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Profiles of Receptive and Expressive Language Abilities in Males with Comorbid Fragile X Syndrome and Autism

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Abstract

Receptive and expressive language profiles were examined for a group of verbal male children and adolescents who had fragile X syndrome along with varying degrees of autism symptoms. A categorical approach for assigning autism diagnostic classification, based upon the combined use of the ADI-R and ADOS, and a continuous approach for representing autism symptom severity, based upon ADOS severity scores, were utilized in two separate sets of analyses. All analyses controlled for nonverbal IQ and chronological age. Nonverbal IQ accounted for significant variance in all language outcomes with large effect sizes. Results of the categorical analyses failed to reveal an effect of diagnostic group (FXS+AUT, FXS-No AUT) on standardized language test performance. Results of the continuous analyses revealed a negative relationship between autism symptom severity and all of the standardized language measures. Implications for representing autism symptoms in FXS research are considered.

More than 90% of males with fragile X syndrome (FXS) display behaviors that are characteristic of individuals with idiopathic autism, and the presence and severity of autism symptoms are important sources of variability in the behavioral phenotype of males with FXS (Bailey, Hatton, Mesibov, Ament, & Skinner, 2000; Feinstein & Reiss, 1998). Autistic-like behaviors in FXS include perseveration, motor stereotypies, repetitive speech, and poor eye contact (Hagerman, 1999; Merenstein, Sobesky, Taylor, Riddle, Tran, & Hagerman, 1996). There is consensus that as many as 25% to 30% of males with FXS meet diagnostic criteria for a comorbid diagnosis of autistic disorder (Bailey, Mesibov, Hatton, Clark, Roberts, Mayhew, 1998; Brown et al., 1982; Demark, Feldman, & Holden, 2003; Hagerman, Jackson, Levitas, Rimland, & Braden, 1986; Hatton et al., 2006; Kau et al., 2004; Kaufmann et al., 2004; Lewis et al., 2006; Rogers, Wehner, & Hagerman, 2001; Sabaratnam, Murthy, Wijeratne, Payne, & Buckingham, 2003), with an additional 30% falling within the range of an autism spectrum disorder (ASD; Harris et al., 2008). It is unclear, however, whether individuals with FXS who meet criteria for autism (or have more symptoms of autism) represent simply the most severely affected end of a continuum of impairment in FXS or whether they present with a different constellation (or profile) of challenges than do their non-autistic peers affected with FXS (Bailey et al., 2004; Lewis et al., 2006).

In this study, we focused on profiles of language impairment as an approach to addressing this issue. Finding differing profiles of language strengths and weaknesses, after controlling for nonverbal cognition, would suggest a qualitative difference between individuals with comorbid FXS and autism when compared to individuals with FXS only. In contrast, finding

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a similar profile of strengths and weaknesses across domains of language, after controlling for differences in nonverbal cognition, would support the premise that autism in FXS reflects only differences in severity of cognitive impairment (Kover & Abbeduto, 2010).

Previous studies examining the language profiles of individuals with FXS with and without autism have yielded inconsistent findings. Several studies, with samples spanning the ages of 20 months to young adulthood, have found that receptive language is more severely impaired in males with FXS who also have an autism or ASD diagnosis than in those without the comorbid diagnosis (Philofsky, Hepburn, Hayes, Rogers, & Hagerman, 2004; Lewis, et al., 2006; Roberts, Mirrett, & Burchinal, 2001; Rogers, Wehner, & Hagerman, 2001); however, this difference has not emerged in other studies in which participants were of comparable ages (Kaufmann et al., 2004; Price, Roberts, Vandergrift, & Martin, 2007; Roberts, Price, Barnes, Nelson et al., 2007). Similar inconsistency in findings has characterized studies of expressive language (Kover & Abbeduto, 2010; Philofsky et al., 2004; Lewis, et al., 2006; Price et al., 2007; Roberts et al., 2001; Roberts et al., 2007; Rogers et al., 2001). In fact, Kaufmann et al. (2004) even found that expressive language scores, assessed with the Preschool Language Scales (Zimmerman, Steiner, & Pond, 1992), were positively correlated with both autism diagnosis and total scores on the Autism Diagnostic Interview – Revised (ADI-R; Lord, Rutter, & LeCouteur, 1994) in their sample of young males with FXS.

These inconsistent findings may be traced to a number of methodological differences and limitations across studies. First, several studies have failed to control for differences in nonverbal IQ (Philofsky et al., 2004; Rogers et al., 2001), which is problematic because IQ is lower on average in individuals with comorbid FXS and autism than in those with FXS alone (Bailey, Hatton, Skinner, & Mesibov, 2001; Kaufmann et al., 2004; Lewis et al., 2006). In such studies, it is impossible to unambiguously determine whether observed differences in language are attributable to IQ or to autism status (or autism symptom severity).

Second, several studies have utilized global measures of language ability, which aggregate over multiple dimensions of language. Philofsky et al. (2004) and Rogers et al. (2001), for example, relied on the language subscales of the Mullen Scales of Early Learning (MSEL; Mullen, 1989), which distinguish between receptive and expressive language but not between vocabulary and emerging syntax. Similarly, Lewis et al. (2006) distinguished between vocabulary, morphology, and syntax in the receptive domain through the use of the Test for Auditory Comprehension of Language (TACL; Carrow-Woolfolk, 1985), but relied on the Oral Expression Scale of the Oral and Written Language Scales (OWLS; Carrow-Woolfolk, 1995), which yields but a single expressive language summary score despite including items indexing everything from vocabulary to discourse-level structure. Reliance on such global measures is likely to mask potentially important differences in language profiles associated with autism status or symptom severity (Abbeduto & McDuffie, 2010).

In this regard, Kover and Abbeduto (2010) separately analyzed several dimensions of expressive language elicited through sampling of spontaneous language in two contexts and found that adolescents and young adult males with comorbid FXS and autism were less intelligible than those with FXS only, with no group differences in measures of vocabulary diversity, syntax complexity, fluency, or talkativeness. However, the subgroup with comorbid autism studied by Kover and Abbeduto (2010) included only 8 individuals and a larger sample size is likely required to detect additional differences attributable to autism status. Results of Kover and Abbeduto (2010) serve to reinforce the notion that a comprehensive and highly nuanced battery of measures is needed to fully characterize the relationship between autism status and language profiles in FXS.

In the current study, we examined language understanding and spoken expression in the domains of vocabulary and syntax. These structured aspects of language can be assessed reliably using standardized tests to yield an adequate characterization of an individual's mastery of the fundamentals of language that can contribute to problems in communication that are common to both fragile X syndrome and autism. In addition, idiopathic autism has been found previously to be associated with more severe impairments in receptive than expressive language (Ellis Weismer, Lord, & Esler, 2010; Hudry et al., 2010; Kjelgarrd & Tager-Flusberg, 2001; Rapin & Dunn, 2003; Williams, Botting, & Boucher, 2008) and thus, it was important to assess both receptive and expressive modalities.

Third, there has been considerable variation across studies in the approach used to assess autism status and characterize autism symptoms. Although the combined use of the ADI-R and Autism Diagnostic Observation Schedul*e* (ADOS; Lord, Rutter, DiLavore, & Risi, 1999) represents the current gold standard for establishing a diagnostic classification of autism for research purposes, studies examining the impact of autism on language development in FXS (Lewis et al., 2006; Roberts et al., 2001) often have used checklists or rating scales, such as the Autism Behavior Checklist (ABC; Krug, Arick, & Almond, 1980) or the Childhood Autism Rating Scales (CARS*;* Schopler, Reichler, & Renner, 1988). Other studies have used either the ADI-R or the ADOS, but not both or have used these instruments in nonstandard ways (Hernandez et al., 2009; Kaufmann et al., 2004; Price et al., 2007; Roberts et al., 2007).

Finally, participants have been grouped into discrete diagnostic categories in virtually all previous studies. Some authors have grouped participants with autistic disorder and ASD together (Roberts et al., 2007), whereas others have grouped those participants who are more mildly affected, or for whom a diagnostic classification is unclear, with participants without autism (Kover & Abbeduto, 2010; Lewis, et al., 2006; Philofsky et al. 2004; Rogers et al., 2001). Such differences in grouping strategy can impact study results. More importantly, findings of both population- and clinic-based studies suggest that a single, continuously-distributed, underlying factor may better characterize the behavioral manifestations of autism across individuals with idiopathic autism than does a categorical approach (Constantino, Gruber, Davis, Hayes, Passanante, & Pryzbeck, 2004; Spiker, Lotspeich, Dimiceli, Myers, & Risch, 2002; Waterhouse, Fein, & Modahl, 1996). Lack of support for behaviorally defined subgroups of individuals with autism (Spiker et al., 2002), as well as interpretive issues that result from use of categorical classification systems, suggest that it would be useful to employ a metric that represents the severity of autism symptoms in a continuous manner (Gotham, Risi, Pickles, & Lord, 2007).

In fact, Gotham and colleagues (2009) have introduced a method for computing autism severity scores from the ADOS, based upon raw scores obtained through the use of the revised algorithms for ADOS modules 1, 2, and 3. Such a metric allows data from all participants in a research study to be included in statistical analyses without making arbitrary decisions about group assignment. Autism severity scores, computed from the ADOS, range from 1 - 10 with higher scores representing more severe affectedness. Severity scores are indexed to ADOS module, as well as to the chronological age and language level of the participant. Use of the severity metric has the potential to facilitate comparisons across modules and time points for a given individual by representing the degree of autistic affectedness while taking into account impairments in spoken language use.

In the current study, therefore, we sought to extend the literature characterizing language profiles of individuals with FXS by: (1) controlling for differences in nonverbal cognitive ability; (2) assessing vocabulary and syntax separately within the domains of receptive and expressive language; (3) using gold standard diagnostic instruments to characterize autism

status; and, (4) using both a categorical approach to diagnostic classification (comorbid FXS with autism vs. FXS without autism) and a continuous metric of autism symptom severity.

The following research questions were addressed for a group of 34 males with FXS: (1) When using a categorical approach to autism classification, are there between-group differences in receptive or expressive vocabulary or grammar after controlling for nonverbal IQ? (2) Does autism symptom severity, scored continuously, account for unique variance in predicting receptive or expressive vocabulary or grammar scores after controlling for nonverbal IQ? In addressing both questions, our primary interest was in characterizing within-syndrome differences in language profiles displayed by males with FXS according to comorbid autism symptoms. Our secondary interest was in examining how the choice of metric for representing autism status (i.e., categorical vs. continuous) might influence resultant language profiles and which metric might best facilitate our understanding of variability in language profiles within the FXS behavioral phenotype.

Method

Participants

Participants were 34 males with FXS, who were part of a larger, longitudinal study of language development in FXS. All participants had the FMR1 full mutation, according to either cytogenetic or molecular genetic testing completed prior to entry into the study. During the study, diagnoses were confirmed by molecular genetic testing conducted on peripheral blood samples for all but 6 participants (1 declined to be retested and blood samples were not obtained for the other 5 participants for logistical reasons). Of the 28 participants who were retested, all had the FMR1 full mutation, although 7 also were mosaic (in methylation status or repeat size). Of the 6 participants for whom molecular genetic testing was not completed during the study, 1 had cytogenetic and 5 had molecular genetic diagnoses of the FMR1 full mutation.

Additionally, all participants were native English speakers who used spoken language as their primary means of communication and produced three-word phrases on a regular basis according to parent report. Participants were between the ages of 10 and 16 years at the time of data collection and 80% were reported to be taking some form of medication for behavioral issues. The proportion of participants taking medication did not vary by autism status. The most frequent symptoms for which medication was prescribed were attention and anxiety. Parents were instructed to treat the testing situation as a school day and to administer any prescribed medications accordingly.

Information is not available indicating whether the participants in this study had been previously diagnosed with a speech and language disorder. As individuals with an intellectual disability, however, we would assume that all of our participants would have displayed delays in speech and/or language throughout development. What we do know is that 30 of the 33 participants were receiving speech and language services at the time of their participation in this study (one participant had missing data for this question), with mothers reporting an average prior history of 9 years of such services (SD = 2.76 years, range 3-13 years).

Participants were recruited nationally through mailings to professionals, attendance at national and regional parent meetings, postings to internet listservs and websites, advertisements on nationally syndicated radio shows and in newspapers in selected urban areas, and through a university registry of families with children with developmental disabilities. The participant sample overlaps with those reported in McDuffie et al. (2010) and Kover, McDuffie and Abbeduto (in prep), although the focus of the analyses and the

primary measures utilized varied across these reports. Descriptive characteristics of the participants are presented in Table 1.

Assessments and Measures

Autism status—Two different metrics of autism status – one categorical and the other continuous – were employed. Both metrics were based upon administration of the Autism Diagnostic Interview-Revised (ADI-R; Rutter, LeCouteur, Lord, 2008) and/or the Autism Diagnostic Observation Schedule (ADOS, Lord et al., 1999).

The ADI-R is a standardized interview, conducted by a trained examiner, which elicits information relevant to early development and the domains of Reciprocal Social Interaction, Communication, and Restricted Interests and Stereotyped Behaviors. For items in the three domains, the presence or extent of autism symptoms is scored from 0 to 3, with a rating of 3 being most severe, for the three months immediately preceding the interview (Current ratings) and for the time period between the ages of 4 to 5 years or ever in the participant's lifetime (Lifetime ratings). Items querying developmental history are used to confirm age of onset. A diagnostic algorithm, based upon Lifetime scores for a specified set of 37 items, yields a dichotomous classification of autism versus no autism.

As part of the larger longitudinal study, a research-reliable examiner administered an abbreviated version (Seltzer, Krauss, Shattuck, Orsmond, Swe, & Lord, 2003; Shattuck et al., 2007) of the ADI-R to the biological mother of each participant. The abbreviated protocol included three items, designed to gather age of onset information, as well as the 37 individual items that constitute the diagnostic algorithm. For purposes of ADI-R scoring, all participants were considered to be verbal (as indicated by parent report) and the following domain cutoffs were used: Reciprocal Social Interaction (10), Communication (8), Restricted Interests/Repetitive Behaviors (3), Developmental History (1).

The ADOS, originally developed for use in conjunction with the ADI-R, provides a standardized context for direct observation of the participant. The ADOS consists of a series of activities and materials, presented with systematic prompts and used to elicit a sample of an individual's social and communication behaviors. There are four ADOS modules, each designed for a particular developmental and language level, ranging from no expressive language in preschool-aged children to verbally fluent adults. This system of organization allows the observation to take place within the context of an interaction appropriate for the individual's expressive language level. The current study used the revised ADOS diagnostic algorithms, as specified by Gotham and colleagues (2007, 2008). These module-specific algorithms consist of a Social Affective domain (comprised of items representing reciprocal social interaction as well as communication) and a Restricted, Repetitive Behaviors domain. Scores for these domains are summed and the total score is compared to thresholds resulting in an ADOS classification of autism, autism spectrum, or nonspectrum.

Categorical and continuous diagnostic metrics—Two different approaches to diagnostic classification were used in the current study: (a) a categorical classification of autism versus no autism based upon combined use of the original ADI-R algorithm and the Gotham et al. (2007) revised ADOS algorithms; and (b) a continuous metric of autism symptom severity derived from the ADOS according to procedures described in Gotham et al. (2009). For the first (i.e., categorical) approach, participants who received a diagnostic classification of autism according to the ADI-R algorithm and a diagnostic classification of autism according to the Gotham et al. (2007, 2008) revision of the ADOS algorithm were assigned to the FXS+AUT subgroup (n = 16). Participants who did not exceed the diagnostic threshold for autism according to the original ADI-R algorithm and also failed to exceed the diagnostic threshold for either autism or autism spectrum according to the

Gotham et al. (2007, 2008) revision of the *ADOS* algorithm were assigned to the FXS-NoAUT subgroup (n = 8). Ten participants, who received other combinations of diagnostic classifications, were not assigned to a diagnostic subgroup; of these participants, five met criteria for autism on the ADI-R but were nonspectrum on the ADOS, three met criteria for autism on the ADOS but were nonspectrum on the ADI-R, one met criteria for ASD on the ADOS and was nonspectrum on the ADI-R, and one met criteria for ASD on the ADOS and met criteria for autism on the ADI-R. These ambiguous cases were excluded from the analyses based on the categorical approach to autism diagnosis.

For the second (i.e., continuous) approach, all participants (N = 34) received an autism severity score based upon chronological age, language status, and total score for the ADOS module they had received, according to Gotham et al. (2009). For each module, a total score was calculated from the Social-Affective domain and the Restricted Interests and Repetitive Behaviors domain (Gotham et al., 2007; 2008). This total score was used to assign a severity score, based upon the individual's age and the ADOS module administered. ADOS severity scores range from 1 - 10, with scores of 1 - 3, 4 - 5, and 6 - 10 indicating mild, moderate and severe degree of autistic impairment, respectively (Gotham et al., 2009).

Nonverbal cognition—The Leiter-R Brief IQ Screener, comprised of the Figure Ground, Form Completion, Sequential Order, and Repeated Patterns subtests from the Visualization and Reasoning Battery (Roid & Miller, 1997), was administered to each participant to provide an assessment of nonverbal cognition. For each participant, the nonverbal brief IQ score was used as the metric of nonverbal cognition in all analyses.

Receptive vocabulary—The Peabody Picture Vocabulary Test, Third Edition (PPVT-3; Dunn & Dunn, 1997) is a norm-referenced, individually administered instrument used to measure comprehension of single vocabulary words. During administration of this test, a page consisting of four pictures is presented and the participant is asked to point to the picture that best corresponds to the meaning of the target word spoken by the examiner. For the current study, A and B versions were each given to approximately half of the participants. Median coefficient alpha for the PPVT-3 is reported as .95, across the range of ages for which the PPVT-3 is normed, median alternate form reliability is reported as .95 for raw scores and .94 for standard scores, and test-retest reliability is above .90 for both A and B version for age ranges from 12- to 17-years. For the current study, PPVT-3 raw scores were used as the measure of receptive vocabulary.

Receptive grammar—The Test for Reception of Grammar, Second Edition (TROG-2; Bishop, 2003) is a norm-referenced, individually administered instrument designed to assess understanding of grammatical contrasts that are marked by inflection, function words, and word order in English. During administration of the TROG-2, a page containing four pictures is presented and the participant is asked to point to the picture that best represents the grammatical or lexical element contained in a target sentence produced by the examiner. The TROG-2 consists of items organized into blocks of four items; each block tests a single grammatical form. According to the manual, split-half reliability for the TROG-2 is .88. For the current study, the number of individual items passed on the TROG-2 was used as the measure of receptive grammar.

Expressive vocabulary—The Expressive Vocabulary Test (EVT, Williams, 1997) is a norm-referenced, individually administered instrument used to measure retrieval and production of single vocabulary words. Items include pictures that the participant must label in response to the examiner's questions as well as pictures for which the participant must provide a synonym in response to a word or words produced by the examiner. The median coefficient alpha is .95 across the age ranges for which the EVT is normed and test-retest

reliability ranges from .77 to .90. The EVT is co-normed with the PPVT. For the current study, raw scores from the EVT were used as the measure of expressive vocabulary.

Expressive grammar—The Syntax Construction subtest of the Comprehensive Assessment of Spoken Language (CASL; Carrow-Woolfolk, 1999) was administered to assess the production of words, phrases, and sentences that require the use of a variety of morphosyntactic rules (e.g., verb tense, plurals, interrogatives, pronouns). Administration of this subtest requires the participant to respond to a picture by imitating the examiner, completing a sentence, answering a question designed to elicit a specific syntactic form, formulating a sentence to tell a story, and using a model sentence to generate a similar sentence. Split-half reliabilities for the Syntax Construction subtest range from .80 to .88 for the age ranges of the participants in the current study. Test-retest reliabilities range from .74 to .81. For the current study, raw scores from the CASL Syntax Construction subtest were used as the measure of expressive grammar. One participant in each group was missing a score for the CASL.

Procedure

All participants were tested over a period of two days, with a maximum of two sessions per day separated by about an hour for lunch. For each participant, the ADI-R was administered to the mother while her child was completing the testing battery. Language and cognitive scores reported for the current study were collected at the visit concurrent with administration of the ADI-R and ADOS.

Analysis Strategy

Two separate sets of analyses were conducted. Raw scores from one of the four standardized language measures served as the dependent variables in each analysis. The first set of analyses utilized the categorical approach to autism status and involved a series of ANCOVAs with Group (FXS+AUT, FXS-NoAUT) as the between-subjects factor. Nonverbal IQ was used as a covariate in these analyses as was chronological age, which happened to differ between the groups, $t(22) = 2.35$, $p < .03$, two-tailed, $d = 1.05$.

The second set of analyses utilized the continuous approach to representing severity of autism symptoms (Gotham et al., 2009). Chronological age, nonverbal IQ, and the continuous metric of autism symptom severity were entered in stepwise fashion into four different linear regression analyses, each predicting raw scores from one of the standardized language measures.

Results

Analyses Using Categorical Autism Classification

Covariate-adjusted mean scores for each standardized language test are presented in Table 2. Results of the ANCOVAs are presented in Table 3.

Receptive vocabulary—Chronological age, $F(1, 20) = 5.74$, $p < .03$, *partial* $\eta^2 = .22$, and nonverbal IQ, $F(1, 20) = 17.66$, $p < .001$, *partial* $\eta^2 = .47$, were significantly related to PPVT raw scores. The effect of group (FXS+AUT, FXS-NoAUT) failed to reach significance and accounted for minimal variance (*partial* $\eta^2 = .02$) after controlling for age and nonverbal IQ.

Receptive grammar—Chronological age, $F(1, 20) = 9.16$, $p < .01$, *partial* $\eta^2 = .31$, and nonverbal IQ, $F(1, 20) = 59.44$, $p < .001$, *partial* $\eta^2 = .75$, were significantly related to number of items passed on the TROG. The effect of group failed to reach significance and

accounted for negligible variance (*partial* η^2 = .001) after controlling for age and nonverbal IQ.

Expressive vocabulary—Nonverbal IQ, F (1, 20) = 37.43, p < .001, partial η^2 = .65 was significantly related to EVT raw scores, but chronological age was not, F (1, 20) = 2.94, p = .10, *partial* η^2 = .13. After controlling for chronological age and nonverbal IQ, the effect of group failed to reach significance, F(1, 20) = 2.53, p = .13, *partial* η^2 = .11), but did account for a nontrivial amount of variance in spoken vocabulary.

Expressive grammar—Chronological age was significantly related to CASL raw scores, F(1,18) = 7.46, p = .01, *partial* η^2 = .29, as was nonverbal IQ, F (1,18) = 34.77, p < .001, *partial* η^2 = .66. The effect of group failed to reach significance after controlling for age and nonverbal IQ, F (1,18) = 1.22, p = .28, *partial* η^2 = .06.

In summary, there were no significant differences on the standardized language measures between participants with FXS+AUT or FXS-NoAutism after controlling for chronological age and nonverbal IQ. Age and nonverbal IQ significantly predicted receptive vocabulary, receptive grammar and expressive grammar. Nonverbal IQ also predicted expressive vocabulary, with chronological age and group membership accounting for similar, albeit nonsignificant, variance in expressive vocabulary scores.

Analyses Using Continuous Autism Severity Metric

Results of the hierarchical regression analyses using chronological age, nonverbal IQ, and the continuous autism symptom severity metric as predictors of each standardized language measure are presented in Table 4. Results of the final steps of each regression model are described below. One-tailed p-values were used in these analyses as it was expected that nonverbal IQ and chronological age would be positively related to, and autism symptom severity would be negatively related to, the language outcome measures.

Receptive vocabulary—Nonverbal IQ (t = 5.16, p < .001, one-tailed, semipartial r = .63), chronological age (t = 1.81, p = .041, one-tailed, semipartial r = .22), and autism symptom severity score (t = −2.18, p = .018, one-tailed, semipartial r = −.27) each accounted for unique variance in predicting receptive vocabulary

Receptive grammar—Nonverbal IQ (t = 7.43, p < .001, one-tailed, semipartial r = .77) and chronological age (t = 2.59, p = .007, one-tailed, semipartial r = .27) each accounted for unique variance in predicting number of items passed on the TROG. Autism severity score was a marginally significant predictor of receptive grammar, (t = −1.53, p = .068, one-tailed, semipartial r = −.16).

Expressive vocabulary—Nonverbal IQ (t = 6.64, p < .001, two-tailed, semipartial r = .74) and chronological age (t = 3.08, p = .002, one-tailed, semipartial r = .34) each accounted for unique variance in predicting raw scores on the EVT. Autism severity score was not a significant predictor of expressive vocabulary (t = −1.10, p = .14, one-tailed, semipartial r = −.12).

Expressive grammar—Nonverbal IQ (t = 6.01, p < .001, one-tailed, semipartial r = .70) and chronological age (t = 3.63, p < .001, one-tailed, semipartial r = .42) each accounted for unique variance in predicting raw scores on the CASL. Autism severity score was not a significant predictor of expressive grammar, (t = −.90, p = .19, one-tailed, semipartial r = −.11).

In summary, nonverbal IQ and chronological age positively predicted performance on each of the language measures. For the domain of receptive language, autism symptom severity was negatively and significantly related to vocabulary and the negative association between autism symptom severity and grammar was marginally significant.

Discussion

Although it is commonly acknowledged that the presence and severity of autism contributes to variability within the FXS behavioral phenotype, it is not yet clear whether autistic-like behaviors merely are an additional sequelae of severity of impairment or represent a qualitatively different disorder within FXS. One approach to understanding the relationship between FXS and autism is to examine how autism affects language profiles in FXS after controlling for nonverbal IQ, which is known to be lower in those individuals with comorbid FXS and autism. If autism represents a distinct disorder within FXS, well-defined profiles of strengths and weaknesses that are unique to this subgroup might emerge once the contribution of nonverbal cognition is partialed out and when ability is compared across different domains of language competence. Previous studies examining this issue, however, have yielded inconsistent findings due to a variety of measurement issues. The primary goal of the current study was to examine how autism status and autism symptom severity are related to language profiles of males with FXS, after controlling for nonverbal cognition, using standardized measures of vocabulary and syntax in the domains of both receptive and expressive language, and using gold standard measures to provide research diagnoses of autism.

A secondary aim of the study was to examine whether language profiles would vary according to the metric that was chosen to represent autism status. Thus, we conducted our analyses using either a categorical metric for diagnostic classification or a continuous metric of autism symptom severity. We also controlled for chronological age, which unexpectedly differed significantly between participants when the categorical grouping approach was utilized and which would be expected to influence the absolute level of an individual's language achievements.

Use of the Categorical Metric for Autism Classification

Results from the analyses using the categorical grouping variable failed to reveal that the presence or absence of an autism diagnosis accounted for significant variance in any of the language measures. Group membership (i.e., FXS+AUT vs. FXS-NoAUT) did, however, account for 11% of the variance in predicting expressive vocabulary - a small effect size - over and above the contribution of nonverbal IQ.

Nonverbal IQ made a significant and substantial contribution to all measured domains of language, accounting for anywhere between 47% (receptive vocabulary) and 75% (receptive grammar) of the variance in language competence. Chronological age, while accounting for less variance than nonverbal IQ, was a significant predictor of all domains of language tested, with the exception of expressive vocabulary. The contribution of chronological age ranged from 13% (expressive vocabulary) to 31 % (receptive grammar) of the variance in language competence. Taken together, these findings suggest that nonverbal IQ has a substantial impact on the language profile of males with FXS, but that chronological age makes a smaller, but important, contribution to language achievements.

Group membership (i.e., autism status) and chronological age both made a similar contribution to explaining variance in expressive vocabulary scores, although neither variable emerged as significant in the analysis. It does seem plausible, however, that increased levels of social anxiety could interfere with the ability of participants with

comorbid FXS and autism to demonstrate their spoken vocabulary knowledge within a testing situation. This raises the question of how to differentiate language competence from language performance when evaluating the results of standardized testing. One potential explanation for a relative deficit in expressive vocabulary would be that producing a spoken response to an examiner press during administration of the EVT may require more motivation to communicate and more confidence in a potential response than producing a point in response to the forced choice format of the PPVT. Although these standardized tests were selected for administration in the current study based upon our confidence in their ability to provide a valid and reliable estimate of language competence, this does not fully exclude performance factors as potentially accounting for error variance in individual cases.

Our results using the categorical grouping strategy, differ from previous studies employing a categorical approach to autism classification. Previous studies of individuals with comorbid FXS and autism have described a profile in which receptive language is relatively more impaired than expressive language (Rogers et al., 2001; Philofsky et al., 2004) and nonverbal cognition (Lewis et al., 2006). The methods of these previous investigations, however, have differed from the current study in potentially important ways. The studies conducted by Rogers and colleagues (Rogers et al., 2001; Philofsky et al., 2004) examined performance in participants who were considerable younger than our participants, used global language measures (i.e. the receptive and expressive language subtests of the Mullen Scales of Early Learning), and did not control for nonverbal IQ.

The discrepancy between the current findings and those reported by Lewis et al. (2006) may be attributable to the nature of the group comparisons in each study. Lewis and colleagues (2006) used a clinical interview and DSM-IV criteria (i.e., the standard system for the clinical classification of mental disorders; American Psychiatric Association, 2000) to assign autism diagnoses. Diagnoses of PDD-NOS (Pervasive Developmental Delay – Not Otherwise Specified; a diagnosis that may be provided to children who do not meet all the criteria for autistic disorder) were not assigned and all individuals who did not meet the criteria for a diagnosis of autistic disorder were included in the FXS only subsample. In the current study, we chose to implement strict grouping criteria for the categorical comparison of FXS+AUT and FXS-NoAutism by including only participants who (1) unambiguously met criteria for autistic disorder on both the ADOS and the ADI-R or (2) were nonspectrum on both the ADOS and the ADI-R. It was expected that this method of dividing participants (i.e., excluding the ambiguous cases) would be most likely to reveal true differences in language profiles between males with FXS based upon autism status. Furthermore, the method of controlling for nonverbal IQ employed by Lewis and colleagues was to match participants with comorbid FXS and autism with participants with FXS only who had received the lowest standard score possible (i.e., 36) on three subtests of the Stanford-Binet, 4th edition (Thorndike, Hagen, & Sattler, 1986) (i.e., Bead Memory, Pattern Analysis, and Copying). Utilizing the Leiter-R Brief IQ standard scores minimized the problem of floor effects in the current study. This approach also allowed us to detect the effects of nonverbal IQ on specific aspects of language ability. Overall, findings of the current study suggest that nonverbal IQ and chronological age are better predictors of performance on standardized measures of language than is a categorical metric of autism status.

Use of the Continuous Metric of Autism Symptom Severity

The regression analyses, which utilized the continuous metric of autism symptom severity and included the entire participant sample, revealed a different pattern of results. As expected, there was a negative relationship between autism symptom severity and language performance for all of the standardized language measures. After controlling for chronological age and nonverbal IQ, autism symptom severity was a significant predictor of receptive vocabulary and a marginally significant predictor of receptive grammar. The

amount of unique variance accounted for by autism symptom severity ranged from 11 % for expressive grammar to 27% for receptive vocabulary.

As was the case for the categorical analyses, nonverbal IQ made a significant and unique contribution to all language outcomes, accounting for between 63% (receptive vocabulary) and 77% (receptive grammar) of the variance, all large effect sizes. Chronological age was, similarly, a unique predictor of all language measures, but accounted for less variance than nonverbal IQ. The unique variance accounted for by chronological age ranged from 22% (receptive vocabulary) to 42% (expressive grammar). It is worth noting that, given the substantial amount of variance in language performance accounted for by nonverbal IQ, a relatively small amount of variance remained to be explained by any other predictor. Despite this, the continuous metric of autism symptom severity emerged as a significant and unique negative predictor of variance in receptive vocabulary and grammar. It seems likely that children with FXS who display more symptoms of autism will engage in fewer positive and sustained social interactions, thereby limiting the amount of language facilitating verbal input they receive from communicative partners. Less exposure to verbal input embedded within social interactions may cause a relative deficit in the acquisition of both vocabulary and grammar in the receptive domain (Dale, Dionne, Eley, & Plomin, 2000; Hoff, 2003; Warren et al., 2010).

The relative weakness in receptive vocabulary and grammar for participants with increased autism symptoms, detected using the continuous severity metric, is concordant with the finding of previous studies of individuals with comorbid FXS and autism (Rogers et al., 2001; Philofsky et al., 2004; Lewis et al., 2006). Lewis and colleagues found that three aspects of receptive language, as measured by subtests of the Test for Auditory Comprehension of Language (TACL; Carrow-Woolfolk, 1999), were impaired in participants with comorbid FXS and autism relative to nonverbal cognitive ability and expressive language ability. Such a finding is theoretically and clinically interesting, given the correspondence of this language profile to that observed for individuals with idiopathic autism. Specifically, previous research has suggested that individuals with idiopathic autism have significant impairments in vocabulary comprehension and language processing in the presence of more moderate impairments in grammatical aspects of expressive language (Ellis Weismer et al., 2010; Hudry et al., 2010; Kjelgarrd & Tager-Flusberg, 2001; Rapin & Dunn, 2003; Williams et al., 2008). Observing a similar uneven profile of language strengths and weaknesses in males with comorbid FXS and autism may support the notion of a common cognitive mechanism underlying idiopathic autism and autism within FXS.

Representing Autism Status and Symptoms in Research on Fragile X Syndrome

When using the same standardized language measures, but two alternate metrics to represent autism status, chronological age and nonverbal IQ had a similar positive relationship to language ability; however, results differed in terms of autism status. The lack of correspondence across analysis strategies in the current study underscores the critical influence of diagnostic decision making for subsequent empirical findings. Use of the ADI-R and ADOS in combination resulted in diagnostic classification that, by definition, excluded some participants from the analyses. Using the continuous metric of autism symptom severity, while allowing data from all participants to be included, did not incorporate information gathered from the ADI-R. Thus, some may argue that ADOS scores can only be viewed as contributing to diagnostic classification, a process that should ideally rely upon results from the ADOS, ADI-R, cognitive testing, and best-estimate clinical decision-making.

While we acknowledge the value of combining multiple sources of information for diagnostic purposes, it is our position that the metric of autism symptom severity derived

from administration of the ADOS is inherently preferable for the purposes of research on the overlap in symptoms between autism and other neurodevelopmental disorders, such as FXS. First, the ADOS score is based upon a current observation of an individual's behavior, while use of diagnostic algorithm scores from the ADI-R reflects behavior at some previous point during the individual's lifetime (i.e., during ages 4-5 or ever in the individual's lifetime). This distinction is perhaps most important for individuals with intellectual disability, who might have displayed social impairments early in life that were, at least in part, attributable to cognitive delays. Second, use of a categorical approach is likely to result in a subset of individuals whose scores place them in an unclear diagnostic category. The categorical approach to diagnostic classification used in the current study eliminated approximately one-third (10) of the participant sample from our analyses. This surely decreased our power to detect significant between-group differences and illustrates a major drawback to use of a categorical metric of autism status. If the goal is to reflect all sources of variability within the FXS phenotype, eliminating these individuals from an analysis results in the loss of important information. We do recognize, however, that some researchers may choose to include participants with a diagnosis of ASD in the group of participants with comorbid FXS and autism - as did Rogers and colleagues; (Rogers et al., 2001; Philofsky et al., 2004) - while others may choose to include these same participants in the group with FXS only, as did Abbeduto and colleagues (Lewis et al., 2006). In such cases, these differences in grouping strategies must be considered in interpreting study results and may make it more difficult to reach a consensus across studies. Lastly, a continuous metric of autism symptom severity may correspond more closely to the manner in which symptoms of autism are distributed in the population of individuals with idiopathic autism.

Limitations—The current study has at least three limitations. As is often the case, our failure to observe between-group differences in language profiles or a significant predictive association between autism symptom severity and language ability may reflect issues with measurement rather than a lack of an actual association. There may have been a floor effects for our measures of grammar, in particular, thus limiting our ability to observe a significant effect of autism in either analysis approach. One way in which we attempted to address this limitation for receptive grammar was to use the number of individual items passed on the TROG as our dependent variable, rather than using the number of blocks passed which is the conventional way in which the TROG is scored for clinical purposes. Secondly, any interpretation of how language improved with age for participants in the current study is limited by the cross-sectional study design. A more complete understanding of this process will require longitudinal analyses of how various dimensions of language change across time within individuals.

Finally, while we were able to detect differences in the domain of receptive language using the continuous metric of autism symptom severity, it is possible that individuals with FXS also differ in their expressive language skills based upon autism symptoms. While the structured format of standardized test administration might be expected to scaffold expressive language performance, standardized tests of expressive vocabulary and syntax may not be sufficient to reveal subtle differences in spoken language ability or to assess how language production may vary across contexts that differ in their social demands. Thus, other standardized assessment procedures are important to supplement the use of standardized language tests. In particular, the use of language sampling in multiple contexts (e.g., conversation and narration) can systematically vary the amount of support for language production and has the potential to provide more nuanced information about how spoken language may differ across situations that require language to be used in naturalistic contexts.

Future directions—There is a clear need for longitudinal data to examine how individual profiles of receptive and expressive language performance change with age over childhood and adolescence. If there is a difference in the extent of language delay based upon autism symptoms, a longitudinal analysis would reveal the manner in which this profile emerges with development as well as which language domains are affected. Our cross-sectional data suggest that language ability does increase with chronological age in males with FXS, giving us reason to expect that longitudinal studies also will reveal a pattern of growth. In addition, prior to concluding that individuals with comorbid FXS and autism display a relative deficit in receptive - but not expressive - language, it is necessary to examine expressive language performance using measures and procedures that may provide a more nuanced characterization of language production across varied contexts. Finally, the current study examined only males with FXS. There is considerable variation in nonverbal cognition and language ability in females with FXS, which also merits further attention.

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Table 1

Participant Characteristics: Means and (Standard Deviations)

	Participant Groups							
	Total sample (*N* = 34)		**Fragile X syndrome with autism (*n* = 16)**		**Fragile X syndrome without autism (*n* = 8)**		**Fragile X syndrome unclear autism dx (n = 10)**	
Variable	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
Chronological age	13.02	(1.73)	12.71	(1.62)	14.29*	(1.37)	12.52	(1.80)
Leiter-R Brief IQ								
Standard Score	45.62	(8.44)	43.25	(5.36)	45.38	(10.13)	49.60	(10.28)
Age-equivalent	5.31	(1.03)	5.01	(0.87)	5.83	(1.25)	5.39	(1.02)
Autism severity[a]	5.65	(3.06)	8.00	(1.51)	2.13	(0.84)	4.70	(2.87)
	Frequency		Frequency		Frequency		Frequency	
Caucasian	31		15		7		9	
Family income[b]	21		10[d]		5		6[e]	
Maternal education[c]	17		9		4		4[e]	

*FXS-NoAUT vs FXS+AUT, $p < .05$; FXS-NoAUT vs FXS-Unclear Diagnosis, $p < .05$.

[a]Scores derived from ADOS (Lord et al., 1999) according to Gotham et al., (2009).

[b]Family income >50K per year.

[c]Mothers who obtained college degree or higher.

[d]n = 15.

[e]n = 9.

Table 2

Covariate Adjusted Language Raw Scores (and Standard Errors)

	Fragile X syndrome with autism (*n*=16)		**Fragile X syndrome with no autism (*n*=8)**	
Measure	Mean	(SE)	Mean	(SE)
PPVT	80.05	(5.81)	86.53	(8.59)
TROG[1]	26.39	(2.27)	26.98	(3.35)
EVT	51.16	(2.80)	59.55	(4.14)
CASL	11.17[2]	(1.39)	14.24[3]	(2.18)

[1] Number of items passed.

[2] n = 15

[3] n = 7

Table 3

Results of the Analyses of Covariance Using Categorical Autism Classification

Source	Mean Square	df	F	Partial η^2
PPVT				
CA	2816.21	1	5.74	.30
Leiter IQ	8661.79	1	17.66**	.22
Group	171.96	1	.35	.02
Error	490.50	20		
TROG				
CA	682.72	1	9.16**	.31
Leiter IQ	4429.54	1	59.44**	.75
Group	1.42	1	.00	.00
Error	74.52	20		
EVT				
CA	334.99	1	2.94	.13
Leiter IQ	4258.49	1	37.43**	.65
Group	288.15	1	2.53	.11
Error	113.78	20		
CASL				
CA	189.94	1	7.46**	.29
Leiter IQ	885.66	1	34.77**	.66
Group	31.14	1	1.22	.06
Error	25.47	18		

* $p < .05$,

** $p < .01$

Table 4

Results of Regression Analyses Using Continuous Metric of Autism Symptom Severity

	Language Test Scores							
	PPVT		TROG		EVT		CASL	
	ΔR^2	β	ΔR^2	β	ΔR^2	β	ΔR^2	β
Step 1	.02		.01		.04		.09	
Chronological Age		.13	.	.10		.20		.30
Step 2	.46**		.64**		.59**		.54**	
Chronological Age		.35*		.36**		.41**		.51**
Nonverbal IQ		.71**		.84**		.80**		.76**
Step 3	.07**		.03		.02		.01	
Chronological Age		.25		.30*		.37**		.47**
Nonverbal IQ		.67**		.82**		.78**		.74**
Autism Severity		−.28*		−.17		−.13		−.11
Total R^2	.55**		.68**		.64**		.64**	

** p<.01

* p<.05