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Modeling Family Dynamics in Children with Fragile X Syndrome

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Abstract Few studies have examined the impact of children with genetic disorders and their unaffected siblings on family functioning. In this study, the reciprocal causal links between problem behaviors and maternal distress were investigated in 150 families containing a child with fragile X syndrome (FXS) and an unaffected sibling. Both children's behavior problems appeared to have strong, direct effects on maternal distress, but maternal distress did not appear to have any reciprocal causal effects on either child's behavior problems. Surprisingly, there were no significant differences in the effects of the two children's behavior problems on maternal distress. These data suggest that the problem behaviors of children with FXS, as well as their unaffected siblings, can have a substantial and additive impact on maternal depression and anxiety. Future research efforts should employ longitudinal research designs to confirm these findings.

Keywords Problem behaviors · Maternal distress · Fragile X syndrome · Structural equation modeling

Introduction

Caring for a child with a developmental disability can have an adverse effect on family functioning (Dyson, 1997). Several investigators have reported decreased feelings of well-being (Essex, Seltzer, & Krauss, 1999), increased stress (Beckman, 1991) and marital conflict (Rivers & Stoneman, 2003; Willoughby & Glidden, 1995) in the parents of children with developmental disabilities. For example, Bristol and colleagues (Bristol, Gallagher, & Schloper, 1988) reported that the risk for depression in the mothers of children with developmental disabilities appeared to be twice as high as the risk for the mothers of typically developing children. In addition, the fathers of children with developmental disabilities reported significantly more marital difficulties than the fathers of typically developing children.

Investigators have also reported decreased sibling well-being (Gold, 1993; Rossiter & Sharpe, 2001) and negative effects on other family members (Hastings, 2003a) in families with children with developmental disabilities. The child's age, degree and type of disability, (Cameron & Orr, 1989; Orr, Cameron, Dobson, & Day, 1993), and severity of problem behaviors (Donenberg & Baker, 1993; Quine & Pahl, 1985; Rossiter & Sharpe, 2001) appear to influence the degree of distress that families experience (Mash & Johnston, 1983). Several investigators have also reported that caring for a child with autism appears to be more stressful than caring for a child without autism (Hastings, 2003b; Koegel et al., 1992; Konstantareas & Homatidis, 1989; Wolf, Noh, Fisman, & Speechley, 1989).

Researchers have begun to examine the impact of children with specific types of genetic disorders on maternal distress (Hodapp, Fidler, & Smith, 1998; Stores, Stores, Fellows, & Buckley, 1998). Children with genetic syndromes display a characteristic profile of intellectual, emotional and behavioral features–a so-called "behavioral phenotype" (Finegan, 1998). For example, children with Prader-Willi syndrome generally have mild mental retardation and display characteristic hyperphagia, food-hoarding and self-injurious behaviors (Thornton & Dawson, 1990). Children with Rett syndrome have severe to profound mental retardation and display a characteristic form of stereotypic behavior (Oliver, Murphy, Crayton, & Corbett, 1993), and children with

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FXS have mild to severe mental retardation and typically show a broad array of dysfunctional behaviors that include social avoidance, stereotypic behaviors and hyperactivity (Baumgardner, Reiss, Freund, & Abrams, 1995; Hall, DeBernardis, & Reiss, 2006).

Previous studies have reported that mothers of children with either fragile X syndrome (FXS) or Prader-Willi syndrome had higher levels of stress than mothers of typically developing children (Sarimski, 1997) and that the parents of girls with Rett syndrome had higher levels of marital dissatisfaction than a normative sample, as well as increased scores on the Parenting Stress Index (Perry, Sarlo-McGarvey, & Factor, 1992). However, these investigators found no association between the degree of developmental disability and parental stress scores. This may have resulted from a lack of variability in the degree of developmental disability in their sample, since all of the girls with Rett syndrome had severe to profound mental retardation. Given the greater variability in intellectual and behavioral functioning in children with FXS, a study of these families offers a unique opportunity to study the impact of the children's dysfunctional behaviors on levels of parental distress, as well as the potential impact of parental distress on the behavior of the children.

FXS affects approximately 1 in 4000 individuals in the general population (Crawford et al., 1999) and is the most common known cause of inherited mental retardation. The syndrome is caused by a mutation to the FMR1 gene on the long arm of the X chromosome at Xq27.3 (Verkerk et al., 1991). The gene contains a sequence of CGG nucleotides that repeats approximately 5 to 45 times in unaffected individuals but can expand to over one thousand repeats in persons affected by the disorder. If the sequence expands to between 55 and 200 repeats, individuals display few or no symptoms of the disorder, but are carriers of the premutation form of the gene. If, in contrast, the sequence expands to over 200 repeats, individuals have the full mutation and hyper-methylation of the promoter region of the gene occurs. The mutation prevents the production of the Fragile X Mental Retardation Protein (FMRP), a protein that is involved in synaptic pruning in the brain. As a result, the mutation produces impairments in brain development along with deficits in intellectual functioning and behavior. Girls with fragile X are less affected by the disorder because the mutation is present on only one of their two X chromosomes. As a result, brain levels of FMRP are higher, so the effect on the developing brain is less severe.

In a previous study of 75 boys and girls with FXS, Johnston and colleagues (Johnston et al., 2003) reported that the children's behavior problems were significantly associated with maternal distress, but their ages and degree of disability were not. Johnston et al. (2003) used the Parenting Stress Index (PSI) (Abidin, 1995) as a measure of maternal distress. This measure assesses maternal distress specifically related to parenting, so it is not surprising that there were associations between child behavior problems and parental distress (Baker et al., 2003). Johnston et al. (2003) did not examine the impact of unaffected siblings on maternal distress, perhaps because it is commonly assumed that unaffected siblings would be unlikely to cause maternal distress. In addition, these investigators did not consider the possibility that mothers and their children might be involved in a system of circular causality. In other words, the association between maternal distress and the children's behavior problems could result from a causal effect of the children on their mothers, a causal effect of the mothers on their children, or both.

Patterson (1982) has suggested that mothers and their children are often engaged in cyclical mutual reinforcement "traps." In other words, the behavior of the child affects the behavior of the mother, which in turn affects the behavior of the child, and so on (Patterson, 1982, 2002). This notion of reciprocal influence, or "control and counter-control" (Skinner, 1988), has been proposed as a crucial process in child and adult interactions, and may be responsible for the maintenance and escalation of problem behaviors in families with typically developing children as well as children with developmental disabilities (Carr & Durand, 1985; Hall, Oliver, & Murphy, 2001).

However, the analysis of systems with bidirectional, reciprocal causal effects presents the investigator with formidable statistical challenges. Any system in which a variable can affect itself indirectly through a circular feedback loop is called a "non-recursive" system (Hanushek & Jackson, 1977). Non-recursive systems cannot be estimated with ordinary least squares (OLS) statistical techniques such as multiple regression because the parameter estimates will be inconsistent (Hanushek & Jackson, 1977; Tomarken & Waller, 2003). This methodological limitation is not trivial, since the percent bias in parameter estimates can be infinite. Furthermore, these errors of estimation are non-detectable.

In contrast, structural equation modeling (SEM) techniques (Bollen, 1989; Burns & Nolen-Hoeksema, 1992; Tomarken & Baker, 2003) can help behavioral scientists evaluate systems with reciprocal feedback loops. In addition, SEM allows the investigator to estimate measurement models, to assess the adequacy of each theorized model, to compare competing models, to test for the effects of mediator or moderator variables, to provide consistent parameter estimates in the presence of missing data and to estimate non-recursive models. SEM techniques can also be used to detect the presence of unobserved "third" variables that create spurious correlations between two variables with no actual causal linkages.

However, it's important to understand what SEM can and cannot do. Although the investigator can say that the data are consistent or inconsistent with this or that causal model, the investigator cannot conclude with certainty that she or he has confirmed any model or causal effect. What the investigator hopes is that the data will be consistent with one model, and inconsistent with all reasonable alternative models. Promising results must be replicated in independent samples and can also be investigated more rigorously using experimental techniques as well as longitudinal analyses of changes in the variables over time.

In the present investigation, we wanted to extend the findings of the Johnston et al. (2003) study by investigating the simultaneous impact of a child with FXS, as well as an unaffected sibling, on measures of maternal distress, while controlling for any reciprocal causal effects of maternal distress on the children's behaviors. Specifically, we wanted to measure two important aspects of maternal distress, depression and anxiety, since there is some suggestion in the literature that individuals with the premutation form of the gene (i.e., CGG repeat lengths of 55 to 200) may be more likely to suffer from social anxiety and mood disorders (Franke et al., 1998; Thompson et al., 1994). In addition, we wanted to determine whether the child's intellectual functioning or behavior problems had a greater impact on maternal distress. We predicted that:

- Children with FXS would show more behavior problems than their unaffected siblings.
- The IQ's and problem behaviors of children with FXS would have a greater impact on maternal distress than the IQs and problem behaviors of their unaffected siblings.
- The IQs and problem behaviors of children with FXS would have independent and additive causal effects on maternal distress.
- Maternal distress would have a causal impact on the behaviors of both children, but the impact on the child with FXS would be greater.
- The impact of the family environment on the behaviors of the children with FXS would be greater than the impact on their unaffected siblings.

Method

Subjects

Participants were parent-child quartets from 150 families. Each quartet consisted of a child diagnosed with fragile X syndrome (FXS), an unaffected sibling and the biological mother and father of the children. Criteria for inclusion were: (1) a child had received a diagnosis of FXS, (2) an unaffected biological sibling also lived in the home, (3) the children were both at school, and (4) the mother of the children was a carrier of FXS. If families had more than one typically developing sibling in the target age range, a same-gender sibling closest in age to the child with FXS was chosen to take part in the study. If families had more than one child with FXS in the target age range,[1] a female child with FXS closest in age to a typically developing sibling was chosen. This was done in order to increase the number of females and gender-matched siblings in the sample. Demographic characteristics of the sample are shown in Table 1.

Table 1 Demographic characteristics: Means (*SD*) and percentages

Variable	
FXS gender (% boys)	62.7
Sibling gender (% boys)	46.7
FXS age (yrs.)	10.9 (3.2)
Sibling age (yrs.)	11.2 (3.2)
Sibling (% older than FXS)	56.0
Age difference between sibling and FXS (yrs.)	0.3 (3.4)
FXS-sibling pair	
Male-Male (%)	34.7
Female-Female (%)	25.3
Male-Female (%)	28.0
Female-Male (%)	12.0
Other siblings in family	0.8 (0.9)
Mother age (yrs.)	40.0 (4.9)
Mother education[a]	4.3 (1.0)
% Married	83.5
Income[b]	3.0 (0.9)
Ethnicity (% white)	82.7

[a] 1 = 8th grade or less, 2 = partial high school, 3 = high school graduate, 4 = partial college, 5 = college graduate, 6 = graduate degree.

[b] 1 = less than \$20,000, 2 = \$20,000 to \$50,000, 3 = \$50,000 to \$100,000, 4 = \$100,000 to \$150,000, 5 = over \$150,000.

Families were recruited from across the United States (West: 28.9%, South: 26.3%, Northcentral 24.6%, NorthEast: 15.8%) and Canada (4.4%) through the National Fragile X Foundation, flyers distributed to special interest groups, local contacts, and our research website. Written informed consent was obtained from the parents of all participants. 63 (55%) of the children with FXS were taking medication at the time of the study. Medications included stimulants (40% of the sample), antidepressants (27%), antihypertensives (4%), and antipsychotics (3%). 18% of the children with FXS were taking more than one class of medication. One unaffected sibling was taking a stimulant and an antidepressant medication.

Carrier status of all mothers was confirmed by PCR analysis. Diagnostic status of affected and unaffected children was confirmed by PCR and Southern Blot DNA analyses

[1] Some children with FXS also had siblings with FXS, although diagnosis was not always confirmed.

(Kimball Genetics, Inc). All children with FXS had CGG repeat lengths greater than 200 (full mutation range) while all unaffected children had CGG repeat lengths less than 40 (normal range). None of the siblings were therefore carriers of FXS. Twenty-one (22.3%) of the males with FXS and six (10.7%) of the females with FXS were mosaic for FXS.

Measures

Family information

Parents were asked to complete a family information form detailing the age and gender of family members, marital status, ethnicity, parent education, and family income.

Intellectual functioning

The Wechsler Intelligence Scale for Children–Third Edition (WISC-III) (Wechsler, 1991) and the Wechsler Adult Intelligence Scale–Third Edition (WAIS-III) (Wechsler, 1997) are standardized measures of intellectual functioning for children aged 6 to 16 years and for adults aged 17 years and over respectively. Each test contains 5 verbal subtests and 5 performance subtests yielding Performance IQ (PIQ), and Verbal IQ (VIQ) standard scores. Standard scores have a population mean of 100 and a standard deviation of 15. Twelve (12.8%) boys with FXS were unable to complete the IQ test and therefore were assigned a score of 46, the lowest possible score for VIQ and PIQ. A further 27 (28.7%) boys with FXS completed the test but received the lowest possible score. This "floor effect" could bias the results of the analyses. To control for this, VIQ and PIQ scores for all children were converted to an ordinal scale: IQ's of 46 were re-coded to "1", IQ's of 47 to 50 to "2", IQ's of 51 to 60 to "3", IQ's of 61 to 70 to "4" etc.[2]

Parent and teacher perceptions of child behavior problems

The Child Behavior Checklist (CBC) (Achenbach, 1991a) is a 118-item rating scale of behavior problems for children aged 4 to 18 years. Parents rate each item as "not true" (scored 0), "somewhat or sometimes true" (scored 1), or "very true or often true" (scored 2), taking the child's behavior over the past 6 months into account. The Externalizing scale (CBC-EXT) contains 33 items with 2 subscales: delinquent behavior (13 items; e.g., "swearing or obscene language") and aggressive behavior (20 items; e.g., "physically attacks people," "screams a lot"). The Externalizing scale *T* score was employed as the dependent measure. *T* scores have a population mean of 50 and a standard deviation of 10. Scores greater than 60 are considered to be in the "clinical range." Inter-rater reliability is .80 and test-retest reliability is .93 over a one-week period. The child's mother was the respondent.

The Teacher's Report Form (TRF) (Achenbach, 1991b) is a comparable 118-item rating scale of behavior problems for children aged 5 to 18. The scale is similar to the CBC but is filled out by teachers who have known the child for at least two months. Teachers score each item as "not true" (scored 0), "somewhat or sometimes true" (scored 1), or "very true or often true" (scored 2), taking the child's behavior over the past 2 months into account. The Externalizing scale (TRF-EXT) *T* score was employed as the dependent measure. Scores greater than 60 are considered to be in the "clinical range." Inter-rater reliability is .66 and test-retest reliability is .92 over a 15-day period. The child's school teacher was the respondent.

Maternal distress

The Symptom Checklist-90-R (SCL-90-R) (Derogatis, 1994) is a 90-item self-report inventory of psychological symptoms that have occurred over the past week. Respondents rate the intensity of each symptom from 0 (not at all) to 4 (extremely). The depression (DEP) and anxiety (ANX) scale *T* scores were used as dependent measures in this study. *T* scores have a population mean of 50 and a standard deviation of 10. Scores greater than 60 on the SCL-90 are considered to be in the "clinical range." Items from the depression subscale include "feeling hopeless about the future," "feeling everything is an effort" and "feelings of worthlessness." Items from the anxiety subscale include "suddenly scared for no reason," "feeling tense or keyed up" and "spells of terror or panic." Internal consistency of the depression and anxiety scales is .90 to .88 respectively, and the test-retest correlations are .75 and .80 over 10 weeks, respectively (Derogatis, 1994).

Family Environment Scale (FES) (Moos & Moos, 1994)

The FES is a 90-item self-report inventory concerning the quality of the family environment. The scale consists of nine positive subscales and one negative subscale, each with nine items: The positive subscales include Cohesion (e.g., "family members help and support one another"), Expressiveness (e.g., "we tell each other our personal problems"), Achievement orientation (e.g., "in our family we try hard to succeed"), Active-recreational (e.g., "we go to the movies, sports events, camping etc'), Independence (e.g., "in our family, we are encouraged to be independent"),

[2] We also performed the analyses treating the lowest scores as missing data. The results of these analyses were very similar.

Intellectual-cultural (e.g., we are interested in cultural activities"), Moral-religious ("we say prayer in our family"), Control (e.g., there are rules to follow in our family"), and Organization (e.g., "we are generally very neat and orderly"). The negative subscale is called Conflict (e.g., "we fight a lot in our family"). Items were scored on a five-point scale from "not at all" (scored 1) to "always" (scored 5). Mothers and fathers of the children filled the scales out independently. The Conflict subscale was not used because of the concern that it might be tautologically related to the children's problem behavior scales.[3] The total score on the nine positive subscales was used in this study (possible range = 81 to 405). On these nine subscales, typical families obtain a mean score of 280, with ratings averaged for the mother and father in each family (Plomin & De Fries, 1985).

Procedures

Packets of questionnaires were mailed to the parents approximately two weeks prior to an in-home visit. The packet contained a set of questionnaires with a cover letter containing instructions. An additional packet of questionnaires was addressed to each child's teacher and the parents were asked to give the envelope to the child's teacher. The packet contained a stamped return envelope so the teachers could mail the questionnaires directly to the research office. During the home visit, two research assistants administered the WISC-III or WAIS-III, as appropriate, to each child on the same day and collected the questionnaires. A $100 honorarium was paid to each family upon completion of their participation.

Data analysis

Statistical analyses were conducted with AMOS, Version 6.0 (Arbuckle, 2005) using maximum likelihood methods. Several fit indices were used to evaluate model fit including the χ^2, the χ^2/DF, the Tucker-Lewis Index (TLI) (Bentler & Bonett, 1980), the Comparative Fit Index (CFI; Bentler, 1990) and the Root Mean Square Error of Approximation (RMSEA) (Browne & Cudeck, 1993) with a 90% confidence limit. The TLI, CFI and RMSEA fit indices are commonly recommended and are less affected by sample size than the chi-square test (Tomarken & Waller, 2003). CFI or TLI values close to 1.0 indicate a good fit while Browne and Cudeck (1993) have advised that RMSEA values below .05 indicate a close fit of a model in relation to the degrees of freedom, whereas values greater than .1 indicate that a model should not be accepted. Changes in chi-square values relative to changes in degrees of freedom (chi-square difference tests) were used to compare nested models. The significance levels of model parameters were determined by examining the critical ratios (*CR*), a statistic comparable to a *t* statistic with infinite degrees of freedom. Missing data models were estimated using the direct full-information maximum likelihood method (Arbuckle, 1996).[4] Differences in mean scores on the scales were examined using χ^2 difference tests, since the sample means in each group were estimated in AMOS using Direct FIML. In each nested test, the sample means in each group were set to be the same. If the means are significantly different in the groups, the nested test will detect this and provide the precise probability value for the difference.

Results

The variance-covariance matrix for the variables is shown in the Appendix. Table 2 shows the mean scores, standard deviations and ranges for the IQ and behavioral measures broken down by gender and diagnosis. The Mean VIQ and PIQ's of the boys with FXS were significantly lower than the girls with FXS, and the mean TRF-EXT scores of the boys with FXS were significantly higher. Mean VIQ and PIQ scores and mean CBC-EXT and TRF-EXT scores of the unaffected boys and girls were not significantly different from each other. The VIQs and PIQs of the combined group of boys and girls with FXS were significantly lower than the VIQs and PIQs of their unaffected siblings, as expected. In addition, the CBC-EXT and TRF-EXT scores of the children with FXS were significantly higher than their unaffected siblings.

The mean mothers' score on the FES was 272.75 ($SD = 21.59$, range = 213 to 331) while the mean fathers' score was 268.83 ($SD = 19.44$, range = 216 to 312). The mean maternal DEP scale score on the SCL-90 was 52.71 ($SD = 10.36$, range = 34 to 80) and the mean ANX scale score was 48.29 ($SD = 9.39$, range = 37 to 72).

Measurement model

The measurement model is presented in Fig. 1. In this model, circles represent unobserved variables (factors and error terms) and rectangles represent observed variables

[3] The correlation between the Conflict subscale of the FES and the CBC-EXT scale of the CBC was 0.23 for children with FXS and 0.46 for unaffected siblings.

[4] This method can provide consistent parameter estimates in the presence of missing data, even when the data are not missing completely at random. Three alternative methods of estimating models with missing data include mean substitution, listwise deletion, and pairwise deletion. These methods are less efficient and provide consistent estimates only under the stronger assumption that any missing data are missing completely at random.

Table 2 Means, standard deviations (SD) and ranges for the IQ and behavior measures in children with FXS and unaffected siblings, with chi-square tests of the assumption that there were no significant differences in each mean across groups

Measure			χ^2	p	Effect size
	Boys with FXS ($N = 94$)	Girls with FXS ($N = 56$)			
VIQ[a]					
M	2.01	5.23	68.49	<0.001	1.91
SD	1.26	2.02			
range	1–8	2–9			
PIQ[a]					
M	2.02	5.16	70.58	<0.001	2.02
SD	1.16	1.87			
range	1–7	2–10			
CBC-EXT					
M	52.99	50.02	2.48	n.s.	0.28
SD	9.21	12.05			
range	30–71	32–75			
TRF-EXT					
M	59.02	52.85	16.25	<0.001	0.73
SD	7.66	9.13			
range	48–82	42–71			
	Unaffected boys ($N = 70$)	Unaffected girls ($N = 80$)			
VIQ[a]					
M	8.17	8.28	0.25	n.s.	0.08
SD	1.34	1.25			
range	4–11	5–11			
PIQ[a]					
M	8.13	8.24	0.24	n.s.	0.08
SD	1.42	1.25			
range	5–11	5–11			
CBC-EXT					
M	47.15	43.74	3.82	0.05	0.32
SD	10.79	10.38			
range	30–73	32–69			
TRF-EXT					
M	48.72	47.25	0.82	n.s.	0.15
SD	11.63	7.60			
range	39–80	39–65			
	Boys and girls with FXS ($N = 150$)	Unaffected boys and girls ($N = 150$)			
VIQ[a]					
M	3.21	8.23	252.44	<0.001	2.75
SD	2.21	1.35			
range	1–9	4–11			
PIQ[a]					
M	3.19	8.19	255.50	<0.001	2.85
SD	2.08	1.35			
range	1–9	5–11			
CBC-EXT					
M	51.95	45.34	45.53	<0.001	0.63
SD	10.41	10.66			
range	30–75	30–73			
TRF-EXT					
M	56.77	48.08	52.86	<0.001	0.94
SD	8.82	9.68			
range	42–82	39–80			

Effect sizes are also shown.

Note. VIQ: Verbal IQ; PIQ: Performance IQ; CBC EXT: Child Behavior Checklist - Externalizing subscale; TRF EXT: Teacher Report Form–Externalizing subscale.

[a]VIQ and PIQ scores were converted to an ordinal scale where 1 = 46, 2 = 47–50, 3 = 51–60, 4 = 61–70, 5 = 71–80, 6 = 81–90, 7 = 91–100, 8 = 101–110, 9 = 111–120, 10 = 121–130, 11 = 131–140.

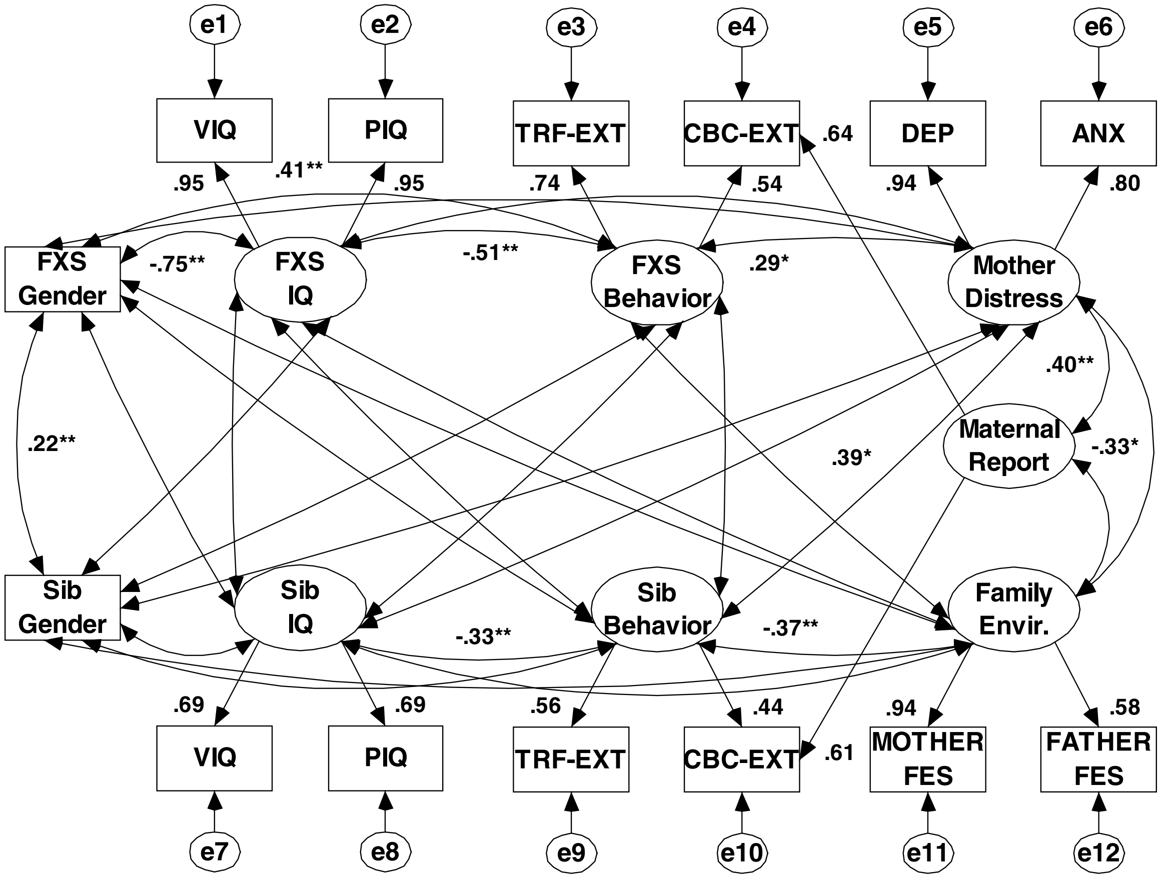

Fig. 1 Measurement model illustrating the factor structure for the IQ, behavior problems, family environment and maternal distress factors in children with FXS and their unaffected siblings. E1 to E12 are error terms for the scales. Two-headed arrows represent correlations, and one-headed arrows represent directional effects. Factor loadings are placed next to each factor indicator. *R*-square values for each indicator can be obtained by squaring the standardized factor loadings. Only significant correlations are shown. $^{*}p < .05$; $^{**}p < .01$

(scale scores). The genders of the siblings are coded 0 for females and 1 for males. One-headed arrows represent causal effects, and two-headed arrows represent correlations.

The PIQ and VIQ scales load on the FXS IQ factor for children with FXS and on the Sib IQ factor for the unaffected siblings. The TRF-EXT and CBC-EXT scales load on the FXS Behavior and Sib Behavior factors. The DEP and ANX scales of the SCL-90 load on the Mother Distress factor. The parents' estimates of the family environment (MOTHER FES and FATHER FES) load on the Family Environment factor. E1–E12 are the error terms for the measures.[5] A "Maternal Report" latent variable was also included in the model because the mothers filled out the CBC-EXT scales on both of their children. Therefore, these two scales might be expected to share systematic variance.[6] The measurement model was identified by setting one unstandardized factor loading for each factor (i.e., PIQ, CBC-EXT, Father FES, and ANX variables) to 1.0. The unstandardized factor loadings for the error terms were also set to 1.0.

The fit of the measurement model was good [$\chi^2(48, N = 150) = 46.37$, $p = .54$; $\chi^2/DF = 0.97$; TLI = 1.00; CFI = 1.00; RMSEA = 0.00 (0.00–0.05)]. A nested test was conducted in which six restrictions were applied to the measurement model. In this restricted model, the regression coefficients for the VIQ variables were declared to be

[5] Some investigators prefer to call these terms "Other Causes," since they contain all the unexplained variance of each observed variable, including unknown systematic causes as well as random measurement errors.

[6] One cannot assume that this is actually a method factor resulting from maternal bias. It could also represent the fact that the two children's behaviors at home may be more highly correlated than their behaviors at school. This would not be surprising, since the home environment as defined here is identical, while the two school environments for the children will be significantly different. This "method factor" could just as easily be represented as a correlated error term. Statistically, this would be an alternative but equivalent representation of the same phenomenon.

1.0 in both FXS IQ and Sib IQ factors. In addition, within each factor, the intercepts and error variances for the PIQ and VIQ variables were set to be the same. The increase in chi-square in this nested model was not significant [$\chi^2(6, N=150)=2.24$, $p=.90$], indicating that both IQ factors were super-parallel.[7] A second nested test was conducted to determine whether the factor loadings for the TRF-EXT scale in the children with FXS and in their unaffected siblings were equal. The increase in chi-square was not significant [$\chi^2(1, N=150)=.21$, $p=.65$], indicating that the factor structures were the same. The fit of the final measurement model, with the seven additional restrictions, was excellent [$\chi^2(55, N=150)=48.82$, $p=.71$, $\chi^2/DF=0.89$; TLI = 1.02; CFI = 1.00; RMSEA = 0.00 (0.00–0.04)].

Gender was significantly correlated with the IQ factor in the children with FXS [$r(150)=-0.75$, $p<.001$], as expected, since boys with FXS have substantially lower IQs than girls. In contrast, gender and IQ were not significantly correlated in the unaffected siblings, as expected. Gender was positively correlated with the behavior factor in children with FXS ($r(150)=.41$, $p<.001$) indicating that males with FXS showed greater behavior problems than females with FXS.

The behavior factors were negatively correlated with the IQ factors in the children with FXS ($r(150)=-0.51$, $p<.001$) and in their siblings ($r(150)=-0.33$, $p<.001$). The Mother Distress factor was positively correlated with the FXS Behavior factor ($r(150)=0.29$, $p<.05$) and with the Sib Behavior factor ($r(150)=0.39$, $p<.001$), indicating that higher levels of dysfunctional behaviors were associated with higher levels of maternal distress in both groups of children. The Family Environment factor was significantly correlated with the Sib Behavior factor [$r(150)=-0.37$, $p<.001$] indicating that a positive family environment was associated with lower levels of problem behaviors in the unaffected siblings, but was not significantly correlated with the FXS Behavior factor. Finally, the Family Environment factor was negatively correlated with the Mother Distress factor ($r(150)=-0.33$, $p<.05$) indicating that a positive family environment was associated with lower levels of maternal distress.

In summary, the measurement model indicated that lower IQs were associated with more behavior problems in the affected and unaffected children. Contrary to predictions, maternal distress was not significantly correlated with the IQs of the affected or unaffected children, but was significantly correlated with the behavior factors of both groups of children. In addition, the Family Environment factor was associated with fewer behavior problems in the unaffected children, but not in the children with FXS.

Structural equation model

The correlations in the measurement model provide no information about the causal links between these variables, or the sizes of these effects. For example, we could ask why the behavior factors were positively correlated with maternal distress. This correlation could result from the effects of the children's behaviors on maternal distress, or from the effect of maternal distress on the children's behaviors, or from an unknown third variable with simultaneous causal effects on the children's behavior as well as maternal distress.

In the structural equation model in Fig. 2, the genders of both siblings are exogenous variables with direct effects on the IQ factors of the children. The IQ factors, in turn, have direct effects on the corresponding behavior factors.[8] The Family Environment factor also has direct effects on the behavior factors. The relationship between the two behavior factors and the Mother Distress factor are represented by reciprocal causal loops. E1 to E12 are the error terms for the observed variables, and E13 to E17 represent the errors terms for the factors.

The fit of the model was excellent [$\chi^2(75, N=150)=68.87$, $p=.68$; $\chi^2/DF=.92$; TLI = 1.01; CFI = 1.00; RMSEA = 0.00 (0.00–0.04)] and the fit of the structural component of the model was also excellent [$\chi^2(20, N=150)=20.05$, $p=.45$][9] (Tomarken & Waller, 2003).

Effects of child IQ and family environment on the behavior factors

FXS Gender accounted for 56% of the variance in the FXS IQ factor [$B=-3.18$ ($se=.25$), $p<.0001$] but the effect of Sib Gender on the Sib IQ factor was not significant, as expected. There were significant negative effects of the IQ factors on the behavior factors in the children with FXS [$B=-1.42$ ($se=0.32$), $p<.0001$)] as well as their unaffected siblings [$B=-2.39$ ($se=1.05$), $p<.05$)]. When these coefficients were declared equal, the increase in chi-square was not significant [$\chi^2(1, N=150)=0.85$, $p=.36$]. The negative regression coefficient (-1.52) indicated that lower IQ scores

[7] In a tau-equivalent factor, the regression coefficient for all the indicators are equal, indicating that they all contain the same amount of factor variance. In a parallel factor, all the error variances are also equal, indicating they all have identical r-square values. In a super parallel factor, the regression coefficients, error variances, and intercepts for all the indicators are equal.

[8] One could argue that the behavior factors might conceivably have causal effects on the IQ factors. In fact, some investigators have proposed such a causal linkage. We tested this possibility in a non-recursive model and found that it was grossly inconsistent with the data, and could be rejected.

[9] This test was performed by subtracting the χ^2 and df of the measurement model from the χ^2 and df of the structural model.

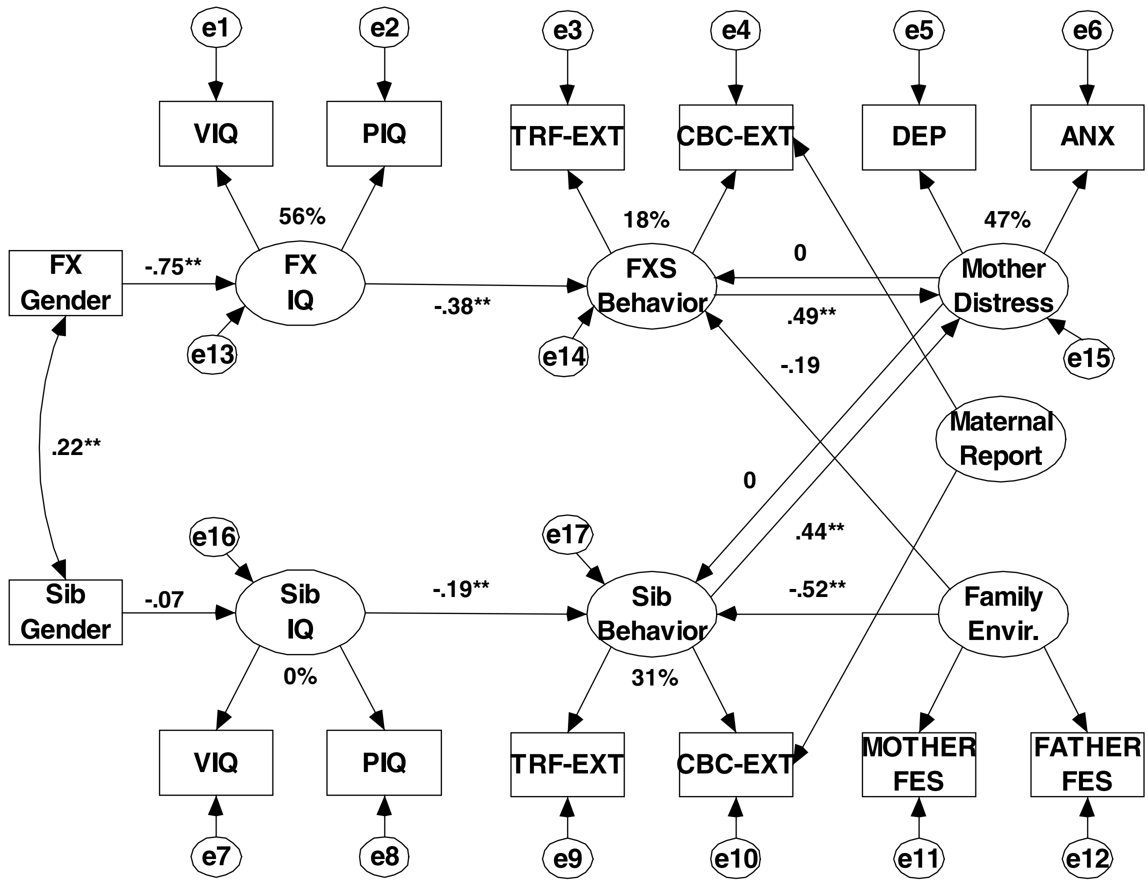

Fig. 2 Structural equation model of the reciprocal effects linking the behavior factors with the Maternal Distress factor. E1 to E12 are the error terms for the factor indicators, while E13 to E17 are the error terms for the factors. Directional effects are next to one-headed arrows, *R*-square values are indicated next to the dependent variables, and correlations are indicated next to two-headed arrows. $^{*}p < .05$; $^{**}p < .01$

were associated with significantly more behavior problems in both groups of children.

To illustrate the magnitude of the effect of IQ on the behavior of the children, we can imagine two children with FXS whose IQs differ by 3 ordinal points (i.e., approximately 30 standardized IQ points). This difference will be associated with a difference of approximately 4.5 points (3×1.52) on their CBC-EXT scores and 2.7 points on their TRF-EXT scores ($3 \times 1.52 \times .60$, since the unstandardized factor loading on the TRF-EXT scale was .60). Given the substantial range on the CBC-EXT and TRF-EXT scales in Table 2, the size of this effect would appear to be small.

There was a significant effect of the Family Environment factor on the Sib Behavior factor [$B = -0.29$ ($se = .09$), $p < .0001$)], but not on the FXS Behavior factor ($p > .05$). These findings indicated that a positive family environment was only associated with improved behavior in the unaffected siblings.

In the model in Fig. 2, gender has only indirect effects on the children's behavior. One could argue that gender might also have direct effects on the children's behavior. For example, boys might exhibit more problem behaviors than girls, when controlling for IQ and family environment. In order to test this possibility, two additional paths were added to the model, directly linking gender with the two behavior factors. When these paths were set to zero, the increase in chi-square for the model was not significant [$\chi^2(2, N = 150) = 2.45$, $p = .29$]. These findings were consistent with the hypothesis that the effects of gender on the behavior of both groups of children were indirect, and mediated by their effects on the IQs of the affected and unaffected children.

Reciprocal effects linking the children's behaviors with maternal distress

To test the direction of the causal effects linking the two behavior factors with maternal distress, two nested tests were conducted. In the first test, the effects of the Mother Distress factor on the child behavior factors were set to zero. The increase in chi-square was not significant [χ^2(2,

$N = 150) = 4.87, p = .09$]. This result was not consistent with our prediction that maternal distress would have causal effects on the children's behavior.

In the second test, the effects of the two behavior factors on the Mother Distress factor were set to zero. The increase in chi-square was highly significant [$\chi^2(2, N = 150) = 17.74$, $p < .0001$] and was consistent with the hypothesis that increases in the children's behavior problems would lead to increases in maternal distress. The unstandardized parameter estimate for the effects of the behavior factors on the Mother Distress factor were 0.44 ($SE = 0.13$, $p < .0001$) in the FXS group and 0.53 ($SE = 0.18$, $p < .005$) in the unaffected sibling group. When these two regression coefficients were declared to be equal, the increase in chi-square was not significant [$\chi^2(1, N = 150) = .26$, $p = .61$]. This result indicated that there were no significant differences in the effects of the behavior of the two groups of children on maternal distress when the effects of maternal distress on the two behavior factors were controlled for. The two behavior factors accounted for 47% of the variance in the Mother Distress factor, a surprisingly large amount of the variance.

The causal effect of behavior on maternal distress was $B = .47$ ($SE = .11$, $p < 0.001$) in both groups of children. To illustrate the magnitude of this effect, we can imagine two unaffected children whose CBC-EXT scores differed by 20 points (i.e., two standard deviations). This difference will be associated with a difference of approximately 9.4 points ($20 \times .47 \times 1.0$) on the mothers' SCL-90 anxiety scores (since 1.0 was the unstandardized factor loading for the ANX variable) and 12.6 points ($20 \times .47 \times 1.34$) on the mothers' SCL-90 depression scores (since 1.34 was the unstandardized factor loading for the DEP variable). Given that the mean scores for mothers on the ANX and DEP scales were approximately 48 and 53, respectively, these increases would appear to be substantial, and could push a mother's scores into the clinical range. Furthermore, the increase in maternal distress resulting from the behavior problems of the children with FXS would be additive.[10]

In these models, the effect of the children's IQs on the mothers' distress scores are indirect, and mediated entirely by their effects on the behaviors of the children. One could argue that the IQs of the children might have direct causal effects on maternal distress. For example, the mothers of children with lower IQs might experience more distress, even when controlling for the effects of the children's behavior and family environment.

To test this possibility, two additional causal effects were included in the model, linking the FXS IQ and Sib IQ factors to Mother Distress. When these parameters were set to zero, the increase in chi-square was not significant [$\chi^2(2, N = 150) = 3.00, p = .22$]. In contrast, when the effects from the two behavior factors to Mother Distress were set to zero, the increase in chi-square was highly significant [$\chi^2(2, N = 150) = 35.86$, $p < .0001$]. These findings were consistent with the hypothesis that the effects of the children's IQs on maternal distress were indirect, and mediated by their effects on the children's behavior.

Finally, it is possible that the behaviors of the two children could have had indirect effects on maternal distress via their effects on the quality of the family environment. That is, the children's behavior problems could lower the quality of the family environment and this, in turn, could trigger maternal stress. To test this possibility, two causal paths from the behavior factors to the Family Environment factor, as well as a causal path from the Family Environment factor to the Mother Distress factor, were included in the model. The fit of the model was excellent [$\chi^2(75, N = 150) = 72.78$, $p = .55$; $\chi^2/DF = .97$; TLI = 1.0; CFI = 1.00; RMSEA = 0.00 (0.00–0.04)], but the effect of the family Environment factor on maternal distress was not significant. In addition, when the effect of the Family Environment on maternal distress was set to zero, the increase in chi-square was not significant [$\chi^2(2, N = 150) = 0.003$, $p = 0.95$]. In contrast, when the effect of the behavior factors on maternal stress were set to zero, the increase in chi-square was highly significant [$\chi^2(2, N = 150) = 22.76, p < .0001$]. These findings were consistent with the hypothesis that the effects of the behavior factors on maternal distress were direct, and were not mediated via their effects on the quality of the family environment.

Discussion

In this study we used structural equation modeling techniques to examine the simultaneous reciprocal effects linking the behavior problems of children with FXS and their unaffected siblings with the emotional distress of their mothers. As expected, boys with FXS had lower IQ scores and more behavior problems than girls with FXS. When compared to their unaffected siblings, children with FXS had lower IQ's and more behavior problems. Although these findings were consistent with our first prediction, none of our other predictions were supported by the data. Specifically, we found that:

- The IQ's of the children with FXS did not appear to have any direct effects on maternal distress.

[10] Five females and 15 males with FXS scored in the "autism" range on the Autism Behavior Checklist (Krug, Arick, & Almond, 1993) and these children had significantly elevated scores on the CBC-EXT and TRF-EXT. Inclusion of autism status in the model, however, indicated that children who showed symptoms of autism did not directly influence mothers' level of anxiety or depressive symptoms.

- The problem behaviors of the children with FXS did not appear to have a greater impact on maternal distress than the behaviors of their unaffected siblings. In fact, the mothers appeared to be equally affected by both children, and these effects were surprisingly large.
- Maternal distress did not appear to have any effects on the dysfunctional behaviors of either child.
- The family environment appeared to have a significant impact only on the behaviors of the unaffected children.

While gender is not ordinarily thought to have significant causal effects on IQ, gender had large effects on IQ in the FXS group, as expected. The mutation in the gene that causes FXS switches off the production of FMRP, a protein that is involved in synaptic pruning in the brain. The deficiency of this protein in the brain causes cognitive dysfunction. Because females have two X chromosomes, they are less affected by FXS because the unaffected X chromosome still produces some FMRP.[11]

The effect of IQ on behavior was small in both groups of children. This indicates that genetic or environmental variables that were not included in the model explain the majority of the variance in the children's behavior problems. There were no direct effects of the IQs of the children on maternal distress, when controlling for the children's behavior, confirming the results of a previous studies by Johnston et al. (2003) and Baker et al. (2003).

One surprising finding in this study was that maternal distress appeared to be equally influenced by the behavior problems of the children with FXS and their unaffected siblings. This finding indicates that the mothers are equally sensitive to the behaviors of both children and that the behavior problems of the affected and unaffected siblings should be considered in studies of families with children with developmental disabilities. In addition, behavioral interventions that lead to improvements in the behavior problems of the children should lead to reductions in maternal distress.

We were equally surprised that maternal distress did not appear to influence the dysfunctional behaviors of either child, and that the effects of the family environment were significantly associated with only the behaviors of the unaffected children. This suggests that the problematic behaviors of children with FXS may be relatively immune to family influences, at least as measured by this instrument. Additional studies will be needed to confirm our result and to evaluate the effects of a stressful family environment on the behaviors of the children, along with studies of the parenting strategies that may be effective in modifying the problematic behaviors of children with FXS.

The mothers of the children in this study were carriers of the premutation form of the gene (i.e., one of their X chromosomes contained between 60 and 180 repeats of the CGG sequence). It has been suggested that premutation mothers may be "at risk" for psychological distress, particularly those with a high number of CGG repeats (Johnston et al., 2001). It is possible that some proportion of the unexplained variance in maternal distress may have been explained by the premutation status of the mothers. To date however, studies of premutation-associated clinical features are inconclusive and methodological issues (e.g., sample size, potential ascertainment bias, control groups and interview procedures) limit the conclusions that can be drawn from these studies. Johnston et al. (2001) reported that premutation mothers with larger trinucleotide CGG repeat lengths were more likely to suffer from depression (as measured by the depression subscale of the SCL). However, this association was modest ($r = .22$) and no other correlations were found between CGG repeat size and the other SCL subscales. This raises the possibility that this finding may be the result of chance. In our sample, the correlation between mother CGG repeat size and the DEP and ANX scales were not significant [$r(150) = .13$ and .11 respectively].

Although the IQ measures we employed were fairly precise, the behavior problems and distress scales assess a variety of dimensions simultaneously. Further studies will be needed to determine which aspect of the children's behaviors were the most strongly influenced by their IQs, and what types of behavioral variables, in turn, had the strongest effects on maternal distress. Although the means of the behavior scales and maternal distress measures were not in the clinically significant range, the variance in these measures was substantial. Still, it is possible that causal effects of maternal distress on the children's behaviors might have been detected with a larger group with a greater range on the behavioral and maternal distress measures. In addition, it is possible that components of maternal distress that we did not measure could affect their children's behaviors.

Omitted variables can significantly bias estimates of effects in experimental or survey research. Furthermore, included variables that appear to have significant causal effects may be proxies for other variables not included in the model. If the basic pattern we report can be replicated and confirmed in other studies, more refined analyses will be needed. For example, are there certain aspects of intelligence that have the strongest causal effects on behavior, and what aspects of behavior are the most affected by intelligence?

Another important limitation is that the design of the study was cross-sectional (Cole & Maxwell, 2003). Confirming these results with longitudinal studies could be of considerable value since maternal distress could affect the children's behaviors over time (Baker et al., 2003). In our study, we

[11] We measured FMR Protein levels in these children, and plan to report those results separately.

found that child behavior problems also affected maternal distress in the short-term.

Although we made every effort to ensure that our sample was representative of the population of families with FXS, the sample consisted primarily of white middle-class families. Inclusion of socioeconomic status (SES) in the model, as measured by parental education and income did not significantly influence the parameter estimates. Future studies with a greater ethnic and socioeconomic diversity would help establish the generalizability of these results. Barry and colleagues (Barry, Dunlap, Cotten, Lochman, & Wells, 2005) reported that low SES was significantly associated with both mother- and teacher-reported behavior problems in 215 typically developing boys aged 9 to 12 years. However, we were not able to confirm this finding in our study, perhaps due to range restriction problems. Perhaps even more important would be the replication of our model in families without children with FXS, so that we can determine whether the results reported here will generalize to the population as a whole. Such a confirmation might contribute significantly to our understanding of the causes of depression and anxiety in women.

Our study was limited in several other ways. First, there were additional siblings in some households, some of whom may have had FXS. We do not know whether the behavior problems of these additional children would have had additive effects on maternal distress. When the number of additional siblings living in the household was introduced in the model, it was not associated with maternal distress. Second, it should be noted that the mothers filled out the behavior scales for both children. To overcome the problem of source variance, we included the teachers' estimates of both children's behavior problems at school and analyzed the variance shared by the two measures, since this variance was not likely to be influenced by maternal bias. Furthermore, this shared variance is the component of the child's behavior that is stable across two different environments, and is much less likely to be influenced by maternal bias. Future studies could profitably employ ratings of the children's behaviors from multiple sources, as well as direct observation by researchers.

In our study, maternal distress was directly influenced by the severity of the children's behavior problems, and this effect was large. One clinical implication might be that any strategy that leads to an improvement in the dysfunctional behaviors of the children should lead to an improvement in maternal depression and anxiety. In children with autism, (Lovaas, 1987) found that behavioral treatments designed to strengthen the children's adaptive behaviors and decrease problem behaviors were successful if they were applied early in the child's life (Cohen, Amerine-Dickens, & Smith, 2006). If similar strategies can be successfully employed in families with children with FXS, it might reduce family dysfunction.

Appendix 1 Variance-covariance matrix

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
FXS														
1. GENDER	0.23													
2. VIQ	−0.75	4.83												
3. PIQ	−0.73	4.25	4.53											
4. CBC EXT	0.69	−5.98	−5.67	104.19										
5. TRF EXT	1.45	−6.47	−6.63	34.16	59.78									
Sibling														
6. GENDER	0.05	−0.13	−0.15	0.28	−0.12	0.25								
7. VIQ	−0.04	0.42	0.43	−1.52	−1.05	−0.03	1.65							
8. PIQ	−0.02	0.24	0.38	−2.72	−0.38	−0.03	0.81	1.71						
9. CBC EXT	−0.29	−0.16	−0.73	49.46	16.91	0.84	−2.27	−1.96	110.73					
10. TRF EXT	−0.02	1.94	1.53	−1.77	3.33	0.38	−1.70	−0.82	20.40	73.75				
Parent														
11. Mother FES	−0.09	3.69	3.64	−36.70	−10.84	−0.32	1.27	0.14	−73.55	−29.01	462.42			
12. Father FES	−0.39	4.08	5.30	−13.03	−6.46	−1.32	0.58	−0.56	−39.69	15.26	220.29	378.16		
13. DEP	0.14	−2.19	−2.68	44.28	16.13	−0.08	−1.87	−2.09	37.95	20.64	−68.23	−33.69	106.81	
14. ANX	0.21	−1.60	−1.89	36.24	7.91	0.22	−1.31	−2.11	35.56	13.91	−39.99	−29.81	73.63	87.87

Note. VIQ: Verbal IQ; PIQ: Performance IQ; CBC EXT: Child Behavior Checklist–Externalizing subscale; TRF EXT: Teacher Report Form–Externalizing subscale; FES: Family Environment Scale; DEP: Symptom Checklist–Depression subscale; ANX: Symptom Checklist–Anxiety subscale.

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