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Chronological age, but not FMRP levels, predicts neuropsychological performance in girls with fragile X syndrome

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Abstract

The effect of FMRP levels and chronological age on executive functioning, visual-spatial abilities and verbal fluency tasks were examined in 46 school-age girls with fragile X syndrome (FXS). Results indicated that FMRP levels were not predictive of outcome on the neuropsychological tests but that performance on the executive functioning task tended to worsen with chronological age. This age effect was not observed on the tests of visual-spatial abilities or verbal fluency. These data indicate that relative deficits in executive functioning in girls with FXS become more pronounced with age. In contrast, the relative deficits in spatial and verbal abilities of these girls did not appear to increase with age, suggesting that these abilities may be spared.

Keywords

Fragile X syndrome; FMRP; executive function

Introduction

Fragile X syndrome (FXS) is the most common known inherited cause of developmental disability affecting approximately 1 in 4000 males and 1 in 8000 females in the general population (Crawford et al 1999). The syndrome is caused by a mutation to the *FMR1* gene located 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 5–45 times in unaffected individuals. If the sequence expands to approximately 200 repeats or more, individuals have the full mutation of the disorder that is invariably associated with DNA methylation of the promoter region of the *FMR1* gene. Methylation of the gene switches off production of the “fragile X mental retardation protein” (FMRP), the protein product of the *FMR1* gene. FMRP is thought to actively participate in the translational machinery that converts messenger RNA into protein (Brown et al 2001). Low levels of FMRP appears to increase the risk for the physical, cognitive, and behavioral manifestations of the disorder (Taylor et al 1994). Females, who have the mutation on only one of their two X chromosomes, consequently have higher levels of FMRP than males with FXS and are therefore less affected by the disorder.

The characteristic cognitive profile associated with the full mutation includes deficits in the following cognitive domains: visual memory and perception, mental manipulation of visual-spatial relationships among objects, visual-motor coordination, processing of sequential

information, processing of arithmetical stimuli, and attentional/executive function (Freund and Reiss 1991; Grigsby et al 1990; Hagerman et al 1992; Hinton et al 1995; Kemper et al 1986; Mazzocco et al 1992; Mazzocco et al 1993; Miezieski et al 1986; Munir et al 2000; Reiss et al 1995; Riddle et al 1998; Schapiro et al 1995; Sobesky et al 1994; Theobald et al 1987). In contrast, studies assessing verbal-based skills show females with FXS to have relative strengths or spared abilities in this area (Freund and Reiss 1991; Grigsby et al 1992; Grigsby et al 1990; Kemper et al 1986; Mazzocco et al 1992; Mazzocco et al 1993; Miezieski et al 1986).

Few studies have investigated the effect of FMRP level on cognitive outcomes, both global (IQ) and specific (e.g., memory, attention, executive function). To date, investigations have produced mixed findings with some studies indicating a connection between FMRP levels while others indicating no definitive relationship (Bennetto et al 2001; Cornish et al 1998; Cornish et al 2001). Further, the association between FMRP and cognitive ability appears to differ between males and females with FXS. Tassone and her colleagues (Tassone et al 1999) examined the relationship between FMRP expression and full scale IQ in males and females with FXS. The highest correlation between FMRP and IQ was found in males with a partially methylated full mutation. In females with the full mutation, FMRP explained only 24% of the variance in full-scale IQ scores. Similarly, Loesch et al. (Loesch et al 2004) demonstrated that approximately 28% of the variance in IQ was accounted for by FMRP levels in females with a full and pre-mutation of FXS while FMRP levels accounted for close to 75% of the variance in IQ scores in males with FXS.

Given the differences in findings, as well as the paucity of well controlled studies examining the effect of FMRP levels on neuropsychological functioning in females with FXS, the present study administering tests of executive functioning, visual-spatial skills and verbal memory to 46 school-aged girls with FXS. In order to compare neuropsychological functioning to an environmental control group, we also administered these same tests to an unaffected sibling living in the same household as the child with FXS. We also compared the performance on these tests to an age and IQ-matched group of children with developmental delay. We hypothesized that FMRP levels would be significantly associated to the children's IQ's and to neuropsychological performance. In addition, by examining neuropsychological functioning in school-age girls with FXS, in comparison to these control groups, we wanted to determine whether there was a significant slowing in neuropsychological performance with age, particularly in executive functioning. To our knowledge, this is the first study to examine the effect of FMRP and age on developmental outcomes on these tests in a large group of girls with FXS while controlling for IQ.

Method

Participants

Forty-six females diagnosed with FXS, 46 unaffected siblings, and 33 children diagnosed with non-specific developmental delay participated in the study. Females with FXS were aged between 5 and 23 years ($M = 11.16$, $SD = 3.86$), unaffected siblings (28 females and 18 males) were aged between 6 and 20 years ($M = 11.507$, $SD = 3.39$) and children with non-specific developmental delay (12 females and 21 males) were aged between 7 and 18 years ($M = 12.63$, $SD = 2.44$). The mean age difference between the girls with FXS and their unaffected siblings was 2.84 years, $SD = 1.86$. Twenty-eight (60.9%) girls with FXS had an older unaffected sibling, 15 (32.6%) had a younger unaffected sibling, and 3 (6.5%) siblings were DZ twins.

The ethnic distribution of the sample was 86.7% Caucasian and 13.3% Other (Asian, Pacific Islander, Hispanic, or Mixed). Fragile X diagnoses were confirmed by Southern Blot DNA

analysis as detailed by Taylor et al. (1994). Seven (15.2%) of the girls with FXS were diagnosed with mosaicism. Participants were recruited from across the United States and Canada through advertisements, referrals, and word of mouth for participation in a study of children and families affected by fragile X syndrome.

Materials

Fragile X Mental Retardation Protein (FMRP)—Blood kits and consent forms were mailed directly to each family in order to obtain FMRP levels for the child with FXS. Blood draws were performed by a local physician and samples were mailed directly to Kimball Genetics using overnight mail. FMRP immunostaining, an indirect alkaline phosphatase technique, was used (Willemsen et al 1997). Slides were analyzed under the microscope, distinguishing lymphocytes from other blood cell types by morphology. For each slide, 200 lymphocytes were scored, and the percentage of lymphocytes expressing FMRP was determined. Scoring was performed in blinded fashion with respect to DNA results.

IQ—The IQs of the children aged 6-16 were measured with the Wechsler Intelligence Scale for Children - Third Edition (WISC-III) (Wechsler 1991). Participants aged 17 and over (3 females with FXS, 3 unaffected siblings and 1 child with developmental delay) received the Wechsler Adult Intelligence Scale - Third Edition (WAIS-III) (Wechsler 1997). Both tests yield Full Scale IQ scores with a mean of 100 and a standard deviation of 15.

Executive functioning—Executive functioning was assessed using the Contingency Naming Task (Taylor 1988). This test is modeled after the Stroop Color Word Test and is a measure of the ability to inhibit, but also to switch, “mental set”. In this test, participants were presented with a laminated sheet of paper containing drawings of 27 shapes (circles, squares and triangles, colored either pink, green or blue). Within each shape, there was a smaller circle, square or triangle. The shapes were presented in 3 rows, with each row containing nine shapes. Participants were first asked to name the colors of the 27 shapes, starting with the top row of shapes, proceeding to the middle and bottom rows, and moving across each row from left to right. Participants were then asked to name the 27 outside shapes, ignoring the smaller shapes inside each shape.

Once participants had completed these preliminary tests, each participant was then asked to name the shapes or colors of the shapes according to a predetermined rule: “If the inside shape matches the outside shape, name the color, otherwise, name the outside shape”. Each participant received up to five practice trials prior to beginning the test to ensure that the participant understood the procedure. Time to completion and number of errors were recorded. Time to completion was defined as the number of seconds it took for the participant to name all 27 items in the test. An error was recorded if the participant said the wrong color or shape. The dependent variable was the number of correct responses per minute, calculated by dividing the number of correct responses by the time taken to complete the 27 items, and multiplying by 60.

Verbal Fluency—Verbal fluency was assessed using the “F, A, S” test (Spreen and Benton 1977). In this test, participants were given one minute to say as many words they could think of beginning with the letter “F”. They were then given one minute to say as many words beginning with the letter “A,” and finally, they were given one minute to say as many words beginning with the letter “S”. The dependent variable was the number of correct responses per minute, calculated by summing the number of correct responses made in the “F”, “A” and “S” conditions and dividing by three.

Visual-spatial ability—Visual-spatial ability was assessed using the Spatial Relations test, a subtest of the Woodcock-Johnson Tests of Cognitive Ability (Woodcock and Johnson 1990). The test consists of 33 puzzles, presented to each participant in a booklet. Each puzzle contains a shape followed by several individual pieces, some of which, when rotated and put together, make the whole shape. The participant must name all pieces correctly in order to score one point for that puzzle. The test is discontinued if the subject receives a score of zero on six consecutive items. Each participant received four practice trials prior to starting the test. The dependent variable was the number of puzzles solved correctly.

Procedure

For the FXS and unaffected sibling groups, two researchers arrived at each participant's home at 8:00 AM and conducted a variety of cognitive and behavioral evaluations of the target child and their unaffected sibling throughout the day. Cognitive testing was administered in the morning, beginning with the IQ test and followed by the Contingency Naming, FAS, and Spatial Relations tests. For the group of children with developmental disabilities, all tests were administered in the laboratory.

Data Analysis—Group means were compared using one-way analysis of variance. A post hoc analysis of differences between groups was performed using Tukey's HSD test. To determine the degree to which FMRP level was associated with performance on the neuropsychological tests, a series of multiple regression analyses were conducted. In girls with FXS, three regression models were tested, with contingency naming, FAS and spatial relations test scores employed as the dependent variable in each analysis respectively. FMRP level, child age and child IQ were entered in one block as the independent variables in each analysis. In the unaffected siblings group, three regression models were also tested, with gender, age and IQ entered in one block as the independent variables in each analysis, with contingency naming, FAS and spatial relations test scores as the dependent variables respectively. The same analysis was also conducted for the developmental delay group. For all multiple regression analyses, the alpha value for statistical significance was .01 (two-tailed). In order to compare the slopes of the regression lines between the three groups, the standard error for the difference between the slopes was calculated and a test of the null hypothesis that the slopes were the same in each group was computed (Bland 2000).

Results

Descriptive statistics

In females with FXS, the mean percentage FMRP level was 53.51 ($SD = 18.39$), range 14% to 95.5%. Table 1 shows the means obtained for each measure in each group. As expected, females with FXS received significantly lower IQ scores than their unaffected siblings, and received significantly lower scores on the neuropsychological tests. In comparison to the group of children with non-specific developmental delay however, children with FXS scored significantly lower on the spatial relations test, but not on the tests of executive functioning or verbal fluency.

In the FXS group, the association between percentage FMRP and IQ failed to reach statistical significance, ($r(45) = .27$, $p = 0.08$). Percentage FMRP was also uncorrelated with age ($r(45) = -.19$, $p = 0.22$), and age was uncorrelated with IQ ($r(45) = -.14$, $p = 0.36$). There was no association between age and IQ in the unaffected sibling and developmental delay groups.

Multiple regression analyses

Table 2 shows the results of the multiple regression analyses for the three groups. Adjusted R^2 values for each regression indicated that the independent variables explained a significant proportion of the variance in the dependent variables.

Effect of FMRP levels on neuropsychological performance

When controlling for age and IQ, there was no effect of FMRP levels on contingency naming scores [$B = -.53$, $se = .07$, $p > .05$], spatial relations scores [$B = .03$, $se = .03$, $p > .05$] or verbal fluency scores [$B = .03$, $se = .02$, $p > .05$] in females with FXS.

Effect of age on neuropsychological performance

In the FXS group, when controlling for IQ and FMRP levels, there were highly significant effects of age on contingency naming scores ($B = 1.30$, $se = 0.37$, $p < .001$), verbal fluency scores ($B = .67$, $se = .11$, $p < .001$) and spatial relations scores ($B = .72$, $se = .15$, $p < .001$). In the unaffected siblings group, when controlling for IQ and gender, the effect of age was also highly significant on contingency naming ($B = 3.00$, $se = .33$, $p < .001$), verbal fluency ($B = .57$, $se = .12$, $p < .001$) and spatial relations ($B = .99$, $se = .17$, $p < .001$). In the developmental delay group, when controlling for IQ and gender, the effect of age was significant on contingency naming ($B = 2.27$, $se = .52$, $p < .001$), but not on verbal fluency ($B = .36$, $se = .15$, $p < 0.05$) or spatial relations ($B = .24$, $se = .27$, $p > 0.05$).

Statistical comparison of the slopes between the groups indicated that the effect of age on contingency naming was significantly lower in the FXS group than in unaffected sibling group ($z = 3.46$, $p < 0.01$) and developmental delay groups ($z = 1.98$, $p < 0.05$). There were no significant differences between the groups for the effect of age on verbal fluency scores or spatial relations scores.

Discussion

There appeared to be no effect of FMRP levels on neuropsychological functioning in girls with FXS when controlling for age and IQ. In addition, we found that percentage FMRP was uncorrelated with intellectual functioning in FXS, accounting for only 7% of the variance in IQ scores. These findings indicate that FMRP levels, as detected in white blood cells, does not completely reflect intellectual functioning in girls with FXS, and suggests that additional genetic, environmental or interactive factors may be involved in the impaired intellectual development of these children. It is also possible that blood levels of FMRP are imprecise indicators of FMRP levels in the brain, in particular as white blood cells are derived from a different embryonic tissue than the brain. Identifying additional factors that contribute to intellectual dysfunction in children with FXS, particularly early in the child's life, might provide us with a better understanding of this disorder, and may lead to new treatment strategies.

Bennetto and colleagues (Bennetto et al 2001) reported that the proportion of *FMR1* gene activation of females with FXS, a measure comparable to FMRP, was significantly associated with neuropsychological functioning. In contrast, Cornish and colleagues (Cornish et al 1998) did not find any correlation between activation ratio and specific tasks of spatial ability. Further, in a study of adult males with FXS, no relationship was found between CGG repeat length and performance on specific tasks of working memory, attention, and executive function (Cornish et al 2001). Such inconsistencies may result from the smaller sample sizes used in these studies, range restriction problems, or other methodological differences amongst the studies. It further may be an indication that FMRP

is a potential predictor of global intellectual functioning but not of more specific areas of strengths and weaknesses (Cornish et al 2001).

In comparison to an age and IQ-matched group of children, females with FXS scored significantly lower on a test of visual-spatial ability but scored at comparable levels on a test of executive functioning and verbal fluency. In order to examine the impact of age on neuropsychological functioning in school-age girls with FXS, we used multiple regression techniques and compared the resulting regression parameters (i.e., slopes) between the groups. Comparison of these coefficients indicated that girls with FXS evidenced a significant slowing with age on the test of executive functioning when compared to their unaffected siblings and to a developmental age-matched group. In contrast, there appeared to be no slowing of performance with age on tests of verbal fluency and spatial ability. These data support the contention that executive functioning abilities such as working memory and set shifting are more difficult for children with FXS (Bennetto et al 2001; Keenan and Simon 2004; Mazzocco et al 1992; Munir et al 2000). Specifically, we found that these difficulties increase with age.

An important limitation of the study is that the gender of our environmental control group and IQ matched control group was mixed. Although we found no effect of gender on neuropsychological performance in these control groups, future studies should endeavor to include a same gender age-matched environmental control group as well as an age, gender and IQ-matched control group.

We hope to validate these results by conducting repeated assessments of neurocognitive functioning over the school-age years. Cornish et al (2004) have speculated that the decline in cognitive performance in the middle-late teens commonly seen in children with FXS may not in fact represent an actual regression in intellectual level e.g., (Fisch et al 1999), but rather, the inability of the children to keep pace with their peers in specific cognitive areas. While the data from this study would appear to support this contention, we believe that further studies are needed to examine the specificity of the neurocognitive deficit in children with FXS, with particular emphasis on determining whether additional components of executive functioning (e.g., inhibition, updating) are also implicated in this disorder. Further refinements in the methodology for assessing FMRP levels in individuals with FXS are also warranted.

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Table 1

Mean scores and standard deviations for each group on the Contingency Naming, Verbal Fluency and Spatial Relations tests. The results of the analysis of variance and a post-hoc analysis are also given.

	A. Females with FXS (N = 46)	B. Siblings without FXS (N = 46)	C. Children with Developmental Delay (N = 33)	F (2,122)	p	Tukey's HSD
Age	11.16 (3.86)	11.57 (3.39)	12.63 (2.44)	1.893	n.s.	
IQ	75.51 (20.93)	110.42 (12.69)	79.94 (21.58)	45.839	<.001	B>AC
Contingency naming	22.83 (8.41)	35.22 (12.89)	24.23 (10.17)	15.970	<.001	B>AC
Verbal fluency	6.17 (3.56)	9.48 (3.20)	6.90 (3.17)	12.069	<.001	B>AC
Spatial relations	14.38 (5.42)	22.72 (5.21)	18.91 (5.51)	25.671	<.001	B>C>A

Table 2

Results of the multiple regression analyses predicting neuropsychological test scores in each group. B is the unstandardized regression coefficient, se is the standard error of the slope.

Group	Independent Variables	Dependent variables					
		Contingency naming		Verbal fluency		Spatial relations	
		B (se)	p	B (se)	p	B (se)	p
FXS (N = 46)	% FMRP	-.05 (.08)	ns	.03 (.02)	ns	.03 (.03)	ns
	Age	1.30 (.37)	.00	.67 (.11)	.00	.72 (.15)	.00
	IQ	.15 (.07)	.00	.06 (.02)	.00	.18 (.03)	.00
		Adj. R ² = .31, p = .004		Adj. R ² = .54, p < .0001		Adj. R ² = .65, p < .0001	
Unaffected Siblings (N= 46)	Gender	3.11 (2.18)	ns	.10 (.77)	ns	-.52 (1.23)	ns
	Age	3.00 (.33)	.00	.57 (.12)	.00	.99 (.17)	.00
	IQ	.19 (.09)	ns	.05 (.03)	ns	.08 (.05)	ns
		Adj. R ² = .70, p < .0001		Adj. R ² = .41, p < .0001		Adj. R ² = .49, p < .0001	
Developmental Delay (N = 33)	Gender	-4.12 (2.58)	ns	-1.26 (.76)	ns	-2.24 (1.33)	ns
	Age	2.27 (.32)	.00	.36 (.15)	ns	.24 (.27)	ns
	IQ	.26 (.06)	.00	.11 (.02)	.00	.20 (.03)	.00
		Adj. R ² = .51, p < .0001		Adj. R ² = .56, p < .0001		Adj. R ² = .58, p < .0001	