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Cognitive, Behavioral, and Adaptive Functioning in Fragile X and Non-Fragile X Retarded Men

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A Comparison of Language Characteristics of Mentally Retarded Adults with Fragile X Syndrome and Those with Nonspecific Mental Retardation and Autism[1]

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Fragile X syndrome is a recently identified form of mental retardation that is associated with a chromosomal abnormality and inherited in an X-linked manner. Previous studies have suggested that distinctive speech and language characteristics are associated with the syndrome. Twelve adult male residents of an institution for the retarded (aged 23 to 51 years) were compared on a series of speech and language measures to 12 adult males with nonspecific forms of MR who were residents of the same institution and were matched on age and IQ. A second contrast group consisted of similarly matched autistic men. Results revealed that there were no significant differences among the groups' performance, with the exception of increased rates of echolalia in the autistic group. A nonsignificant trend toward poorer performance on expressive measures on the part of the fragile X group was noted. The implications of these findings for further research on the syndrome are discussed.

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The fragile X syndrome is a recently identified form of mental retardation (MR) with a characteristic physical and behavioral phenotype that is associated with a chromosomal abnormality and is transmitted within families in an X-linked manner—that is, through generally unaffected female carriers to sons who demonstrate the syndrome (Lubs, 1969; see Paul, Cohen, Breg, Watson, & Herman, 1984, for review of history of this syndrome). The condition is diagnosed by observing a pinched area or constriction (fragile site) at the tip of the long arm of some of the X chromosomes in affected males and some female carriers, when cells are grown in media deficient in folic acid or in other specialized culture media (Sutherland, 1977).

Clinical features of the syndrome include a broad range of intellectual ability varying from profound to borderline levels of functioning (de la Cruz, 1985). A few normal males with the marker have been reported (Daker, Chidiac, Fear, & Berry, 1981), and apparent transmission through phenotypically normal males has been documented (Popovich, Vekemans, Rosenblatt, & Monroe, 1982; Webb, Rogers, Pitt, Halliday, & Theobald, 1981). About one-third of the female "carriers" show some degree of impairment, ranging from mild learning disabilities to mental retardation (Turner, Brookwell, Daniel, Selikowitz, & Zilibowitz, 1980). While this form of retardation is not always associated with obvious physical abnormalities, males affected with the fragile X syndrome tend to have abnormally large, low-set ears, slightly enlarged head circumference, long and narrow face with some midface hypoplasia, prominent mandible, and connective tissue dysplasia (de la Cruz, 1985). Testicular enlargement, or macroorchidism, is the most frequent physical abnormality seen in postpubertal males, although testicular size in young boys may be enlarged but is usually normal (Escalante, Grunspun, & Frota-Pessoa, 1971; Meryash, Cronk, Sachs, & Gerald, 1984).

X-linked forms of mental retardation have been found to be quite common. Turner and Turner (1974) estimated that X-linked forms of MR (about half of those with X-linked MR have the fragile X syndrome) could be responsible for 20% or more of the moderately retarded male population. Current estimates for the occurrence of the fragile X syndrome of 1 in 2,000 males (Turner & Jacobs, 1983) suggest that this form of MR may be second only to Down's syndrome in prevalence, and it is certainly one of the most common diagnosable forms of mental retardation.

Behavioral features include some association with autism (Brown et al., 1982; Meryash, Szymanski, & Gerald, 1982; Levitas et al., 1983; Watson et al., 1984; Blomquist et al., 1985), although estimates of the degree of association between the two syndromes vary from 5 to 15% in larger series (Watson et al., 1984) to more than 50% in a small series (Levitas et al., 1983). Pervasive hyperactivity has been reported in boys with the syndrome (Hagerman & McBogg, 1983), but this appears to abate in adulthood.

One of the first observations of geneticists studying this syndrome was that affected individuals showed peculiar speech characteristics (Allen, Herndon, & Dudley, 1944; DeRoover, Fryns, Parloir, & VanDenBerghe, 1977; Hagerman & McBogg, 1983; Lehrke, 1974; Martin & Bell, 1943; Renpenning, Gerrard, Zaleski, & Tabata, 1962; Snyder & Robinson, 1969; Yarborough & Howard-Peebles, 1976). Language characteristics reported include poor auditory reception (Howard-Peebles, Stoddard, & Mims, 1979), a characteristic rhythmic "litany-like" intonational pattern (Turner et al., 1980), dyspraxic characteristics and dysfluency (Paul et al., 1984), perseverative speech (Herbst, Dunn, Dill, Kalousek, & Krywaninik, 1981), and high rates of palilalia and echolalia (Hagerman & McBogg, 1983). While all these characteristics can be found in mentally retarded individuals of any etiology, there has been the strong suggestion in the literature on this syndrome that the constellation of speech disorders seen in affected individuals forms a distinctive pattern. However, none of these studies has systematically compared language characteristics of males with the fragile X syndrome to those of similarly retarded males who do not exhibit the marker X chromosome. The present study contrasts language performance of males with the fragile X syndrome to that of males with other, nonspecific forms of retardation known not to have the fragile X trait who are matched to the experimental subjects on chronological age, mental age, and institutional status. In addition, the fragile X group's language characteristics will be compared to those seen in similarly matched autistic individuals who do not show the marker X chromosome.

METHOD

Subjects

Fifteen adult males (mean age 38 years) who were long-term residents of a state institution for the retarded were identified as showing the fragile X syndrome. Peripheral blood lymphocytes were cultured in medium 199 with 2% fetal calf serum as previously described (Lubs, Watson, Breg, & Lujan, 1984). Not all residents of the institution were screened for the syndrome. These men were identified on the basis of family history of mental retardation, testicular enlargement, and/or physical appearance. This was not, then, a complete ascertainment of fragile X syndrome within the institution. Because 3 of the subjects were subsequently placed outside the institution, they were not included in the study. The remaining 12 subjects were able to undergo the complete battery of measures. There were two sibships in the fragile X sample, one of two brothers and one of three. All had nor-

mal hearing. Two had been diagnosed as autistic on the basis of behavioral characteristics before they had been identified as having fragile X syndrome.

The contrast group consisted of 12 males, all unrelated to each other or to subjects in other diagnostic groups, living in the same institution, who had no family history of mental retardation, no known syndrome of retardation, and no evidence of a marker X chromosome on the basis of laboratory studies. These individuals were matched to the fragile X men on chronological age, IQ, and length of residence within the institution. One contrast subject had a moderate hearing loss in one ear, the rest had normal hearing. None had ever been diagnosed as autistic. A second contrast group consisted of 12 males who had been identified by institutional records as autistic and had no family history of mental retardation, no other known syndromes, and no evidence of marker X chromosomes on the basis of laboratory studies. These men were also matched to the fragile X group on chronological age, IQ, and length of stay in the institution. Table I displays the average age at study, age at admission to the institution, Stanford-Binet (Terman & Merrill, 1973) mental age, and Leiter International Performance Scale (Arthur, 1952) nonverbal mental age (both ascertained independently by us, using clinicians blind to subjects' diagnosis) for each group. Analysis of variance revealed no differences among the groups on any of these matching variables. In addition, no significant differences were found between primarily verbal (Stanford-Binet) and nonverbal (Leiter) estimates of intelligence for any of the diagnostic groups.

Procedure

A battery of standardized language tests measuring reception, expression, and articulation was administered to each subject by trained clinicians

Table I. Means (and Standard Deviations) of Subject Characteristics and F and p Values for Comparisons Among Diagnostic Groups

Variable	Group Fragile X	Nonspecific MR	Autistic	F	p
Age	37.83 (8.9)	39.58 (7.1)	37.50 (9.8)	.20	.82
Age at admission to institution	10.33 (5.6)	12.33 (7.6)	12.00 (5.9)	.33	.72
Standord-Binet mental age	3.28 (1.1)	3.92 (1.4)	3.80 (1.6)	.72	.49
Leiter mental age	2.70 (1.0)	3.90 (1.8)	4.13 (3.0)	1.45	.25

Table II. Tests and Measures Used in Study

Area of Assessment	Assessment instruments
Receptive vocabulary	Peabody Picture Vocabulary Test (PPVT; Dunn & Dunn, 1981)
Receptive language	Test of Auditory Comprehension of Language (TACL; Carrow, 1973) Grammatical Understanding subtest of Test of Language Development (TOLD-GU; Newcomer & Hammill, 1977)
Expressive vocabulary	Expressive One-Word Picture Vocabulary Test (EOWPVT; Gardiner, 1979)
Expressive language	Grammatical Completion subtest of Test of Language Development (TOLD-GC; Newcomer & Hammill, 1977) Mean length of utterance (MLU; Brown, 1973; Miller, 1981)
Sentence imitation	Sentence Imitation subtest of Test of Language Development (TOLD-SI; Newcomer & Hammill, 1977)
Articulation	Goldman-Fristoe Test of Articulation (Goldman and Fristoe, 1969)
Vocal quality	Speech sample rating
Vocal volume	Speech sample rating
Rate of speech	Speech sample rating
Intonational pattern	Speech sample rating
Intelligibility	Speech sample rating
Dysfluency	Speech sample rating
Echolalia	Speech sample rating
Palilalia	Speech sample rating
Perseveration	Speech sample rating

blind to subjects' diagnosis. These measures are listed in Table II. In addition to a comparison of scores on individual measures, comparisons were made among composite scores for receptive language—obtained by averaging the age-equivalent scores derived from the Peabody Picture Vocabulary Test (Dunn & Dunn, 1981), the Test of Auditory Comprehension of Language (Carrow, 1973), and the Grammatical Understanding subtest of the Test of Language Development (Newcomer & Hammill, 1977). This is referred to as the Receptive Composite Score. Similarly, composite scores for expressive language—derived by averaging the age scores obtained from the Expressive One-Word Picture Vocabulary Test (Gardiner, 1979), the Grammatical Completion subtest of the Test of Language Development (New-

comer & Hammill, 1977), and the mean length of utterance (Miller, 1981), and referred to as the subject's Expressive Composite Score—were compared among the three groups.

Samples of each subject's spontaneous speech were also audiorecorded and transcribed. In each of the three diagnostic groups there were three subjects who did not produce enough speech to allow ratings to be done. There were, then, nine speech samples rated in each group. Mean length of utterance in morphemes (MLU) was derived from the transcriptions of the speech samples according to Brown's (1973) rules. Speech samples were collected by clinicians who had become familiar to the subjects after several sessions spent collecting the standardized test data. Conversations were generally around normal social topics (discussion of plans for the weekend, subjects' job assignments, and so on). Conversations with very low-functioning subjects used pictures to stimulate verbal output when this normal conversational style failed to elicit speech. Samples were 5 to 10 minutes in length and contained 40 to 100 utterances per subject. The audiorecordings were rated by a trained speech-language pathologist blind to the subjects' diagnosis for the following characteristics: vocal quality (normal, harsh, or breathy), rate of speech (normal, fast, slow, or fluctuating), volume (normal, loud, soft, or fluctuating), intonational pattern (normal, exaggerated, or monotonic), percent of dysfluent syllables (defined as those containing rapid repetitions of consonant sounds, prolongations, or silent blocks), number of instances of echolalia, number of instances of palilalia, topics on which the subject perseverated, percent of unintelligible words in a 100-word sample, and a rating of intelligibility (good, moderate, or poor).

A second trained clinician, also blind to the subjects' diagnosis, rated a randomly selected sample of 10 of the 27 speech samples on each of the above variables. Interrater reliabilities were calculated using a kappa statistic for the nominal ratings (quality, rate, volume, intonation, perseveration, and intelligibility) and Pearson product-moment correlations for the numerical ratings (dysfluency, echolalia, and percent unintelligible words). There were too few instances of palilalia to do reliability measures. Kappa values ranged from 1.0 to .48 and all were statistically significant. Correlations ranged from .86 to .65 and all were statistically significant. Tables III and IV list the reliability values for each of the ratings made on the speech samples.

Table III. Kappa Values for Reliability Studies on Nominal Ratings on Speech Samples

Variable	Kappa value	$p <$
Vocal quality	.81	.001
Vocal volume	.74	.001
Rate of speech	.57	.005
Intonational pattern	.84	.001
Perseveration	.48	.002

Table IV. Correlation Coefficients for Reliability Studies on Numerical Ratings of Speech Samples

Variable	R	R^2	$p <$
Dysfluency	.65	.42	.05
Echolalia	.80	.64	.003
Percent unintelligible words	.86	.75	.001

RESULTS

Average scores for each of the three diagnostic groups on each of the individual speech and language measures, as well as on the receptive and expressive composite scores, are given in Table V. Analyses of variance among the three groups were performed on the raw scores for each language measure, as well as on the averaged age scores for the composite measures. Chi-squared tests were used to test for group differences on the nominal ratings. These chi-squared values are given in Table VI.

As Tables V and VI show, the only difference to reach significance ($F = 3.90, p < .03$) was the average number of instances of echolalia, 16.33 for the autistic group as opposed to 2.22 for the fragile X and 4.11 for the nonspecific. Thus, the autistics, as would be expected, were using much more echolalia than were either of the other two groups. Two other differences approached significance: the difference among the groups on MLU ($F = 2.15, p < .13$) and vocal quality ($\chi^2 = 2.40, p < .13$). The autistic and fragile X subjects had lower MLUs than the nonspecific MRs, with autistics' MLUs being the lowest. Autistic and fragile X subjects received ratings of "harsh" vocal quality more often than did the nonspecific MR group.

Two-way comparisons were also made between the fragile X and nonspecific MR groups, as well as between the fragile X and autistic groups. Here, all differences failed to reach significance, except the difference in echolalia in the latter comparison ($F = 5.78, p < .03$), indicating higher frequencies of echolalia for the autistic group. The only two-way comparison to approach significance ($F = 2.49, p < .13$) was that between the fragile X and the nonspecific MR groups on the Expressive Composite Score, sug-

Table VI. Chi-Squared Values for Comparisons of Nominal Speech Sample Ratings for Three Diagnostic Groups

Variable	χ^2	$p <$
Vocal quality	12.40	.13[a]
Vocal volume	4.26	.64
Rate of speech	5.63	.47
Intonation pattern	4.21	.37
Intelligibility rating	1.40	.50

[a]Difference approaches significance.

Table V. Mean Scores (and Standard Deviations) and F and p Values of Comparisons of Language Measures Among Three Diagnostic Groups

Variable	Fragile X	Nonspecific MR	Autistic	F	$p <$
Receptive composite age score	3.05 (.88)	3.24 (1.06)	3.17 (1.13)	.10	.91
Expressive composite age score	2.48 (.98)	3.25 (1.39)	2.88 (1.55)	1.02	.37
PPVT raw score	24.83 (19.87)	33.10 (26.09)	29.25 (22.00)	.39	.68
TACL raw score	47.75 (18.26)	51.67 (25.37)	40.08 (24.18)	.80	.46
TOLD-GU raw score	5.50 (4.08)	3.92 (3.37)	5.08 (4.60)	.49	.62
TOLD-SI raw score	1.42 (2.43)	.42 (.79)	1.00 (1.28)	1.11	.31
TOLD-GC raw score	1.42 (2.39)	3.25 (4.79)	2.92 (5.57)	.58	.57
EOWPVT raw score	28.42 (19.11)	37.25 (26.67)	38.33 (24.93)	.63	.54
MLU	3.00 (1.76)	3.75 (2.13)	2.14 (1.68)	2.15	.13[a]
Goldman-Fristoe raw score	50.83 (21.47)	52.40 (18.67)	60.38 (12.29)	.69	.51
Percent dysfluent syllables	2.88 (3.79)	2.75 (3.99)	2.00 (2.24)	.14	.87
Topic perseverations per sample	3.44 (6.14)	9.22 (14.29)	8.00 (11.22)	.68	.51
Instances of echolalia	2.22 (5.59)	4.11 (9.80)	16.33 (16.70)	3.90	.03[b]
Instances of palilalia	.11 (.33)	.00 (.00)	1.33 (3.04)	1.58	.22
Percent unintelligible words	24.03 (16.60)	29.01 (25.13)	42.23 (35.04)	.85	.44

[a]Difference approaches significance.
[b]Significant difference.

gesting a trend toward poorer performance on standardized measures of expressive language on the part of the fragile X group.

DISCUSSION

These results may seem rather surprising in light of the previously cited reports on the apparently distinctive speech and language characteristics of individuals with the fragile X syndrome. One reason for our failure to find such differences may be the relatively small size of the sample, particu-

larly for the measures of expression, where only nine subjects per group produced enough speech to rate. Two differences that approached significance, the difference in MLU among the three groups and the difference between the fragile X and the nonspecific MR group in the Expressive Composite Score, suggest that the fragile X individuals do show deficits in several areas of expressive syntax and morphology relative to individuals with nonspecific MR (MLUs in the autistic group were lower than those of the fragile X subjects owing to a general sparsity of speech that contributed to receiving a diagnosis of autism). A larger sample of individuals with some spontaneous speech may have allowed these comparisons to reach significance. It is important to be aware that the scores reported here reflect, for the most part, skills on formal language measures and do not look at interactive abilities or conversational skill, which would presumably highlight the communicative difficulties of autistic individuals.

The effects of institutionalization may also have contributed to this outcome. That is, these subjects had spent an average of over 25 years of their lives in an institutional setting. Most had entered the institution in early adolescence or before. Studies of deinstitutionalization suggest that institutionalized individuals show reduced language performance relative to similar individuals in other settings (Kleinberg & Galligan, 1983). The effects of institutionalization may, then, have diluted any group differences that might have been present.

Pilot work on longitudinal changes in performance on standardized language and IQ measures by individuals with fragile X syndrome (Leckman & Paul, 1985) and on language performance by children with the syndrome (Paul et al., 1984) may also be relevant to these findings. In these initial investigations, fragile X individuals appeared to make rapid progress in receptive vocabulary and mental age until very early adolescence, at which point they plateaued quite suddenly and failed to make further gains. This pattern of development contrasts with that of other retarded individuals who seem to advance more slowly in mental age throughout childhood, but continue to make gains until later in adolescence (Fisher & Zeaman, 1970). Studies of the language of children with the syndrome (Paul et al., 1984; Hagerman & McBogg, 1983), while employing no contrast groups, suggest that comprehension skills are similar to those expected on the basis of mental age, while speech characteristics such as developmental dyspraxia accompanied by some dysfluency are typical of the syndrome in childhood. Like the hyperactivity observed in fragile X children, these characteristics may abate in adulthood, leaving perhaps only slightly depressed performance in general expressive language skills.

The picture of the institutionalized adult with the fragile X syndrome drawn from this study includes comprehension skills similar to those of com-

parable retarded individuals, and some limitations in syntax and morphology relative to adults with nonspecific MR. The study suggests that fragile X individuals generally produce more spontaneous speech—at least as indexed by MLU—and less echolalia than retarded adults who are considered by institutional staff to be autistic, although some fragile X individuals will also meet behavioral criteria for the diagnosis of autism (in this sample, 17%). However, other speech and language deficits that have been reported in the literature—such as intonational differences, increased dysfluency, perseveration, palilalia, and poor auditory reception—do not apear to distinguish institutionalized individuals with fragile X syndrome from adults with similar retardation of different etiology. If there is a pattern of language skills within the institutionalized adult fragile X population, it is likely to consist of a general depression in productive language ability rather than a unique constellation of speech and language peculiarities. These findings are consistent with other recent studies of fragile X individuals, suggesting that some of the phenotypic characteristics previously considered pathognomonic, such as macroorchidism, are in fact more variable than previously thought (Fryns, 1984).

Several research strategies remain to be explored in order to refine further the knowledge of the behavioral characteristics of the fragile X syndrome, and their development throughout the life-span. First, controlled studies involving larger samples of subjects are needed, as are studies of noninstitutionalized individuals. These studies can help to clarify some of the sampling issues raised by the present report. Second, controlled studies of language and other behavioral characteristics of children are needed in order to evaluate the speculation made here that distinctive characteristics present in childhood may disappear by the adult years. Finally, controlled studies of the developmental course of cognitive and language patterns of the fragile X syndrome, in contrast to other forms of retardation, will serve to broaden the understanding of the natural history of this condition, and will have implications for identification and treatment as well.

If, for example, our preliminary observations—suggesting that children with the fragile X syndrome show rapid rates of cognitive and receptive language growth in early childhood, followed by specific types of expressive language difficulties during the school years, with an early plateauing of all skill areas in early adolescence and limited expressive skills, relative to comprehension in adulthood—are substantiated by larger-sample controlled studies, certain therapeutic practices would be indicated. Children with fragile X syndrome would be especially likely targets for early intervention, since their learning potential appears greatest during the preschool and early school years. Expressive language skills would be targeted from the beginning, since they would be likely to plateau earlier than do other abilities.

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