Cultural and Contextual Perspectives on Developmental Risk and Well-Being

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Fragile X-Associated Disorders: How the Family Environment and Genotype Interact

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The family system has long been recognized as a central context for human development, with family-level processes acting as sources of both risk and protection for children, parents, and other family members across the life course. Following a developmental psychopathology perspective, development is the result of dynamic transactions between individuals and their contexts over time wherein individuals simultaneously shape and are shaped by their environments (Cummings, Davies, & Campbell, 2000). Further, in order to adequately understand the interplay of personal and contextual contributions to lifespan development, research should delineate genetic and environmental risk factors as well as focus on how and why interaction processes work in specific subgroups (Rutter et al., 1997).

In this chapter, we explore the family as a context for children's development among families of children with fragile X syndrome (FXS), a unique population in which to investigate the interactive effects of genes and environment. FXS is an inherited genetic disorder, resulting in biologically compromised development of varying degrees in individuals with this mutation. In some cases, mothers of children with FXS and other extended family members are also affected with different and milder symptoms if they are "premutation" carriers. As such, within samples of families of individuals with FXS, it is possible to explore the influence of environmental factors at varying levels of genetic liability. For instance, developmental risk for children with FXS may be moderated by the presence of protective factors in the family environment. As another example, the level of genetic risk for mothers with the premutation may explain individual differences in reactivity to environmental stressors and adaptation over time. Thus, in this chapter, we specifically examine how family environmental
factors (e.g., family emotional climate, responsive parenting, child-related parenting stress) contribute to child and maternal development in the context of genetic risk, using the special case of families of children with FXS.

Fragile X syndrome (FXS) is the most prevalent inherited cause of intellectual disability (Crawford, Acuna, & Sherman, 2001). Children with FXS may have any number of phenotypic characteristics such as intellectual disability, hyperactivity, gaze avoidance, unintelligible speech, perseverative and stereotypic behaviors, and passivity (Abbeduto, Brady, & Kover, 2007; Bailey, Hatton, & Skinner, 1998; Sterling & Warren, 2008), although there is great heterogeneity in the degree of affectedness, with males typically more severely affected than females in this X-linked condition. It is estimated that approximately 15% to 25% of individuals (mostly males, but some females) with FXS meet the diagnostic criteria for autism (Clifford et al., 2007; Rogers, Wehner, & Hagerman, 2001). Regardless of codiagnosis, 50% to 90% of males with FXS are reported to show some of the symptoms of autism, including self-injurious behaviors, stereotypic movements (i.e., rocking, hand flapping), perseverative speech, tactile defensiveness, and poor eye contact (Bailey et al., 1998; Clifford et al., 2007; Feinstein & Reiss, 1998). Males with both FXS and autism typically have more severe language and social impairments and lower IQ scores than children with FXS without autism (Bailey et al., 1998; Bailey, Hatton, Mesibov, & Skinner, 2000) and similarly have more severe behavior problems than children with FXS without autism (Smith et al., 2012).

FXS results from a mutation in the 5' untranslated region of the FMR1 gene located on the X chromosome (Brown, 2002). In the healthy allele, there are approximately 40 or fewer repetitions of the CGG sequence of nucleotides comprising the FMR1 gene. In the full mutation of FXS, there is an expansion to 200 or more repetitions. Importantly, smaller expansions of the CGG sequence are also associated with adverse phenotypic consequences. Individuals who have between 55 and 200 CGG repeats in the gene are said to carry the premutation. The premutation can expand to the full mutation when passed on from mother to child (Nolin et al., 1996). In addition, a sizeable proportion of individuals with the premutation display many of the same behavioral features of individuals with FXS, albeit typically in a less severe form (Bailey, Raspa, Olmstead, & Holiday, 2008). Specifically, premutation carriers are at risk for difficulties in attention, verbal memory, and executive function (Freund, Reiss, & Abrams, 1993; Sobesky, Hull, & Hagerman, 1994); additionally, women with the premutation of FXS are more prone to depression and social anxiety and may be more affectively labile than unaffected women (Hagerman & Hagerman, 2002; Mazzocco,
2000; Sobesky et al., 1994; Thompson, Rogeness, McClure, Clayton, & Johnson, 1996).

The premutation is also associated with elevated risk for two disorders that do not occur in individuals with the FMR1 full mutation: Fragile X-Associated Primary Ovarian Insufficiency (FXPOI), which includes a continuum of ovarian dysfunction, including infertility, irregular menstrual cycles, and premature menopause, and Fragile X-Associated Tremor-Ataxia Syndrome (FXTAS), a late-onset neurodegenerative disorder (Cornish, Turk, & Hagerman, 2008). These difficulties are not uncommon, with prevalence rates for female carriers over the age of 50 reported to be 18.6% and 16.5% for FXPOI and FXTAS, respectively (Rodriguez-Revenga et al., 2009). Families that include one or more member who has FXS or even the FMR1 premutation, therefore, are likely to experience higher levels of stress and nonnormative life experiences as a (direct or indirect) result of the characteristics and behaviors of the affected family members (Murphy & Abbeduto, 2005; Smith et al., 2012).

Fragile X-associated disorders, thus, constitute a multigenerational set of conditions affecting children, their parents and grandparents, and potentially other members of the extended family. Children with FXS inherit the problem gene from their mother, who would be a carrier of either the premutation or the full mutation (Nolin et al., 1996). (For more details about the inheritance profile of the FMR1 gene, see Hagerman, 1999.) Some parents (and grandparents) of children with an expanded FMR1 allele will be affected by many of the same challenges as their children, which may well make them less able to deal with life stressors, including those associated with their child's condition (Esbensen, Seltzer, & Abbeduto, 2007). Consequently, understanding the functioning of any individual in a family affected by an FMR1 expansion will require examination both of his or her own genetic status and of experiences within the family, which is the underlying premise of our program of research.

The full mutation of FXS affects 1 in approximately 4,000 individuals. The premutation is much more prevalent, but it has only recently begun to be investigated. Prevalence studies have been conducted in Canada, Israel, Spain, Taiwan, and Japan, and prevalence rates vary widely, reflecting significant ethnic variation, likely a function of founder effects (i.e., mutations that appear in the DNA of individuals that are founders of a distinct population and that are passed down to other generations). In a review of the world literature, Song and colleagues (2003) pooled estimates across all studies and arrived at a premutation prevalence of 1 in 643 males and 1 in 149 females. However, pooling data from studies of different ethnic groups
and sex distributions could be misleading because of the wide variation in prevalence across ethnicities and between men and women. In the first U.S. population-based prevalence study of premutation prevalence conducted on an unselected sample of Whites largely of Northern and Central European ancestry, Seltzer, Baker, and colleagues (2012) reported a prevalence of 1 in 468 males and 1 in 151 females. Two other recently published population-based prevalence studies (one by our group) provide converging evidence regarding the validity of these prevalence estimates (Maenner et al., 2013; Tassone et al., 2012).

The purpose of this chapter is to summarize our group's research findings on the family context of FXS and the premutation of FMR1. Specifically, we draw mainly on our published findings to elucidate how environmental factors (particularly the family environment) and genotype interact to affect the functioning and well-being of family members. We begin with an overview of our research program. Next, we turn to questions of how the family influences the development of children with the full mutation of FXS. With this life course perspective, we examine first how early maternal behavior (in particular, maternal responsivity) longitudinally affects the development of language in young children with FXS and subsequently how the family emotional climate is associated with behavior problems in individuals with FXS in childhood, adolescence, and adulthood. In the next section of the chapter, we consider the premutation of the FMR1 gene in mothers of children with the full mutation and examine how carrier mothers are affected by the behavior problems of their children as well as other stresses in the larger environment. Thus, our goal is to examine the reciprocal relations between mother and child across the life course in the context of variations in FMR1 genotypes.

STUDY OF FAMILY ADAPTATION TO FXS: VARIATIONS ACROSS THE LIFE COURSE

This chapter draws on data collected as part of a multisite, ongoing study on family adaptation to FXS and how the family context is associated with heterogeneity in life course patterns of development and functioning of individuals with FXS (Bailey, Hatton, Tassone, Skinner, & Taylor, 2001; Seltzer, Barker et al., 2012; Warren, Brady, Sterling, Fleming, & Marquis, 2010). This multisite study is part of an NICHD-funded Fragile X Research Center that includes 199 families in total: 52 children, 96 adolescents, and 51 adults with FXS. Documentation from laboratory or medical records confirming that the son/daughter has the full mutation of the gene causing
FXS was a requirement for participation. Families were recruited through service agencies, clinics, foundations across the United States, and university-based research registries of families having a child with developmental disabilities.

Mothers of young children with FXS \((n = 52)\) have participated in a longitudinal study of family adaptation to FXS thus far spanning more than 8 years (Warren, Brady, Sterling, Fleming, & Marquis, 2010). Children’s ages ranged from 10 to 40 months at the first data collection point (in 2004), and all lived in the parental home. In families with two or more children with FXS, the youngest child was the focal child for the study. Their median household income was between $50,000 and $80,000 in 2008, with incomes ranging from less than $15,000 to $100,000 or more. The majority of mothers are White (90%), currently married (73%), and had at least some college education (85%).

Mothers of adolescents \((n = 96)\) and adults \((n = 51)\) with FXS are participating in a companion longitudinal study of family adaptation to FXS (Greenberg et al., 2012; Seltzer, Barker et al., 2012; Smith et al., 2012). Median household income was between $80,000 and $89,000 at the start of the study in 2008, but a range in income was represented (< $9,999 to $160,000 or more). Most mothers are White (95%), currently married (82%), and had at least some college education (85%), similar to the sample of families of younger children described previously.

When considering the combined sample, the majority of individuals with FXS are sons (81%, 77%, and 94% of the children, adolescents, and adults, respectively) and have intellectual disability (ID; 83%, 79%, and 84%, respectively). The percentage of sons (vs. daughters) differs across the three age groups (Chi square = 6.18, \(df = 2\), \(p < .05\)). However, the percentage of those with ID (vs. average intelligence) does not vary across the three stages of life.

Family Influences on the Development of Individuals with Fragile X Syndrome

There has been a long tradition of research aiming to identify aspects of the family environment that can enhance the well-being of children with intellectual and developmental disabilities (IDD; see review by Hatton & Emerson, 2003). For example, Mitchell and Hauser-Cram (2009) studied longitudinally families of children with developmental delays and found that a more positive family climate when the child was of age 3 predicted lower levels of both internalizing and externalizing behavior problems at
age 5; in a companion study, this group of investigators linked a positive family climate at age 3 to growth in social skills at age 10 (Hauser-Cram, Warfield, Shonkoff, & Krauss, 2001). Maternal responsiveness is associated with the development of children with IDD (see Warren & Brady, 2007, for a review), while high levels of maternal criticism are associated with an increase in behavior problems of individuals with autism and other types of IDDs (Baker et al., 2011; Greenberg, Seltzer, Hong, & Orsmond, 2006; Wamboldt, O'Connor, Wamboldt, Gavin, & Klinnert, 2000).

With regard to the impact of the family environment on individuals with FXS, the initial literature points to the family as an important context for development. In a study examining the effect of the quality of the family environment on children with FXS (based on a larger evaluation of 80 boys and 40 girls with FXS between the ages of 6 and 17 (mean age = 10.8 years), the quality of the home environment was found to be related to fewer autistic symptoms (Hessl et al., 2001), better cognitive outcomes (Dyer-Friedman et al., 2002), and better adaptive behavior (Glaser et al., 2003).

One overall purpose of our program of research, therefore, is to investigate how parenting style and the broader family environment affect the development of children with FXS across the life course. In this section of the chapter, we focus on two aspects of the family context that we have studied and found to be associated with the development of children with FXS: maternal responsiveness, which is a specific type of parenting style, and expressed emotion, which is an indicator of the emotional climate of the family.

MATERNAL RESPONSIVITY AND LANGUAGE DEVELOPMENT IN CHILDREN WITH FXS

Maternal responsiveness refers to a healthy, growth-producing parent–child relationship characterized by warmth, nurturance, and stability as well as specific behaviors such as responding contingent on child initiations. In studies of the general population, maternal responsiveness has been shown to have a cumulative impact on children’s cognitive, emotional, social, and language development (Landry, Smith, Miller-Loncar, & Swank, 1998; Landry, Smith, Swank, Assel, & Vellet, 2001). A highly responsive parent will often engage in a style of interaction that maintains the child’s focus of attention, expands on the child’s initiations, and only occasionally redirects the child’s attention to a new topic. In contrast with highly responsive parent–children interactions, high rates of directiveness, which are typically defined as maternal control of children’s behavior and/or attention,
may negatively impact children's emotional, cognitive, and language development (Farran, 2001; Mahoney & Neville-Smith, 1996; Marfo, 1992; Warren & Brady, 2007).

Maternal responsivity represents a complex, dyadic interaction involving both child and maternal factors. Certain maternal variables, such as low educational attainment (i.e., less than a high school education), mild intellectual disability, substance abuse, and depression may substantively impact a mother's ability to maintain a highly responsive style of parenting (Hooper, Burchinal, Roberts, Zeisel, & Neebe, 1998; Miller, Heysek, Whitman, & Borkowski, 1996; Osofsky & Thompson, 2000; Rutter & Quinton, 1984). As the biological mothers of children with FXS are themselves premutation carriers of FXS (a small portion have the full mutation as well), they are at risk for a range of subtle to severe cognitive or emotional problems that could impact their interactions with their children. These risk factors have been associated with lower maternal responsivity (Goldsmith & Rogoff, 1995; Osofsky & Thompson, 2000).

Characteristics of the son or daughter with FXS also may pose risks to maternal responsivity. A mother with the best intentions may nevertheless have difficulty employing and maintaining a highly responsive style with a child with a developmental disability (Stormont, 2001). The elevated levels of behavior problems, hyperactivity, unintelligible speech, autism, and other characteristics that are often displayed by children with FXS could make a highly responsive interaction difficult. Over time, such behaviors may cause caregivers to become less responsive even to appropriate initiations (Murphy & Abbeduto, 2005). For example, Sterling and colleagues (Sterling, Warren, Brady, & Fleming, 2013) have shown that for young children with FXS, the child's developmental level and language abilities have a significant impact on how responsive their mothers are across a variety of contexts, while maternal IQ is a strong predictor of the mother's behavior toward the child even after controlling for child developmental level.

The presence of autism symptoms, in particular, may contribute to difficulties in establishing and maintaining responsive parent–child interactions. Since the severity of behavior problems is a predictor of maternal well-being, autistic symptoms are an important variable to examine in determining the impact of the child's behavior on maternal parenting style. Later in this chapter, we will return to the question of how child behavior and other sources of stress affecting the family may put mothers at risk for poor functioning, especially in the context of genetic vulnerability. However, we first turn to the examination of the effects of maternal parenting style on child development for children with FXS.
As noted earlier, in 2004, Warren, Brady, and Sterling initiated a study to investigate maternal responsivity in a cohort of 55 children with the full mutation of FXS and their biological mothers from across the United States. The children’s ages ranged between 10 and 40 months when the study commenced. Fifty-two of the mothers were premutation carriers and three mothers had the full mutation of the FMR1 gene. The study has continued through middle childhood. Fifty-two of these families have continued to participate in the longitudinal study. Each of these families has thus far been visited five to six times at approximately 18-month intervals. The original sample included 44 boys and 11 girls with full-mutation FXS.

At each visit, we completed several standardized tests and interviews and also videotaped mother–child interactions in several different contexts (reading a book, making and eating a snack, unstructured play, and a 30-minute naturalistic sample). During the naturalistic context, parents were instructed to conduct an everyday activity such as putting dishes away, folding clothes, or playing together. Five minutes from the book, snack, and play contexts and 10 minutes from the naturalistic context were digitized for coding, yielding a total of 25 minutes of interaction, an amount of coded interaction similar to that reported in other studies of maternal responsivity (Warren & Brady, 2007). These interactions were coded for child communication behaviors, maternal responsivity, and maternal behavior management.

Our first goal was to investigate the relation between early maternal responsivity and later child communication outcomes in these young children (Warren, Brady, Sterling, Fleming, & Marquis, 2010). The findings indicated that early maternal responsivity significantly predicted later receptive and expressive language scores on standardized tests, as well as the rate of the number of different words used by the child and the child’s total communication (including both verbal and nonverbal communication) at 36 months. We measured autism symptoms using the Childhood Autism Rating Scale (CARS; Schopler, Reichler, & Renner, 1988) and overall child developmental level using the learning composite score of the Mullen Scales of Early Learning (MSEL; Mullen, 1995). Children of highly responsive mothers had better language outcomes than did children with less responsive mothers, but the effect was dampened for children with high degrees of autism symptoms. For example, children with less responsive mothers but no evidence of autism outperformed children with high autism symptoms and highly responsive mothers (see Figure 11.1). The presence of autism symptoms placed significant constraints on language development even in the context of highly responsive parent–child interactions.
We additionally explored maternal responsivity as the children in our study moved into middle childhood. Our data indicated stability in terms of general maternal affect: there were virtually no changes in the mothers’ demonstrations of positive affect, warmth, physical control, verbal discipline, or punitive tone with their children. There was evidence of a slight increase in levels of maternal flexibility and responsiveness in their interactions with their child with FXS. Thus, one important conclusion of our research to date is that parenting style is established early in these families, and this style continues well into middle childhood.

Naturally, the types of activities in which mothers engaged their child with FXS changed by middle childhood. For example, reading as an activity had increased. Subsequent analyses indicated that the relation between early maternal responsivity and later vocabulary development actually strengthened as the children aged. However, the presence of autism symptoms continued to constrain the impact of maternal responsivity on language development during middle childhood (Brady et al., 2013).

In a second line of research with these families, we sought to determine how well the mothers adjust their parenting style to match their child’s behavioral needs. In other words, would the mothers be consistent in their
parenting style with all of their children (those with FXS and those not affected) regardless of the developmental level of the child, or would they instead make appropriate adjustments based on the needs of each child? To investigate this question, we selected 13 children with FXS from our original cohort of 55 families (Sterling, Barnum, Skinner, Warren, & Fleming, 2012) and compared them with a typically developing sibling. The two children within a family were tested when they were the same age. To establish a chronological age match, we first completed the assessment with whichever child in the sibling pair was older. For seven of the sibling pairs, this was the child with typical development; in five of the sibling pairs, the child with FXS was the older child, and the last pair involved dizygotic twins. Seven of the pairs were same gender (male-male), and six were male-female; all of the children with FXS were males. We waited until the younger sibling was the same chronological age to conduct the assessment with the younger sibling (within a 1-month window). The average age difference between the siblings at the time of the assessment was just 2 weeks. The chronological age matches controlled for history of interaction with the mother. The children were between 16 and 70 months of age at the time of this assessment (M = 46 months). We thus used a within-family design to directly compare a mother’s parenting style with her child with FXS and one of her other children with typical development.

The mothers and children participated in the same interactional contexts described earlier, and the videotapes were coded for both maternal and child behaviors. In order to provide more contextual information on mothers’ descriptions of interactions with their children and to provide concrete examples of maternal responsivity and behavioral management strategies, we conducted semistructured interviews before administering the quantitative assessments. These interviews elicited information on a number of domains (e.g., quality of life, impact of diagnosis), and included a section devoted to maternal responsivity.

The quantitative analysis and the interview data indicated that, in general, mothers used the same types of parenting strategies with both children (i.e., the child with FXS and the typically developing sibling) and that they made developmentally appropriate alterations in their level of interaction and expectations of the two children. The findings from this study were positive, as mothers used the same levels of praise and warmth with both children regardless of differences in developmental level. The differences in parenting focused on maternal behaviors central to either diffusing problematic child behaviors or in their use of a more conversational style of language with their children with typical development. The mothers did
not exhibit high levels of differential parenting between siblings but rather employed a responsive style of parenting with both of their children that made appropriate accommodations for the developmental differences in the children. Furthermore, they were aware that they were making these accommodations and were able to describe them to the interviewer.

In summary, our findings indicated that many of the mothers in our study displayed a stable, positive affect with their child and used growth-enhancing parenting techniques well into middle childhood. However, the findings from the Warren and colleagues (2010) study indicate that for the children with high levels of autism symptomatology, the effect of maternal responsivity was more constrained than for the children with fewer autism symptoms.

FAMILY EMOTIONAL CLIMATE AND BEHAVIOR PROBLEMS ACROSS THE LIFE COURSE

Despite the clear patterns of gains in language and learning and the mothers’ ability to both adapt to and support their children from early to middle childhood, the behavioral challenges posed by children with FXS remain considerable and may increase with age. Thus, we sought to understand how families and children with FXS manifest different profiles of behavior problems at different stages of the life course and particularly if the association between the family emotional climate and the child’s behavioral functioning is different in childhood, adolescence, and adulthood. To do so, we compared the families described earlier with two additional groups of families of children with FXS in our multisite study, namely families of adolescents with FXS and families of adults with FXS. To obtain a common measure of the family emotional climate across these three stages of life, we turned to the concept of expressed emotion.

Expressed emotion (EE) is a measure of the emotional climate of the family. EE was originally studied in families of adults with schizophrenia, with high levels of EE found to be related to an exacerbation of symptoms and relapse (Brown, Birley, & Wing, 1972). Among persons with disabilities, high levels of EE (i.e., an emotionally charged family environment) predict symptom exacerbations across a broad range of mental health disorders and medical conditions, including mood disorders, eating disorders, Alzheimer’s disease, asthma, diabetes, and Parkinson’s disease (Asarnow, Thompson, Woo, & Cantwell, 2001; Bledin, Kuipers, MacCarthy, & Woods, 1990; Kim & Miklowitz, 2004, Vitaliano, Young, Russo, Romano, & Magana-Amato, 1993; Wearden, Tarrier, Barrowclough, Zastowny, & Rahill, 2000). More recently, investigators have applied this concept in research on families of children
with autism and other developmental disabilities and found a similar pattern: high levels of EE in the family predicted increasing levels of behavior problems in the sons and daughters with developmental disabilities (Baker et al., 2011; Greenberg et al., 2006).

Our group is the first to examine the relation between EE and behavior problems in individuals with FXS across different stages of the child's life course (Greenberg et al., 2012). We examined two primary research questions with respect to the influence of the family emotional climate on the lives of individuals with FXS: (1) Are there differences in the family emotional climate in families of children with FXS at three stages of the family life course: childhood, adolescence, and adulthood? and (2) Are the associations between aspects of the family emotional climate and behavior problems similar across the three stages of life?

This analysis is part of our larger multisite study of family adaptation to FXS described previously. A total of 167 families of children (n = 48), adolescents (n = 85), and adults (n = 34) with FXS were included in this analysis (i.e., only mothers with the premutation and those for whom there were complete data on specific study measures). The sample of children included in this analysis ranged in age from 6 to 8 at the time when the expressed-emotion data were collected (mean = 7.2 years), while the sample of adolescents ranged in age from 12 to 21 (mean = 15.9), and the sample of adults ranged in age from 22 to 43 (mean = 27.4). Their mothers' ages were similarly diverse (means = 38.5, 46.8, 55.8 years, respectively).

The Five Minute Speech Sample (FMSS) was developed as a brief but valid measure of EE (Magaña et al., 1986). A common protocol for transcribing the speech samples was used for families in all three life stages, which were transcribed by an independent researcher. The mother was asked to speak for 5 minutes to describe her relationship with the target son or daughter with FXS and her thoughts and feelings about this child. The FMSS is coded with respect to both verbal content and vocal tone and yields ratings for multiple dimensions of the parent–child relationship, including levels of criticism, emotional overinvolvement, and parental warmth. It includes a count of the number of positive remarks made by the parent about the child as well as an overall EE rating. For criticism, emotional overinvolvement, and warmth, the codes were used to classify mothers into categories (e.g., high, borderline, moderate, low) on the particular EE dimension. Classification was performed by an independent rater with more than 30 years of experience coding the FMSS for all aspects of EE.

The mothers also completed the Child Behavior Checklist (CBCL; Achenbach & Rescorla, 2001) for their sons and daughters who were
18.5 years of age or younger and the Adult Behavior Checklist (ABCL; Achenbach & Rescorla, 2003) for their sons and daughters who were older than 18.5 years of age. The reliability and validity for the CBCL and ABCL are well established (Achenbach & Rescorla, 2001). The scores for the three summary scales, Total Problems, Internalizing Problems, Externalizing Problems, were computed.

Our first research focus concerned age-related differences in the family's emotional climate. We compared EE in families of children versus adolescents versus adults with FXS. As reported by Greenberg and his colleagues (2012), the data indicated that level of maternal criticism significantly varied across the age groups, with follow-up tests indicating that mothers of children were rated as expressing higher levels of criticism of their child than mothers of adolescents. Whereas 31% of the mothers of children with FXS and 29% of the mothers of the adults were classified as high in criticism, only 16% of the mothers of the adolescents were rated as high in this dimension. A different pattern was evident with regard to emotional overinvolvement. There was a trend for levels of emotional overinvolvement to differ among the three groups, with the mothers of adolescents showing a higher level of overinvolvement than the mothers of children. Whereas approximately 10% of the mothers of children and a similar percentage of the mothers of adults were rated as high or borderline with respect to overinvolvement, 23% of the mothers of adolescents were rated as high or borderline on overinvolvement.

However, across the three stages of life, the mothers were very similar with respect to positive dimensions of the family emotional climate. The majority of the mothers in all three life stages had high or moderate levels of warmth (73% to 88%). They averaged around three positive remarks during the FMSS, and this dimension was similar across the three life course groups. Thus, with respect to our first research question, negative measures of the family emotional climate (i.e., criticism and overinvolvement) varied across the three age groups, whereas positive dimensions of the family emotional climate (i.e., positive remarks and warmth) were more stable across the life course.

Unfortunately, we do not have access to normative data about the family emotional climate using the FMSS paradigm in families of typically developing children, adolescents, and adults. However, the pattern of findings regarding positive dimensions of the emotional climate of the family was consistent with the findings regarding maternal responsivity. The longitudinal observational data suggest stability of maternal positive affect and warmth during the child's early childhood and continuing into the school
years. The cross-sectional data derived from FMSS codes similarly show rates of parental positivity that are consistent over a much longer stretch of the life course and that characterize the family emotional climate well into the son's or daughter's adult years. Our finding that mothers of adolescents and adults expressed less criticism than mothers of children was foreshadowed by the longitudinal maternal responsivity data of an increase in flexibility and responsiveness from the early childhood to the school-age period.

We next extended this life course investigation to ask whether similar associations are found between the indicators of the family emotional climate and the son's or daughter's behavior problems across the three life stages (Greenberg et al., 2012). Regarding the negative dimensions of the family emotional climate (criticism and emotional overinvolvement), we found that the associations with behavior problems were mainly similar across the three life stages. Maternal criticism was significantly related to externalizing symptoms for each of the three age groups, whereas criticism was unrelated to internalizing symptoms at any life stage. Consistent with prior research on families and individuals with developmental disabilities (Greenberg et al., 2006), emotional overinvolvement was not related to internalizing, externalizing, or total problems scores for any of the three age groups. Thus, for the population with developmental disabilities, parental behavior that has been classified in psychiatric research as reflecting overinvolvement might not have a negative effect because of the lifelong nature of the disability.

The absence of association between emotional overinvolvement and behavior problems in individuals with developmental disabilities, including FXS, suggests that for this population, descriptions of the child that in other contexts would signify unhealthy levels of overinvolvement do not result in elevated behavior problems in individuals with developmental disabilities. However, criticism is associated with higher levels of behavior problems in those developmental disabilities, consistent with other populations that have been studied. Furthermore, for individuals with FXS, the patterns reported above are the same for all age groups.

In contrast, an age-related pattern was evident in the relation between positive dimensions of the family emotional climate and behavior problems for children, adolescents, and adults. For children and adults with FXS, higher numbers of positive remarks made by mothers during the FMSS were related to significantly lower levels of behavior problems in their sons and daughters with FXS. However, for adolescents, positive remarks by the mother in the FMSS were unrelated to behavior problems. Similarly, for children and adults with FXS, a higher level of maternal warmth was
significantly associated with lower levels of behavior problems, but these associations only showed a trend level effect in families of adolescents. Thus, for children and adults with FXS, higher levels of maternal warmth and positive remarks were associated with lower levels of behavior problems, but for adolescents such associations were either absent or weak.

The finding that the behavior of adolescents with FXS may be less responsive to their mothers’ expressions of positivity suggests that they may be similar to adolescents in general in their struggles for autonomy. However, this interpretation warrants further exploration in longitudinal research. For children and adults, however, the significant cross-sectional associations between both positivity and negativity in the family emotional climate and the behavior problems of the sons and daughters with FXS underscores findings reported earlier from our longitudinal observations of maternal responsivity, namely that the functioning of parents and their children co-occur and that early patterns and associations are long lasting across many decades of the life course.

Challenges Facing Premutation-Carrier Mothers of Individuals with FXS

Since parenting a child with FXS has been shown to be stressful (Hartley et al., 2011) and since the mothers in these families are themselves affected by instability in the gene that causes FXS, we examine how stressful parenting and more generally how life events affecting the family may impact mothers’ psychological well-being and physiological stress response. Therefore, in this section of the chapter, we describe our studies of the health and mental health of premutation-carrier mothers and then report analyses that we have conducted to examine how mothers respond to the behavior problems manifested by their son or daughter with FXS and to other life events that they or their family experienced in the previous year, and how maternal genotype may interact with their response. Understanding how mothers with the premutation respond to stress will contribute to a more complete picture of family adaptation to FXS.

OVERVIEW OF HEALTH AND MENTAL HEALTH OF PREMUTATION CARRIERS

Although premutation carriers were originally considered to be unaffected, at least some premutation carriers display signs of impairment, with high levels of premutation-containing messenger RNA (mRNA) suspected to result in “toxicity” leading to disease (Berry-Kravis & Potanos, 2004). In addition
to the premutation-related conditions of FXTAS or FXPOI, risks to physical health and psychological well-being may also be a part of the premutation-carrier phenotype (Bailey et al., 2008; Chonchaiya et al., 2010; Coffey et al., 2008). Next we review the findings regarding these aspects of the premutation-carrier phenotype, including findings from our own study.

Premutation-carrier status has been linked with a variety of physical health problems. For instance, Coffey and colleagues (2008) found increased prevalence of thyroid disease, hypertension, seizures, peripheral neuropathy, and fibromyalgia in female carriers with FXTAS; carriers without FXTAS also had higher rates of muscle pain and history of tremors than women without FMR1 expansions (Coffey et al., 2008). High rates of thyroid disease and chronic muscle pain similarly have been reported for female carriers in other studies (Rodriquez-Revenga et al., 2009). Some premutation-related problems may produce subthreshold symptomatology (i.e., a profile of problems that fails to meet clear diagnostic criteria for a particular disease) but still produce discomfort or pain. In a sample of daughters of men with FXTAS, premutation women had higher prevalence of symptoms including tremors, balance problems, memory problems, dizziness, menopausal symptoms, sleep problems, and anxiety than noncarriers (Chonchaiya et al., 2010). Chonchaiya and colleagues (2010) concluded that symptoms in premutation carriers still may be related to mRNA toxicity, although they may not be elevated consistently enough or sufficiently to meet diagnostic criteria (Chonchaiya et al., 2010).

Similar to findings regarding physical health symptoms in premutation carriers, individuals with the premutation may experience an elevated severity of neuropsychological symptoms even if the symptoms do not reach a clinical threshold (Hunter et al., 2008b). Accordingly, female carriers have been found to have heightened levels of negative affective symptoms compared to unaffected women of the same age (Bailey et al., 2008; Hunter et al., 2008a; Lachiewicz et al., 2010).

Given the potential for subthreshold symptomatology in premutation carriers, in our own work we have examined daily physical health symptoms and daily affect using a Daily Diary methodology (Almeida, Wethington, & Kessler, 2002). For our Daily Diary Study, respondents were interviewed by telephone each evening for a period of 8 days. The daily telephone interview, which lasted approximately 15 to 25 minutes, included questions about experiences in the previous 24 hours. The questions focused on time use, daily stressors, positive events, mood, and physical health symptoms.

We compared the daily health symptoms of mothers of adolescents and adults with fragile X syndrome (FXS; \(n = 112\)) to a nationally representative
sample of mothers of similarly aged children without disabilities \((n = 230)\) as well as to a sample of mothers of adolescents and adults with autism spectrum disorders \((n = 96\); Smith, Seltzer, & Greenberg, 2011). Health symptoms \((e.g., \) headache, backache, muscle soreness, fatigue, joint pain, muscle weakness, dizziness, nausea, diarrhea, constipation, menstrual-related symptoms, and hot flashes or flushes) experienced in the previous 24 hours were recorded during telephone interviews on the 8 consecutive days of the Daily Diary Study. We found that both mothers of a son or daughter with FXS and mothers of a son or daughter with ASD had a higher proportion of days with headaches, backaches, muscle soreness, fatigue, and hot flashes than mothers of children without disabilities. The premutation-carrier mothers experienced at least one health symptom on 75% of days in the 8-day study, suggesting that the vast majority of time, premutation-carrier mothers need to cope with their own health difficulties even as they provide care for their children (Smith et al., 2011).

Using the same Daily Diary methodology as our examination of physical health symptoms, we also explored daily levels of positive and negative affect among premutation-carrier mothers (Smith et al., 2011). We found that mothers of adolescent and adult children with FXS reported higher levels of daily negative affect than mothers of similarly aged children without disabilities, although mothers of a son or daughter with FXS did not differ significantly in positive affect from mothers of children without disabilities. Further, even after controlling for child behavior problems, mothers in the FXS group had higher levels of positive affect than mothers in the ASD group (Smith et al., 2011). This finding raises questions regarding possible protective mechanisms for premutation-carrier mothers. Given that higher levels of positive affect have been repeatedly associated with better health in other populations (Cohen & Pressman, 2006; Xu & Roberts, 2010), a valuable area for future research will be to consider both what contributes to positive affect in premutation-carrier mothers and how positive affect may relate to their long-term health outcomes. Further, findings confirming the relation between positive affect and health outcomes for families with full mutation children with FXS would suggest that interventions aimed at addressing positivity may be beneficial.

In conclusion, in our work we have found evidence of significantly elevated levels of daily physical health symptoms and negative affect among premutation-carrier mothers relative to noncarrier women of the same age. However, levels of health symptoms among mothers of adolescents and adults with FXS in our sample did not differ from those of mothers of similarly aged children with ASD (Smith et al., 2011). As others have noted,
the development and maintenance of health symptoms in women with the premutation may be due, at least in part, to environmental factors such as the heightened level of stress these mothers experience while caring for a child with FXS (Bourgeois et al., 2009; Hunter et al., 2009). Importantly, they also experience normative levels of positive affect, which emerge as important strengths in this group of caregiving mothers.

**GENE BY ENVIRONMENT INTERACTIONS: HOW MATERNAL GENOTYPE INTERACTS WITH STRESS**

The *FMR1* premutation offers a unique opportunity to examine how stressful parenting interacts with genotype to impact the well-being of carrier mothers. There are a number of genetic markers associated with the premutation, and we have examined how two of these – activation ratio and CGG repeat length – interact with stress in premutation-carrier mothers.

**Activation Ratio x Child Behavior Problems**

In our ongoing study, we examined how the stress of parenting an adolescent or adult with full mutation FXS might interact with maternal genotype to take a toll on premutation-carrier mothers’ physiological functioning (Hartley et al., 2011). In this analysis, we employed a diathesis-stress model in which a genetic vulnerability (diathesis) interacts with environmental adversity (stress) to affect functioning. This model has not previously been tested directly in women with the *FMR1* premutation, but it has been of great value for examining psychological functioning in the general population (Caspi et al., 2002; Caspi et al., 2003; Fowles, 1992; McKeever & Huff, 2003; Monroe & Simons, 1991).

In our application of the diathesis-stress model, maternal diathesis is measured by the activation ratio (defined below) and the stressful challenge of parenting a child with FXS is indexed by child behavior problems. Although the activation ratio is just one of the several genetic markers of mutations in the *FMR1* gene, we focus on this indicator of genetic vulnerability to stress because it is an individual difference variable that reflects the degree of biochemical affectedness. Similarly, although child behavior problems are just one source of environmental stress experienced by mothers, they are a prominent stressor documented in past research to be of significance in FXS (Bailey et al., 2008; Cornish et al., 2008).

Mothers with the premutation of the *FMR1* gene vary widely in terms of their biochemical affectedness (e.g., Tassone et al., 2000). This variation is
due in part to \textit{X inactivation}. The process of \textit{X} inactivation occurs early in embryological development in all females, and it results in the "turning off" of one \textit{X} chromosome in each cell. In females with the \textit{FMR1} premutation, the relative proportion of active and inactive \textit{FMR1} expansion mutation-carrying alleles varies from person to person (Tassone et al., 2000). The percentage of cells with a normal \textit{X} as the active \textit{X} is known as the activation ratio. The activation ratio has been identified as a potentially important biological indicator of the extent to which various biochemical pathways are altered. A low activation ratio may put premutation-carrier mothers at risk for poor psychological well-being and physical health (Hessl et al., 2005; Seltzer, Abbeduto et al., 2009). Thus, a low activation ratio may serve as a diathesis, which increases the degree to which mothers with the premutation may be negatively impacted by child-related stress.

We examined the interactive effects of activation ratio and child behavior problems on maternal awakening cortisol. We selected this dependent variable because cortisol dysregulation is affected by both acute and chronic stress (McEwen, 1998) and because we have shown that the chronic stress of parenting an adolescent or adult child with autism is associated with lower or blunted maternal cortisol profiles (Seltzer et al., 2010). Our specific prediction in the present analysis was that the extent to which premutation-carrier mothers of individuals with FXS are negatively affected by their child's behavior problems will be influenced by their own genetic vulnerability. Mothers with a greater genetic vulnerability (i.e., those who have a lower activation ratio) were expected to be more negatively impacted by child-related stress, leading to a hypocortisolemic response to their child's behavior problems. In contrast, mothers with less genetic vulnerability (i.e., those who have a higher activation ratio) may have a more typical response to their son or daughter's behavior problems, resulting in a pattern of a hypercortisolemic activity in response to behavior problems.

For this analysis, we focus on a subsample of mothers ($n = 76$) drawn from our study of families of adolescents and adults with FXS who participated in the 8-day telephone Diary Study and who supplied saliva samples from which cortisol levels were measured. In the Daily Diary Study, the mothers reported on the behavior problems manifested by their son or daughter at the end of each day. Saliva samples were collected at four time points (awakening, 30 minutes after awakening, before lunch, and before bed) each day on Days 2 through 5 of the Diary Study and analyzed in the Kirschbaum laboratory (Dresden, Germany); results regarding the awakening time point are reported in this section of the chapter. Maternal activation ratio was measured through DNA analysis of blood samples conducted
by Kimball Genetics. Multilevel models were used to analyze daily variables nested within individuals across time.

We found that behavior problems were frequent in these adolescents and adults with FXS. The two most frequently occurring behavior problems during the 8-day Diary Study were unusual or repetitive behavior and uncooperative behavior, which occurred on approximately one third and one quarter of diary days, respectively. Socially offensive behavior, withdrawn or inattentive behavior, and disruptive behavior were less frequent, evident on 12% to 14% of days. Behaviors involving hurting oneself, hurting others, or destroying property occurred much less frequently, on approximately 3% to 5% of days. The large majority (85.7%) reported to have exhibited at least one episode of behavior problems during the 8-day Diary Study period.

For the present analysis, we used measures of behavior problems manifested by the child the day before to predict maternal cortisol level the next morning, and we predicted that maternal activation ratio would interact with child behavior problems. Indeed, as we hypothesized, the interaction between mothers’ activation ratio and the number of previous-day behavior problems manifested by the child was a significant predictor of maternal cortisol at awakening the next morning (see Figure 11.2). Mothers with lower and higher activation ratios showed markedly different awakening cortisol values depending on the prior day’s experience of child behavior.
problems. For mothers with low activation ratios (i.e., a smaller proportion of normal cells), the greater the number of behavior problems on the previous day, the lower the morning cortisol level (an abnormal response to stress). In contrast, for mothers with a high activation ratio (i.e., a larger proportion of normal cells), the greater the number of behavior problems yesterday, the higher the morning level of cortisol, which is a more typical neuroendocrine response to environmental stress.

Further evidence that chronic exposure to stressful parenting is associated with hypocortisolism is provided by our finding that low morning cortisol was characteristic of mothers in the present study who had more than one child with a disability. In our sample, 54% of the mothers had another child with a disability (including 36% with at least one additional child who had FXS and 18% with at least one child with another disability). Having multiple children with disabilities was predictive of low morning cortisol, consistent with our previous research on mothers with adolescent and adult children with ASD (Seltzer et al., 2010).

Our findings indicate that the activation ratio of mothers with the premutation is an important biological vulnerability factor that influences the extent to which mothers are affected at the neuroendocrine level by the behavior problems of their adolescent or adult child with FXS. Low morning cortisol level is the “biological signature” associated with feelings of fatigue and exhaustion among people who experience chronic stress (Cleare, 2003; Fries et al., 2005; Sonnenschein et al., 2007). Females with the FMR1 premutation share this biological profile, along with increased prevalences of fibromyalgia and chronic pain (Coffey et al., 2008; Hagerman & Hagerman, 2002; Smith et al., 2011).

Thus, our own research as well as the findings of past studies suggest that the elevated level of health symptoms reported in premutation-carrier mothers may be attributed to both their genetic vulnerability and their exposure to the stress of daily behavior problems in their son or daughter with FXS. Future longitudinal research is needed to determine the magnitude and direction of the pathways between child behavior problems, maternal genetic vulnerability, maternal cortisol dysregulation, and health problems in premutation-carrier mothers.

CGG Repeat Length x Stressful Life Events

In an additional analysis, we examined whether another genetic marker of the premutation and other types of environmental stress have a similar interactive effect on mothers’ functioning. To do so, we asked a related
question as before, only rather than focusing on daily child behavior problems as the source of stress, we instead examined whether stressful life events experienced by the family during the previous year would interact with premutation-carrier mothers' genetic vulnerability to predict not only cortisol levels but also maternal depression and anxiety (Seltzer, Barker et al., 2012). Stressful life events included change in marital status, employment status, and caring for an aging parent among others. Events that occurred in the lives of the mother, her husband, and/or her children were considered. In this analysis, which included 82 of the mothers from our larger study of families of adolescents and adults with FXS, we measured genetic vulnerability by the number of CGG repeats. We built on past findings that revealed curvilinear associations between CGG repeat number and vulnerability to various aspects of the premutation phenotype, such as depression (Roberts et al., 2009) and age at menopause (Allen et al., 2007; Ennis, Ward, & Murray, 2006; Sullivan et al., 2005). One explanation for this nonlinear effect is that individuals with low repeat lengths are close to normal in the amount of the mRNA produced by the FMR1 gene, but as the sequence of CGG repeats expands, there is an overproduction of mRNA, which has a toxic effect. However, as the expansion comes closer to the full mutation (i.e., closer to 200 repeats), the gene begins to shut down its production of mRNA, which results in less toxicity for those with the largest repeats. Thus, those with mid-size repeats have the highest mRNA toxicity and therefore the greatest vulnerability to stress.

Our findings were again consistent with a gene × environment interaction effect (Seltzer, Barker et al., 2012). Premutation-carrier mothers with mid-size repeats who experienced the greatest number of negative life events in the previous 12 months had the highest levels of depression (portrayed in Figure 11.3) and anxiety and the most blunted cortisol awakening response (defined as the difference between cortisol level upon awakening and 30 minutes later). These mothers with mid-size repeats (in this study, between 90 and 105 CGG repeats) were more vulnerable to stressful life events than mothers with either a smaller or larger number of repeats, consistent with past research.

This analysis of the association between genotype and environmental stress also revealed that there was a positive side to the gene × environment interaction among the mothers with a mid-sized number of repeats, but only when they were not exposed to stressful life events in the previous year. Following a year of relative stability, the mothers with mid-sized repeats had the best outcomes in the sample—the lowest levels of depression and anxiety and the most normative cortisol awakening response. This pattern of
response is consistent with the differential susceptibility hypothesis (Belsky et al., 2007; Pluess & Belsky, 2009), according to which people with certain genotypes are more likely to manifest either poorer or better outcomes depending on the nature of their environmental exposures. As Pluess and Belsky (2009) noted in their review, “the very same individuals who may be most adversely affected by many kinds of stressors may simultaneously reap the most benefit from environmental support and enrichment (including the absence of adversity)” (p. 886), which is exactly the pattern of results we found in the present study. More generally, these findings highlight that variations in the environment can inform genetic investigations, and this underscores the importance of examining the environment when seeking to elucidate genetic effects.

The present study has implications for counseling premutation-carrier mothers. Fully one quarter of the mothers in the present study had clinically elevated levels of depressive symptoms and more than 15% had clinically elevated levels of anxiety. As mothers become increasingly aware of their CGG repeat length, understanding the risks associated with a midsize repeat length may help them anticipate their vulnerability to stressful life events and therefore to more actively seek appropriate familial and professional support.
Summary and Agenda for Future Research

Our program of research on family adaptation to FXS brings together an interdisciplinary and multimethod approach to understanding fragile X-associated disorders in the family context. Our study’s data include genetics (CGG repeat length, activation ratio), neuroendocrine measures (salivary cortisol), maternal health (daily symptoms), maternal psychological functioning (depression, anxiety, negative and positive affect), child behavioral measures (language, autism symptoms, challenging behaviors), and measures of the family context (maternal responsivity, family emotional climate, stressful events in the lives of family members). Although our studies are ongoing, new knowledge about family adaptation to FXS across the life course is already coalescing.

We have shown that the family environment, including parenting style, stabilizes early and appears to be somewhat constant across the stages of the family life course, particularly with respect to maternal warmth and responsiveness. Furthermore, indicators of the family context (maternal responsivity, family emotional climate) are associated with behavioral development and functioning in sons and daughters with FXS, evident in both cross-sectional and longitudinal analyses. Thus, optimizing parenting style and supporting a nurturing family environment are important goals for family-focused services, especially for the minority of families who are struggling with a child who has co-occurring autism, more severe behavior problems, and higher levels of parental stress. For such families, psychoeducational interventions that have been shown to enhance positive family functioning in other populations could be adapted for families with FXS. Intervention studies are a necessary next step to determine whether family treatments designed to lower expressed emotion and promote positivity have a similar beneficial effect on families of children with FXS across the life course.

The family processes described in this study are bidirectional. Improved child communication both flows from responsive parenting and is likely to be associated with positive maternal outcomes because better child communication decreases frustrations and is associated with fewer behavior problems (Abbeduto & Murphy, 2004; Brady, Warren, & Sterling, 2010; Reichle & Wacker, 1993; Warren & Abbeduto, 1992). Given the health and mental health risks of mothers with the premutation, targeting early communication and behavior problems in children with FXS could alleviate some of the significant stress that parents experience. In terms of language development in young children with FXS, the impact of early language intervention coupled with parent training and support has been found
to produce optimal language outcomes in children with developmental disabilities in general and would likely benefit families of children with FXS (Brady, Warren, & Sterling, 2010; Girolametto & Weitzman, 2006). This type of program would allow parents to facilitate language development while learning to diffuse problematic behaviors. Thus, interventions that improve responsive parenting are likely to have pervasive benefits for the child and family.

In addition to highlighting valuable new directions for clinical practice and services, our findings point to several areas for future research. In our sample of young children, we found that early maternal responsibility prospectively predicted language development well into middle childhood, although the presence of autism symptoms significantly constrained the benefits of positive parent–child interactions for children with FXS. Research is needed to better understand mechanisms that support developmental gains for children with FXS who have additional risk factors such as a diagnosis of autism or challenging behaviors.

Our studies also indicate that the genotype of premutation-carrier mothers interacts with environmental risk (child behavior problems, life stressors) in predicting patterns of salivary cortisol. However, we do not yet know how dysregulation of daily cortisol expression may influence long-term health outcomes in premutation-carrier mothers or how protective factors such as positive affect may moderate these associations. More work is needed in exploring the interactive effects of genotype and environmental factors in the development of cognitive, affective, and physical problems in premutation women across the life course.

To conclude, the dynamic and bidirectional influences of families and children with FXS play out in the context of the genetics of fragile X-associated disorders. As a result of a mutation in a single gene, children with the full mutation have compromised functioning, with males more seriously affected than females, on average. But such children also display strengths, gaining new language and cognitive skills as they mature and develop. Their mothers are also genetically vulnerable, but there is considerable heterogeneity in carrier women in part because of individual differences in activation ratio and CGG repeat length. Thus, the extent of genetic liability will vary considerably from family to family based on maternal genetics, child gender, and other factors discussed in this chapter. According to our data, the extent of maternal genetic vulnerability contributes to and interacts with the child's behavioral phenotype to sculpt the functioning of all family members. Further, although family patterns show continuity from one life stage to the next, there is also individual-level change accompanying
maturation of all members of the family across the life course. The research summarized in this chapter emphasizes the value of the gene × environment approach and the lifespan developmental approach in elucidating the family as a context for risk and protection for children and parents, even when the children have conditions with well-defined genetic causes.

ACKNOWLEDGMENTS

This study was supported by a grant from the Eunice Kennedy Shriver National Institute of Child Health and Human Development to the University of North Carolina (P30 HD003100-S1) to support a Fragile X Research Center at three additional sites (Research Triangle Institute International, the University of Kansas, and the University of Wisconsin–Madison), which is led by Donald B. Bailey, Jr. The present analyses were based on data collected at the University of Kansas site (S. Warren, PI) and at the UW–Madison Waisman Center site (M. Mailick, PI). We gratefully acknowledge the contributions of our research teams (at Kansas, Kandace Fleming, PhD, and Janet Marquis, PhD; at Wisconsin, Jason Baker, PhD, Erin Barker, PhD, Sigan Hartley, PhD, and Renee Makuch). We are also extremely appreciative of the families who participated in this study, without whom our research would not have been possible. We would like to thank the National Fragile X Foundation for providing informational materials to share with families. We are also grateful for the support we received from the Kansas and Waisman Center Core Grants (P30 HD002528, J. Colombo, PI; P30 HD03352, M. Mailick, PI).

REFERENCES


International review of research on mental retardation (pp. 37). New York: Academic Press.


