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CHAPTER SEVEN

BIOMARKERS IN THE STUDY OF FAMILIES OF CHILDREN WITH DEVELOPMENTAL DISABILITIES

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Abstract

Research during the past 20 years on families of children with developmental disabilities (DD) has yielded a rich body of knowledge about the risk and protective factors that result in profiles of family resilience versus vulnerability at various stages of the family life course. Virtually all of this research has been based on data collected from self-report or observational measures, and has examined family interactions, family relationships, and the psychosocial well-being of individual family members. The present chapter focuses on different sources of data, namely biomarkers, which have the potential to expand our understanding of the biological mechanisms by which the stress of parenting a child with developmental disabilities can take its toll on parents' physical and mental health. We focus on two examples: (1) variations in the *FMR1* gene, *FMRP*, and *FMR1* messenger RNA in mothers of children with fragile X syndrome and the association of these measures with maternal depression and anxiety and (2) profiles of cortisol in mothers of children with disabilities and the association of cortisol with daily measures of caregiving stress. These biomarkers extend past behavioral and psychosocial measures of family adaptations.

1. INTRODUCTION

The demands of parenting a child with a developmental disability can take a significant toll on the physical, financial, and psychological well-being of the rest of the family (Orsmond, Lin, & Seltzer, 2007; Seltzer, Greenberg, Floyd, & Hong, 2004), although profiles of resilience are frequently noted (Glidden & Schoolcraft, 2003). Selye (1956), the father of modern stress research, distinguished between external demands, or *stressors*, and the individual's physiological response to these demands, which he referred to as the *stress syndrome*. Glidden (1993) expanded on this distinction, particularly as it applies to family research within the field of developmental disabilities. Previous family research investigating the challenges of parenting a child with developmental disabilities has relied largely on self-report indicators of the stress syndrome, such as perceived physical health or perceived level of distress (Abbeduto, Seltzer, Shattuck, Krauss, Orsmond, et al., 2004; Seltzer, Greenberg, Floyd, Pettee, & Hong, 2001). The pathways of influence between parenting stressors and parental physiological functioning remain virtually unexplored among parents of individuals with developmental disabilities. The study of biomarkers thus has the potential to add to our

understanding of caregiving stress by giving insight into the mechanisms by which caregiving demands takes a toll on health and well-being.

According to an NIH study group (Biomarkers Definitions Working Group, 2001), a biomarker is "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention." Only a few studies on parenting a child with a disability have incorporated biomarkers into the research design. For example, one recent study by Gallagher, Phillips, Drayson, and Carroll (2009) reported that parents of children with developmental disabilities mounted a poor antibody response to pneumococcal vaccination, particularly in the context of high levels of child behavior problems.

Another study that incorporated biomarkers was conducted by Epel et al. (2004), who reported that, in parents who have a child with autism or other developmental or chronic disability, longer duration of caregiving was associated with greater telomere shortening (a sign of cellular aging) and elevated oxidative stress, controlling for maternal age. In addition, this study estimated the toll taken by perceived parenting stress, and concluded that cellular aging was accelerated by 9–17 years in the highest stress group, relative to those in the lowest stress group (Epel et al., 2004). These patterns provide strong evidence of the link between the experiences of parents of children with disabilities and their biological functioning.

The purpose of the present chapter is to review research on two other types of biomarkers that have been used to investigate associations between parenting stress and parental psychosocial well-being. We first review research on parents of children with fragile X syndrome and examine how variation in their profiles of the *FMR1* gene, *FMRP* levels, and *FMR1* messenger RNA are associated with parental levels of depression, anxiety, and other dimensions of psychological well-being. In this example, variation in the biomarker is conceptualized as *increasing vulnerability to parenting stress*. Next, we examine how daily parenting stress is associated with dysregulation of cortisol, a stress hormone, in parents of children with disabilities. In this example, variation in the biomarker is conceptualized as the *consequence of parenting stress*. Thus, in this chapter, we aim to review literature on biomarkers as both antecedents to and consequences of the stress that is associated with parenting a child with disabilities. We note that the biomarkers discussed in this chapter are just two examples of a wide range of biomarkers that can be included in family research, and the selection of the particular biomarker in a given study should be guided by an understanding of the biology of the specific disorder (in the case of antecedents) and by hypotheses regarding the physiological impacts of parenting a child with a disability (in the case of consequences).

2. FRAGILE X SYNDROME AND RELATED CONDITIONS

Fragile X syndrome (FXS) is the most common inherited cause of intellectual disability (Crawford, Acuna, & Sherman, 2001) and the single leading known cause of autism (Demark, Feldman, & Holden, 2003). 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 55 or fewer repetitions of the CGG sequence of nucleotides comprising the *FMR1* gene (Nolin, Glicksman, Houck, Brown, & Dobkin, 1994). In FXS, there is an expansion to 200 or more repetitions. Importantly, lesser variations in the *FMR1* gene 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, Sideris, Roberts, & Hatton, 2008). The premutation is also associated with elevated risk for two disorders that do not occur in individuals with the *FMR1* full mutation: *primary ovarian insufficiency* (POI), which includes premature menopause, and *Fragile X-associated Tremor-Ataxia syndrome* (FXTAS), a late-onset neurodegenerative disorder (Cornish, Turk, & Hagerman, 2008). Families that include one or more children who have FXS or even the *FMR1* premutation, therefore, are likely to experience elevated levels of stress and non-normative life experiences as a (direct or indirect) result of the characteristics and behaviors of their affected children (Murphy & Abbeduto, 2005).

FXS is, therefore, a multigenerational disorder and its effects on families do not emanate only from the affected children, but also from parents and grandparents. In the case of a child with FXS, the child will have inherited the problem gene from his or her mother, who would be a carrier of either the premutation or the full mutation (Nolin et al., 1996). In the case of children with the *FMR1* premutation, sons will have inherited the gene from their mothers and daughters from either their mother or father (Nolin et al., 1996) (for more details of the inheritance profile of the *FMR1* gene, see Hagerman, 1999). Some parents (and grandparents) of children with an expanded *FMR1* allele will thus 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, 2008). Consequently, understanding the functioning of any individual in a family affected by an *FMR1* expansion will require examination of his or her own genetic status and experiences within the family.

To date, the identification of biomarkers of risk in FXS and related conditions has been conceptualized largely in terms of the prediction of trajectories of cognitive, linguistic, and social-affective development in affected *individuals*. We believe, however, that it is also useful to view those biomarkers as predictors of risk for the *family* and for individuals trying to meet various *family roles*, especially the role of parent, which is the focus of the remainder of this section on FXS and related conditions. In addition to reviewing the published literature, we present new data from our own research linking *FMR1* biomarkers and parental psychological well-being.

2.1. Biochemical alterations and phenotypic correlates

Variation in *FMR1* CGG repeat size is a useful biomarker of various types of risk that could affect parents, as it defines differences between "healthy" and "affected" and between full mutation and premutation carriers. At the same time, however, there are a variety of additional "downstream" biochemical processes that may be even better indicators of risk because they not only reflect the effects of the *FMR1* expansion, but also the moderating effects of various background genes and environmental events (Belmonte & Bourgeron, 2006). Thus, we now briefly review studies of the measurable biochemical changes associated with variation in the *FMR1* gene and the phenotypic correlates of those variations. Although these studies have not focused specifically on individuals who are parents of affected children, they provide a useful context for understanding parental well-being in families with members who carry an *FMR1* expansion. We then review the published studies of psychological well-being in parents, with an emphasis on studies that have included *FMR1* biomarkers. Throughout our review, we consider both the full mutation and the premutation case. We do so because although premutation carriers are more likely than full mutation carriers to be having children and raising families: (1) individuals with the full mutation are not sterile and (2) studies in which mothers have been recruited through an affected child have found more than 10% of the mothers to be carriers of the *FMR1* full mutation (e.g., Bailey, Raspa, Olmsted, & Holiday, 2008).

2.1.1. *FMR1* full mutation

The full mutation typically leads to hypermethylation and transcriptional silencing so that the *FMR1* gene does not produce, or produces at greatly reduced levels, the protein (FMRP) it normally would (Oostra & Willemsen, 2003). FMRP is an RNA-binding protein that regulates translation of biochemical "messages" into proteins at the synapse (Jin & Warren, 2003) and thus, it is involved in important ways in experience-dependent neural development and functioning (Klintsova & Greenough, 1999). The function of FMRP appears to be largely inhibitory in that it prevents activity

in various biochemical pathways and thereby ensures that neural activation occurs in a "controlled" manner (Cornish et al., 2008). In a sense, reduced FMRP leads to exaggerated biochemical reactions that adversely affect neural function. It is known, for example, that lowering the level of FMRP leads to activity in the mGluR5 pathway that would otherwise be blocked (Huber, Gallagher, Warren, & Bear, 2002), which then leads to long-term depression (LTD), or reduced responsiveness to stimuli, in the hippocampus and other regions of the brain involved in learning and memory (Bear, Huber, & Warren, 2004).

In addition to intellectual disability, the FMRP deficit in FXS leads to a characteristic behavioral phenotype, which includes both neurocognitive and social-affective features. In the neurocognitive domain, the full mutation is associated with especially severe delays or impairments in sequential processing (Burack et al., 1999; Dykens, Hodapp, & Lecman, 1987), working memory (Ornstein, Schaaf, Hooper, Hatton, Mirrett, et al., 2008), and attention (Bailey, Raspa, et al., 2008), particularly inhibitory control and inattentiveness (Cornish, Scerif, & Karmiloff-Smith, 2007). In the social-affective domain, hyperarousal (Wisbeck, Huffman, Freund, Gunnar, Davis, et al., 2000), hyperactivity (Baumgardner, Reiss, Freund, & Abrams, 1995; Dykens, Hodapp, Ort, & Finucane, 1989; Freund, Reiss, & Abrams, 1993; Mazzocco, Pennington, & Hagerman, 1993), and anxiety (Bailey, Sideris, et al., 2008), particularly social anxiety (Bregman, Leckman, & Ort, 1988; Mazzocco, Baumgardner, Freund, & Reiss, 1998), are frequent in individuals with the full mutation. Autistic-like behaviors are also common in FXS (Bailey, Hatton, & Skinner, 1998; Bailey, Hatton, Skinner, & Mesibov, 2001; Bailey, Mesibov, Hatton, Clark, Roberts, et al., 1998; Feinstein & Reiss, 1998), with 25% to 50% of affected individuals meeting diagnostic criteria for comorbid autism (Bailey, Roberts, Hooper, Mirrett, Roberts, et al., 2004; Brown et al., 1982; Demark et al., 2003; Hatton et al., 2006; Kaufmann et al., 2004; Lewis et al., 2006a; Rogers, Wehner, & Hagerman, 2001; Sabaratnam, Murthy, Wijeratne, Buckingham, & Payne, 2003). Numerous studies have found that variations in both the neurocognitive and social-affective features of the phenotype are correlated with FMRP level among those with the full mutation (e.g., Bailey, Hatton, Skinner, et al., 2001; Bailey, Hatton, Tassone, Skinner, & Taylor, 2001; Cohen, Nolin, Sudhalter, Ding, Dobkin, et al., 1996; Kwon et al., 2001; Loesch, Huggins, Bui, Epstein, Taylor, et al., 2002; Loesch, Huggins, & Hagerman, 2004; Loesch et al., 2005; Menon, Kwon, Eliez, Taylor, & Reiss, 2000), making FMRP level a useful biomarker of risk for individuals with the *FMR1* full mutation. In terms of parental well-being, the FMRP level of a parent with the *FMR1* full mutation could be viewed as a biomarker of the psychological resources available to deal with stressful experiences and thus, as an indicator of vulnerability or risk for less optimal outcomes.

The full mutation leads to FXS in about 1 in 4000 males and 1 in 6000–8000 females (Crawford et al., 2001). On average, males and females have similar phenotypes, although with milder effects in females (Bailey, Raspa, et al., 2008). This sex difference in affectedness is the result of the fact that males have a single X chromosome, whereas females have two. Moreover, the process of X inactivation early in embryological development in females results in the "turning off" of one X chromosome in each cell, which effectively reduces the impact of the *FMR1* mutation in females relative to males (Tassone, Hagerman, Chamberlain, & Hagerman, 2000). The relative proportions of active and inactive mutation-carrying X chromosomes contribute to differences in affectedness among females, making the *activation ratio* another useful biomarker of vulnerability to parenting stress, albeit only for females.

2.1.2. *FMR1* premutation

There is a complex pattern of alterations in several biochemical processes important for neural development in individuals carrying the *FMR1* premutation. In particular, there appears to be a decrease in FMRP levels for some, but not all, individuals who have large premutations (i.e., >100 CGG repeats; Tassone et al., 2000). Perhaps more importantly, Tassone et al. (2000) have found levels of *FMR1* messenger RNA (mRNA) that are 2–8 times the levels seen in individuals with the healthy *FMR1* allele, with a correlation between mRNA levels and CGG repeat number (Allen, He, Yadav-Shah, & Sherman, 2004). This elevation is thought to lead to RNA toxicity, which in turn has numerous adverse phenotypic consequences (Greco et al., 2006; Hagerman & Hagerman, 2004). Not surprisingly, such substantial alterations in neural development and function are associated with numerous adverse physical and behavioral outcomes, including some not found in FXS (Cornish et al., 2008).

Nearly one-fourth of women with the premutation are affected by POI, a condition associated with premature menopause (i.e., before age 40) and decreased fertility (Cronister, Schreiner, Wittenberger, Amiri, Harris, et al., 1991). The condition is also accompanied by increased levels of several hormones and endocrine problems (Welt, Smith, & Taylor, 2004). Interestingly, the risk of POI has been found in a recent study (Sullivan et al., 2005) to be associated with premutation size in a nonlinear manner, increasing with CGG repeat number up to 100 CGG repeats, but declining a bit thereafter. Thus, there is much to be learned about the relationship between POI and the biomarkers discussed thus far. Moreover, although it is reasonable to suppose that the hormonal changes associated with POI as well as the psychological impact of early menopause and decreased fertility could affect psychological well-being and adaptation to the role of parent of a special needs child, this area has yet to be investigated.

Males and, to a lesser extent, females with the premutation are also at elevated risk during late adulthood for FXTAS (Hagerman & Hagerman, 2004). FXTAS is characterized by intention tremor and ataxia, which become increasingly severe with age (Hagerman, Ono, & Hagerman, 2005). The disorder also has cognitive and social-affective features, including problems in memory and executive function and increased anxiety and disinhibition (Berry-Kravis et al., 2007; Cornish et al., 2008; Grigsby et al., 2006). These physical and psychological challenges will no doubt affect the quality of life of individuals with FXTAS; however, the condition might have other indirect effects on the family. The mother of a young child with FXS, for example, might have to deal with the emotional and financial demands of simultaneously caring for an affected parent and these additional demands may further limit her ability to deal effectively with the needs and challenges of her own child. Unfortunately, empirical tests of this and other possible indirect effects of FXTAS on families have yet to be conducted.

Other features of the *FMR1* premutation phenotype are similar, but less severe, than are those observed in the full mutation case (Bailey, Raspa, et al., 2008). Males with the premutation have problems (relative to typically developing age-matched peers) in several cognitive domains, including executive function, long-term memory, and social perception (Aziz et al., 2003; Cornish et al., 2008; Hessel et al., 2007; Moore et al., 2004). These males are also at elevated risk for various forms of psychopathology, such as ADHD, anxiety, obsessive-compulsive disorders, and autism (Aziz et al., 2003; Goodlin-Jones, Tassone, Gane, & Hagerman, 2004; Hessel et al., 2005). Females with the premutation, especially those with larger premutations (and thus, lower FMRP and higher *FMR1* mRNA levels), are at elevated risk for anxiety, depression, obsessive-compulsive disorder, and features of autism (Goodlin-Jones et al., 2004; Hessel et al., 2005). There is little evidence, however, in support of a cognitive phenotype for premutation females (Allen et al., 2005; Moore et al., 2004; Steyaert, Borghgraef, & Fryns, 2003). Again, it is reasonable to suppose, although this has yet to be investigated empirically, that many of the features of the premutation phenotype we have described can limit a parent's psychological resources and thereby increase his or her vulnerability to parenting stress.

In addition to differences between premutation carriers and individuals with a healthy *FMR1* allele, there is considerable variation at both the genetic and behavioral levels among individuals who have the premutation. Moreover, there is strong evidence of correlations between measurable biochemical variables and several important features of the premutation phenotype. FMRP correlates with cognition and brain activation patterns in premutation cases (Loesch et al., 2004; Moore et al., 2004). More recently, *FMR1* mRNA levels have been found to correlate with measures of psychopathology in males and females with the premutation (Hessel et al., 2005). CGG repeat size and activation ratio have also been found to

correlate with depression and other symptoms of psychopathology in females (Johnston et al., 2001), although recent evidence (described below) suggests that the relationship may be nonlinear. Thus, these variables are likely to be useful indices of potential vulnerability to stress and lower levels of well-being among parents of individuals with an *FMR1* expansion.

2.2. Stress and well-being of parents of individuals with FXS

Nearly all of the studies on stress and well-being in parents of individuals with FXS or *FMR1*-related conditions have focused on mothers. These studies have clearly demonstrated that mothers of children, adolescents, and young adults with FXS display high rates of stress and mental health symptoms and lower quality of life as compared with mothers of similarly aged typically developing individuals, although there is considerable inter-individual variability in the former group. In one such study, Roberts et al. (2009) estimated the rates of psychopathology in 93 mothers of children who carried the premutation and had children with FXS, and compared them with mothers of unaffected children. The comparison group was selected from the National Comorbidity Survey Replication (NCS-R), which includes more than 9000 respondents 18 years of age and older who were interviewed during 2001 and 2002 (<http://www.umich.edu/~ncsum>). Structured psychiatric interviews with the mothers of the children with FXS yielded higher rates of lifetime major depressive disorder, lifetime panic disorder (without agoraphobia), and current agoraphobia without panic disorder than age- and gender-matched subset of NCS-R participants. In another study, Head, Chavis, Serafin, Maddocks, and Abbeduto (2008) conducted clinical interviews with 33 mothers of children with FXS and found a lifetime rate of major depressive disorder that was lower than that in the Roberts et al. study, but still in excess of that expected for women in the general population. Head et al. also found, however, that the most frequent diagnosis was lifetime anxiety disorder, which was observed in 70% of the women, which is well in excess of expectations for the general population. Studies using self-report measures of currently experienced (rather than lifetime history of) mental health symptoms (e.g., the Symptom Checklist-90-R—SCL-90-R), and measuring additional negative facets (e.g., parenting stress) and positive facets (e.g., optimism) of well-being, have also suggested that a relatively high proportion of biological mothers of individuals with FXS have psychological symptoms severe enough to warrant a psychiatric diagnosis or professional intervention (e.g., Bailey, Sideris, et al., 2008).

There is also evidence that mothers of individuals with FXS may have more stress and mental health challenges, as a group, than mothers parenting individuals with several other types of developmental disabilities. In a study focused on currently experienced psychological well-being, Abbeduto et al. (2004)

found that mothers of adolescents and young adults with FXS were more pessimistic about their child's future and believed that their children felt less close to them compared to mothers of age-matched individuals with Down syndrome. In addition, the mothers of the youth with Down syndrome displayed better functioning than a comparison group of mothers of age-matched youth with autism on virtually every measure administered in the Abbeduto et al. study. In contrast, the mothers of the youth with FXS seldom differed from the mothers of the youth with autism. In general, mothers of youth with autism have been found to be among the most stressed of those parenting a son or daughter with developmental disabilities (Esbensen et al., 2008). It should be noted that the FXS sample in the Abbeduto et al. study did not include any son or daughter who met criteria for autistic disorder and thus, a more inclusive sample of mothers would be expected to fare even more poorly on measures of psychological well-being (Lewis et al., 2006b). Thus, it appears that mothers of individuals with FXS, as a group, fall on the upper end of the risk continuum.

In addition to documenting the extent of psychological challenges among mothers parenting sons and daughters with FXS, researchers have begun to address the sources of these challenges. In fact, there is now compelling evidence that, in addition to elevated risk conferred by the biomarkers of FXS, maternal psychological distress and well-being can be traced, at least in part, to characteristics of the son or daughter with FXS, most notably the extent of challenging behavior. Indeed, there is evidence that currently manifested symptoms of depression (Abbeduto et al., 2004; Bailey, Sideris, et al., 2008; Orland, Griffith, Abbeduto, Brown, & Dobkin, 2008), anxiety (Orland et al., 2008; Roberts et al., 2009), and parenting stress (Bailey, Raspa, et al., 2008; Johnston et al., 2003) are predicted by concurrently measured child challenging behavior, as are more general measures of maternal well-being, such as optimism and quality of life (Bailey, Sideris, et al., 2008). Although other personal and contextual factors, such as number of affected children, parent education, and income also contribute to the prediction of such measures, child challenging behavior consistently emerges as a strong predictor of currently manifested symptoms of psychological distress for mothers of individuals with FXS (Esbensen et al., 2008), as it does for mothers parenting children with other developmental disabilities.

In contrast to the many studies examining child and other environmental contributions to maternal psychological well-being for mothers carrying an *FMR1* expansion, few parenting studies have included relevant maternal biomarkers. Moreover, most studies addressing the contribution of maternal genotype to well-being have relied on CGG repeat size as the only biomarker of interest, and with inconsistent results.

In one study focused on currently manifested mental health symptoms, Johnston et al. (2001) found a positive correlation between self-reported

symptoms of depression on the SCL-90-R and CGG repeat number in a sample of mothers carrying the premutation who had children with FXS. In contrast, Bailey, Raspa, et al. (2008) administered a large battery of self-report measures and conducted clinical interviews to assess the currently experienced levels of well-being of 108 mothers who carried the premutation ($n = 95$) or full mutation ($n = 13$) and who had a child with FXS. Bailey did not find any contribution of maternal CGG repeat number to the mothers' currently experienced levels of maternal well-being. In particular, there was no difference between premutation and full mutation mothers in scores on the well-being measures, and no correlation between maternal CGG repeat number and well-being for the premutation mothers.

Abbeduto and colleagues have recently examined the relationship between *FMR1* allele size and currently manifested mental health symptoms in a small sample ($n = 27$) of mothers of adolescents and young adults with FXS. Characteristics of the sample are provided in Table 7.1. All were biological mothers identified through their adolescent or young adult son or daughter with FXS. The sample of mothers was largely White, in their 40s, married, and carried the premutation. The mothers completed the SCL-90-R, which yields several *t*-scores, including for depression and anxiety.

Table 7.1 Families of adolescents or young adults with FXS: selected characteristics of mothers, children, and families

Characteristic	Mean	SD	Min.	Max.
<i>Maternal</i>				
Number of CGG repeats	98.7	24.7	70	155
Age (in years)	45.3	6.6	33.5	61.7
IQ ^a	109.4	13.6	86	134
Education ^b	5.6	1.7	3	8
<i>Child</i>				
Challenging behavior ^c	- 9.1	9.6	- 40	2
<i>Family</i>				
Income ^d	7.9	2.7	3	11
Number of children	2.3	1.2	1	5
Number of children w/DD	1.6	0.6	1	3
% Single parent	22	-	-	-

^a Based on administration of the Kaufmann Brief Intelligence Test.

^b Based on a rating scale of from 1 (grade 8 or less) to 8 (advanced graduate degree), with a rating of 6 signifying a college graduate.

^c Based on scores from the Problem Behavior Scale of the Scales of Independent Behavior—Revised. Scores derived from administrations to teacher and/or father. Lower scores reflect greater problems with challenging behaviors. Not available for three children.

^d Based on a rating scale of from 1 (annual income \$10,000 or less) to 16 (annual income \$150,000 or more) in \$10,000 increments. Not available for three children. Not available for one family.

The target child's father or teacher or both completed the Problem Behavior Scale of the Scales of Independent Behavior—Revised, which assesses behavior problems. It should be noted that these mothers were functioning relatively well according to their SCL-90-R scores, as only eight met the definition of "caseness" (i.e., a *t*-score of 63 or above, reflecting the likelihood of symptoms severe enough to warrant a diagnosis) for depression and three for anxiety, although other data we collected suggested that many more mothers had dealt with mental health problems at previous points in their lives. Similarly, the mean score of the adolescents and young adults with FXS fell at the edge of the "normal" range on the Problem Behavior Scale, suggesting that, as a group, they too were functioning relatively well.

As can be seen in Table 7.2, SCL-90 depression scores were significantly correlated with several maternal characteristics, child challenging behavior, and family characteristics. In contrast, scores for anxiety were correlated with a more narrow set of variables, suggesting the possibility of different causal pathways for depression and anxiety in this population. Most importantly for present purposes, maternal *FMR1* allele size (i.e., CGG repeat

Table 7.2 Families of adolescents or young adults with FXS: bivariate correlations between maternal mental health measures and selected characteristics of mothers, children, and families

Characteristic	Depression (SCL-90-R)	Anxiety (SCL-90-R)
<i>Maternal</i>		
Number of CGG repeats	−0.58****	−0.49***
Age (in years)	−0.34*	−0.27
IQ ^a	−0.42**	−0.41**
Education ^b	−0.42**	−0.30
<i>Child</i>		
Challenging behavior ^c	−0.35*	−0.31
<i>Family</i>		
Income ^d	−0.41**	−0.26
Number of children	−0.10	−0.06
Number of children w/DD	−0.03	0.00

* $p \leq 0.10$, ** $p \leq 0.05$, *** $p \leq 0.01$, **** $p \leq 0.005$, with all tests two-tailed.

^a Based on administration of the Kaufmann Brief Intelligence Test.

^b Based on a rating scale of from 1 (grade 8 or less) to 8 (advanced graduate degree), with a rating of 6 signifying a college graduate.

^c Based on scores from the Problem Behavior Scale of the Scales of Independent Behavior—Revised. Scores derived from administrations to teacher and/or father. Lower scores reflect greater problems with challenging behaviors and thus, the negative correlation reflects the fact that higher rates of maternal mental health symptoms are associated with higher rates of child challenging behavior. Not available for three children.

^d Based on a rating scale of from 1 (annual income \$10,000 or less) to 16 (annual income \$150,000 or more) in \$10,000 increments. Not available for three children. Not available for one family.

number) was correlated with both maternal depression and anxiety in this sample of mothers, consistent with the notion of a genetic susceptibility to some types of mental health problems in premutation cases. Surprisingly, however, the correlation between allele size and SCL-90-R scores was negative; that is, larger *FMR1* expansions in the premutation range were associated with fewer and/or less intense symptoms of depression and anxiety. A negative relationship also emerged when allele size in mothers meeting criteria for caseness was compared against those not meeting caseness criteria, although only for depression, $t_{(1,24.06)} = 2.54$, $p = 0.018$, with the former averaging fewer CGG repeats.

Abbeduto and colleagues also explored the relationships displayed in Table 7.2 in a series of regression analyses and found that maternal CGG repeat number and child challenging behavior made independent contributions to current symptoms of maternal health as assessed by the SCL-90-R. In a regression that included four predictor variables (maternal CGG repeat number and IQ, child challenging behavior, and family income) and SCL-90-R anxiety scores as the dependent variable, β was -0.51 for maternal repeat number, $t = 2.6$, $p = 0.018$, and -0.41 , $t = 2.3$, $p = 0.033$ for child behavior. In the same analysis for SCL-90-R depression scores, β was -0.57 for maternal repeat number, $t = 3.1$, $p = 0.006$, and -0.46 , $t = 2.7$, $p = 0.016$ for child behavior. Regressions including additional maternal and family variables did not change the results appreciably. Thus, smaller maternal premutations and more serious child challenging behaviors predicted worse current levels of mental health in the mothers. Moreover, the negative relationship between mental health and CGG repeat number was not explained by correlated differences on any of the other variables, although the small sample size precluded an examination of all variables of interest or their interactions.

The findings reported by Abbeduto and colleagues are consistent with a model in which the *FMR1* premutation is thought to confer increased risk for mental health problems over and above the contribution of child challenging behaviors and other factors "external to the mother." Nevertheless, the findings regarding premutation size are surprising in that they suggest that it is only the smaller premutations that increase vulnerability to psychological distress. This interpretation must be considered speculative until the biological mechanisms underlying differences in risk and premutation size are more fully understood. Caution is also required because our finding is at odds with those of Johnston et al. (2001) who found a positive correlation between maternal repeat number and currently manifested symptoms of depression. Nevertheless, it is important to note that Roberts et al. (2009) also found a negative correlation between lifetime mental health problems and repeat number in their larger sample of biological mothers of children with FXS, suggesting that our findings did not emerge because of some unidentified idiosyncratic feature of

our sample. Roberts et al. suggested that the larger *FMR1* premutations might serve a protective function.

Ultimately, understanding the pathways from maternal genetic status to mental health outcomes will require that researchers move beyond CGG repeat number and instead rely on biomarkers that capture more "downstream" biochemical processes (e.g., FMRP and mRNA levels), reflecting the influence of other background genes and environmental events as well as the *FMR1* mutation. Moreover, it is likely that the use of a combination of several biomarkers may well be most informative, as each reflects somewhat different biochemical processes and thus, each may make a unique contribution to maternal mental health. This possibility is illustrated in a recent study by Hessel et al. (2005), who found a positive correlation between *FMR1* mRNA levels and self-reported current symptoms of anxiety (measured by the SCL-90-R) for a sample of women with the premutation (largely mothers of children with FXS); however, this correlation emerged only for women who had activation ratios reflecting a higher proportion of active X chromosomes containing the premutation (rather than the healthy allele). Such findings serve as a reminder of the complexity of development, even in the case of a single-gene disorder (Belmonte & Bourgeron, 2006) and thus, of the need to create a comprehensive battery of well-characterized and understood biomarkers when attempting to evaluate risk.

It is important, as well, to reiterate that other factors, such as child challenging behavior, also contribute to maternal mental health. Indeed, contextual factors, such as number of affected children in the family and family income, as well as maternal characteristics, such as education, have been found to contribute to psychological well-being (Abbeduto et al., 2004). Moreover, other genes make independent contributions to mental health and may well interact with the *FMR1* gene to affect risk. Thus, maternal *FMR1* status is only part of the picture needed to understand an individual's risk for mental health challenges or the most effective path to prevention or treatment.

In concluding this section, it is interesting to consider a study by Franke et al. (1998), which demonstrates a particularly creative approach to investigating the role of biological variables in the psychological distress and well-being of mothers of individuals with FXS. These investigators included mothers who themselves carried the *FMR1* premutation and relied on diagnostic interviews and observation to determine whether they met criteria for various psychiatric disorders. Franke et al. also included several control groups of women (e.g., mothers of children with autism, premutation women without affected children) in an attempt to parse out the contributions of maternal genetic status, parenting *per se*, and parenting a child with FXS. In general, the women who carried the premutation and who had children with FXS were found to be at greatest risk for several psychiatric

conditions. They were the most likely to be diagnosed with an anxiety disorder or a major depressive episode, and they were more likely to be so diagnosed than were women who had the premutation, but had no affected children. Again, such findings suggest that, although the biochemical alterations associated with the *FMR1* expansion do increase the risk of mental health challenges, there are many other factors that contribute, including, of course, those associated with parenting a son or daughter with FXS.

2.3. Limitations of the *FMR1* biomarkers and measures of psychological well-being

It is important to acknowledge that although significant correlations between the *FMR1*-related biomarkers and measures of neurocognitive and social-affective functioning and mental health problems have been found in numerous studies, the magnitude of the correlations generally suggests that these biomarkers are accounting for only a rather small proportion of phenotypic variance. These modest correlations may reflect the fact that the biomarkers are calculated only from peripheral blood rather than from neural tissue, which obviously cannot be sampled except under "unusual" circumstances, such as from postmortem tissue under autopsy. Although estimates of FMRP and other *FMR1* biomarkers from lymphocytes can be assumed to be virtually identical to their distribution in brain for males with the full mutation, they can provide only approximations for females and mosaic males (Brown, 2002). In studies of mothers of affected children, then, the biomarkers contain considerable error, a problem that is compounded by the small numbers of participants in most studies. It is likely, therefore, that the current set of biomarkers available in human studies will seriously underestimate the contribution of genetic variation in stress and well-being among parents of individuals with FXS and related conditions.

Throughout this section, we have noted considerable variation in the ways in which psychological well-being has been measured, and these variations in measurement strategy may have important consequences for understanding the ways in which *FMR1* biomarkers confer risk. Importantly, some investigators measure whether a participant has met criteria for a clinical diagnosis at some point during his or her life whereas other investigators use current symptoms of a clinical condition that are nonetheless below the threshold for receipt of a clinical diagnosis. It is possible, for example, that for individuals who are prone to depression, anxiety, or other conditions, carrying an *FMR1* expansion functions as an additional "hit," pushing them from subthreshold levels to clinical levels of mental health concerns. In this case, the most sensitive measure of the role of the biomarker would be lifetime history of psychiatric diagnosis rather than an index of current symptom severity. Unfortunately, there are not yet a

sufficient number of studies and there are too many inconsistencies in results across studies, including those employing the same measurement strategy, to discern a clear pattern between these two types of measurement strategies. Substantially more research on this issue is needed.

2.4. Summary and directions for future research

There is considerable evidence from decades of research that the biomarkers we have considered are broadly predictive of "affectedness" in individuals with an *FMR1* expansion. Those with a full mutation typically display a characteristic phenotype that includes high rates of intellectual disabilities and social-affective problems, including anxiety and autism. Individuals who carry the premutation are at risk for milder cognitive and social-affective symptoms, but also for conditions, such as POI and FXTAS, that do not occur in the full mutation case. The biomarkers we have considered also appear to be predictive of psychological well-being in women who carry the premutation and are raising sons and daughters with FXS, although the relations among the biomarkers and psychological symptoms are complex and inconsistent across studies. In the case of these mothers, it appears that they have poorer mental health outcomes, as a group, because of a genetic vulnerability to mental health problems and are less well equipped to deal with the stresses of life, including those that arise (directly and indirectly) from parenting a child with challenging behavior.

Knowing that the *FMR1* expansion produces a vulnerability to psychological stress in mothers, however, is only the beginning of an explanation. Additional research is needed to determine more fully the causal pathways and mediators involved in producing mental health outcomes for these mothers. There is a need for research at multiple levels of analysis, from that focusing on biochemical processes at the synapse and the structural and functional integrity of neural systems, to that focused on the ways in which the psychological and biological characteristics of a woman who carries the problematic allele affects her reactions to stress at various points in development both before and after the birth of her affected child, as well as the ways in which those reactions are tempered by the broader context in which she lives.

There is also a need for more research on mothers who carry the full mutation. Most studies focused on maternal well-being have generally included only women with the premutation or have included so few women with the full mutations that drawing conclusions has been difficult. From a clinical perspective, it is important to understand the mental health challenges and needs of women across the full range of *FMR1* expansions, especially as one might suppose that full mutation carriers may be even more vulnerable to the stresses of parenting an affected child. From a basic science perspective, there is still much we do not know about how the various

biomarkers considered here map onto phenotypic outcomes and the ways in which these biomarkers operate similarly and differently across full mutation and premutation cases.

Research is also needed on other members of the family and the ways in which the *FMR1* biomarkers can help us understand family risk more broadly. How do fathers who carry the *FMR1* premutation deal with parenting stress? Do they display the same vulnerabilities as mothers? What of siblings who carry the premutation? Are they less able to deal with challenges within the family relative to siblings who carry the healthy allele? As we address these questions and continue to learn more about the pathways from gene to behavior in FXS we may be able to move beyond conceptions of risk for *individuals* and toward conceptions of risk for *families* that take into account the genetic and psychological vulnerabilities of all family members and the dynamic relationships among them.

Finally, it is important to acknowledge that establishing biomarkers of risk in families affected by FXS and its associated disorders does not provide a direct path to intervention. Although such biomarkers can be useful indicators of who is likely to be most in need of interventions or preventive supports, there remains considerable work to be done in specifying the nature of those interventions and supports. No doubt, psychoeducational therapeutic programs and psychopharmacological agents used to treat depression and anxiety disorders should be evaluated in individuals with *FMR1* expansions. In addition, a variety of promising pharmaceuticals that target neural pathways that are specifically impaired in FXS are beginning to be tested and hold promise (Hagerman et al., 2009). Nevertheless, the path from identification of biomarkers of risk in carriers of *FMR1* expansions to treatment is likely to involve many steps and considerable scientific effort.

3. CORTISOL PROFILES IN PARENTS OF CHILDREN WITH DISABILITIES

Whereas the biomarkers of FXS and the premutation appear to increase the *vulnerability* of parents to poor mental health outcomes and to reduced ability to deal with caregiving stress, other biomarkers are useful indicators of the *consequences* of parenting children with disabilities. One such biomarker that has been shown to be a sensitive measure of the effects of life stressors is cortisol, which is produced in the adrenal cortex and is an indicator of the activity of the hypothalamic-pituitary-adrenocortical (HPA) axis. A large body of research has demonstrated that disruption of the HPA axis is associated with physical and mental health problems (Gunnar & Vasquez, 2001), suggesting its widespread physiological effects. Cortisol plays a vital role in linking stress exposure to health problems

(McEwen, 1998). However, prior to our own research (Seltzer et al., 2009), this pathway had not been examined in parents of children with disabilities. Therefore, in this section of the chapter, we review the literature on cortisol and stressful life circumstances, drawing from studies of other subgroups of the population, and then we present data from our program of research, which has examined cortisol in parents of children with disabilities.

3.1. Stress and cortisol

Cortisol normally peaks shortly after waking in the morning and then gradually declines throughout the rest of the day. Diurnal cortisol (i.e., the pattern of cortisol expressed throughout the day) provides a window into individuals' chronobiology (Keenan, Licinio, & Veldhuis, 2001). The early morning and evening levels of cortisol reflect daily engagement and disengagement, respectively, of the brain with peripheral physiology, and hence with the external environment. Failure to *activate* the HPA axis in the morning may indicate difficulty in responding to the ordinary challenges that are faced every day. Failure to *deactivate* the HPA axis in the evening may indicate difficulty in disengaging from external demands, leading to inhibition of restoration and recovery processes associated with sleep (Sapolsky, Krey, & McEwen, 1986). (Note that the phrases "failure to activate" and "failure to deactivate" do not imply that cortisol is under the intentional control of the individual; rather, these phrases reflect physiological processes.)

Short-term increases in cortisol are thought to reflect a "normal" physiological response to exposure to a stressor (Sapolsky et al., 1986). However, individual differences as well as variation in the nature of stressors may influence the magnitude of such responses, leading to exaggerated (hyper) or diminished (hypo) responsiveness. The impact of variation in cortisol reactivity is thought to accumulate over time in response to repeated or chronic stressor exposure, thereby leading to persistently high or low levels of circulating cortisol (which in turn can influence multiple aspects of physiological functioning). Both hyper- and hyporesponsive cortisol reactivity are symptomatic of poor physical health, generally interpreted as wear and tear on the HPA axis (Kiecolt-Glaser et al., 1986; Segerstrom & Miller, 2004). The measurement of daily cortisol rhythms provides a useful window into stress physiology, yielding information about overall levels and fluctuations in cortisol levels across the day, and the association of these characteristics of cortisol with exposure to stressful experiences.

Daily stressors have been shown to be important predictors of individual and family functioning (Crnic & Greenberg, 1990; DeLongis, Folkman, & Lazarus, 1988). Studying cortisol in parents of children with disabilities offers a new opportunity to examine how daily life experiences influence

daily physiology and are significantly associated with indicators of health and well-being.

Research has shown that individuals who experience *acute* stressors display elevations in cortisol levels at waking and 30 min after waking as compared to individuals who do not experience acute stress (Dickerson & Kemeny, 2004). For example, Kirschbaum, Pirke, and Hellhammer (1993) demonstrated that when research participants were given a stressful laboratory task such as having to give a speech or perform mental arithmetic, this led to a two- to fourfold elevation in cortisol levels above their baseline level.

However, a different pattern of cortisol is evident in the context of *chronic* life stressors. Although exposure to acute stressors leads to elevations in cortisol, hypoactivity of the HPA axis has been documented in the face of chronic stressors, such as unemployment, bereavement, environmental disasters, chronic fatigue syndrome, fibromyalgia, PTSD, and parenting children with cancer (Baum, Schaeffer, & Lake, 1985; Demitrack et al., 1991; Griep, Boersma, & de Kloet, 1993; Jacobs, Mason, Kosten, Kasl, Ostfeld, et al., 1987; Meewisse, Reitsma, De Vries, Gersons, & Olf, 2007; Miller, Chen, & Zhou, 2007; Ockenfels, Porter, Smyth, Kirschbaum, Hellhammer, et al., 1995; Scott & Dinan, 1998). Pruessner, Hellhammer, and Kirschbaum (1999) found that teachers scoring high on burnout showed lower overall cortisol secretion relative to peers who are low on burnout. Adam and Gunnar (2001) found that mothers who worked more hours and had more children at home had lower morning cortisol values and a less pronounced decline in cortisol levels across the day than mothers working fewer hours and having fewer children. Similarly, in a study of parents of children with cancer, Miller, Cohen, and Ritchey (2002) found that these parents had lower levels of cortisol secretion 1-h postawakening than parents of healthy children, and showed a flatter diurnal decline in cortisol. In a meta-analysis of 37 studies of 828 people with PTSD and 800 controls, Meewisse et al. (2007) found that individuals with PTSD had significantly lower levels of cortisol than controls who had not been exposed to trauma.

Thus, cortisol shows a different pattern with chronic than acute stressful life events: Acute stressful life events are associated with sharper elevations in the morning rise of cortisol, whereas chronic stressful life circumstances are associated with a flatter pattern of low levels of cortisol throughout the day, that is, a lower morning rise and a less pronounced decline at the end of the day.

Apart from our program of research (described in the next section), no previous study has extended the investigation of cortisol dysregulation to parents dealing with the demands of caring for a child with disabilities. However, based on past research on other populations experiencing chronically stressful life circumstances, we hypothesized that parents of children with disabilities would exhibit patterns of hypoactivation of cortisol.

3.2. Measurement of daily stress and the diurnal rhythm of cortisol

Our research protocol for the measurement of daily caregiving challenges and salivary cortisol is based on the methods developed by Almeida, Wethington, and Kessler (2002) for the National Study of Daily Experiences (NSDE), one of the projects that comprise the National Survey of Midlife in the United States (MIDUS; Carol Ryff, PI). MIDUS is a national probability sample of English-speaking, noninstitutionalized adults who were aged 25–74 in 1994 (MIDUS I; Brim, Ryff, & Kessler, 2004). Follow-up data were collected from 2003 to 2005 (MIDUS II; $n = 4032$).

A subset of MIDUS II sample members was also included in the National Study of Daily Experiences (NSDE; David Almeida, PI), which is the source of data for the daily diary study analyses we present in this chapter. The NSDE consists of 15–25-min telephone interviews at the end of each of 8 consecutive days. The NSDE daily telephone interview includes questions about daily experiences in the past 24 h concerning the number of stressors and positive events, and daily measures of positive and negative affect (Almeida et al., 2002).

As part of the NSDE, salivary cortisol samples are collected 16 times (i.e., four times each day on days 2–5 of the 8-day study). Respondents receive a Home Saliva Collection Kit 1 week prior to their initial phone call. Sixteen numbered and color-coded “salivettes” are included in the collection kit, each containing a small absorbent wad, about 3/4 of an inch long, as well as a detailed instruction sheet. In addition to written instructions, telephone interviewers review the collection procedures and answer any questions.

The four saliva samples collected each day are scheduled to provide data about the characteristic diurnal rhythm of cortisol: one upon waking, one 30 min after getting out of bed, one before lunch, and one at bed time. Data on the exact time respondents provided each saliva sample are obtained from the nightly telephone interviews and on a paper-pencil log sent with the collection kit. In addition, approximately 25% of the respondents received a “smart box” to store their salivettes. These boxes contain a computer chip that recorded the time respondents opened and closed the box. The correlations between self-reported times and the times obtained from the “smart box” ranged from 0.75 for the evening occasion to 0.95 for the morning, substantiating the reliability of the self-reported times of saliva collection.

Measures of salivary cortisol derived from the samples include the absolute values at each of the four collection times (upon awakening, 30 min later, before lunch, before bedtime), as well as two parameters of diurnal rhythm: morning rise and daily decline. *Morning rise* is an indicator of how high an individual’s cortisol rises, measured from awakening to 30 min after awakening. *Daily decline* refers to the slope from the typically

highest point in the day, measured at 30 min after awakening, through the collection before bed.

3.3. Study samples: Parents of children with disabilities and comparison group parents

All parents in the MIDUS study were asked if any of their children had a developmental or a mental health problem, and if so, which child had the condition and the name of the particular diagnosis the child had received. Approximately one in ten (10.5%) MIDUS participants responded affirmatively, of whom nearly half (46.3%) had a child with a developmental problem, about the same number (42.7%) had a child with a mental health problem, and the remaining 11% had a child with another type of neurological disability.

A subsample of the MIDUS II participants who also participated in the NSDE ($n = 806$ at the time of the present analysis) had a child with a developmental or mental health problem ($n = 82$). About half (47.6%) had developmental disorders and the others (52.4%) had mental health diagnoses. Among the developmental disorders were intellectual disability, cerebral palsy, Down syndrome, hydrocephalus, muscular dystrophy, pervasive developmental disorders, specific genetic disorders (e.g., cri du chat syndrome), ADHD, seizure disorders, traumatic brain injury, etc. Among the mental health diagnoses were schizophrenia, bipolar disorder, depression, anxiety disorders, eating disorders, alcohol and drug abuse, etc. Thus, the present sample was characterized by a heterogeneous set of disabilities.

We selected as a comparison group a sample of NSDE respondents who had at least one living child, but no child with a disability or chronic health condition, and who never provided care to a family member. For this comparison group, we selected the 82 individuals most similar to the parents of children with a disability with respect to parent gender, parent age, number of children in the household, child age, whether the target child lives with the parent, parent marital status, and parent educational attainment (see Seltzer et al., 2009 for details of the methods and findings). Table 7.3 portrays the characteristics of the sample of parents of children with disabilities and the comparison group, and shows that the two groups were very similar.

As shown in Table 7.3, the sons and daughters in both groups were nearly 30 years of age and their parents were in their late 50s, on average. Most of the parents were mothers (almost 60%), and nearly all were non-Hispanic whites. The two groups were similar with respect to marital status (about 80% were married) and employment status (about 60% were employed), and both groups averaged about 2 years of education beyond high school. The one variable on which the two groups differed was the percentage who had children still living at home, with the comparison

Table 7.3 Parents of children with disabilities: descriptive statistics (mean with standard deviation in parenthesis) of parents of children with disabilities ($n = 82$) and comparison group parents ($n = 82$)

Variables	Parents of children with disabilities	Comparison group
<i>Parent's characteristics</i>		
Age	57.4 (13.0)	57.4 (13.1)
Gender (1 = female/0 = male)	0.59 (0.50)	0.59 (0.50)
Race (1 = non-Hispanic white/0 = others)	0.96 (0.19)	0.97 (0.16)
Marital status (1 = married/0 = not married)	0.79 (0.41)	0.84 (0.37)
Employment status (1 = employed/0 = not employed)	0.57 (0.50)	0.61 (0.49)
Years of education	14.4 (2.65)	14.5 (2.35)
Total household income	\$74,400 (49,800)	\$78,300 (50,100)
Number of children	3.29 (1.91)	3.21 (1.26)
<i>Child's characteristics</i>		
Age	29.3 (13.4)	29.9 (13.4)
Gender (1 = female/0 = male)	0.40 (0.49)	0.40 (0.49)
Living with parents (1 = yes/0 = no)	0.41 (0.50)	0.32 (0.47)

group less likely to have coresident children than the group of parents of individuals with disabilities (32% vs 41%), which is to be expected given the ability differences between the two groups of children.

3.4. Daily stress in parents of children with disabilities and the comparison group

As described in Seltzer et al. (2009), this sample of parents of children with disabilities diverged considerably in daily experiences from parents in the comparison group, despite demographic similarity. As shown in Table 7.4, parents of children with disabilities reported a significantly higher number of days during the daily diary study when they had arguments and a higher number of days when they experienced tense moments but avoided arguments, relative to the comparison group. The former also reported experiencing a greater number of stressors each day, a greater number of days when they experienced at least one stressor, a greater severity of stressors, and a greater number of stressors that occurred at home, than the comparison group. The parents of children with disabilities also reported

Table 7.4 Parents of children with disabilities: mean comparisons between parents of children with disabilities ($n = 82$) and comparison group parents ($n = 82$) on type and severity of stressors, mood, and symptoms

Variables	Parents of children with disabilities		Comparison group		<i>t</i> -test
	Mean	SD	Mean	SD	
<i>Stressors</i>					
Arguments ^a	0.13	0.15	0.08	0.12	2.36*
Avoided arguments ^a	0.18	0.17	0.13	0.13	2.21*
Number of stressors/day (mean)	0.74	0.64	0.52	0.42	2.60**
Days with any stressors (%)	0.50	0.26	0.40	0.25	2.49**
Work stressors ^a	0.07	0.10	0.08	0.14	-0.57
Home stressors ^a	0.13	0.14	0.09	0.11	2.30*
Network stressors ^{a,b}	0.02	0.07	0.01	0.03	1.28
Severity of stressors (mean) ^c	2.51	1.32	2.09	1.00	2.27*
<i>Positive events</i>					
Number of positive events/day (mean)	1.09	0.66	1.04	0.63	0.49
Days with any positive event (%)	0.69	0.28	0.69	0.26	-0.13
<i>Affect</i>					
Negative affect ^d	0.20	0.18	0.14	0.15	2.17*
Positive affect ^e	2.57	0.73	2.78	0.66	-1.88 ⁺

⁺ $p = 0.06$, * $p < 0.05$, ** $p < 0.01$.

^a Reflects the percent of days in the daily diary study when the type of stress was reported.

^b Defined as stress in the lives of individuals in the respondent's social support network.

^c Severity was rated from "not at all stressful" to "very stressful."

^d The negative affect scale (10 items) measured anxiety, hostility, and depression on a five-point scale from "none of the time" to "all of the time."

^e The positive affect scale (10 items) measured enthusiasm, alertness, and vitality. The rating scale was the same as for negative affect.

significantly elevated levels of negative affect, reflecting more anxiety and depression on a daily basis, than the comparison group, and a marginally lower level of positive affect.

However, the parents of children with disabilities did not differ from the comparison group in all respects; they were not different in the number of days when they experienced a stressor at work or when members of their social support network experienced stress, and they reported an equal number of positive events per day and days with a positive event during the 8-day diary study.

Thus, parents of children with disabilities had daily lives that were similar to the norm in their experience of positive events, stressors at work, and stress experienced by members of their social support network. However, their lives were characterized by elevated levels of negative affect, stressors at home, arguments, tense moments, and several other measures of stressful life circumstances that were assessed during the 8-day diary study.

We next asked whether there is a “biological signature” of this level of daily stress, namely whether parents of children with disabilities differed from the comparison group in their level and pattern of cortisol.

3.5. Cortisol in parents of children with disabilities and the comparison group

Using multilevel modeling, we examined group differences in the diurnal rhythm of cortisol. We found that parents of children with disabilities and comparison parents did not differ significantly in the slope of the morning rise, but parents of children with disabilities exhibited significantly less pronounced daily decline slopes (see Fig. 7.1; the full results of the multilevel models are available in Seltzer et al., 2009). This pattern indicates that parents of children with disabilities are significantly less likely to deactivate the HPA axis at the end of the day than their counterparts in the comparison group, suggesting inhibition of restoration and recovery processes for parents of children with disabilities. This pattern remained significant even after controlling for the residential status of the child.

We also examined whether the amount of time parents spent with their children on a given day predicted variation in diurnal pattern of cortisol and other indicators of daily psychological well-being. Specifically, we investigated if there were within-person associations between time spent with children, on the one hand, and negative affect and the cortisol measures, on the other, and compared parents of children with disabilities and unaffected parents. For this analysis, we focused only on the coresident subgroup to ensure a closer association between daily contact with children and parental psychological and biological response.

We found that there was a significant interaction between parental status (having a child with a disability vs having unaffected children) and time spent with coresident children, with respect to parental well-being outcomes and cortisol (see Seltzer et al., 2009 for the data). On days when they spent more time with their children, parents of children with disabilities reported significantly higher levels of negative affect compared to days when they spent less time with their children, whereas parents in the comparison group did not evidence a difference in negative affect based on the amount of time they spent with their children. In addition, parents of children with disabilities had a less pronounced daily decline of cortisol on days when they spent more time with their children as compared to days

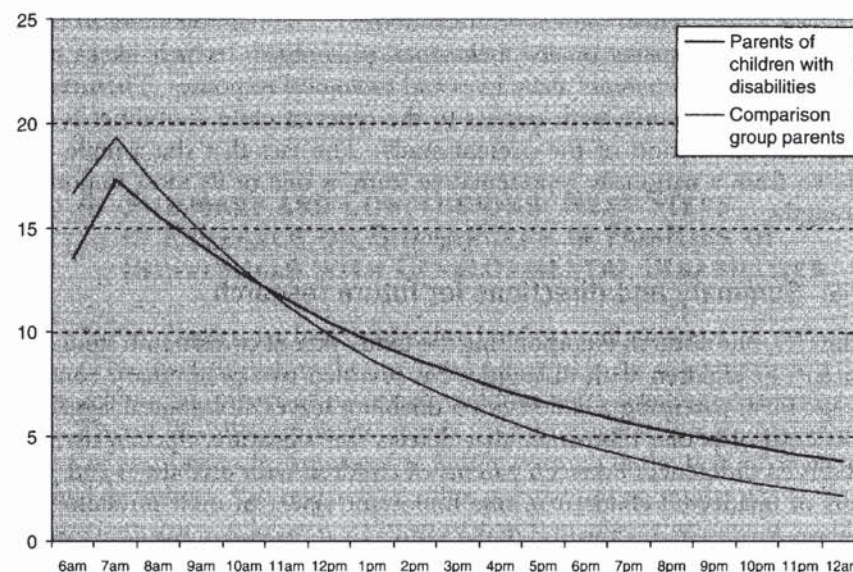


Figure 7.1 Diurnal rhythm of cortisol in parents of children with disabilities and comparison group parents.

they spent less time, whereas the opposite pattern was evident for the parents in the comparison group. These findings suggest that parents of children with disabilities were less likely to deactivate the HPA axis during days when they spent more time with their children than on days when they spent less time with their children.

Based on these analyses, we have tentatively concluded that there indeed is a biological signature of parenting a child with disabilities. Such parents experience elevated levels of stress and are less likely to show the characteristic daily decline pattern of cortisol, particularly on days when they spend more time with their coresident children. These findings suggest that, at the end of the day, the brain is less likely to be disengaged from peripheral physiology in parents of children with disabilities than in parents whose children do not have disabilities. However, in this analysis, parents of children with disabilities did not differ from the norm in the slope of their morning rise of cortisol, suggesting that they “gear up” for the day’s challenges as well as their peers who do not have children with disabilities. This pattern of normative daily rise but flatter daily decline is only partially characteristic of a classic chronic stress response.

One explanation for this partial chronic stress response concerns the heterogeneity of the diagnoses represented in the sample. Some of the diagnoses are chronic and long-lasting, while others are more transitory. Furthermore, some of the diagnoses reflect developmental problems,

whereas others reflect mental health problems. The heterogeneity in child diagnosis encompasses diverse behavioral phenotypes, which likely have diverse effects on parents' daily lives and biological responses. The heterogeneity of the sample with respect to the types of child disabilities is one important limitation of the present study. The fact that the sample was drawn from a nationally representative study is one of its most important strengths.

3.6. Summary and directions for future research

Thus far, our research incorporating the biomarker of cortisol into studies of parents of children with disabilities has revealed two preliminary conclusions. First, parenting a child with a disability leaves a biological signature and cortisol is one biomarker that detects this signature. Specifically, we observed differences between parents of children with disabilities and parents of unaffected children in one important aspect of their physiological response, namely deactivation of the HPA axis at the end of the day. Parents of children with disabilities were significantly less likely to deactivate their HPA axis at the end of the day than unaffected parents, and this was particularly the case on days when they spent more time with their children. These findings may suggest a pileup of stress during the day. It is also possible that these findings suggest an adaptive response to long-term exposure to stressors. Future longitudinal research that explores the relationship between the pattern of cortisol evident in this analysis and the health of mothers of individuals with disabilities will be useful in elucidating possible adaptive effects.

Second, we believe that it will be profitable to disaggregate samples of parents of children with disabilities according to the specific diagnosis of their child. We are currently applying this same daily diary and cortisol collection methodology in studies focusing on distinct groups defined by the specific developmental disability of their child—autism, fragile X syndrome, and Down syndrome. Past research (e.g., Abbeduto et al., 2004; Dykens, Hodapp, & Finucane, 2000; Ly & Hodapp, 2002) has shown that these three groups of mothers differ in their level of self-reported parenting stress, with mothers of individuals with autism reporting the highest level of parenting stress, mothers of individuals with Down syndrome reporting the lowest levels of parenting stress, and mothers of individuals with FXS close to the level experienced by those whose child has autism. By extending this line of comparative self-report research to include the biomarker of cortisol, we will be able to determine the extent to which self-reported differences in stress correlate with the biological data.

These studies are currently ongoing. Within the sample of mothers of individuals with FXS, we will be particularly interested to separate those whose son or daughter has a comorbid autism diagnosis from those

who have FXS only, and to determine whether the biomarkers of fragile X alter the pattern of maternal stress reactivity as evidenced in their cortisol patterns.

4. SUMMARY AND CONCLUSIONS: NEXT STEPS IN RESEARCH ON BIOMARKERS IN FAMILIES OF INDIVIDUALS WITH DEVELOPMENTAL DISABILITIES

In this chapter, we have highlighted only a small subset of the potential array of biomarkers that might prove to be fruitful in the investigation of the biopsychosocial impact of parenting children with developmental disabilities. Therefore, one important agenda for future research is to expand the range of biomarkers incorporated in family research in the field of developmental disabilities. Past research on other populations points the way toward biomarkers that would potentially be profitable in advancing developmental disabilities family research.

For example, cellular aging and allostatic load are both promising biomarkers that are receiving increasing attention in research. Such biomarkers can increase our understanding of the mechanisms by which exposure to stressors takes a psychosocial and biological toll to ultimately impact health. These biomarkers may help to identify family members at increased risk for morbidity and mortality, as well as those who evidence profiles of resilience.

4.1. Cellular aging

Telomere length is a promising measure of cellular aging. Specifically, telomeres are the distal structures of chromosomes. They serve to protect chromosome ends from damage during replication, but shorten with each cell division. Telomere attrition has therefore been proposed as a biomarker of cellular aging (Bekaert, De Meyer, & Van Oostveldt, 2005; Harley, Vaziri, Counter, & Allsopp, 1992) because telomeres shorten naturally with each cell division and, when exhausted, are associated with cell death (Hayflick, 1965). Moreover, cells subjected to oxidative stress *in vitro* show an accelerated rate of telomere attrition (Serra, Grune, Sitte, Saretzki, & Von Zglinicki, 2000; von Zglinicki, Saretzki, Docke, & Lotze, 1995), suggesting that oxidative stress, such as that associated with depression (Forlenza & Miller, 2006; Irie, Asami, Ikeda, & Kasai, 2003) and perceived stress (Irie, Asami, Nagata, Miyata, & Kasai, 2001) may hasten human aging at the cellular level through accelerated telomere attrition (Epel et al., 2004). One implication of this process is that biological, or cellular, aging may proceed at a dramatically different pace in different individuals with similar chronological ages, and this may be a function of stressor exposure.

The utility of telomere length as a biomarker has been established through studies demonstrating correlations between reduced telomere length and aging-related illnesses, including cardiovascular ailments (Nakashima, Ozono, Suyama, Sueda, Kambe, *et al.*, 2004), metabolic dysfunctions (Demissie *et al.*, 2006; Gardner *et al.*, 2005; Valdes *et al.*, 2005), cancer (Broberg, Bjork, Paulsson, Hoglund, & Albin, 2005), and dementia (Panossian *et al.*, 2003; von Zglinicki *et al.*, 2000). Short telomeres have also been linked to significantly higher mortality rates from infectious disease and heart disease (Cawthon, Smith, O'Brien, Sivatchenko, & Kerber, 2003). Epel *et al.* (2004) were the first to show that telomere length is inversely correlated with the duration of parenting a child with developmental disabilities.

Much research remains to be conducted. There is substantial individual variability in response to stressful life events, likely related to individual differences in stress appraisal and biological reactivity (Biondi & Picardi, 1999). Therefore, there is a need to understand both cellular aging and the self-perceived impact of stress among parental caregivers of children with developmental disabilities.

4.2. Allostatic load

A different approach to examining the physiology of stress is via a composite index, referred to as allostatic load. It is operationalized by biomarkers of cardiovascular, immune, and HPA axis dysfunction, with higher allostatic load indicating greater dysfunction (Singer & Ryff, 2001). Conceptually, allostatic load reflects the impact of psychosocial experience, including stress, on health, and has been shown to result in adverse health outcomes over the life course (McEwen, 1998, 2000; Singer & Ryff, 2001). Higher exposure to stress has been shown to result in poorer cardiovascular functioning, poorer immune response, and a more dysregulated HPA axis (Singer & Ryff, 2001). Higher levels of allostatic load are, in turn, associated with declines in physical and cognitive functioning (Seeman, Singer, Rowe, Horwitz, & McEwen, 1997) and an increased risk of mortality (Seeman, McEwen, Rowe, & Singer, 2001).

Although, on average, elevated levels of stress are associated with higher levels of allostatic load, there is great diversity in individual response to stress, including presumably in response to the challenge of parenting a child with a developmental disability. Composite measures of allostatic load have not yet been incorporated in studies of parents of children with developmental disabilities, although several first steps have been taken with components of allostatic load, including cortisol (reflective of HPA function; Seltzer *et al.*, 2009) and antibody response to pneumococcal vaccination (reflective of immune function; Gallagher *et al.*, 2009).

Finally, by incorporating measures such as allostatic load into research on parenting children with disabilities, and investigating individual differences,

it may also be possible to discover pathways to resiliency in such parents by identifying the characteristics of families whose allostatic load scores are normative.

4.3. Avenues for future research

Future research should prioritize longitudinal studies that have the potential to clarify the long-term impact of childhood developmental disability, and variations in parental risk, on parents' health across the life course. Virtually all studies on parents of children with developmental disabilities have examined only concurrent relationships between biomarkers and psychological outcomes. As a result, we do not know which factors move an individual from having a biological vulnerability to actually having an anxiety disorder, depression, or other adverse mental health outcome. Knowledge of such "triggering" factors will be critical for preventing adverse outcomes in parents of children with disabilities. It is likely that these factors will include both parental background genes and exposure to various stressors over the life course.

In addition, studies will need to employ interdisciplinary methodologies that allow for the examination of dynamic and complex effects of caregiving on the family. Current methods often do not account for the direct, indirect, and interactive effects of childhood developmental disability on the family. Future research should provide a critical link between subjective measures of parenting stress and objective measures of parents' physiological response in order to improve understanding of both disease risk among parent caregivers and the implications of parental psychobiology for the quality of life of children with developmental disabilities. Furthermore, quantitative studies—which examine the complex interrelationships between the physiological, behavioral, and social factors that contribute to caregiver vulnerability and resiliency, as well as qualitative studies, which examine the "lived experience" of parents of children with developmental disabilities—will be essential to develop interventions to improve the well-being of such families.

Finally, allostatic load, cortisol, and other biomarkers that serve as indices of the effects of caregiving demands on parents have the potential to be useful in evaluating the effects of various psychosocial and pharmacological treatments. In fact, these biomarkers may be especially sensitive indicators of treatment effectiveness as they reflect changes in adaptation to stressors that may precede changes in measurable psychological and behavioral outcomes. Although the inclusion of biomarkers in family interventions may not be immediately on the horizon, successful interventions that enable parents to better cope with stress may be enhanced by the inclusion of biomarkers, with better coping hopefully leading to altered physiological reactions to stress, and ultimately to reduction in mental and physical health symptoms.

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