) an anxiety disorder category consisting of any diagnosis of social phobia, specific phobia, generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, agoraphobia, or posttraumatic stress disorder.

CHAPTER 4

Results

Preliminary Analysis

Preliminary analyses were conducted to assess the distributions and inter-correlations of all variables and to test the assumptions of the models employed. Distributions of all the scaled measures, including the PSI, CBCL, and WASI met assumptions of normality. A significance level of $p < .05$ was established *a priori.* To control for multiple comparisons, all p-values were adjusted using the Benjamini-Hochberg method (Benjamini & Hochberg, 1995).

Group Selection

Child and maternal demographics and characteristics are provided in Table 2. Maternal IQ was the only demographic variable that failed to meet the pre-determined selection criteria set of less than .5 standard deviation between groups, specifically, the mothers of children with autism had a higher mean group IQ than either of the other two groups. T-tests between the group means tested this difference statistically. Maternal IQ in the autism group was significantly higher than maternal IQ in the FXS only [$t(89.64) = -4.70$, $p < .001$] and FXS/autism groups [$t(25.96) = -2.25$, $p = .033$]. As a result, maternal IQ is controlled for in the analyses.

The Vineland Adaptative Behavior composite scores were used to assure that the adaptive functioning in the group of children with autism matched the adaptive functioning

in the groups of children with FXS and FXS/autism. See Figure 1 for a detailed look at how the ABC scores are distributed. The standard scores indicate the children, overall, displayed significant delays. Vineland scores were not available for three children, including two in the FXS group and one in the FXS/autism group. Thus, for analyses using the Vineland, the sample is 110. As expected, the FXS group had the highest mean ABC score (M = 57.30), the children with autism had a mean score between the FXS group and FXS/autism group (M = 54.21), and the FXS/autism group had the lowest mean scores (M = 48.67). The standard deviations and ranges are noted in Table 2. The difference between the children with FXS only and the children with FXS/autism was statistically significant [t(35.78), p = .031). No differences were found between the autism and the FXS group or the autism and the FXS/autism group, suggesting an appropriate match on adaptive behavior.

Table 3 displays the Pearson correlations computed on the continuous variables, and Table 4 displays the Phi correlations computed on the categorical variables.

Descriptives

Descriptive statistics for the child and maternal characteristics are provided in Table 2. Maternal mood and anxiety, as measured by the SCID, are reported by lifetime frequency in Table 3 and by current frequency in Table 4.

Maternal stress, as measured by the PSI, is depicted in Figure 2. For analyses using the PSI, the sample is 98, because five participants did not complete the PSI and 10 participants had significant scores on the defensive scale rendering their scores invalid (eight from the FXS only group, one from the FXS/autism group, and one from the autism group). Within the whole sample, 48% (n = 47) of the mothers who validly completed this measure reported experiencing clinically significant levels of parenting stress (greater than the 90th

percentile). The types of stress experienced in the total sample were examined: 28% (n = 27) reported clinically significant stress due to general parenting stress (not to the target child in particular), 51% (n = 50) reported clinically significant stress specific to the dysfunction within the parent-child interaction, and 37% (n = 36) reported clinically significant stress related to raising this difficult child. Pearson correlations between the individual subtests scores and the total stress scores demonstrated statistically significant correlations among all. As a result, total parent stress scores will be used for later analyses.

Figure 3 shows how maternal stress was experienced by mothers of the three different samples. When group means were compared, mothers of children with FXS reported significantly less total stress than mothers of children with FXS/autism [$t(30.62) = -2.08$, $p = .05$] and mothers of children with autism only [$t(81.49) = -3.61$, $p < .01$]. No difference was found between the FXS/autism group and the autism group on total maternal stress.

Child problem behavior, as measured by the CBCL is shown in Figure 5. For analyses using the CBCL, the number is 108, as five participants did not complete the CBCL. Within the whole sample, 38% (n = 41) of the mothers reported problem behaviors in the clinically significant range, and 13% (n = 14) reported problem behaviors in the borderline range. When group means were compared, children with FXS were described as having significantly less total problem behavior than the children with FXS/autism [$t(40.12) = -3.42$, $p = .001$] and children with autism only [$t(83.42) = -4.58$, $p = < .001$]. There was no difference in total problem behavior between the FXS/autism and autism group.

Full Model Analyses

Question 1: What is the frequency of current and lifetime mood and anxiety disorders within and across diagnostic classes in mothers of children with FXS, FXS/autism, and autism?

Frequency of each DSM-IV disorder was calculated in terms of lifetime history and current status. Results are depicted in Table 5 and Table 6. Because of the uneven sample sizes of the groups, the percentage of individuals who met for each disorder was calculated and a mean percentage was obtained for all three groups. That mean frequency percentage was applied to the sample size of each group to compute an expected sample frequency. The individual group's expected sample frequency was then compared, via chi-square analysis, to the actual frequency of each group. To control for a false discovery rate of multiple testing, p-values were adjusted via the Benjamini-Hochberg method (Benjamini & Hochberg, 1995). The p-values were adjusted separately for lifetime frequency and current frequency. Using the same method, the frequencies of diagnoses grouped categorically were compared via a chi-square analysis using the disorder class groupings of any mood disorder lifetime, any anxiety disorder lifetime, any mood disorder current, and any anxiety disorder current. These p-values were also adjusted via the Benjamini-Hochberg method. Results are depicted in Table 7.

After adjustment, one significant difference in frequency existed among the three groups, a difference in the frequency of lifetime history of generalized anxiety disorder [$X^2(2, N = 113) = 14.3, p = .01$]. Pair-wise post-hoc analyses demonstrated a greater frequency of generalized anxiety disorder in mothers of the autism group than in mothers of the FXS only group [$X^2 (1, N = 94) = 11.11, p < .01$] and the FXS/autism group [$X^2 (1, N = 57) = 5.64, p = .02$]. No differences existed between the two FXS groups.

Because maternal IQ was higher in mothers of children with autism than in the other two groups, an individual ANOVA including the entire sample tested whether a difference in IQ existed between those who did and did not meet for a mood or anxiety disorder. No

difference was found. Additionally, using the entire sample, mean maternal IQ scores were compared for those who did and did not meet for generalized anxiety disorder. No difference was found.

Although maternal IQ was the only selection variable that did not meet the predetermined criteria, t-tests were used to examine group differences for all other selection variables. Group differences were found in maternal age and child age. Mothers in the autism only group were significantly older than mothers in the FXS only [$t(68.09) = -2.93$, $p = .005$] and FXS/autism [$t(32.43) = -2.44$, $p = .02$] groups. Children in the autism only group were significantly older than the children in the FXS only [$t(91.44) = -2.24$, $p = .028$] and the FXS/autism [$t(55) = -2.10$, $p = .026$] groups. The association between maternal and child age and maternal mood and anxiety, was tested using an individual ANOVA across the entire sample. There was no difference in maternal or child age for those who met for a mood or anxiety disorder and those who did not.

To assess whether mothers across the groups experienced a different quantity of disorders, a chi-square analysis compared the number of diagnoses for mothers in each group. First, a count of how many diagnoses each mother had was generated. Next, frequencies of mothers who met for none, one, two, and three or more disorders were formulated per group. Because of the uneven sample sizes of the groups, the percentage of individuals who met for each number of disorders was calculated and a mean percentage was obtained for each count for all three groups. That mean frequency percentage was applied to the sample size of each group to compute an expected sample frequency. The expected frequency of each individual group was then compared, via chi-square analysis, to the actual frequency count in each group. Results of this analysis are depicted in Table 8. An overall

significant difference was found [$X^2(5, N = 113) = 11.46, p = .04$] and pair-wise post hoc analyses showed that the significant difference existed between the FXS only group and autism only group [$X^2(3, N = 94) = 8.33, p = .04$]. The mothers of children with autism appear less likely to have never had a mood or anxiety disorder and more likely to have experienced two and three or more disorders. Therefore, the prediction that mothers of children with FXS/autism would experience a greater frequency and number of mood and anxiety disorders was not supported.

Question 2: If a mood or anxiety disorder has been identified, was the age at first onset before the birth of the target child with FXS, FXS/autism, or autism? Is this different across groups?

Another set of chi-square analyses assessed differences across groups in whether mothers experienced a mood or anxiety disorder before the birth of the target child. First, the date of onset for mothers who met for a mood or anxiety diagnosis was compared to the birth date of the target child. A count was generated for all mothers who met for a diagnosis prior to the birth of the child. Table 9 depicts these frequencies. Next, three separate chi-square analyses compared the frequencies of having a mood disorder, anxiety disorder, and either mood or anxiety disorder prior to the birth of their target child. No differences were found among the groups. The prediction that more than half of all mothers that have a diagnosed mood or anxiety disorder will experience the onset prior to the birth of their child with FXS and/or autism was supported.

Question 3: Does child problem behavior predict maternal mood, anxiety, or stress? Is this prediction different across the three groups?

To examine whether child problem behavior is predictive of mood and anxiety disorders, a set of binary logistic regressions investigated this association using disorders grouped by class (see Table 1). Each regression initially included an interaction in order to assess whether the magnitude of the association between the behavior and the psychiatric diagnosis was different among the different groups. Separate regressions were run for lifetime mood, lifetime anxiety, current mood, and current anxiety as dependent variables. Additionally, in order to account for the difference found among the groups for maternal IQ and child age, they were added to the model to control for their possible contributions. No group effects or interactions for these regression models were significant at the .05 significance level for any of the four outcome variables, suggesting that the CBCL does not predict mood or anxiety differently per group status. Thus, the regression models were run again without group as an interaction in order to analyze the main effects more clearly. CBCL scores significantly predicted all four outcome variables. Problem behavior predicted maternal lifetime incidence of mood disorders [X^2 (1, N = 105) = 5.62, p < .02; OR = 1.06, 95% CI = 1.01-1.11], lifetime incidence of anxiety disorders [X^2(1, N = 105) = 7.96, p = <.01; OR = 1.08, 95% CI = 1.03-1.15], current mood disorders [X^2 (1, N = 105) = 4.74, p = .03; OR = 1.10, 95% CI = 1.01-1.20], and current anxiety disorders [X^2 (1, N=105) = 3.74, p = .05; OR = 1.07, 95% CI = .99-1.14].

A two-way analysis of variance was conducted to examine whether child problem behavior was predictive of maternal stress. First, due to group differences in maternal IQ, and maternal and child age, Pearson correlations (Table 3) were examined to better understand the contribution of each variable to maternal stress. No association was found between maternal or child age and stress. However, a significant association was evident between

maternal IQ and parental stress, ($\beta = .27$, $p < .001$), indicating a need to use maternal IQ as a control variable.

The first model included an interaction to assess whether the association varied across the groups. To account for the difference found among the groups for maternal IQ, it was added as a control variable. Results indicated a main effect for CBCL ($F = 51.30$, $p < .01$), but no effect for group, and no interaction. This model was run again without the interaction to secure parameter estimates. Again, there was no group effect. However, the effect of the CBCL remained significant ($F = 56.39$, $p < .01$), suggesting that for every one point change in the CBCL there is an increase in total stress of 1.28. Thus, the prediction that child problem behavior would not predict maternal mood or anxiety disorders measured at the diagnostic level was not supported. However, the prediction that higher levels of child problem behavior would predict significantly increased stress in mothers was supported.

Question 4: Regardless of diagnostic category, do ratings of autistic behavior predict maternal stress?

Group effects were not examined because the groups are defined by differences in autistic behavior, as measured by the CARS. A univariate analysis of variance revealed that CARS scores do predict stress in mothers ($F = 9.34$, $p < .01$) suggesting that for every one point change in the CARS, there is an increase in total stress of .84. These results support the prediction that mothers of children with higher levels of autistic behavior will report significantly increased levels of stress.

CHAPTER 5

Discussion

Integration of Findings

The goal of this study was to describe and compare maternal mood, anxiety, and stress across mother-child dyads categorized into three groups (those with children affected by FXS only, FXS/autism, and autism only).

Frequency of Mood and Anxiety in the Three Groups

While there was no precedent in the literature that examined mood and anxiety disorders in mothers of children with FXS/autism, it was predicted that this group would experience a significantly greater frequency of mood and anxiety disorders. This hypothesis was based on a theory that the additive impact of FXS/autism on mothers would be greater than that of either disorder alone. This prediction was not statistically supported. However, despite a lack of statistical difference among groups, descriptively, a pattern of equal or greater mood and anxiety disorders in mothers of children with autism, regardless of FXS status, exists. It may be that the small sample sizes and resulting limits on statistical power prevent these differences from reaching statistical significance. Nevertheless, an examination of the numbers suggests a trend for more mood and anxiety disorders in mothers of children with more autistic behavior, independent of their FXS status. This trend is more evident when lifetime or current mood and anxiety disorders are grouped by class, as occurrence appears to increase from the FXS only to the FXS/autism to the autism only group. This

trend suggests that autism group affiliation and/or greater autistic symptomatology is associated with more mood and anxiety in mothers.

It was also predicted that mothers of children with FXS/autism would experience a greater number of mood and anxiety disorders than the other two groups. This hypothesis was not supported. Instead, the number of mood and anxiety disorders experienced by the mothers of children with autism was significantly different from the group of mothers of children with FXS only. Mothers of children with autism were less likely than the mothers of children with FXS only to have no mood or anxiety disorder (26% and 46% respectively), and more likely to have experienced two (24% and 9% respectively) and three or more (18% and 7% respectively) disorders, suggesting a "worse" mental health profile for mothers of children with autism (Table 8). Because there was no precedent for a count of disorders in the FXS or autism literature, this initial finding needs to be replicated before conclusions are drawn. Nevertheless, understanding differences in maternal mental health profiles is quite important to understanding mental health prognosis.

Regarding group differences, the three groups were similar across all mood and anxiety disorders with the exception of generalized anxiety disorder. Mothers of children with autism experienced the disorder with greater frequency than mothers of children with FXS or FXS/autism. While no previous studies reported the frequency of generalized anxiety disorder in mothers of children with autism, two studies that examined generalized anxiety disorder in parents or first degree relatives of individuals with autism found no difference between their rates and those of controls (Piven et al., 1991; Smalley et al., 1995). It should be noted that 29% of the mothers of children with autism in this sample reported a lifetime history of generalized anxiety disorder, over four times that of the 7.1% (N = 9,282)

prevalence in women reported in large community sample (Kessler, 2005). The community prevalence of 7.1% is more in line with the frequency found in the mothers of children with FXS (4%) and mothers of children with FXS/autism (5%) in the current study. Therefore, this new finding suggesting an elevated risk of generalized anxiety disorder in mothers of children with autism should be explored further to better understand its contribution to the broader autism phenotype and the support/intervention needs of mothers of children with autism. In future studies, it will be crucial for relatives of individuals with autism to be grouped by their relationship to the child, as generalized anxiety disorder may affect mothers and not fathers or siblings, thereby explaining why past studies have not found such a high occurrence.

Lifetime frequency of obsessive compulsive disorder was significant prior to the adjustment, with mothers of children with autism demonstrating a higher frequency of the disorder than the other two groups. In fact, obsessive compulsive disorder was not experienced by any of the mothers of children with FXS or FXS/autism in the current sample. This finding is similar to that of Franke and colleagues (1998), whose sample of mothers with the premutation of FXS (n = 61) lacked obsessive compulsive disorder, while a high proportion of their sample of mothers of children with autism met criteria (9.5%; n = 42). Thus, an elevated risk of obsessive compulsive disorder in mothers of children with autism should be explored further to better understand its contribution to the broader autism phenotype. An elevated rate of obsessive compulsive disorder in mothers of children with autism is not surprising given that obsessive and compulsive behaviors are typically seen in the autistic phenotype.

No significant differences were found between the groups in social phobia. As mentioned, Smalley and colleagues (1995) found a high incidence rate of social phobia (20.2%) in first degree relatives of children with autism compared to that of controls (2.4%; relatives of individuals with seizure disorders). Additionally, Franke et al. (1998) found significantly elevated rates of social phobia in premutation mothers of children with FXS (18%) compared to mothers of children with autism (4.8%). There were no differences among the groups in frequency of social phobia in the current sample. Community prevalence rates of social phobia in women are reported as 13% (Kessler et al., 2005), while rates in this sample were 7% (FXS), 11% (FXS/autism), and 11% (autism). A possible explanation for these findings may be differences in diagnostic criteria, as both of the earlier studies diagnosed social phobia based on the DSM-III or DSM-III-R, which did not include impairment in functioning in their criteria. However, the SCID, used in the current study, is based on the DSM-IV which includes impairment in functioning as a diagnostic criterion.

While not directly tested, all three groups demonstrate a higher frequency of major depressive disorder than typically found in community samples. Specifically, Kessler and colleagues (2005) reported lifetime prevalence estimates of major depressive disorder in women as 20% (N = 9,282), much lower than the 43%, 37%, and 61% found in this sample of mothers. This supports previous findings of a higher frequency of major depressive disorder in mothers of children with FXS and mothers of children with autism when compared to community or control samples (Franke et al., 1998; Reiss et al., 1993; Sobesky et al., 1994; Smalley et al., 1995; Thompson et al., 1994). Note that the group chi-square comparisons in this study were calculated using an average of the percentages from the three groups. Thus, without comparing these numbers to that of a community sample, one can only

speculate on their difference from the population. Nevertheless, the findings seem to support literature that suggests having a child with a significant disability is a risk factor for depression (Singer, 2006).

Regarding the overall frequency of anxiety disorders in this sample, the FXS only group's reported 23% appears to be in line with the 28.8% reported in a large community sample (Kessler et al., 2005), while the 37% found in the FXS/autism and 45% found in the autism groups appear higher. Again, these comparisons are descriptive, and were not directly tested. Nevertheless, the high incidence of anxiety in mothers of children with autism is partially supported by previous literature that found more anxiety disorders in first degree relatives of individuals with autism than in controls (Micali, Chakrabarti, & Fombonne, 2004; Piven et al., 1991).

Age of Onset

Based on the literature reviewed, it was predicted that more than half of all mothers who experienced a mood or anxiety disorder would have experienced onset prior to the birth of the target child. This prediction was supported. As a result, the high frequency of major depressive disorder seen in this population of mothers cannot be entirely explained by psychosocial factors of raising a child with a developmental disability, as 53% of the mothers within the total sample who reported a mood disorder experienced the onset of at least one mood disorder prior to the birth of the target child. This finding supports previous research stating that the majority of the individuals with depression report onset prior to the birth of their target child (Franke et al., 1998; Micali et al., 2004; Piven et al., 1991; Smalley et al., 1995). Also in support of the literature, a majority (87%) of the mothers who reported anxiety disorders within the total sample reported onset prior to the birth of the target child

(Piven et al., 1991; Smalley et al., 1995). No difference existed across the three groups in the percentages of mothers whose disorder onset was prior to the child's birth.

It should be noted, however, that these findings are limited for at least two reasons. First, the birth date of the target child was used, not the birth date of the first child. As a result, mothers could have onset of a diagnosis prior to the birth of the target child but after the birth of an older child, possibly one with a disability. Second, due to the heritable components of autism and FXS, and the broader phenotypic expression found in families of individuals with either disorder, mothers were possibly exposed to family environments that were not typical during their childhood and young adult years. Thus, it is possible that a diagnosis of a mood or anxiety disorder prior to the birth of a child may be a result of other stressors and or disabilities that were not directly measured or controlled for, yet existed within these families.

Problem Behavior and Maternal Mood and Anxiety

While much of the literature suggests that problem behavior is associated with current depressive symptoms, it was predicted that problem behavior would not predict maternal mood and anxiety measured at a diagnostic level, as the threshold for clinical mood and anxiety disorders is high. Additionally, the current study measured lifetime incidence of mood and anxiety while the CBCL measured current problematic behavior.

Results did not support this prediction. In fact child problem behavior predicts both current and lifetime incidence of maternal mood and anxiety, the same across groups. As mentioned above, there was no precedent in the FXS or autism literature for examining the impact of problem behavior on mood and anxiety disorders. However, several studies examined its impact on maternal depressive and anxious symptoms using current rating

scales. These findings support those of Hall et al. (2007) who found that problem behavior of children with FXS (as well as the difficult behavior of their unaffected siblings), had a substantial and additive impact on current symptoms of maternal depression and anxiety.

Regarding depressive symptoms, these findings support those of Abbeduto and colleagues (2004) who found the extent and severity of problem behavior to be the most consistent predictor of current depressive symptoms in the mothers of children with FXS. However, their measure of problem behavior actually measured autism-spectrum behaviors, not the broad range of problem behaviors measured by the CBCL. In contrast, Lewis, Abbeduto, Murphy, Richmond, Giles, Bruno, Schroeder, Anderson, et al. (2006) did not find current symptoms of depression (current rating scale) to be linked to child autistic behavior in their comparison of maternal well-being across groups of children with FXS, FXS/autism, and Down syndrome.

This finding that child problem behavior predicts maternal mood and anxiety suggests that not all of the "psychological risk" factors for these mothers are genetic in nature. Still, the course and direction of this association needs further exploration, as it is possible that mothers with a history of a mood or anxiety disorder are biased in their perception of their children's behavior. For example, mothers may rate their children's behavior more negatively or problematic due to their own low threshold, or they could be more aware of symptoms in their child after having experienced difficult symptoms themselves.

Problem Behavior and Maternal Stress

Based on a plethora of literature documenting an association between child problem behavior and maternal stress, it was predicted that higher levels of problem behavior would significantly predict increased stress in mothers. This prediction was supported. Within this

sample, elevated levels of maternal stress are reported by mothers across groups. As reported in other studies of stress in mothers of children with autism or FXS, stress in this sample (Figure 2) appears associated with child factors, as the parent distress subscale accounts for less of the total stress than the other subscales (Johnston et al., 2003; Kasari & Sigman, 1997). In fact, across all three groups, the subscale with the highest percentage of scores above clinical significance is the parent-child dysfunctional interaction subscale. Notably, the difficult child subscale is elevated in the FXS/autism group and the autism only group, when compared to the FXS only group.

Previous research has suggested that the type of disability is an important variable in parental stress (Hodapp et al., 1997; Hodapp et al., 1998). As noted in the results section, the mothers of children with FXS/autism and autism reported significantly more stress than the mothers of children with FXS alone. While child problem behavior was found to predict maternal stress, it did so in all groups, without an interaction effect, despite the differing level of stress experienced among the groups. These findings support those of previous studies in which problem behavior predicted stress in mothers of children with FXS (Johnston et al., 2003; Sarimski, 1997; Wheeler et al., in press) and in mothers of children with autism or ASD (Hastings et al., 2005; Lecavalier, Leone, & Wiltz, 2006; Sharpley et al., 1997). However, McCarthy and colleagues (2005) did not find behavioral problems (on the BASC) to predict stress in mothers of children with FXS ($N = 40$). It is not clear why McCarthy et al. (2005) had disparate findings; however, they used an Australian sample, and it is possible that cultural differences may account for the differences found among in their study and others which were conducted in the United Sates.

Autistic Behavior and Maternal Stress

There was little precedent in the FXS literature for examining the association between autistic behavior and maternal stress, as much of the literature focused instead on child problem behavior. Based on the findings from the autism literature, it was predicted that children who demonstrated higher levels of autistic behavior would have mothers with increased levels of stress. Results supported this prediction. Undoubtedly, child problem behavior and autistic behavior overlap, as reflected in the significant positive correlation between them (.42, $p < .01$) shown in Table 3. However, the CARS provides a more precise measure of autistic symptomatology, that may differentially impact mothers. The finding that autistic behavior predicts maternal stress seems of particular importance for those who provide services to families with children with FXS, as children with more autistic symptoms appear to cause more maternal stress. This result supports findings that autistic symptomatology predicted elevated levels of parental stress in the autism literature (Hastings & Johnson, 2001). Still, a recent study by Hastings and colleagues (2005) found child problem behavior, but not autistic behavior, predicted maternal stress; however, this study only included children with autism. Therefore, a strength of the present study is the ability to examine the impact of a wider spectrum of behaviors.

Limitations

As with many research studies of families of children with autism and FXS, this sample was non-randomly selected and relied on families to volunteer their participation in research. For this study in particular, slightly different methods of recruitment were used for the group of mothers of children with autism. The mothers of children with FXS were asked, and subsequently volunteered, to participate in a study that assessed family adaptation to

FXS using a broad range of measures. In contrast, the mothers of children with autism volunteered for a study specifically detailing maternal well-being as the focus. Thus, it is possible that mothers of children with autism were less likely to volunteer for this study because of having symptoms of mood, anxiety, or stress. However, it is also plausible that mothers with mental health difficulties volunteered believing that they would be good candidates for this study based on their history of depression, anxiety, or stress.

It should be recognized that the associations between child characteristics and maternal outcomes are correlational not causal in nature, and should be interpreted with caution. In fact, these associations may be transactional in nature and act to intensify one another. For example, child problem behavior may increase parental stress, which may then be reflected in the parent child interactions, only to trigger an increase in difficult child behavior. Likewise, the measures given were completed by one individual, the mother. Thus, the responses may be biased based on the personality style of this mother. As mentioned previously, mothers may rate their child differently, for example on the CBCL, because of their own experience, frustration threshold, and/or their level of stress. Thus, in future studies, taking into account ratings completed by others (fathers or teachers) will provide another approach to examine these associations.

Another limitation of this study is the lack of FXS testing for all individuals in the autism only group. Although extant data were examined when available and family markers (e.g., history of FXS or MR in the family) were discussed, it is possible that individuals in the autism group could have FXS and should then be in the FXS/autism group. Literature suggests that FXS accounts for roughly 4% of the total cases of autism (Dykens & Volkmar, 1997).

This study was limited by small sample sizes, especially considering that of the FXS/autism group (n = 19). Larger sample sizes would provide a better estimation of the frequency of mood and anxiety disorders in these groups, and possibly make differences and interpretations of such differences more robust. In fact, many of the *a priori* predictions were made based on a theory that the additive impact of both FXS and autism would predict greater mood and anxiety disorders in mothers of children with FXS/autism. It is possible that the small sample size of this group resulted in the lack of such findings. Future studies could alleviate this limitation by including a larger FXS/autism group.

While this study examined several dimensions of child and maternal characteristics across three groups, it lacks generalizability in that it doesn't include a comparison group consisting of mothers of typically developing children. Thus, it remains unclear whether the association between increased problem and autistic behavior and increased maternal mood, anxiety, and stress is specific to children with FXS and autism. Additionally, without statistical comparisons of rates of mood and anxiety between these mothers and a community sample, one can only speculate about how they compare to the community. Thus, it will be important to follow up this study with one that compares the frequency of these disorders with prevalence rates from women in an epidemiological study.

Another limitation of this study was the lack of genetic data on mothers of children with autism. While, genetic documentation proves that all mothers of children with FXS and FXS/autism in this sample were carriers of the gene that caused FXS in their child, the route of possible genetic transmission in the children with autism is still unknown. Thus, it is possible that the children with autism inherited their disorder from their father, or from a combination of both parents' genetics. Without genetic data, direct comparisons of maternal

gene-behavior influence cannot be made. Furthermore, additional exploration of the genetic status of the mothers of the children with FXS may uncover genetic differences between mothers of children with FXS and mothers of children with FXS/autism. The recent findings that link elevated levels of mRNA to psychological symptoms in premutation women with FXS could also inform this study. Future studies that compare mood and anxiety disorders measured at a diagnostic level to quantity of mRNA are vital.

As mentioned above, this study is also limited by the use of a target child for child variables. Using a target child, rather than the first born child or first affected child, limits the conclusions that can be drawn from the findings that most mood and anxiety disorders were present prior to the birth of the target child. Although over 60% of this sample are first born children, many children in this study may have older siblings that have FXS, FXS/autism, or autism whose diagnosis or behavior could have contributed to the onset of disorder. Additionally, using variables related to a target child limits our interpretation of maternal stress, as there may be parental stress related to the characteristics of other children and/or the contributory affect of several children.

Implications for Intervention

This study provides important descriptions of maternal mood, anxiety, and stress in mothers of children with disabilities and the complex and likely interactive impact of child behavior. In addition, this study has important implications for intervention. The most noteworthy of these is the high number of mothers across all three groups who report major depressive disorder. Maternal depression can have potentially negative impacts on the cognitive, emotional, and social development of infants (Coyl, Roggman, & Newland, 2002; Siefer & Dickstein, 2000). Infants of depressed mothers have been shown to have more

difficulty with social referencing (Gewirtz & Paleaez-Nogueras, 1992), differentiating facial expressions (Hernandez-Reif, Field, Diego, Vera, & Pickens, 2006), social-perceptual skills (Murray, 1990), and more problem behavior (Ashman, Dawson, Panagioti, Yamado, & Wilknoson, 2002; Chi, & Hinshaw, 2002). Moreover, infants of depressed mothers are at greater risk for insecure attachments, depressed affect, and negative styles of interaction, (Seifer & Dickstein, 2000). Whether this depression is due to a genetic vulnerability, the stressful home environment of raising a severely developmentally disabled child, or likely both, the risk of depression needs to be recognized and responded to through intervention and support.

While this study highlighted an increased risk of depression in all groups of mothers, establishing intervention and/or preventative services for this depression is complicated, given that the majority of mothers who reported depression experienced episodes prior to the birth of their child. Because of the direct heritability of FXS and the availability of genetic testing, women who have individuals with FXS in their family may be aware of their carrier status prior to having children. For these women, it will be important for service providers and/or genetic counselors to facilitate awareness of the symptoms of depression and inform premutation carrier women of their increased risk. For mothers of children with autism and mothers who learn of their FXS carrier status at the diagnosis of their child, it will also be important to facilitate awareness of their risk for depression. It is possible that these women have already experienced depression. Thus, a careful examination of each mother's current and history of depression and or depressive symptoms should be completed. Mothers should be informed of their increased risk and given resources to utilize currently or if difficulties should arise.

Findings from this study also highlighted an increased risk for anxiety in mothers of children with autism, mainly a risk for generalized anxiety disorder and obsessive compulsive disorder. Given that 77% of mothers of children who reported anxiety disorders had experienced onset prior to the birth of their child, many mothers will have already struggled with symptoms of anxiety. Therefore, at the time of the child's diagnosis and or follow-up visits, mothers of children with autism should be screened for anxiety, informed of the increased risk of certain anxiety disorders, and given treatment resources if needed.

Both depression and anxiety are treatable disorders which typically respond to therapy, counseling, medication, or a combination of medication and therapy. For mental health service providers, differential diagnosis of depression, anxiety, or comorbid depression and anxiety in these mothers will be important to consider for individualized treatment planning.

The high levels of stress experienced by women across all maternal groups in this study cannot be ignored. As shown, much of this stress was associated with child variables. Thus, it is important that interventions focus on comprehensive parental education and support including behavioral management techniques and the identification of individualized interventions that focus on specific mother and child relationships. Mothers may also benefit from interventions designed to help them understand and cope with their child's behavior, especially those who have children with increased autistic symptomatology. Additionally, mothers could benefit from education on personal stress reduction techniques.

Table 1

Categorical Variables of the SCID-I/NP

Mood Module
Major depressive disorder
Minor depression
Dysthymia
Bipolar I disorder
Bipolar II disorder
Anxiety Module
Panic disorder with agoraphobia
Panic disorder without agoraphobia
Social phobia
Specific phobia
Obsessive compulsive disorder
Posttraumatic stress disorder
Generalized anxiety disorder

Table 2

Child and Maternal Demographics

	Total Sample *N* = 113	**FXS only Group** *n* = 56	**FXS/Autism Group** *n* = 19	**Autism Group** *n* = 38
Child Age (in months)				
Mean	77.76	71.43	67.79	92.08
Standard Deviation	47.96	55.11	44.12	34.33
Range	11-175	11-175	27-155	33-171
Child Ethnicity				
Non-European American	28 (25%)	16 (29%)	4 (21%)	8 (21%)
European American	85 (75%)	41 (71%)	15 (79%)	30 (79%)
Maternal Age				
Mean	36.48	35.46	34.37	39.03
Standard Deviation	6.06	5.04	7.05	6.24
Range	20-51	21-46	20-43	26-51
Maternal IQ				
Mean	111	106	110	118
Standard Deviation	13.34	13.39	13.66	9.99
Range	73-135	75-131	73-127	88-135
Low Income	*n* = 111			*n* = 36
(<200% poverty level)	25 (23%)	15 (27%)	4 (21%)	6 (17%)
Maternal Education				
High School or Less	8 (7%)	3 (6%)	3 (16%)	2 (5%)
Some College	40 (36%)	27 (48%)	5 (26%)	8 (22%)
Some Post College	64 (57%)	26 (46%)	11 (58%)	27 (73%)
Maternal Employment				
Mothers that work outside of the home	68 (60.2%)	37 (66%)	8 (42%)	23 (60.5%)
Other Children				
Percent with other children	73%	73%	63%	79%
Percent other children w/ DD	34%	39%	43%	26%
Vineland ABC (SS)				
Mean	54.82	57.30	48.67	54.21
Standard Deviation	16.12	16.44	13.29	16.41
Range	20-93	24-93	21-64	20-84
CBCL (Total Problem)				
Mean	59.17	54.72	62.68	63.86
Standard Deviation	10.26	10.25	8.08	8.51
Range	27-83	27-71	49-75	47-83
PSI (Total Problem)				
Mean	90.18	84.49	93.61	95.74
Standard Deviation	19.12	18.74	20.44	17.29
Range	47-137	47-130	56-130	58-137
CARS Total Score				
Mean	29.91	24.49	34.92	35.40
Standard Deviation	6.76	3.22	5.08	4.72
Range	17.5-50	17.5-29.5	30.5-47.5	30-50

Table 3

Pearson Correlation Matrix for Continuous

		Mom Age	Income	Child Age	CARS Total	Vineland ABC	CBCL	WASI IQ	Total Stress
Mom Age		1							
	n	113							
Income		.09	1						
	n	111	111						
Child Age		.49*	-.30**	1					
	n	113	111	113					
CARS Total		.18	-.08	.13	1				
	n	113	111	113	113				
Vineland ABC		-.32**	.28**	-.69**	-.37**	1			
	n	110	108	110	110	110			
CBCL Problem Behavior		.03	-.17	.20*	.42**	-.27**	1		
	n	108	107	108	108	105	108		
WASI IQ		.23*	.30**	-.04	.28**	.05	.30**	1	
	n	110	108	110	110	109	105	110	
Total Stress		-.05	-.09	.09	.30**	-.26*	.67**	.27**	1
	n	98	96	98	98	95	95	95	98

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

Table 4

Phi Correlation Matrix of Categorical Maternal and Child Variables and Outcomes

		European American	Low Income	Mom Job	Mom Education	Meet for Mood	Meet for Anxiety	Group
European American		1						
	n	113						
Low Income		-.13	1					
	n	111	111					
Mom Job		.08	-.01	1				
	n	113	111	113				
Mom Education		.18	-.50**	.07	1			
	n	112	111	112	112			
Meet for Mood		.09	.38**	.01	.30	1		
	n	113	111	113	112	113		
Meet for Anxiety		.05	.13	-.09	.06	.27**	1	
	n	113	111	113	112	113	113	
Group		.09	-.11	.17	.30*	.17	.21	1
	n	113	111	113	112	113	113	113

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

Table 5

Lifetime Frequency of DSM-IV Disorders Across Samples: Frequency (Percentage)

DSM-IV Disorder	Total Sample $N = 113$	FXS only $n = 56$	FXS/Autism $n = 19$	Autism Only $n = 38$	X^2	p-value	adjusted p
Mood Disorders							
Major depressive disorder	54 (48%)	24 (43%)	7 (37%)	23 (61%)	3.99	.14	.39
Minor depression	4 (4%)	1 (2%)	1 (5%)	2 (5%)	.96	.62	.68
Dysthymia	3 (3%)	1 (2%)	0	2 (5%)	1.94	.38	.70
Bipolar I	3 (3%)	1 (2%)	2 (11%)	0	4.38	.11	.40
Anxiety Disorders							
Generalized anxiety	14 (12%)	2 (4%)	1 (5%)	11 (29%)	14.3	< .00**	.01**
Panic disorder	14 (12%)	5 (9%)	4 (21%)	5 (13%)	2.08	.35	.77
Social phobia	10 (9%)	4 (7%)	2 (11%)	4 (11%)	.42	.81	.81
Specific phobia	8 (7%)	3 (5%)	1 (5%)	4 (11%)	1.04	.59	.72
Posttraumatic stress	6 (5%)	2 (4%)	2 (11%)	2 (5%)	1.38	.50	.69
Obsessive-compulsive	3 (3%)	0	0	3 (8%)	6.14	.05*	.28
Agoraphobia without panic	2 (2%)	1 (2%)	1 (5%)	0	1.69	.43	.68

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

Table 6

Current Frequency of DSM-IV Disorders Across Samples: Frequency (Percentage)

DSM-IV Disorder	Total Sample $N = 113$	FXS only $n = 56$	FXS/Autism $n = 19$	Autism Only $n = 38$	X^2	p-value	adjusted p
Mood Disorders							
Major depressive disorder	11 (10%)	3 (5%)	1 (5%)	7 (18%)	4.94	.08	.40
Minor depression	0	0	0	0			
Dysthymia	1 (1%)	0	0	1 (3%)	2.01	.37	.74
Bipolar I	1 (1%)	0	1 (5%)	0	3.04	.22	.73
Anxiety Disorders							
Generalized anxiety	10 (9%)	1 (2%)	1 (5%)	8 (21%)	10.28	.01*	.10
Panic disorder	3 (3%)	1 (2%)	1 (5%)	1 (3%)	.67	.72	.80
Social phobia	10 (9%)	4 (7%)	2 (11%)	4 (11%)	.42	.81	.81
Specific phobia	8 (7%)	3 (5%)	1 (5%)	4 (11%)	1.04	.59	.74
Posttraumatic stress	1 (1%)	0	0	1 (3%)	2.01	.37	.62
Obsessive-compulsive	1 (1%)	0	0	1 (3%)	2.25	.32	.80
Agoraphobia without panic	2 (2%)	1 (2%)	1 (5%)	0	1.69	.43	.61

*$p < .05$.

Table 7

Frequency of DSM-IV Disorders Grouped by Class Across Samples

DSM-IV Disorder	Total Sample *N* = 113	FXS only *n* = 56	FXS/Autism *n* = 19	Autism Only *n* = 38	X^2	*p*-value	adjusted *p*
Any Disorder							
Any Mood Disorder (Lifetime)	61 (54%)	26 (46%)	10 (53%)	25 (66%)	3.49	.17	.23
Any Anxiety Disorder (Lifetime)	37 (33%)	13 (23%)	7 (37%)	17 (45%)	5.02	.08	.16
Any Current Mood Disorder	13 (12%)	3 (5%)	2 (11%)	8 (21%)	5.25	.07	.28
Any Current Anxiety Disorder	22 (20%)	8 (14%)	3 (16%)	11 (29%)	3.28	.19	.19

Table 8

Number of Different Diagnoses Mothers Experience

	Total Sample ***N*** **= 113**	**FXS only** ***n*** **= 56**	**FXS/Autism** ***n*** **= 19**	**Autism Only** ***n*** **= 38**	**Total** X^2	***p*-value**
Did not have any disorder	42 (37%)	26 (46%)[§]	6 (32%)	10 (26%)		
Met for 1 disorder	42 (37%)	21 (38%)[§]	9 (47%)	12 (32%)		
Met for 2 disorders	15 (13%)	5 (9%)[§]	1 (5%)	9 (24%)		
Met for 3 or more disorders	14 (12%)	4 (7%)[§]	3 (16%)	7 (18%)		
Number of Diagnoses					**11.46**	**.042***

*$p < .05$.
[§] significantly different from the autism group, $p < .05$

Table 9

Onset of Disorder Prior to Birth of Target Child Across Groups: Frequency (Percentage)

	Total Sample	**FXS only**	**FXS/Autism**	**Autism only**	X^2	***p*-value**
Onset of **either** mood or anxiety disorder before birth of target child	47 (66%)	21 (70%)	9 (69%)	17 (61%)	0.73	.73
Onset mood disorder before birth of target child	32 (53%)	15 (58%)	5 (50%)	12 (48%)	0.52	.77
Onset anxiety disorder before birth of target child	32 (87%)	12 (92%)	7 (100%)	13 (77%)	4.06	.13

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

Figure 1. Vineland ABC scores by group.

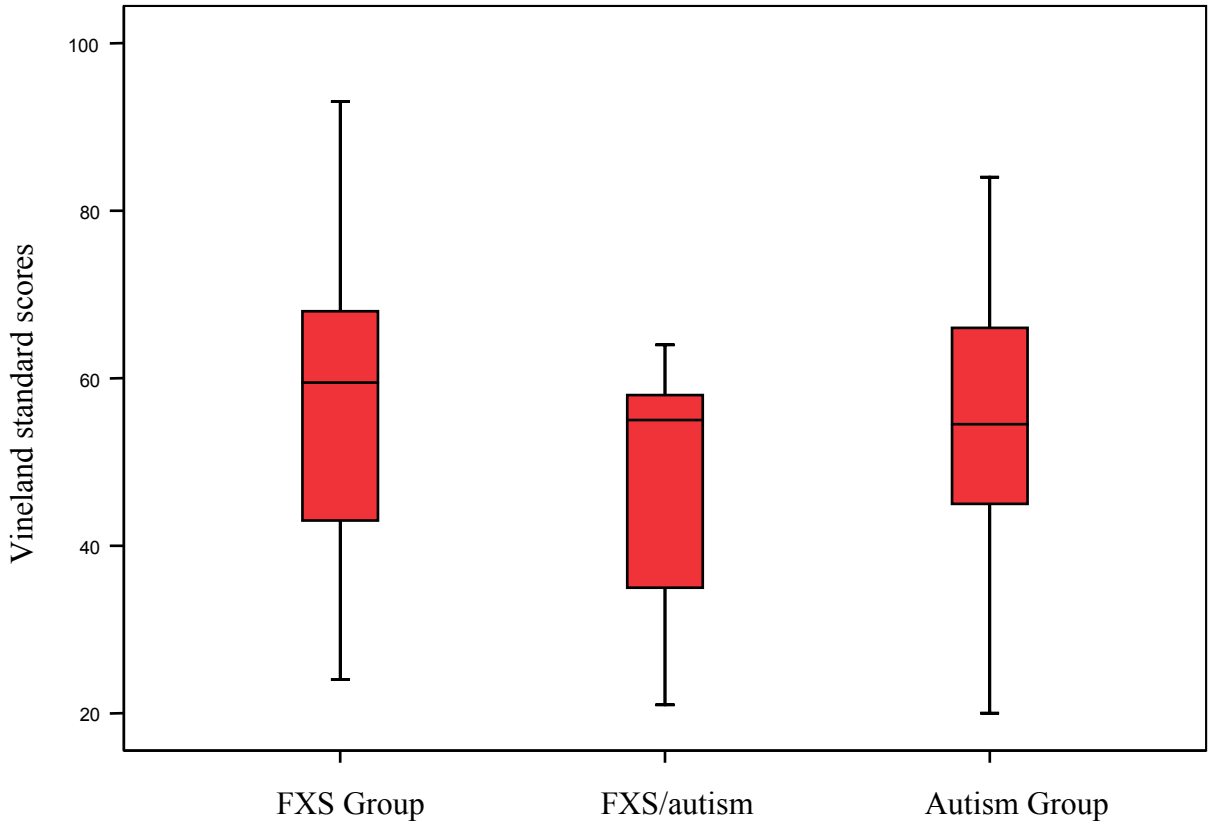


Figure 2. Clinically significant maternal stress as measured by the PSI.

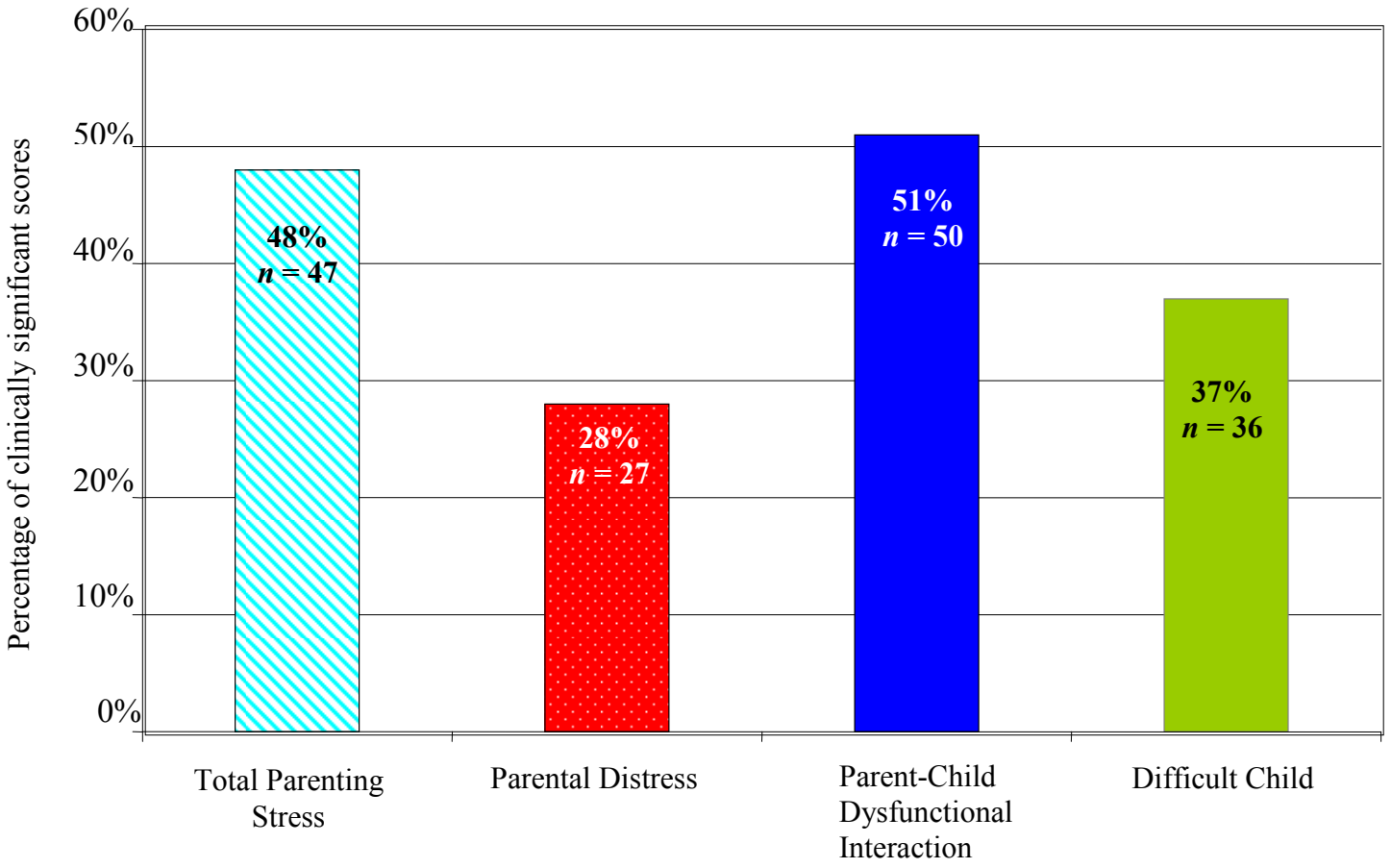


Figure 3. Percentage of clinically significant subtest scores on the PSI across groups.

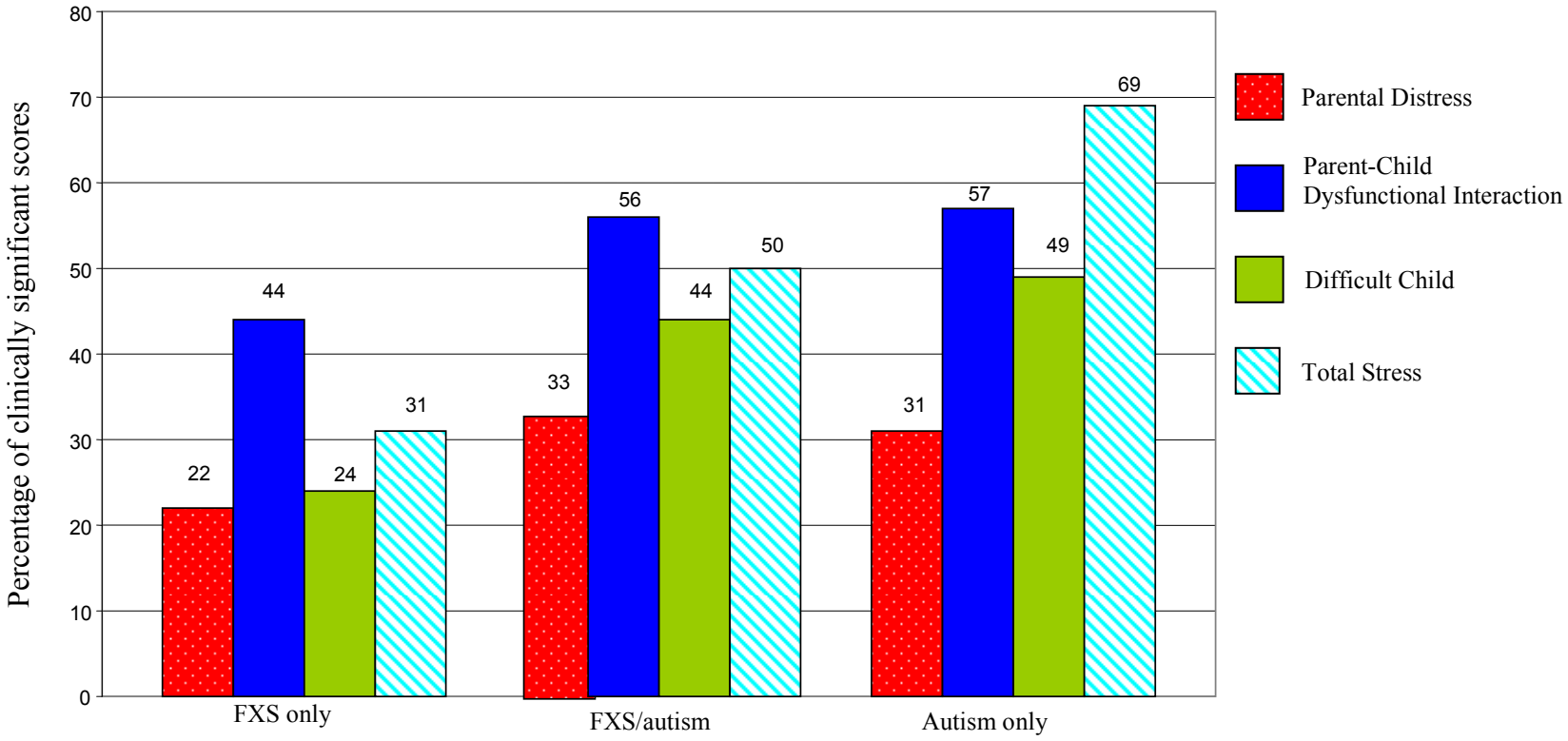
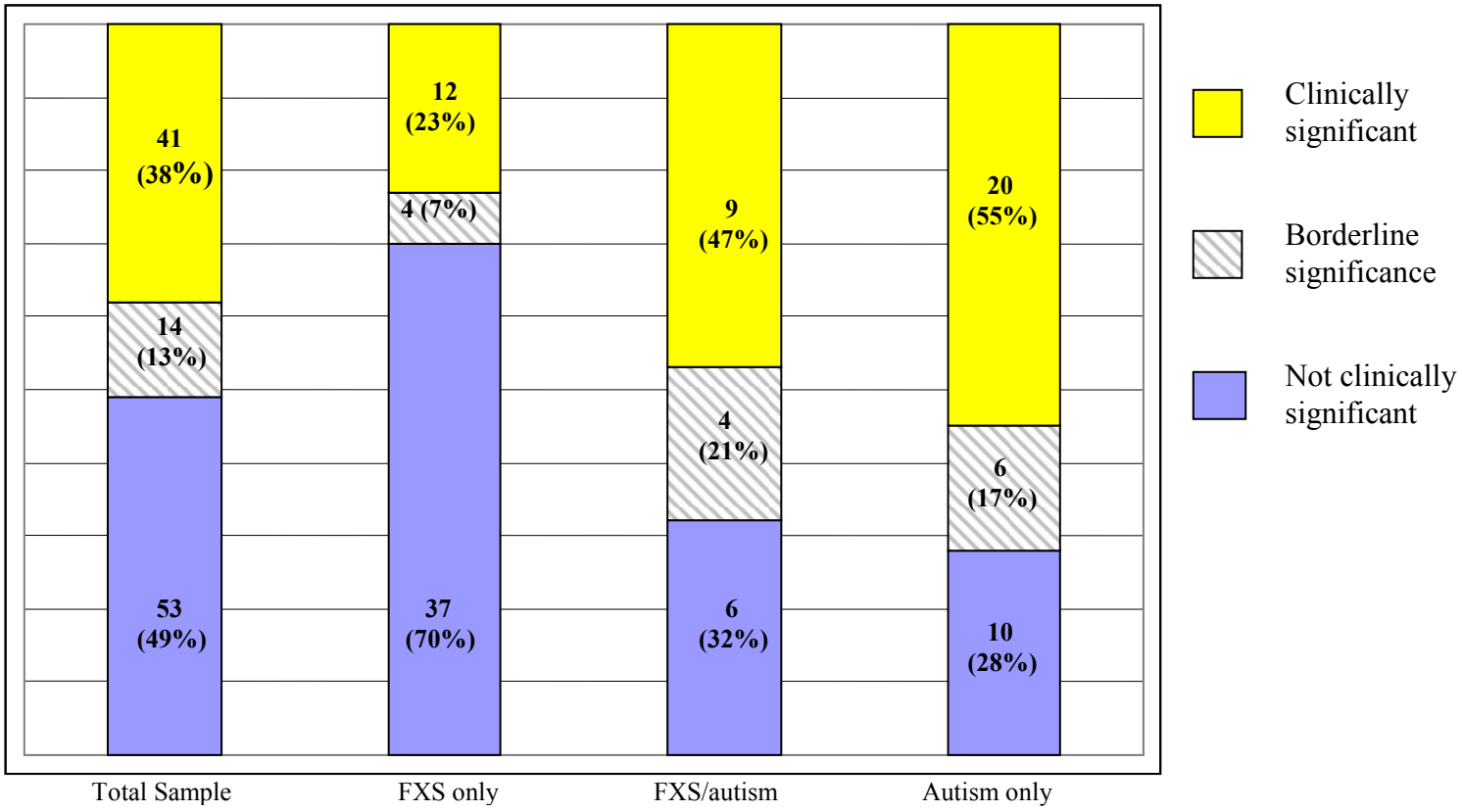


Figure 4. Percentage of children that scored in the clinical range on CBCL: Total sample and across groups.



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