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Social Communication Delay in an Unbiased Sample of Preschoolers With the *FMR1* Premutation

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ABSTRACT

Purpose: The *Fragile X Messenger Ribonucleoprotein-1* (*FMR1*) premutation (FXpm) is a genetic variant that is common in the general population and is associated with health symptoms and disease in adulthood. However, poor understanding of the clinical phenotype during childhood has hindered the development of clinical practice guidelines for screening and intervention. Given that social communication difficulties have been widely documented in adults with the FXpm and are linked with reduced psychosocial functioning, the present study aimed to characterize the communication profile of the FXpm during early childhood.
Method: Eighteen children with the FXpm who were identified through cascade testing (89%) or screening at birth (11%) were compared to 21 matched typically developing children, aged 2–4 years. Participants completed standardized assessments of language (Mullen Scales of Early Learning) and adaptive communication (Vineland Adaptive Behavior Scales-II). Social communication was rated from seminaturalistic interaction samples using the Brief Observation of Social Communication Change.
Results: Children with the FXpm showed delayed social communication development, with the magnitude of group differences highlighting social communication as a feature that distinguishes children with the FXpm from their peers (p = .046, η_p^2 = .12). The groups did not differ on the standardized language and adaptive communication measures (ps > .297, η_p^2s < .03).
Conclusions: Early screening and treatment of social communication delays may be key to optimizing outcomes for children with the FXpm. Further research is needed to replicate findings in a larger sample, delineate the trajectory and consequences of social communication difficulties across the life span in the FXpm, and determine the potential epidemiological significance of *FMR1* as a mediator of developmental communication differences within the general population.

Trinucleotide cytosine-cytosine-guanine (CGG) expansion of > 200 repeats on *Fragile X Messenger Ribonucleoprotein-1* (*FMR1*) is the cause of fragile X syndrome, the most common inherited cause of intellectual disability and most common single-gene cause of autism (Abbeduto et al., 2021; Crawford et al., 2020). Shorter expansions of the *FMR1* CGG sequence of 55–200 repeats result in the *FMR1* premutation (FXpm), a risk allele that is also associated with increased burden of disease. The FXpm is prevalent in the general population, with 1:151–291 females and 1:468–845 males carrying this risk allele (Hantash et al., 2011; Hunter et al., 2014; Seltzer et al., 2012). However, population screening is not conducted, so most FXpm carriers are unaware of their genetic status. Carriers of the FXpm are at risk for two adult-onset

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disorders that are caused by the FXpm: fragile X–associated tremor/ataxia syndrome (FXTAS), a late-onset neurodegenerative disorder that affects 40% of males and 15% of females with the FXpm (Jacquemont et al., 2004; Rodriguez-Revenga et al., 2009), and fragile X primary ovarian insufficiency (FXPOI), a cause of early menopause that affects 20%–30% of FXpm women (Sullivan et al., 2011). A group of neuropsychiatric symptoms and disorders, collectively referred to as fragile X–associated neuropsychiatric disorders (FXAND; Hagerman et al., 2018) and fragile X premutation associated conditions (FXPAC; Johnson et al., 2020), have also recently been recognized as phenotypic characteristics common in the FXpm. These include anxiety and mood disorders, attentional difficulties, and other executive deficits, as well as social challenges and differences in the use of pragmatic (social) language. Disease pathogenesis in the FXpm is associated with several molecular processes that contribute mitochondrial and cellular dysfunction, including repeat-associated non-AUG translation resulting in aggregation of polyglycine-containing protein, glial dysregulation, co-transcriptional R loop formation, altered expression of long noncoding RNAs, and neurotoxic levels of *FMR1* mRNA (Dias et al., 2023; Elizur et al., 2019; Gohel et al., 2021; Kraan et al., 2019; Loomis et al., 2014; Todd et al., 2013; Usdin & Kumari, 2015).

Given the absence of routine screening for *FMR1* conditions, children with the FXpm are most commonly identified (a) through cascade testing after a family member is diagnosed with a fragile X condition or (b) after presenting clinically and being referred for genetic testing themselves. Therefore, it is rare for FXpm children to be identified very early in life (i.e., infancy), and research on early developmental characteristics of FXpm children is sparse. In the research that has been conducted, conclusions are often limited by small samples and/or biased cohorts of clinically referred children who may show more severe phenotypes than what is typical of the larger FXpm population. From this research, however, a preliminary clinical picture of the childhood FXpm phenotype is beginning to unfold, with autism-related traits emerging as potentially associated features. Several small studies suggest that the likelihood of autism spectrum disorder in children with the FXpm is elevated relative to the population base rate of 2% (Shaw et al., 2023). However, as has been seen in other studies of the FXpm, rates vary based upon ascertainment method and sex. For example, studies have found that 68%–79% of clinically identified males and 8%–25% of males identified through cascade testing meet diagnostic criteria for autism (Chonchaiya et al., 2012; Farzin et al., 2006). As would be expected, likelihood of autism appears to be lower in females, as Clifford et al. (2007) detected autism in 5% in females aged 5–80 years (9% clinically referred; 91% identified through cascade testing). Finally, in a study that did not separate the predominantly male sample by ascertainment method or sex, 33% of children with FXpm met diagnostic criteria for autism (Aishworiya et al., 2022). Taken together, these studies of small samples of children with the FXpm suggest that the FXpm allele may confer elevated likelihood for autism, even among children with the FXpm who were not identified due to clinical concerns.

While the full clinical expression of autism has been the developmental outcome of interest in several investigations of the childhood FXpm phenotype, there has been less attention to the expression of broader autism phenotypes, which mirror the core traits of autism but do not meet full diagnostic criteria. Elevated expression of the broad autism phenotype has been widely documented in adult carriers of the FXpm (Losh et al., 2012; Schneider et al., 2016). In particular, social communication aspects of the broad autism phenotype have been well characterized in women with the FXpm, who are more likely than control women to violate social-pragmatic rules that govern conversation such as conversational turn-taking, staying on topic, avoiding ambiguity, or providing necessary background information (Klusek et al., 2019; Losh et al., 2012). Women with the FXpm also display nonverbal social communication differences in the form of reduced eye contact and atypical attentional allocation to the eyes and faces (Klusek et al., 2017; Winston et al., 2020). Although the social communication differences seen in FXpm adults are typically considered to be mild, they are not without clinical impact. Social communication difficulties in women with the FXpm are associated with depression, loneliness, and decreased life satisfaction (Klusek, Thurman, & Abbeduto, 2022; Moser et al., 2021). Mothers with the FXpm who struggle with social communication skills report poorer family relationship quality, have less synchronous interactions with their children, and their children show more autism symptoms and poorer language skills (Klusek et al., 2016; Losh et al., 2012; Moser et al., 2021). Additionally, some research suggests that communication difficulties in women with the FXpm may extend beyond social language use to also encompass language weaknesses in the areas of semantics and syntax. These weaknesses manifest as disfluent speech, word finding difficulties, and reduced lexical diversity (Bredin-Oja et al., 2021; Klusek, Fairchild, et al., 2022; Klusek, Porter, et al., 2018; Movaghar et al., 2019; Sterling et al., 2013). These language weaknesses have shown CGG-dependent associations in some reports (Klusek, Porter, et al., 2018).

In contrast to the growing body of research on the communication phenotype of the FXpm during adulthood, very little is known about the developmental emergence and profile of communication differences in children

with the FXpm. Current understanding of the FXpm communication profile in early childhood comes primarily from Wheeler et al. (2016), which followed 26 infants with the FXpm who were identified through a pilot newborn screening study and participated in developmental assessments between 5 and 42 months of age. Because infants entered the study at different ages and participated in varying numbers of assessments (one to seven), the sample size was relatively small and fluctuated across age bands (e.g., n = 22 at 5–7 months, n = 11 at 35–42 months). Relative to matched infants who screened negative for *FMR1* expansion in the newborn screening study, infants with the FXpm exhibited comparable receptive and expressive language abilities and comparable adaptive communication abilities. However, the infants with the FXpm performed more poorly on the gesture and emotion and eye gaze subscales of the Communication and Symbolic Behavior Scales (CSBS; Wetherby & Prizant, 2002), a standardized measure of early communicative competence. Differences in gesture use emerged in infancy and were consistent across the developmental period sampled. Differences on the emotion and eye gaze subscale, which measures joint attention, shared enjoyment, and communication of affect, emerged later (after 12 months) and became more pronounced as the infants with the FXpm approached their third birthday. These findings suggest that communicative differences in FXpm may be subtle in infancy but likely become more pronounced across the first few years of life.

Taken together, the preliminary evidence on communication development in young children with the FXpm suggests that social communication delays, but perhaps not broader delays in receptive and expressive language development, may represent a key feature of the FXpm neurodevelopmental phenotype. Much remains to be known, however, about the clinical profile of social communication impairments in FXpm during early development. Such knowledge is critical to facilitating early identification of communication delays in children with the FXpm and enabling the early implementation of social communication interventions, which are known to yield the greatest positive impact when provided in early childhood (Fuller & Kaiser, 2020). This is especially important because early social communication skills serve as a critically important foundation for development in other domains. For example, strong social communication skills early in childhood are known to protect children at elevated risk for anxiety from developing anxiety later in childhood (Coplan & Weeks, 2009; Rodas et al., 2017). Given that anxiety is a key feature of the FXpm phenotype across the life span (Bailey et al., 2008; Bourgeois et al., 2009; Cordeiro et al., 2015), improved understanding of early social communicative development in the FXpm may enable opportunities to improve long-term outcomes in not just social communication but a variety of other high-impact domains.

In the present study, we built on this emerging research through characterization of communication skills in an unbiased sample of 2- to 4-year-old children with the FXpm, who were identified through cascade testing or fragile X screening at birth. Children with the FXpm were compared to neurotypical control children, who served as a reference point for normative development in the general population. We focused on the age range of 2–4 years because several key social communication behaviors (e.g., distal pointing, requesting information, acknowledging) are not mastered until 15–18 months (Orr, 2018; Paul et al., 2018; Tomasello et al., 2007) and because focus on the developmental period when most neurotypical children will have acquired these skills allowed us to detect skill deficiencies. We employed a comprehensive assessment battery that included standardized measures of language and adaptive communication as well as a novel, validated observational measure of social communicative skills, the Social Communication Scale of the Brief Observation of Social Communication Change (BOSCC; Grzadzinski et al., 2016). Relative to other available social communication measures, the BOSCC has several properties that maximize its sensitivity to subtle variation in behavior, such as use of a naturalistic sampling context and a rating system that encapsulates a wide range of possible scores. Finally, because anxiety symptoms are elevated in both adults and children with the FXpm (Bailey et al., 2008; Bourgeois et al., 2009; Cordeiro et al., 2015), and could interface with communication difficulties (Coplan & Weeks, 2009; Rodas et al., 2017), we tested associations between early anxiety symptoms and communication skills. We hypothesized that children with the FXpm would show delayed social communication development relative to the control group but would not differ from the control group in their performance on standardized measures of language and adaptive communication skills. We also expected anxiety symptoms to relate to social communication difficulties, but not to performance on the standardized measures of language or adaptive communication.

Method

Participants

Participants were 18 children with the FXpm (eight boys, 10 girls) and 21 neurotypical control children (12 boys, nine girls), aged 23–49 months (M = 30). Participants were drawn from a larger longitudinal study that

focused on the early emergence of anxiety and autism symptoms in infants and preschoolers with fragile X syndrome at the University of South Carolina (Roberts et al., 2020). While the primary focus of the larger study was on children with the full mutation of fragile X syndrome, supplemental funding allowed expansion of the aims to include children with the FXpm. The larger study involved longitudinal assessment at standard time points of 24, 36, 48, and 60 months, with assessments typically scheduled within a 1-month window of their standardized assessment target month. Recruitment targeted 24-month-olds but children with the FXpm were enrolled in the larger study if they were 60 months or younger at the age of the first assessment. Inclusion criteria for the larger study included gestation age of ≥ 36 weeks and normal or corrected-to-normal vision and hearing. Children with a history of serious medical conditions were excluded. Additionally, control children were excluded if they had a developmental delay or autism diagnosis, as reported by caregivers and verified through the research protocol. Control children were also excluded if they had a first-degree relative with autism or a family history of fragile X syndrome. The FXpm (55–200 CGG repeats on 5'UTR of *FMR1*) was confirmed for all participants via review of clinical genetic testing records or completion of genetic testing through the larger study. Recruitment for the FXpm sample was conducted nationally in the United States via word-of-mouth and web-based dissemination of recruitment materials targeting preschools who had been diagnosed with the FXpm and referrals from research collaborators at other institutions. Control children were recruited locally in South Carolina via word-of-mouth and dissemination of study information within the community and on the web.

The present study is a convenience study reflecting secondary analysis of data from the larger study. To rule out bias related to identification due to clinical concerns, FXpm participants were selected for inclusion in the present study if they had been identified with the FXpm either through cascade testing (89%) or through fragile X screening at birth (11%), as reported by the caregiver. One participant from the larger study was excluded because he had been identified with the FXpm after presenting clinically. FXpm participants were also excluded from the present study if they did not have data available at 48 months or younger. When multiple time points were available for FXpm participants, the youngest assessment was selected for inclusion (73% of the sample reflected the 24-month, 22% the 36-month, and 5% the 48-month assessments). Data from control children were randomly selected from the larger data set and group matched to the FXpm sample on age and sex. As shown in Table 1, this matching strategy yielded groups that matched on age and ratio of males to females, as well as race, mother's educational attainment, or nonverbal developmental level

Table 1. Group characteristics.

Characteristic	Group		Test of group differences	
	FXpm *n* = 18	Control *n* = 21	Test statistic	*p*
Age (months)				
M (*SD*)	28.41 (7.68)	30.31 (9.03)	0.81[b]	.423
Range	22.68–49.98	23.78–48.53		
Sex ratio (M:F)	8:10	12:9	0.63[c]	.429
Nonverbal developmental level, age equivalent[a]				
M (*SD*)	29.56 (7.32)	32.62 (10.61)	1.03[b]	.309
Range	19.00–46.00	17.00–52.00		
Nonverbal developmental level, *T* score[a]				
M (*SD*)	54.28 (10.70)	54.10 (11.00)	–0.05[b]	.959
Range	37.00–79.00	32.00–75.00		
Race (%)				
Black or African American	0%	14%	3.59[c]	.166
White	78%	76%		
More than one race	22%	10%		
Maternal education level (%)				
Less than bachelor's	17%	19%	3.73[c]	.155
Bachelor's degree	17%	43%		
Graduate degree	66%	38%		

Note. FXpm = *Fragile X Messenger Ribonucleoprotein-1* premutation.

[a]Estimated by the Mullen Scales of Early Learning Visual Reception Scale. [b]*T* value. [c]χ^2.

as estimated by the Visual Reception Scale of the Mullen Scales of Early Learning (MSEL; Mullen, 1995).

Procedure

The research battery consisted of about 4 hr of direct behavioral and developmental assessment. Assessments were spread across two testing days to allow for sufficient breaks and reduce risk of fatigue. A team of two research specialists conducted the assessments. Assessors were either postdoctoral or doctoral level trainees, or full-time research specialist employees with bachelor-level qualifications; all assessors had extensive training and experience with neurodevelopmental conditions and reliable administration of the research protocol. Assessments were completed in either the participant's home or a university research laboratory, depending on family preference. Informed consent was provided by the participant's caregivers. All study procedures were approved by the Institutional Review Board of the University of South Carolina.

Measures

Standardized Assessments of Language and Adaptive Communication

Receptive and expressive language development was evaluated with the Receptive and Expressive Language subscales of the MSEL (Mullen, 1995). The MSEL is appropriate for children up to 69 months of age and provides a direct assessment measure of development across five domains: Gross Motor, Fine Motor, Receptive Language, Expressive Language, and Visual Reception. Items on the language subscales focus on word production and comprehension. *T* scores for each subscale were used in analyses ($M = 50$, $SD = 10$). Internal reliability for all MSEL subtests is adequate, ranging from .75 to .83 (Mullen, 1995). Consistent with prior work, *T* scores from the Visual Reception subscale were also used in the present study as an estimate of nonverbal developmental level (e.g., Will et al., 2019).

The Vineland Adaptive Behavior Scales–Second Edition (VABS-II; Sparrow et al., 2005), a parent interview, was administered, and the Communication subscale was used to measure adaptive communication skills. The Communication subscale addresses the functional use of receptive and expressive language, such as the ability to use words and sentences to express oneself or to understand instructions. Standard scores were computed, which have an M of 100 ($SD = 15$). The VABS-II shows good internal consistency with reliability coefficients ranging from .88 to .94 on the communication domain in children ages 0–5 years, and test–retest reliability for children ages 0–6 years is excellent (Sparrow et al., 2005).

Observational Rating of Social Communication Skills

The BOSCC (Grzadzinski et al., 2016) was used as a behavioral coding scheme to capture social communication skills sampled from a seminaturalistic context. The BOSCC Social Communication Scale consists of eight items: Eye Contact, Facial Expressions, Gestures, Vocalizations, Integration of Vocal and Nonvocal Modes of Communication, Social Overtures, Social Responses, and Engagement. Each item is coded on a scale of "0" (*abnormality not present*) to "5" (*abnormality is present and significantly impairs functioning*), using operational definitions and decision trees to determine the frequency and severity of each social communication difficulty. A higher score indicates greater social communication impairment.

Social communication behaviors on the BOSCC were scored from two 6-min videotaped segments of the Autism Diagnostic Observation Schedule–Second Edition (ADOS-2; Lord et al., 2012). The first segment consists of 3 min of Free Play and 3 min of Bubble Play, and the second segment comprises of 3 min of Birthday Party/Bath Time and 3 min of Anticipation of Routine with Objects. This selection and order of ADOS-2 tasks are recommended by the developers of the BOSCC. Each segment is scored independently and averaged to yield an overall score (Grzadzinski et al., 2016). The ADOS-2 provides an ideal context for sampling social communication skills as it provides a flexible yet standardized seminaturalistic interaction between an examiner and the child from which to observe behavior, which maximizes the likelihood that the skills observed reflect use in real-life contexts (e.g., Adams, 2002; Tager-Flusberg et al., 2009). The ADOS-2 has several modules to choose from, based on the age and language level of the child. The modules used in the present sample included the Toddler Module for children assessed at 24 months (72%) and Module 2 for children assessed at 36 months or older (28%). These modules were represented at similar proportions across the two groups ($\chi^2 = 2.20$, $p = .138$).

Although the BOSCC was originally designed to be used to detect change over time, in the present study, we used the scale to capture variation in social communication skills at a single time point, given the useful properties of this scale. A key advantage of the BOSCC is that the items were designed to allow for a greater range of possible scores relative to the ADOS-2 and many other available social communication measures, thus increasing the tool's sensitivity to subtle differences in behavior. BOSCC items were also developed to achieve a normal distribution over the coding range, which optimizes variability and minimizes floor and ceiling effects (Grzadzinski et al., 2016). Another advantage of the BOSCC is the use

of observational ratings of behavior sampled from a semi-naturalistic sampling context, as naturalistic observation is considered the gold standard for obtaining an ecologically valid index of social communication ability (Adams, 2002). Psychometric properties of the BOSCC Social Communication Scale are strong, with higher interrater and test–retest reliability and internal structure supported by confirmatory factor analysis (Grzadzinski et al., 2016; Kim et al., 2019; Kitzerow et al., 2016). In the present study, internal consistency for the Social Communication Scale was $\alpha = .93$.

The BOSCC was coded by five independent raters. All raters contributed to the coding of samples from both participant groups and were naïve to the participant's group membership. One rater (KC) completed research training with the BOSCC developers and trained the additional raters who were undergraduate and postbaccalaureate research assistants. Training reliability was established by scoring within 1 point for over 80% of items on each segment and within 4 points on total segment scores with KC for three consecutive videos. Twenty percent of samples were randomly selected and second-scored by an independent rater for reliability. Interrater reliability was examined via intraclass correlation coefficients (ICCs). ICCs (3,4) were 0.83 for the Social Communication Scale.

Anxiety Symptoms

The DSM-Oriented Anxiety Problems Scale of the Child Behavior Checklist (CBCL; Achenbach, 2013; Achenbach & Rescorla, 2000) form for ages 1.5–5 years captured parent-reported anxiety symptoms. This scale comprises of six items, rated on a scale from 0 (*not true*) to 2 (*very true*), that correspond with Diagnostic and Statistical Manual of Mental Health Disorders, Fifth Edition (DSM-5; American Psychiatric Association, 2013) diagnostic criteria for anxiety disorders and captures symptoms of generalized anxiety, specific phobia, and social anxiety disorder. Normalized *T* scores were computed, with a *T* score of 50 indicating scores at the 50th percentile. Psychometric properties of the CBCL include good test–retest reliability, convergent and discriminant validity, good internal consistency, and validated factor structure (Achenbach & Rescorla, 2000; Koot et al., 1997; Pandolfi et al., 2009).

Analytic Approach

Analyses were conducted in SAS (Version 9.4; SAS Institute, 2013). In preliminary analyses, descriptive statistics were computed, and variables were examined for normality. Skew was observed for the BOSCC Social Communication Scale and the individual items on this scale, so a BoxCox power transformation (Box & Cox, 1964) was applied to normalize these distributions as follows: Directed Vocalizations $\lambda = -1.5$; Social Overtures items $\lambda = -0.50$; Facial Expressions and Engagement items $\lambda = -0.25$; Eye Contact item $\lambda = -0.00$; Social Communication Subscale and Social Response item $\lambda = 0.25$; and Gestures and Integration of Vocal and Nonvocal Modes of Communication $\lambda = 0.5$. Transformed data were used in all analyses. A covariance matrix with Spearman's correlations was then computed to describe associations among study variables to inform model specification (see Table 2). A general linear model testing group as a predictor of the CBCL Anxiety Problems Scale was run to characterize anxiety symptoms across the groups.

To determine whether children with the FXpm exhibit differences in language and communication relative to their neurotypical peers, a series of general linear models tested group as a predictor of the standardized language and communication measures (MSEL Receptive and Expressive Language subscales, VABS-II Communication subscale). Another general linear model employed group as a predictor to test group differences in observed social communication skills (BOSCC Social Communication Scale). Covariates in the models included race (coded as a three-level variable: Black/African American, White, or more than one race) and maternal education level (coded as a three-level variable: highest attainment of less than a bachelor's degree, bachelor's degree, or graduate degree). Inclusion of these covariates allowed us to

Table 2. Covariance matrix.

Variable	1	2	3	4	5
1. Receptive Language Subscale *T* Score, MSEL	1.00				
2. Expressive Language Subscale *T* Score, MSEL	.53**	1.00			
3. Adaptive Communication Standard Score, VABS-II	.58**	.57**	1.00		
4. Social Communication Scale, BOSCC	–.11	–.18	.15	1.00	
5. Visual Reception Subscale *T* Score, MSEL	.31*	.33*	.32*	.01	1.00

Note. MSEL = Mullen Scales of Early Learning; VABS-II = Vineland Adaptive Behavior Scales–Second Edition; BOSCC = Brief Observation of Social Communication Change.

*$p < .050$. **$p < .001$.

examine variability in development related to social determinates of health. Sex was considered as a potential covariate but was not included in final models because sensitivity analyses indicated that its inclusion did not change model inference and it accounted for negligible variance explained in the models (all partial eta squared [η_p^2s] < .01). Nonverbal developmental (MSEL Visual Reception Scale) was also considered as a covariate but its inclusion did not change model inference (and it was moderately correlated with the standardized measures, introducing potential multicollinearity), and so was not included in the final models.

Primary analyses were followed by an exploratory item-level analysis of the BOSCC Social Communication Scale to inform specific social communication skills that may be particularly affected in children with the FXpm. Item analyses consisted of a series of general linear models testing group as a predictor, covarying for race and maternal education level. Correction for multiple comparisons was not applied to the item analysis, given it was exploratory in nature. The η_p^2 effect sizes were computed and interpreted using Cohen's "rule of thumb" benchmarks of η_p^2 = .01 denoting a small effect, η_p^2 = .06 denoting a medium effect, and η_p^2 = .14 denoting a large effect (Cohen, 1988). Effect sizes index the magnitude of an effect. While *p* values convey statistical significance, they are not a reliable indicator of effect magnitude (e.g., Cohen, 1994). Additionally, the ability to detect a statistically significant effect, as indicated by *p* values, is strongly hampered by small samples sizes. Therefore, examination of effect sizes in conjunction with *p* values can offer a more comprehensive understanding of practical significance of an effect, even in the absence of statistical significance (Nakagawa & Foster, 2004). The second research question regarding associations between communication skills and anxiety symptoms in children with the FXpm was addressed via Spearman correlations between each of the communication measures and the CBCL Anxiety Problems score.

Results

Descriptive Statistics

The FXpm sample was composed of children recruited from western (47%), eastern (43%), and southeastern (10%) regions of the United States. Eighty percent learned of the study through word of mouth or study advertisements and 20% were referred from research collaborators at other institutions. Information on the reason for testing was gathered from caregivers. For 11 of the 18 families (61%), the participant's mother was the first in the family identified as a FXpm carrier through prenatal expanded carrier screening, which prompted testing of the child. Two additional participants (11%) also had mothers who were identified with the FXpm during prenatal genetic testing, although these mothers had a known history of fragile X in the family (brother, nephew) that motivated participation in testing. Five participants (28%) inherited the FXpm from their father. Two of these participants were the first in their family identified, at birth and with no known family history, through participation in a research study at their birth hospital that offered fragile X screening. The remaining three participants had fathers who had been identified with the FXpm (n = 2) or full mutation (n = 1) prior to the child's birth. All but one of the FXpm participants were tested prenatally or at birth (one participant, whose father was a known carrier prior to her birth, was not tested until 3 years old when her younger sibling was born and the family decided to test both children). Two participants (11%) had a sibling with fragile X syndrome. Eight participants (44%) had a sibling with the FXpm.

FMR1 CGG repeat length data were available for 15 of the 18 FXpm participants. CGG repeat length ranged from 55 to 100, with an *M* of 74 (33% had CGGs of 55–65 repeats, 25% had CGGs of 66–75 repeats, 5% had CGGs of 76–85 repeats, 11% had CGGs of 86–95 repeats, and 11% had CGGs of 96–100 repeats).

Descriptive statistics for the communication and anxiety measures are shown in Table 3. None of the children with the FXpm and one of the control children exceeded the cutoff score (*T* score > 69) for "clinically significant" anxiety symptoms on the CBCL Anxiety Problems Scale (Achenbach, 2013). The mean score on the Anxiety Problems Scale did not differ across groups, $F(1, 29) = 0.83$, p = .370, η_p^2 = .03. Three of the 18 children with the FXpm (17%) scored above the cutoff scores for autism spectrum disorder on the ADOS-2.

Group Comparisons on Standardized Assessments of Language and Adaptive Communication

The general linear models did not support group differences on the MSEL Receptive Language subscale (p = .845, η_p^2 < .01), MSEL Expressive Language subscale (p = .686, η_p^2 < .01), or the VABS-II Adaptive Communication subscale (p = .297, η_p^2 = .03); see Table 4 for full model results. Race accounted for significant variance in expressive language performance and demonstrated a large effect size (p = .041, η_p^2 = .18). Post hoc comparisons indicated that the expressive language scores of White children (M = 53.30) were significantly higher than the expressive language scores of Black/African American children (M = 36.74), p = .014. The mean score of children identifying as more than one race was 48.97, which did not significantly differ from the other racial groups

Table 3. Descriptive statistics.

Variable	Group	
	FXpm	Control
	M (*SD*), range	*M* (*SD*), range
Receptive Language Subscale *T* Score, MSEL	54.11 (8.70), 33.00–68.00	53.19 (10.17), 20.00–71.00
Expressive Language Subscale *T* Score, MSEL	53.22 (10.09), 33.00–70.00	50.00 (11.00), 28.00–69.00
Adaptive Communication Standard Score, VABS-II	105.78 (13.03), 81.00–140.00	98.10 (9.36), 81.00–119.00
Social Communication Scale, BOSCC	11.61 (7.12), 3.00–26.50	9.12 (7.48), 1.00–26.50
Social Communication Scale, BOSCC (transformed)	3.31 (1.11), 1.66–5.16	2.78 (1.20), 0.76–5.20
Anxiety Problems *T* Score, CBCL	51.15 (2.61), 50.00–57.00	52.94 (6.71), 50.00–73.00

Note. FXpm = *Fragile X Messenger Ribonucleoprotein-1* premutation; MSEL = Mullen Scales of Early Learning; VABS-II = Vineland Adaptive Behavior Scales–Second Edition; BOSCC = Brief Observation of Social Communication Change; CBCL = Child Behavior Checklist.

(*p*s > .117). Although not a statistically significant predictor, maternal education level accounted for variance in adaptive communication scores with an effect size consistent with medium-to-large magnitude (p = .166, η_p^2 = .10). The highest performance was associated with maternal attainment of a graduate degree (M = 104.29), followed by maternal attainment of a bachelor's degree (M = 99.19), and with the lowest scores obtained by children whose mother's highest educational attainment was lower than the bachelor's level (M = 94.16).

Group Comparisons on Observational Rating of Social Communication Skills

Significant group differences were observed on the BOSCC Social Communication Scale, with a medium–large effect size (p = .046, η_p^2 = .12), in that the FXpm exhibited higher scores (i.e., more social communicative impairments; see Figure 1). The covariates for maternal education level and race did not account for significant variance in the model; however, it is notable that both effects were of medium–large effect sizes (η_p^2s = .11; see Table 4). On average, Black/African American children showed the most social communication difficulties (M = 4.33) followed by children of more than one race (M = 3.20), and with the lowest level of social communication difficulties observed in White children (M = 2.87). Children whose mother's highest degree was at the bachelor's level had poorer social communication abilities (M = 4.05) than those whose mothers had obtained a graduate degree (M = 3.32). Unexpectedly, maternal educational attainment of less than a bachelor's degree was associated with the least social communication difficulties on the BOSCC in this model (M = 3.03).

Item analysis of social communication features. Table 5 shows group differences on the items of the BOSCC Social Communication Scale. Children with the FXpm obtained significantly higher (i.e., more impaired) scores on the Gesture item, with a large effect size (p = .011, η_p^2 = .18), and on the Social Response item with a medium–large effect size (p = .035, η_p^2 = .13). Given the relatively small sample size, it is also notable that group effects with medium effect sizes were observed for the Eye Contact and Engagement items, although these differences were not statistically significant.

Relationships Between Anxiety Symptoms and Communication Skills in Children With the FXpm

No significant associations were detected between the communication measures and anxiety symptoms on the CBCL (see Table 6). However, the relations between

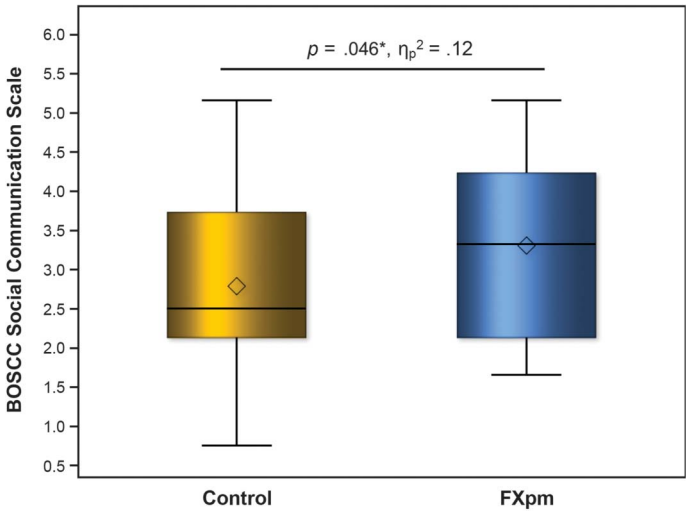
Table 4. Group comparisons on language and communication measures.

Predictor	MSEL Receptive Language			MSEL Expressive Language			VABS-II Adaptive Communication			BOSCC Social Communication		
	F	*p*	η_p^2	*F*	*p*	η_p^2	*F*	*p*	η_p^2	*F*	*p*	η_p^2
Group	0.04	.845	< .01	0.17	.686	< .01	0.30	.297	.03	**4.29**	**.046***	**.12**
Maternal education	0.58	.565	.03	0.05	.947	< .01	1.90	.166	.10	1.99	.153	.11
Race	1.58	.221	.09	3.52	.041*	.18	1.56	.225	.07	1.97	.156	.11

Note. MSEL = Mullen Scales of Early Learning; VABS-II = Vineland Adaptive Behavior Scales–Second Edition; BOSCC = Brief Observation of Social Communication Change.

*p < .050.

Figure 1. Social communication differences across groups. Higher scores indicate greater impairment. BOSCC = Brief Observation of Social Communication Change; FXpm = *Fragile X Messenger Ribonucleoprotein-1* premutation. *$p < .050$.



adaptive communication and anxiety, as well as between expressive language and anxiety, were observed to be between small and medium effect size per Cohen's (1988) guidelines.

Discussion

The FXpm is a genetic risk allele that is prevalent in the general population and associated with increased likelihood of adult-onset symptoms and disease. However, clinical management of the FXpm is hindered by poor understanding of how FXpm symptoms manifest during childhood, which potentially undermines opportunities to intervene early when treatments may be most effective. The present study adds to emerging research on communication deficits associated with the FXpm genotype in children, through focus on an unbiased sample of preschool-aged children with the FXpm who were identified through cascade testing or fragile X screening at birth through a research study, with no family history. Compared to control children, children with the FXpm showed delayed development of social communication skills, with group differences of medium-to-large magnitude of effect. Social communication deficits have been well documented in adults with the FXpm and are linked with depression and low life satisfaction in this group. The present study demonstrates that social communication differences are

Table 5. Item analysis of Brief Observation of Social Communication Change Social Communication Scale.

	Group		Test of group differences	
	FXpm	Low risk control		
Item	*M (SE)*	*M (SE)*	*p*	η_p^2
Eye contact	0.92 (0.12)	0.84 (0.12)	.162	.06
Facial expressions	0.71 (0.17)	0.46 (0.43)	.177	.05
Gestures	**1.78 (0.21)**	**1.18 (0.17)**	**.011***	**.18**
Vocalizations directed to others	0.33 (0.08)	0.25 (0.07)	.334	.03
Integration of vocal and nonvocal	1.69 (0.24)	1.37 (0.20)	.239	.04
Social overtures	0.61 (0.14)	0.45 (0.12)	.314	.03
Social response	**1.37 (0.17)**	**0.94 (0.14)**	**.035***	**.13**
Engagement	0.69 (0.14)	0.47 (0.11)	.143	.06

Note. Covariate-adjusted means, controlling for maternal education level and race. Higher scores indicate greater impairment. Boldface text indicates items on which groups differed significantly. FXpm = *Fragile X Messenger Ribonucleoprotein-1* premutation.

*$p < .05$.

Table 6. Associations between language/communication measures and anxiety symptoms in FXpm children.

Variable	CBCL anxiety problems *T* score		
	n	*r*	*p*
Receptive Language Subscale *T* Score, MSEL	13	−.01	.966
Expressive Language Subscale *T* Score, MSEL	13	−.23	.441
Adaptive Communication Standard Score, VABS-II	13	−.14	.638
Social Communication Scale, BOSCC	13	.08	.798

Note. CBCL = Child Behavior Checklist; MSEL = Mullen Scales of Early Learning; VABS-II = Vineland Adaptive Behavior Scales–Second Edition; BOSCC = Brief Observation of Social Communication Change.

evident in early childhood in the FXpm, highlighting social communication impairment as a key neurodevelopmental phenotype of the FXpm that emerges early in life and persists across the life span. More research is needed to determine how early social communication delays in children with the FXpm impact daily living and whether they contribute to the emergence of other FXpm symptoms (e.g., anxiety) through childhood and into adulthood, which will inform recommendations for screening, monitoring, and intervention. However, given that social communication difficulties continue to distinguish carriers of the FXpm from healthy individuals into adulthood and have been associated with negative clinical effects, early screening for social communication delays, and initiation of treatment if indicated, would likely be beneficial for children who are known to carry the FXpm genotype.

The primary finding of this study was that 2- to 4-year-old children with the FXpm showed delayed development of social communication skills relative to control children. The magnitude of the effect size for group differences was medium to large, indicating that social communication delay is a feature that distinguishes children with the FXpm from children who do not carry this genotype. This finding aligns with other emerging evidence of social communication difficulties and higher rates of autism in children with the FXpm (e.g., Aishworiya et al., 2022; Chonchaiya et al., 2012; Clifford et al., 2007; Wheeler et al., 2016). The consistency of social communication findings across emerging independent studies involving children with the FXpm is notable and highlights social communication differences as a key aspect of the FXpm neurodevelopmental phenotype. The FXpm group in this study did not differ from the control group on standardized measures of receptive or expressive language, which suggests that early differences in communication development may be constrained to the social use of language to communicate, rather than structural aspects of language such as the ability to use and comprehend words and sentences.

Social communication differences have been documented in adults with the FXpm and are linked with poorer clinical outcomes for both FXpm carriers and their families, including depression, loneliness, and decreased life satisfaction, poor family relationship quality, less synchronous parent–child interactions, and higher autism symptoms and poorer language skills in their children with fragile X syndrome (e.g., Klusek et al., 2017, 2019; Klusek, Ruber, & Roberts, 2018; Klusek, Thurman, & Abbeduto, 2022; Losh et al., 2012; Maltman et al., 2021). Longitudinal research is needed to clarify the lifetime trajectory of FXpm social communication difficulties to inform treatment recommendations. Research on pragmatic language impairment in children without the FXpm suggests that the majority of children continue to face persistent problems in adulthood, with substantial impact on social functioning throughout the life span (Conti-Ramsden et al., 2001; Coplan & Weeks, 2009; Geurts et al., 2004; Jobe & White, 2007; Ketelaars et al., 2010; Laws et al., 2012; Whitehouse et al., 2009). Thus, it seems likely that, if left untreated, social communication differences in children with the FXpm will persist, or even become more impairing, in adulthood. Our research team is continuing to follow the present cohort longitudinally to report back on the trajectory of symptoms across childhood. Considering the potential lifetime psychosocial consequences of social communication deficits, early screening and treatment of social communication delays in children with the FXpm may be critical to promoting the health and well-being of children with the FXpm genotype across the life span.

It is unclear whether the routine developmental screening practices currently employed by pediatricians in the United States are sufficient to detect early social communication delays in children with the FXpm. Current American Academy of Pediatrics guidelines recommend the use of developmental and autism-specific screening tools at well-child visits, paired with universal developmental surveillance (Lipkin et al., 2020). However, uptake of these recommendations has been suboptimal (Mazurek et al., 2021), and it is not known whether these procedures are sensitive to specific delays in social communication development, particularly in the absence of broader developmental delays. If evidence continues to point toward the FXpm as a genetic risk factor for social communication impairment, targeted universal screening for social communication delays may be indicated for children known to carry the FXpm. Several validated,

norm-referenced tools are available for this purpose, including parent report tools that require little time or training to administer, such as the Language Use Inventory (O'Neill, 2007) and the CSBS Developmental Profile (Wetherby & Prizant, 2002).

This study raises a host of follow-up questions regarding how early emerging differences in the ability to communicate socially may constrain the experiences of children with the FXpm and initiate developmental cascades that could influence the expression of other FXpm phenotypes over time (e.g., Masten & Cicchetti, 2010). For example, early social communication delays could plausibly increase risk for anxiety and internalizing disorders, which are significant problems for children and adults with the FXpm (Bailey et al., 2008; Bourgeois et al., 2009; Cordeiro et al., 2015). Research on other clinical populations clearly demonstrates that children who are at risk for internalizing problems due to genetic/temperamental factors are more likely to develop these problems later in life if they also demonstrate weak social communication skills. Strong social communication skills, on the other hand, protect at-risk children from developing problems such as social anxiety, social withdrawal, and loneliness (Coplan & Weeks, 2009; Hallett et al., 2010; Rodas et al., 2017). The relationship between early social communication delays and later internalizing problems may be accounted for within a developmental cascade framework. Early social communication impairments could pave the way for internalizing problems via more frequent communication breakdowns and negative social interactions. Repeated negative social interactions could create an environmental context that reinforces the tendency of anxiety-prone children to overestimate the probability of threats in the environment and selectively attend to them, creating a self-reinforcing cycle that escalates anxiety symptoms over time (Hofmann, 2007; Muris & Field, 2008). In the present study, we did not detect an association between social communication skills and concurrent anxiety symptoms, but we may have been limited by our reliance on a broad-band parent report anxiety symptom scale, concurrent measurement, small sample size, and the young age of the sample. The finding that the association between two of the social communication skills subscales (i.e., adaptive communication, expressive language) and anxiety symptoms was between small and medium effect size further points to the value of continuing to explore these relationships in future work. Larger longitudinal or experimental studies are needed to determine whether childhood social communication deficits could play a role in the development of anxiety in the FXpm—or possibly other FXpm phenotypes—which would inform early intervention as a possible means to alter the lifetime trajectory of FXpm disease.

Although social communication difficulties have been discussed in the adult FXpm literature for over a decade, it has been unclear until now whether the social communication phenotype of the FXpm was of a neurodevelopmental or neurodegenerative origin. The present findings support a neurodevelopmental onset, with social communication differences distinguishing children with the FXpm from their peers as early as the second year of life. However, it is important to note that our findings do not preclude the possibility that neurodegenerative processes may also play an independent, additive, or interactive role in the expression of the FXpm social communication phenotypes across the life span. Although social communication deficits are often associated with neurodevelopmental conditions such as autism, they are also characteristic of a range of neurodegenerative disorders, including Parkinson's, primary progressive aphasia, amyotrophic lateral sclerosis, and multiple sclerosis (Bambini et al., 2016; Carotenuto et al., 2017; Goldberg et al., 2021; Montemurro et al., 2019) and thus may plausibly arise from either neurodevelopmental or neurodegenerative processes (or both). Efforts to distinguish neurodevelopmental and neurodegenerative features of the FXpm could promote mechanistic understanding of disease expression and progression, as it has been suggested that these features could arise from functionally and pathologically independent mechanisms (Brown & Stanfield, 2015). For example, fragile X messenger ribonucleoprotein protein (FMRP), which is mildly reduced in FXpm carriers (Kenneson et al., 2001; Primerano et al., 2002), is thought to play a major role in neurodevelopmental problems as this protein is responsible for regulating the translation of many gene targets that are critical for brain development (Casingal et al., 2020; Darnell & Klann, 2013; Darnell et al., 2011). Significant overlap between FMRP targets and autism susceptibility genes suggests that FMRP could play a role in disrupted social communication development as well (Casingal et al., 2020). It is notable that the specificity of FMRP-related disruptions to early development is unclear, however, as FMRP also controls signaling pathways associated with neurodegenerative disease (Koeglsperger et al., 2020; Sokol et al., 2011). We did not have access to molecular genetic data in the current study, which would have been informative in beginning to explore associated mechanisms. Inclusion of neuroimaging data in future research would also be helpful in delineating gene–brain–behavior pathways, with the amygdala and cerebellum potentially implicated as brain regions that are affected in the FXpm and are involved in social communication (Adolphs, 2008; Birch et al., 2015; Hessl et al., 2007, 2011; Olson et al., 2023; Wang et al., 2017).

While the present study adds to a growing evidence base linking the FXpm to social communication difficulties,

the methods of the present study do not allow us to tease apart the relative contributions of genetic and environmental influences on the observed social communication phenotype. In particular, it is notable that, due to inheritance patterns, children with the FXpm typically have a parent who is also a FXpm carrier and may also express unique communication patterns associated with their genetic status. Considerable empirical and theoretical evidence (e.g., transactional model, social-interactionist perspectives) shows that caregiver communication style is a salient characteristic of the child's learning environment, with certain caregiver behaviors better scaffolding child development than others (McDuffie & Yoder, 2010; Sameroff & Fiese, 2000; Siller & Sigman, 2002, 2008; Tomasello, 1992). For example, language and communication development of children is enhanced when caregivers are highly responsive, elaborate on their child's attentional focus, and respond contingently (Baumwell et al., 1997; Landry et al., 2006; Tamis-LeMonda et al., 2001). This effect holds true in studies of fragile X, which show that higher expression of pragmatic language difficulties and lower responsivity in mothers with the FXpm is associated with less synchronous mother–child interactions and poorer language skills in their children with fragile X syndrome (Klusek et al., 2016; Moser et al., 2021; Warren et al., 2010; Wheeler et al., 2007). Given the familial nature of *FMR1*-associated conditions, investigation of potential environmental influences on the development of young children with the FXpm will be important for understanding modifiable aspects of the child's environment that can be targeted in intervention (e.g., Mahoney & Perales, 2005; Yoder & Warren, 2001).

A notable strength of the present study is the inclusion of an unselected sample of children with the FXpm who were young and relatively homogeneous in age. Through focus on a FXpm sample identified through cascade testing or screening at birth, this study builds confidence that the observed social communication difficulties are representative of the clinical profile associated with the FXpm genotype in the population and not just a subset of individuals with FXpm with more significant clinical involvement. The participants' young age at enrollment in the present study further reduces the potential for recruitment bias toward children whose parents had clinical concerns. Given recent increase in the clinical availability and uptake of pre/perinatal expanded carrier screening (Krstić & Običan, 2020; Sagaser et al., 2023), the identification of the FXpm genotype in young children who have no known family history of fragile X is becoming increasingly common. This has resulted in an urgent and critical need to develop clinical practice and counseling guidelines that accurately reflect clinical risk associated with the FXpm genotype in the population. The current study contributes to these efforts by adding to the emerging literature on social communication differences in unbiased samples of children with the FXpm.

While inclusion of an unbiased sample is a significant strength, difficulties ascertaining this specific population also resulted in a small sample size. However, is important to note that ascertainment of unbiased FXpm samples is a major challenge, particularly when the focus is on young children, and our sample size is comparable to other published studies including unselected samples of children with the FXpm (Farzin et al., 2006; Wheeler et al., 2016). Nonetheless, our sample size may have reduced our ability to detect subtler effects; we reported effect sizes to aid interpretation. Recruitment challenges also made it difficult to achieve a sample that reflects the diversity of the U.S. population. On average, the FXpm children in this study were predominantly White and their mothers were more highly educated than what is typical of the current demographics of children in the United States (Ryan & Siebens, 2012; The Annie E. Casey Foundation, 2023). While we had good representation of children of more than one race, there were no Black/African American children represented in the FXpm group that limits interpretation of effects specific to this racial category. Our analyses did support variance in development accounted for by race and maternal education level, which is consistent with a large body of research on social determinates of health inequities (Letourneau et al., 2013; Williams & Cooper, 2019).

In conclusion, this study builds on the currently limited literature on the clinical expression of the FXpm during childhood. We documented social communication development that was delayed in children with the FXpm during the preschool years and strongly differentiated children with this genotype from their peers. Although more research is needed, including replication in larger samples and longitudinal observation, it is likely that early identification and treatment of social communication delays would improve the outcomes of children with the FXpm, given that childhood social communication deficits typically persist into adulthood and impact psychosocial functioning. A growing number of studies have shown that the FXpm genotype is connected to atypical social communication features across this life span, suggesting potential epidemiological significance of *FMR1* as a mediator of developmental communication differences within the population.

Data Availability Statement

Data are available from the corresponding author on reasonable request.

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