Early Predictors of Later Language Ability in Children with Fragile X Syndrome

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Abstract

The predictive ability of early language skills on later expressive language was examined in children with Fragile X Syndrome (FXS) and children with FXS with co-morbid autism. Children were visited in their homes and mother-child interactions were videotaped, coded and transcribed behavior-by-behavior. Females with FXS were higher performing than males with FXS, and both were higher performing than males and females with FXS and autism. Early language ability and autism symptomatology were predictive of later productive vocabulary size. These findings provide further evidence for differences in language ability based on sex and autism status in children with FXS.

Keywords: Fragile X, language, autism

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Fragile X Syndrome (FXS) is a neurodevelopmental disorder caused by excessive repeats of a CGG nucleotide triplet on the *FMR1* gene, which is located on the X chromosome (Verkerk, Pieretti, Sutcliffe, Fu, & Kuhl, 1991). The elongated coding sequence causes hypermethylation of the coding region on *FMR1*, which results in the loss or reduction of proteins (FMRP) produced by the gene (Darnell, Warren, & Darnell, 2004). This causes a broad range of emotional, cognitive, and linguistic deficits and delays, which differ by gender due to the X-linked nature of the disorder. Males are more severely affected than females, but individuals of either gender who have comorbid autism are lower performing than their non-autistic counterparts. This suggests four distinct subphenotypes in Fragile X syndrome: males with FXS-only, males with FXS and ASD, females with FXS-only, and females with FXS and ASD. In addition to being the most common inherited cause of intellectual disability, FXS is the most common known genetic cause of autism, with the Centers for Disease Control (2016) estimating that 46% of males and 16% of females with FXS also have an autism spectrum disorder (ASD). The presence of autism may negatively influence cognitive and linguistic abilities in children of both genders with FXS.

It has been well-established that young children with FXS, particularly males, are delayed in the onset of language and in general cognitive development compared to typically developing (TD) peers. Roberts, Stoel-Gammon, and Barnes (2008) reported that on average boys with FXS speak their first words at 28 months of age. Brady, Skinner, Roberts, and Hennon (2006) suggested an even more delayed timeline: In a longitudinal study of 55 children with FXS, parents reported that their boys were nonverbal at 26 months of age, had emerging verbal skills around 28 months of age, but were not considered verbal until the third year of life, around 36 months. Another study based on retrospective parent-reports demonstrated that boys with FXS were on average delayed in speaking their first word by 8.2 months, only beginning to speak around 26 months (Hinton, Budimirovic, Marschik, Talisa, Einspieler, Gipson, & Johnston, 2013). Regardless of the specific timeline, it is quite clear that onset of spoken language is delayed in male children with FXS. Roberts, McCary, Shinkareva, and Bailey (2016) suggested that infant boys with FXS have a developmental profile that is distinct from typically developing peers and non-FXS peers who are at risk for autism. They reported that pervasive differences in cognitive development were evident by six months of age, and when the Mullen Scales of Early Learning was administered, a significant delay was observed for children with FXS compared to TD and at-risk-for-ASD peers.

Despite many overlapping symptoms, there are differences between FXS and ASD. It is important to note that Fragile X autism is distinct from non-syndromic autism (Abbeduto, McDuffie, & Thurman, 2014). Individuals with FXS and ASD have lower IQs on average than those with non-syndromic ASD. They also have fewer atypical communicative behaviors and lower rates of repetitive behaviors. Those with FXS and ASD are also more socially responsive and have less impaired social communication than individuals with non-syndromic ASD. These factors alone can impact language development and cognition to a great extent.

Rinehart, Cornish, and Tonge (2010) discussed a distinct profile for individuals with FXS and comorbid autism. Several studies have demonstrated that impairment in verbal ability is a hallmark trait of FXS and comorbid ASD (see Loesh, 2007 and Philofsky, 2004, as reviewed in Rinehart et al., 2010). These studies both showed a link between low verbal ability and dual diagnoses. Furthermore, Hinton and colleagues (2013) reported that young boys with FXS and ASD were delayed by an average of 13 months in the onset of language, and Warren et al. (2010)

found that the language of children with FXS and high autism symptomatology developed at a slower speed than that of those with FXS and low autism symptomatology. This suggests that autism symptomatology may play an important role in language development in children with FXS. A small subset of females with FXS also meet diagnostic criteria for ASD. These females have delays and deficits that pattern more closely with males with FXS and FXS with ASD.

While it is clear that language development is abnormal in children with FXS, and that certain factors, such as dual diagnosis with autism, may impact language development, relatively little is known about early predictors of language development in children with FXS. It is pertinent to examine the impact that early variables may have on later language development in children with FXS, as this may inform clinical and therapeutic practices. Additionally, an understanding of the impact of early ability and environment on later language in FXS may help further characterize the cognitive phenotype of the disorder. Previous research on children with ASD is relevant to studies of children with FXS given the high prevalence of comorbidity between the two disorders, and a considerable literature exists on early predictors and factors that impact language development in children with autism. This body of research indicates that early consonant inventory, intentional communication, parent linguistic responses, and non-verbal social communication including response to bids for joint attention are predictive of later language ability (Yoder, Watson & Lambert, 2015; Sigman & McGovern, 2005). The current study focused on intentional communication and consonant inventory, previously unstudied early predictors in children with FXS, as predictors of later expressive language in boys and girls with FXS and FXS and ASD. The current study aimed to answer the following research questions:

1) What amount of variance in later productive vocabulary do the early predictors (intentional communication and consonant inventory) explain?

    a. How much variance in later productive vocabulary do early intentional communication and consonant inventory account for together in children with FXS? *It was predicted that together the early variables would account for a significant amount of variance in later productive vocabulary ability.*
    b. What amount of variance in later productive vocabulary ability does each early variable account for uniquely in children with FXS? *It was predicted that intentional communication and consonant inventory would each account for a significant amount of variance in later productive vocabulary ability in children with FXS.*

2) Does adding autism symptomology into the model change the amount of variance in productive vocabulary ability accounted for by the early predictors? *It was predicted that adding autism symptomology to the model would explain more variance. It was further hypothesized that when autism symptomology was added as a unique predictor, variables that previously accounted for unique variance would have lessened variance due to shared effects of autism symptomology.*
3) How do gender and autism impact early language ability? *It was predicted that males with FXS and ASD would be lower performing than males with FXS only. The same was predicted for females with FXS and females with FXS and ASD. It was predicted that females with FXS would be higher performing than males with FXS and that both would outperform males and females with FXS and ASD.*

Language Development in FXS. As previously noted, language delays and cognitive impairments are prevalent in young children with Fragile X syndrome, especially males. It is hypothesized that as boys with FXS age, impaired cognition limits language development, resulting in delayed and impaired language comprehension (McDuffie, Chapman, & Abbeduto, 2008). Studies of boys with FXS have shown delayed expressive and receptive language compared to mental age expectations, as well as impaired pragmatic abilities (Roberts, Chapman, Martin, & Moskowitz, 2008). Similarly, language production is challenging for males. A distinct and peculiar tone of speech, involving rapid accelerations in rate of speech, and segmental errors in speech production, including liquid simplification (/l, r/ become the glide, /w/) and cluster reduction (eg. /st/ becomes /t/) have been reported for some males (Roberts et al., 2008). Speech production and expressive and receptive vocabulary are delayed in boys with FXS when compared to TD peers (Roberts et al., 2007). Morphosyntax is similarly delayed in young males with FXS (Sterling, Rice, & Warren, 2012).

While similar deficits are evident in females with FXS and comorbid ASD, the same is not true for females with FXS-only. Parents of female children in the Brady et al. (2006) study did not report delayed onset of language. Sterling and Abbeduto (2012) demonstrated that school age girls with FXS-only use syntactically complex language in conversation, and have generally strong receptive vocabulary skills. They additionally have mean length of utterances (MLUs) that are near normal.

Pragmatic skills in children of both genders with FXS are impaired and/or delayed. Mazzocco et al. (2006) performed a three-way comparison between females with FXS, Turner’s syndrome, and typical development who were chronologically age matched. They concluded that females with FXS had fewer total utterances, fewer questions, and more repetitions than the other two groups. Abbeduto and Hagerman (1997) reported that males with FXS use more repetitive language than females with FXS, and Murphy and Abbeduto (2007) found that they use a more repetitive conversational style and repeat more rote phrases than females. McDuffie et al. (2008) reported that while males are more talkative than females, many studies suggest that males use perseverative language excessively (McDuffie et al., 2008; Murphy & Abbeduto, 2007; Abbeduto & Hagerman, 1997). Perseverative language use has also been tightly correlated to autistic symptoms. It has been suggested that pragmatics is an area of relative weakness for both males and females with FXS, and becomes more problematic over time (Dykens et al. as referenced in McDuffie et al., 2008).

Early Predictors in Fragile X. Deficits in expressive and receptive language, in combination with impaired pragmatic skills contribute to further delay and impairment as the child matures (McDuffie et al., 2008). Therefore it is critical to understand what factors may impact language development in young children with FXS in order to anticipate and potentially minimize further difficulties. In order to do this, it is necessary to examine literature on children with autism in addition to the literature on children with FXS, since the disorders are so frequently co-occurring. A number of early predictors have been extensively studied in FXS, but these are not as all-encompassing as those studied in children with ASD. Early predictors that are implicated in ASD need further examination in children with FXS. Maternal responsivity and maternal communication style have been well-researched in the FXS literature (Warren et al., 2010; Brady, Warren, Fleming, Keller, & Sterling, 2014; Hahn, Zimmer, Brady, Romine, & Fleming, 2014; Warren, Brady, Fleming, & Hahn, 2017). Parent linguistic response has been suggested as a predictive factor in the autism literature, as has nonverbal social communication (Sigman & McGovern, 2005; Yoder et al., 2015). Additionally, early predictors of language ability have been studied in the ASD population including consonant inventory and intentional communication (Yoder et al., 2015; Woynaroski et al., 2015). It is clear that many factors can have long-lasting effects on the language development of children with neurodevelopmental disorders. Nevertheless, an aggregate of multiple early factors may provide the best prediction of language ability in children with FXS.

Maternal responsivity has been shown to impact language development in children with FXS (Brady et al., 2014; Warren et al., 2010). An active line of research has demonstrated that early (Warren et al., 2010) and sustained (Brady et al., 2014) maternal responsivity predicts expressive and receptive language ability over time even when gender, autism symptomatology, and maternal education level are controlled for. Maternal responsivity includes a variety of maternal behaviors such as warmth, nurturance, and contingent and positive responses to child communication leads. Increased amounts of these and other characteristics of highly responsive parenting styles significantly affected the child's expressive and receptive vocabulary scores and number of different words used by the child during video-recorded interactions (Brady et al., 2014). As Warren, Brady, Fleming, and Hahn (2017) discuss, high levels of responsivity provide the child with a supportive environment, and contingent responses to child initiations of communication help shape the form and function of the child's language. This in turn advances the child's language use. Consistency and flexibility are important aspects of responsivity, and children whose mother's demonstrated variable levels of responsivity fared worse than those whose mother's had sustained high responsivity (Warren et al., 2017) in terms of their development of communication skills in middle childhood. Similarly, Hahn, Brady, Warren, and Fleming (2014) examined maternal gesture use during toddlerhood in a sample of children with FXS and found that children were more likely to respond using speech when mothers used a gesture in combination with speech. This finding held true for two later age periods, suggesting that maternal use of gestures has an evocative effect on child speech production over time.

A specific piece of maternal or parental responsivity is parental linguistic response to child communication or attentional leads. Parent use of an appropriate linguistic response to his/her child's communication bid has been demonstrated as a robust predictor of language development in children with autism (Woynaroski et al., 2016; McDuffie & Yoder, 2010; Yoder et al., 2015). McDuffie and Yoder (2010) determined that parent verbal responses were predictive of productive vocabulary six months later in a sample of young children with ASD. They suggested that responding to the child's verbal communicative act though linguistic mapping, expansion, and/or repetition, and responding to the child's focus of attention through commenting and/or directing, enhance early vocabulary acquisition (McDuffie & Yoder, 2010). Warren et al. (2010) further support this claim by demonstrating that early maternal responsivity, including child-directed speech, predicts rate of total communication and rate of number of different words at 36 months of age.

During the interaction between parent and child, both participants must serve as adept conversational partners. However, the young child is rarely an experienced and proficient conversational partner. While important, parental responses alone are not sufficient for language development; the child too must respond and interact. Nonverbal social communication, in the form of child responses to parent bids for joint attention has been thoroughly explored in studies of autism (Yoder et al., 2015; Sigman & McGovern, 2005). By responding to the parent's request for joint attention the child is enhancing their language learning opportunities in several ways. Primarily, they are learning to assign meaning to objects, which assists in the development of the lexicon. The child is also learning pragmatic skills necessary for social interactions, such as turn taking and topic maintenance. Research suggests that response to bids for joint attention is a robust predictor of later language ability in children with autism (Sigman & McGovern, 2005; Yoder et al., 2015).

Early Predictors in Autism Spectrum Disorders. Additional factors that influence early speech and language abilities and their development have been extensively studied in children with autism spectrum disorders (Woynaroski et al., 2016; Yoder et al., 2015; Plumb & Wetherby, 2013; Schoen, Paul, & Chawarska, 2011; Paul, Chawarska, Cicchetti, & Volkmar, 2008). Paul et al. (2010) found early receptive vocabulary and stereotypic behaviors contribute significantly to a stepwise regression model predicting expressive language outcome in a sample of toddlers with ASD. Yoder, Watson, and Lambert (2015) studied theoretically- and empirically-motivated early predictors of expressive and receptive language growth in 87 initially nonverbal preschoolers with ASD. They proposed nine predictors of expressive language growth and seven predictors of receptive language growth. Of the nine proposed predictors of expressive language, they found that intentional communication, consonant inventory, response to joint attention, and parent linguistic responses were “value-added predictors” of expressive language. Value-added predictors being those which “account for significant variance … after controlling for intercorrelation among other predictors” (Yoder et al., 2015; p. 1256). Motor imitation, non-imitative oral motor skills, attention to child-directed speech, and play were not value-added predictors of expressive language growth. Similarly, intentional communication, response to joint attention, parent linguistic responses, receptive vocabulary, and autism symptomatology were value-added predictors of receptive language growth. Again, motor imitation, play, and attention to child-directed speech were not predictive of receptive language growth.

In a related study using the same sample, Woynaroski, et al. (2016) found that intentional communication and parent linguistic responses were predictive of consonant inventory growth in children with ASD. Diversity of key consonants used in communication increased at a faster rate for children who had initially higher scores on those two measures, yet children with comparatively lower intentional communication and parent linguistic response scores still showed growth in consonant inventory throughout the longitudinal study (Woynaroski et al., 2016). The presence of intentional communication and parent linguistic responses, regardless of their quantity, appears to be highly influential in language development. In this case quality maybe more important than quantity. Clearly, intentional communication and parent linguistic response are robust environmental predictors of multiple aspects of language development in young children with ASD (Woynaroski et al., 2015; Yoder et al., 2015). However, little is known about the effect of early intentional communication in particular on language development in children with FXS.

Intentional Communication. Intentional communication encompasses purposeful and meaningful communication acts produced by the child. This takes the form of child initiations, responses, and topic maintenance. Yoder and Warren (1999) summarize the theoretical implications necessitating intentional communication in the prelinguistic stage of language acquisition. The use of intentional communication suggests that the child understands the means-end and social agency functions of communication (Yoder & Warren, 1999). That is, they are able to request something and understand that a communicative partner, typically an adult or parent, can fulfill their request. This sets the stage for responsivity on the communicative partner’s side, giving them the opportunity to respond to the child. The use of intentional communication by the young, prelinguistic child is predictive of expressive and receptive language and overall cognitive ability later in childhood in children with autism. This is supported by findings from several studies (Yoder et al., 2015; Plumb & Wetherby, 2011; Sigman & McGovern, 2005). Initiation of requesting behavior was predictive of language development from preschool to adolescence in children with ASD (Sigman & McGovern 2005). As Yoder et al. (2015) further demonstrated, intentional communication was predictive of both expressive and receptive language growth in children with autism. An investigation of this relationship in children with FXS is necessary to inform clinical practices and early interventions for children at risk for language delays. This will also help determine the unique and overlapping aspects of the four Fragile X subphenotypes (males with FXS-only, males with FXS and ASD, females with FXS-only, and females with FXS and ASD).

Consonant Development and Inventory. Consonant inventory is an additional robust predictor of expressive language ability in autism. In order to understand why consonant inventory may be predictive, it is relevant to briefly discuss canonical vocalizations. Canonical vocalizations are those that contain a true consonant and a true vowel in quick succession. Roberts et al. (2007) propose that the increased use of complex babbling in young children and infants with FXS is linked to better performance on speech and language measures after the onset of speech. Complex babbling includes vocalizations that use adult-like and variegated consonants. Hochmann, Benavides-Varela, Nespor, and Mehler (2011) suggest that consonants and vowels trigger different learning mechanisms during early language acquisition. They propose that consonants are used for word identification and processing, whereas vowels are more important for generalization of structural relations (Hochmann et al., 2011). The use of canonical vocalizations has also been argued to be a building block of successful speech production. It can be further argued that the use of consonants during early language acquisition sets the child up for diverse use of consonants during later acquisition.

Consonant inventory, a measure of the diversity of the total number of consonants used rather than the frequency with which consonant sounds are produced, is an important early predictor. Yoder et al. (2015) found that expressive, not receptive, language growth is predicted by consonant inventory in children with ASD. In a study by Sokol and Fey (2013), the speech sound development of 26 young children with Down syndrome (DS) was compared to that of age-matched developmentally-delayed peers with non-Down syndrome etiologies. Sokol and Fey (2013) found that their DS toddlers, who were roughly 25 months of age, had extremely restricted consonant inventories when compared to 14 month-olds with ASD and 11-13 month-olds with TD. The DS toddlers produced on average four different consonants, while the ASD infants produced on average 6.5 consonants and the TD infants averaged 7.5 consonants (Schoen, Paul, & Chawarska, 2011). This information has not been previously reported for children with FXS. Woynaroski et al. (2016) further assessed consonant inventory in preschoolers with ASD and discovered that diversity of consonants used in communication was predicted by intentional communication and parent linguistic responses. Much more is known about early consonant inventories of children with autism than those with FXS.

No known studies have examined the impact that the previously discussed early variables have on language outcomes in children with FXS. Intentional communication and consonant inventory are clearly predictive of later language ability in children with autism. The current study examined the impact that intentional communication and consonant inventory in toddlerhood have on the growth of expressive language abilities over time in children with FXS and FXS with comorbid ASD. Because previous literature concerned with these variables focuses on children with autism, and due to the high comorbidity of FXS and ASD, and the distinct linguistic profile of children with FXS and ASD, autism symptomatology was included as a third predictor of later productive vocabulary size, a measure of expressive language growth.

Finally, the current study investigated the gender differences in early language ability for young children with FXS and FXS with comorbid ASD. An examination of differences in language ability in childhood by gender and autism status could be informative for our understanding of the four subphenotypes of Fragile X syndrome.

Method

Participants

The current study utilized a pre-existing database from the Fragile X Research Lab at the University of Kansas (PIs Steven F. Warren and Nancy C. Brady). Fifty-five children with full-mutation FXS and their biological mothers were enrolled in a longitudinal study spanning a ten year period (See Warren et al. 2010). Given that the disorder is relatively rare, the participants represent a sample of convenience, recruited from across the United States. Therefore, race, socioeconomic status, and maternal education were not controlled although there was some variance in the sample on these variables. Table 1 includes demographic information for the 46 children included in the current analyses.

Child Characteristics. Forty-six children with full mutation FXS (10 females) participated in the study, beginning in toddlerhood (see Table 1 for participant characteristics). At Time 1, the children were between 19 and 36 months of age (M_{age} = 30.4, SD = 5.29) and at Time 2, roughly six and a half years later, the children were between 104 and 119 months (M_{age} = 113.3, SD = 3.29).

Fourteen children in the current analyses had consistently high autism symptomatology during the time of the home visits based on results from the Childhood Autism Rating Scale

(CARS; Schopler, Reichler, & Renner, 1988). Parents additionally reported their child had a diagnosis of autism provided by either a pediatrician, developmental pediatric neurologist, or psychologist.

Seven children were nonverbal at Time 2. This was reported by the mother, and confirmed with the Expressive Vocabulary Test (Williams, 2007). Nonverbal status indicates that the child did not use verbalizations, or words, to communicate. Nonverbal children may use signs, gestures, or alternative and augmentative communication (AAC) systems to communicate.

Maternal Characteristics. Maternal age at the first observation ranged between 20.0 and 41.00 years, with a mean of 32.8 (SD = 4.70) years. Age at the final observation ranged from 27.0 to 48.0 years, with a mean of 39.8 (SD = 4.68) years. Two of the mothers were full mutation (>200 CGG repeats), and 44 were premutation carriers (55-200 repeats).

Measures

Data were collected during five or six home visits, depending on the child’s age at the time of the first visit. For the current study, data come from an early visit and from a visit roughly six and a half years later. Time 1 refers to early visits when the children were on average 30.4 months of age (2.5 years), and Time 2 refers to late visits that occurred when the children were on average 113.3 months of age (9.5 years). At each visit, the research team administered standardized assessments of language and cognitive ability, and then the child and mother were videotaped during three structured contexts that each lasted five minutes. For Time 1, the contexts were: playing together, making a snack together, and reading a book together. At Time 2, the contexts were similar: making a craft together, making a snack together, and reading a book together. Table 1 shows child demographics and scores on standardized assessments, including the Mullen Scales of Early Learning (Mullen, 1995) at Time 1 and the Peabody Picture Vocabulary Test (Dunn & Dunn, 2007) and Expressive Vocabulary Test (Williams, 2007) at Time 2.

Trained graduate research assistants coded the videotaped mother-child interactions for each visit using the Noldus Observer software (Noldus Information Technology, 2008). This software allowed for behavior-by-behavior coding of the child's communicative acts. Child verbal (both vocalizations and verbalizations) and nonverbal (gestures, points, and signs) communication acts were identified based on their clear communicative intent. These were further broken down into initiations and responses. Transcripts from the Noldus observations were reformatted and entered into the Systematic Analysis of Language Transcripts software (SALT; Miller & Chapman, 1985). This software determines mean length of utterance (MLU), total number of utterances, and total number of different words used, among other counts.

During Time 1 structured mother-child interactions, number of intentional communicative acts and number of partially acquired consonants for the child were obtained. This included 15 minutes of videotaped interactions. For the Time 2 interactions, total number of different words was obtained, again from 15 minutes of interaction.

Intentional Communication. Intentional communication was the total sum of all communicative acts across the three structured mother-child interactions at the Time 1 visit. Again, communicative intent was defined as meaningful and adult-directed for the purpose of this study. Communicative acts included verbalizations, vocalizations, gestures, and signs that had clear communicative intent, based on the Noldus transcripts. Furthermore, communicative acts were coded as either social interaction, joint attention, or behavior regulation. Social interaction occurred when the child attracted the adult's attention in order to engage in a social routine. Joint attention occurred when the child directed the adult’s attention to an object or event. Behavior regulation occurred when the child regulated the adult’s behavior. Thus, intentional communication was a count of the total number of child communicative acts that occurred during three types of mother-child interactions, regardless of modality or specific function.

Partially Acquired Consonants. Child consonant inventory was measured using the pre-identified vocal and verbal communication acts. A trained coder listened to each communicative act at most three times to determine which, if any, consonant was present in the act. Glottal stops and glottal fricatives were not considered consonants. However, glides were considered consonants. Voicing distinctions were not considered, such that /p/ and /b/ and other voiced/voiceless minimal pairs were considered a single consonant. This was due to difficulties in distinguishing voicing encountered by the coders. The maximum consonant inventory was 14, and included the sounds found in Table 2. For each consonant the child produced during the mother-child interactions, s/he was given credit, regardless of the locations within the act (syllable-initial, etc.). While a more stringent method for including a child’s consonants in their acquired consonant inventory is used for acquisition studies, the current study took all consonant productions into account. This way, the child was credited for each consonant they produced regardless of how often or where in the syllable the consonant was produced. A total count of different consonants heard by the coder was obtained.

Number of Different Words. Productive vocabulary size was determined using the number of different words the child spoke during the Time 2 interactions. All three structured contexts were used to measure vocabulary size. A total number of different words was derived from the SALT analyses.

Autism Symptomatology. Autism symptomatology was measured at each data collection visit using the Childhood Autism Rating Scale (CARS; Schopler, Reichler, & Renner, 1988). The CARS is a 15-item rating scale that provides a general impression of autistic behavior. Scores under 30 indicate no autistic symptoms. Children who score over 30 display mild to moderate autistic symptoms. Children who score over 37 display symptoms consistent with severe autism. Although the CARS alone cannot be used to diagnose ASD, it is a good indicator of autistic symptomatology displayed at the time of the home visit. CARS score at the Time 2 visit was used for analyses, because at Time 1 the children were too young to reliably assess using the CARS.

Reliability

See previous publications from our lab for further information regarding reliability (Brady et al., 2014; Warren et al., 2010). Intra-class correlation coefficients (ICCs) were calculated between primary and secondary scores for intentional communication and number of different words. ICCs were both .99. Consonant inventory was coded by a primary coder, and a secondary coder performed reliability on 31% of the children. Agreement was calculated based on how many times the coders agreed on the total number of consonants present out of all possible consonants per child. Percent agreement was 95%.

Statistical Analyses

The statistical software SPSS (IBM Corp., 2013) was used to run multiple regression analyses.

Results

The results of this study are organized into three analyses, based on the research questions. First, multivariate regression was employed to determine the predictive ability of consonant inventory and intentional communication (referred to as early linguistic predictors) on later number of different words, also referred to as productive vocabulary size. This included an analysis for the entire sample, as well as one for the subsample (39 of the 46 subjects) who were verbal at Time 2. Next, a multivariate regression was performed to determine whether adding autism symptomatology would strengthen the model. This again included two analyses, one of the whole group and one of the verbal subsample. Finally, the predictive ability of the early predictors and autism symptomatology was differentiated by gender, to examine the impact the early predictors and autism symptomatology on productive vocabulary for each gender.

Table 3 presents descriptive summaries of each variable and correlational information between the variables. All the early predictors were significantly correlated with the dependent variable, and with one another. Multi-collinearity tests suggested no confound of collinearity in Model 2a, which included all three predictors, see Table 4. Variance inflation factors (VIFs) ranged from 1.47 to 4.05, which were below the cut-off of 10. Similarly, tolerances were all above the .10 threshold (range from .247 to .680). The condition index for CARS score was near 15, at 13.828. However, this only suggests a mild multi-collinearity problem, and was not of a great enough magnitude to raise concern. Furthermore, although significant, the correlation between predictors and the dependent variable were moderate in magnitude, further reducing multi-collinearity concerns. The one exception to this was the correlation between the two early predictors, intentional communication and consonant inventory, which was .852. This high correlation suggests that a hierarchical method of variable entry would be preferable. However, a stepwise regression method was used since neither intentional communication nor consonant inventory were theoretically more salient than the other, giving no compelling reason why one should be entered first. Yoder et al. (2015) and Woynaroski et al. (2016) demonstrated that both intentional communication and consonant inventory are predictive of expressive language growth in children with ASD. Furthermore, the research questions were concerned with the impact that CARS score had on the established model. Thus, if CARS score accounted for the most variance of the independent variables, the early linguistic predictors would never be entered into the model and the research questions would be unanswerable.

Early Linguistic Predictors. To answer the first research question, whether the early linguistic variables predicted later expressive language ability, a multiple regression was performed. Consonant inventory and intentional communication were used as predictors for productive vocabulary size. A simultaneous entry method was used. There was one instance of missing data, which was handled using listwise deletion. Thus, all data from the subject with missing data was removed from the analyses.

Two statistical analyses were performed. The first model utilized the entire sample (n=45, due to missing data), and a second model utilized the subsample of participants who were verbal at Time 2 (n=39). Tables 5 and 6 show a summary of the models. In the whole sample, the early linguistic variables were significantly related to vocabulary size. When both predictors were included, they explained significantly more variance in vocabulary size than a null model alone, $F(2,43)=7.64$, $p<0.01$, and accounted for an adjusted R-square of .23. Consonant inventory alone was significantly predictive of number of different words, $t(43)=3.27$, $p<.01$. Intentional communication was not significant, however it neared significance, see Table 5.

When reducing this model to only include children who were verbal at Time 2 (n=39), the two predictors did not account for significantly more variance in vocabulary size than the null model. The adjusted R-square was reduced in magnitude to .097, $F(3,36)=3.09$, $p>0.05$. Consonant inventory remained significantly predictive, $t(36)=2.13$, $p<.05$, while intentional communication remained non-significant. Verbal status seems to make a difference in these models.

Adding Autism Symptomatology. The second research question was concerned with the impact that autism symptomatology, as measured by the CARS, might have on the above models. When CARS score was included as an additional predictor in the complete sample, the adjusted R-square value increased from .23 to .46, $F(3,42)=13.85$, $p<0.01$. Furthermore, autism symptomatology alone provided unique predictive value ($t(42)=-4.43$, $p<0.01$) above and beyond the early linguistic variables. See Tables 5 and 6 for further model information. When autism symptomatology was added to the regression, consonant inventory and intentional communication were both significantly predictive of number of different words, $t(42)=2.29$, $p<0.05$ and $t(42)=-2.10$, $p<0.05$, respectively. It is clear that all three variables should be included in the model.

Autism symptomatology had a lesser effect on vocabulary size when nonverbal children were removed from the sample. The adjusted R-square value was .20, $F(3,36)=4.15$, $p<0.05$ for the reduced model. Autism symptomatology remained a significant predictor in the verbal-only model, $t(36)=-2.35$, $p<0.05$. Consonant inventory and intentional communication were both non-significant, see Table 6.

Gender Difference. The final analyses concerned the gender differences in predictive ability for the three independent variables (consonant inventory, intentional communication, and autism symptomatology). There were too few females in the sample to run a multiple regression, but for males, the model accounted for an R-square of .45, which was significant ($F(3,32)=10.75$, $p<0.01$), see Table 7. Autism symptomatology was the only predictor with significant predictive ability, $t(32)=-4.32$, $p<0.01$.

Group differences by gender and autism status are apparent upon visual inspection of the data, see figures 4 and 5. However, given the difference in sample size for each gender and diagnosis, an analysis of variance (ANOVA) yields cautious results and thus is not reported here. Ideally, an ANOVA to compare the difference between groups should include groups of equal size. This is tricky given the prevalence of FXS in the general population and the X-linked nature of the disorder. The sample used in this study is representative of the disorder by gender and autism status in the general population, however. Table 8 provides an overview of the mean performance for each group (males with FXS, males with FXS and ASD, females with FXS, and females with FXS and ASD). CARS score is clearly higher for both FXS and ASD groups, while consonant inventory and intentional communication are both higher for the FXS-only groups. Number of different words is also higher for the FXS-only groups.

Discussion

These findings suggest that together early consonant inventory, intentional communication, and autism symptomatology are predictive of later productive vocabulary size in children with FXS. As Table 5 demonstrates, two early linguistic variables and a later cognitive variable are significantly predictive of number of different words in late-middle childhood. However, this effect is reduced in verbal-only samples and in single-gender samples. A subset of children who were verbal in late-middle childhood did not show as robust an effect as the whole sample. Nor did subsets of boys-only or girls-only. This suggests that the findings are representative of a mixed-gender and mixed-ability group.

Although the aggregate of the two linguistic variables explained significant variance, only consonant inventory uniquely explained significant variance. Unique variance accounted for by each predictor may have been impacted by the high correlation between the two predictors. A high correlation prevents each predictor from contributing uniquely to the variance in productive vocabulary size. Although there were no problems with collinearity in the statistical analyses, the early predictors are theoretically highly related in the following way. Intentional communication acts were first coded. Each act was then designated as either canonical or noncanonical. Each identified canonical communication act was coded for the consonant(s) used. A null consonant inventory maps directly to a low proportion of canonicals, which is indicative of fewer communicative acts. Essentially, the two measures share variance because they co-occur to a large degree.

An additional reason that intentional communication was nonsignificant may be due to the presence of late talkers and nonverbal children. At Time 1, sixteen children had not yet begun using canonical verbalizations or vocalizations, and as a result had null consonant inventories. Although they may have used gestures and other means of intentional communication, they did not use verbalizations or canonical vocalizations. This skews the sample towards the nonverbal children. A more uniform sample of children who were closer in age and ability at Time 1 may have different results. Running the second regression was intended to overcome this problem.

Given that seven participants were nonverbal throughout childhood, it is reasonable to suspect that these participants impacted the regression model. A second model was performed that did not include children who were unable to complete the EVT at Time 2 due to experimenter and/or parent report of nonverbal status. When the second model was analyzed, the amount of variance explained by the set of predictors actually decreased between the complete and subsampled models. Consonant inventory remained significant in the linguistic predictor model. However, without a skew towards the nonverbal participants, the early linguistic predictors were no longer significant when combined with autism symptomatology.

Another possible explanation for the lack of unique variance accounted for by intentional communication could be due to the nature of the sample analyzed. Although there was a fair amount of variability in productive vocabulary size (mean= 98.98, range 1-193), there could have been an influence of gender on the results. Males with FXS are generally more severely affected than females since the disorder is X-linked. Separate analyses by gender would be warranted. It could be expected that an analysis of males only would yield significant results of a greater magnitude as the high performance of females may have impacted the model fit. Based on the results of a male-only analysis (Table 7), it is likely that by including the females in the analysis there was a bias towards significance. A regression of females only was not performed due to limitations in sample size, so it is not definite that females affected the significance of the results.

When examining early ability by gender and by autism diagnosis, clear patterns arise. Figure 1 shows the number of different words by autism symptomatology score, the most robust predictor in each model. For the females there is a clear difference in number of different words between diagnostic categories: girls with high autism symptomatology have fewer number of different words than girls with lower autism symptomatology in late-middle childhood. Similarly, as autism symptomatology increases in severity, number of different words decreases for boys with FXS.

Children with FXS only and those with FXS and ASD may perform differently on consonant inventory, based on previous research. Profiles of consonant acquisition in toddlers with ASD vary from those of toddlers with TD, and DS (Schoen, Paul, & Chawarska, 2011). Toddlers with ASD produce more varied consonants than those with DS, suggesting a more typically developing profile. There are no known studies that report consonant inventory size in the population studied here, but our analyses suggest that children with FXS produce around 4 consonants on average during the toddler period studied, when collapsed over gender. This is lower than previous findings from studies of children with ASD and TD, and on par with toddlers with DS (Sokol & Fey, 2013; Schoen et al., 2011). However, when this is more closely examined, it appears there are gender differences in consonant inventory. As shown in Table 8, the difference in consonant inventory between diagnostic groups is striking. Although children with ASD-only seem to have relatively spared early consonant inventories, children with FXS and ASD of both genders have deficient early consonant inventories. Males with FXS-only have similar early consonant inventories to their peers with DS, and females perform similarly to TD peers (see Schoen et al., 2011). This supports the assertion that gender differences are pervasive in FXS.

A dual diagnosis of FXS and ASD, or FXS with high autistic symptomatology, generally represents a significant reduction in ability and likely affects the families' qualities of life. When autism symptomatology was included above and beyond the early linguistic predictors in each regression model, it uniquely accounted for significant variance in later productive vocabulary size. Aside from a proposed distinct language profile for children with a dual diagnosis (Rinehart et al., 2010), several potential reasons explain why children with FXS and ASD may underperform compared to peers with just FXS. Deficits in social interaction may limit the quality of the language learning environment available to the young child with ASD. Schoen et al. (2011) suggested that toddlers with ASD have difficulty attending and listening to child-directed speech, which may impact their ability to acquire their native language phonemes, including consonants. Schoen et al. (2011) and Plumb and Wetherby (2013) demonstrated that young children with ASD use a high proportion of atypical vocalizations compared to their TD and different etiology peers. Plumb and Wetherby (2014) further argue that toddlers with ASD have “higher levels of temperamental negative affect” (p. 730), which may impact the quality of the video interactions and data obtained from them. Although distinct from non-syndromic ASD, FXS and ASD may negatively impact the child’s ability to learn language from social interaction and the environment.

Many variables relating to language growth in children with FXS and other neurodevelopmental disorders have been studied. In the current study, early linguistic predictors were able to explain a small but significant amount of variance in later productive vocabulary. The inclusion of autism symptomatology increases the variance accounted for, but there is still a large portion of variance unexplained by the early linguistic predictors and autism symptomatology. As previous research has indicated, maternal responsivity and linguistic input have a significant impact on language development in children with FXS and/or language delays (Warren et al., 2010; Kryski et al., 2009). Warren et al. (2010) showed that having a highly responsive mother early in childhood predicted better expressive language outcomes and increased rates of communication in later childhood. Kryski et al. (2009) showed that quantity and sophistication of maternal vocabulary was indicative of child vocabulary development, and that lower maternal mean length of utterance (MLU) had an effect on the child’s language development. A responsive environment that fosters conversation and positive discourse features provides the child with models for language that set a foundation for a diverse consonant inventory and the use of complex syllables. Intentional communication on the child’s part is reinforced through responsive parenting. Clearly there is a larger picture beyond the three variables studied that explains variance in expressive language development. Furthermore, the prevalence of nonverbal children with FXS and FXS and ASD suggests additional mechanisms at the heart of productive language development.

A central strength of the current study is the true longitudinal nature of its data. Other studies have followed their participants for 18 months, or only through several shorter data collection periods (Woynaroski et al., 2016; Yoder et al., 2015; Warren et al., 2010). This study followed participants from toddlerhood through middle childhood, with Time 2 following Time 1 by roughly six years. Additionally, attrition was minimal as all but two of the families have remained in the study for five or six data collection visits. This is a strength of which few longitudinal studies can boast. Data is now being collected from this sample in middle adolescence, and new analyses with more recent data may yield more robust results.

Unfortunately, this study is limited in statistical power since the sample is relatively small, which obviously limits the kinds of analyses that can be performed. A component analysis of multiple vocal and environmental factors in this population is certainly a potential direction for future study. The feasibility of a large study of children with a rare neurodevelopmental disorder, however, may be difficult due to budget and time constraints. Although, there is little racial and ethnic diversity in the sample, given that it is a sample of convenience, previous findings with this sample have demonstrated strong effects (c.f. Warren et al., 2010, Brady et al., 2014, Warren et al., 2017).

The current study did not use standardized measures of expressive vocabulary as an outcome variable. The outcome variable, productive vocabulary size, was the child's number of different words obtained during fifteen minutes of video-recorded interactions between the mother and child. This short sample period may present difficulties with estimating actual productive vocabulary abilities, and the use of a non-standard outcome variable may have limited the generalizability of our findings. In lieu of spontaneous productive vocabulary size, raw scores from the EVT could be studied as the dependent variable, however spontaneous productive vocabulary size was selected as the dependent variable for this study since it is a relative strength of the longitudinal study as a whole to contain data beyond standardized assessments. It is also a more representative measure of the child's ability since it does not rely on fidelity of administration and represents the child's level of talkativeness. The child's talkativeness in and of itself is important in day-to-day life, perhaps more so than his ability to recall items during standardized testing. Furthermore, in our sample, EVT and number of different words were strongly and significantly correlated (.63, $p<.01$).

As is the case in many neurodevelopmental disorders, there was a great amount of variation in ability in the current sample. Sex and autism status clearly impact early and later language ability in children with FXS. Although early consonant inventory, intentional communication, and autism symptomatology explained nearly half the variance in later expressive language ability, other factors may also contribute. These include parent linguistic response and overall responsivity, and child social communication skills. It is evident that a variety of factors impact language development, and an understanding of their impact on atypical language development is critical for elucidating an underlying language mechanism in neurodevelopment.

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Appendices

Table 1: Child Characteristics and Demographics

		Mean/%	SD	Range
Age (Months)	Time 1	30.4	5.29	19-36
	Time 2	113.3	3.29	104-119
MSEL (Time 1)	Receptive Raw Score	17.23	5.25	4-30
	Expressive Raw Score	15.45	5.98	5-27
PPVT (Time 2)	Verbal	86.43	34.75	17-163
	Non-verbal	38.17	15.38	15-56
EVT (Time 2)	Verbal	64.38	27.71	9-131
	Non-verbal	0.00	0.00	0
Ethnicity	Caucasian	91.5%		
	Other	8.5%		
Household Income	< $30,000	21.30%		
	$30,000-$80,000	31.90%		
	> $80,000	40.40%		
	No Report	6.40%		

MSEL: Mullen Scales of Early Learning (Language domain scores reported)
PPVT: Peabody Picture Vocabulary Test, raw score
EVT: Expressive Vocabulary Test, raw score

Table 2: Consonants of the English Language Included in Consonant Inventory

	Bilabial	Labio-dental	Dental	Alveolar	Post-alveolar	Velar
Stop	p, b		t, d			k, g
Nasal	m			n		ŋ
Fricative		f, v	Θ, ð	s, z	ʃ, ʒ	
Approximant			ɹ			
Lateral approximant			l			
Affricate	ts, dʒ					

Table 3: Descriptive Statistics and Correlations

Correlations	1	2	3	4	Mean	SD
Intentional Communication	–	.852**	.281*	-.492**	35.50	41.10
Consonant Inventory		–	.464**	-.565**	4.02	4.39
Number of Different Words			–	-.657**	98.98	57.14
Autism Symptomatology				–	26.40	6.48

Note: ** *p*<.01, * *p*<.05

Table 4: Multi-collinearity Tests

Predictor	Tolerance	VIF	Eigenvalue	Condition Index
(Constant)			3.172	1.000
Intentional Communication	.275	3.641	.083	6.186
Consonant Inventory	.247	4.053	.728	2.087
Autism Symptomatology	.680	1.470	.017	13.828

Table 5: Multiple Regression Analyses Predicting Productive Vocabulary Size from Early Predictors and Autism Symptomatology in the Full Sample

	Early Predictors						
	Model 1a: Early Predictors			Model 2a: Early Predictors and Autism Symptomatology			
Predictor	β	t	Sig.	β	t	Sig.	Partial Correlation
(Constant)	-	7.55	.000	-	6.45	.000	
Intentional Communication	-0.415	-1.66	.104	-0.438	-2.10	.042*	-.308
Consonant Inventory	0.817	3.27	.002*	0.505	2.29	.027*	.333
Autism Symptomatology				-0.588	-4.43	.000**	-.565
Total R^2 (Adjusted)			.262 (.228)**				.497 (.461)**
n			45				45

Note: Betas are standardized. ** $p < .01$.

Table 6: Multiple Regression Analyses Predicting Productive Vocabulary Size in the Verbal Only Sample from Early Predictors and Autism Symptomatology

	Early Predictors						
	Model 1b: Early Predictors			Model 2b: Early Predictors and Autism Symptomatology			
Predictor	β	t	Sig.	β	t	Sig.	Partial Correlation
(Constant)	-	9.76	.000	-	4.63	.000	
Intentional Communication	-0.335	-1.15	.259	-0.424	-1.52	.137	-.232
Consonant Inventory	0.622	2.13	.040*	0.497	1.77	.085	.264
Autism Symptomatology				-0.395	-2.35	.024*	-.366
Total R^2 (Adjusted)			.143 (.097)				.257 (.195)*
n			39				39

Note: Betas are standardized. * $p<0.05$.

Table 7: Multiple Regression Analyses Predicting Productive Vocabulary Size in Boys with FXS and FXS with ASD

	Early Predictors and Autism Symptomatology		
	Model 3: Boys		
Predictor	β	t	Sig.
(Constant)	-	5.94	.000
Intentional Communication	-0.195	-0.89	.382
Consonant Inventory	0.305	1.33	.193
Autism Symptomatology	-0.619	-4.32	.000*
Total R^2 (Adjusted)			.502 (.455)**
n			35

*p<.05. **p<.01.

Table 8: Mean Performance for Males and Females with FXS and FXS and ASD

	FXS Males	FXS and ASD Males	FXS Females	FXS and ASD Females
# Intentional Communication Acts	37.1 (±33)	14.6 (±12.5)	68.3 (±69.8)	10.5 (±.7)
Consonant Inventory	4.7 (±3.8)	.9 (±1.8)	7.6 (±5.8)	0.00 (±0)
CARS Score	23.9 (±2.7)	34.8 (±4.3)	19.8 (±3.2)	33.0 (±2.8)
Number of Different Words	121.4 (±45.5)	47.2 (±51.5)	128.6 (±30.8)	22.5 (±23.3)
Age (T1)	31.6 (±5.2)	28.9 (±6.3)	30.4 (±4.1)	27 (±4.2)
Age (T2)	113.8 (±2.8)	113.5 (±2.9)	112.8 (±4.6)	108.0 (±1.4)
Sample Size	24	12	8	2

Figure 1: Number of Different Words by Sex and Diagnosis

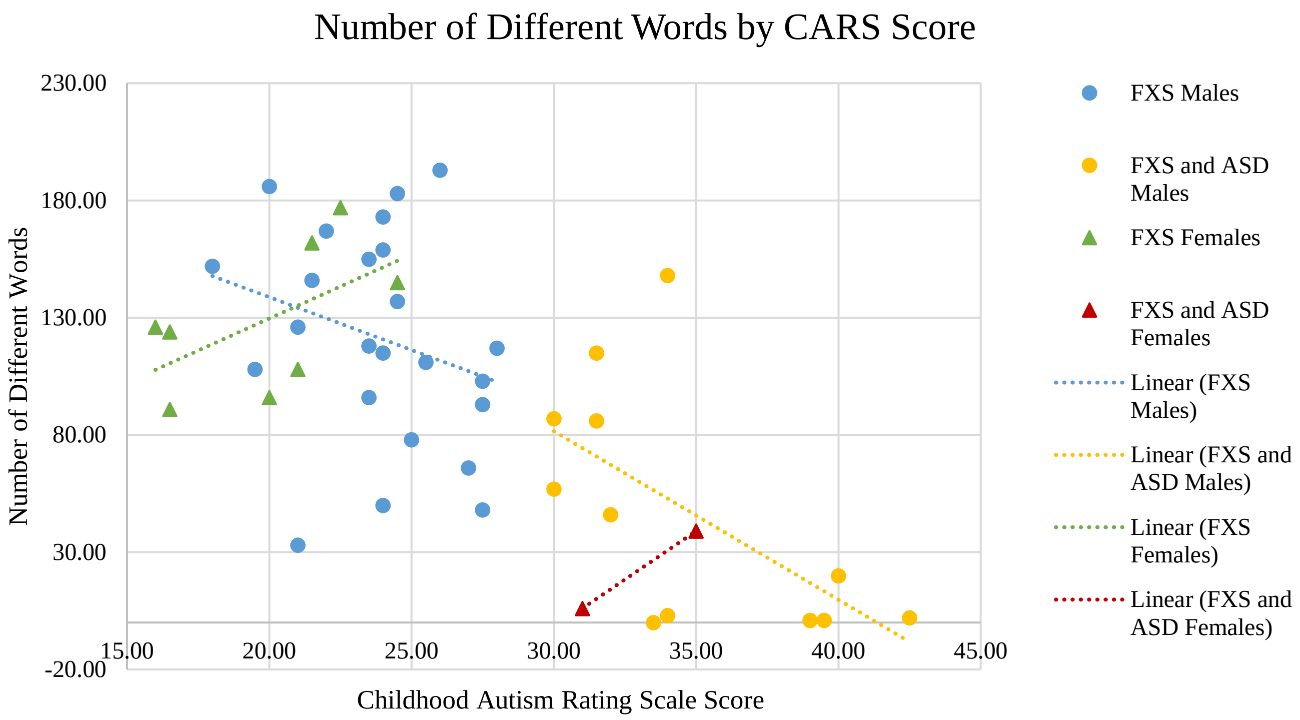

Figure 2: Intentional Communication Acts by Sex and Diagnosis

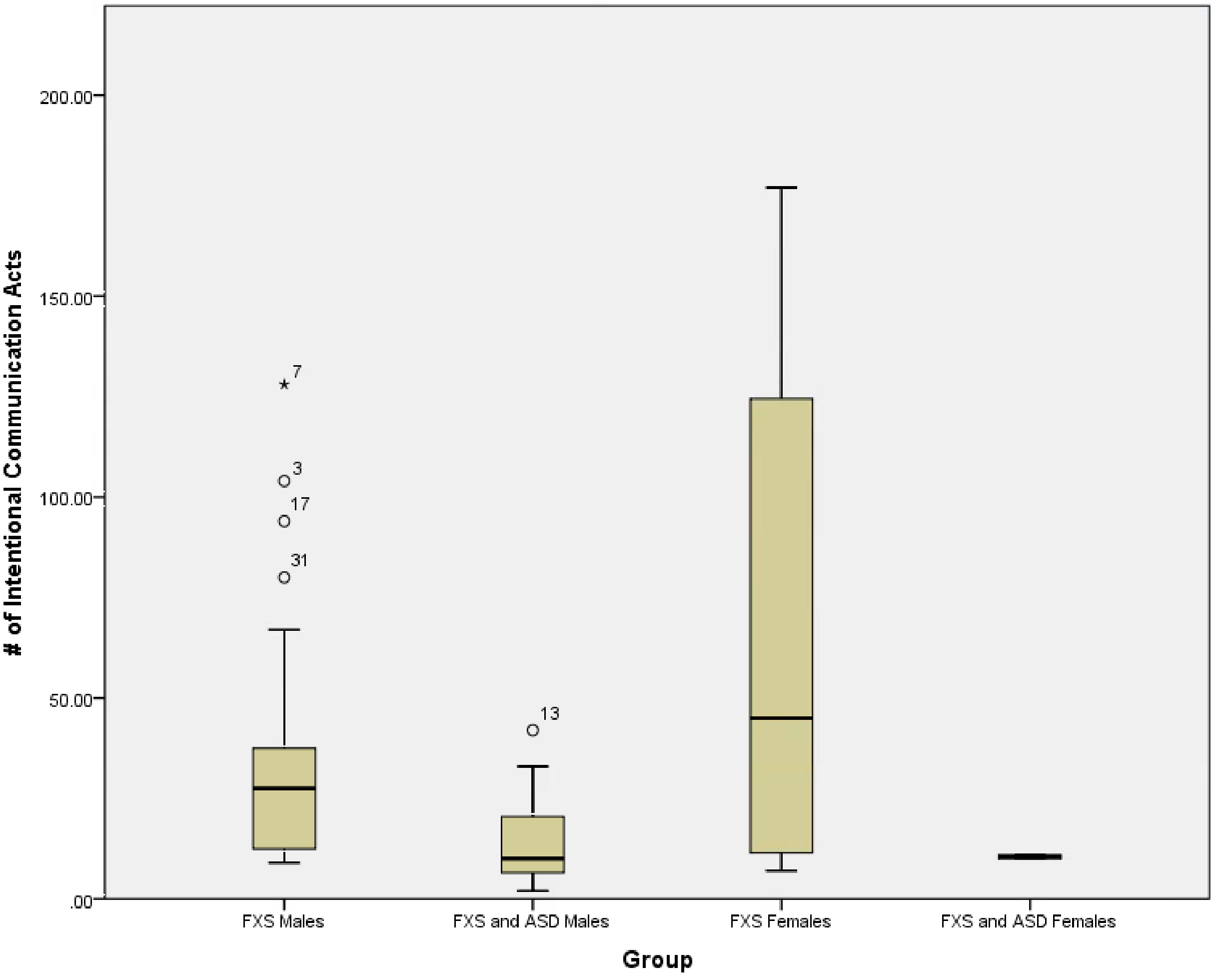

Figure 3: Consonant Inventory by Sex and Diagnosis

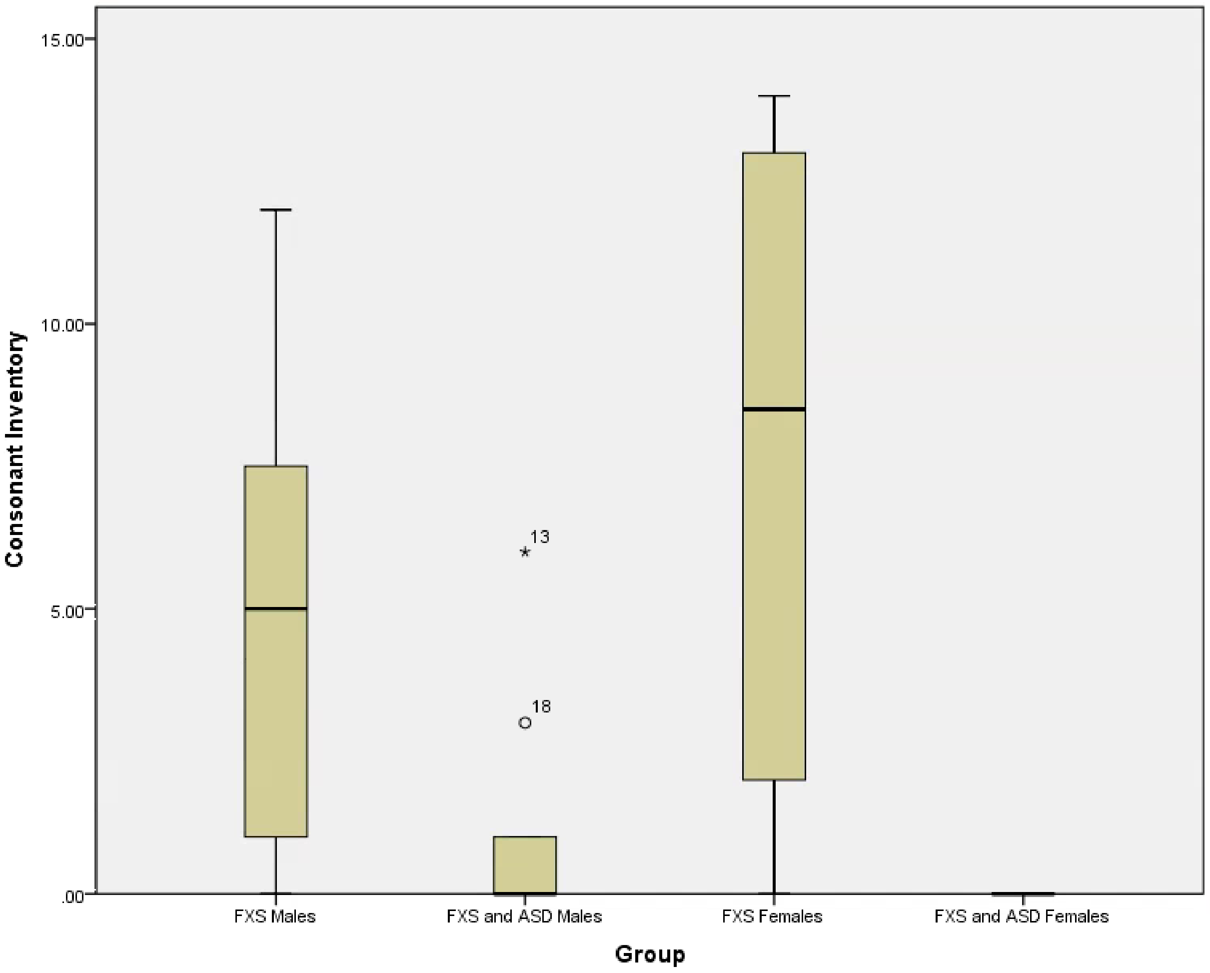

Figure 4: Number of Different Words by Sex and Diagnosis