Social Behavior Profile in Young Males With Fragile X Syndrome: Characteristics and Specificity

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The present study characterizes distinctive and specific features of social behavior impairment, termed social behavior profile (SBP), in young males with fragile X syndrome (FraX). Fourteen males with FraX and autism (FraX+Aut), ages 3–8 years, were compared with either 41 FraX boys without autism (Aut), 7 age-matched males with developmental language delay and autism (DLD+Aut), or with 11 boys with non-selected (for language delay) idiopathic autism (IA), on several standardized instruments assessing social behavior and autistic features (i.e., autism diagnostic interview-revised, ADI-R). We found that FraX+Aut subjects displayed more impairment in overall cognition, problem/aberrant behavior, and adaptive behavior than the rest of the FraX cohort, even when individuals with pervasive developmental disorder (PDD) were included in the latter. Compared to both DLD+Aut and IA, FraX+Aut males were less impaired in ADI-R reciprocal social interaction (RECS) domain. However, boys with FraX+Aut were in general comparable to DLD+Aut subjects in problem/aberrant and adaptive behaviors. Based on the contrast between FraX+Aut and non-autistic FraX and DLD+Aut, we were able to identify measures (e.g., child behavior checklist (CBCL) withdrawn subscale) that better define social interaction impairment in FraX. Comparisons with DLD+Aut and IA led to the conclusion that communication impairment (COMM) and stereotypic behavior contribute relatively more to the diagnosis of autism in FraX+Aut. In agreement with recent studies, our data suggest that FraX+Aut, and more generally SBP, is a distinctive subphenotype among boys with FraX, which may share some pathophysiological mechanisms with IA.
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KEY WORDS: fragile X; social behavior profile; autism; autism diagnostic interview; child behavior checklist; social withdrawal

INTRODUCTION

Fragile X syndrome (FraX) is the most common cause of heritable mental retardation, affecting approximately 1:4,000 males and 1:6,000 females [Kaufmann and Moser, 2000]. FraX is associated with an unstable expansion of a polymorphism within the 5′ untranslated region of the *FMR1* gene, located in the X chromosome [Kaufmann and Reiss, 1999]. Based on the size of the repeat, alleles are classified as normal (5–40 repeats), intermediate or gray zone (41–60 repeats), premutation (PM, 61–199 repeats), or full mutation (FM, >200

repeats). A mixed PM+FM pattern is termed mosaicism [Kaufmann et al., 2002]. While FM alleles are associated with hypermethylation, gene silencing, and severe phenotype, typical and methylation mosaicism show a generally milder cognitive impairment [Hagerman et al., 1994; Kaufmann and Reiss, 1999; Kaufmann et al., 1999]. Males are typically more affected, particularly those with FM, presenting with not only cognitive impairment but also behavioral abnormalities. Although the behavioral phenotype of males with FraX has been delineated in general terms [Reiss and Freund, 1992; Freund, 1994; Kerby and Dawson, 1994; Lachiewicz et al., 1994; Baumgardner et al., 1995; Freund et al., 1995; Kau et al., 2000], the variability and specificity of the manifestations are still controversial issues [Turk and Graham, 1997; Bailey et al., 1998; Rogers et al., 2001].

Autism (Aut) is one of the most severe behavioral abnormalities associated with FraX [Hagerman et al., 1986; Baumgardner et al., 1995; Cohen, 1995; Bailey et al., 1998; Kaufmann and Reiss, 1999]. As in the case of other developmental disorders [Gath and Gumley, 1986; Kent et al., 1999], autistic features seem to concentrate among those FraX individuals with more severe cognitive impairment [Cohen, 1995; Bailey et al., 2000; Rogers et al., 2001]. A recent focus of attention has been on the identification of specific features that distinguish males with FraX and autism (FraX+Aut) from those with Aut of unknown cause. Bailey et al. [1998] found that boys with FraX+Aut had a comparable "Childhood autism rating scale (CARS)" profile to a large group with idiopathic Aut, although the severity of manifestations was milder in the FraX group. In contrast, Rogers et al. [2001] reported that young boys with FraX+Aut had similar "Autism diagnostic interview-revised (ADI-R)" and "Autism diagnostic observation schedule-generic (ADOS-G)" patterns to those of matched idiopathic Aut subjects. Despite their discrepant findings, these two studies are among the first attempts at using standardized instruments for the evaluation of autistic features in males with FraX.

The importance of a more precise delineation of the FraX+Aut profile is underscored by the fact that this subgroup of FraX boys appears to display other behavioral abnormalities. Hatton et al. [2002] recently reported that total problem behavior scores, measured by the "Child behavior checklist (CBCL)," were related to autistic behavior as determined by CARS scores. Rogers et al. [2001] found that young males with FraX had lower developmental equivalent scores of adaptive behavior, assessed by the "Vineland adaptive behavior scales (VABS)" [Sparrow et al., 1984], than a developmentally delayed contrast group but similar to group with Aut. Nonetheless, the FraX+Aut group was more impaired than non-autistic FraX subjects in adaptive behavior. In agreement with previous data showing a direct relationship between adaptive behavior and overall cognitive level [Fisch et al., 1994], the FraX+Aut Aut group had also a significantly lower performance on the Mullen scales of Early Learning [Rogers et al., 2001], a standardized developmental test for infants and young children [Mullen, 1995]. Altogether, the latter findings

have been interpreted as a demonstration that the FraX+Aut is a distinctive FraX subphenotype, with considerable similarities to idiopathic Aut [Rogers et al., 2001].

The above mentioned studies [Rogers et al., 2001; Hatton et al., 2002], as well as our own previous research [Freund et al., 1995; Kau et al., 2000], suggest that autistic behavior, problem/aberrant behavior, and adaptive behavior are interrelated in boys with FraX. This notion is supported by prior studies of children with other developmental disorders, such as Williams syndrome and idiopathic Aut [Rescorla, 1988; Greer et al., 1997; Bolte et al., 1999]. A further elucidation of this aspect of the FraX phenotype, which we have termed "Social behavior profile (SBP)," particularly in terms of the overlap between FraX and idiopathic Aut, may be of significance for understanding the genetic and neurobiologic mechanisms underlying these disorders. Characterizations of the SBP of boys with FraX could also provide additional information about the spectrum of the FraX+Aut subphenotype. Considering that previous studies have indicated that the frequency of autistic features [Hagerman et al., 1986; Baumgardner et al., 1995; Bailey et al., 1998], and prominence of other related behavioral abnormalities [Fisch et al., 1999; Kau et al., 2000; Hatton et al., 2002], is higher in very young males with FraX, a focused study of this subgroup of males with FraX could also be quite informative. Consequently, the present investigation intended to determine:

1. whether there is a distinctive SBP, specifically of problem and adaptive behaviors, in young boys (i.e., under the age of 8 years) with FraX+Aut.
2. if such a SBP is found, whether there are differences between very young males (i.e., under the age of 5 years) and the rest of the FraX+Aut cohort.
3. whether the pattern of autistic features, as measured by the ADI-R, of young males with FraX+Aut is different from the one exhibited by boys with idiopathic Aut.
4. whether the SBP of young males with FraX+Aut is different from the one displayed by boys with idiopathic Aut.

MATERIALS AND METHODS

Subjects

The present study included boys with FraX syndrome with (FraX+Aut) and without autism (FraX), respectively, and two contrast cohorts: developmental language delay with autism (DLD+Aut) and a group with non-selected for language delay idiopathic autism (IA). A total of 55 boys with FraX (mean age: 57.4 ± 13.9 months, mean IQ: 54.8 ± 16.6) and a total of 22 boys with DLD (mean age: 56.5 ± 11.6, mean IQ: 70.4 ± 25.2) were recruited as part of a study of cognitive and social behavior of young males with FraX at the Kennedy Krieger Institute (Baltimore, MD). All participants with FraX, DLD, or IA were screened for FraX by the use of standard Southern blotting techniques [Rousseau et al.,

1991], followed by clinical examination. Of the 55 FraX subjects, 41 individuals (approximately 72%) were diagnosed with full mutation; the remaining were mosaic for the *FMR1* mutation. Fourteen of the 55 FraX subjects met the criteria for autism as determined by the ADI-R [Lord et al., 1989, 1994], (FraX+Aut) (mean age: 60.1 ± 16.9, mean IQ: 43.1 ± 14.1), and the DSM-IV. Twelve of the FraX+Aut subjects were diagnosed to have *FMR1* full mutation and two were mosaic.

The first contrast group, the DLD group, was included in the study due to the characteristic speech and language [Freund, 1994] and adaptive communication delay [Fisch et al., 1999] in the FraX population. Approximately 32% or 7 subjects met the ADI-R criteria of autism (DLD+Aut) (mean age: 59.2 ± 13.7, mean IQ: 52.4 ± 21.2). The second contrast group consisted of eleven subjects with non-selected IA, who were recruited as part of a larger study of neuroanatomical variation in monozygotic twins discordant for autism (mean age: 107.4 ± 32.7, mean IQ: 66.3 ± 18.1). The IA group, which was included on the basis of no specified language delay, was recruited primarily through the Autism Society of America, the psychiatry, neurology, and developmental pediatrics clinics at the Kennedy Krieger Institute, and by "word-of-mouth." Children were initially screened with the "Autism behavior checklist (ABC)" [Nordin and Gillberg, 1996], and enrolled in the study if the score on the ABC was >57. Then, the IA subjects were administered the ADI-R for confirmation of the diagnosis of autism. All autistic subjects, under study, FraX+Aut, DLD+Aut, and IA met DSM-IV diagnostic criteria for autism. A summary of the characteristics of the subjects under study is shown in Table I.

This study was approved by the authors' Institutional Review Board and written informed consent was obtained from all parents or legal guardians of the subjects, after the procedures were fully explained.

Instrumentation

Cognitive evaluation. To assess the cognitive ability of the subjects with FraX and DLD, the Stanford Binet-IV (SB-IV) [Thorndike et al., 1986] or the Bayley Scales of Infant Development II (BSID-II)-Mental Scales [Bayley, 1993] was administered. The SB-IV was administered to all participants who were able to establish a true basal. The remaining subjects were evaluated by the BSID-II, in order to obtain the "Mental developmental index (MDI)." If the child's chronological age was >42 months, a BSID-II-estimated IQ was calculated by dividing the mental age-equivalent by the chronological age and multiplying the ratio by 100. All but one child with IA were administered the SB-IV; measures of cognitive abilities for the non-tested subject are not reported. Level of cognitive impairment was not used to exclude subjects (i.e., severe-profound mental retardation). The test composite score from SB-IV, the MDI, and the BSID-II-estimated IQ, representing levels of overall cognitive abilities, were labeled as "IQ" for data analysis purposes (see Table I).

Autistic behavior. Autism related features were assessed by the Autism Diagnostic Interview-Revised (ADI-R) [Lord et al., 1994], a standardized semi-structured diagnostic interview conducted with the child's mother to obtain detailed descriptions of behavioral symptoms associated with criteria for DSM-IV diagnosis of "Pervasive developmental disorder (PDD)" and autism (Aut). The ADI-R depends on descriptions of behaviors that indicate developmental deviance rather than developmental delay. The ADI-R provides total and separate scores in three areas: "Communication impairment (COMM)," "Reciprocal social interaction (RECS)," and "Repetitive behaviors and stereotyped patterns (REPS)." A diagnosis of autism was given if the participant met the cut-off criteria for each of the three areas and the developmental deviance occurred before age 3 years.

The ADI-R was administered to the participant's mother by a trained interviewer; two interviewers, who were blind to group membership, were used in this study to administer the ADI-R interview. The interviewers were trained by a psychologist who was authorized by Catherine Lord, Ph.D. to administer the ADI-R. Reliability of total scores for the three domains was established between the psychologist and the two interviewers. Reliability intraclass correlation coefficients ranged between 0.88 and 0.94.

Problem/aberrant behavior assessment. Problem/aberrant behaviors were assessed by the CBCL and the "Aberrant behavior checklist-community (ABC-C)." The CBCL is a well-standardized and widely used parent report instrument given to assess several factors of common childhood behavior and emotional problems. Depending on the age of the participant, the 2–3 year version [Achenbach, 1992] or the 4–18 year version [Achenbach, 1991] of CBCL was completed by the parent. There are six subscales and eight subscales in

TABLE I. Characteristics of Participants

Diagnosis	Subjects (n)	Age (mo.) (mean, SD)	IQ (mean, SD)	Behavioral measures
Fragile X				
With autism (FraX+Aut)	14	60.1, 16.9	43.1, 14.1[a,b]	ADI-R, CBCL, ABC-C, VABS
Without autism	41	56.4, 13.1	59.3, 15.4[a,b]	ADI-R, CBCL, ABC-C, VABS
Language-delayed				
With autism (DLD+Aut)	7	59.1, 13.6	52.4, 21.2[a,b]	ADI-R, CBCL, ABC-C, VABS
Idiopathic autism (IA)	11	102.4, 28.9	66.3, 18.0[b]	ADI-R, VABS[c]

[a]IQ-equivalent by BSID-II.
[b]FSIQ by SB-IV.
[c]Analyses based on a sample of six subjects.

the 2–3 year and 4–18 year versions, respectively. The majority of the syndrome subscales are grouped within two domains: Internalizing and Externalizing behaviors. The Internalizing behavior domain includes, in the 2–3 year version, Withdrawn and Anxious/depressed subscales. In the 4–18 year version, the Internalizing domain also includes the Somatic complaints subscale, which in the 2–3 year version is analyzed separately. The Externalizing domain includes the Aggressive and Destructive behavior subscales, in the 2–3 year version, and the Aggressive and Delinquent behavior subscales in the 4–18 year version. Additional syndrome subscales include, in the 2–3 year version, Sleep problems, and in the 4–18 year version Social problems, Thought problems, and Attention problems. T scores can be generated for each syndrome subscale, as well as for both the Internalizing and Externalizing behavior domains. A total T score, combining all subscales can also be calculated. For the Internalizing and Externalizing behavior domains and the Total Composite T score, T scores between 60 and 63 are considered to be in the borderline clinical range, while T scores above 63 are in the clinically significant range. T scores for all the syndrome subscales between 66 and 70 are considered to be in the borderline clinical range, while T scores above 70 are in the clinically significant range.

The feasibility of applying CBCL to developmental disabled populations, in general, and to FraX in particular, was recently reviewed by Hatton et al. [2002].

The ABC-C [Aman and Singh, 1986] is also a parent report measure of inappropriate and maladaptive behaviors in individuals, between 3–18 years, with developmental disabilities. All five subscales, Irritability, Lethargy/social withdrawal, Stereotypic behaviors, Hyperactivity, and Inappropriate speech, were included in the data analysis.

Adaptive behavior evaluation. Adaptive behavior was assessed using the "Vineland adaptive behavior scales, survey from, Interview edition (VABS)" [Sparrow et al., 1984]. The VABS, which was administered through a semi-structured interview with the parent, provides a general assessment of adaptive behavior from birth to 18 years of age. The VABS provides Adaptive behavior composite scores and four domain scores (communication, daily living skills, socialization, and motor skills). Age equivalents of all five scores were used in the data analysis.

Problem/aberrant behavior, in combination with adaptive behavior, and ADI-R diagnosis are referred in the following sections of the article as SBP.

Data Analysis

Several statistical tests and approaches were used for data analysis. Descriptive statistics helped to determine distribution of values and interpretation of results from non-parametric tests. Considering that many parameters, particularly in the FraX+Aut and DLD+Aut groups, were not distributed normally and that the aforementioned groups were relatively small, we conducted all analyses using non-parametric tests employing the Mann–Whitney U test for two-group comparisons. Taking into account that preliminary analyses of the subjects' characteristics demonstrated differences in age and IQ between several groups, we conducted where appropriate additional analyses of co-variance (ANCOVA). As in previous publications [Cutting et al., 2002], we selected posthoc analyses that complement the non-parametric tests. Specifically, the Scheffe's test was applied since it is robust to violations of assumptions, non-normal distribution, unequal *ns*, and heterogeneous variances [Scheffe, 1953]. Following earlier studies [Kaufmann et al., 2000], we considered biologically significant only those results that were concordant on both Mann–Whitney and ANCOVAs. For reading simplicity, mainly Mann–Whitney P values are cited in the text. Most analyses were hypothesis-driven and performed in a hierarchical fashion. For instance, in the case of the CBCL and ADI-R, we examined first domains and, when these were found to be significant, their subcomponents (e.g., CBCL internalizing behavior domain followed by its syndrome subcomponents: withdrawn, somatic complaints, anxious/depressed).

RESULTS

Preliminary Analyses of FraX and Autism Cohorts

Table I illustrates the characteristics of the subjects under study. The FraX cohort consisted of 55 boys, which according to ADI-R criteria were distributed as follows: 14 FraX+Aut, 18 FraX+PDD, and 23 FraX-only (without PDD or autism by ADI-R and DSM-IV). The entire DLD cohort was analyzed only with the purpose of describing the population from which the language-delayed autistic subjects were identified. It consisted of 7 subjects with Aut, 3 with PDD, and 12 without ADI-R/DSM-IV abnormal diagnosis. Only the 7 DLD+Aut subjects were further analyzed in this study. The IA cohort consisted of 11 subjects, all of them with ADI-R/DSM-IV-based diagnosis of Aut. In terms of age, there was no difference between the FraX and DLD cohorts, the FraX subgroups, or between the FraX+Aut and DLD+Aut groups. The IA group was significantly older ($P = 0.0004$) than the FraX+Aut group (mean ages: 102.4 months and 60.1 months, respectively). In terms of IQ, (all) FraX subjects were significantly more impaired than the entire DLD cohort (55.2 ± 16.5 vs. 70.4 ± 25.1, $P = 0.02$). Differences in IQ between the FraX subgroups, or the FraX+Aut and the two autistic groups are shown in Table I and mentioned in the following sections.

SBP of Autistic and Non-Autistic FraX Males

Considering that a large proportion (~33%) of our FraX sample was diagnosed as having PDD and that, at present, there is no clear neurobiological distinction between individuals with PDD and those with Aut, we conducted two sets of analyses. In the first one, we compared the 14 FraX+Aut subjects with the 41 non-autistic FraX boys. We then repeated the analyses excluding the 18 FraX+PDD subjects, with emphasis on

those parameters that differentiated autistic and non-autistic FraX subjects in the first analysis. Essentially, both set of analyses yielded the same results. In terms of overall cognition (i.e., IQ), the FraX+Aut group was significantly ($P = 0.0014$) more impaired than the non-autistic FraX group (mean IQ: 43.1 vs. 59.3). When the FraX+PDD subjects were excluded, these differences remained (43.1 ± 14.1 vs. 63.7 ± 12.9, $P = 0.0002$). Considering the high agreement between the FraX+Aut vs. FraX+PDD/FraX-only and FraX+Aut vs. FraX-only comparisons, the data summary presented below illustrates only the FraX+Aut vs. FraX+PDD/FraX-only analyses. Complementing the latter information, Table II summarizes the comparisons between the FraX+Aut and the FraX+PDD/FraX-only (non-autistic FraX) groups.

Regarding problem behavior (Table II), CBCL total scores were higher in the FraX+Aut (mean score: 61.9 vs. 57.1, $P = 0.012$). Among the composite scales, the internalizing behavior domain was a contributor to these differences, since T scores were significantly higher for the FraX+Aut group (mean score: 58.1 vs. 51.6 for the non-autistic FraX group, $P = 0.02$). No differences were found for the externalizing behavior domain. Among the syndrome subscale components of the internalizing domain, T scores for the Withdrawn were higher in the FraX+Aut group (mean score: 63.4 vs. 56.1, $P = 0.001$). The attention problems subscale was also higher in the FraX+Aut group (mean score: 72.3 vs. 66.2, $P = 0.02$). Despite these differences, the attention problems scale reached the borderline-clinical range (i.e., T score > 66) for both groups. Although ANCOVAs (co-varying for IQ) did not show differences in CBCL total scores, they confirmed the significance of the higher scores in the internalizing domain and the withdrawn and attention problems subscales in the autistic FraX group.

Analyses of the five ABC-C scales also demonstrated higher scores of aberrant behavior in the FraX+Aut group (Table II). As for the CBCL Withdrawn, the ABC-C lethargy/social withdrawal scale was significantly different in FraX+Aut (mean score: 10.3 vs. 3.4, $P = 0.0004$). Scores for the stereotypic behaviors scale were again higher in the FraX+Aut group (6.8 vs. 3.5, $P = 0.02$). Mann–Whitney and ANCOVAs were concurrent.

Comparison of age-equivalent (months) scores on the VABS showed a greater impairment (i.e., reduction) in adaptive behavior, across all four domains, in the FraX+Aut with respect to non-autistic FraX subjects (Table II). In the Communication domain, mean scores were 23.9 and 31.8, respectively ($P = 0.01$). However, after co-varying for IQ, there were no differences in this domain between the two FraX groups. In contrast, for all other VABS comparisons Mann–Whitney and ANCOVAs were concordant. Daily living skills mean age-equivalents were 24.7 and 36.8, for FraX+Aut and non-autistic FraX+Aut, respectively ($P = 0.003$). For the VABS motor skills domain, mean age-equivalent scores were 26.9 and 34.1, respectively ($P = 0.04$). Scores on the VABS socialization domain showed the greatest differences between autistic and non-autistic FraX subjects

TABLE II. Problem/Aberrant and Adaptive Behavior Profiles

Behavioral measure	Scale	FraX+Aut			Non-autistic FraX			DLD+Aut		
		Mean	SD	n	Mean	SD	n	Mean	SD	n
Total	CBCL	61.9	7.1	13*	57.1	6.4	39	65.7	9.1	7
Internalizing	CBCL	58.1	6.8	13**	51.6	8.5	38	63.3	9.7	7
Withdrawn	CBCL	63.4	6.4	13***	56.1	6.7	39	71.7	9.6	7 [#]
Anxious/depressed	CBCL	53.5	5.3	13	53.6	5.1	39	52.0	3.1	6
Externalizing	CBCL	52.5	9.8	13	51.2	8.0	38	56.8	14.3	6
Aggressive behavior	CBCL	55.1	7.1	13	53.9	6.1	39	60.0	11.9	7
Delinquent behavior	CBCL	51.4	3.1	9	53.1	4.9	28	56.8	11.0	4
Attention problems	CBCL	72.3	5.6	9****	66.2	6.9	28	68.7	12.5	4
Social problems	CBCL	63.7	3.5	9	60.9	8.8	28	60.0	5.6	6
Thought problems	CBCL	66.5	5.1	9	62.1	8.4	28	69.3	3.8	4
Irritability	ABC-C	9.9	7.8	13	9.5	7.4	36	14.0	3.9	7
L/SW[a]	ABC-C	10.3	6.8	13[##]	3.4	3.5	36	15.7	13.9	7
SB[b]	ABC-C	6.8	4.6	13[###]	3.5	3.2	36	6.0	4.8	7
Hyperactivity	ABC-C	20.1	8.1	13	17.9	9.0	36	21.3	9.9	7
Inappropriate speech	ABC-C	2.8	3.2	13	2.6	2.2	36	3.0	3.9	7
Composite	VABS	23.8	12.1	14[&]	34.9	11.7	41	25.4	16.8	7
Communication	VABS	23.9	16.8	14[&]	31.8	13.5	41	20.9	17.7	7
Daily living	VABS	24.7	9.8	14[&]	36.8	13.1	41	26.3	20.6	7
Motor	VABS	26.9	8.7	12[&]	34.1	9.2	37	34.8	17.9	6
Socialization	VABS	20.4	12.0	14[&]	36.6	13.3	41	20.7	18.7	7

*Mann–Whitney; FraX+Aut vs. non-autistic FraX, $P = 0.01$.
**Mann–Whitney; FraX+Aut vs. non-autistic FraX, $P = 0.02$.
***Mann–Whitney; FraX+Aut vs. non-autistic FraX, $P = 0.002$.
****Mann–Whitney; FraX+Aut vs. non-autistic FraX, $P = 0.02$.
[#]Mann–Whitney; FraX+Aut vs. DLD+Aut, $P = 0.057$.
[##]Mann–Whitney; FraX+Aut vs. non-autistic FraX, $P = 0.0004$, [a]Lethargy/social withdrawal scale.
[###]Mann–Whitney; FraX+Aut vs. non-autistic Frax, $P = 0.02$, [b]Stereotypic behaviors scale
[&]Mann–Whitney; FraX+Aut vs. non-autistic FraX, $P \leq 0.01$.

(mean score: 20.4 and 36.6, respectively, $P = 0.0003$). In accordance with the aforementioned data, the VABS composite score was also significantly lower in the FraX+Aut group (mean score: 23.8 vs. 34.9, $P = 0.003$).

SBP in FraX Males With Autism Stratified by Age

Taking into consideration previous reports indicating that frequency, and perhaps severity, of autistic features is greater in very young males with FraX [Rogers et al., 2001], we performed exploratory analyses comparing our six youngest FraX+Aut subjects (under age 5 years) with those FraX+Aut boys between 5–8 years ($n = 8$) in terms of SBP. Both groups did not differ in IQ, problem behavior, or aberrant behavior. In line with the differences in chronological age, there were differences in adaptive behavior between the two FraX+Aut groups. On two of the four VABS domains, the Daily living skills and motor skills as well as on the VABS composite score, the younger FraX+Aut exhibited lower age-equivalent scores (mean scores: 16.0 and 31.2, $P = 0.003$; 18.8 vs. 32.7, $P = 0.0045$; 15.2 vs. 30.1, $P = 0.017$). Interestingly, differences were not significant in the socialization (mean scores: 13.3 vs. 25, $P = 0.053$) and communication (mean scores: 14.5 vs. 30.9, $P = 0.15$) domains. These results are in agreement with the longitudinal evaluation of adaptive behavior, by VABS, reported by Fisch et al. [1999], which demonstrated an increase over time in daily living skills in boys with FraX.

Profiles of Autistic Behavior in FraX and IA

The specificity of the autistic profile of the FraX+Aut group was examined by comparing ADI-R scores of the FraX+Aut with those of an age-matched language delayed group of autistic boys (DLD+Aut) and with those of a group of non language-selected autistic boys (IA). The first comparison addresses the issue of the characteristic language/COMM exhibited by FraX boys [Freund, 1994; Baumgardner et al., 1995; Kau et al., 2000], by controlling for language delay. Consequently, since ADI-R (and DSM-IV) evaluates three areas of autistic behavior (Table III), namely Communication, Social Reciprocity, and Restricted Interests/Behaviors

[Lord et al., 2001], differences between subjects with FraX+Aut and those with DLD+Aut will be mainly contributed by the latter two areas and/or by a more severe impairment in Communication in one of the groups. The second analysis intended to confirm in non-selected group of autistic boys the differences in the ADI-R, if any, shown by the first comparison. For this purpose, we included a group of young males with idiopathic Aut (IA) who were recruited, for a parallel study, without any ascertainment bias. Our preliminary analyses (see Table I) showed that the FraX+Aut and DLD+Aut groups had comparable mean ages and that, although higher in DLD+Aut, the differences in IQ were not significant ($P = 0.35$). Therefore, all comparisons between FraX+Aut and DLD+Aut were done exclusively by Mann–Whitney analyses. In contrast, the IA group was significantly older ($P = 0.0004$) and had significantly ($P = 0.0045$) higher IQ than the FraX+Aut Aut group. Consequently, the comparisons between FraX+Aut and IA were conducted by the dual nonparametric/ANCOVA approach.

We found that scores for RECS were significantly lower in the FraX+Aut group than in the DLD+Aut group (mean score: 18.6 vs. 23.1, $P = 0.044$). Continuing our hierarchical approach, we examined which items of RECS domain contributed to these differences. Scores on Social smiling (B1, 43) and seeking to share own enjoyment with others (B3, 47) were significantly lower in the FraX+Aut group (mean scores: 1.0 vs. 2.0, $P = 0.003$ and 0.6 vs. 1.6, $P = 0.008$, respectively). Two other items were lower in the FraX+Aut, but at a trend level: Direct gaze (B1, 42; mean scores 1.17 vs. 1.86; $P = 0.052$) and Offering to share (B3, 46; mean scores: 1.25 vs. 1.85; $P = 0.099$).

Comparisons between the FraX+Aut and IA groups confirmed, to large extent, the milder ADI-R profile of the FraX+Aut found in the first analysis. Although the scores for RECS domain were lower (i.e., less impairment) but not significant ($P = 0.07$; $P = 0.14$ after ANCOVA) in the FraX+Aut group, several of the items within the RECS domain that were informative in the FraX+Aut vs. DLD+Aut comparison were also significantly different in the FraX+Aut vs. IA comparison. Scores on social smiling and seeking to share own

TABLE III. Autistic Behavior Profiles

ADI-R domain/item	FraX+Aut			DLD+Aut			IA		
	Mean	SD	n	Mean	SD	n	Mean	SD	n
Total	36.4	6.8	14	40.7	8.1	7	45.1	9.7	11
Reciprocal social interaction (RECS)*	18.6	4.9	14	23.1	5.0	7	22.0	5.3	11
Direct gaze**	1.17	0.72	12	1.86	0.38	7	1.18	0.60	11
Social smiling*,#	1.00	0.60	12	2.00	0.00	7	1.45	0.68	11
Offering to share**,##	1.25	0.75	12	1.85	0.38	7	1.63	0.80	11
Seeking to share own...*,#	0.58	0.52	12	1.57	0.54	7	1.18	0.75	11
Communication#	12.4	2.8	14	13.0	2.8	7	16.8	4.3	11
Repetitive behaviors	5.4	1.7	14	4.5	1.3	7	6.3	1.3	11

*Items showing significant differences ($P < 0.05$) between FraX+Aut and DLD+Aut.
**Items showing trend level ($0.10 < P > 0.05$) differences between FraX+Aut and DLD+Aut.
#Items showing significant differences ($P < 0.05$), by ANCOVA (age, IQ) between FraX+Aut and IA.
##Items showing trend level ($0.10 < P > 0.05$) differences, by ANCOVA (age, IQ) between FraX+Aut and IA.

enjoyment with others were lower, at trend or near trend level by Mann–Whitney, and became significant in FraX+Aut after age/IQ correction ($P = 0.027$ and 0.0009, respectively). One of the two other items that were lower, at a trend level in the FraX+Aut vs. DLD+Aut comparison, Offering to share showed also a trend ($P = 0.055$ after ANCOVA) towards lower scores in FraX+Aut when contrasted with the IA group. Surprisingly, if one considers the language impairment of the FraX+Aut group, COMM scores were significantly ($P = 0.01$; $P = 0.016$ after ANCOVA) higher (i.e., more impairment) in the IA group. Scores on the REPS domain were also lower, but not significantly ($P = 0.15$ after ANCOVA), in the FraX+Aut group.

SBP of Autistic FraX and Idiopathic Autistic Boys

Based on the findings presented above, indicating that there is a distinctive SBP in boys with FraX+Aut that distinguishes them from non-autistic FraX males and that the ADI-R profile of FraX+Aut subjects appears to be milder than in boys with idiopathic Aut, we hypothesized that the problem/aberrant behavior and adaptive behavior areas will be less affected in the FraX+Aut than in idiopathic Aut. Two sets of analyses were performed; the first one was modeled after the FraX+Aut vs. non-autistic FraX comparison, including CBCL, ABC-C, and VABS data of FraX+Aut and DLD+Aut subjects (Table II). The second analysis, contrasting the 14 FraX+Aut subjects with 6 IA boys, was restricted to VABS due to data availability.

Only scores on CBCL withdrawn subscale were lower, at a borderline significance level, in the FraX+Aut group with respect to DLD+Aut (mean scores: 63.4 vs. 71.7, $P = 0.057$). As expected from a recent study, which examined children diagnosed as having Aut by ADI-R [Bolte et al., 1999], the DLD+Aut group had high scores (Table II), at the borderline and even clinical range, in several CBCL scales (e.g., internalizing, withdrawn). Adaptive behavior (VABS) scores did not differentiate FraX+Aut and DLD+Aut subjects; however, scores on Daily living skills and Motor skills were higher in the DLD+Aut group. VABS age-equivalent scores on Communication, Daily living, and Socialization were also significantly higher in the IA group; however, after covarying for age and IQ, only differences in communication remained significant.

DISCUSSION

Our data demonstrate that autism co-morbidity in FraX labels a more global problem in social behavior, at least among young boys with FraX. We found that FraX+Aut subjects had lower IQ, higher scores (i.e., more impairment) in problem and aberrant behavior, particularly in items indicating social avoidance (i.e., CBCL withdrawn, ABC-C lethargy/Social withdrawal), and lower age-equivalent scores of adaptive behavior than the rest of the FraX cohort. These findings were irrespective of the inclusion of boys with PDD in the non-autistic FraX group. This profile appeared not to be age-dependent, since no differences were found between younger (under 5 years) and older (5–8 years) FraX+Aut subjects. However, younger FraX+Aut boys had lower age-equivalent Daily living and Motor skills VABS scores than their older counterparts suggesting that males FraX+Aut continue to develop some adaptive skills despite their autistic impairment. The autistic behavior profile of FraX+Aut appeared to be distinctive, in terms of its relatively milder social interaction impairment. Compared to both DLD+Aut and IA, FraX+Aut males were less impaired in ADI-R's RECS. With the exception of CBCL withdrawn, which showed lesser impairment in FraX+Aut, and VABS communication, which indicated greater impairment in FraX+Aut when compared with IA, boys with FraX+Aut were comparable to DLD+Aut and IA subjects in problem/aberrant and adaptive behaviors.

The present study intended to examine several aspects of the behavioral phenotype of males with FraX, which we have termed "social behavior profile (SBP)." Under SBP, we have included measures of one individual's interaction with other subjects, with particular emphasis on behavioral difficulties of clinical significance. Although this conceptual framework is not completely novel, to our knowledge, this is the first attempt at integrating three areas, namely autistic behavior, problem or aberrant behavior, and adaptive behavior, into a single behavioral construct (i.e., SBP). There is considerable evidence for the overlapping and complementary nature of the three aforementioned areas in developmental disabilities [Rescorla, 1988; Greer et al., 1997; Bolte et al., 1999], in general, and FraX in particular [Freund et al., 1995; Kau et al., 2000; Rogers et al., 2001; Hatton et al., 2002]. In a previous study of our FraX cohort, we reported CBCL attention problems scores in the borderline-clinical range [Kau et al., 2000], which were significantly different from those of a contrast group with developmental delay of unknown cause (mean scores of 67.1 and 63.1, respectively) [Kau et al., 2000]. In contrast, CBCL withdrawn and ABC-C lethargy/social withdrawal scores were significantly lower than those of the contrast group [Kau et al., 2000]. Remarkably similar CBCL profiles were found by Hatton et al. [2002], in a slightly older sample. The present investigation corroborated the high scores in the Attention problems subscale in FraX subjects, which were even higher in boys with FraX+Aut. We also confirmed the lesser impairment in the behaviors measured by the CBCL withdrawn and ABC-C lethargy/social withdrawal in FraX subjects. Scores for the CBCL withdrawn in the FraX+Aut group were intermediate between those in the non-autistic FraX boys and the DLD+Aut group. A similar situation involving the scores on CBCL internalizing domain is most likely a reflection of the CBCL withdrawn subscale. Emphasizing that the findings on the CBCL point out to a distinctive behavioral profile (i.e., SBP), ABC-C lethargy/social withdrawal scores paralleled those of CBCL withdrawn (see Table II).

In terms of general neurobehavioral development, the FraX+Aut group showed, as expected from previous reports [Rogers et al., 2001], lower IQ and greater adaptive behavior impairment than its non-autistic

FraX counterpart. Consistent with the existence of a SBP in FraX, the Socialization domain appeared as the most differentially affected component of the VABS in FraX+Aut. However, IQ and VABS differences with the idiopathic autistic groups were milder. IQ was only lower when FraX+Aut was compared with the non-selected autistic group (i.e., IA), probably reflecting the impact of language impairment on the IQ of both FraX+Aut and DLD+Aut. Although a previous study reported lower age-equivalent scores for adaptive behavior in a group of young autistic boys when compared with age-matched males with FraX [Bailey et al., 2000], as in the recent report by Rogers et al. [2001], our FraX+Aut group was comparable on VABS to both DLD+Aut and IA. Only VABS communication was more impaired in FraX+Aut when contrasted with IA, a finding that highlights the marked involvement of language [Freund, 1994] and adaptive communication [Fisch et al., 1999] in boys with FraX. Preliminary comparisons between younger (3–5 years) and older (5–8 years) FraX+Aut subjects did not reveal any difference in problem or aberrant behavior; nonetheless, VABS scores on Daily living and motor skills were higher in the older subgroup. This preliminary (i.e., small sample) and cross-sectional comparison suggests, as previously reported for FraX boys in general [Fisch et al., 1999] as well as for subjects with IA [Freeman et al., 1999; Liss et al., 2001], that impaired males with FraX+Aut continue to acquire some adaptive skills throughout childhood. Nevertheless, a recent report by Fisch et al. [2002] found that, in both FraX and idiopathic autistic boys of comparable age to those in this study, there are longitudinal declines in standardized VABS scores across all domains. As proposed by the latter authors, several aspects of the study design may contribute to the discrepancy among different publications. Certainly, specific longitudinal evaluations of boys with FraX+Aut will be needed to elucidate the developmental progression of these children.

While comparisons of problem and adaptive behaviors with the two groups of autistic boys (i.e., DLD+Aut, IA) only demonstrated slightly less impaired social interaction in FraX+Aut, the distinctiveness of the SBP in FraX is underscored by the fact that even after co-varying for IQ the FraX+Aut cohort still showed greater involvement than its non-autistic FraX counterpart. Additional evidence for the uniqueness of the SBP in FraX comes from the contrast of ADI-R profiles between FraX+Aut and DLD+Aut and IA. Scores on three items of the ADI-R reciprocal social interaction domain were consistently lower (i.e., less impaired) in FraX+Aut than both DLD+Aut and IA. These data are in agreement with Bailey et al. [1998], who studied boys between the ages of 2 and 11 years, and found that the severity of autistic features seems milder in FraX+Aut than in IA. Since there were no other differences in the ADI-R between FraX+Aut and DLD+Aut groups, and the only additional distinction between FraX+Aut and IA was higher scores on Communication in IA, we concluded that COMM and stereotypic behavior had a relatively greater impact on the diagnosis of autism in ADI-R in our FraX+Aut cohort.

The specificity of the autistic features seen in individuals with FraX is one of the most controversial issues in the field [Hagerman, 1992; Reiss and Freund, 1992; Kerby and Dawson, 1994; Lachiewicz et al., 1994; Baumgardner et al., 1995; Turk and Graham, 1997; Bailey et al., 1998; Rogers et al., 2001]. This study intended to address the subject by examining autistic behavior in the context of related measures of social interaction. Despite limitations such as small group size, restricted age range, and use of two different measures for the evaluation of cognitive status, our results indicate that a subset of boys with FraX is uniquely impaired in social interaction, though less than other males with developmental language delay and IA. Whether the relatively similar profile, in the other examined areas, of boys with FraX+Aut and IA reflects common pathogenetic mechanisms or not will require additional studies (e.g., laboratory observational measures of social withdrawal). Correlations between recently reported direct [Brown et al., 2001] and indirect [Sun et al., 2001] molecular targets of FMRP deficit and distinct FraX subphenotypes could also contribute to a better understanding of FraX pathogenesis. Furthermore, molecular-behavioral associations may help in the selection of FraX groups more suitable for certain therapeutic interventions, as well as of potential outcome measures.

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