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Autistic Behavior, FMR1 Protein, and Developmental Trajectories in Young Males with Fragile X Syndrome

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In the context of a longitudinal study, we assessed the relationship between ratings of autistic behavior, FMR1 protein expression (FMRP), and the developmental trajectories of 55 young males with fragile X syndrome. Autistic behavior, as measured by the Childhood Autism Rating Scale, was not related to FMRP expression. However, autistic behavior was a significant predictor of both developmental status and developmental change. Boys with both autistic behavior and fragile X syndrome functioned at significantly lower levels of development and grew at significantly slower rates than those without autistic behavior. FMRP expression accounted for less variance in developmental level than did autistic behavior, and was not significantly related to slope (developmental change over time). No autistic behavior × FMRP interaction was found.

KEY WORDS: FMR1 protein expression; fragile X; autistic behavior.

INTRODUCTION

Males with fragile X syndrome (FXS), an inherited disorder that results in characteristic physical features, mental retardation, and behavioral styles, often exhibit behaviors consistent with those seen in males with autism. Sometimes these behaviors are so significant and persistent as to result in a concurrent diagnosis of autism or the description of behavior as autistic-like. Currently the rate of autism in the population of individuals with fragile X syndrome is estimated at somewhere between 15 and 25% (Bailey, Mesibov, *et al.*, 1998; Bregman, Dykens, Watson, Ort, & Leckman, 1987; Dykens & Volkmar, 1997; Hagerman, Jackson, Levitas, Rimland, & Braden, 1986; Levitas, *et al.*, 1983; Reiss & Freund, 1990; Turk & Graham, 1997).

Why children with FXS exhibit autistic behavior is unknown. FXS results from an expansion of CGG nucleotide repeats at Xq27.3 on the long arm of the X chromosome, effectively reducing or eliminating the production of the FMR1 protein (FMRP) known to be essential for normal brain function (Small & Warren, 1995; Weiler *et al.*, 1997). FMRP expression has been shown to vary in persons with FXS, and this variation accounts for some of the variability seen in developmental function and growth (Bailey, Hatton, Tassone, Skinner, & Taylor, 2001; Tassone *et al.*, 1999). A logical inference is that the absence of FMRP somehow relates to autistic behavior, but the mechanism by which this occurs is unknown. Cohen (1995b) suggested that the cause might be hyperarousal of the autonomic nervous system resulting in heightened anxiety, especially as evidenced in social situations, changes in routines, and demanding tasks.

Also unknown is if autism is a part of the spectrum of FXS, if FXS is part of the spectrum of autism, or if they are two distinct disorders with an increased likelihood of co-occurrence if an individual has FXS (Cohen, Sudhalter, Pfadt, & Jenkins, 1991; Feinstein & Reiss,

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1998). Sudhalter (1996) has argued that despite apparent similarities between individuals with FXS and individuals with autism, the two groups differ fundamentally in many ways, especially with regard to social and communication skills. For example, boys with FXS have been described as socially shy, playful, and conversational, whereas boys with autism have been described as socially oblivious, not playful, and exhibiting little in the way of conversational skills (Sudhalter, 1996).

What are the developmental consequences of having both FXS and autistic behavior? Each disorder results in significant developmental delays evident in the early childhood years. Cross-sectional and longitudinal studies document a wide range of delays in both fragile X syndrome (Bailey, Hatton, & Skinner, 1998; Fisch *et al.*, 1996) and autism (Bailey, Phillips, & Rutter, 1996; Bristol *et al.*, 1996), with both disorders typically resulting in moderate to severe delays. The expected consequence of having both would be development that is impaired to a greater extent than having FXS alone. Only a few studies have addressed this question and typically only as part of a larger investigation of autism status in FXS, but those that have reported relevant data suggest that indeed this assumption may be true. In a study of 50 males with fragile X syndrome, Hagerman *et al.* (1986) found that the 15 males who met the criteria for autism using the Autism Behavior Checklist scored an average of 10 IQ points lower than the males who did not meet the criteria for autism. Reiss and Freund (1990) reported no statistically significant differences between autistic and nonautistic males with FXS, but observed that with one exception, "all fragile X males who had a past or present diagnosis of autism disorder were in the lower composite IQ group" (p. 887). Cohen (1995a) assessed 109 males with FXS, 30 (27.5%) of whom met the DSM-III-R criteria for autistic disorder. A significant difference was found in age-adjusted IQ scores, such that males with FXS and autism had IQ scores that were 20 points lower than males with FXS only. Males with both autism and FXS also were significantly lower on all domains of the Vineland Adaptive Behavior Scales, and a regression analysis (based on cross-sectional data) suggested that slope differences were also evident in all domains.

More recently, Turk and Graham (1997) found a 15-point difference in Vineland developmental quotient scores of FXS males with and without autism. Bailey, Mesibov, *et al.* (1998), in a cross-sectional study of males with FXS, found that ratings on the Childhood Autism Rating Scale (CARS; Schopler, Reichler, & Renner, 1988) accounted for more than 50% of the variance in developmental test scores, with higher ratings of autistic behavior associated with lower developmental scores. And Bailey, Hatton, Mesibov, Ament, and Skinner (2000), in an age-matched sample, found that children with both autism and FXS were substantially more delayed than children with autism alone or FXS alone.

The research to date has been limited to correlations or comparisons between autism status and developmental status at a single point in time. Also, no research has examined the relationship between FMRP expression and autistic behavior, and the extent to which these variables interact or independently relate to development. The present study extends this literature by assessing the relationship between ratings of autistic behavior and developmental trajectories in the context of a longitudinal, prospective study of early development in fragile X syndrome. Three questions are addressed: (a) What is the relationship between FMRP expression and ratings of autistic behavior in males with FXS? (b) To what extent does variability in ratings of autistic behavior account for variability in levels of development as well as the rate or slope of development over time? (c) Do FMRP and ratings of autistic behavior interact in their relationships with development?

METHOD

Participants

The subjects were 55 boys with full mutation FXS, verified by DNA analysis. Each was enrolled in a prospective, longitudinal study of early development and FXS. The average age of enrollment in the study was 46 months (range 24–84 months). Mean age at the time of autism assessment was 58.5 months (range 24 to 95). The participants lived in three contiguous southern states in the U.S. Of the 55, 47 (85%) were European American, 7 (13%) were African American, and 1 (2%) was Hispanic.

Instrumentation

As part of the longitudinal study, each child was assessed at 6- or 12-month intervals using the Battelle Developmental Inventory (BDI; Newborg, Stock, Wnek, Guidubaldi, & Svinicki, 1984). The BDI is administered by a trained tester through a combination of direct testing, observation, and parent interview. The BDI was selected because it covers the full age-span of interest in this study (24–96 months) and because it not only provides a Total development score but also assesses development in five important domains: Cognitive, Communication, Adaptive, Motor, and Personal-Social.

The reliability of the measure is well documented as well as its utility in describing development of children with disabilities (Bailey, Hatton, & Skinner, 1998; Hatton, Bailey, Burchinal, & Ferrell, 1997) and in predicting their later achievement (Behl & Akers, 1996).

Autistic behavior was assessed using the CARS (Schopler *et al.*, 1988). The CARS consists of 15 items (relating to people, imitation, emotional response, body use, object use, adaptation to change, visual response, listening response, taste, smell, and touch response and use, fear or nervousness, verbal communication, nonverbal communication, activity level, intellectual response, and general impressions). Items are rated on a scale from 1 (*within normal limits for age*) to 4 (*severely abnormal for age*) and descriptors and guidelines are provided for scoring each item. Total scores below 30 are considered *nonautistic*, scores from 30 to 36.5 are considered *mildly or moderately autistic*, and scores of 37 or higher are considered *severely autistic*. The CARS was selected for this study because of its documented reliability and usefulness (e.g., Sevin, Matson, Coe, & Fee, 1991) and because it could easily be completed in the context of a regularly scheduled developmental assessment of each child. Generally the diagnosis of autism is not made on the basis of CARS scores alone, and should be based on a more extensive evaluation adhering to DSM-IV criteria (Bristol *et al.*, 1996). Thus for the purpose of this study we refer to the CARS scores as a continuum of ratings of autistic behavior rather than as a diagnosis of autism. For some analysis purposes, the children are differentiated into two groups: those with significant levels of autistic behavior (CARS score of 30 or more) and those without significant levels of autistic behavior (CARS score < 30).

FMRP was assessed through DNA studies performed at Kimball Genetics in Denver, CO, using Southern blot and PCR analysis, as described by Tassone *et al.* (1999). Blood smears from each individual were analyzed for FMRP using the immunocytochemistry approach developed by Willemsen *et al.* (1995). For each child, 200 lymphocytes were scored for the presence or absence of FMRP, resulting in a measure of the percentage of lymphocytes producing FMRP. This is considered an estimate of protein production in the brain.

Procedure

Children were referred to the project by genetics clinics, early intervention programs, and developmental evaluation centers in the three states. All had been identified previously as having FXS during the early childhood years. Most had been identified because of early concerns about behavior and development (Bailey, Skinner, Hatton, & Roberts, 2000), although a few were identified after a relative or other family member had been diagnosed. Once enrolled, each child was assessed once or twice yearly using the BDI, within 3 weeks of each birthday and usually each half birthday. Assessments were conducted in the child's home or school, depending upon parent preference. Project staff with extensive training in use of the BDI and extensive experience in assessing young children with disabilities conducted all developmental assessments. The data in this paper represent a total of 290 assessment occasions. The average number of assessments per child was 5, with a range from 2 to 10.

During a 6-month period in the prospective study, all children were rated using the CARS. The research staff received training on the CARS from experts in its use and practiced using it in videotaped and live observations. Following the training, the next assessment occasion for each child was scheduled for the CARS evaluation. Immediately following the BDI assessment session, the examiner completed the CARS rating based on observational impressions of the child's behavior.

RESULTS

Autistic Behavior

Of the 55 boys, 14 (25%) were rated as exhibiting a significant amount of autistic behavior (CARS score of 30 or above). Twelve (22%) had scores in what the CARS characterizes as mildly to moderately autistic (30–36.5) and two (2%) had scores in the severely autistic range (37 or higher). Across the entire sample, the mean total CARS score was 26.1 (SD = 4.7, Range 18.5–37.5). As reported earlier (Bailey, Mesibov, *et al.*, 1998), the CARS differentiation of the two groups (autistic vs. nonautistic) was not based on differences in a few items, but rather higher average ratings on all items on the measure.

FMRP

The average percentage of lymphocytes expressing FMRP was 8.6 per child. The range was from 1 to 40% (SD = 8.03). Thus, this is a sample of individuals with very low levels of FMRP expression.

Analysis Procedures

We used a hierarchical linear models (HLM) approach (Bryk & Raudenbush, 1987; Burchinal, Bailey,

& Snyder, 1994; Willet, 1989) to describe and compare developmental change for time for fragile X children with and without autistic behavior. The HLM approach constructs individual growth curves for each subject and uses them as a basis for computing estimated population growth curves. HLM is particularly well suited to a study such as this in which the children varied in terms of age at study entry (24–84 months), length of time in the study (6–60 months), and number of assessment occasions (2–10).

HLM was used to examine developmental age (DA) during early childhood as a function of chronological age (CA), FMRP, and autistic behavior, controlling for maternal education. Linear, quadratic, and cubic growth curve slopes were estimated to describe patterns of development. The linear term estimated the extent to which DA increases with CA, reflecting a stable rate of growth over time. The quadratic term was included to test for changes in the rate of development over time (such as acceleration or deceleration in the rate of change). The cubic term was included to test for a second (later) change in rate of growth. Maternal education was entered as a covariate to control for possible differences in development as a function of family education and resources. In addition, an interaction term between maternal education and CA was included to test for differences in rates of growth due to differences in maternal education status. Thus the HLM models used to analyze these data related DA scores to the individual child and CA as within-subject random-effects variables. Age-squared, age-cubed, maternal education, the interaction between maternal education and CA, autistic behavior, the interaction between autistic behavior and CA, FMRP, and the interaction between FMRP and CA were entered as fixed-effects variables. Age was centered on the mean value (60 months).

Findings

Initially we tested for a relationship between FMRP and autistic behavior by running a *t* test comparing FMRP levels for boys with and without autistic behavior. Both groups exhibited low levels of FMRP. Although the boys with FXS alone had slightly higher levels of FMRP expression than boys with FXS and autistic behavior ($M = 9.43$ vs. 6.29), this difference was not statistically significant, $t(1, 53) = 1.27$, $p < .21$.

Data regarding the HLM analyses for total BDI scores and scores in each of the five developmental domains are summarized in Table I. For the total score and all domain scores, fragile X boys with autistic behavior achieved significantly lower development and grew at significantly lower rates than those without autistic behavior. With respect to developmental status, at the centered mean CA of 60 months, fragile X boys with autistic behavior had a mean overall DA of 22.7 months, compared with a mean overall DA of 33.4 months for fragile X boys without autistic behavior. Similar discrepancies were evident across all developmental domains, with the largest mean differences in the personal social (12 months), language (11.7 months), and adaptive (11.3 months) domains. Maternal education was not related to the level or rate of development in any domain.

Table I. Parameter Estimates for Level and Slope

	Total	Cognitive	Language	Adaptive	Motor	Personal-social
FXS Intercept[a]	33.35[e]	32.14[e]	30.04[e]	34.33[e]	35.14[e]	32.18[e]
Aut Intercept[b]	22.65[e]	22.98[e]	18.31[e]	23.02[e]	25.45[e]	20.78[e]
FXS* Age (slope)	.5343[e]	.5420[e]	.5093[e]	.5566[e]	.4861[e]	.5181[e]
Aut* Age (slope)	.2754[e]	.2967[e]	.2355[e]	.3481[d]	.3141[e]	.2232[e]
Age squared	.0002	.0009	.0002[c]	–.0007	–.0011	–.0005
Age cubed	–.00003[d]	–.00003[d]	–.00003[c]	–.00003[c]	–.00000	–.00002
Maternal educ.	.4169	.3429	.1301	.5406	.2986	.6961
FMRP	.1340[c]	.2424[c]	.2003[c]	.2535[c]	.2989[c]	.2176[c]
FMRP* Age	.0029	.0033	.0004	.0029	.0033	.0025
FMRP* Aut	–.1144	–.1792	–.2018	–.0040	–.1059	–.1383

[a] Mean developmental age of boys with fragile X syndrome only at a chronological age of 60 months.
[b] Mean developmental age of boys with both fragile X syndrome and autistic behavior at a chronological age of 60 months.
[c] $p < .05$.
[d] $p < .01$.
[e] $p < .001$.

Individual slopes based on chronological age, age-squared, and age-cubed were calculated. Estimated group trajectories for total and domain scores are displayed in Figures 1–6 and Table I. As is evident from both Table I and the figures, boys with both FXS and autistic behavior had significantly lower rates of development than those with FXS alone across all developmental domains. The slope for total scores of boys with FXS and autistic behavior was 0.26, less than half of the rate of growth (0.53) of children with FXS alone. Similar differences were observed across developmental domains, with the largest slope differences again evident in the personal social and language domains.

FMRP expression was significantly related to level of total development and level of development in each of the five domains (Bailey, Hatton, *et al.*, 2001). However, FMRP expression was not related to rate of development over time. The effect of autistic behavior was substantially greater than that of FMRP. The autistic behavior × FMRP interaction was not significant, suggesting that the relationship between autistic behavior and development is independent of the relationship between FMRP and development.

Quadratic and cubed effects were estimated to test for changes in the rate of development over time (curvilinear effects). A significant squared effect would indicate at least one point of change in the rate of growth. A significant cubed effect would indicate a second point of change in the rate of growth. The direction and magnitude of these changes determine the shape of the trajectories in Figures 1–6. To estimate subtle changes in growth, it is necessary to have more observations over time than the number of changes you want to estimate. In our analyses, the number of observations on each child ranged from 2–10, with an average of 5 per child, and the length of the growth period was limited to 24–96 months. Although this is sufficient for estimating two points of change in growth rates for the whole sample, we did not feel it was sufficient to estimate separate points of change for the 14 children with autistic behavior as a separate group. Therefore, the general shape of the curve is assumed to be the same for both groups of boys. Only the mean level and the overall linear slopes were allowed to differ.

None of the quadratic effects were significant. Cubic effects were significant for the total BDI score, indicating two points of change in rate of growth for the sample overall. Examination of the five domains suggested that this acceleration and deceleration occurred in the cognitive, language, and adaptive domains. Visual inspection of the trajectories suggests that growth may speed up around 36 months, then slow a bit after 72 months. The magnitude of these shifts in the rate of growth do not appear to be dramatic, but do make a significant difference in how much progress the child makes over time.

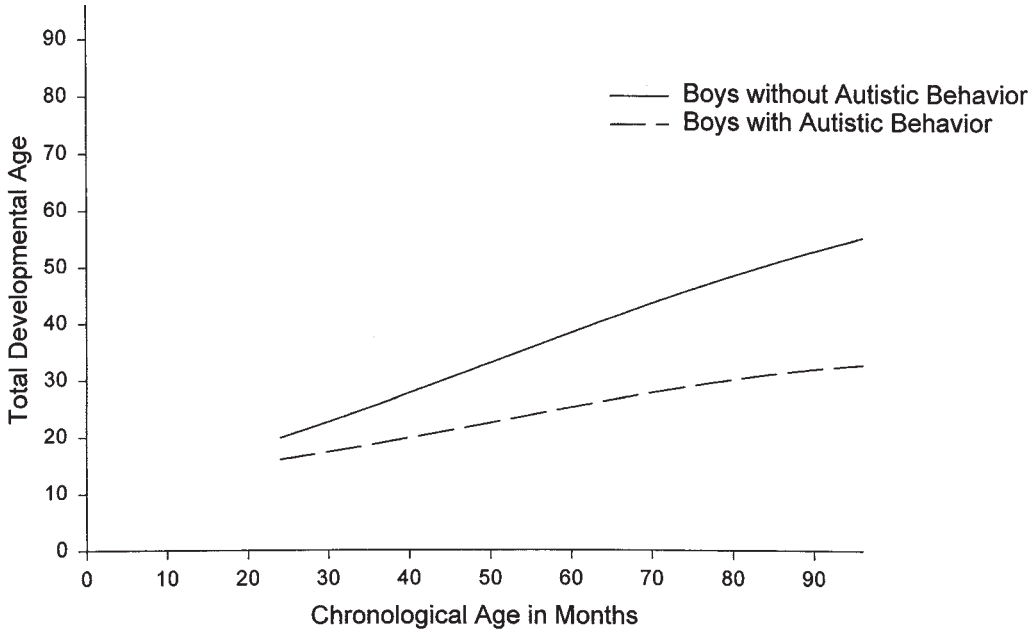

Fig. 1. Predicted growth curves for Total Development Score.

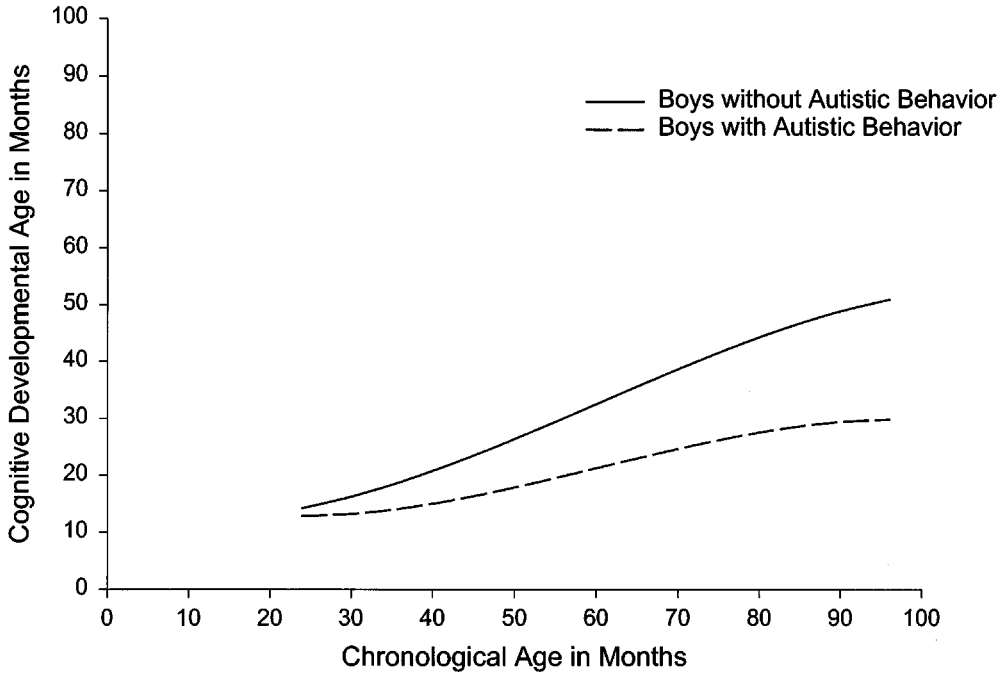

Fig. 2. Predicted growth curves for Cognitive Development.

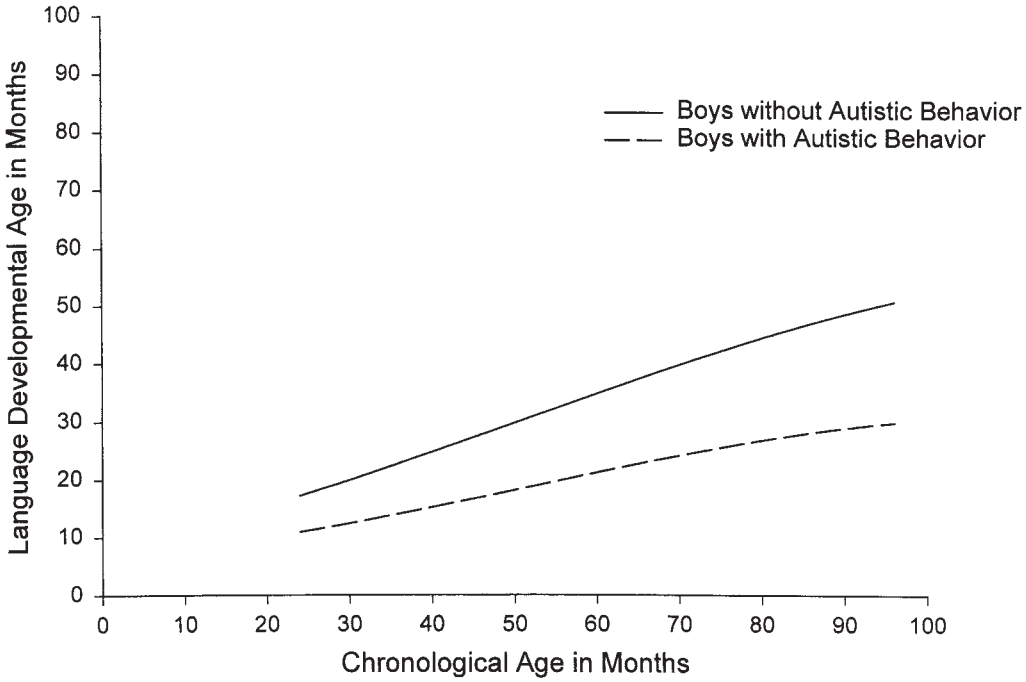

Fig. 3. Predicted growth curves for Language Development.

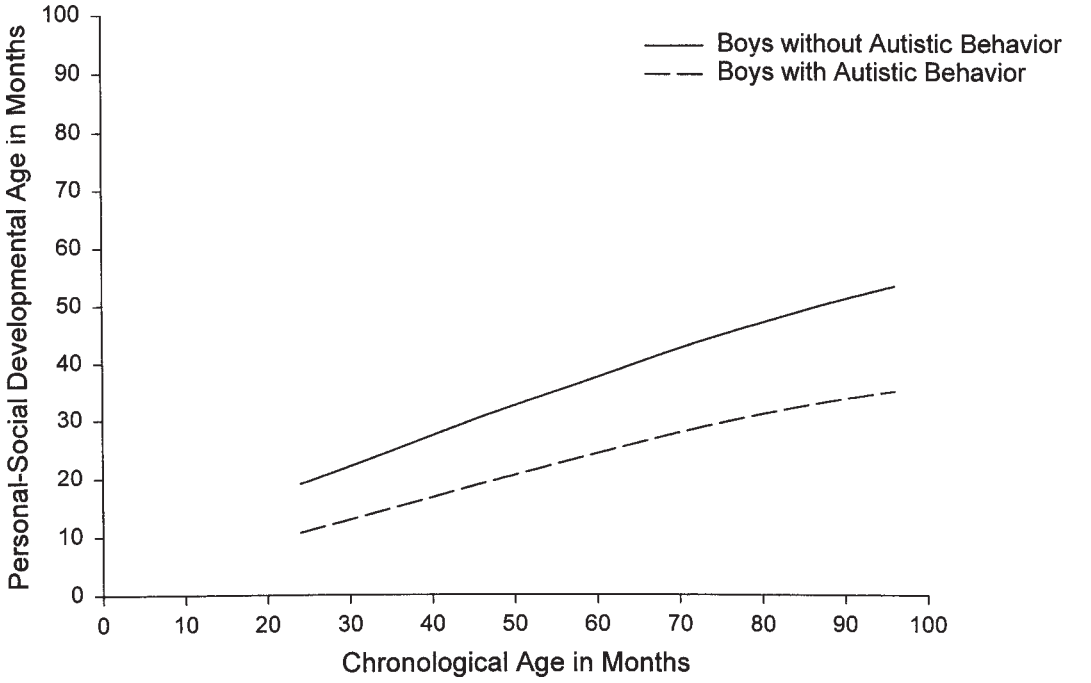

Fig. 4. Predicted growth curves for Personal-Social Development.

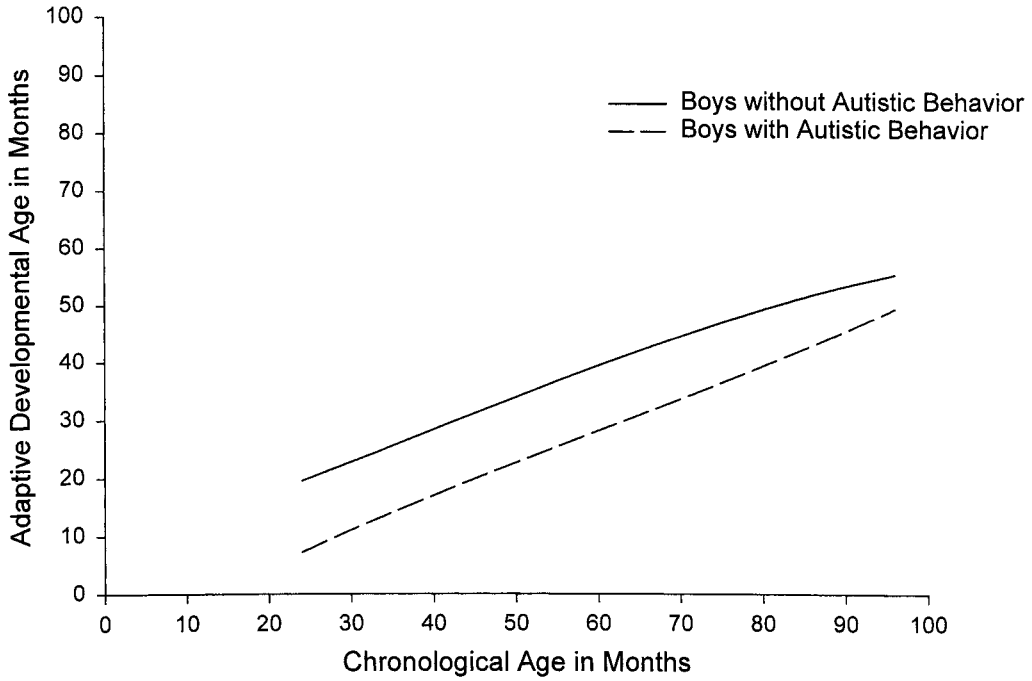

Fig. 5. Predicted growth curves for Adaptive Development.

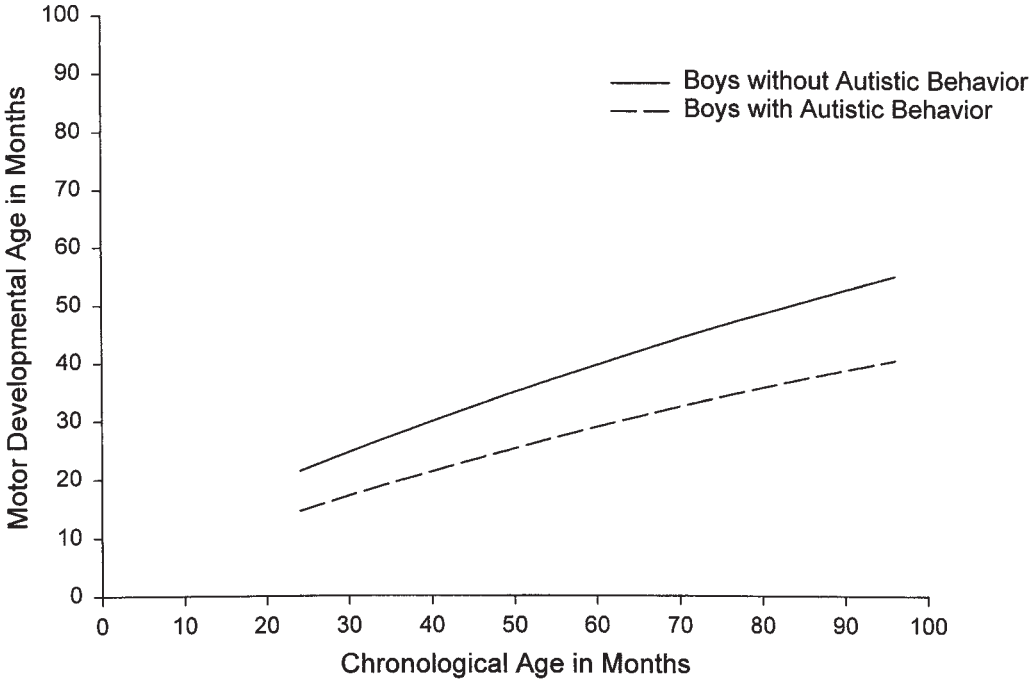

Fig. 6. Predicted growth curves for Motor Development.

DISCUSSION

This study assessed the relationships among autistic behavior, FMRP, and development in young males with fragile X syndrome. Drawing on multiple assessments of 55 children in the context of a prospective, longitudinal study, we used hierarchical linear modeling to construct growth curves to determine whether autistic behavior was associated with greater developmental delay and slower developmental trajectories. The results indicate a clear and strong relationship between autistic behavior (as measured by the CARS) and developmental status. Boys with both FXS and autistic behavior had significantly lower developmental levels and slower trajectories of growth than did boys with FXS only.

The differences are both statistically and clinically significant. For example, the slope for overall development of boys with autistic behavior and FXS was less than half the rate of that seen with boys with FXS alone. Furthermore, the relationship was true for almost all of the children. In a visual inspection of the individual child data, there appear to be two groups of children, one group on a very low trajectory of development and one on a higher trajectory. With one exception, the low trajectory group contains only those boys with autistic behavior. Likewise with one exception the higher trajectory group contains only those boys without autistic behavior. Thus there is a consistent pattern of association across the sample.

In addition, the general findings are true for both overall development as well as development in each of the five domains of the BDI: Cognitive, Language, Personal-Social, Motor, and Adaptive. Although the extent of difference varied somewhat across domains, each was large and significant. For example, developmental age scores for the group with both FXS and autistic behavior ranged from 9.2 to 12 months lower than those for children with FXS alone. This suggests that the pattern of relationship between autistic behavior and development occurs in multiple domains of development, not just the areas of language and social development which seem to differentiate children with autism from children with fragile X syndrome and other forms of mental retardation (Bailey *et al.*, 1998; Carpentieri & Morgan, 1996; Jacobson & Ackerman, 1990; Sudhalter, Cohen, Silverman, & Wolf-Schein, 1990).

FMRP expression and autistic behavior were not related in this sample. This may be due in part to the fact that we had overall low levels of FMRP in all children, and a relationship may be evident in a sample that includes children with higher levels of FMRP. FMRP expression was related to level but not rate of development,

and there was no interaction between FMRP and autistic behavior in testing relationships with development.

These findings lend support to the hypothesis that when autistic behavior and FXS co-occur, the effect is additive in its impact on development. However, an alternate explanation is that lower IQ in general results in an increased incidence of autistic features, and thus further research is needed. This finding needs to be replicated with other samples and verified further in studies in which a more complete autism diagnostic evaluation is completed on individuals with fragile X syndrome. Despite the singular measure of autistic behavior, however, the findings are both clear and compelling. If substantiated by further research, they suggest that children with both fragile X and autism are at increased risk for severely compromised development during the early years, and more intensive or specialized approaches to intervention may be warranted.

The mechanisms by which these findings occur are not clear from this study or from the literature (Cohen *et al.*, 1991; Feinstein & Reiss, 1998), but several explanations are possible. One scenario is that FXS and autistic behavior are two separate disorders which, when co-occurring, have an additive impact on the level and rate of development. This suggests that two different mechanisms are affected, and thus having both impairments would be more deleterious than either alone. A second possibility is that within the continuum of FXS and other causes of mental retardation, persons who are severely affected by the syndrome are more likely to exhibit autistic behavior than those who are less severely affected. This suggests that only one mechanism is affected, but along a continuum of severity, one end of which also resembles mild or moderate forms of autism. A third possibility reflects various combinations of the first two. For example, autistic behavior and FXS may co-occur in most individuals with FXS, yet both are on continua that vary from mild to severe. This suggests that when both are severely affected, development is more likely to be compromised. Future research is needed involving more comprehensive evaluations of children with FXS, but the ultimate answer may depend upon the discovery of genetic or neurobiological mechanisms underlying autism.

Regardless of the explanation, these findings suggest that children with both FXS and autistic behavior have significant developmental impairments over and above those evident in FXS alone. In our sample, the magnitude of these differences is large and likely to be of clinical and functional significance. Future research should focus on educational and therapeutic implications and systematically test the effectiveness of a wide range of behavioral, therapeutic, and pscychopharmocological interventions that could alter what appears to be severely compromised development.

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