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Language Development and Fragile X Syndrome: Profiles, Syndrome-Specificity, and Within-Syndrome Differences

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Fragile X syndrome (FXS) is the leading inherited cause of mental retardation. In this article, we review what is known about the language and related problems of individuals with FXS. In doing so, we focus on the syndrome-specific features of the language phenotype and on the organismic (i.e., genetic and individual neurocognitive and behavioral) and environmental factors associated with within-syndrome variation in the phenotype. We also briefly review those aspects of the behavioral phenotype of FXS that are relevant for understanding syndrome-specific features of, and within-syndrome variability in, language. The review includes summaries of research on the prelinguistic foundations for language development and on each of the major components of language (i.e., vocabulary, morphosyntax, and pragmatics). Throughout the review, we point out implications of existing research for intervention as well as directions for future research. © 2007 Wiley-Liss, Inc.
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Fragile X syndrome (FXS) is the leading inherited cause of mental retardation [Crawford et al., 2001]. The syndrome results from a mutation in the *FMR1* gene, which is located on the X chromosome at Xq27.3 [Brown, 2002]. In the healthy allele, there are approximately 55 or fewer repetitions of the CGG sequence of nucleotides comprising the *FMR1* gene [Nolin et al., 1994]. In FXS, there is an expansion to 200 or more repetitions. This full mutation typically leads to hypermethylation and transcriptional silencing so that the gene's protein (FMRP) is not produced [Oostra and Willemsen, 2003]. Expansions in the *FMR1* gene that are less than 200 repetitions but that exceed 55 or so are termed premutations, and they too can be associated with reduced FMRP levels [Nolin et al., 2003]. FMRP is normally involved in "synaptic maturation, synaptic plasticity, axonal guidance, and experience-dependent learning and related synaptic pruning" [Hagerman et al., 2005], and thus, reduced FMRP levels lead to physical and behavioral consequences [Hagerman, 1999]. In this article, we review what is known about the language and related problems of individuals with the FMR1 mutation. In doing so, we focus largely on the full mutation and the syndrome-specific features of the language phenotype; however, we also consider the organismic and environmental factors associated with within-syndrome variation in the phenotype.

IMPLICATIONS OF THE BEHAVIORAL PHENOTYPE FOR LANGUAGE LEARNING AND USE

There is considerable evidence that FXS is associated with a characteristic behavioral phenotype, defined by a profile of relative strengths and weaknesses in various neurocognitive domains and a heightened probability of various forms of psychopathology [for comprehensive reviews see Hagerman, 1999; Dykens et al., 2000; Hagerman and Hagerman, 2002b; Kau et al., 2002; Keysor and Mazzocco, 2002]. Nevertheless, there is substantial within-syndrome variability in the severity of affectedness, as well as in the precise profile of impairments and psychopathology manifested [Mazzocco, 2000; Kaufmann, 2002; Loesch et al., 2004]. Moreover, there is emerging evidence that even the FMR1 premutation is associated with a distinctive phenotype [Johnston et al., 2001; Aziz et al., 2003; Goodlin-Jones et al., 2004; Moore et al., 2004; Allen et al., 2005; Hessl et al., 2005]. In the next sections, we briefly review those aspects of the phenotype and its variable manifestations that are relevant for understanding the language difficulties of this population.

Syndrome-Specificity

Numerous cognitive skills thought to be important for language learning are impaired in FXS [Belser and Sudhalter, 1995; Cohen, 1995; Munir et al., 2000; Mirrett et al., 2003; Murphy and Abbeduto, 2003; Cornish et al., 2004]. Cognitive skills that are especially delayed or impaired include those involved in auditory short-term memory [Freund and Reiss, 1991], the processing of sequential information [Dykens et al., 1987; Burack et al., 1999], and the directing and sustaining of attention [Dykens et al., 1987; Bregman et al., 1988; Mazzocco et al., 1993]. In contrast, some cognitive skills are relatively strong in FXS, including those

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involved in processing simultaneous information [Dykens et al., 1989], entering and retrieving information from long-term memory [Freund and Reiss, 1991], and distinguishing between the self's and other people's representations of the world [Garner et al., 1999]. This profile of (relative) cognitive strengths and weaknesses differs from the profiles of other neurodevelopmental disorders, such as Down syndrome [Dykens et al., 2000], which suggests that the profile and causes of linguistic impairments in FXS will be different compared to other disorders [Abbeduto and McDuffie, 2007].

FXS is also characterized by high rates of psychopathology and challenging behaviors, which can adversely affect language learning and use [Abbeduto and Chapman, 2005]. This psychopathology includes hyperarousal [Wisbeck et al., 2000], hyperactivity [Baumgardner et al., 1995; Bregman et al., 1987; Dykens et al., 1989; Freund et al., 1993; Mazzocco et al., 1993], and social anxiety [Bregman et al., 1988b; Mazzocco et al., 1998]. Similar rates of psychopathology are not seen in Down syndrome or many other neurodevelopmental disorders [Dykens and Kasari, 1997]. The behaviors associated with these psychopathologies might lead the individual with FXS to avoid or have difficulties with participation in social interaction, thereby impacting language learning in ways that are not common to other neurodevelopmental disorders such as Down syndrome [Cornish et al., 2004; Murphy and Abbeduto, in press].

Autistic-like behaviors are also frequent in FXS [Feinstein and Reiss, 1998; Bailey et al., 2000a] and are often sufficient to warrant a comorbid diagnosis of autism, with its core features of deficits in communication, social relations, and repetitive and stereotyped behaviors and interests [Dykens et al., 2000]. The rate of autism among individuals with FXS has generally ranged from 10 to 40%, with a consensus near 25% [Rogers et al., 2001; Demark et al., 2003; Sabaratnam et al., 2003; Bailey et al., 2004], although it should be noted that large-scale population-based studies of the prevalence of this comorbidity are yet to be conducted. This relatively high rate of comorbidity with autism is not characteristic of all neurodevelopmental disorders. Delays in areas of language heavily dependent on social experience would be expected to be more substantial in FXS than in neurodevelopmental disorders not as strongly associated with autism and autistic-like behavior [Abbeduto and McDuffie, 2007].

In summary, theories of language development that ascribe an important role to cognitive capacities and social experiences in language learning, such as the social-interactionist approach, emergentism, or connectionism [Abbeduto et al., 2001], would predict (1) not only delays in language learning for those with FXS, (2) but also an uneven profile of linguistic impairments (i.e., relative strengths and weaknesses) reflecting the uneven cognitive and psychological foundation upon which language must be constructed and (3) a linguistic profile that is distinct from that of other neurodevelopmental disorders [for a fuller discussion, see Abbeduto and Chapman, 2005; Abbeduto et al., 2006a; Abbeduto and McDuffie, 2007].

Within-Syndrome Variability

The considerable within-syndrome variability that characterizes the behavioral phenotype of FXS is related to several factors, both organismic and environmental. Perhaps, the most important organismic factor is biological sex. As expected for an X-linked disorder, FXS differentially affects the sexes. Thus, the prevalence of affected individuals is one in 4,000 males and one in 8,000 females [Crawford et al., 2001]. Males with the full mutation typically meet diagnostic criteria for mental retardation [Hagerman, 1999]. Only about half of all females with the full mutation have intelligence quotients (IQs) in the range of mental retardation, the remainder has learning disabilities and/or social affective challenges [Keysor and Mazzocco, 2002]. Despite differences in severity of affectedness, males and females with the full mutation display similar profiles of neurocognitive deficits and psychopathology [Kau et al., 2002; Keysor and Mazzocco, 2002], which suggests that they will have similar types of language learning problems albeit to varying degrees [Murphy and Abbeduto, 2003].

Thus, the negative effects of the FMR1 mutation and premutation are clearly developmental in nature, with different symptoms emerging or intensifying at different points in the life course . . . It is interesting, therefore, that so few studies of language in this population have involved a developmental design. . .

There is also considerable phenotypic variation within each sex due, in large measure, to biological differences [Brown, 2002]. Among males with the full mutation, there is variation in terms of the size of the CGG expansion, the extent to which there is methylation across cells, and whether some cells contain the premutation rather than the full mutation [Nolin et al., 1994]. Indeed, as many as 40% of males with FXS may be mosaic as regards methylation or the inclusion of premutation-size expansions [Nolin et al., 1994]. Among females, there are rather large variations in the relative proportion of active X chromosomes containing the mutation [Tassone et al., 2000a]. These variations among the full mutation males and females are important because they are associated with variations in FMRP levels, and thus with many dimensions of the phenotype, including the neurocognitive and the psychopathological dimensions [e.g., Cohen et al., 1996; Menon et al., 2000; Bailey et al., 2001a,b; Kwon et al., 2001; Loesch et al., 2002, 2004]. It is reasonable to suppose that various aspects of the linguistic phenotype should also be correlated with FMRP and the other measures of FMR1 variation, although few studies have addressed this relationship.

Recent evidence has demonstrated that there is also a phenotype associated with the FMR1 premutation. For example, males with the premutation have impairments in executive function, long-term memory, and social cognition and behavior [Aziz et al., 2003; Moore et al., 2004], and are at elevated risk for various forms of psychopathology, including attention deficit/hyperactivity disorder (ADHD), anxiety, obsessive-compulsive disorders, and autism spectrum disorders (ASD) [Aziz et al., 2003; Goodlin-Jones et al., 2004; Hessl et al., 2005], but see Moore et al., [2004] for contrary findings. Females with the premutation, especially those with larger expansions, are at an elevated risk of depression, obsessive-compulsive disorder, anxiety, and ASD [Goodlin-Jones et al., 2004; Hessl et al., 2005]. The evidence for a cognitive phenotype in premutation females, however, is more equivocal [Steyaert et al., 2003; Moore et al., 2004; Allen et al., 2005]. In large measure, the premutation phenotype results from lower FMRP levels and elevated levels of FMR1 messenger RNA [Allen et al., 2005]. Aging premutation carriers, both males and females, are also at

greatly elevated risk for developing FXTAS (Fragile X Associated Tremor/Ataxia Syndrome), which is characterized by increasingly severe intentional tremors, problems in gait, memory, and related cognitive problems that can transition into dementia [Hagerman et al., 2005]. Thus, the negative effects of the FMR1 mutation and premutation are clearly developmental in nature, with different symptoms emerging or intensifying at different points in the life course [Murphy and Abbeduto, 2005]. It is interesting, therefore, that so few studies of language in this population have involved a developmental design [Murphy and Abbeduto, 2003].

Despite the fact that FXS is a genetic disorder, there is also theoretical and empirical support for an environmental contribution to the phenotype [Murphy and Abbeduto, 2005]. In particular, IQ and other indices of more specific cognitive functions are predicted by measures of the home environment (such as enrichment opportunities and economic status) for boys [Dyer-Friedman et al., 2002; Glaser et al., 2003] and girls [Dyer-Freidman et al., 2002] with the full mutation. At the same time, there is evidence that challenging child behaviors and a lack of social and professional support, as well as maternal premutation vulnerabilities, lead to lower levels of psychological well-being among some mothers [Roy et al., 1995; York et al., 1999; Bailey et al., 2000b; Johnston et al., 2003; Abbeduto et al., 2004; Poehlmann et al., 2005] and thus, perhaps, a less than optimal environment within which their children with FXS must learn language [Murphy and Abbeduto, 2005].

In summary, there is considerable within-syndrome variability in the profile of neurocognitive impairments and psychopathology that is related to biological sex, variation in the FMR1 mutation, and the affected individual's environment, as well as interactions between these variables. Variations in language learning and use are likely to be similarly related to these variables.

LANGUAGE LEARNING AND USE IN INDIVIDUALS WITH FXS

In the following sections, we review what is known about language learning and use in FXS. We begin with the prelinguistic foundations for language development and then consider in turn each of the major components of language (i.e., vocabulary, morphosyntax, and pragmatics). We conclude by reviewing research on the impact of the environment on language learning.

Prelinguistic Foundations

Children typically communicate with gestures and vocalizations before they start to talk. By about 9 months of age, typically developing children intentionally communicate, that is, there is evidence of purposefully conveying an intent towards a communication partner [Bates et al., 1987; Volterra et al., 2005]. This prelinguistic stage of development is often protracted in children with developmental disabilities, such as Down syndrome and autism. In fact, it is not uncommon for children with severe disabilities to communicate prelinguistically (with gestures, vocalizations, or a few single words) well into later childhood, adolescence, or even adulthood [McLean et al., 1998; Brady et al., 2004].

Recent evidence suggests that a large number of children with FXS are also prelinguistic communicators well past the typical age associated with transition into linguistic communication [Levy et al., 2006; Brady et al., in press]. Brady and colleagues reported the results of interviewing 55 biological mothers of young boys ($n = 44$) and girls ($n = 11$), ranging in age from 18 to 36 months, with full mutation FXS [Brady et al., in press]. According to the children's mothers, 42 of the 55 children communicated nonverbally or only produced a few words at the time of the interview. Levy et al. [2006] recruited 21 potential participants between 9 and 13 years of age for a study of language development in boys with FXS. Of these 21 boys, seven were found to be prelinguistic communicators.

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Within-syndrome differences in prelinguistic development in FXS are poorly understood. There have, for example, been no studies of premutation carriers. Little is known even about differences in the prelinguistic functioning of males versus females with FXS. Although the majority (35) of the 42 children who reportedly communicated prelinguistically in the Brady et al. study was boys, 7 of the 11 girls communicated prelinguistically. The mean chronological age of the girls reported to be nonverbal was 18.5 months, however, compared to 26.4 months for boys, suggesting a greater delay in development for boys. However, little is known about the early communication development of girls with FXS because, to date, most studies have limited their focus to boys [e.g., Roberts et al., 2001, 2002; Levy et al., 2006]). There is a need for further research on prelinguistic communication development in both boys and girls with FXS.

The role of autism in the prelinguistic functioning of individuals with FXS also needs further attention. Studies seeking to learn more about phenotypic profiles of language development in children with FXS have often excluded children who meet the diagnostic criteria for autism [e.g., Roberts et al., 2002; Abbeduto et al., 2003; Levy et al., 2006]. In a study of language development that included children with comorbid FXS and autism, Roberts and colleagues found that the presence of autism was associated with an increased degree of language impairment [Roberts et al., 2001]. Autism may also negatively impact prelinguistic communication. Children with autism often show deficits in prelinguistic skills, such as joint attention and pointing [Mundy and Crowson, 1997; Wetherby et al., 1998; Hanson, 1999; Kasari et al., 2001]. One would also expect similar deficits in children who have both FXS and autism.

Vocabulary

Receptive and expressive vocabulary have been described as relative strengths for children with FXS [Abbeduto et al., 2003; Rice et al., 2005]. Receptive vocabulary refers to how well an individual understands words spoken to them, and expressive vocabulary refers to the number of different words spoken by an individual. Although studies have often looked at composite language scores, a few have specifically considered development of receptive and/or expressive vocabulary in children and youth with FXS.

In a study of receptive language, Abbeduto et al. [2003] found that receptive vocabulary was commensurate with the participants' nonverbal mental ages (MA). The mean age of participants with FXS in this study was 16 years. Significant correlations were found between nonverbal MA scores and scores on the Word Classes and Relations subtest of the Test for Auditory Comprehension of Language [Carrow-Woolfolk, 1985], a standardized

test of language comprehension. That is, measured vocabulary was below chronological age expectations but similar to expectations based on nonverbal cognition.

Although the onset of spoken language is usually delayed relative to chronological age expectations, once children with FXS begin to talk they continue to develop expressive vocabulary [Roberts et al., 2001, 2002]. Roberts et al. [2002] examined early communication profiles in a group of 21- to 77-month-old boys with FXS who were functioning between 12 and 28 months in terms of their developmental ages. The children were all given the Communication and Symbolic Behavior Scales [CSBS; Wetherby and Prizant, 2003], a structured assessment of early social communication development. Scaled scores within certain domains of the CSBS can be compared to each other to identify profiles of relative strengths and weaknesses. Mean scores for the boys in this study were highest for use of different words and different word combinations. Language comprehension, including comprehension of vocabulary, was not a relative strength for this sample, however. The relatively lower receptive vocabulary scores for children in the Roberts et al. [2002] study compared to the Abbeduto et al. [2003] study may reflect the ages of participants. It is often difficult to measure receptive language in developmentally young children [Tomasello and Mervis, 1994], such as those studied by Roberts et al. [2002].

Again, little is known about within-syndrome differences in vocabulary development in FXS. Males in the Abbeduto et al. [2003] study performed significantly worse than females. However, the differences between nonverbal MA and age-equivalent scores on the TACL were similar between males and females, indicating a global delay in language that is greater in males than females. Other studies of vocabulary, however, have purposely excluded females with FXS [Roberts et al., 2001, 2002; Philofsky et al., 2004] and thus, little information is available about vocabulary development in girls.

Children who have ASDs in addition to FXS are likely to show poorer vocabulary skills than children with only FXS. Although both the Abbeduto et al. [2003] and Roberts et al. [2002] studies excluded participants with autism, other studies of language development have found the presence of autism to detrimentally affect language scores [Roberts et al., 2001; Philofsky et al., 2004]. Philofsky et al. [2004] found that children with both FXS and autism performed worse on both the expressive and receptive scales of the Mullen Scales of Early Learning [Mullen, 1995], compared to children with only FXS or only autism. These scales measure aspects of language other than vocabulary, however, and the specific effect on vocabulary is not known. Lewis et al. [2006], however, found lower receptive vocabulary scores in adolescents with comorbid FXS and autism than in adolescents with FXS only. Although there have been no studies of vocabulary development in premutation carriers, the risk of autism and autism-like symptoms in carriers suggests that there is a need for such research.

Morphosyntax

Morphosyntax refers to the rules that describe the ways in which linguistic units, such as words, are combined into phrases, clauses, and sentences. In English, for example, these rules include those involving word order (e.g., articles and adjectives precede nouns in noun phrases, as in "the red hat") and rules concerning the use of grammatical morphemes to modulate meaning (e.g., the use of the grammatical morpheme "ed" to convey past tense and the use of grammatical morphemes to mark subject-verb agreement, as in "boy is" and "boys are"). For decades, morphosyntax has been the center of debates about the nature of language and its development [Abbeduto et al., 2001]. In fact, the nativist claim [e.g., Chomsky, 1965] that children are biologically prepared to acquire morphosyntactic knowledge with little or no support from other cognitive functions has fueled considerable research on neurodevelopmental disorders, including, most notably, Williams syndrome [Mervis et al., 2003]. It is surprising, therefore, that our knowledge of the development of morphosyntax in individuals with FXS is relatively limited, especially as regards within-syndrome variation along the dimensions of gender, mutation status (e.g., full mutation compared to the premutation), and the presence of comorbid conditions (e.g., autism).

There is strong evidence that morphosyntactic abilities are significantly delayed relative to chronological age expectations in males with FXS and in those females with FXS whose impairments are severe enough to warrant a diagnosis of mental retardation [Abbeduto and Hagerman, 1997]. Although language skills, including morphosyntax, generally improve with age in FXS [Roberts et al., 2001], age is generally a poor predictor of morphosyntactic maturity in this population [Fisch et al., 1999]. In contrast, cognitive ability, at least as reflected in broad measures such as nonverbal MA, is a far better predictor of morphosyntactic development in FXS [Roberts et al., 2001; Abbeduto et al., 2003]. The latter finding is consistent with theories that assume an important role of domain-general cognitive abilities in language development, such as emergentism [Abbeduto et al., 2001].

Nevertheless, the relationship between cognitive ability and morphosyntactic development in FXS is not a simple one. The evidence to date suggests that receptive morphosyntax keeps pace with nonverbal cognitive abilities in FXS. For example, Abbeduto et al. [2003] found that, as a group, adolescent and young adult males and females with FXS did not differ from typically developing 3- to 6-year-olds matched on nonverbal MA in their age-equivalent scores on any of the subtests of the TACL-R, including those measuring multiword combinatorial rules and grammatical morphemes. Paul [1984] and Paul et al. [1987] also found MA-consistent receptive morphosyntactic performance in a small sample of males, most of whom were adults. Thus, individuals with FXS achieve levels of development in receptive morphosyntax appropriate for their levels of nonverbal cognitive development during adolescence and young adulthood. It would be useful to determine whether such synchrony characterizes the earlier phases of development as well.

The extent to which expressive morphosyntax is delayed relative to nonverbal cognition is less clear. Paul et al. [1987] found that delays in expressive morphosyntax in conversation exceeded nonverbal MA expectations in males with FXS. In contrast, Madison et al. [1986] analyzed conversational samples and found that mean length of utterance (MLU), which is a gross measure of morphosyntactic maturity, was at or, in advance of, nonverbal MA-expectations in males with FXS. The males in the Madison et al. study, however, were members of a single extended family and thus, the generalizability of their findings is suspect.

In a more recent investigation conducted in Israel, Levy et al. [2006] examined the expressive language skills of 15 Hebrew-speaking boys with FXS who were between the ages of 9 and 13 years. None of the boys had a diagnosis of autism as determined by the childhood autism rating scale [Schopler et al., 1980]. As noted previously, seven of these boys were completely nonverbal or produced only single words or syllables and were excluded from further analyses, leaving the sample quite small and the findings in need of replication. Language samples produced by the participants with FXS were compared to those produced by typically developing children ($n = 20$) who were

matched to the FXS sample on MLU and the percentage of utterances five or more morphemes in length. The boys with FXS did more poorly than the comparison children on some measures of language (e.g., using fewer complex clauses), but did better on many measures (e.g., making fewer errors on number agreement as in the "the boys is"), particularly in language samples that were solicited in a narrative, or storytelling, rather than in a conversational context. These findings suggest that the grammatical complexity of speech produced by boys with FXS is more advanced in some respects than expected based on MLU, at least in a context defined by considerable structure and visual support, as in Levy et al.'s narrative context. These findings also raise the possibility that morphosyntactic development is not simply delayed but also different in FXS. The Levy et al. study also suggests that reliance on only MLU can sometimes mask a more complicated profile of morphosyntactic strengths and weaknesses in FXS. It is important to note, however, that in the Levy et al. study, the children were learning Hebrew, which has a complex morphology relative to, for example, English, and thus, their conclusions might not characterize children with FXS learning other languages.

There is considerable within-syndrome variation in morphosyntactic development, much of which appears to be related to individual characteristics, although our knowledge here is quite sketchy. As with cognitive development [Hagerman, 1999], there are gender differences in morphosyntactic development, with females being less impaired, on average, than males [Fisch et al., 1999; Abbeduto et al., 2003]. Despite these differences in degree of impairment, however, males and females display synchrony between morphosyntax and nonverbal cognition and between multiword combinatorial rules and grammatical morphology, at least in the receptive modality [Abbeduto et al., 2003]. There is a need, however, for additional direct comparisons under comparable testing conditions with large samples of participants before firm conclusions will be possible.

The few studies of language in premutation carriers have relied almost exclusively on gross measures, such as verbal IQ [Tassone et al., 2000b]. Moore et al. [2004], however, included a more specific measure in their study of language issues in individuals with the FMR1 premutation. Moore et al. found no significant differences between male premutation carriers and a comparison group of age-, IQ-, and handedness-matched males on any of their language measures, including the Token test [Spreen and Benton, 1977], which requires that individuals respond to increasingly morphosyntactically (and semantically) complex instructions (e.g., "together with the yellow circle, pick up the blue circle"). Further studies are necessary to confirm that individuals with the premutation have no language or morphosyntax-specific deficit.

As mentioned previously, researchers have found that, on an average, language development of young males with comorbid FXS and autism is more impaired than in males with FXS without autism [Bailey et al., 2001a; Philofsky et al., 2004]. In general, however, these studies have relied on gross measures of language that do not allow for examination of morphosyntax separately from other domains of language and communication.

These investigators found that receptive language was more impaired than nonverbal cognition in adolescents and young adults with FXS who had comorbid autism than in those with FXS only. Moreover, the same degree of delay relative to nonverbal cognition was seen in grammatical morphology, multi word combinatorial rules, and vocabulary . . .

An exception however, is a study by Lewis et al. [2006] that examined the relationship between morphosyntax and the autism diagnosis in FXS. These investigators found that receptive language was more impaired than nonverbal cognition in adolescents and young adults with FXS who had comorbid autism than in those with FXS only. Moreover, the same degree of delay relative to nonverbal cognition was seen in grammatical morphology, multiword combinatorial rules, and vocabulary, suggesting that receptive language in general, including morphosyntax, is affected by autism status. Replications are needed, however, with larger samples of varying ages and with a more comprehensive battery of measures of morphosyntax.

Although not great in number, a few studies have compared the morphosyntactic performance of individuals with FXS to other populations with developmental disabilities associated with language impairments. Ferrier et al. [1991] compared expressive language skills in a conversational context in three groups of adult males: FXS, autism, and Down syndrome. Ferrier et al. found that although males with FXS used more partial self-repetition and more eliciting forms than the other two groups, they did not differ from either comparison group in expressive morphosyntax. In a more recent study, males and females with FXS scored significantly higher on total scores of the TACL than individuals with Down syndrome [Abbeduto et al., 2003]. While performance was even across subtests for individuals with FXS, those with Down syndrome scored lower on the grammatical morphemes and elaborated sentences subtests, which reflect morphosyntax-related comprehension, than on word classes & relations, a subtest of receptive vocabulary. Thus, adolescents with FXS differ from those with Down syndrome in that morphosyntax does not seem to be a particular weakness in FXS, although further comparisons among these and other populations are warranted.

Pragmatics

Pragmatics refers to the ability to use language in social interaction to convey one's needs, interests, and intentions, as well as to discern the meanings intended by other speakers, and to do so in a way that conforms to various principles of informativeness and social appropriateness. Pragmatic skills would be displayed, for example, in the decision to use a pronoun (e.g., "it") only if the entity referred to can be assumed to be clear to the listener because of what has already been said or because of accompanying nonverbal information, such as a pointing gesture by the speaker. Deciding to express a request to a teacher by using the polite, "Can I have another?" rather than the impolite "Give me another" would also be evidence of pragmatic skills.

There is considerable evidence that the pragmatic development of most males and many females with FXS (i.e., the full mutation) is delayed relative to chronological age expectations [Murphy and Abbeduto, 2003]. For example, summary measures, such as the communication domain score from the vineland adaptive behavior scales (VABS) [Sparrow et al., 1984], which includes a number of pragmatic skills (as well as other verbal and nonverbal skills), indicate a level of skill closer to MA than chronological age expectations for

males with FXS [Dykens et al., 1989]. Moreover, communication domain scores from the VABS and other similar summary measures lag behind scores in other adaptive skill domains, suggesting that pragmatics is an area of relative weakness [Dykens et al., 1989; Bailey et al., 1998; Fisch et al., 1999]. Such summary measures, however, often include skills that are outside of the pragmatic domain. Moreover, such measures do not allow for determining whether some facets of communication pose greater challenges than do other facets for individuals with FXS [Murphy and Abbeduto, 2003].

Studies employing measures of more narrowly defined pragmatic skills have reinforced the notion that pragmatics is an area of special challenge for individuals with FXS while also providing a more nuanced characterization of their problems in this domain. In a study examining non-face-to-face talk in a laboratory-based task that required describing novel shapes, Abbeduto et al. [2006b] found that adolescents and young adults with FXS were less adept in some facets of the task than in others. In particular, the participants with FXS were more likely to create ambiguous, and thus, incomprehensible, descriptions of their intended referents (e.g., using "the muffin" to refer to two or more different shapes) than were MA-matched typically developing children. The participants with FXS were also more likely than either the typically developing children or MA-matched participants with Down syndrome to reformulate their previously successful descriptions on subsequent trials (e.g., using "muffin" to refer to a shape on one trial, but "house" to refer to the same shape on subsequent trials), which also decreased comprehensibility. At the same time, however, the participants with FXS were more adept at using linguistic forms that helped to scaffold their listener's understanding than were the participants with Down syndrome (e.g., by stating "It looks kind of like a house" rather than simply "It's a house"). Thus, FXS is characterized by an asynchronous profile of pragmatic strengths and weaknesses, some features of which may be syndrome specific [Abbeduto and Murphy, 2004].

Perhaps, the most studied aspect of pragmatics in FXS has been perseveration. Males with FXS produce high rates of self-repetition of words, phrases, and topics [Sudhalter et al., 1990; Ferrier et al., 1991; Belser and Sudhalter, 2001]. Many in the field have argued that such perseveration is a unique and defining characteristic of individuals with FXS [Bennetto and Pennington, 1996; Abbeduto and Hagerman, 1997]. Indeed, several studies have demonstrated that males with FXS produce more perseverative language than do typically developing children at similar linguistic levels [Levy et al., 2006] or developmental level-matched males with Down syndrome, autism, or other forms of mental retardation [Sudhalter et al., 1990, 1991, 1992; Ferrier et al., 1991; Belser and Sudhalter, 2001], but see Paul et al. [1987] for contrary results.

Several hypotheses about the causes of perseveration in individuals with FXS have been proposed. First, it has been suggested that abnormalities in the frontal lobes of the brain result in a deficit in inhibiting high strength, salient, or previously activated responses, which results in repetitions of previously uttered forms and content or the intrusion of idiosyncratic material [Abbeduto and Hagerman, 1997]. In support of this hypothesis is the well-documented finding that individuals with FXS have impairments in attention and impulsivity that make it difficult for them to focus or direct their behavior for extended periods of time [Baumgardner and Reiss, 1994; Lachiewicz et al., 1994; Baumgardner et al., 1995; Cohen, 1995; Hagerman, 1996; Hatton et al., 1999; Miller et al., 1999]. Second, it has been suggested that impaired regulation of the autonomic nervous system, which results in hyperarousal, may exacerbate problems in inhibitory control, particularly in socially demanding or otherwise anxiety-provoking situations [Belser and Sudhalter, 1995; Cohen, 1995]. In support of this hypothesis is the finding that youth with FXS, particularly males, display higher cortisol levels than typical controls and show physiological and behavioral signs of an inability to adapt in a timely fashion to stressful or demanding situations [Belser and Sudhalter, 1995; Miller et al., 1999; Wisbeck et al., 2000; Hessl et al., 2006]. Third, it has been suggested that perseveration may reflect an attempt to deal with conversational demands in the face of limited linguistic capabilities [Ferrier et al., 1991]; however, support for this hypothesis is lacking [Sudhalter et al., 1992].

It is likely, therefore, that multiple, probably interacting, factors account for perseveration in FXS, which suggests that any therapies designed to reduce its occurrence will need to be multipronged as well.

Recent research by Murphy and Abbeduto [in press], however, suggests that the manifestations and causes of perseveration may be more complex than previously recognized. In particular, these investigators reported that the rates of repetition of different types of verbal units (i.e., topics, rote conversational phrases, or within-utterance syllables, words, or phrases) by adolescent males and females with FXS were influenced by different variables, with some types of repetition differing in rate between male and female speakers and other types differing in rate between contexts (i.e., conversation and narration). It is likely, therefore, that multiple, probably interacting, factors account for perseveration in FXS, which suggests that any therapies designed to reduce its occurrence will need to be multipronged as well.

There have been very few studies of pragmatics in females with FXS and fewer still in which gender differences in pragmatics have been systematically investigated. Several case studies are suggestive of pragmatic difficulties in females with FXS, including those who are otherwise high-functioning. In a descriptive study, Canales [1994] found that the picture descriptions of five women with FXS were characterized by long-windedness and a lack of coherence relative to age-matched women with the FMR1 premutation and typical controls, although no inferential statistics were conducted. Madison et al. [1986] examined several aspects of the language skills of females in a single extended family and reported that the females displayed an overly detailed, repetitive, and run-on style of recounting personal events.

Larger-sample experimental investigations support these anecdotal accounts of pragmatic problems in females with FXS. Simon et al. [2001] found that females with the full mutation had difficulty in selecting appropriate humorous endings for stories that they read relative to IQ-matched women without FXS. Simon et al. concluded that the females with FXS failed the task because they were unable to follow and make connections between the elements and propositions of a discourse (i.e., establish coherence). Although the generalizability of these results to the on-line performances more typical of every-day pragmatics is not clear [Murphy and Abbeduto, 2003], the Simon et al. [2001] findings are notable, because the women displayed pragmatic problems despite having normal-range IQs, suggest-

ing that the pragmatic domain may be specifically challenging for females with FXS.

There has been relatively little empirical research on the pragmatic skills of individuals with the FMR1 premutation. In a recent investigation of a small sample of boys with the premutation, Aziz et al. [2003] reported that several boys conveyed the clinical impression of having poor conversational skills, including those who did not qualify for an ASD diagnosis. It may be hypothesized that premutation carriers who also have ASD may show pragmatic difficulties because of the high occurrence of pragmatic difficulties associated with ASD [Wetherby and Prizant, 2000]; however, additional research is needed to verify this hypothesis because most studies of premutation carriers have relied largely on verbal IQ and other measures of language that do not provide data on pragmatics directly.

Environmental Influences

Few would argue against the importance of a responsive environment to language development. Communication is about conveying one's message to another person, and hence the scaffolding and feedback offered by that other person are of paramount importance. For this reason, there have been a number of investigations of such responsivity in the communication partners of typically developing children and of children with developmental disorders. For our purposes, interest is in the responsivity of the primary caregivers, typically the parents.

Maternal responsivity has been tied to language outcomes in typically developing children [Masur, 1982; Bornstein and Tamis-LeMonda, 1989; Hart and Risley, 1995; Tamis-LeMonda et al., 1996], children at risk of delays [Landry et al., 2001; Barwick et al., 2004], and in children with various developmental disabilities [Mahoney, 1988; Yoder and Warren, 1999; Hauser-Cram et al., 2001; Siller and Sigman, 2002]. In general, children of mothers who interact more with their children and provide more linguistic input are more advanced linguistically and cognitively, compared to children of parents who are less interactive and talk less to their children. A specific interaction style in which parents are highly responsive to child initiations and not overly directive has been described as particularly facilitative for language development [Girolametto et al., 1986; MacDonald and Carroll, 1992; Spiker et al., 2002].

Interventions aimed at improving responsivity by mothers and other care providers have been developed and researched with children with developmental disabilities, although not specifically with children with FXS [Girolametto et al., 1986; Tannock et al., 1992; Girolametto et al., 1994; Fey et al., 2006]. This research has demonstrated that the interventions are successful in promoting change in care-provider behaviors. Concomitant changes have been reported for child communication behaviors, such as joint attention (i.e., communicating about a common referent). However, Spiker and colleagues observed that certain child behaviors make it difficult to be highly responsive [Spiker et al., 2002]. For example, if a child frequently engages in challenging behaviors, as is the case in FXS, it may be difficult to use the responsive interaction strategies taught in these interventions.

Responsivity and FXS

There are several variables associated with FXS that may decrease responsivity, particularly by mothers. First, characteristics of mothers of children with FXS may impact responsivity. Biological mothers of children with FXS either carry the premutation or have the full mutation themselves. Mothers with the full mutation may have cognitive deficits, increased social anxiety, and depression [Abbeduto et al., 2004]. Although less is known about women who carry the premutation, some reports indicate increased rates of affective disorders [Hagerman and Hagerman, 2002a]. Abbeduto et al. [2004] found that mothers of adolescents with FXS were more pessimistic and had more depressive symptoms than did mothers of adolescents with Down syndrome. The mothers of the children with FXS were more similar to mothers of children with autism—a fact that may reflect the high proportion of similar characteristics of children with autism and children with FXS. Information about the full-mutation versus premutation status of the mothers of children with FXS was not available in the Abbeduto et al. [2004] study.

Second, behaviors often observed in children with FXS are likely to impact mother–child interactions. The following child behaviors have been described as phenotypic for children with FXS, and each of these may impact responsivity: gaze avoidance or atypical eye gaze, hypersensitivity to sensory input, social anxiety and shyness, perseveration, stereotypical and challenging behaviors, delayed speech, unintelligible speech, and problems with conversational discourse [Abbeduto and Hagerman, 1997; Bailey et al., 1998]. With the possible exception of social anxiety and shyness, each of these behaviors appears more pronounced in boys than in girls. Thus, one would expect more disruption in maternal responsivity to boys with FXS than to girls with FXS. Research is needed to document differences in caregiver responsivity toward boys versus girls, however.

Third, the presence of ASDs or behaviors associated with ASDs could also impact responsivity. Symptoms such as an intolerance for variation in routine, or gaze aversion may impede development of facilitative, reciprocal interactions. It seems reasonable that the number and severity of autistic symptoms would relate to stress in maternal–child interactions. Although this has not yet been specifically investigated, more maternal stress in general, as reported on the Parenting Stress Index [Abidin, 1986], was associated with an increased severity of child behavior problems in a recent study with mothers of children with FXS [Johnston et al., 2003].

Despite these speculations, research on responsivity in mother–child dyads with FXS has not yet been reported. This is unfortunate in light of the existence of interventions to improve responsivity and possibly child outcomes.

CONCLUSIONS

Research to date indicates that individuals with the full FMR1 mutation are, on average, delayed relative to age expectations in traversing the milestones of the prelinguistic communication period and in their progress in all domains of language, including vocabulary, morphosyntax, and pragmatics. In general, vocabulary and receptive morphosyntax are highly correlated with nonverbal cognition and display similar rates of development. The course of expressive morphosyntax is less clear, but there does appear to be an asynchronous profile, with some morphosyntactic achievements being less delayed than others. Pragmatics is an area of special challenge for individuals with FXS, with verbal perseveration and referential communication being especially problematic. There are some aspects of the linguistic profile of FXS that may be syndrome-specific, distinguishing it both from Down syndrome and from autism. Males with FXS are more impaired in language, on overage, than are females with FXS. This sex difference appears to be one of degree rather than of kind and reflects largely differences in cognitive functioning. And finally, there is clear evidence that individuals with co-morbid FXS and autism have serious language delays, especially in the receptive mode.

Despite three decades of research on language in FXS, however, there is still much that we do not know and several limitations on the interpretability of existing data.

1. There is a pressing need for more information about the early de-

velopmental period for children with FXS. Information about the nature of early prelinguistic communication would help inform practitioners and family members about variability in development and what types of interventions may be most effective. For example, adolescent girls with FXS do not show the same degree of language impairment as do boys [Abbeduto et al., 2003; Rice et al., 2005]; yet, some girls have language delays that extend the prelinguistic period much longer than expected. It is not known whether this finding reflects a proportion of girls that remain delayed in expressive language over time, or if girls may show these early delays but "catch up" in their skills more readily than boys.

2. There is a growing evidence base for interventions that are specific to the prelinguistic period. In addition to early interventions that target augmentative or alternative forms of communication (AAC), interventions have been developed that specifically target child prelinguistic communicative behaviors and partner responsivity in children with disabilities [Girolametto et al., 1994; Yoder and Warren, 2002; Fey et al., 2006]. Based on the descriptive studies conducted with children with FXS thus far, there is reason to expect that these interventions would be similarly effective with children with FXS. However, research is needed to verify this assumption.
3. Studies of vocabulary development have not found this to be an area of special concern for FXS. Nevertheless, these studies are few in number and have generally focused on assessing mastery of rather concrete vocabulary, leaving specific lexical domains (e.g., mental state terms, such as "know" and relational terms, such as "bigger") unexplored. More importantly, there have been no studies that have focused on the processes by which individuals with FXS learn new words. Do they, for example, engage in the same types of fast mapping processes as do typically developing children and children with Down syndrome [Abbeduto and Chapman, 2005].
4. Studies of morphosyntactic development have largely been confined to rather broad measures, such as MLU, which may mask important differences in the profile of impairments in FXS. Moreover, inadequate attention has been paid to the ways in which the language samples yielding the morphosyntactic variables of interest have been collected. Inadequate standardization of language sampling procedures makes it impossible to know whether morphosyntactic differences across groups or individuals reflect something about the speaker or about the context. Moreover, reliance on conversational contexts for collecting language samples may have led to an underestimation of morphosyntactic skills in individuals with FXS [Abbeduto et al., 1995]. More generally, there is a need to assess morphosyntax under a broader range of speaking tasks and contexts, both from a research and a clinical perspective. Information on the sequence of morphosyntactic acquisitions and on the types of errors made prior to mastery will be important for providing insights into the learning process. Indeed, information about morphosyntactic on-line learning will be crucial to the development of interventions.
5. In the pragmatic domain, there is a need to move beyond a focus on only the linguistic dimensions of communication to examine the gestural and prosodic features of the communicative process. Indeed, there are preliminary data suggesting that gestural communication may be especially impaired among young boys with FXS [Roberts et al., 2002]. There is also a need for more research into the ways in which pragmatic performance and development are shaped by other features of the FXS behavioral phenotype, especially the executive function [Cornish et al., 2004] and attention problems [Mirrett et al., 2003] that are so characteristic of affected individuals.
6. There is considerable evidence to suggest that the mental health challenges faced by many mothers who carry the full or premutation of the *FMR1* gene and the maladaptive behavior of their children may conspire to disrupt parent–child interactions, limiting the extent to which those interactions are responsive and optimal for language learning. There are, however, no studies examining parent–child interactions directly. Moreover, there is a need not only to simply document disruptions in those interactions but also to evaluate their impact on language learning and use over time. The need for these data is particularly acute as there are interventions that could be implemented should parental responsivity be a problem area.
7. There is a need for additional research regarding syndrome specificity and within-syndrome variation across all domains of language. Syndrome comparisons have involved Down syndrome almost exclusively. This makes it impossible to conclude whether the profile of language strengths and weaknesses observed is truly syndrome specific, or just different from Down syndrome [Dykens et al., 2000]. Studies in which males and females with FXS have been compared under similar task conditions are quite rare. Although it is difficult to conduct such studies because of the inherent confounding of IQ and gender, such comparisons are possible [Murphy and Abbeduto, in press] and are needed if we are to be certain whether gender differences in language are quantitative or qualitative in nature [Murphy and Abbeduto, 2003]. Additionally, we have only begun to examine differences in the language profiles of individuals with FXS who do and do not have a comorbid diagnosis of autism and to determine whether there is a language profile associated with the FMR1 premutation.
8. Most studies that have examined the developmental trajectory of language have relied on gross summary measures, such as a language age or verbal IQ, which collapse across multiple domains of language (e.g., vocabulary, morphosyntax, and pragmatics). Developmental studies using narrowly defined measures of language, focusing on a specific domain (e.g., vocabulary) or even on different types of skills or content within a domain (e.g.,

concrete versus abstract or relational words, or nouns versus verbs), have been rare. Cross-sectional studies in which groups of different ages are compared have also been rare, as have studies employing more time-consuming and logistically difficult longitudinal designs. Such studies are needed, however, because there is clear evidence that the FXS phenotype emerges and changes dramatically over time. Without more information about the developmental course of language, it will be impossible (a) to provide information to families and professionals about "what to expect," (b) to identify the factors leading to better or worse outcomes in language, or (c) to develop interventions that optimize language outcomes. ■

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