MENTAL RETARDATION AND DEVELOPMENTAL DISABILITIES
RESEARCH REVIEWS *3: 313–322 (1997)*

LANGUAGE AND COMMUNICATION IN FRAGILE X SYNDROME

Leonard Abbeduto[1,2]* and Randi Jenssen Hagerman[3,4]

[1]Department of Educational Psychology, University of Wisconsin-Madison, Madison, Wisconsin

[2]Waisman Center on Mental Retardation and Human Development, University of Wisconsin-Madison, Madison, Wisconsin

[3]Department of Pediatrics, University of Colorado Health Sciences Center, Denver, Colorado

[4]Child Development Unit, Children's Hospital, Denver, Colorado

In this article, we describe the language and communication problems of individuals with fragile X syndrome (FXS). FXS is a common genetic disorder resulting from a single-gene mutation on the X chromosome. It is associated with a wide spectrum of physical, behavioral, cognitive, and language problems. Males are typically more severely affected than females, with the vast majority of males having mental retardation. Language and communication are negatively affected by problems in oral-motor structure and function and by conductive hearing loss associated with recurrent otitis media. Speech problems of males with FXS include variability in rate and stuttering-like repetition of sounds. The pattern of speech problems displayed by males is unique to FXS and may reflect a form of developmental dyspraxia. Lexical development is serious delayed in males with FXS. It is less clear, however, whether lexical development keeps pace with achievements in cognitive development and whether receptive and expressive vocabularies are equally impaired. Morphosyntactic development is delayed in males with FXS, with receptive morphosyntax being mental-age-appropriate. It is less clear whether expressive morphosyntactic keeps pace with mental age in affected males. Communication problems are characteristic of both males and females and include features that are syndrome-specific. Most notable among the features displayed by males with FXS is perseveration on a word, phrase, or topic in conversation. Several hypotheses have been advanced to explain this perseveration, but the most promising focus is on hyperarousal and frontal-lobe-executive function deficits. Females with FXS display a run-on, disorganized, and tangential style of conversation that may result from their well-documented frontal-lobe-executive function deficits. Language and communication intervention for affected individuals requires coordination of medical and behavioral approaches, with the involvement of professionals from several disciplines. Future research must focus on females, on language problems suggested by clinical experience, and on connections between language and communication problems and problems at the neurological and molecular genetic levels.

MRDD Research Reviews 1997;3:313–322.

Key Words: fragile X syndrome; speech; language; communication

Fragile X syndrome (FXS) is a common genetic disorder associated with a broad spectrum of problems [Dykens et al., 1994; Hagerman, 1996a]. Some affected individuals may present with only mild language, cognitive, or behavioral problems, whereas others may display mental retardation or even fail to develop any spoken language. Despite this heterogeneity, there is a characteristic pattern of language development and use associated with FXS. In fact, this profile is frequently what first alerts clinicians to the possibility of an FXS diagnosis. In this article, we describe what is known about the language problems of individuals with FXS. We focus on both the nature and severity of their problems and, where possible, distinguish between those problems that may be unique to FXS and those shared with other syndromes (e.g., Down syndrome, autism). We also consider problems in language within the broader context of the behavioral and neurological development of affected individuals. We begin, however, with a brief review of the genetic mechanisms underlying the syndrome and of the nonlinguistic dimensions of the behavioral phenotype.

BACKGROUND

FXS is the most common (known) inherited cause of mental retardation. Early studies demonstrated a prevalence of 1 per 1,200 in males and 1 per 2,500 in females [Webb et al., 1986]. More recent molecular studies have suggested a prevalence in males closer to 1 per 4,000 [Turner et al., 1996]. FXS results from a mutation on the X chromosome. Cytogenetically, this mutation is manifested as a break, or fragile site, at the bottom of the X chromosome. In 1991, the Fragile X Mental Retardation 1 Gene (FMR1) was discovered and a trinucleotide repetitive sequence $(CGG)_n$ was found at the beginning of the gene [Verkerk et al., 1991]. In most non-FXS individuals, there are approximately 5 to 50 CGG repeats [Imbert and Mandel, 1995]. In FXS carriers, the repeat number is 53 to 200, which is termed the premutation. The premutation does not cause intellectual disability but there is a high risk of expansion when the premutation is passed to the next generation through a female [Imbert and Mandel, 1995]. Individuals affected by FXS have more than 230 CGG repeats, and this is termed a full mutation [Imbert and Mandel, 1995]. In the full

Grant sponsor: National Institute of Child Health and Human Development; Grant numbers: R01 HD24356, P30 HD03352; Grant sponsor: Maternal and Child Health; Grant number: MCJ089413; Grant sponsor: March of Dimes; Grant number: 12-FY96-0492.
*Correspondence to: Leonard Abbeduto, University of Wisconsin-Madison, Waisman Center, 1500 Highland Avenue, Madison, WI 53705-2280. E-mail: abbeduto@waisman.wisc.edu

mutation, the FMR1 gene typically is methylated, a process that shuts off the gene and prevents the normal production of the FMR1 protein (FMRP), which (as discussed below) is thought to be important for brain development [Hagerman, 1996a; Oostra, 1996].

The phenotype of males with FXS is comprised of both physical and behavioral features. Physical features include a long face, prominent ears, and large testicles in adolescent or adult males [Hagerman, 1996a]. Prepubertal males typically do not have a long face, but the ears are usually prominent. There is evidence of a connective tissue dysplasia or loose connective tissue in FXS leading to hyperextensible finger joints, soft and smooth skin, flat feet, and double-jointed thumbs. Although these physical features are seen in the majority of individuals with FXS, young children may not have obvious physical features and so clinicians must rely on the behavioral manifestations of FXS when considering the diagnosis.

In terms of behavioral features, males with FXS often display limited attention spans and hyperactivity [Baumgartner et al., 1995]. They also may be oversensitive to tactile, auditory, olfactory, or visual stimuli. Many males with FXS also avoid eye contact [Cohen et al., 1991] and may display autistic-like stereotypies (e.g., hand flapping, hand biting) beginning in the second or third year of life [Hagerman, 1996a]. In fact, approximately 6% of boys with autism also have FXS [Brown et al., 1986; Cohen et al., 1991]. It is important in studies of language and FXS, therefore, to examine the relation between language problems and the social-emotional features that define FXS and to discriminate between affected individuals with and without autism.

Cognitive deficits in males can be severe. Mental retardation occurs in approximately 85% of males with the full mutation [Hagerman et al., 1994b]. Young boys with FXS may have an IQ above 75 [Freund et al., 1995] only to show declines in IQ by late childhood or adolescence [Wright-Talamante et al., 1996]. Most males with FXS but without mental retardation have a variant DNA pattern, such as a full mutation without complete methylation or a mosaic pattern (i.e., the premutation in some cells with the full mutation and complete or partial methylation in others). These males may be higher functioning because their cells contain a limited amount of FMRP [Tassone et al., unpublished data]. Mean IQ is 41 for males with a completely methylated full mutation, 60 for males with a mosaic pattern, and 88 for males with an unmethylated or partially unmethylated full mutation [Merenstein et al., 1996]. It is important in studies of FXS, therefore, that language problems are studied in relation to cognitive impairments and that correlations are examined between variations at the molecular-genetic level and in the language profile. Such data, however, are virtually nonexistent.

Females with FXS are usually less affected than males [Lachiewicz, 1995]. This is the case because females typically have the full mutation on only one of their two X chromosomes and, thus, the unaffected chromosome moderates the effects of the mutation [Imbert and Mandel, 1995]. Approximately 50 to 70% of girls with the full mutation have IQs in the borderline or mentally retarded range [de Vries et al., 1996]. Females with the full mutation but without mental retardation typically have learning problems, including executive function problems that can lead to a limited attention span and impulsivity [Mazzocco et al., 1993; Hagerman et al., 1992; Sobesky et al., 1996]. Social anxiety or avoidant disorder and shyness are also frequent in females with FXS [Freund et al., 1993]. This anxiety in combination with language impairments can lead to selective mutism in females with the full mutation [Hagerman, 1996a]. Because of the phenotypic differences in males and females with FXS, it is important to distinguish between them in language studies.

Recent research on the role of the FMRP in brain development promises to greatly increase our understanding of the mechanisms involved in the development of the FXS behavioral phenotype. In particular, absence of the FMRP in individuals with FXS is hypothesized to interfere with the pruning of neuronal connections that typically occurs early in development, with the result being an enhanced number of neuronal connections [Reiss et al., 1995a]. In fact, Connery et al. [1997] have reported long, thin, and tortuous dendritic spines in FMR1 knockout mice compared to unaffected littermates, which suggests impaired synapse stabilization and pruning without FMRP. Neuroimaging studies in humans have demonstrated increased size of the hippocampus, caudate, and thalamus in individuals with FXS compared to controls, which is also consistent with a lack of normal neuronal pruning in FXS [Reiss et al., 1995a,b; Schapiro et al., 1995]. It is important, therefore, to determine the relation between the language problems associated with FXS, the production of FMRP, and the neural functioning of individuals with FXS. Such analyses, however, are just beginning.

LANGUAGE, COMMUNICATION, AND RELATED DOMAINS

Language is not a unitary ability. It consists of several components (e.g., the lexical and the morphosyntactic) that emerge from different types of experiences and that are tied more or less closely to achievements in other domains of psychological and behavioral functioning [Rondal, 1995]. In this section, we consider the problems that individuals with FXS have in acquiring and using skills in the various components of language.

Physical Structures Related to Language

Expressing one's thoughts through spoken language presupposes a functional oral-motor system. Individuals with FXS, particularly males, suffer from a number of oral-motor problems that could impact speech, including dramatic oral tactile defensiveness [Scharfenaker et al., 1996], drooling because of a failure to swallow reflexively as saliva builds up [Scharfenaker et al., 1996], truncal hypotonia involving the oral-facial muscles [Hagerman, 1996a], and a narrow and high arched palate with dental crowding [Hagerman, 1996a]. In addition, cleft palate is seen in 5% of children with FXS [Partington, 1984], and prognathism occurs but typically only in adults with FXS [Fryns et al., 1987; Loesch et al., 1995]. Although there is little doubt that these functional and structural problems can interfere with speech, their full impact on the development of language and communication in FXS has not been fully explored.

Hearing problems are also common in FXS and may complicate the task of learning language. In a study by Hagerman et al. [1987], for example, 63% of the 30 boys with FXS studied had recurrent bouts of otitis media in early childhood, compared to 15% of their unaffected siblings and 38% of developmentally disabled children without FXS. More recent studies show that 85% of boys with FXS have recurrent otitis media [Hagerman, 1996a]. These problems may result from the combination of changes in facial structure and the loose connective tissue associated with FXS interfering with drainage through the eustachian tube. It is important to note, however, that systematic investigations of

the contributions of recurrent otitis media to the language development of individuals with FXS have not been conducted.

Speech Production

The ability to produce speech sounds and sequence them appropriately is critical for communication. Speech problems can lead to reduced intelligibility (i.e., speech that is difficult for others to understand) and can affect how a speaker is evaluated by others [Kent, 1993]. Speech production is problematic for many individuals with FXS, and some speech problems are claimed to be specific to the syndrome [Schopmeyer and Lowe, 1992].

Most notable among the speech problems observed are those involving speaking rate, which have been well documented in males with FXS [Dykens et al., 1994]. Affected males display an unusual variability is speaking rate that consists of unpredictable shifts from rapid to slower rates [Hanson et al., 1986]. Variability in rate is seen across all levels of IQ [Hanson et al., 1986], but may be more prevalent in adolescents and adults than in boys [Borghgraef, 1987]. Such variability in speaking rate is not seen in age- and cognitively-matched persons with Down syndrome [Wolf-Schein et al., 1987], which leads to the hypothesis that this variability in rate is unique to FXS. Verifying this hypothesis, however, will require comparisons with a greater number of other mental retardation syndromes.

Males with FXS also produce speech of low intelligibility relative to chronological age expectations [Paul et al., 1984], although intelligibility problems may not be any more severe than those seen in other syndromes. Paul et al. [1987], for example, found that ratings of speech intelligibility in conversation did not differ between adult males with FXS and males with Down syndrome and males with autism matched to them on age, IQ, and length of institutionalization. It should be noted, however, that the participants in Paul et al. [1987] had been institutionalized and had limited expressive skills. It remains to be determined whether the intelligibility problems of higher functioning, noninstitutionalized males can be similarly characterized.

Males with FXS also omit, distort, and substitute consonants and vowels in their conversational speech [Hanson et al., 1986; Newell et al., 1983; Vilkman et al., 1988], although there is considerable variability in the rates of such errors even among similarly aged males with FXS [Paul et al., 1984]. These errors reflect simplification processes similar to those of younger, typically developing children rather than an atypical pattern of development [Palmer et al., 1988].

Affected males also have been observed to repeat sounds and syllables at high rates [Newell et al., 1983; Vilkman et al., 1988], although less than in stuttering [Paul et al., 1984]. They also have difficulty repeating nonreduplicated multisyllabic sequences, such as ''pa-ta-ka'' [Paul et al., 1984]. In contrast, they do reasonably well when repeating isolated sounds and words [Niemi et al., 1985; Paul et al., 1984].

The social, cognitive, and morphosyntactic limitations associated with FXS suggest that lexical learning will be seriously disrupted. It is surprising, therefore, how little is known about lexical development in FXS.

It has been argued that the profile of speech problems described for affected males, which Hanson et al. [1986] referred to as *cluttering*, reflects a developmental dyspraxia; that is, problems in planning and controlling the complex motor sequences involved in speaking. In fact, it has been suggested that this dyspraxia is a manifestation of a more general inability to deal with sequential information during both input and output [Dykens et al., 1994]. It remains to be determined whether this problem is common to other syndromes.

In contrast to the abundant research on males, there are virtually no data on females. In addition, little is known about the developmental course of speech production in males or females. There are also dimensions of speech, such as volume, pitch, and harshness, that clinical experience suggests are unusual in FXS, but which have yet to be documented by systematic research.

Lexical Development

Lexical development is a life-long process that is central to many conceptions of intelligence [Rosenberg and Abbeduto, 1993]. Lexical learning depends on expertise in other components of language (e.g., morphosyntax [Gleitman and Gillette, 1995] and on various nonlinguistic, cognitive capacities and processes (e.g., categorization [Barrett, 1995]). The social, cognitive, and morphosyntactic (described below) limitations associated with FXS suggest that lexical learning will be seriously disrupted. It is surprising, therefore, how little is known about lexical development in FXS.

Existing data demonstrate that males with FXS perform well below chronological age expectations on both receptive and expressive measures of vocabulary [Madison et al., 1986; Paul et al., 1987; Sudhalter et al., 1992]. It is less clear, however, whether lexical development keeps pace with achievements in other domains (e.g., cognition). Madison et al. [1986] reported that the adult males they studied, all of whom were members of a single family, scored substantially higher on standardized tests of lexical knowledge than expected from their nonverbal mental ages. In contrast, Paul et al. [1987] found that institutionalized adult males had vocabulary scores similar to those of age- and cognitively-matched males with nonspecific forms of mental retardation and males with autism. And finally, Sudhalter et al. [1992] found that males with FXS supplied more semantically incorrect words in a sentence completion task than did typically developing children matched to them on adaptive behavior. Differences in measures or participant characteristics (e.g., developmental level) may be responsible for these inconsistent results.

It is also not clear whether receptive and expressive vocabularies are impaired to the same degree in affected males. On the one hand, Madison et al. [1986] reported that their adult males achieved higher scores in expression than in comprehension of vocabulary. On the other hand, Paul et al. [1987] reported no differences between the receptive and expressive vocabularies of the institutionalized adult males with FXS they studied. Again, the differences may be due to participant or measurement differences.

We know less about the lexical development of females with FXS than about that of males. The females in the family studied by Madison et al. [1986] (only some of whom had mental retardation) showed little difference between their receptive and expressive vocabularies on average. In addition, we lack data on the strategies that individuals with FXS—whether male or female—use to

learn new words. Typically developing preschoolers, for example, make a variety of assumptions about how words relate to referents (e.g., no word can refer to more than one category), and these assumptions limit the range of potential meanings the children need to consider [Clark, 1995]. It is not known whether persons with FXS make similar assumptions. We also lack data on the developmental course of lexical learning in FXS.

Morphosyntactic Development

Morphosyntax refers to the rules and elements that govern the combination of words into phrases and sentences, mark grammatical functions such as subject and object, and express notions such as plurality and tense. Morphosyntax is the linguistic vehicle for expressing meaning and ''the major source of the infinite combinatorial capability of language users'' [Rosenberg and Abbeduto, 1993, p. 82]. Included in the morphosyntactic competence of most adult speakers of English would be the knowledge that variations in word order signal differences in meaning and knowledge of the ways in which plural and singular nouns are distinguished linguistically.

Affected males have been found to perform below chronological age expectations in both receptive and expressive morphosyntax [Dykens et al., 1994; Schopmeyer and Lowe, 1992]. More interesting are the findings concerning morphosyntactic functioning in relation to nonlinguistic cognitive functioning. Such findings address the issue of whether morphosyntax poses special problems for males with FXS (i.e., over and above those expected based on their intellectual retardation). The results on comprehension are clear: Receptive morphosyntax is commensurate with nonverbal mental age in affected boys [Paul et al., 1984] and men [Paul et al., 1987], although there is a need to address this issue in larger, more diverse samples (e.g., in terms of developmental levels).

Results for expression are less clear. Paul et al. [1984] studied three 10- to 13-year-olds with FXS, all of whom had mental retardation, and found delays in the morphosyntax of their conversational language relative to their nonverbal mental ages. In contrast, the males studied by Madison et al. [1986] displayed MLUs (i.e., mean length of utterances) equal to or in advance of mental-age expectations on average, and neither Ferrier et al. [1991] nor Paul et al. [1987] found differences in expressive morphosyntax between males with FXS and age- and cognitive-ability matched groups of males from several other diagnostic groups. Differences in the results of these studies may be attributable to variations in participant characteristics and the small sample sizes. Moreover, interpretation of the studies is complicated by the lack of appropriately matched typically developing comparison groups.

Research on the morphosyntactic development of females with FXS is virtually nonexistent [Dykens et al., 1994]. Madison et al. [1986], however, did study the members of one extended family that included six females whose IQs fell in the average to moderate range of mental retardation. Although the MLUs of most of the adult females tended to be quite high, the one young girl studied achieved an MLU far lower than expected from either her nonverbal mental age or receptive language age.

In closing this section, it is important to note that the methods of the studies reviewed have been limited in two respects. First, the data collected typically have been summarized by only a few rather gross indices that collapse across performance on many different morphosyntactic elements and rules (e.g., MLU). This has made it impossible to determine whether some aspects of morphosyntax are more impaired than others in males with FXS. More importantly, such measures tell us little about the strategies used by individuals with FXS to learn morphosyntax. Identification of these strategies requires analysis of the sequence of acquisition of specific forms or of errors in the use of specific forms. Second, expressive language samples have been collected almost exclusively in conversational contexts that are poorly standardized in terms of materials, activities, and the behavior of the conversational partner. Without some degree of standardization, it is difficult to interpret comparisons across diagnostic groups or individuals [Abbeduto et al., 1995]. The heavy reliance on conversational samples also has limited the generalizability of results. In fact, there are other naturally occurring language tasks (e.g., story telling) that require expressive language, and morphosyntactic aspects of expressive language vary considerably across tasks for many diagnostic groups [Abbeduto et al., 1995; Dollaghan et al., 1990].

Communication

In this section, we consider the ability of individuals with FXS to communicate with others through language. Problems in communication are to be expected in light of the speech and language impairments already described—individuals with FXS have fewer, less well-developed linguistic tools available for communication than do similarly aged, typically developing individuals. Communication problems also are to be expected from the cognitive and social-emotional limitations associated with FXS because communication draws heavily on such *supporting competencies* [Abbeduto and Rosenberg, 1987]. Communication, however, also requires *pragmatic* skills and knowledge, which are specific to the task of communication [Abbeduto and Rosenberg, 1987]. Pragmatics include, for example, knowledge of the procedures for taking turns at talking [Sack et al., 1974] and the ability to solicit the information needed to resolve comprehension failures [Clark, 1996]. It appears that persons with FXS have special difficulty in acquiring and using pragmatic skills. Simply put, their communication is often less adequate than expected on the basis of their speech, language, cognitive, and social-emotional impairments.

This conclusion is supported by studies of *adaptive behavior*. Adaptive behavior refers to the ability to meet age-appropriate demands imposed by the daily life tasks typical for the culture [Dykens, 1995]. Many such tasks require communication and, thus, communicative behaviors are included in measures of adaptive behavior [Dykens, 1995]. In fact, the Vineland Adaptive Behavior Scales (VABS) [Sparrow et al., 1984], which is a commonly used informant measure [Dykens, 1995], yields scores in four domains, one of which is Communication. Interestingly, the only longitudinal data available on communication in FXS come from studies of adaptive behavior.

The scores of males with FXS are significantly below chronological age expectations for all domains of the VABS, including communication [Dykens, 1995]. In fact, the VABS scores of affected males are closer to their mental ages than to their chronological ages [Dykens et al., 1988]. Although problems in communication characterize males with FXS throughout development, studies of adaptive behavior suggest that these problems may become more severe in adolescence. In adolescence, the scores of affected males on the Communication and Socialization domains of the VABS begin to lag behind those on Daily Living Skills [Dykens et al., 1989, 1994, 1996; Weigers et al., 1993]. The cause of this change during adolescence is not known [Dykens, 1995]. Perhaps adolescence

brings communication (and socialization) tasks that increasingly involve unfamiliar people and settings. Males with FXS find unfamiliar social situations to be stressful [Cohen, 1995] and their communication may suffer as a result (see below).

In an attempt to better understand the nature of these communication problems, researchers have turned to direct observation of the behavior of affected males in either naturally occurring or semistructured social interactions. In these studies, males with FXS consistently perform below chronological age expectations on virtually all dimensions of communication examined. In fact, there is evidence that they perform more poorly than do developmental level-matched individuals with other diagnoses (e.g., autism, Down syndrome, nonspecific mental retardation) on some dimensions of communication, including the overuse of highly routinized phrases [e.g., Madison et al., 1996; Paul et al., 1987; Sudhalter et al., 1990] and the production of utterances that are only loosely related (i.e., tangential) to the conversational topic [Sudhalter, 1996].

Most notable among the findings to date, however, are those concerning perseveration (i.e., excessive self-repetition of a word, phrase, sentence, or topic). Perseveration is frequent in the language production of many males with FXS [Borghgraef et al., 1987; Hanson et al., 1986; Sudhalter et al., 1990; but see Paul et al., 1987]. In fact, males with FXS have been found to engage in more self-repetition than do age- and IQ-matched males with Down syndrome or with nonspecific forms of mental retardation [Ferrier et al., 1991; Reiss and Freund, 1992; Wolf-Schein et al., 1987]. Moreover, males with FXS who do not meet diagnostic criteria for autism are more likely to produce self-repetitions than are non-FXS males with autism [Ferrier et al., 1991]. Such findings suggest that perseveration may be unique to FXS, although comparisons with a wider range of mental retardation syndromes than studied to date are needed to decide the issue. Interestingly, males with FXS—at least those without autism—do not engage in frequent echolalia (i.e., repetition of the linguistic contributions of other people [Ferrier et al., 1991]), which suggests that the perseveration observed in FXS does not reflect a general tendency to repeat any previous behavior. In a later section we consider research on the cause(s) of perseveration.

In concluding this section, it is important to note several limitations of the research on pragmatics. First, little research has been conducted on the communication problems of females with FXS, although it has been suggested that they display a run-on, disorganized, and tangential style of talking that is related to their executive function deficits [Benetto and Pennington, 1996; Mazzocco et al., 1993; Sobesky et al., 1996]. Second, communication has been assessed almost exclusively within a single context—conversation—and with a limited range of partners—almost always a familiar caregiver or an experimenter. But communication occurs in many other contexts (e.g., story telling, entering the ongoing activities of others) and with a variety of partners (e.g., peers, teachers), each of which requires somewhat different skills and knowledge [Rosenberg and Abbeduto, 1993]. The ability of individuals with FXS to communicate in these other contexts and with other important partners remains to be determined. Third, there has been no serious attempt to characterize the ability of individuals with FXS to fulfill the requirements of the listener's role despite the fact that their attentional deficits make comprehension problems especially likely. And, finally, there have been few attempts to trace the emergence of the communicative problems of affected individuals over the course of development [Dykens et al., 1994].

Causes of Perseveration

Because of the pervasive, disruptive effects of perseveration on the conversations of males with FXS, researchers in this area have devoted considerable attention to its explanation. In this section, we briefly consider the four explanations that have been offered. The first can be termed the *deficient expressive morphosyntax* hypothesis [Sudhalter et al., 1991]. According to this hypothesis, perseveration represents a strategy for participating in conversation when a failure to master morphosyntax makes meaningful contributions all but impossible. The problem with this hypothesis is that it is not clear why perseveration rather than echolalia or some other pattern of suboptimal language performance should arise as a strategy for the individual with FXS. Nor is the hypothesis supported by the data: Sudhalter et al. [1991] did not find a correlation between measures of expressive syntactic maturity and the rate of perseveration in a group of 19 males with FXS.

The *word-retrieval deficit* hypothesis of Sudhalter et al. [1992] is the second explanation offered for the perseveration of FXS males. According to this hypothesis, perseveration is a strategy emerging from the need to talk in the face of an inability to find the words needed to express intended meanings. Sudhalter et al. [1992] tested this hypothesis by comparing the sentence-completion performance of males with FXS to typically developing boys and girls who were matched to them in terms of their communication ages as determined by the VABS. The sentences presented could be completed with a single word and differed as to whether they imposed high or low constraints on the word to be selected. Sudhalter et al. found that the males with FXS were more likely than the typically developing children to produce semantically incorrect lexical responses, especially for sentences with low constraints. They interpreted this finding as supporting the word-retrieval hypothesis. Note, however, that these findings demonstrate only that males with FXS have difficulties with both perseveration and word-retrieval, not that these two problems are causally related. Testing the word-retrieval hypothesis would require demonstrating that the rate of perseveration is correlated with the rate of word-retrieval difficulties.

The third hypothesis is that perseveration is a reflection of *hyperarousal*. Both Cohen [1995] and Belser and Sudhalter [1995] have argued that males with FXS are excessively aroused by various classes of stimuli, especially those that include an interpersonal component, and that this heightened arousal causes the high rates of perseveration. In support of this hypothesis, they point out that perseveration co-occurs with a variety of nonverbal behaviors reflective of anxiety, including self-stimulation (e.g., hand flapping) and social avoidance (e.g., actively avoiding eye contact with others). These anxiety-related behaviors also occur at higher rates in males with FXS than in age- and IQ-matched males with Down syndrome [Belser and Sudhalter, 1995] and increase in socially stressful situations [Cohen, 1995]. In a direct test of this hypothesis, Belser and Sudhalter found that the skin conductance levels of two males with FXS were higher when their conversational partner initiated eye contact than when eye contact was not initiated. Belser and Sudhalter also found no variation in skin conductance across the eye contact conditions for two control participants, one of whom had Down syndrome and one of whom had ADHD. Because of the small sample size, however, the generalizability of the relationships observed by Belser and Sudhalter and their specificity to FXS

require further study. It is also necessary to specify the psychological mechanisms by which hyperarousal exerts its effects and, thereby, why this particular pattern of linguistic performance occurs rather than some other pattern of suboptimal performance [see Cohen, 1995, for some interesting suggestions in this regard].

The final hypothesis relates perseveration to executive function deficits and frontal lobe dysfunction. Executive function deficits have been well documented for females with FXS [Mazzocco et al., 1993; Sobesky et al., 1996] and are suspected in males with FXS, although their deficits have been more difficult to measure because of their lower levels of intellectual functioning. Executive function deficits are thought to reflect frontal lobe dysfunction and deficits in inhibition [Bennetto and Pennington, 1996]. A lack of appropriate inhibition of a high-strength response and repetition of that response could lead to perseveration. In fact, neuroimaging studies have demonstrated that the caudate, which is involved in the frontal circuits necessary for effective functioning, is enlarged in males (and females) with FXS [Abrams and Reiss, 1995]. It is thought that enlargement of the caudate may reflect a failure of the processes involved in pruning neuronal connections [Comery et al., 1997; Reiss et al., 1994, 1995a,b]. It is possible that these problems in neuronal connectedness facilitate activation of high-strength linguistic responses and without appropriate frontal inhibition, perseveration could result. Problems in excessive neuronal connectedness also may be the basis of the hyperarousal associated with FXS.

In summary, the cause of perseveration in males with FXS is not clear. Although deficits in expressive morphosyntax and word-retrieval are not the basis of perseveration, deficits in other aspects of language may well be involved. The hyperarousal hypothesis is promising and offers the additional advantages of explaining several dimensions of the social behavior of affected males (e.g., self-stimulation and body orientation) and of connecting the verbal (i.e., perseveration) and nonverbal (e.g., gaze avoidance) dimensions of their communicative behavior. The frontal-executive function hypothesis promises to explain several dimensions of the FXS behavioral phenotype (e.g., the inability to inhibit responses to external as well as internal stimuli) and offers the advantage of tying together work on FMRP expression, brain development, and communicative behavior.

INTERVENTION

Because of the broad spectrum of involvement in FXS, it is important to individualize each therapy program to the child's strengths and weaknesses. Vastly different approaches must be utilized with the nonverbal child who has moderate retardation compared to a child who presents with only mild auditory processing problems and a mild deficit in comprehension. Nevertheless, the consistent problems described for males and females who are significantly affected by FXS warrant specific approaches in therapy. Suggestions about intervention, however, must be based only on clinical experience because data on treatment effectiveness are virtually nonexistent.

Medical intervention must be organized for the problems that impact speech and language development, including conductive hearing loss, significant attention problems or ADHD, and anxiety. Aggressive use of PE tubes for a conductive hearing loss is essential in early childhood [Hagerman et al., 1987]. ADHD can be significantly improved with medication, including stimulants and/or clonidine [Hagerman, 1996b; Hagerman et al., 1988, 1995]. These medications can make a dramatic difference in the ability of a child with FXS to sit and focus on the language intervention. Stimulants also improve auditory processing and motor coordination, which can impact oral motor coordination [Barkley, 1990]. Because anxiety can worsen perseveration and interfere with speech production [Sudhalter, 1992], aggressive treatment of anxiety is essential. The use of selective serotonin reuptake inhibitors (SSRIs) can dramatically decrease anxiety and improve mood [Hagerman, 1996a]. The first SSRI on the market, Prozac, has a significant activation effect which may improve social interactions and in some cases social aspects of language [Hagerman et al., 1994a; Kramer, 1993]. Prozac also is the treatment of choice for selective mutism [Black and Uhde, 1994].

Children with FXS demonstrate low tone in the trunk as well as the oral area. Poor trunk support can sometimes lead to ''fixing'' oral structures in an attempt to gain needed stability. Poor separation of tongue, lip, and jaw movements then occurs, affecting sound production skills. Working with an occupational therapist (OT) and physical therapist (PT) on strengthening stability in the trunk may benefit speech production. Increased oral tone can be achieved through hands-on oral resistance exercises or through more adaptive activities using blow toys and whistles or foods of variable textures. Blow toys such as harmonicas, kazoos, and various other ''action'' whistles need differing amounts of tongue and lip strength to activate. Additionally, the graded respiration needed to work these whistles can help regulate arousal state [Oetter et al., 1995].

Snacking on crunchy and chewy foods such as Bazooka bubble gum, fruit leather, bagels, and pretzels, or chewing on rubber tubing can help children with FXS achieve increased jaw stability and may decrease oral defensiveness and gag reflexes. Direct deep pressure input through massage to the face, lips, and gums under the guidance of a speech-language pathologist or OT also may help reduce oral defensiveness.

A significant concern in the development of children with FXS is the IQ decrease over time in approximately 30% of cases [Wright-Talamante et al., 1996]. Because cognitive capabilities are essential for acquiring new language skills and using them in communication, abstract reasoning skills should be a focus in language therapy. For preschool and kindergarten children, early reasoning concepts, including sorting and categorizing, can be topics for therapy, with more complex reasoning tasks addressed as the individual with FXS matures and in high-functioning individuals.

For the most severely involved nonverbal individual with FXS, the use of combined speech and language therapy and occupational therapy is helpful [Scharfenaker et al., 1996]. The utilization of movement, rhythm, and music with sensory integration techniques provided by an OT and singing may help to stimulate language. A total communication approach in which signing is used as a bridge to speech also can facilitate language development. Augmentative communication devices, ranging from a communication picture board to computers, are also helpful. Computer software helpful for children with FXS [Scharfenaker et al., 1996b] and computer technology resource centers in the United States can be found in Scharfenaker et al. [1996c].

Young children with FXS and moderate to severe retardation often benefit from training programs designed for children with severe autism. The TEAACH program from North Carolina and other programs for autistic children that emphasize language development and social interaction [Rogers et al., 1986, 1991] are often helpful for children with FXS. In the case of more mildly affected children, milieu approaches,

which introduce new language forms in the context of naturally occurring attempts to communicate [Rosenberg and Abbeduto, 1993], should be used over more didactic approaches whenever possible.

Utilization of the imitation strengths in FXS can help to improve articulation and social skills by modeling appropriate speech in social settings. Individuals with FXS may also have intense interest areas that can be pulled into therapy to improve their attention and willingness to verbalize. Themes of interest can be the basis of language stimulation. Word processors that utilize visual and auditory feedback are particularly motivating for expanding written language.

Pragmatics must be an important therapy focus and may be best treated in a group therapy situation. Again, milieu rather than didactic approaches should be used whenever possible. Intervention can also include field trips to restaurants or stores to develop the language skills needed in these highly scripted events. As the individual with FXS moves into adolescence and adulthood, the pragmatic aspects of various vocational settings should be addressed in therapy and tied to job skills training. Intervention techniques developed for other populations of adults with mental retardation [e.g., Calculator and Bedrosian, 1988] might prove useful for adults with FXS as well.

FUTURE RESEARCH

Despite the considerable research conducted on the language and related problems associated with FXS, more work is needed. Here are our suggestions for future research.

1. There is a desperate need for more research on the language and communication problems of females with FXS. Many of the language problems described for males with FXS are apt be shared with females (albeit in less severe forms, on average). Nevertheless, differences in the cognitive and social-emotional development of affected males and females, as well as the different life histories normally experienced by males and females in our culture, make it likely that there will be gender-specific language and communication problems as well.
2. We know little about the developmental course of language in FXS. This is unfortunate in light of clear evidence that cognitive and social functioning decline during the adolescent and early adult years. These declines, together with a demand for more abstract forms of language in school and in peer relationships during adolescence, suggest that the language problems of individuals with FXS may worsen over the course of development. Both cross-sectional and longitudinal data are needed, especially those focused on the transition into adolescence.

Recent neuroimaging research, however, has uncovered changes in many brain structures with ties to many psychological functions. Establishing the connections between these and other atypical neural patterns and the language and connection problems of individuals with FXS is an important challenge for future research.

3. Much of the research to date has focused on determining how far individuals with FXS have progressed in language and communication relative to some standard (e.g., developmental level-matched peers). What is lacking, however, are data on the strategies that these individuals use to acquire new language skills. Ultimately, effective intervention for individuals with FXS will require data on learning strategies because it is those strategies that must be improved if we are to prevent some of the language and communication problems that characterize these individuals.
4. There is a need for data on the ability of persons with FXS to meet the communicative challenges of the varied language tasks that they encounter in school, at home, and in the workplace. Research to date has focused almost exclusively on conversation with familiar caregivers or with an experienced researcher or clinician. Future research should examine tasks such as narration, entering ongoing play groups, academically oriented problem-solving tasks, and non-face-to-face interactions such as talking on the telephone. Partners should be more varied as well, and include teachers, peers, and adults who vary in their familiarity with the participant. Such variations in task and partner are associated with differing language and communication demands [Rosenberg and Abbeduto, 1993] and may uncover heretofore hidden communication impairments or strengths in individuals with FXS.
5. Several language and communication problems have been hypothesized to be unique to FXS (e.g., perseveration). These hypotheses about syndrome uniqueness have been based largely on comparisons with autism, Down syndrome, or nonspecific forms of mental retardation. Additional data involving comparisons with a wider variety of mental retardation syndromes are needed to confirm these hypotheses.
6. Explaining the within-group variability in language and communication problems seen in FXS will require that we look to variations at the molecular genetic level. Variations in FMRP expression have already been tied to some features of the behavioral phenotype [Hagerman, 1996a; Tassone et al., 1997]. It seems likely that ties to language and communication problems also exist.
7. There is a need to examine the relations between atypical patterns in brain structure and function and the development and use of language. We have already noted the possibility that executive function deficits and frontal lobe dysfunction may play a role in the per-

severation typical of males with FXS. Recent neuroimaging research [Abrams and Reiss, 1995], however, has uncovered changes in many brain structures (e.g., the caudate nucleus, hippocampus, and thalamus) with ties to many psychological functions (e.g., executive function, attention, emotional control, motor programming). Establishing the connections between these and other atypical neural patterns and the language and communication problems of individuals with FXS is an important challenge for future research.

8. There are several language-related problems that have been observed clinically, but that have yet to be investigated systematically. Two examples are selective mutism (i.e., the failure to speak in selected contexts) and self-talk (i.e., talking aloud but not for purposes of communicating with others). Selective mutism has been observed in some girls with FXS and may reflect the debilitating effects of anxiety on the use of existing language and communication skills. Research verifying this relationship is needed, as is research on the role of SSRIs in alleviating this condition. Self-talk has been noted in many individuals with FXS, especially males. It has many interesting characteristics, including shifts in register and voice. It also often takes the form of ''mumbling.'' There is a need to document the frequency of self-talk as well as to determine its functions for the individual and the conditions that elicit it. Such research is needed before decisions can be made about whether and how to modify the self-talk of affected individuals.
9. There is an urgent need for controlled outcome studies regarding specific therapy approaches in FXS. Clinically, we have seen the combined approaches of medication, occupational therapy, and speech and language therapy to work well synergistically, although, again, data are lacking for outcome research.
10. Many families and researchers are looking to the future for the benefits of protein therapy or gene therapy in FXS. However, the hurdles to be overcome before protein or gene therapy becomes a reality are monumental [Rattazzi and Ioannou, 1996]. Until that time, new pharmacological interventions will no doubt be more helpful for enhancing cognitive function. The nootropics that may improve memory and learning through enhancement of cholinergic systems are presently undergoing animal studies. These may prove to be useful in FXS along with other medication innovations.
11. And finally, our focus here has been on those individuals with FXS who develop some language. In fact, some severely affected individuals, particularly males, fail to develop spoken language at all. Clinical experience suggests that this failure to speak is not solely a function of the degree of mental retardation characterizing the individual. It is important to identify the predictors of the transition into spoken communication so that we can identify individuals most at risk as well as develop interventions to promote their acquisition of spoken language. ■

ACKNOWLEDGMENTS

Preparation of this article was supported by National Institute of Child Health and Human Development grants R01 HD24356 to L. Abbeduto and P30 HD03352 to the Waisman Center and by grants MCJ089413 from Maternal and Child Health and 12-FY96-0492 from the March of Dimes awarded to Dr. Hagerman.

REFERENCES

Abbeduto L, Rosenberg S. Linguistic communication and mental retardation. In: Rosenberg S, ed. Advances in applied psycholinguistics. Vol. 1: Disorders of first language development. Cambridge: Cambridge University Press, 1987:76–125.

Abbeduto L, Benson G, Short K, et al. Effects of sampling context on the expressive language of children and adolescents with mental retardation. Ment Retard 1995;33:279–288.

Abrams MT, Reiss AL. The neurobiology of fragile X syndrome. Ment Retard Dev Disabil Res Rev 1995;1:269–275.

Barkley RA. Attention Deficit Hyperactivity Disorder: a handbook for diagnosis and treatment. New York: Guilford Press, 1990.

Barrett M. Early lexical development. In: Fletcher P, MacWhinney B, eds. The handbook of child language. Oxford: Blackwell, 1995:362–392.

Baumgardner T, Reiss AL, Freund LS, et al. Specifications of the neurobehavioral associations in males with fragile X syndrome. Pediatrics 1995;95:744–752.

Belser RC, Sudhalter V. Arousal difficulties in males with fragile X syndrome: A preliminary report. Dev Brain Dysfunct 1995;8:270–279.

Bennetto L, Pennington BF. The neuropsychology of fragile X syndrome. In: Hagerman RJ, Cronister AC eds. Fragile X syndrome: diagnosis, treatment, and research. 2nd edition. Baltimore, MD: Johns Hopkins University Press, 1996:210–248.

Black B, Uhde TW. Treatment of elective mutism with fluoxetine: A double blind placebo controlled study. J Am Acad Child Adoles Psychiatry 1994;33:1000–1006.

Borghgraef M, Fryns JP, Dielkins A, et al. Fragile X syndrome: A study of the psychological profile in 23 prepubertal patients. Clin Genet 1987;32:179–186.

Brown WT, Jenkins EC, Friedman E, et al. Fragile X and autism: A multicenter survey. Am J Med Genet 1986;23:341–352.

Calculator SN, Bedrosian JL, eds. Communication assessment and intervention for adults with mental retardation. Boston: Little, Brown, 1988.

Clark EV. Later lexical development and word formation. In Fletcher P, MacWhinney B (eds): The handbook of child language. Oxford: Blackwell, 1995:393–412.

Clark HH. Using language. New York: Cambridge University Press, 1996.

Cohen IL. A theoretical analysis of the role of hyperarousal in the learning and behavior of fragile X males. Ment Retard Dev Disabil Res Rev 1995;1:286–291.

Cohen IL, Sudhalter V, Pfadt A, et al. Why are autism and the fragile X syndrome associated? Conceptual and methodological issues. Am J Hum Genet 1991;48:195–202.

Comery TA, Harris JB, Willems PJ, et al. Abnormal dendritic spines in fragile X knockout mice: Maturation and pruning deficits. Proc Natl Acad Sci USA 1997;94:5401–5404.

Cromer R. A case study of dissociations between language and cognition. In: Tager-Flusberg H, ed. Constraints on language acquisition: Studies of atypical children. Hillsdale, NJ: Erlbaum, 1994:141–153.

deVries BBA, Wiegers AM, Smits APT, et al. Mental status of females with an FMR1 gene full mutation. Am J Hum Genet 1996;58: 1025–1032.

Dollaghan CA, Campbell TF, Tomlin R. Video narration as a language sampling context. J Speech Hear Res 1990;55:582–590.

Dykens EM. Adaptive behavior in males with fragile X syndrome. Ment Retard Dev Disabil Res Rev 1995;1:281–285.

Dykens EM, Leekman J, Paul R, et al. Cognitive, behavioral, and adaptive functioning in fragile X and non-fragile X retarded men. J Autism Dev Disord 1988;18:41–53.

Dykens EM, Hodapp RM, Leckman JF. Adaptive and maladaptive functioning of institutionalized and noninstitutionalized males with fragile X syndrome. J Am Acad Child Adolesc Psychiatry 1989;28:427–430.

Dykens EM, Hodapp RM, Ort SI, et al. Trajectory of adaptive behavior in males with fragile X

syndrome. J Autism Dev Disord 1993;23:135–145.
Dykens EM, Hodapp RM, Leckman JF. Behavior and development in fragile X syndrome. Thousands Oak, CA: Sage, 1994.
Dykens EM, Ort S, Cohen I, et al. Trajectories and profiles of adaptive behavior in males with fragile X syndrome: Multicenter studies. J Autism Dev Disord 1996;26:287–301.
Ferrier LJ, Bashir AS, Meryash DL, et al. Conversational skills of individuals with fragile-x syndrome: A comparison with autism and Down syndrome. Dev Med Child Neurol 1991;33:776–788.
Freund LS, Reiss AL, Abrams M. Psychiatric disorders associated with fragile X in the young female. Pediatrics 1993;91:321–329.
Freund LS, Peebles CD, Aylward E, et al. Preliminary report on cognitive and adaptive behaviors of preschool aged males with fragile X. Dev Brain Dys 1995;8:242–251.
Fryns JP, Haspeslagh M, Dereymaeker AM, et al. A peculiar subphenotype in the fra(X) syndrome: Extreme obesity, short stature, stubby hands and feet, diffuse hyperpigmentation. Further evidence of disturbed hypothalamic function in the fra(X) syndrome? Clin Genet 1989;32:388–392.
Gleitman LR, Gillette J. The role of syntax in verb learning. In Fletcher P, MacWhinney B (eds): The handbook of child language. Oxford: Blackwell, 1995:413–428.
Goldson E, Hagerman RJ. Fragile X syndrome and failure to thrive. AJDC 1993;147:605–607.
Hagerman RJ. Molecular and clinical correlations in fragile X syndrome. Ment Retard Dev Disabil 1995;1:276–280.
Hagerman RJ. Physical and behavioral phenotype. In: Hagerman RJ, Cronister A, eds. Fragile X syndrome: diagnosis, treatment, and research. 2nd edition. Baltimore, MD: Johns Hopkins University Press, 1996a:3–87.
Hagerman RJ. Medical follow-up and psychopharmacology. In: Hagerman RJ, Cronister A, eds. Fragile X syndrome: diagnosis, treatment, and research. 2nd edition. Baltimore, MD: Johns Hopkins University Press, 1996b:283–331.
Hagerman RJ, Altshul-Stark D, McBogg P. Recurrent otitis media in boys with the fragile X syndrome. Am J Dis Child 1987;141:184–187.
Hagerman RJ, Murphy MA, Wittenberger M. A controlled trial of stimulant medication in children with fragile X syndrome. Am J Med Genet 1988;30:377–392.
Hagerman RJ, Jackson C, Amiri K, et al. Fragile X girls: Physical and neurocognitive status and outcome. Pediatrics 1992;89:395–400.
Hagerman RJ, Fulton MJ, Leaman A, et al. Fluoxetine therapy in fragile X syndrome. Dev Brain Dysfunt 1994a;7:155–164.
Hagerman RJ, Hull CE, Safanda JF, et al. High functioning fragile X males: Demonstration of an unmethylated, fully expanded FMR-1 mutation associated with protein expression. Am J Med Genet 1994b;51:298–308.
Hagerman RJ, Riddle J, Roberts LS, et al. A survey of the efficacy of clonidine in fragile X syndrome. Dev Brain Dys 1995;8:336–344.
Hanson DM, Jackson A, Hagerman R. Speech disturbances (cluttering) in mildly impaired males with Martin-Bell/Fragile X syndrome. Am J Med Genet 1986;23:195–206.
Imbert G, Mandel J. The fragile X mutation. Ment Retard Dev Disabil 1995;1:251–262.
Kent RD. Speech intelligibility and communicative competence in children. In: Kaiser AP, Gray DB, eds. Enhancing children's communication: Research foundations for intervention. Baltimore, MD: Brooks, 1993:223–239.
Kramer PD. Listening to Prozac. New York: Viking/Penguin, 1993.
Lachiewicz AM. Females with fragile X syndrome: A review of the effects of an abnormal gene. Ment Retard Dev Disabil Res Rev 1995;1: 292–297.
Lachiewicz AM, Hoegerman SF, Holmgren G, et al. Association of the Robin sequence with the fragile X syndrome. Am J Med Genet 1991;41:275–278.
Loesch DZ, Huggins RM, Hoang NH. Growth in stature in fragile X families: A mixed longitudinal study. Am J Med Genet 1995;58:249–256.
Lowe F, Schopmeyer B, Kaye S. Combined treatment. In Schopmeyer BB, Lowe F (eds): The fragile X child. San Diego: Singular Publishing, 1992:173–195.
Madison LS, George C, Moeschler JB. Cognitive functioning in the fragile-X syndrome: A study of intellectual, memory, and communication skills. J Ment Defic Res 1986;30:129–148.
Mazzocco M, Pennington B, Hagerman R. The neurocognitive phenotype of female carriers of fragile X: Further evidence for specificity. J Dev Behav Pediatr 1993;14:328–335.
Merenstein SA, Sobesky WE, Taylor AK, et al. Molecular-clinical correlations in males with an expanded FMR1 mutation. Am J Med Genet 1996;64:389–394.
Newell K, Sanborn B, Hagerman R. Speech and language dysfunction in the fragile X syndrome. In Hagerman RJ, McBogg PM (eds): The fragile X syndrome: diagnosis, biochemistry, and intervention. Dillon, CO: Spectra, 1983:175–200.
Neimi J, Vilkman E, Ikonen U. Fragile X speech in Finnish: Phonological observation. In: Niemi J, Koiveselka-Sallienene, eds. Neurolinguistic papers: proceedings of the 2nd Finnish Conference of Neurolinguistics, 1985.
Oetter P, Richter E, Frick S. M.O.R.E.—Integrating the mouth with sensory and postural functions, 2nd edition. Hugo, MN: PDP Press, 1995.
Oostra BA. FMR1 protein studies and animal model for fragile X syndrome. In: Hagerman RJ, Cronister AC, eds. Fragile X syndrome: diagnosis, treatment, and research. 2nd edition. Baltimore, MD: Johns Hopkins University Press, 1996:193–209.
Palmer KK, Gordon JS, Coston GN, et al. Fragile X syndrome: Its relation to speech and language disorders. Proceedings, Greenwood Genetic Center 1988;7:93–97.
Partington MW. The fragile X syndrome. II. Preliminary data on growth and development in males. Am J Med Genet 1984;17:175–194.
Paul R, Cohen DJ, Breg WR, et al. Fragile X syndrome: Its relation to speech and language disorders. J Speech Hear Disord 1984;49:328–332.
Paul R, Dykens E, Watson M, et al. A comparison of language characteristics of mentally retarded adults with fragile X syndrome and those with non-specific mental retardation. J Autism Dev Disord 1987;17:457–468.
Pieretti M, Zhang F, Fu Y-H, et al. Absence of expression of the FMR-1 gene in fragile X syndrome. Cell 1991;66:817–822.
Rattazzi MC, Ioannou YA. Molecular approaches to therapy. In Hagerman RJ, Cronister A (eds): Fragile X syndrome: diagnosis, treatment, and research. 2nd edition. Baltimore, MD: Johns Hopkins University Press, 1996: 412–452.
Reiss AL, Freund L. Behavioral phenotype of fragile X syndrome: DSM-III-R autistic behavior in male children. Am J Med Genet 1992;43:35–46.
Reiss AL, Lee J, Freund L. Neuroanatomy of fragile X syndrome: The temporal lobe. Neurology 1994;44:1317–1324.
Reiss A, Abrams M, Greenlaw R, et al. Neuro developmental effects of the FMR-1 full mutation in humans. Nat Med 1995a;1:159–167.
Reiss AL, Freund LS, Baumgardner TL, et al. Contribution of the FMR1 gene mutation to human intellectual dysfunction. Nat Genet 1995b;11:331–334.
Rogers S, DiLalla. A comparative study of the effect of a development based preschool curriculum on young children with autism and young children with other disorders of behavior and development. TECSE 1991;11:29–47.
Rogers SJ, Herbision JM, Lewis HC, et al. An approach for enhancing symbolic communicative interpersonal functioning of young children with autism or severe emotional handicaps. J Dis Early Child 1986;10:135–148.
Rondal JA. Exceptional language development in Down syndrome: implications for the cognition-language relationship. Cambridge, UK: Cambridge University Press, 1995.
Rosenberg S, Abbeduto L. Language and communication in mental retardation: Development, processes, and intervention. Hillsdale, NJ: Erlbaum, 1993.
Rousseau F, Rouillard P, Morel M-L, et al. Prevalence of carriers of premutation-sized alleles of the FMR1 gene and implications for the population genetics of the fragile X syndrome. Am J Hum Genet 1995;57:1006–1018.
Rousseau F, Morel M-L, Rouillard P, et al. Surprisingly low prevalence of FMR1 premutation among males from the general population. Am J Hum Genet 1996;59(suppl A188): 1069.
Sacks H, Schegloff E, Jefferson G. A simple systematics for the organization of turn-taking in conversation. Language 1974;50:696–735.
Scarborough HS, Rescorla L, Tager-Flusberg H, et al. The relation of utterance length to grammatical complexity in normal and language-disordered groups. APS 1991;12: 23–45.
Schapiro MB, Murphy DGM, Hagerman RJ, et al. Adult fragile X syndrome: Neuropsychology, brain anatomy and metabolism. Am J Med Genet 1995;60:480–493.
Scharfenaker S, O'Connor R, Stackhouse T, et al. An integrated approach to intervention. In Hagerman RJ, Cronister A (eds): Fragile X syndrome: diagnosis, treatment, and research, 2nd edition. Baltimore, MD: Johns Hopkins University Press, 1996a:349–411.
Scharfenaker S, O'Connor R, Stackhouse T, et al. In: Hagerman RJ, Cronister A, eds. Fragile X syndrome: diagnosis, treatment, and research, 2nd edition. Baltimore, MD: Johns Hopkins University Press, 1996b:453–462.
Scharfenaker S, O'Connor R, Stackhouse T, et al. Appendix 2: Computer Technology Resource Centers. In: Hagerman RJ, Cronister A, eds. Fragile X syndrome: diagnosis, treatment, and research, 2nd edition. Baltimore, MD: Johns Hopkins University Press, 1996c: 463–466.
Schopmeyer BB. Speech and language characteristics in fragile X syndrome. In: Schopmeyer BB, Lowe F, eds. The fragile X child. San Diego: Singular Publishing, 1992:71–89.

Sobesky WE, Taylor AK, Pennington BF, et al. Molecular/clinical correlations in females with fragile X. Am J Med Genet 1996;64:340–345.

Sparrow SS, Balla D, Cichetti D. Vineland Adaptive Behavior Scales. Circle Pines, MN: American Guidance Service, 1984.

Sudhalter V. The language system of males with fragile X syndrome. In Hagerman RJ, McKenzie P (eds): 1992 international fragile X conference proceedings. Dillon, CO: Spectra Publishing, 1992:165–166.

Sudhalter V. The emergence of tangential language in fragile X. Paper presented at the 29th annual Gatlinburg Conference on Mental Retardation and Developmental Disabilities, Gatlinburg, TN, March 1996.

Sudhalter V, Cohen IL, Silverman W, et al. Conversational analyses of males with fragile X, Down syndrome, and autism: Comparison of the emergence of deviant language. Am J Ment Retard 1990;94:431–441.

Sudhalter V, Scarborough H, Cohen IL. Syntactic delay and pragmatic deviance in the language of fragile X males. Am J Med Genet 1991;38:493–497.

Sudhalter V, Maranion M, Brooks P. Expressive semantic deficit in the productive language of males with fragile X syndrome. Am J Med Genet 1992;43:65–71.

Turner G, Webb T, Wake S, Robinson H. Prevalence of the fragile X syndrome. Am J Med Genet 1996;64:196–197.

Verkerk AJ, Pierettl M, Sutcliffe JS, et al. Identification of a gene (FMR-1) containing a CGG repeat coincident with a breakpoint cluster region exhibiting length variation in fragile X syndrome. Cell 1991;65:905–914.

Vilkman E, Niemi J, Ikonen U. Fragile X speech phonology in Finnish. Brain Lang 1988;34:203–222.

Webb TP, Bundey S, Thake A, et al. The frequency of the fragile X chromosome among school children in Coventry. J Med Genet 1986;23:396–399.

Weigers AM, Curfs LM, Vermeer EH, et al. Adaptive behaviors in the fragile X syndrome: Profile and development. Am J Med Genet 1993;47:216–220.

Wolf-Schein EG, Sudhalter V, Cohen IL, et al. Speech-language and the fragile X syndrome: Initial findings. J Am Speech Hear Assoc 1987;29:35–38.

Wright-Talamante C, Cheema A, Riddle JE, et al. A controlled study of longitudinal IQ changes in females and males with fragile X syndrome. Am J Med Genet 1996;64:350–355.