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Research Article

Noncomprehension Signaling in Males and Females With Fragile X Syndrome

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Purpose: This study used a prospective longitudinal design to evaluate the trajectory and predictors of noncomprehension signaling in male and female youth with fragile X syndrome (FXS).
Method: A direction-following task in which some of the directions were inadequate was administered. Participants were 52 youth (36 boys, 16 girls) with FXS. Upon study entry, participants ranged from 10 to 16 years. The average number of annual assessments per participant was 3.65 (range = 1–4), providing 198 data points for analysis.
Results: Participants with FXS were less likely to signal noncomprehension than younger, typically developing, cognitively matched children. The average rate of change in noncomprehension signaling was not significantly different from 0 for either boys or girls, suggesting a plateau. Both FMRP and nonverbal IQ were significant independent predictors of noncomprehension signaling for boys. Variability in noncomprehension signaling among girls was not explained by any of the predictors, but trends similar to those observed for boys were observed.
Conclusions: Noncomprehension signaling appears to be an area of weakness for individuals with FXS. Because the failure to signal noncomprehension can have negative, cumulative effects on comprehension, the results suggest a need for interventions targeting the requisite cognitive skills.

Successful communication with others extends beyond a listener's knowledge of words or the rules for combining words into sentences. Conversations are created and influenced by the abilities of each participant (e.g., Wilkes-Gibbs & Clark, 1992; Nilsen & Mangal, 2012). Therefore, a listener's ability to successfully negotiate this reciprocal social interaction requires the real-time coordination of skills across a variety of domains as well as an appreciation for the rules that govern communicative exchanges, that is, pragmatic competence (e.g., Nilsen, Mangal, & MacDonald, 2013). Consequently, difficulties in any one of several domains, from the cognitive to the social, can negatively affect a listener's contribution to the conversation in addition to their ability to form an accurate representation of what has been said (e.g., Ninio & Snow, 1996; Wilkes-Gibbs & Clark, 1992; Yule, 1997). Individuals with neurodevelopmental disorders are at increased risk for difficulties in navigating these communicative exchanges. For example, fragile X syndrome (FXS), one of the most common genetic causes of intellectual disability, is associated with pervasive cognitive, linguistic, and sociocognitive impairments, all of which are likely to contribute to the difficulties individuals with FXS have in reciprocal social interactions. In this study, we sought to map the trajectory of development of a key aspect of a listener's communicative success—the ability to signal when noncomprehension has occurred—across late childhood and adolescence in boys and girls with FXS. In addition, we explored factors contributing to within-syndrome variability in noncomprehension signaling.

Noncomprehension Signaling

As a listener, one is responsible for monitoring comprehension of what the speaker has said, identifying any problems with the speaker's message, and, if necessary, formulating a response indicating that a problem has occurred and the nature of that problem. These activities and the skills they entail are critical to conversational success (Glucksberg,

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Krauss, & Higgins, 1975). By 9 years of age, typically developing (TD) children demonstrate virtually adult-level competence in the listener's role in referential communication tasks (Glucksberg et al., 1975). In such tasks, the speaker's goal is to convey information that will enable a listener to identify a target referent from confusable alternatives; the listener's goal is to correctly identify the referent or inform the speaker when the target referent cannot be identified (e.g., Morisseau, Davies, & Matthews, 2013; Nilsen, Mangal, & MacDonald, 2013; Rosenberg & Cohen, 1964). Younger TD children and children with intellectual disabilities, however, have difficulty with such noncomprehension signaling in referential tasks (Abbeduto et al., 2008; Ackerman, 1981; Beal & Belgrad, 1990; Fujiki & Brinton, 1993; Robinson & Whittacker, 1985). For example, it has been shown that 5- to 6-year-old TD children encounter difficulty with regard to consistently evaluating utterances for their referential adequacy, particularly when presented with ambiguous directions (i.e., directions that refer equally well to multiple entities; Ackerman, 1981; Robinson & Whittacker, 1985). When considering noncomprehension signaling in adults with mild to moderate intellectual disability, Fujiki and Brinton (1993) reported a similar pattern of poor performance on referentially ambiguous messages. Furthermore, difficulties with noncomprehension signaling have been documented in individuals with a variety of genetic conditions associated with intellectual disability (e.g., autism spectrum disorder [ASD], Down syndrome, FXS, Williams syndrome; e.g., Abbeduto et al., 2008; Asada, Tomiwa, Okada, & Itakura, 2010; John, Rowe, & Mervis, 2009; Loveland, Tunalia, McEvoy, & Kelley, 1989; Skwerer, Ammerman, & Tager-Flusberg, 2013). Thus, difficulties with regard to a listener's role in conversational exchanges appear to persist in individuals with intellectual disabilities far longer than is observed in TD. These difficulties likely have a significant negative impact on myriad situations, from school and work to conversational exchanges with peers or caregivers, making this an important area of investigation.

FXS

FXS, which results from the mutation of a single gene (*FMR1*) on the X chromosome, affects 1 in 4,000 males and 1 in 6,000 females (Crawford, Acuña, & Sherman, 2001; Fernandez-Carvajal et al., 2009; Hagerman, 2008). FXS accounts for approximately 40% of the cases of X-linked intellectual disability (Coffee et al., 2009). In individuals with FXS, a repetitive sequence of trinucleotides (i.e., CGG repeats) is found in the fragile X gene promotor region, which undergoes an intergenerational expansion from 54 or fewer repeats to more than 200 repeats and is referred to as the *full mutation.* Methylation is an epigenetic mechanism used by cells to stop gene expression. In FXS, the expansion to the full mutation leads to hypermethylation and transcriptional silencing of the gene, reducing or completely preventing the production of its associated protein, FMRP (Oostra & Willemson, 2003). FMRP has been shown, in both animal and human studies, to be critical for experience-dependent neural development, affecting both the maturation and pruning of synapses (Klintsova & Greenough, 1999). Variability in FMRP expression is considered to be partially responsible for the significant within-syndrome variability that characterizes the FXS phenotype. Importantly, because of the presence of a second unaffected X chromosome in females, which continues to produce FMRP, biological sex and FMRP expression are inherently confounded when exploring the FXS phenotype, with females being less severely affected on average. In females, FMRP variability appears to be related to intercellular variation in methylation status and X inactivation. In males, three general molecular groups have been described: (a) fully methylated full mutation (i.e., those with little to no FMRP expression; Kaufman, Abrams, Chen, & Reiss, 1999; Tassone et al., 1999), (b) partially methylated full mutation (i.e., those with the gene methylated in some cells and unmethylated in others), and (c) mosaic (i.e., those who have some cells with the premutation, which express FMRP, and some with the full mutation). Most males appear to be categorized as fully methylated full mutations, but the actual distribution of these types remains unclear. These gender differences highlight the importance of characterizing the phenotype in males and females with FXS separately.

To date, several studies have been published providing evidence supporting a relation between FMRP expression and phenotypic variation in FXS. For example, Tassone et al. (1999) found that the percentage of lymphocytes that expressed FMRP was significantly correlated with IQ scores for mosaic males, males with partially methylated full mutation, and females with the full mutation. No association was observed between IQ and FMRP in males with a fully methylated full mutation, although it is important to point out that there is little variation in FMRP expression within this group. Although our understanding of the impact of FMRP on the FXS phenotype is still in its infancy, the evidence documenting associations in both the neurocognitive and psychiatric domains of the phenotype highlights the importance of exploring the impact of FMRP expression on the FXS phenotype in both males and females (e.g., Cohen et al., 1996; Menon, Kwon, Eliez, Taylor, & Reiss, 2000; Bailey, Hatton, Skinner, & Mesibov, 2001; Bailey, Hatton, Tassone, Skinner, & Taylor, 2001; Kwon et al., 2001; Loesch et al., 2002; Loesch, Huggins, & Hagerman, 2004).

The FXS phenotype is associated with a number of cognitive, linguistic, and sociocognitive difficulties. In terms of a cognitive profile, relative weaknesses have been observed in the areas of executive function, visual memory/perception, spatial reasoning, and short-term memory. Verbal reasoning and simultaneous processing are areas of relative strength (Huddleston, Visootsak, & Sherman, 2014). Language difficulties are also commonly observed in individuals with FXS (e.g., Abbeduto & Hagerman, 1997). Finally, a number of behavioral difficulties have been noted. For example, social anxiety and/or social avoidance are observed in nearly all individuals with FXS (e.g., Budimirovic et al., 2006; Hall, DeBernardis, & Reiss, 2006; Hessl, Glaser,

Dyer-Friedman, & Reiss, 2006; Roberts, Weisenfeld, Hatton, Heath, & Kaufmann, 2007). In addition, symptoms such as gaze avoidance, inattention, hyperactivity, and hyperarousal are commonly associated with FXS (e.g., Chromik et al., 2015; Cornish, Sudhalter, & Turk, 2004; Tonnsen, Grefer, Hatton, & Roberts, 2015; Wisbeck et al., 2000). Collectively, the aforementioned symptoms are often significant enough to draw parallels between the FXS and ASD phenotypes.

Importantly, there is considerable variability among individuals with FXS. In terms of intellectual abilities, much of the variability is related to sex/FMRP. Nearly all males with FXS full mutation have an IQ score that is less than or equal to 85, and a substantial majority demonstrate IQs that fall within the intellectual disability range (Dykens, Hodapp, & Finucane, 2000; Hessl et al., 2009). In contrast, females with FXS are less cognitively impaired than their male counterparts, with less than half of females with the FXS full mutation presenting with an intellectual disability, with the remainder presenting with a learning disability or cognitive performance in the normal range (Keysor & Mazzocco, 2002).

Linguistic abilities below chronological age (CA)–level expectations are observed in most males with FXS and in a large proportion of females with FXS, once again demonstrating that females with FXS are less severely affected than males. Generally, when considering both receptive and expressive language ability, males with FXS have been shown to demonstrate below CA expectations on measures of both vocabulary and syntax, with syntax sometimes below cognitive-level expectations (e.g., Abbeduto, Brady, & Kover, 2007; Finestack & Abbeduto, 2010; Oakes, Kover, & Abbeduto, 2013; Price et al., 2008; Sudhalter, Maranion, & Brooks, 1992). Furthermore, males with FXS have been shown to demonstrate a number of pragmatic language difficulties, including frequent use of perseverative language and tangential speech as well as difficulties with turn-taking and topic maintenance (e.g., Roberts et al., 2007; Losh, Martin, Klusek, Hogan-Brown, & Sideris, 2012; Sudhalter & Belser, 2001). Investigations of language outcomes experienced by females with FXS have been less frequent (Mazzocco, Singh Bhatia, & Lesniak-Karpiak, 2006; Sterling & Abbeduto, 2012). Nevertheless, there is evidence that females with FXS, like their male counterparts, display strength in receptive vocabulary performance relative to nonverbal cognition (Sterling & Abbeduto, 2012), with asking questions and selecting appropriate endings for stories read being areas of substantial weakness (Mazzocco et al., 2006; Simon, Keenan, Pennington, Taylor, & Hagerman, 2001). Again, however, these difficulties are less severe, on average, than those in males.

Finally, both males and females with FXS have been shown to be at high risk for difficulties in social interactions. In fact, FXS is one of the most common single-gene mutations observed in individuals with ASD (Betancur, 2011; Cohen et al., 2005; Geschwind, 2011), with as many as 60% of males with FXS presenting with symptoms severe enough to warrant a comorbid diagnosis of ASD (e.g., Bailey et al., 1998; Clifford et al., 2007; Demark, Feldman, & Holden, 2003; Harris et al., 2008). Although frequent, ASD is less commonly observed in females with FXS. For example, Mazzocco, Kates, Baumgardner, Freund, and Reiss (1997) observed a rate of autism near 20% in their sample of 30 females with FXS. Other behavioral difficulties, such as social avoidance or anxiety (e.g., Cordeiro, Ballinger, Hagerman, & Hessl, 2011; Thurman, McDuffie, Hagerman, & Abbeduto, 2014) and the presence of hyperactivity and inattention (Cordeiro et al., 2011; Thurman et al., 2014), are also common, especially in males. In sum, the developmental trajectories for males and females with FXS differ rather dramatically, with outcomes that are more variable for females than for males. In this study, we add new data on the language phenotype of FXS, focusing on the severity of impairment and predictors of developmental trajectories in both males and females with FXS.

The behavioral difficulties associated with the FXS phenotype are likely to place individuals with FXS at particular risk for impaired use of language in social settings, such as the ability to signal when noncomprehension has occurred. In fact, Abbeduto et al. (2008) examined the ability of 18 adolescents and young adults with FXS (13 boys, 5 girls; mean CA = 17.58 years) to signal noncomprehension of the spoken messages of others, using a direction-following task in which some of the messages were inadequate because (a) the speaker referred to an unavailable object (Incompatible), (b) the speaker's direction was too nonspecific to indicate which object of several available was the intended object (Ambiguous), or (c) the speaker's direction contained an adjective unknown to the participant (Unfamiliar). Abbeduto et al. found that the youth with FXS were less likely to signal noncomprehension of inadequate messages than were younger, nonverbal mental age–matched TD children. In addition, the Ambiguous and Unfamiliar directions were particularly likely to be "missed" by these participants, which reflects the same order of difficulty seen for much younger TD children. Furthermore, even after controlling for differences in nonverbal mental age, males with FXS signaled noncomprehension less often than their female peers with FXS. Numerous potential predictors of noncomprehension signaling also were examined; however, only receptive language ability was a significant predictor. Thus, difficulties in (a) monitoring comprehension and/or (b) creating and executing a plan for requesting clarification from the speaker are part of the FXS phenotype, especially in males, and (c) may arise in part from a broader language deficit.

The Abbeduto et al. (2008) study, however, suffered from a number of limitations that restrict its clinical utility. In particular, the study had a cross-sectional design, relatively small sample size, and/or a very wide age range of participants. Together, these limitations make it difficult to determine the age-related developmental course of noncomprehension signaling in this population and provide limited insight into the predictors that shape the course of that development and account for gender-related differences. Moreover, the study was not designed to address the

role of genetic variation, particularly in terms of FMRP levels, in relation to the extent of impairments in noncomprehension signaling. The present study was designed to overcome these limitations and provide a richer characterization of the development of noncomprehension signaling in FXS.

In the present study, we used a prospective longitudinal design, with four annual assessments, to evaluate noncomprehension signaling in individuals with FXS. To begin, we sought to place the findings into a broader developmental context by comparing the trajectory of noncomprehension signaling for FXS to that for younger TD children at a comparable level of cognitive development. We hypothesized that we would see growth in the TD participants during this developmental period. In addition, we hypothesized that the individuals with FXS would demonstrate delay in noncomprehension signaling relative to even younger TD children at similar nonverbal cognitive levels. The first aim of the study was to investigate the trajectory of development of noncomprehension signaling for a large sample of male youth (10–18 years) with FXS and to identify the predictors of noncomprehension signaling that contribute to within-syndrome variability in males with FXS. We hypothesized that the trajectory would indicate that the development of noncomprehension may plateau during adolescence for males with FXS. Moreover, we hypothesized that variations in the trajectory of noncomprehension signaling would be related to nonverbal IQ, receptive language ability, autism symptom severity, and FMRP level. The second aim of the study was to present exploratory data with regard to the trajectory of noncomprehension signaling for a small sample of female youth (10–18 years) with FXS and provide insight into the predictors of noncomprehension signaling that contribute to within-syndrome variability, thereby setting the stage for future hypothesis-driven studies of females. We were interested in whether there was growth in noncomprehension signaling in females with FXS and explored some possible predictors of within-group variability.

Method

Participants

Participants were 52 youth with FXS (36 boys, 16 girls) and 46 younger TD children (28 boys, 18 girls) who were selected so that they demonstrated the same range of nonverbal growth scores (≤ 502) as did the participants with FXS ($p = .14$). All participants were drawn from a larger project focused on the language and communicative development of children and adolescents with FXS or Down syndrome relative to younger TD children. Findings in this project have been reported in several publications (Kover, McDuffie, Abbeduto, & Brown, 2012; Kover, Pierpont, Kim, Brown, & Abbeduto, 2013; McDuffie et al., 2010; McDuffie, Kover, Abbeduto, Lewis, & Brown, 2012; Oakes, Kover, & Abbeduto, 2013; Pierpont, Richmond, Abbeduto, Kover, & Brown, 2011), but none have focused on measures of noncomprehension signaling. Families were recruited by advertisements in local newspapers, mailings to local educators and administrators of genetic clinics, notices to families enrolled in a university research registry, postings on Internet website and listservs, and announcements in the newsletters of national organizations focused on developmental disabilities. Written informed consent was obtained from the parent or legal guardian of each participant. All participants with FXS provided reports of either molecular genetic ($n = 48$) or cytogenetic ($n = 4$) testing upon entry into the project. The reports indicated that 40 participants had the full mutation, whereas 12 others (all boys) were mosaic (i.e., 10 with a mix of full mutation and premutation cells and two who were methylation mosaics).

With regard to the participants with FXS, six mixed-gender sibling pairs were included in the present analyses. Upon entry into the study (Time 1), participants ranged in age from 10 to 16 years, with a mean CA of 12.64 years ($SD = 1.65$), with a nonverbal growth score of 471.10 ($SD = 12.71$; range = 446–502). Time 1 participant characteristics as a function of gender are presented in Table 1. The racial/ethnic composition of the sample was 90% Caucasian, 4% African American, 2% Hispanic, 2% Native American, and 2% other. In this sample, 19.2% of mothers held an advanced degree, 30.8% held no higher than a college degree, and an additional 50% held no higher than a high school degree. The average number of annual assessments per participant was 3.65 (range = 1–4). This provided a total of 198 potential data points for the analyses.

With regard to the TD participants, upon entry into the study (Time 1), participants ranged in age from 3 to 8 years, with a mean CA of 5.66 years ($SD = 1.54$; range = 3.1–8.99), with an average nonverbal growth score of 475.5 ($SD = 14.5$; range = 442–502). The racial/ethnic composition of the sample was 94% Caucasian, 4% Hispanic, and 2% African American. In this sample, 17.4% of mothers held an advanced degree, 54.3% held no higher than a college degree, and an additional 28.3% held no higher than a high school degree. The average number of annual assessments per participant was 3.73 (range = 1–4). This provided a total of 172 potential data points for the analyses.

Standardized Measures

The following measures assessed domains hypothesized to be important for the ability to recognize and resolve comprehension failures. In most cases, the measures were administered on the same day, or within a few days, of the noncomprehension signaling task (described below). Scores from each of the following measures at the first annual assessment served as a predictor of performance on the noncomprehension signaling task across time.

Nonverbal Cognition

Nonverbal cognitive ability was assessed with the four Brief IQ subtests from The Leiter International Performance Scale–Revised (Leiter-R; Roid & Miller, 1997):

Table 1. Descriptive statistics (*M, SD,* and range) as a function of gender at the first annual assessment.

Descriptive measure	TD participants (all; *n* = 46)			FXS boys (*n* = 36)			FXS girls (*n* = 16)		
	M	*SD*	Range	*M*	*SD*	Range	*M*	*SD*	Range
Chronological age (years)	5.66	1.54	3.11–8.99	12.88	1.71	10.18–16.00	12.10	1.40	10.19–15.59
Nonverbal IQ SS[a]	116.35	15.59	87–159	46.44	9.11	36–71	69.00	15.69	46–98
Receptive vocabulary SS[b]	117.17	13.06	87–146	59.64	17.15	40–96	89.50	13.72	59–106
Autism symptom severity[c]	—	—	—	5.60	3.03	1–10	3.25	2.70	1–9
FMRP	—	—	—	0.04	0.08	0.00–0.30	0.48	0.05	0.34–0.51

Note. TD = typically developing; FXS = fragile X syndrome; SS = standard score.

[a]Leiter-R IQ standard score. [b]Peabody Picture Vocabulary Test–III standard score. [c]Autism Diagnostic Observation Schedule–Generic.

Figure Ground, Form Completion, Sequential Order, and Repeated Patterns. The Leiter-R is individually and nonverbally administered. The mean Brief IQ for the general population is 100, with a standard deviation of 15. Nonverbal IQ from the first annual visit (or the first annual visit with valid data on the noncomprehension signaling task for the three participants without valid data at the first annual visit) served as a putative predictor. For one participant, nonverbal IQ at the first annual assessment was imputed because of missing data on two subtests. Growth scores were used for comparisons between TD participants and participants with FXS. All other analyses used nonverbal IQ standard scores; 11% of participants earned scores at floor.

Receptive Vocabulary

Receptive vocabulary ability was assessed based on administration of the Peabody Picture Vocabulary Test–III (PPVT-III; Dunn & Dunn, 1997). The PPVT-III is an individually administered, untimed measure of receptive vocabulary, normed for participants 2½ to 90+ years of age. The mean for the general population is 100 (*SD* = 15). PPVT standard score was used in all analyses; 12% of participants earned scores at floor. Receptive vocabulary was chosen as the language measure in the present study because the experimental stimuli exemplified a very simple grammatical structure (i.e., single-clause imperatives) that was held constant across all items and conditions, with vocabulary being the primary difference across stimuli.

Autism Severity

The severity scores (Gotham, Pickles, & Lord, 2009) from the Autism Diagnostic Observation Schedule–Generic (ADOS; Lord, Rutter, DiLavore, & Risi, 2002) were used as the measure for autism severity. The ADOS is a semi-structured standardized assessment in which the examiner creates specific situations to observe the participant's social, communication, and play/imaginative behaviors and scores these behaviors based on the live administration. The ADOS consists of four modules that contain a set of activities designed to be used for children and adults at different developmental and language levels. ADOS scores were available for all but one participant. The module most appropriate based on expressive language skills and CA was administered to the participant, as required in the published manual. In the present study, two participants received a Module 1, seven participants received a Module 2, 40 participants received a Module 3, and two participants received a Module 4. Two participants whose data were analyzed received the ADOS at the second visit instead of the first because of scheduling difficulties. Twenty-two of 35 male participants and five of 16 female participants earned ADOS scores above the ASD cutoff. Note, ADOS data were missing for one male participant. Project staff who administered the ADOS were graduate-level professionals who had completed standard requirements for research reliability. Overall ADOS comparison/severity scores were used in analyses.

FMRP Level

To examine the contributions of variations in the genetic mutation causing FXS, blood samples were collected from 44 participants (30 boys, 14 girls) upon entry into the study. Using the procedures described by Willemsen et al. (1997), the proportion of cells that expressed the FMRP protein was determined for each participant (using a sample of 200 cells for boys and 400 cells for girls). The average percentage of cells that expressed the protein for boys was 4% (*SD* = 8, range = 0–30; 21 of 30 boys expressed no FMRP) and 48% for girls (*SD* = 5; range = 34–51).

Noncomprehension Signaling Task

Task Overview

This task, which was modeled after Abbeduto et al. (2008), was designed to individually assess each participant's ability to verbalize when the referent in a speaker's one-sentence direction could not be identified with certainty. Two examiners were involved in the administration: a primary examiner who explained the task instructions and a second experimenter who served as the "speaker." The participant (the "listener") and the speaker sat at a table opposite of one another, each with an easel book in front of them. For the participant, each page of the easel book contained a colorful scene (e.g., a beach). Moveable magnetic pieces, each with a colored drawing of an object (e.g., a beach ball), were situated at the bottom of each page. A magnet was located in the scene indicating where the participant

should place the piece identified by the speaker. Although the participant's easel book contained scenes with a missing piece, each page of the speaker's easel book contained a colorful scene complete with the piece missing in the participant's easel book. The participant was unable to see the speaker's scene. For each page of the book, the speaker produced a one-sentence direction that indicated the piece/referent that the participant needed to move into the scene (e.g., "Put the blue hat on the lady.") to make the participant's scene identical to the speaker's scene.

Each page belonged to one of four conditions. Items from all four conditions were presented to each participant. Examples of each condition are presented in Table 2. In the Informative condition, the speaker's direction allowed the intended referent to be unambiguously identified. The remaining three conditions were designed to create different types of situations in which the participant had to signal noncomprehension and thereby solicit more information to be sure of making a correct referent choice. These conditions were (a) the Incompatible condition, in which the speaker's direction referred to a piece that was not available; (b) the Ambiguous condition, in which the speaker's direction failed to contain an adjective to indicate which piece was the intended piece; and (c) the Unfamiliar condition, in which the speaker's direction contained an adjective whose meaning was highly unlikely to be known by the participant. In addition to condition, the number of potential referents available per page was also manipulated across items, with either two, four, or six available referents.

Materials

The participant's book contained 35 pages (three practice items and 32 experimental items). With regard to the experimental items, each participant received 14 trials in the Informative direction condition and six trials in each of three noncomprehension signaling conditions. The number of potential referents available per page varied across items, with two (11 items), four (11 items), or six (10 items) potential referents available. Scripts were created for the directions provided by the speaker as well as for the speaker's responses to possible participant responses. More specific information regarding the task materials and scripts can be found in Abbeduto et al. (2008). Two versions of the easel book were created, each composed of a different set of 32 experimental items with no more than two in a row of any one type. Version assignment was alternated between participants within the larger study. In addition, the version was alternated between annual visits for each participant.

Procedure

The primary examiner explained at the start of the task that the participant was going to play a matching game together with a second adult (a confederate who played the role of speaker) and stressed the need to listen carefully and achieve an exact match with the speaker. The primary examiner also explained that the participant could "talk with [speaker's name], ask him/her questions, or say anything to him/her to make sure your pictures match" to assure the participant that there were no prohibitions against talking, thereby ensuring the validity of this task (Abbeduto, Short-Meyerson, Benson, & Dolish, 1997).

The three practice items each involved an Informative direction and varied with regard to the number of potential referents available (i.e., one practice item had two, one had four, and one had six available referents). The participant and speaker were allowed to compare their pages after each direction with either positive or negative corrective feedback provided as necessary for each practice item. During the experimental items, the participant and speaker were not allowed to compare pages, and no corrective feedback was given. Noncontingent general praise (e.g., "I like how you're listening.") was delivered according to a script throughout the task.

To avoid conveying the impression that the speaker necessarily expected a verbal response, the speaker looked at his or her own book rather than at the participant during the production of each direction and maintained that focus until the participant had either signaled noncomprehension or moved a potential referent into the scene. The speaker responded verbally to signals of noncomprehension according to the script. The speaker did not provide a response when the participant simply moved a potential referent into the scene.

Scoring Noncomprehension Signals

The referent selected whether or not a signal of noncomprehension was produced, and the type of noncomprehension signal produced was coded from video by a trained coder. The classifications of participant's responses that were scored as signals of noncomprehension are presented in Table 3 and followed Abbeduto et al. (2008), with the exception of our addition of requests for repetition as an

Table 2. Examples of speaker directions as a function of condition.

	Condition			
Example	**Informative**	**Incompatible**	**Ambiguous**	**Unfamiliar**
Scene	Box of crayons half full	Dinner table	A blank sheet of paper	Blue sky and clouds
Speaker's direction	"Put the red crayon on the box."	"Put the black fork on the table."	"Place the brush on the page."	"Place the azure balloon in the sky."
Referents available	Yellow crayon, red crayon, green crayon, blue crayon	Blue fork, green fork, red fork, yellow fork	Red brush, blue brush, yellow brush, green brush	Blue hot air balloon, yellow hot air balloon

Table 3. Types of noncomprehension signals.

Type of signal	Example
Request for confirmation	The blue hat?
	This one? (plus holds up card for the speaker to see)
Request for definition	What's *russet* mean?
	What's *tawny*?
	What's a _____? (uttered with an intonation suggesting that completion by the speaker is expected)
Request for specific information	Which one?
	Which fork do you mean?
Statement of nonexistence	There is no brown book.
	There's not one like that.
	I can't find that one.
Statement of existence	There are four forks.
	There are lots of those you know.
Request for repetition	What?
	Huh?
Other	For example, participant holds up a potential referent to show the examiner while looking expectantly.

Note. From "Signaling noncomprehension of language: A comparison of fragile X syndrome and Down syndrome," by Abbeduto et al., 2008, *American Journal on Mental Retardation*, *113*, 214–230. Copyright © by American Association on Intellectual and Developmental Disabilities. Reprinted with permission.

additional type of signal. Interrater agreement was calculated for 44 participants (13, 12, 12, and nine per time point, respectively) and distributed across participant groups (21 participants with FXS; 23 with TD). Cohen's kappa (TD: $\kappa = .95$, FXS: $\kappa = .92$) indicated very high reliability for classification of the type of signal first produced by participants across the larger study.

The dependent variable of interest was the total number of problematic messages, collapsed across conditions, on which the participant signaled noncomprehension. In several instances, no data were available from the noncomprehension signaling task at a given assessment time point for a participant (seven total time points were missing across four different participants with FXS and 10 total time points were missing across eight different TD participants). In these cases, data were missing due to nonstandard administrations ($n = 2$), participants not returning for follow-up visits ($n = 6$), missing videotape ($n = 2$), and unknown ($n = 7$). In these instances, data were retained for the other visits in which valid data were obtained. A small number of participants had missing data within an administration; in these cases, data were imputed as the proportion of signals (within the same visit) for the condition in question given the number of valid signaling opportunities obtained. For each session, data were imputed by first taking the number of trials for which the participant signaled noncomprehension multiplied by the total number of trials that were to be completed by that participant during that session. This number was then divided by the total number of trials the participant actually completed. In all, the number of signals was imputed for only 16 data points out of the total 370 possible data points.

Analysis Plan

Preliminary analyses were conducted using data from the 46 TD children to provide a broader developmental context for noncomprehension signaling. First, hierarchical linear modeling was used to determine whether the slope for change with CA would be significantly greater than zero for our younger sample of TD participants who performed in the same nonverbal cognitive range as the participants with FXS. Additional preliminary analyses were then carried out to determine if the participants with FXS, as had been found by Abbeduto et al. (2008), demonstrated a weakness in noncomprehension signaling relative to TD participants of similar nonverbal cognitive level.

To address the first aim, we first conducted preliminary analyses to ensure that the experimental task functioned as intended for boys with FXS. We then used hierarchical linear modeling to determine whether the slopes for change with CA in boys with FXS would be significantly greater than zero. We centered CA at 14 years, which was the overall mean age of the combined sample (boys and girls) across the four visits. We then tested putative predictors of noncomprehension signaling with data from the participants with valid data for the predictors. We considered Leiter-R IQ standard scores and PPVT-III standard scores at the first available assessment as time-constant predictors, as well as autism symptom severity and FMRP level. Correlations between these variables were estimated to assess collinearity; variables with a correlation greater than 0.6 were not included in a model together. In boys, Leiter-R IQ and PPVT-III standard scores were highly correlated ($r = .73$, $p < .001$), but none of the other variables were correlated (absolute correlations $< .33$, $p > .05$). Our interest was in the participant characteristics that predicted individual differences in level of noncomprehension signaling (intercept) or slope. This led us to test a model that included as predictors FMRP, Leiter-R IQ, and autism symptom severity and then a second model that included FMRP, the PPVT-III standard score, and autism symptom severity. Both models included a random intercept. Leiter-R IQ, PPVT-III standard score, and autism symptom severity were centered

on the grand mean. FMRP was neither centered nor transformed.

The second aim was to consider noncomprehension signaling in girls with FXS. Because of the small sample size, these analyses were exploratory and designed to provide preliminary results that have the potential to be helpful in guiding future research. First, we conducted preliminary analyses to ensure that the experimental task functioned as intended for girls with FXS. Additional preliminary analyses were conducted, comparing the girls to boys with FXS, to verify the between-gender differences in affectedness that have been documented within the literature. Next, using the same approach that was used for the boys, we used hierarchical linear modeling to estimate whether the slopes for change with CA would be significantly greater than zero and tested putative predictors of noncomprehension signaling. For the girls with FXS, none of the putative predictors were correlated (absolute correlation < .48, $p > .05$).

Results

Preliminary Analyses

The 46 TD children had an average nonverbal Leiter-R growth score of 475.5 (SD = 14.5; range = 442–502) at Time 1. The noncomprehension signaling task was administered annually over 4 years (M = 3.74. SD = 0.68, range = 1–4 annual assessments per child). Children with average Leiter-R nonverbal growth scores made, on average, one additional noncomprehension signal per year ($\beta = 1.20$, $SE = 0.23$, $p < .001$). At the same time, however, a higher nonverbal Leiter-R growth score was associated with less improvement per year (interaction between Leiter-R growth score and age: $\beta = -0.04$, $SE = 0.01$, $p < .001$), such that a Leiter-R growth score 10 points higher than the average was associated with nearly half a signal less improvement per year ($-0.04 \times 10 = -0.40$). This finding is likely a reflection of the fact that there was less room for improvement on the noncomprehension signaling task from the first annual assessment for the higher-functioning children. Individuals with FXS did not differ from the TD children on the nonverbal Leiter-R growth score at Time 1 (M = 471.10, SD = 12.71, range = 446–502, $p = .12$) but still used fewer noncomprehension signals at Time 1 (TD: M = 12.93, SD = 6.74; FXS: M = 7.65, SD = 7.37; $p < .001$). These data replicate the finding of an especially severe impairment in noncomprehension signaling for FXS, an impairment more severe than expected for this level of nonverbal cognitive development (Abbeduto et al., 2008).

Noncomprehension Signaling in Boys With FXS

We completed further preliminary analyses designed to ensure that the noncomprehension signaling task functioned as intended for the boys with FXS. High referent selection accuracy was observed in the Informative condition (M proportion correct = .91, SD = .14, range = .43–1.00), indicating that, as a group, the boys with FXS in our sample were able to complete the task successfully when the speaker's message was referentially precise. Furthermore, the rate of noncomprehension signaling in the Informative condition was extremely low, as would be expected, reflecting the fact that the participants were generally able to understand the task requirements and the form of the directions to be processed and were able to refrain from using noncomprehension signals indiscriminately. We also examined the rate of noncomprehension signaling across the three Uninformative directions (i.e., Incompatible, Ambiguous, and Novel) and found that for boys with FXS, there was no significant difference in frequency of noncomprehension signaling at Time 1 as a function of direction type, $F(1.84, 64.55) = 2.25$, $p = .12$, $\eta p2 = .06$. This contrasts with the findings from Abbeduto et al. (2008) and may reflect the younger ages of our participants. Descriptive information regarding noncomprehension signaling performance as a function of condition is presented in Table 4. Finally, consideration of the Time 1 data indicated that, after controlling for nonverbal IQ, rate of noncomprehension signaling in the Informative condition was significantly correlated with the total rate of noncomprehension signaling in the Noninformative conditions ($r = .68$, $p < .001$) but not proportion of item accuracy in the Informative condition ($r = .06$, $p = .732$). These latter findings suggest that there may be some level of "talkativeness" at play in determining rate of noncomprehension signaling for boys with FXS.

In terms of the primary analyses, we found that the average rate of change across CA for the 36 boys with FXS did not differ from zero, $p = .57$. In examining the predictors of those trajectories, 29 of the 36 boys with FXS had data for each of the predictors (no missing data) and so were included in the analyses. Leiter-R IQ and PPVT-III standard scores were too highly correlated to include in the same model. In the model including FMRP, Leiter-R IQ, and autism symptom severity, Leiter-R IQ and FMRP were positive predictors of level (i.e., intercept) of noncomprehension signaling (Table 5). A significant interaction between FMRP level and age also was found, indicating that the slope in boys differed according to FMRP level; for example, a boy with 0 FMRP was not significantly changing (estimated annual change = −0.24, SE = 0.34, $p = .49$; Table 5), whereas a boy with a 15% increase in FMRP level was improving by one noncomprehension signal per year of age (estimated annual change = $-0.24 + 0.15 \times 9.12 = 1.13$, $SE = 0.51$, $p = .03$; Figure 1). If the PPVT-III standard score was used in place of Leiter-R IQ, only FMRP was significantly associated with level of noncomprehension signals ($\beta = 30.59$, $SE = 13.45$, $p = .03$) and change with age ($\beta = 9.62$, $SE = 3.99$, $p = .02$); there was no significant change for a boy with 0 FMRP ($\beta = -0.33$, $SE = 0.35$, $p = .35$).

Noncomprehension Signaling in Girls With FXS

We completed preliminary analyses designed to ensure that the noncomprehension signaling task functioned as intended for girls with FXS. Descriptive statistics

Table 4. Descriptive statistics (*M*, *SD*, and range) for number of noncomprehension signals in each condition and total signals for noninformative conditions as a function of gender and time point.

	FXS boys (*n* = 36)					FXS girls (*n* = 16)				
Time point	Informative	Incompatible	Ambiguous	Unfamiliar	Total signals in noninformative conditions	Informative items	Incompatible	Ambiguous	Unfamiliar	Total signals in noninformative conditions
1	0.42 (0.97; 0–4)	1.77 (2.20; 0–6)	1.33 (2.18; 0–6)	1.61 (2.26; 0–6)	4.72 (6.27; 0–17)	0.25 (0.58; 0–2)	5.31 (1.54; 0–6)	4.56 (2.48; 0–6)	4.38 (1.78; 0–6)	14.25 (5.09; 0–18)
2	0.33 (1.14; 0–6)	2.18 (2.77; 0–6)	1.30 (1.91; 0–6)	1.42 (1.88; 0–6)	4.90 (6.08; 0–18)	0.25 (0.45; 0–1)	4.88 (2.28; 0–6)	3.88 (2.80; 0–6)	3.19 (2.48; 0–6)	11.94 (6.80; 0–18)
3	0.61 (1.02; 0–3)	2.55 (2.72; 0–6)	1.90 (2.33; 0–6)	2.10 (2.61; 0–6)	6.55 (7.25; 0–18)	0.07 (0.27; 0–1)	5.21 (1.72; 0–6)	4.21 (2.52; 0–6)	4.36 (2.31; 0–6)	13.79 (6.03; 0–18)
4	0.60 (1.79; 0–9)	2.23 (2.73; 0–6)	1.83 (2.57; 0–6)	1.59 (2.24; 0–6)	5.65 (7.23; 0–18)	0.00 (0.00; 0)	4.64 (2.53; 0–6)	4.07 (2.79; 0–6)	3.79 (2.69; 0–6)	12.50 (7.45; 0–18)

Table 5. Estimates for predictors of total number of noncomprehension signals.

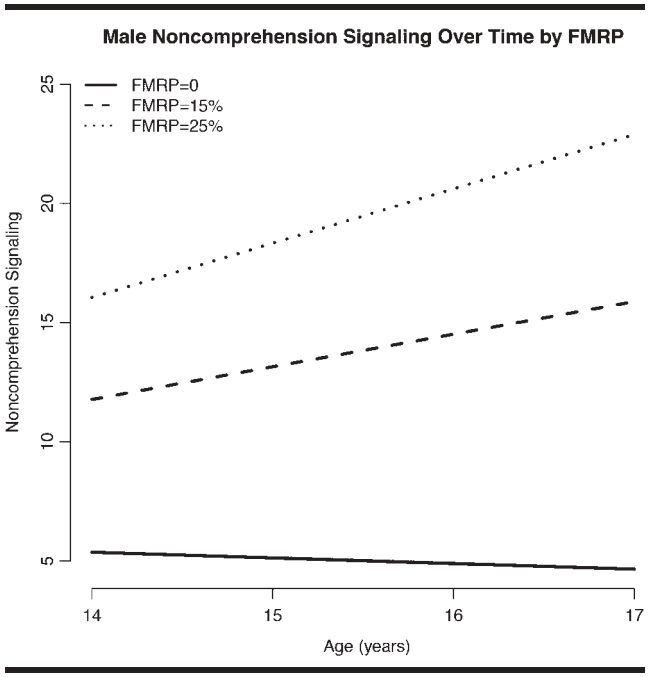
	FXS full sample (*n* = 41)			FXS boys (*n* = 29)			FXS girls (*n* = 14)		
Fixed effect	**β**	***SE***	***p***	**β**	***SE***	***p***	**β**	***SE***	***p***
Total noncomp signals									
Intercept (mean)	–7.74	0.82	< .001*	–5.60	1.23	< .001*	–27.11	19.21	.19
Leiter-R IQ SS	28	0.06	< .001*	.29	.10	.006*	.16	.08	.07
PPVT-III SS	—	—	—	—	—	—	–.05	.15	.75
Autism severity	.11	.29	.69	.51	.32	.12	–.22	.63	.73
FMRP	—	—	—	33.62	12.22	.007*	79.42	42.09	.07
Slope									
Age (rate of change)	.06	.25	.80	–.24	.34	.49	.13	.41	.74
FMRP*Age	—	—	—	9.12	3.90	.02*	—	—	—

Note. Intercept reflects a chronological age of 14 years. All predictors except for FMRP were grand-mean centered. SS = standard score; PPVT-III = Peabody Picture Vocabulary Test–III.

*$p < .05$.

for the number of noncomprehension signals in each condition (collapsed across array size) and for the total number of collapsed across Noninformative conditions (collapsed across array size) were considered for girls with FXS (Table 4). High item selection accuracy was observed in the Informative condition (M proportion correct = 0.99, SD = 0.01 range = 0.93–1.00), indicating that, as a group, the girls with FXS in our sample were able to complete the task successfully when the speaker's message was fully informative. Furthermore, there were very few noncomprehension signals produced by girls during the Informative condition, reflecting the fact that the participants were able to understand the task requirements and the form of the directions to be processed. We also found that, like for the boys with FXS, noncomprehension signaling did not vary as a function of Uninformative direction type at Time 1 for girls with FXS, $F(1.28, 19.28) = 2.60$, $p = .12$, $\eta_p^2 = .15$. Finally, consideration of the Time 1 data indicated that, after controlling for nonverbal IQ, the proportion of item accuracy in the Informative condition ($r = .17$, $p = .55$) was not correlated with the total rate of noncomprehension signaling in the Noninformative conditions. This latter finding differs from that observed for boys with FXS, likely because of the reduced heterogeneity in performance and smaller sample size observed for girls as compared with boys.

Figure 1. Male noncomprehension signaling over time by FMRP.



In a further set of preliminary analyses, girls with FXS were compared with boys with FXS. Descriptive statistics on measures administered in the project at Time 1 indicated that girls with FXS had significantly higher nonverbal IQ, $t(50) = 6.55$, $p < .001$, and receptive vocabulary standard scores, $t(50) = 6.14$, $p < .001$, and significantly lower (less severe) autism symptomatology severity scores, $t(49) = -2.66$, $p = .01$, than did boys with FXS (Table 1). Furthermore, after controlling for nonverbal IQ, girls with FXS were more likely to signal noncomprehension than were their male counterparts, $F(1, 48) = 5.67$, $p = .02$, $\eta_p^2 = .10$. These differences are consistent with previous findings of greater affectedness on multiple dimensions of behavior in boys than girls with FXS because the disorder is X-linked (e.g., Abbeduto et al., 2008; Hagerman, 1999).

In terms of the primary analyses, the average rate of change across CA for the 16 girls with FXS did not differ from zero, $p = .67$. Because the putative predictors were not significantly correlated in girls, all predictors were included in the same predictive model. There were no significant predictors of noncomprehension signals in the 14 girls who had data on all predictors (Table 5) when the model included FMRP, Leiter-R IQ, PPVT-III, and autism severity. As a note, within this model, nonsignificant trends were observed for higher Leiter-R IQ and FMRP to be associated with an increased level of noncomprehension signaling.

Discussion

Successful communication requires a listener to use all sources of information to identify a speaker's intended meaning. One key aspect of the listener's role is the requirement to signal in cases of noncomprehension so that the speaker can provide clarification. Previous research suggests that noncomprehension signaling is an area of relative weakness for adolescents and young adults with FXS, with performance below levels expected based on nonverbal cognitive ability (Abbeduto et al., 2008). Our data replicate this finding in a somewhat younger sample of 10- to 15-year-olds with FXS.

Importantly, little is known about the course of development or the characteristics that account for the variation in noncomprehension signaling observed in the disorder. To address this issue, the present study used a prospective longitudinal design with four annual assessments to map the trajectories of this key aspect of communicative ability across late childhood and into adolescence in boys and girls with FXS. In addition, we explored the factors contributing to within-syndrome variability, for both boys and girls, by considering the roles of nonverbal IQ, receptive vocabulary ability, autism symptom severity, and FMRP on the age-related trajectories of noncomprehension signaling.

Noncomprehension Signaling in Boys With FXS

Our first aim was to characterize the trajectory of development of noncomprehension signaling for male youth (10–16 years at their first assessment) with FXS. We were especially interested in whether boys with FXS would show age-related improvement during late childhood and into adolescence despite their especially severe impairment in noncomprehension signaling. Our data indicated that although the slope computed was positive, it was not significantly different from zero for our sample. In other words, not only are boys with FXS less likely to signal noncomprehension than expected for their levels of nonverbal cognitive ability, they also appear to have plateaued with virtually no improvement from late childhood through adolescence. Furthermore, our preliminary analyses of the trajectory of noncomprehension signaling in younger TD participants of similar cognitive ability level to the participants with FXS demonstrated that across the 4-year study period, TD participants continued to improve in noncomprehension signaling. This latter finding is evidence that the task used was sensitive to developmental change and further highlights the substantial magnitude of the impairment in noncomprehension signaling among boys with FXS. In light of the importance of noncomprehension signaling to successful participation in real-world linguistic interactions, our findings suggest a pressing need for interventions to encourage more careful monitoring of comprehension and the use of adaptive strategies for soliciting clarification in this population.

A wide range of interindividual variability in noncomprehension signaling was observed for the boys with FXS. Thus, we also sought to determine the predictors of noncomprehension signaling that contribute to this within-syndrome variability. We considered the impact of FMRP, nonverbal IQ, receptive vocabulary ability, and autism symptom severity on the signaling of noncomprehension. In the boys, however, nonverbal IQ and receptive vocabulary ability were highly correlated; this led us to test two multilevel models: one that included FMRP, nonverbal cognition, and autism symptom severity and a second that included FMRP, receptive vocabulary ability, and autism symptom severity. In the first model, our findings indicated that nonverbal IQ was a significant, independent predictor of noncomprehension signaling performance. This relationship is not surprising given the many cognitive skills on which noncomprehension signaling no doubt depends, including, for example, auditory memory, which has been shown to predict other aspects of language performance and growth in FXS (Pierpont, Richmond, Abbeduto, Kover, & Brown, 2011). Other cognitive skills captured in IQ, such as those involved in executive functioning, also are likely to be at the core of successful noncomprehension signaling.

We also found that FMRP made an independent and unique contribution to noncomprehension signaling for boys with FXS over and above the contribution of nonverbal IQ. This finding raises the possibility that aspects of neural developmental specifically affected by FMRP beyond those reflected in an omnibus measure of cognitive ability may also be important in noncomprehension signaling. Indeed, it is likely that the prefrontal cortex, with its ties to skills such as planning, inhibition, and other executive functions, is also critically related to noncomprehension signaling, perhaps through these skills, all of which are severely impaired in FXS (e.g., Hooper et al., 2008; Rubia et al., 2006; Wilding, Cornish, & Munir, 2002). Brain regions involved in other cognitive and noncognitive domains, including attention and arousal, also are affected by reduced FMRP, and they too may be affecting noncomprehension signaling. More generally, the close relationship between noncomprehension signaling and the core biological deficit of FXS suggests that the former may have potential as an outcome measure for use in clinical trials of pharmacological agents in FXS (Berry-Kravis et al., 2013). Of course, use as an outcome measure would require additional research on the psychometric properties on the noncomprehension signaling, as assessed in the present study (e.g., to document test-retest reliability), as well as a greater understanding of other potential mediators of the noncomprehension signaling-FMRP relationship.

Because FXS results from a mutation in a single gene (*FMR1*) that causes a lack or reduction of its associated protein (FMRP), there is considerable interest in elucidating the mechanisms by which the absence of this protein produces the FXS phenotype. Recent studies have found the amount of FMRP expressed in peripheral blood cells to be linked to physical characteristics and neurocognitive abilities (e.g., Kover, Pierpont, Kim, Brown, & Abbeduto, 2013; Loesch et al., 2004; Tassone et al., 1999). Our findings demonstrate that FMRP levels account for a significant

amount of the variability in the noncomprehension signaling of youth with FXS. Moreover, we observed a significant interaction between FMRP level and age. Specifically, for boys with 0% FMRP, we observed no change in noncomprehension signaling; however, for example, men with 15% FMRP were observed to improve in noncomprehension signaling at a rate of one signal per year.

In the present study, receptive vocabulary ability was not found to be a significant predictor of noncomprehension signaling performance when included in a model with FMRP and autism symptom severity. Previously, Abbeduto et al. (2008) found that receptive language, as measured by the Test for Auditory Comprehension of Language-3 (TACL-3; Carrow-Woolfolk, 1999), was a significant predictor of overall noncomprehension signaling. Importantly, our study differs from that of Abbeduto et al. (2008) in terms of methodological approach. To begin, in Abbeduto et al. (2008), receptive language was found to predict overall noncomprehension signaling in a model that included TD participants along with participants with FXS or Down syndrome. Thus, the relation between receptive language and noncomprehension signaling may be a result of the inclusion of these other diagnostic groups. In addition, unlike the measure used in the present study, the receptive language domain of the TACL-3 not only assesses the ability to understand vocabulary but also assesses grammatical morphemes and syntactic rules and relations. Importantly, however, the grammatical morphemes and syntactic structures exemplified in the task stimuli were simple and constant between the informative and problematic messages. Moreover, the former messages were processed adequately by the boys with FXS, as reflected in the accuracy of their referent selection and their infrequent use of noncomprehension signaling relative to the problematic messages. A strong contribution of grammatical ability to noncomprehension signaling in our task, therefore, seems unlikely. Nevertheless, more research is needed to better understand the impact of language ability on noncomprehension ability.

Finally, autism symptom severity was not found to significantly predict noncomprehension signaling for boys in the present study. Previous studies have demonstrated significant associations between autism symptom severity, nonverbal cognitive ability, and FMRP in individuals with FXS. However, the correlations between FMRP and autism symptom severity often do not remain after controlling for differences in nonverbal IQ (e.g., Hatton et al., 2006; Kover et al., 2013; McDuffie et al., 2010; Thurman, McDuffie, Kover, Hagerman, & Abbeduto, 2015). Thus, given that our models of noncomprehension ability included both FMRP and nonverbal cognitive ability and the fact that nonverbal IQ seems to play a role in the presence of ASD symptomatology in FXS, it may not be surprising that autism symptomatology failed to emerge as a significant predictor. Generally speaking, our findings suggest that the poor noncomprehension signaling of individuals with FXS may be best seen as a cognitive problem rather than as a social or social-cognitive problem.

Noncomprehension Signaling in Girls With FXS

Because females with FXS have a second unaffected X chromosome that continues to produce FMRP, biological sex and FMRP are inherently confounded when exploring the FXS phenotype. Females with FXS are usually less severely affected at the phenotypic level and demonstrate more variable outcomes than their male counterparts (Mazzocco, 2000). Because of the lower prevalence rates and this more variable phenotypic presentation in females with FXS, studies of females have been infrequent, with very few focused on language. The second aim of the present study, therefore, was to present exploratory data with regard to the trajectory of noncomprehension signaling for a small sample of female youth with FXS (10–18 years). Despite being small, our sample size was higher than that previously reported by Abbeduto et al. (2008) and longitudinal in nature; thus, these data may be useful for future hypothesis-driven studies of females.

In a previous study, Abbeduto et al. (2008) found females with FXS to have better noncomprehension signaling skills than males with FXS, even after restricting females to only those with IQs in the intellectual disability range and statistically accounting for gender differences in nonverbal mental age (Abbeduto et al., 2008). In the present study, we replicated this pattern of findings. In addition, we found that the average rate of change across CA for our 16 girls with FXS was not significantly different from zero. Thus, females with FXS, like their male peers, appear to have reached a plateau in the development of noncomprehension signaling.

At the same time, however, it is important to acknowledge the wide range of interindividual variability in noncomprehension signaling observed for the girls with FXS. Although some of the girls demonstrated relatively good performance on the noncomprehension signaling task, some girls evidenced more difficulty, allowing many inadequate messages to "slip through," even at Time 4. These instances are likely to lead to inadequate understanding in a range of interactive contexts. Thus, like boys with FXS, some girls with FXS would benefit from targeted intervention in this domain.

We also sought to determine the predictors of noncomprehension signaling that contribute to within-syndrome variability. In addition to FMRP, we considered the impact of nonverbal IQ, receptive vocabulary ability, and autism symptom severity on the signaling of noncomprehension. Unlike boys with FXS, the putative predictors were not significantly correlated; therefore, all predictors (FMRP, nonverbal cognition, receptive vocabulary, and autism severity) were included in the same predictive model. Although no significant predictors emerged, trends for associations between nonverbal cognition and FMRP with noncomprehension signaling were observed. Given the fact that the small sample size included in the present study limited our power to observe a significant effect and that these predictors were also observed to play a role in noncomprehension signaling in boys with FXS, we believe they remain

important factors to consider in future studies. The findings also are interesting in that they suggest that despite being less severely affected than boys, there may not be qualitative differences in the factors shaping noncomprehension signaling in affected boys and girls.

Summary and Implications for Future Research

The results of the present study demonstrate that noncomprehension signaling remains an area of impairment well into the late adolescent years for most individuals with FXS, including at least some girls. Because the failure to signal noncomprehension can have negative, cumulative effects on comprehension of an ongoing discourse in a variety of contexts, from school to informal conversation, there is a need for interventions targeting the requisite skills and behaviors entailed. The results also suggest that cognitive skills should be the particular focus, such as those broadly described as executive function (e.g., monitoring). Intervention could focus on practicing the act of comparison of a referential description to all available alternatives before responding and of pointing out referential mismatches resulting from a lack of systematic evaluation of comprehension. Individuals with FXS might also benefit from being taught the value (i.e., the information naturally solicited) of specific signal types (e.g., "which one?"). Further research in this area should be directed at identification of specific cognitive skills and their relative contributions to successful noncomprehension signaling so that potential intervention targets can be prioritized accordingly.

The results of this study also demonstrated that the rate of noncomprehension signaling is tied to the amount of FMRP expressed in peripheral blood. Currently, there are calls for behaviorally based measures that could be sensitive to changes promoted by new pharmacological agents in clinical trials for FXS (Berry-Kravis et al., 2013). Because noncomprehension signaling is both functional in the individual's daily life and potentially reflects underlying biology, research focused on exploring the psychometric properties of this measure (e.g., test-retest reliability) could be an interesting avenue for future research.

Despite these contributions, it is important to acknowledge the limitations of the present study. First, because of our limited sample size, analyses for girls with FXS were exploratory; it is vital that large-scale studies be done with girls with FXS to characterize the FXS phenotype in this group and how it compares to the phenotype associated with boys with FXS. Second, we did not include a comparison group of individuals with intellectual disability arising from causes other than FXS, and thus, we are unable to determine the syndrome specificity of the findings. Third, the oldest age at which data were collected was 18, and thus, it is possible that further improvement in noncomprehension signaling may occur in the adult years, although this seems unlikely given the large age span studied here. Fourth, the tasks used in this study focused only on noncomprehension arising with a referential task; thus, noncomprehension signaling may display a different pattern in FXS in other types of comprehension tasks (e.g., those requiring processing abstract or hypothetical discourse or retention over longer periods of time). Fifth, we focused here on the individual's explicit linguistic signaling of noncomprehension, ignoring nonverbal signals such as a "puzzled" facial expression. Although this decision was justified in light of evidence that such nonverbal signals do not necessarily reflect an awareness of the source of confusion (i.e., the inadequacy of the speaker's message), they may well serve as useful indices of importance prerequisites to noncomprehension signaling and thus should be explored in FXS. Finally, we have interpreted the poor noncomprehension signaling of the participants with FXS as reflecting a deficit in skill. There are, however, other aspects of the FXS phenotype, most notably, anxiety (e.g., Cordeiro et al., 2011), that could serve to constrain noncomprehension signaling by preventing access and application of existing skills. Future research should focus on the contributions of anxiety and other comorbid mental health symptoms on noncomprehension signaling.

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