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Signaling of noncomprehension in communication breakdowns in fragile X syndrome, Down syndrome, and autism spectrum disorder

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ABSTRACT

The ability to indicate a failure to understand a message is a critical pragmatic (social) language skill for managing communication breakdowns and supporting successful communicative exchanges. The current study examined the ability to signal noncomprehension across different types of confusing message conditions in children and adolescents with fragile X syndrome (FXS), Down syndrome (DS), autism spectrum disorder (ASD), and typical development (TD). Controlling for nonverbal mental age and receptive vocabulary skills, youth with comorbid FXS and ASD and those with DS were less likely than TD controls to signal noncomprehension of confusing messages. Youth with FXS without ASD and those with idiopathic ASD did not differ from controls. No sex differences were detected in any group. Findings contribute to current knowledge of pragmatic profiles in different forms of genetically-based neurodevelopmental disorders associated with intellectual disability, and the role of sex in the expression of such profiles.

Learning outcomes: Upon completion of this article, readers will have learned about: (1) the social-communicative profiles of youth with FXS, DS, and ASD, (2) the importance of signaling noncomprehension in response to a confusing message, and (3) the similarities and differences in noncomprehension signaling in youth with FXS (with and without ASD), DS, idiopathic ASD, and TD.

1. Introduction

Pragmatic, or social, language skills are often impacted, to varying degrees, in individuals with intellectual and developmental disabilities such as fragile X syndrome (FXS), Down syndrome (DS), or autism spectrum disorder (ASD) (Abbeduto, Brady, & Kover, 2007; Rice, Warren, & Betz, 2005; Tager-Flusberg, Edelson, & Luyster, 2011). Pragmatics is a multifaceted domain comprised of a complex array of component skills, such as speech acts, topic maintenance, turn-taking, and repair of communication breakdowns. One critical skill for repairing breakdowns in communication is a listener's ability to indicate when a speaker's message is not understood, or to signal noncomprehension of a confusing or unclear message.

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Typically developing children as young as two and a half years can signal noncomprehension of very noticeable incompatible messages (e.g., asking "Where is it?" when told to do something with an unavailable referent), whereas the skill for managing more difficult messages, such as those containing ambiguity or unfamiliar vocabulary items, continues to develop into the early school-age years (Flavell, Speer, Green, & August, 1981; Lempers & Elrod, 1983; Revelle, Wellman, & Karabenick, 1985).

The failure to indicate misunderstanding of a spoken message is likely to be particularly detrimental for individuals with neurodevelopmental disabilities, who may face communication breakdowns more frequently due to structural language and cognitive deficits or problems understanding and intuiting others' intentions. The current study compares noncomprehension signaling across three genetically-based neurodevelopmental disabilities–FXS, DS, and ASD–in order to determine whether any syndrome-specific differences exist that would inform general knowledge as well as the design of tailored language interventions. In the case of FXS and DS, we also examine sex differences (data were not available from girls with idiopathic ASD). Sex differences in pragmatic language have been documented in typically developing children (Austin, Salehi, & Leffler, 1987; Cook, Fritz, McCornack, & Visperas, 1985; Kothari, Skuse, Wakefield, & Micali, 2013; Leaper, 1991; Sigelman & Holtz, 2013). However, girls with neurodevelopmental disabilities tend to be underrepresented in research, and determining how phenotypes in genetic conditions may be differentially expressed in males and females has important implications for understanding underlying pathophysiology and informing differential assessment and intervention practices (Messinger et al., 2015; Rinehart, Cornish, & Tonge, 2011; Thompson, Caruso, & Ellerbeck, 2003). Finally, we include both males and females with FXS with and without ASD, along with males with idiopathic ASD, to examine the impact of ASD symptomatology on noncomprehension signaling within and across groups. Below we briefly review the literature on pragmatic skills in FXS, DS, and ASD.

1.1. Fragile X syndrome

FXS is the most common heritable cause of intellectual disability (Dykens, Hodapp, & Finucane, 2000; Hagerman & Hagerman, 2002). In FXS, methylation (turning off) of the Fragile X Mental Retardation-1 gene (*FMR1*) on the X chromosome leads to underproduction of the Fragile X Mental Retardation Protein (FMRP), a protein believed to be critical for normal cognitive functioning (Devys, Lutz, Rouyer, Bellocq, & Mandel, 1993; Jin & Warren, 2003; Patel, Loerwald, Huber, & Gibson, 2014). Because females possess two X chromosomes, females with FXS have one healthy FMRP-producing copy of *FMR1*. For this reason, females with FXS are often affected less severely than males (Hagerman & Hagerman, 2002; Loesch et al., 2002; Reiss & Dant, 2003). Whereas males with FXS generally have moderate to severe intellectual disability, females may display mild to moderate intellectual disability or perform in the normal range of intellectual functioning (Saldarriaga et al., 2014; Sterling & Abbeduto, 2012; Warren, Brady, Sterling, Fleming, & Marquis, 2010).

Pragmatic deficits that are beyond expectations for nonverbal cognitive ability are well documented in males with FXS, with characteristic features including noncontingent (tangential or off-topic) and perseverative (repetitive) language (Klusek, Martin, & Losh, 2014; Martin, Losh, Estigarribia, Sideris, & Roberts, 2013; Roberts et al., 2007; Sudhalter & Belser, 2001; Sudhalter, Cohen, Silverman, & Wolf-Schein, 1990). Far fewer studies have focused on the pragmatic language profile of females with FXS. In one study of parent-reported autistic behaviors in FXS, girls with FXS were rated as having more difficulty initiating and sustaining conversation than IQ-matched controls (Mazzocco, Kates, Baumgardner, Freund, & Reiss, 1997). Similarly, compared with age-matched peers, females with FXS took longer to initiate conversation (Lesniak-Karpiak, Mazzocco, & Ross, 2003) and asked fewer questions to maintain a topic (Mazzocco et al., 2006) in two other investigations. On a standardized test of expressive language abilities, Turkstra, Abbeduto, and Meulenbroek (2014) reported that adolescent females with FXS scored significantly lower overall than age-matched females with TD. In addition, 11 of the 20 girls with FXS had below-average scores on a pragmatic subtest. However, the TD group also scored significantly higher in nonverbal cognition and these differences were not controlled for in the language analysis. Because of the differences in general cognitive ability typically observed in boys and girls with FXS, very few studies have directly compared pragmatic language abilities in these groups. One exception is a study of repetitive language where males with FXS used more repetition of rote sayings and phrases (e.g., "that's a wrap") but did not differ from females in topic repetition (Murphy & Abbeduto, 2007).

Further complicating the pragmatic language profile in FXS is the common comorbidity of ASD, a developmental disorder defined in part by pragmatic language impairments. FXS is the most common known single-gene cause of ASD, with 40%–74% of males and 13%–45% of females with FXS meeting ASD criteria (Bailey, Raspa, Olmsted, & Holiday, 2008; Clifford et al., 2007; Hall, Lightbody, & Reiss, 2008; Kaufmann et al., 2004; Klusek, Losh, & Martin, 2014; Philofsky, Hepburn, Hayes, Hagerman, & Rogers, 2004; Rogers, Wehner, & Hagerman, 2001). Of note, IQ is generally lower in individuals with comorbid FXS and ASD (as is the case in many other monogenetic disorders showing strong overlap with ASD, e.g., Leblond et al., 2014) than in those with FXS only (Kaufmann et al., 2004; Philofsky et al., 2004; Rogers et al., 2001), raising the question of whether ASD in the context of FXS may simply reflect more severe cognitive deficits (see Abbeduto, McDuffie, & Thurman, 2014, for a review). However, in several studies that controlled for nonverbal cognitive ability, boys with comorbid FXS and ASD showed more pragmatic language deficits, including more noncontingent language and perseveration, than those without comorbid ASD (Klusek, Martin et al., 2014; Losh, Martin, Klusek, Hogan-Brown, & Sideris, 2012; Martin et al., 2013; Martin, Roberts, Helm-Estabrooks, Sideris, & Assal, 2012; Roberts et al., 2007). In studies using a semi-naturalistic conversational context or standardized test, boys with FXS and ASD also exhibited the same types of pragmatic language errors and severity of pragmatic impairment as boys with idiopathic ASD (Klusek, Martin et al., 2014; Losh et al., 2012).

Studies of broader language abilities further support the importance of studying the ASD phenotype in FXS. A few investigations have found receptive language to be more impaired in comorbid FXS and ASD than in FXS only (Lewis et al., 2006; Philofsky et al., 2004; Rogers et al., 2001), although findings are mixed (Price, Roberts, Vandergrift, & Martin, 2007). For example, Lewis et al. (2006) found that males with comorbid FXS and ASD performed more poorly on receptive language measures than males with FXS without ASD matched on nonverbal cognitive ability. Similarly, McDuffie and colleagues reported that ASD severity in FXS significantly predicted receptive vocabulary skills even after controlling for nonverbal IQ (McDuffie, Kover, Abbeduto, Lewis, & Brown, 2012). Children with idiopathic ASD also show a relative weakness in receptive versus expressive language (Ellis Weismer, Lord, & Esler, 2010; Hudry et al., 2010). Together, these findings provide support for comorbid FXS and ASD constituting a clinically meaningful group where ASD-related language profiles are not simply explained by intellectual disability. To our knowledge, no studies have compared the language skills of females with FXS with and without ASD, an important focus given that intellectual skills are typically less affected in girls.

To date, only one study has examined noncomprehension signaling in individuals with FXS. Abbeduto and colleagues (Abbeduto et al., 2008) reported that adolescents and young adults with FXS were less likely than mental age-matched children with TD to signal noncomprehension. Males with FXS also signaled less often than a small sample of five girls with FXS. Note that this study did not include groups of individuals with comorbid FXS and ASD, nor did this study directly compare girls with FXS to girls with TD.

1.2. Down syndrome

DS is the most common, non-inherited genetic condition associated with intellectual disability (CDC, 2006). The pragmatic language profile of children with DS is characterized by strengths and weaknesses. Whereas children with DS are able to maintain a topic across multiple turns (Beeghly, Weiss-Perry, & Cicchetti, 1990; Tannock, 1988) and are more contingent than children with FXS or ASD (Roberts et al., 2007; Tager-Flusberg & Anderson, 1991), they do show deficits in initiation and elaboration of topics (Roberts et al., 2007; Tannock, 1988). Communicative functions, with the exception of requests, appear to be generally intact (Beeghly et al., 1990; Coggins, Carpenter, & Owings, 1983).

The few studies of communication breakdown in individuals with DS suggest that they will *respond* to requests for clarification (Coggins & Stoel-Gammon, 1982), but may be less likely than mental age-matched TD controls to signal noncomprehension (Abbeduto et al., 2008). However, adolescents and young adults with DS did not differ from a group with FXS in one study (Abbeduto et al., 2008). Note that this latter study included an older group of adolescents and young adults, and utilized mixed-sex groups, so males and females with DS were not examined separately and less is known about noncomprehension signaling in younger children with DS.

Because DS is expected to affect girls and boys similarly, with the genetic basis not at the level of the sex chromosome (as in FXS) and prevalence rates for males and females not dissimilar (as in ASD), potential sex differences in pragmatic language in DS have been largely unexplored. In fact, many studies of language in DS have included only males to ensure sex-matching, as they were included as controls in studies of boys with FXS or ASD. However, one study of young Swedish children with DS found better parent-reported pragmatic language in girls compared to boys (Berglund, Eriksson, & Johansson, 2001). This study and the literature on sex differences in pragmatic skills in typical development (Austin et al., 1987; Cook et al., 1985; Kothari et al., 2013; Leaper, 1991; Sigelman & Holtz, 2013) together provide support for further examination of potential sex differences in DS.

1.3. Autism spectrum disorder

ASD is a developmental disability defined behaviorally by impairments in social interaction and communication, as well as repetitive or restricted behaviors and interests (American Psychiatric Association, 2013). Pragmatic impairment is a defining feature of ASD, and deficits have been well documented in the areas of topic initiation and maintenance, with quality of topic maintenance affected by both noncontingency and nonresponsiveness (Hadwin, Baron-Cohen, Howlin, & Hill, 1997; Hale & Tager-Flusberg, 2005; Hauck, Fein, Waterhouse, & Feinstein, 1995; Jackson et al., 2003; Philofsky, Fidler, & Hepburn, 2007; Tager-Flusberg & Anderson, 1991). Children with ASD also have difficulty appropriately and effectively responding to requests for clarification in order to repair communicative breakdowns (Geller, 1998; Paul & Cohen, 1984; Volden, 2004). No previous studies have examined noncomprehension signaling abilities in individuals with ASD.

Group comparisons of individuals with ASD with and without FXS are particularly significant, as characterizing the phenotypic expression of these disorders, and their potential overlap, may also provide clues to underlying cognitive or neurobiological deficits that could help target meaningful endophenotypes (i.e., genetically-linked traits) shared across disorders. In a series of studies, Losh and colleagues reported substantially overlapping pragmatic profiles between groups using both a standardized test and a comprehensive coding system for assessing pragmatic violations in conversation (Klusek, Martin et al., 2014; Losh et al., 2012). The current study importantly builds on this work by implementing a more structured task designed specifically to examine a discrete pragmatic skill that is critical to conversational competence–the ability to signal noncomprehension of a spoken message.

1.4. Present study

This study contrasts noncomprehension signaling across groups of children and adolescents with different types of genetically-based developmental disability to examine potential syndrome-specific profiles, as well as overlap in this important pragmatic language skill. We include males and females with FXS without ASD, FXS with ASD, DS, and TD, and males with idiopathic ASD. As noted previously, noncomprehension signaling has not before been investigated in ASD or in comorbid FXS and ASD. We also include a larger group of girls with FXS than has been previously studied, along with distinct groups of girls with DS and TD, to further understand potential sex-specific patterns of pragmatic language competence. Additionally, we examine ASD symptomatology within and across the FXS and ASD groups to explore whether overlap exists in cases of ASD with and without FXS. We hypothesized that children with FXS, DS, and ASD would signal noncomprehension less often than children with TD. We further hypothesized that children with both FXS and ASD would signal less frequently than those with FXS only, and that boys with comorbid FXS and ASD would perform similarly to boys with idiopathic ASD. Finally, we expected females with FXS to signal noncomprehension more often than males.

2. Material and methods

2.1. Participants

Participants included 121 male and 81 female children and adolescents with fragile X syndrome (FXS) with and without autism spectrum disorder (FXS-ASD; FXS-Only or FXS-O), idiopathic ASD (ASD-O), Down syndrome (DS), and typical development (TD). All participants were combining three or more words in an utterance and spoke English as their primary language at home. Subjects with FXS had the full mutation of the *FMR1* gene. Participants were excluded for failing a hearing screening (threshold greater than 30 dB HL across 500; 1000; 2000; and 4000 Hz in the better ear) performed with a MAICO MA 40 audiometer. Participants with DS and TD were excluded if they scored as ASD on the Autism Diagnostic Observation Schedule (ADOS; Lord, Rutter, DeLavore, & Risi, 2001).

Participants were broken into 9 groups based on sex and diagnosis (see Table 1 for participant characteristics). Analyses controlled for nonverbal mental age and receptive vocabulary skill. Girls with FXS-O had significantly higher receptive vocabulary scores than boys with FXS-ASD ($p < 0.001$), girls with FXS-ASD ($p < 0.01$), boys with DS ($p < 0.01$), and girls with DS ($p < 0.001$). On mental age, boys with ASD-O scored significantly higher than boys with FXS-ASD ($p < 0.001$), girls with FXS-ASD ($p < 0.05$), and girls with DS ($p < 0.01$). Boys with FXS-ASD also scored significantly lower in mental age than girls with FXS-O ($p < 0.01$) and TD ($p < 0.05$). Boys with ASD-O were significantly younger than boys with FXS-ASD ($p < 0.001$) and DS ($p < 0.01$). There was no comparison sample of girls with ASD-O, given the lower incidence of comorbid FXS and ASD in females as compared to males (Bailey, Bolton, Butler, & Le Couteur, 1993; Bailey et al., 2008; Clifford et al., 2007; Cohen, Brown et al., 1989; Mazzocco et al., 1997) and the lower incidence of ASD in females (CDC, 2014). Participants with FXS, ASD-O, and DS were recruited through the Research Participant Registry Core of the Carolina Institute for Developmental Disabilities (CIDD) at the University of North Carolina at Chapel Hill (UNC), parent support groups, and genetic clinics in the Eastern, Southeastern, and Midwestern U.S. Children with TD were recruited from the CIDD Participant Registry Core, childcare centers, and local schools.

Table 1
Participant Characteristics by Group.

	FXS-O		FXS-ASD		ASD-O	DS		TD	
	Boys (N = 11) *M* (*SD*) Range	Girls (N = 27) *M* (*SD*) Range	Boys (N = 41) *M* (*SD*) Range	Girls (N = 12) *M* (*SD*) Range	Boys (N = 33) *M* (*SD*) Range	Boys (N = 16) *M* (*SD*) Range	Girls (N = 21) *M* (*SD*) Range	Boys (N = 20) *M* (*SD*) Range	Girls (N = 21) *M* (*SD*) Range
Chronological age (years)	11.9 (3.2) 7.8–16.4	10.7 (3.9) 5.6–16.3	12.4 (2.7) 6.9–19.4	9.8 (3.8) 6.2–17.4	9.8 (2.7) 4.9–13.9	12.5 (2.2) 7.9–16.1	10.7 (2.6) 7.1–16.3	6.1 (1.5) 3.8–10.3	6.2 (2.5) 3.6–12.9
Receptive vocabulary age	7.3 (3.0) 3.9–15	9.4 (3.9) 3.9–19.1	6.2 (1.1) 3.8–8.5	6.0 (1.9) 3.9–9.2	7.5 (3.2) 2.6–17	6.2 (1.2) 4–8.3	5.8 (2.1) 2.9–9.7	7.8 (2.4) 3.8–14.8	7.4 (3.2) 2.7–16.3
Nonverbal mental age	5.7 (1.4) 4.1–9.2	7.1 (2.5) 4.3–13.3	5.1 (0.5) 4–6.6	5.2 (0.8) 4–6.3	7.6 (3.3) 3.7–19.7	5.9 (1.1) 3.1–8.3	5.4 (1.0) 3.6–7.7	6.3 (1.3) 4.4–10.5	7.0 (2.7) 4.5–14.9
ADOS severity score	1.8 (1.0) 1–3	1.9 (0.9) 1–3	6.8 (1.5) 4–10	6.4 (1.7) 4–10	7.8 (1.9) 3–10	1.4 (0.7) 1–3	1.6 (0.7) 1–3	1.7 (0.8) 1–3	1.4 (0.7) 1–3

Note: FXS-O = fragile X syndrome only; FXS-ASD = FXS with autism spectrum disorder; ASD-O = ASD only; DS = Down syndrome; TD = typical development; ADOS = Autism Diagnostic Observation Schedule.

2.2. Procedure and assessments

Participants were tested in a quiet room in a laboratory or in their home or school. Testing sessions for the larger study lasted approximately 4–6 h with breaks when necessary. All assessments were audiotaped with a Marantz portable solid state recorder (PMD670) and videotaped with a Sony Digital 8 camcorder (Model DCR-TVR27). Institutional review boards at UNC and Northwestern University approved all study protocols.

2.2.1. Cognition and language

Subtests comprising the Brief IQ composite of the Leiter-Revised (Leiter-R; Roid & Miller, 1997) and the Peabody Picture Vocabulary Test-Third Edition (PPVT-III; Dunn & Dunn, 1997) were used to assess nonverbal cognitive ability and receptive vocabulary skills, respectively. Age equivalents were computed and used in analyses as covariates, to help ensure that findings were not due to differences in general cognitive or language ability. Standard scores, though typically preferable, were not used given that many participants received raw scores that were too low to be converted. Although raw scores themselves may be used in analysis, we have explained previously that age equivalents are more interpretable measures of development (Martin et al., 2013).

2.2.2. ASD

The Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2001) was administered to participants in the ASD-O and FXS groups by trained examiners to confirm ASD diagnosis or determine sub-group membership, respectively. The ADOS consists of a series of semi-structured interactions between an experimenter and a participant, allowing for the observation of developmentally appropriate or inappropriate responses to these social exchanges. Assessments were scored live or from video using the revised algorithms (Gotham et al., 2008; Gotham, Risi, Pickles, & Lord, 2007). Coders were either research reliable (i.e., had achieved reliability through direct training with the test developers) or reliable with a research-reliable member of the project team, following procedures of the test developer. ADOS scores provide classifications of "autism", "spectrum", or "non-spectrum". Because the data come from a larger longitudinal study, multiple ADOSs may have been available for a given child. If two were available, the concurrent ADOS was selected (if not, the more recent was used) where "autism" or "spectrum" were both considered ASD. If ADOS data were available at three time points and results differed, a best-estimate classification was determined. That is, the majority (2 out of 3) classification was used to determine group membership where "autism" or "spectrum" were considered the same classification. For example, if a child scored as "non-spectrum" at Time 1, "spectrum" at Time 2, and "autism" at Time 3, this child was classified as having ASD. Using this procedure, all participants in the ASD-O and FXS-ASD groups were classified as having ASD on the ADOS, with the exception of two boys with ASD-O. While not reaching ASD criteria on the ADOS, both boys met cutoffs on the Autism Diagnostic Interview-Revised (ADI-R; Lord, Rutter, & Le Couteur, 1994), which was administered to the majority of children with ASD-O, and had received a clinical diagnosis of ASD. Thus, these boys were included in analyses. All participants in the FXS-O groups were classified as having no ASD on the ADOS using the procedure described above. The ADOS revised algorithm 10-point severity score (Gotham, Pickles, & Lord, 2009) was used as a predictor in regressions that paralleled original group-comparison models but examined ASD status continuously for the FXS groups.

2.2.3. Noncomprehension signaling task

Subjects participated in an assessment of their ability to signal noncomprehension (i.e., confusion) to the experimenter using a modified version of the barrier task described by Abbeduto and colleagues (Abbeduto et al., 2008). The task was modified to include only items with an array of 4 choices, rather than a mix of 2 and 4 choices, in order to decrease the length of the task for our participants, who were developmentally younger on average than those in the former study. In additional support of this modification, Abbeduto et al. found similar results for the two- and four-referent conditions.

During this task, two experimenters served as the Examiner and the Speaker, and the participant was asked to make their picture match the Speaker's picture based on a request made by the Speaker. The participant could not see the Speaker's picture. Specifically, youth were instructed by the Examiner that they could "talk with [Speaker], ask her questions, or say anything to her. You need to make sure your pictures match." The participant was presented with four images attached to magnets and had to choose the correct image to attach to the picture on his/her easel. The type of information provided by the Speaker was divided into four conditions with varying degrees of missing information (the latter three conditions attempting to elicit a signal of noncomprehension): Informative (no intended confusion), Incompatible (image consistent with direction not available; e.g., telling the child, "stick the black pencil in the cup" when there is no black pencil, only pencils of other colors), Unfamiliar (use of obscure word very unlikely to be known by the child; e.g., telling the child, "put the ursine animal in the zoo"), and Ambiguous (missing adjective to indicate intended image; e.g., telling the child, "put the star in the sky" when there are four different stars to choose from). Color knowledge and discrimination were tested before beginning the task and all participants were required to perform correctly on three practice items (with feedback). The task included 18 test items across the four conditions (6 Informative, 4 Incompatible, 4 Unfamiliar, and 4 Ambiguous).

If a participant signaled noncomprehension of the Speaker's message, this signal was coded as one of nine types from the video recording (see Table 2) by a research team member blind to diagnosis. The coding scheme was modified from that of Abbeduto and colleagues (Abbeduto et al., 2008) to include nonspecific requests for repetition as noncomprehension signals, as well as facial expressions and gestures directed to the Speaker (previously captured under the published system as

Table 2
Noncomprehension Signal Types.

Signal Type	Example
Nonspecific request for repetition	What? Huh?
Request for Confirmation	Is that green? (in reference to new vocabulary) The black fork? You mean the purple umbrella?
Request for Definition	What's *cerulean*? What's *ursine* mean?
Request for Specific Information	Which color?
Statement of Nonexistence	There's no black. I don't see a black pencil.
Statement of Existence	I have four shells. I have brown, green, purple, blue.
Statement of Uncertainty	I don't know. I'm not sure. Got me.
Facial Expression/Gesture	Child shrugs shoulders during eye contact with Speaker.
Other	That one's tricky

"Other"). Data from 21 participants (10% of sample) were scored independently by a second coder for reliability assessment. The average interclass correlation coefficient for all conditions across all signal types was 0.961, with all individual coefficients exceeding 0.93 with the exception of statements of existence (0.79).

For group comparisons, the outcome variable was the total number of noncomprehension signals by condition. For regression analysis, the dependent variable was "appropriate" signaling as defined by Abbeduto and colleagues (Abbeduto et al., 2008): the proportion of signaling in Incompatible, Unfamiliar, and Ambiguous conditions minus proportion signaling in the Informative condition across conditions. As explained by Abbeduto et al. (2008), calculation of the outcome measure in this way controls for indiscriminate signals (i.e., any signals made during the Informative/control condition which were not necessary to repair a communication breakdown).

2.3. Analysis strategy

Group differences on number of noncomprehension signals in each condition were assessed using a series of repeated measures analysis of covariance (rANCOVA), covarying for nonverbal mental age and receptive vocabulary age. First, sex effects were assessed within diagnostic category (all but the ASD-O group, which included no girls). Next, boys (rANCOVA with FXS-O, FXS-ASD, ASD-O, DS, TD) and girls (rANCOVA with FXS-O, FXS-ASD, DS, TD) were compared independently. Follow-up ANCOVAs and post-hoc comparisons were used when appropriate. In all cases, Mauchley's test indicated that the sphericity assumption was not met for the within subjects variable of condition, and Greenhouse-Geisser statistics are reported for all comparisons of condition.

Linear regressions were run for the FXS-ASD and FXS-O groups collapsed for both sexes, with predictors being nonverbal mental age, receptive vocabulary age, and ASD severity (ADOS severity score), in order to assess ASD as a continuous variable as complementary analysis to the group comparisons. Predictors were entered stepwise if the probability of F was <0.05.

3. Results

3.1. Sex differences

No significant main effects of sex or interactions between sex and condition for any diagnostic group were found (for all omnibus tests, $p > 0.140$). Despite the lack of sex differences, we analyzed data separately for boys and girls given the systematic differences between the groups in sex make-up (i.e., the lack of girls with ASD-O).

3.2. Boys

While there was no main effect of condition for boys, $F(2.457, 280.106) = 0.558$, $p = 0.643$, a main effect of diagnostic group, $F(4, 114) = 3.776$, $p < 0.01$, indicated that boys in the FXS-ASD and DS groups made fewer noncomprehension signals overall

Table 3
Estimated Marginal Means (M) and Standard Errors (SE) for Noncomprehension Signaling by Group and Condition (Boys).

	FXS-O		FXS-ASD		ASD-O		DS		TD	
	M	*SE*	*M*	*SE*	*M*	*SE*	*M*	*SE*	*M*	*SE*
Informative	0.32[a]	0.27	0.31[a]	0.15	0.55[a]	0.17	0.25[a]	0.23	0.14[a]	0.21
Incompatible	2.38[a]	0.50	1.22[b]	0.27	2.24[a]	0.32	1.05[b]	0.42	2.20[a]	0.38
Unfamiliar	1.87[a,b]	0.47	0.72[c]	0.26	2.17[a]	0.30	0.95[b,c]	0.39	2.36[a]	0.35
Ambiguous	1.78[a,b]	0.47	0.72[c]	0.25	1.94[a]	0.30	0.86[b,c]	0.39	1.98[a]	0.35

Note: FXS-O = fragile X syndrome only; FXS-ASD = FXS with autism spectrum disorder; ASD-O = ASD only; DS = Down syndrome; TD = typical development. Different superscripts within a row indicate significant differences. If groups share the same letter, differences were not significant.

than boys in the ASD-O and TD groups (p values <0.05). Boys with FXS-ASD also made fewer signals overall than did boys with FXS-O ($p < 0.05$). A significant interaction of diagnostic group and condition, $F(9.828, 280.106) = 3.199$, $p < 0.01$, was driven by group differences in the Incompatible, $F(4, 114) = 2.858$, Unfamiliar, $F(4, 114) = 5.386$, and Ambiguous, $F(4, 114) = 3.673$, conditions (p values <0.05). In the Incompatible condition, boys with FXS-ASD and DS made fewer signals than boys with ASD-O, TD, and FXS-O (p values <0.05). The FXS-ASD and DS groups also made significantly fewer signals in Unfamiliar and Ambiguous conditions than the ASD-O and TD groups, with boys with FXS-ASD also signaling less often in both conditions than boys with FXS-O (p values <0.05). There were no group differences in the Informative (control) condition, $F(4, 114) = 0.660$, $p = 0.621$. See Table 3.

3.3. Girls

There was a marginally significant main effect of condition for girls, $F(2.510, 188.284) = 2.480$, $p = 0.073$, with girls making the fewest signals in the Informative condition (p values <0.001), but also making more signals in the Incompatible condition than the Unfamiliar and Ambiguous conditions (p values <0.01). A main effect of diagnosis, $F(3, 75) = 3.736$, $p < 0.05$, indicated that girls with FXS-ASD and DS made fewer signals overall than girls with TD (p values <0.05). The significant diagnostic group by condition interaction, $F(7.531, 188.284) = 2.983$, $p < 0.01$, was driven by group differences in Incompatible, $F(3, 75) = 6.273$, and Ambiguous, $F(3, 75) = 3.041$, conditions (p values <0.05), with girls with FXS-ASD and DS making fewer signals than girls with TD in both conditions, and girls with DS also making fewer signals than girls with FXS-O in the Incompatible condition (p values <0.05). There were no group differences for the Informative, $F(3, 75) = 0.747$, $p = 0.527$ or Unfamiliar, $F(3, 75) = 2.111$, $p = 0.106$, conditions. See Table 4.

3.4. Linear regressions

When collapsing across boys with FXS-ASD and FXS-O, 30% of variance in appropriate signaling was predicted by receptive language age (a covariate for group comparisons) and autism severity (adjusted $R^2 = 0.323$, standardized β for receptive language = 0.394, standardized β for autism severity = −0.345, $F(2, 49) = 13.170$, $p < 0.001$). When collapsing girls with FXS-ASD and girls with FXS-O, autism severity was not a significant predictor of appropriate signaling across the three inadequate conditions, $F(1, 37) = 7.6$, $p = 0.259$.

4. Discussion

The ability to signal noncomprehension of unclear spoken messages is a critical skill for successfully managing communication breakdowns. The present study investigated this skill in children and adolescents with different forms of developmental disability associated with genetic conditions–FXS, DS, and ASD–in order to expand our knowledge of

Table 4
Estimated Marginal Means (M) and Standard Errors (SEs) for Noncomprehension Signaling by Group and Condition (Girls).

	FXS-O		FXS-ASD		DS		TD	
	M	*SE*	*M*	*SE*	*M*	*SE*	*M*	*SE*
Informative	0.29[a]	0.17	0.06[a]	0.24	0.37[a]	0.18	0.51[a]	0.18
Incompatible	2.58[a,b]	0.33	1.42[b,c]	0.47	0.97[c]	0.36	3.00[a]	0.36
Unfamiliar	1.87[a]	0.35	1.09[a]	0.49	1.08[a]	0.38	2.28[a]	0.38
Ambiguous	1.17[a,b]	0.35	0.88[b]	0.50	1.12[b]	0.38	2.52[a]	0.38

Note: FXS-O = fragile X syndrome only; FXS-ASD = FXS with autism spectrum disorder; DS = Down syndrome; TD = typical development. Different superscripts within a row indicate significant differences. If groups share the same letter, differences were not significant.

potentially variable social language profiles, as well as the overlap between FXS and ASD and potential sex differences in pragmatic skills.

4.1. Noncomprehension signaling in boys

In the present investigation, boys with comorbid FXS and ASD (FXS-ASD) made significantly fewer signals of noncomprehension compared to boys with TD, FXS-O, or ASD-O. This pattern held across Incompatible, Unfamiliar, and Ambiguous conditions, whereas there were no significant differences found for the control (i.e., informative, non-confusing) condition. Similarly, increased ASD severity was associated with fewer signals among all boys with FXS. These findings are consistent with a growing body of research showing a detrimental effect of ASD status on language profiles of boys with FXS using either a comparative or continuous analytical approach (Bailey, Hatton, Skinner, & Mesibov, 2001; Klusek, Martin et al., 2014; Losh et al., 2012; Martin et al., 2013; McDuffie et al., 2012; Roberts et al., 2007; Rogers et al., 2001). Of note, in the one previous study of noncomprehension signaling in FXS (Abbeduto et al., 2008), only individuals with FXS who met criteria for *autistic disorder* according to the DSM-IV (American Psychiatric Association, 1994) were excluded from the FXS group. Thus, groups with FXS-ASD and FXS-O were not compared, and the single group of individuals with FXS likely included some who would meet DSM-5 (American Psychiatric Association, 2013) criteria for ASD. Our findings suggest that ASD status affects noncomprehension signaling in boys with FXS, and that boys with FXS without ASD may not show particular deficits in this area. As noted in Section 1.1, an important question concerns whether ASD symptoms in FXS can be explained by cognitive deficits. Because we controlled for nonverbal mental age and receptive vocabulary skills, our findings suggest that differences in noncomprehension ability are not simply due to the FXS-ASD group being lower functioning in general, but rather that ASD in FXS results in a distinct phenotype that differentially impacts pragmatic language skills. We note, however, that we did not control for receptive syntax, which may contribute to this skill. In fact, receptive syntax may be more impaired in males with FXS-ASD than in mental age-matched males with FXS-O (Lewis et al., 2006), although findings are mixed (Price et al., 2007).

Given that we found ASD symptomatology in FXS to contribute to difficulties in signaling noncomprehension, it was perhaps surprising that the idiopathic ASD group showed no such difficulties in this area. Specifically, boys with ASD-O performed similarly to TD controls and significantly better than boys with FXS-ASD and DS. The difference between the two ASD groups is in contrast to previous studies where pragmatic profiles overlapped in boys with FXS-ASD and ASD-O during a standardized test of pragmatic judgment and a semi-naturalistic conversation (Klusek, Martin et al., 2014; Losh et al., 2012). These previous studies also controlled for expressive language ability, which might help to explain group differences. Although expressive language was not related to noncomprehension ability in FXS or DS in the study by Abbeduto et al. (2008), that study did not include FXS-ASD or ASD-O groups.

Whereas the validity of ASD in FXS has been questioned historically (Cohen, 1995; Cohen, Vietze, Sudhalter, Jenkins, & Brown, 1989; Hall, Lightbody, Hirt, Rezvani, & Reiss, 2010), it would be a mistake to use findings from this study to perpetuate arguments that FXS is not a valid model for understanding the genetic basis of ASD. To the contrary, findings of overlap and difference together underscore the importance of an endophenotype-based research approach, in order to determine specific features associated with ASD which may be linked to the *FMR1* gene in particular. Our findings may suggest that impairment in noncomprehension signaling is not a shared symptom of pragmatic deficit associated with the *FMR1* gene. On the other hand, perhaps a very structured task like the one employed in the current study is not always able to adequately capture core pragmatic impairment, and some individuals are able to adopt a more strategic approach to task performance that is coded to their benefit without them understanding pragmatic cues on a more reflexive level. In fact, studies have shown that individuals with ASD perform better on more structured conversational (Nadig, Lee, Singh, Bosshart, & Ozonoff, 2010) and narrative (Losh & Capps, 2003; Losh & Gordon, 2014) tasks that place less demand on interpersonal interaction. It is possible that examination of noncomprehension signaling in a more naturalistic, conversational setting would have revealed deficits in the ASD-O group as well.

Boys with DS made fewer signals of noncomprehension than boys with TD and ASD-O in Incompatible, Unfamiliar, and Ambiguous conditions, and fewer signals in the Incompatible condition than boys with FXS-O, but did not differ from the FXS-ASD group. While social skills have traditionally been thought to represent a relative strength for individuals with DS, pragmatic deficits have been documented (Abbeduto et al., 2006; Losh et al., 2012; Roberts et al., 2007; Tannock, 1988). The difference between boys with DS and TD reported here is consistent with the findings of Abbeduto et al. (2008), but DS and FXS groups did not differ in that study. Again, the FXS group studied by Abbeduto and colleagues likely included a mix of those with FXS-O and FXS-ASD, making direct comparison of results difficult. Our findings are also consistent with previous findings of reduced initiations and requests in children with DS (Beeghly et al., 1990; Tannock, 1988). Thus, whereas youth with DS may *respond* to requests to repair communication breakdowns (Coggins & Stoel-Gammon, 1982), they may be less likely to *initiate* a request. Further, it could be that receptive syntax, a well documented impairment in DS even relative to receptive vocabulary (Abbeduto et al., 2003; Chapman, Schwartz, & Kay-Raining Bird, 1991; Laws and Bishop, 2003; Price et al., 2007), plays a significant role in this pragmatic skill and should therefore be considered in future studies. Indeed, Abbeduto et al. (2008) found that receptive language predicted noncomprehension signaling in individuals with DS. The receptive language measure used in that study encompassed both vocabulary and syntax, whereas we controlled for receptive vocabulary only.

4.2. Noncomprehension signaling in girls and sex comparisons

The present study was the first to directly compare noncomprehension signaling in girls with FXS, DS, and TD. Group differences followed a similar pattern to that observed for boys, with the FXS-ASD and DS groups signaling significantly less often than the TD group during Incompatible and Ambiguous conditions (with differences for the Unfamiliar condition following this pattern without reaching statistical significance). Girls with FXS-O did not differ from TD controls, and signaled noncomprehension significantly more often than girls with DS in the Incompatible condition, providing some support for ASD status affecting language in girls with FXS. That is, although girls with FXS did not differ significantly from each other based on autism status, only girls with FXS-ASD differed significantly from controls. That at least a subgroup of girls with FXS showed difficulty signaling noncomprehension is consistent with the small body of research showing that females with FXS have difficulty initiating social interaction and asking questions to sustain the interaction (Lesniak-Karpiak et al., 2003; Mazzocco et al., 1997, 2006). Our findings extend this literature to indicate that girls with FXS-ASD may also have specific difficulty initiating repairs of communication breakdowns. Results also add to the literature on language in DS, and indicate that noncomprehension signaling represents a significant pragmatic challenge even when boys and girls are examined independently.

We found no significant main effects of sex or interactions between sex and condition for any group. These findings are not entirely consistent with those of Abbeduto and colleagues (Abbeduto et al., 2008), who reported that sex was not a significant predictor overall in regression analysis but that males with FXS signaled less frequently overall than a preliminary sample of five girls. Based on our findings with larger and expanded samples, the lack of sex differences suggests that the pragmatic skill of noncomprehension signaling is not differentially expressed in males and females when controlling for nonverbal cognitive skills and receptive vocabulary. Although sex differences have been largely unexplored in both FXS and DS, our null findings are somewhat inconsistent with a small amount of research suggesting greater pragmatic deficits in boys with DS than in girls (Berglund et al., 2001) and more repetitive language in males with FXS than in females (Murphy & Abbeduto, 2007). Pragmatics is a complex language domain encompassing a wide array of skills. Although the current study found no sex differences for the discrete skill of noncomprehension signaling, future studies should take a similar fine-grained approach to examining additional skills, such as topic maintenance and turn-taking, to more fully understand the patterns of sex difference and overlap in pragmatic language abilities across groups. For noncomprehension signaling at least, the similarity in impairment level for boys and girls with FXS-ASD and DS suggests that clinical needs may be more comparable than different.

4.3. Clinical implications

For individuals with neurodevelopmental disabilities, who may encounter breakdowns in communication due to cognitive and language deficits, the failure to signal noncomprehension may be particularly detrimental and may compound existing challenges in language development and academic learning. For instance, unsuccessful repair of communication breakdowns may impact other pragmatic skills, causing a child to be nonresponsive to communicative bids or to produce off-topic language due to a misunderstanding of the previous turn. Intervention to increase noncomprehension signaling is indicated for those showing a deficit in this area. Of note, Dollaghan (Dollaghan, 1987; Dollaghan & Kaston, 1986) has described a comprehension monitoring intervention program focused on identifying and responding to insufficiencies in both the speech signal (e.g., rate, noise) and language content (e.g., ambiguous messages, unfamiliar vocabulary). This program was effective in increasing queries of inadequate messages for four children with language impairment, ages five to eight years, with low-average to average nonverbal mental ability (Dollaghan & Kaston, 1986). Similar strategies may also be successful for children and adolescents with FXS, DS, or ASD, although intervention research with these groups in particular is necessary to determine whether such approaches are beneficial for individuals with a range of intellectual abilities. Finally, given that ASD in FXS negatively affected noncomprehension signaling in our sample, the ASD status of a child with FXS should be considered during assessment and intervention.

4.4. Study strengths and limitations

There are several strengths of the current study. First, the sample size of individuals with FXS is large relative to many previous studies, especially with respect to girls. Second, we controlled for nonverbal mental age and receptive vocabulary skill in our analyses, to help ensure that detected group differences in noncomprehension signaling were not due to differences in general cognitive or receptive vocabulary skills. Third, this was the first study to directly compare noncomprehension signaling in girls with FXS, DS, and TD, contributing to our knowledge of language profiles in girls and similarities across sexes. Fourth, the present study included boys and girls with FXS with and without ASD and boys with ASD-O to better understand the effects of ASD status on language in FXS as well as the overlap of FXS-ASD and ASD-O.

This study also has some limitations and related directions for future research. First, adding a comparison group of girls with idiopathic ASD will help to clarify the extent to which sex may affect the overlap of language profiles in FXS and ASD as well as sex differences in pragmatic language profiles in ASD more generally. Second, although we statistically controlled for both mental age and receptive vocabulary ability in our analyses, it is noteworthy that the groups that performed similarly to TD controls (FXS-O, ASD-O) had higher receptive vocabulary abilities than those who performed more poorly (FXS-ASD, DS).

As previously discussed, we also did not include a measure of expressive language skill. For this reason, we did not examine signal types separately, as expressive language ability could be a particular confound in such analyses. Note, however, that Abbeduto and colleagues (Abbeduto et al., 2008), who also did not examine signal types separately, did not find expressive language to be a significant predictor of noncomprehension ability in FXS or DS. Future studies should more closely match groups on both receptive and expressive language ability, including syntax in addition to vocabulary, to ensure that observed differences are not rooted in structural language impairment. Third, future studies should employ more naturalistic, semi-structured language sampling techniques, which may be more sensitive contexts for assessing group differences and clinical needs. Finally, important to note is that approximately 15% of individuals with DS may also have ASD (Hepburn, Philofsky, Fidler, & Rogers, 2008; Richards, Jones, Groves, Moss, & Oliver, 2015). A primary goal of this study was to examine the impact of ASD symptomatology on pragmatic language in FXS, with the DS group originally included as a control for intellectual disability. Therefore, it was beyond the scope of the current investigation to recruit a group with comorbid DS and ASD of adequate size to address this research question in DS. However, the impact of ASD symptomatology on pragmatic language in DS is an important question for future studies.

4.5. Conclusions

In conclusion, examining a discrete pragmatic language skill–the ability to signal lack of understanding of a speaker's message–revealed distinct patterns of noncomprehension signaling behaviors across different genetically-based neurodevelopmental disabilities. Specifically, children and adolescents with comorbid FXS and ASD and youth with DS signaled noncomprehension of confusing messages less often than typically developing controls in this structured task. Further, no sex differences were detected and ASD status negatively impacted performance in both males and females with FXS, above and beyond the impact of general cognitive delay. These findings highlight the importance of teasing out specific pragmatic language skills for examination across genetically-based neurodevelopmental disabilities, in order to further understand complex language profiles across these groups as well as areas of potential overlap and divergence, with important implications for future research and clinical application.

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Appendix A

Continuing Education Questions:

1. True/False: Compared with boys, less research has been conducted on pragmatic language in girls with developmental disabilities.
2. True/False: DS is the most common known inherited cause of ASD.
3. A pragmatic profile including strengths in topic maintenance (i.e., staying on topic across multiple turns), but difficulties with topic elaboration and noncomprehension signaling best describes the following group:
   a fragile X syndrome
4. autism spectrum disorder
5. Down syndrome
6. fragile X syndrome with autism spectrum disorder

- Compared with TD controls, youth with comorbid FXS and ASD and those with DS:
  a were less likely to signal noncomprehension of a confusing message
- were more likely to signal noncomprehension of a confusing message
- were just as likely to signal noncomprehension of a confusing message
- used more nonverbal strategies for signaling noncomprehension
- Sex differences in noncomprehension signaling emerged in:
  a the DS group only
- the FXS group only

- both the FXS and DS groups
- no groups

Answer Key:

1. True
2. False
3. C
4. A
5. D

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