

Autism Spectrum Disorder in Children and Adolescents With Fragile X Syndrome: Within-Syndrome Differences and Age-Related Changes

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Abstract

The Autism Diagnostic Interview-Revised (ADI-R) was used to examine diagnostic profiles and age-related changes in autism symptoms for a group of verbal children and adolescents who had fragile X syndrome, with and without autism. After controlling for nonverbal IQ, we found statistically significant between-group differences for lifetime and current autism symptoms for the Communication and Restricted Interests/Repetitive Behaviors domains, but not the Reciprocal Social Interaction domain. Effect sizes for differences in Reciprocal Social Interaction also were smaller than effect sizes for the other domains, with one exception. Overall, severity of autism symptoms improved with age for all participants, with the least improvement noted for Restricted Interests and Repetitive Behaviors. FMRP did not account for unique variance in autism symptoms over and above nonverbal IQ.

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Fragile X syndrome is the most common inherited cause of intellectual disability. In general, prevalence rates have been reported as 1 in 4,000 males and 1 in 8,000 females (Crawford, Acuna, & Sherman, 2001); however, recent studies have yielded rates closer to 1 in 2,500 (Fernandez-Carvajal et al., 2009; P. Hagerman, 2008). Fragile X syndrome is caused by an expansion of a repetitive CGG nucleotide sequence in the FMR1 gene, located on the X chromosome (Kaufmann & Reiss, 1999). This expansion causes methylation and transcriptional silencing of the gene, resulting in a reduction or absence of the protein that is normally produced (Kaufmann et al., 2004). This protein (FMRP) is critical for the regulation of processes involved in synaptic maturation, axonal guidance, and experience-dependent learn-

ing (Darnell, Warren, & Darnell, 2004; R. Hagerman, Ono, & Hagerman, 2005). Behaviors characteristic of autism are frequent in fragile X syndrome, with many individuals meeting diagnostic criteria for autism (R. Hagerman, 1999). Most estimates place the prevalence of autism in fragile X syndrome at 25%, although in recent studies in which researchers utilized diagnostic criteria for the full spectrum of autism disorders (i.e., inclusive of pervasive developmental disorder—not otherwise specified) they reported rates approaching 50% (Demark, Feldman, & Holden, 2003; Kaufmann et al., 2004; Philofsky, Hepburn, Hayes, Hagerman, & Rogers, 2004). In the present study, we were interested in within-syndrome differences in, and the age-related trajectories of, autism symptoms in fragile X syndrome.

Although the association between fragile X syndrome and autism has been well-documented, the developmental course of autism within fragile X syndrome is not well understood. It is not known whether the symptoms of autism are stable across development in fragile X syndrome or whether there is an abatement of symptoms with age as has been observed for idiopathic autism (Seltzer et al., 2003; Shattuck et al., 2007). The behavioral characteristics that distinguish between individuals with fragile X syndrome with and without a diagnosis of autism are not fully understood. We also lack data on the role of FMRP in autism symptomatology in fragile X syndrome. We designed the present study to address these gaps.

Autism Spectrum Disorder

Autism is a spectrum of behavioral characteristics observable before 3 years of age and characterized by impairments in reciprocal social interactions, language and communication, and repetitive and stereotyped behaviors and restricted interests (American Psychiatric Association, 1994). In contrast to fragile X syndrome, which is diagnosed through DNA testing, a diagnosis of autism is based on behavioral testing and clinical judgment relative to criteria specified in the *Diagnostic and Statistical Manual-Fourth Edition—DSM-IV* (American Psychiatric Association, 1994) and the 10th edition of the *International Classification of Diseases and Related Health Problems—ICD-10* (World Health Organization, 1992).

Although the characteristics of autism vary widely across individuals, poor modulation of eye contact in social interaction is the most widely reported behavioral feature of the disorder (Lord & Spence, 2006). The avoidance of eye gaze is also characteristic of individuals with fragile X syndrome and may contribute to the perceived similarity between the two disorders. Other commonalities between fragile X syndrome and autism include insistence on sameness, hand stereotypies, self-injurious behavior, and inappropriate and repetitive use of objects (Levitas et al., 1983).

Diagnostic Instruments

The recent development of standardized instruments for the diagnosis of autism spectrum disorders has allowed increased precision and

consistency in characterizing the differences between individuals with fragile X syndrome only and individuals with comorbid fragile X syndrome and autism (hereafter, fragile X/autism). The Autism Diagnostic Interview-Revised—ADI-R (LeCouteur, Lord, & Rutter, 2003) is widely regarded as one of the gold standards for the diagnosis of autism. This instrument closely follows the *DSM-IV* and *ICD-10* diagnostic criteria for autism and elicits information, through parent interview, relative to the three domains that define the disorder.

Most of the ADI-R items responses are scored for (a) the current degree of impairment and (b) the greatest impairment noted between ages 4 to 5 or ever in the individual's lifetime. Diagnostic classification is based on computation of an algorithm, composed of a subset of lifetime items (i.e., in reference to ages 4 to 5 or over). When administered to parents of older children and adolescents, the ADI-R offers the potential for examining symptom change retrospectively by comparing behaviors queried in the diagnostic items to queries about current behaviors. In fact, use of the ADI-R in this manner (Seltzer et al., 2003; Shattuck et al., 2007) has yielded results similar to those of prospective longitudinal studies of individuals with idiopathic autism (Howlin, Goode, Hutton, & Rutter, 2004). For the present study, we used the ADI-R to examine age-related symptom change for older children and adolescents with fragile X syndrome by comparing lifetime scores with scores reported for current behaviors.

Age-Related Changes in Symptoms of Autism

Although, by definition, autism is a lifelong disorder and social impairments persist in virtually all individuals diagnosed early in life, there is evidence of significant improvement in symptoms with age in idiopathic autism (Boelte & Poustka, 2000; Gilchrist et al., 2001; Piven, Harper, Palmer, & Arndt, 1996; Seltzer et al., 2003). Seltzer et al. examined diagnostic stability and patterns of symptom change over time by comparing current symptoms of autism with lifetime ratings as measured by the ADI-R in 405 individuals diagnosed with an autism spectrum disorder. Participants were between the ages of 10 and 53 years ($M = 22$) and did not have fragile X syndrome. Significantly fewer participants met diagnostic cutoffs based upon current behavior

than based upon lifetime ratings of past behavior (55% vs. 97%), and a general pattern of symptom abatement in all three ADI-R domains was observed. In a follow-up study, Seltzer and colleagues (Shattuck et al., 2007) conducted a prospective analysis of the current ADI-R profiles of 241 individuals at two time points across 4 years. The results were consistent with the retrospective analyses conducted by Seltzer et al. (2003), suggesting that retrospective analysis of ADI-R scores can be used to obtain a reliable index of age-related symptom change.

Cognitive Impairment and Symptoms of Autism

Cognitive ability is a robust correlate of symptom severity and a predictor of later social functioning and independent living status for adults with idiopathic autism (Howlin et al., 2004; Howlin, Mawhood, & Rutter, 2000). Individuals with autism who have IQs in the range of intellectual disability display slower growth in many cognitive domains (Sigman & McGovern, 2005), and they continue to manifest difficulty as adults in areas such as friendship, work, and independent living (Howlin et al., 2004). Such findings suggest the need to examine the association between autism symptoms and cognitive ability in individuals with fragile X syndrome because a high proportion of this population has intellectual disabilities and because their rate of cognitive development appears to decrease in later childhood and adolescence, as reflected in age-related declines in IQ (Kover, Abbeduto, Kim, & Brown, 2008; Hall, Burns, Lightbody, & Reiss, 2008).

Autism in Fragile X Syndrome

Profile of Symptoms

Results across several studies suggest that children with comorbid fragile X syndrome and autism differ in their symptom profiles from children with fragile X syndrome only, with the former being more similar to individuals with idiopathic autism than to individuals with fragile X syndrome only (Bailey et al., 1998; Demark et al., 2003; Lewis et al., 2006; Rogers, Wehner, & Hagerman, 2001). For example, Rogers et al. examined profiles of autistic behavior in children with fragile X syndrome who were 21 to 48 months of age. Participants received a diagnosis of autism if they met criteria on two of three diagnostic measures: the ADI-R, the Autism Diagnostic

Observation Schedule–ADOS (Lord, Rutter, DiLavore, & Risi, 1999), and a clinical diagnosis. Rogers et al. found no significant differences in ADI-R and ADOS total scores or individual domain scores between the autism only group and the group with comorbid fragile X syndrome and autism. Both groups with autism, however, differed from the fragile X syndrome only group in two ADI-R domains and all three ADOS domains.

Most researchers who have examined autism symptoms in individuals with fragile X syndrome have dichotomized their samples into those with and those without autism, without making distinctions within the broader autism spectrum. In an attempt to make a more fine-grained distinction, Kaufmann et al. (2004) used the ADI-R to characterize 56 mostly nonverbal young boys with fragile X syndrome (ages 3 to 8 years), as fragile X/autism, fragile X syndrome/autism spectrum disorder, or fragile X syndrome only. They found that the fragile X syndrome/autism spectrum disorder group and the fragile X syndrome only group differed significantly on Reciprocal Social Interaction domain scores, whereas the fragile X syndrome/autism spectrum disorder group and the fragile X/autism group differed significantly on Communication domain scores. This profile suggests that the diagnosis of an autism spectrum disorder in fragile X syndrome results largely from differences in social reciprocity and is not merely an artifact of communication challenges in fragile X syndrome. Kaufmann and colleagues have confirmed these results in a follow-up longitudinal study (Hernandez et al., 2009).

Although the Kaufmann et al. (2004) and Hernandez et al. (2009) studies add important information to the question of how characteristics of autism are distributed within the population of individuals with fragile X syndrome, the young age of their participants, their primarily nonverbal status, and the inclusion of only males limits the generalizability of these results. The present study provides an opportunity to extend previous findings by examining ADI-R profiles for a group of older children and adolescents with fragile X syndrome, including both males and females, who met the criterion for having verbal language status.

Age-Related Changes in Autism Symptoms in Fragile X Syndrome

We do not yet have a clear picture of symptom change with age in individuals with

fragile X syndrome. Some researchers suggest that similar to the trajectory observed for those with idiopathic autism, the symptoms of autism in fragile X syndrome abate with age (Baumgardner, Reiss, Freund, & Abrams, 1995; R. Hagerman, Jackson, Levitas, Rimland, & Braden, 1986; Reiss & Freund, 1992; Rogers et al., 2001). Most studies, however, have used cross-sectional comparisons and, thus, are subject to the confounding effect of cohort differences (Hatton et al., 2006). Moreover, there is some inconsistency even in the cross-sectional findings.

In a longitudinal study covering the age span of 1 to 14 years, Hatton et al. (2006) found small but significant age-related increases in symptom severity, as measured by the Childhood Autism Rating Scale–CARS (Schopler, Reichler, & Reynolds, 1988), for a sample of 116 children with fragile X syndrome. These investigators also found that of those 39 participants who exceeded the CARS cutoff for a diagnosis of autism at one or more measurement periods, only 13% improved with age to the point that they no longer exceeded the CARS cutoff. It is important to note that although the Hatton et al. cohort extended into early adolescence, most participants were quite young, with the mean age under 5 years at the initial visit.

In fact, there are few data regarding the age-related course of autism symptoms in fragile X syndrome during adolescence and into adulthood. In the only longitudinal study involving older individuals with fragile X syndrome, Sabaratnam, Murthy, Wijeratne, Payne, and Buckingham (2003) suggested that the symptoms of autism remain stable during adulthood. The mean age of participants in the Sabaratnam et al. study, however, was over 46 years. In addition, the investigators employed a brief caretaker interview that was not specifically designed to assess autism. It is possible that an examination of autism symptoms during an earlier developmental period and with a more appropriate and better validated measure, such as the ADI-R, would reveal a more nuanced picture of longitudinal symptom change.

Cognitive Impairment and Symptoms of Autism in Fragile X Syndrome

On average, cognitive abilities in individuals with comorbid fragile X syndrome and autism are lower relative to individuals with fragile X

syndrome only during childhood, and this profile continues into adolescence and early adulthood (Bailey, Hatton, Mesibov, Ament, & Skinner, 2000; Bailey, Hatton, Skinner, & Mesibov, 2001; Demark et al., 2003; Hernandez et al., 2009; Kau et al., 2004; Kaufmann et al., 2004; Kover et al., 2008; Lewis et al., 2006; Philofsky et al., 2004; Rogers et al., 2001). In turn, cognitive ability has been found to be positively correlated with FMRP levels (Dyer-Friedman et al., 2002; Kover et al., 2008; Loesch, Huggins, & Hagerman, 2004; Reiss, Freund, Baumgardner, Abrams, & Denckla, 1995; Tassone et al., 1999), although some investigators have failed to confirm this relationship (Skinner et al., 2005). Hall and colleagues (2008) recently demonstrated the relationship between IQ and FMRP maintains even after controlling for age and gender, suggesting a unique contribution of FMRP to cognitive ability.

The association between FMRP levels and symptoms of autism is unclear. Although Hatton et al. (2006) found a positive association between FMRP and autism symptoms using the CARS, they did not include IQ as a covariate in their analyses, leaving unresolved the question of whether FMRP accounts for unique variance in autism symptoms over and above the contribution of IQ. Other researchers have failed to detect a positive association between FMRP and autism severity (Bailey et al., 2000; Harris et al., 2008; Hessel et al., 2001). Loesch et al. (2007), however, found that both FMRP and FSIQ were significant predictors of ADOS Communication domain scores for full mutation females and that FMRP was a significant predictor for full mutation males.

Given the high degree of shared variance between FMRP and IQ, Hatton et al. (2006) suggested that null findings in measuring the relationship between FMRP and autism symptom severity may depend, in part, upon whether IQ is included as a covariate. In addition, the choice of instrument to measure the presence of autism symptoms may be critical for detecting such an association. Finally, the association between FMRP and autism symptoms may not be detected within samples of only male participants due to the truncated range of FMRP in males. In the present study, we investigated whether FMRP accounts for unique variance in predicting current symptoms of autism, over and above the contribution of nonverbal IQ, when the ADI-R is used to measure symptoms.

Research Questions

In summary, we addressed the following questions: (a) Which lifetime symptoms of autism distinguish participants with fragile X syndrome only from those with fragile X syndrome who meet diagnostic criteria for autism? (b) Which current symptoms of autism distinguish participants with fragile X syndrome only from those who meet diagnostic criteria for autism? (c) Within each diagnostic group, which symptoms of autism show significant improvement over time? (d) Which symptoms of autism best predict group membership? (e) Do FMRP levels account for unique variance in predicting current symptoms of autism, after controlling for nonverbal cognitive ability?

Method

Participants

Participants were 51 children and adolescents with fragile X syndrome who were part of a larger, longitudinal examination of language development in fragile X syndrome and Down syndrome. All were between the ages of 10 and 16 years at the time of data collection for the current study. They were recruited nationally

through mailings to professionals, attendance at national and regional parent meetings, postings to Internet listservs and websites, advertisements on nationally syndicated radio shows and in newspapers in selected urban areas, and through a university registry of families with children who had developmental disabilities.

The current sample included 35 males and 15 females, all of whom were native English speakers. Six families had 2 children participate; however, there were no sibling pairs in the fragile X/autism group. According to parent report, all participants used spoken language as their primary means of communication and produced three-word phrases on a daily basis. Participants were identified as having autism based on the diagnostic algorithm of the ADI-R as described in detail below. The participants with fragile X syndrome only ($n = 26$, 13 females) and fragile X/autism ($n = 24$, 2 females) did not differ significantly in age (see Table 1). As expected, however, individuals with fragile X/autism had significantly lower nonverbal mental ages and IQs and lower receptive and expressive language age-equivalent scores on standardized measures.

All participants had a diagnosis of fragile X syndrome confirmed through molecular genetic testing prior to entry into the study. We also

Table 1. Participant Characteristics

Characteristic	Fragile X only				Fragile X/autism			
	Female ($n = 13$)		Male ($n = 13$)		Female ($n = 2$)		Male ($n = 22$)	
	Mean	<i>SD</i>	Mean	<i>SD</i>	Mean	<i>SD</i>	Mean	<i>SD</i>
CA	12.35	1.57	13.60	1.85	11.04	0.59	12.89	1.71
Language age equivalents								
Receptive vocabulary ^a	10.65	2.49	7.63	2.68	7.41	1.29	6.04	2.16
Receptive grammar ^b	7.53	2.59	4.60	1.13	4.00	0.00	4.27	0.68
Expressive vocabulary ^c	9.43	2.27	6.35	2.24	6.50	0.59	4.95	1.57
Expressive syntax ^d	8.81	1.96	5.38 ^e	2.37	3.67	2.12	3.56	1.40
Nonverbal cognition								
IQ	70.46	14.33	48.38	10.45	53.00	7.07	42.96	6.63
Mean age equivalent	8.00	1.95	5.80	1.06	5.51	0.84	4.97	0.88
Maternal age	40.26	3.58	42.24	6.89	35.70	4.51	42.43	5.93
Mothers with college degree or higher (%)	46		54		50		48	

^aPeabody Picture Vocabulary Test, Third Edition. ^bTest for Reception of Grammar, Second Edition. ^cExpressive Vocabulary Test. ^dComprehensive Assessment of Spoken Language, Syntax Construction subtest. ^e $N = 12$.

confirmed the diagnosis through use of Southern Analysis and polymerase chain reaction (PCR) testing (Brown et al., 1993; Nolin et al., 2003) conducted on peripheral blood samples for all but 9 participants (2 declined to be retested and blood samples were not available for the other 7 participants for logistical reasons). All participants had the FMR1 full mutation, although 11 males were mosaic (in methylation status or repeat size). Using a sample of 200 cells for males and 400 cells for females and employing the method of Williamson et al. (1997) and Tassone et al. (1999), we found that the average proportion of cells that expressed the protein FMRP in participants with fragile X syndrome only was .04 ($SD = .09$, range = .00 to .30) for males and .48 ($SD = .05$, range = .34 to .51) for females. For those with fragile X/autism, average FMRP expression was .04 ($SD = .07$, range = .00 to .20) for males and .50 ($SD = .00$, range = .50 to .50) for females.

Assessments

Autism status. Autism status for the current study was based on the diagnostic algorithm of the ADI-R. Items from this measure elicit information relevant to early development as well as the domains of Reciprocal Social Interaction, Communication, and Restricted Interests and Stereotyped Behaviors. Individual ADI-R items are scored according to the examiner's judgment of the presence/absence or extent of a given behavior using a scale of 0 (behavior of the type specified not present), 1 (behavior present but not sufficiently severe or frequent to meet criteria for a score of 2), 2 (definite abnormality of the type specified), or 3 (definite abnormality of the type specified and marked in severity). Items are scored for the presence/extent of the behavior (a) during the 3 months immediately preceding the interview (current) or (b) between the ages of 4 to 5 years or ever in the targeted individual's lifetime (lifetime). Some items provide specific age periods for coding (e.g., friendships from 10 to 15 years of age).

Summary scores for current and lifetime ratings are calculated for each domain and provide a quantitative measure of the presence of autism symptoms. Items regarding developmental history are used to reflect the examiner's judgment as to age of onset. In the standard version of the ADI-R, a diagnostic algorithm, based upon domain cutoff scores for lifetime ratings, is calculated using 37 items that have been

shown to have the best discriminative validity between individuals with and those without autism (Lecavalier et al., 2006). In order to prevent a few items from contributing excessively to the calculation of the algorithm, examiners are instructed to convert scores of 3 to 2s. Given the eligibility criteria for the current study, all participants were considered to be verbal for purposes of ADI-R scoring. Domain cutoffs used in the current study to determine a classification of autism/no autism were those provided in the ADI-R for participants with verbal language status.

One of two research-reliable examiners interviewed the biological mothers of participants in the current study using an abbreviated version of the ADI-R, which contained 42 items (Seltzer et al., 2003; Shattuck et al., 2007). The protocol included 3 items designed to gather background and age of onset information and 37 items to compute domain scores for Reciprocal Social Interaction (16 items), Communication (13 items), and Restricted Interests and Repetitive Behaviors (8 items). These 37 items were queried lifetime ratings and constituted the diagnostic algorithm.

In this abbreviated version of the ADI-R, the examiners assessed current behavior using 29 items (11, 10, and 8 of the items in the Reciprocal Social Interaction, Communication, Restricted Interests and Repetitive Behaviors domains, respectively). Although an algorithm to determine diagnostic status based on current symptoms is not available, items for which both lifetime and current ratings were available were used to examine, retrospectively, age-related changes in autism symptoms and between-group differences in current symptoms of autism (e.g., mean scores for ADI-R domains and scores for individual lifetime and current items within each domain are presented in tables below).

Internal consistency. Because the ADI-R was not developed for the fragile X syndrome population, we examined internal consistency of its diagnostic algorithm items for the current sample. Chronbach's α values were .87, .81, and .67 for Reciprocal Social Interaction, Communication, and Restricted Interests and Repetitive Behaviors, respectively. The latter domain may have had slightly lower internal consistency because it contains the fewest items. The coefficients for this sample are similar to those obtained for the same domains by Lecavalier et al. (2006) for

individuals with idiopathic autism (i.e., .84, .76, and .54, respectively).

Interrater agreement. Interrater agreement was computed by having a second research-reliable examiner recode 25% (13) of the ADI-R protocols. We used Cohen's kappa, which corrects for chance agreement by considering base rates of the coded variables, and evaluated the resultant kappas using the benchmarks provided by Landis and Koch (1977): .81 to 1.00 (very good), .61 to .80 (substantial), .41 to .60 (moderate), and .21 to .40 (fair). The kappa for the diagnosis of autism was .58, which was the maximum value possible given the distribution of the rater's marginal scores (Cohen, 1969, p. 42). Kappas for lifetime ratings were 1.00, .70, and .68 for the Reciprocal Social Interaction, Communication, and Restricted Interests and Repetitive Behaviors domains, respectively. Kappa was at the maximum possible value for the latter two domains. Kappa for the ADI-R section used to assess whether symptoms of autism were evident before 36 months of age was .75, also the maximum possible value. Average percentage agreement exceeded 85% for the diagnosis of autism and for each lifetime domain score. Kappa was at the maximum possible value for 33 of the 40 individual lifetime items and for 17 of the 29 items for current behavior. The remaining kappa values ranged between .52 and .83; thus, none of the kappa values for the individual items fell below the moderate level of agreement. Average percentage agreement was 88% for individual lifetime items (range = 69% to 100%, and 89% for individual current items (range = 69% to 100%).

Nonverbal cognition. We administered the Brief IQ Screener (i.e., the Figure Ground, Form Completion, Sequential Order, and Repeated Patterns subtests) of the Leiter-R Visualization and Reasoning Battery (Miller & Miller, 1997). For each participant, age-equivalent scores across the four subtests were averaged to provide a mean age-equivalent, and scaled scores were summed to calculate a deviation IQ.

Procedure

We administered a battery of measures focusing on language and cognition to all participants. The ADI-R was administered to each participant's biological mother. This instrument was completed at the first annual visit for 47 participants and at the second annual visit, for 4

participants. Nonverbal cognitive and language scores were obtained concurrently with the time period in which the ADI-R was administered. We classified participants as fragile X/autism if they met the designated lifetime cutoff scores for all ADI-R domains, including age of onset. Lifetime and current ADI-R scores obtained for each domain are presented in Table 2. Means are reported separately for female and males; however, all analyses collapsed across gender. For all of the analyses in the following sections, we include the ADI-R item numbers corresponding to the symptoms of autism that were identified as significantly differently between the groups, showing age-related changes or predicting group membership.

Results

Diagnostic Symptoms of Autism

We examined between-group differences for each ADI-R domain using separate multivariate analyses of covariance. Group (fragile X syndrome only, fragile X/autism) was a fixed factor and diagnostic algorithm (lifetime) item scores for the individual ADI-R domain under consideration were the dependent variables. Nonverbal IQ was a covariate. Significant multivariate tests were followed by simple effects testing, using Holm's sequentially rejective procedure (Holm, 1979). One-tailed significance levels were used because we expected participants with fragile X/autism to attain higher scores on all ADI-R items than participants with fragile X syndrome only.

Between-group differences in diagnostic algorithm scores from the Reciprocal Social Interaction domain of the ADI-R failed to reach significance when controlling for differences in nonverbal IQ, $F(16, 33) = 1.49$, $p = .16$, *partial* $\eta^2 = .42$. The covariate-adjusted mean scores for algorithm items in this domain are presented in Table 3.

Communication

There was a significant effect of group on diagnostic algorithm scores for the Communication (C) domain, $F(13, 36) = 3.63$, $p < .001$, *partial* $\eta^2 = .57$. This represents a large effect size and indicates that 57% of the variance in algorithm scores for this domain was accounted for by group membership. The univariate tests revealed significant differences for six symptoms of autism: pointing to express interest (C7), stereotyped

Table 2. Lifetime and Current Autism Diagnostic Interview-Revised (ADI-R) Domain Scores

ADI-R ratings	Fragile X only						Fragile X/autism					
	Female (n = 13)		Male (n = 13)		Total (n = 26)		Female (n = 2)		Male (n = 2)		Total (n = 24)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Lifetime												
Social Interaction ^a	6.46	4.46	11.46	4.27	8.96	4.98	13.50	0.71	17.83	4.93	17.48	4.87
Communication ^b	5.31	3.25	6.77	2.31	6.04	2.86	12.50	6.36	14.48	4.03	14.32	4.11
Behavior ^c	2.08	1.32	3.31	1.75	2.69	1.64	8.00	0.00	6.39	2.61	6.52	2.54
Current												
Social Interaction	2.62	2.90	4.62	2.40	3.62	2.80	6.00	5.66	6.91	3.13	6.84	3.22
Communication	1.92	1.44	2.31	1.70	2.12	1.59	5.00	0.00	6.74	3.00	6.60	2.92
Behavior	1.38	1.12	2.54	1.13	1.96	1.25	8.00	0.00	5.39	2.59	5.60	2.58

^aAlgorithm cutoff = 10. ^bAlgorithm cutoff = 8. ^cAlgorithm cutoff = 3.

utterances/delayed echolalia (C1), nodding (C8), head shaking (C9), spontaneous imitation of actions (C11), and imitative social play (C13). The covariate-adjusted means for all Communication algorithm items are presented in Table 4.

Restricted Interests and Repetitive Behaviors

There was a significant effect of group on diagnostic algorithm scores for the Restricted Interests and Repetitive Behaviors domain (R), $F(8, 41) = 3.19, p = .007, partial \eta^2 = .38$. Again, this represents a large effect size. The univariate tests revealed significant differences for three symptoms of autism: repetitive object use/interest in parts of objects (R4), compulsions and rituals (R5), and circumscribed interests (R3). The covariate-adjusted means for all algorithm items within this domain are presented in Table 5.

Current Symptoms of Autism

The same analytic strategy described above was followed to make between-group comparisons for current behavior items within each ADI-R domain:

Reciprocal Social Interaction. Between-group differences in current autism symptoms in the Reciprocal Social Interaction domain failed to reach significance, $F(11, 38) = 1.57, p = .15, partial \eta^2 = .31$. (See Table 3 for presentation of the covariate-adjusted mean scores for current items in the Reciprocal Social Interaction domain.)

Communication. There was a significant effect of group, $F(10, 39) = 3.57, p = .002, partial \eta^2 = .48$, for current items in the Communication domain, reflecting a large effect size. Univariate tests revealed significant between-group differences for 2 items: stereotyped utterances/delayed echolalia (C1) and reciprocal conversation (C3). (See Table 4 for presentation of the covariate-adjusted mean scores for current items in the Communication domain.)

Restricted interests and repetitive behaviors. There was a significant effect of Group, $F(8, 41) = 3.13, p = .007, partial \eta^2 = .38$, for current items in the Restricted Interests and Repetitive Behaviors domain, reflecting a large effect size. Univariate tests revealed a significant between-group difference for 3 items: circumscribed interests (R3), compulsions and rituals (R5), and unusual sensory interests (R6). (See Table 5 for the covariate-adjusted mean scores for current items in the

Table 3. Autism Diagnostic Interview-Revised (ADI-R) Reciprocal Social Interaction Domain Scores

	Fragile X syndrome only (<i>n</i> = 26)				Fragile X syndrome/autism (<i>n</i> = 25)			
	Lifetime		Current		Lifetime		Current	
	Adj. mean	SE ^a	Adj. mean	SE	Adj. mean	SE	Adj. mean	SE
Social Interaction (S) domain								
S1. Use of other's body to communicate	.37	.18	.01	.05	.58	.18	.11	.05
S2. Imaginative play with peers	1.03	.19			1.92	.19		
S3. Direct gaze	1.00	.18			1.48	.18		
S4. Social smiling	.40	.16	.26	.14	1.06	.17	.77 ^b	.14
S5. Showing and directing attention	.40	.22	.11	.13	1.26	.23	.45 ^b	.14
S6. Offering to share	1.17	.23	.67 ^b	.18	1.54	.24	.75 ^b	.18
S7. Seeking to share enjoyment	.48	.17	.12	.13	.98	.18	.43 ^b	.13
S8. Offering comfort	.36	.16	.15	.10	.58	.17	.13 ^b	.10
S9. Quality of social overtures	.74	.17	.33 ^b	.12	1.30	.18	.53 ^b	.13
S10. Range of facial expressions	.17	.14	.07	.10	.59	.15	.21	.10
S11. Inappropriate facial expression	.49	.16	.37	.14	.97	.16	.66	.14
S12. Appropriateness of social responses	1.07	.16	.80	.11	1.69	.17	1.17 ^b	.12
S13. Interest in children	1.01	.19			1.59	.19		
S14. Response to approach of children	.65	.17			1.17	.18		
S15. Group play with peers	1.01	.19			1.91	.19		
S16. Friendships	1.23	.22	1.24	.22	1.52	.23	1.45	.22

^aStandard error. ^bItems for which significant within-group improvement was observed from lifetime to current time periods,

Restricted Interests and Repetitive Behaviors domain.)

Age-Related Change in Autism Symptoms

Twenty-nine items are included in both the lifetime and the current item pool of the ADI-R. For these individual items, we computed difference scores by subtracting current scores from lifetime scores; thus, a difference score greater than zero indicated age-related improvement for the behavior under consideration, whereas a difference score less than zero indicated worsening of the behavior. We used one sample *t* tests to detect significant differences from zero as well as two-tailed *p* values and a Bonferroni correction to adjust for multiple significance tests within each domain. Prior to conducting these analyses, we examined the bivariate correlations between chronological age (CA) and lifetime scores, current scores, and difference scores. None of these correlations were significant, indicating that CA of the participants did not contribute to the profile of age-related changes in autism symptoms.

Fragile X Syndrome Only Group

Of the 11 items in the Reciprocal Social Interaction (S) domain used for both the lifetime and current behavior, scores for 2 items improved significantly with child age: offering to share (S6), $t(25) = 3.73$, $p < .001$, $d = .73$, and quality of social overtures (S9), $t(25) = 3.43$, $p = .002$, $d = .67$. These effect sizes were in the medium range. Examination of the means for the other 9 items in this domain indicated that scores for these items were all at or below 1 for both the lifetime and current ratings.

Of the 10 items in the Communication domain used for both the lifetime and current ratings, 2 showed significant age-related improvement: social verbalization/chat (C2), $t(25) = 4.50$, $p < .001$, $d = .88$, and reciprocal conversation (C3), $t(25) = 5.28$, $p < .001$, $d = 1.03$. These effect sizes are large. Examination of the means for the other items in this domain indicated that scores were all at or below 1 for both lifetime and current ratings, with the following 4 items at or close to zero for both ratings: neologisms/

Table 4. Autism Diagnostic Interview-Revised (ADI-R) Communication Domain Lifetime and Current Scores

Communication (C) domain	Fragile X only (n = 26)				Fragile X/autism (n = 25)			
	Lifetime		Current		Lifetime		Current	
	Adj. mean	SE ^a	Adj. mean	SE	Adj. mean	SE	Adj. mean	SE
C1. Stereotyped utterances/echolalia	.67 ^b	.18	.61 ^b	.14	1.82	.18	1.44	.14
C2. Social verbalization/chat	1.07	.17	.26 ^c	.15	1.53	.17	.77 ^c	.15
C3. Reciprocal conversation	1.40	.15	.36 ^{b,c}	.16	1.79	.15	1.30 ^c	.15
C4. Inappropriate questions/statements	.79	.16	.67	.15	.93	.16	.91	.15
C5. Pronominal reversal	.77	.25	.25	.19	1.48	.25	.66 ^c	.19
C6. Neologisms/idiosyncratic language	.00	.08	.01	.05	.28	.08	.11	.05
C7. Pointing to express interest	.37 ^c	.13	.23	.13	1.35	.13	.61 ^c	.13
C8. Nodding	.04 ^c	.13	.02	.09	.84	.13	.38 ^c	.09
C9. Head shaking	.00 ^c	.11	.01	.06	.51	.11	.16	.06
C10. Conventional/instrumental gestures	.10	.14	-.01	.04	.57	.14	.09 ^c	.04
C11. Spontaneous imitation of actions	.20 ^c	.20			1.12	.21		
C12. Imaginative play	.98	.19			1.31	.20		
C13. Imitative social play	.47 ^c	.18			1.23	.18		

^aStandard error. ^bItems for which significant between group differences were observed at lifetime or current time periods. ^cItems for which significant within group improvement was observed from lifetime to current time periods.

idiosyncratic language (C6), nodding (C8), head shaking (C9), and conventional/instrumental gestures (C10).

None of the 8 items in the Restricted Interests and Repetitive Behaviors domain used for both lifetime and current ratings showed age-related

improvement; however, means for these items were all at or below 1 for both ratings.

Fragile X/Autism Group

Of the 11 items in the Reciprocal Social Interaction domain (S) used for both lifetime and

Table 5. Autism Diagnostic Interview-Revised (ADI-R) Restricted Interests and Repetitive Behaviors Domain Scores

Restricted Interest and Repetitive Behavior (R) domain	Fragile X only (n = 26)				Fragile X/autism (n = 25)			
	Lifetime		Current		Lifetime		Current	
	Adj. mean	SE ^a	Adj. mean	SE	Adj. mean	SE	Adj. mean	SE
R1. Verbal rituals	.17	.16	.16	.15	.63	.16	.60	.16
R2. Unusual preoccupations	.24	.18	.08	.17	.87	.19	.76	.17
R3. Circumscribed interests	.47 ^b	.18	.29 ^b	.15	1.16	.18	1.06	.16
R4. Repetitive object use/interest in parts of objects	.45 ^b	.16	.31	.14	1.18	.17	.80 ^c	.14
R5. Compulsions and rituals	.35 ^b	.20	.30 ^b	.18	1.20	.20	1.05	.19
R6. Unusual sensory interests	.46	.14	.34 ^b	.13	.80	.14	.64	.13
R7. Hand and finger mannerisms	.92	.21	.70	.18	1.28	.21	.95 ^c	.18
R8. Other complex mannerisms	.50	.20	.32	.16	1.12	.21	.79	.17

^aStandard error. ^bItems for which significant between-group differences were observed at lifetime or current time periods. ^cItems for which significant within-group improvement was observed from lifetime to current time periods.

current ratings, 7 showed significant age-related improvement, all with medium to large effect sizes: social smiling (S4), $t(25) = 3.36, p = .003, d = .67$, showing and directing attention (S5), $t(25) = 3.66, p < .001, d = .73$, offering to share (S6), $t(25) = 5.28, p < .001, d = 1.05$, seeking to share enjoyment (S7), $t(25) = 3.53, p = .002, d = .70$, offering comfort (S8), $t(25) = 3.38, p = .002, d = .68$, quality of social overtures (S9), $t(25) = 3.84, p < .001, d = .77$, and appropriateness of social responses (S12), $t(25) = 4.30, p < .001, d = .86$.

Of the 10 items in the Communication domain used for both lifetime and current ratings, scores for 6 items showed significant age-related improvement, with medium or large effect sizes: social verbalization/chat (C2), $t(24) = 4.94, p < .001, d = .99$, reciprocal conversation (C3), $t(24) = 4.24, p < .001, d = .85$, pronominal reversal (C5), $t(24) = 3.76, p < .001, d = .75$, pointing (C7), $t(24) = 4.93, p < .001, d = .98$, nodding (C8), $t(24) = 3.12, p < .005, d = .62$, and conventional/instrumental gestures (C10), $t(24) = 3.16, p = .004, d = .63$. Examination of the remaining 4 items in this domain revealed means that were at or below 1 for both lifetime and current ratings, with the exception of stereotyped utterances/delayed echolalia. This latter item had a mean lifetime score of 1.79 (.15) and a mean current score of 1.44 (.14). Although the ability to engage in reciprocal conversations did improve significantly with age, the mean current score for this item remained elevated at 1.30 (.15).

For the 8 items in the Restricted Interests and Repetitive Behaviors domain (R) queried for both lifetime and current ratings, 2 showed significant age-related improvement with medium effect sizes: repetitive object use/interest in parts of objects (R4), $t(24) = 3.46, p = .002, d = .69$, and hand and finger mannerisms (R7), $t(24) = 3.17, p = .004, d = .63$.

Prediction of Group Membership

Using a series of discriminant analyses, we sought to determine the combination of diagnostic (lifetime) items within each ADI-R domain that best predicted group membership. Nonverbal IQ and the diagnostic algorithm items from one domain were included in each respective analysis using a stepwise method. For each domain, the value of the squared canonical correlation reflects a measure of effect size and indicates the percentage of variation in group assignment

accounted for by the significant independent variables in each discriminant analysis. A significant Wilk's lambda allowed us to (a) reject the null hypothesis that the fragile X syndrome only and fragile X/autism groups had the same mean discriminant function score and (b) conclude that the model for that ADI-R domain was discriminating. Finally, the standardized discriminant function coefficients indicate the relative importance of the independent variables in predicting the dependent variable, similar to the standardized betas in a regression analysis.

Reciprocal Social Interaction. The groups were significantly discriminated, canonical $R^2 = .45, A = .55, \chi^2(4) = 28.59, p < .001$, by 3 items: group play with peers (S15), nonverbal IQ, and social smiling (S4). The pooled within-group correlations between the three discriminating variables and the standardized discriminant function were .72, $-.68$, and $.52$, respectively, with algorithm items positively related and nonverbal IQ inversely related to the single discriminant function. Functions at the group centroids (i.e., the mean variate scores for each group) were $-.87$ for the fragile X syndrome only group and $.91$ for the fragile X/autism group. The combination of group play with peers, nonverbal IQ, and social smiling correctly classified 80% of participants with fragile X syndrome only and 88% of participants with fragile X/autism.

Communication. The groups were significantly discriminated, canonical $R^2 = .65, A = .35, \chi^2(4) = 49.83, p < .001$, by 4 items: stereotyped utterances/delayed echolalia (C1), pointing to express interest (C7), nodding (C8), and nonverbal IQ. The pooled within-group correlations between the four discriminating variables and the standardized discriminant function were $.58, .54, .53$, and $-.45$, respectively, with algorithm items positively related and nonverbal IQ inversely related to the discriminant function. The functions at the group centroids were -1.32 for the fragile X syndrome only group and 1.37 for the fragile X/autism group. The combination of these four variables correctly classified 96% of participants with fragile X syndrome only and 92% of participants with fragile X/autism.

Restricted Interests and Repetitive Behaviors. The groups were significantly discriminated, canonical $R^2 = .41, A = .59, \chi^2(4) = 25.19, p < .001$, by 3 items: repetitive object use (R4), circumscribed interests (R3), and verbal rituals (R1). We note that nonverbal IQ did not contribute significantly

to group separation for this domain. The pooled within-group correlations between the three discriminating variables and the standardized discriminant function were .68, .58, and .47, respectively, with these algorithm items positively related to the discriminant function. The functions at the group centroids were $-.80$ for the fragile X syndrome only group and $.84$ for the fragile X/autism group. The combination of these three algorithm items correctly classified 80% of participants in the fragile X syndrome only group and 72% of participants in the fragile X/autism group.

FMRP and Current Symptoms of Autism

A large and positive association was detected between FMRP and nonverbal IQ, $r(42) = .65$, $p < .01$, two-tailed. The correlations between FMRP and the three current ADI-R domain scores were moderate and negative, with values ranging between $-.31$ and $-.39$, all $ps < .05$, as were the correlations between nonverbal IQ and current domain scores, which ranged between $-.42$ and $-.49$, all $ps < .01$. We examined the issue of whether FMRP accounted for unique variance in predicting current symptoms of autism, over and above nonverbal IQ, using a separate stepwise multiple regression equation for each domain score. In each regression, the percentage of cells expressing FMRP was entered at the first step, followed by nonverbal IQ at the second step. When entered as the sole predictor, the contribution of FMRP was significant for Reciprocal Social Interaction, Communication, and Restricted Interests and Repetitive Behaviors, $F(1, 40) = 7.07$, $p < .01$, $F(1, 40) = 4.32$, $p = .04$, and $F(1, 40) = 4.48$, $p = .04$, two-tailed, respectively. Each overall regression equation remained significant when nonverbal IQ was entered into the model, $F(2, 39) = 5.70$, $p < .01$, $F(2, 39) = 5.95$, $p < .01$, and $F(2, 39) = 5.00$, $p < .01$, two-tailed, respectively. However, for all three analyses, the proportion of cells expressing FMRP failed to account for unique variance in current ADI-R scores over and above the contribution of nonverbal IQ. Results of these analyses are presented in Table 6. We note that there were no significant differences in FMRP level between males with fragile X syndrome only and those with fragile X/autism or between females with fragile X syndrome only and those with fragile X/autism.

Discussion

We used the ADI-R to examine the behavioral symptoms that distinguish between older children and adolescents with fragile X syndrome with and without autism. We also took advantage of the fact that the ADI-R queries the informant about the target individual at two points in the life course (i.e., through lifetime and current ratings) to examine, retrospectively, age-related changes in the symptoms of autism. Finally, we examined the contribution of FMRP to the manifestation of autism symptoms in fragile X syndrome.

Deficits in social reciprocity are considered to reflect the essential and defining feature of idiopathic autism (Volkmar & Klin, 2005). After controlling for nonverbal IQ, however, we did not detect statistically significant differences between the groups in either the lifetime or current symptoms of autism that are queried in the ADI-R Reciprocal Social Interaction domain. Moreover, although effect sizes for the between-group differences in this domain were large, and perhaps clinically important, they were smaller than the effect sizes obtained for lifetime and current ratings in the Communication domain as well as current ratings in the Restricted Interests and Repetitive Behaviors domain.

Based upon our findings, it appears that impairment in the Reciprocal Social Interaction domain is not the primary feature distinguishing individuals with fragile X syndrome with and without a comorbid autism diagnoses. The current findings differ, however, from those reported by Kaufmann and colleagues (Hernandez et al., 2009; Kaufmann et al., 2004), who found that the Reciprocal Social Interaction domain represented the most significant determinant of autistic behavior in a group of young, largely nonverbal males with fragile X syndrome. It is important that Kaufmann and colleagues did not covary IQ in the various regression models that they used to explore profiles of symptoms of autism in individuals with fragile X syndrome. Thus, the problems that individuals with fragile X syndrome display in the Reciprocal Social Interaction domain may reflect cognitive impairments that influence their ability to experience and share enjoyment and interest with a social partner rather than a social indifference or a lack of motivation to engage with others.

In contrast, we did find significant between-group differences for 6 diagnostic items within the

Table 6. Hierarchical Regression Predicting Autism Diagnostic Interview-Revised Domains: Current Total Score

Domain/Step	<i>B</i>	<i>SE B</i>	β	<i>Semipartial r</i>
Reciprocal Social Interaction ^a				
Step 1				
Constant	6.61	.66		
FMRP	– 6.24	2.35	– .39**	– .38
Step 2				
Constant	10.40	2.05		
FMRP	– 2.47	2.99	– .15	– .12
Nonverbal IQ	– .09	.04	– .36	– .27
Communication ^b				
Step 1				
Constant	5.12	.63		
FMRP	– 4.66	2.24	– .31*	– .31
Step 2				
Constant	9.86	1.89		
FMRP	.07	2.76	.00	.00
Nonverbal IQ	– .11	.04	– .49**	– .37
Restricted Interests & Repetitive Behaviors ^c				
Step 1				
Constant	4.67	.55		
FMRP	– 4.14	1.96	– .32*	– .32
Step 2				
Constant	8.28	1.69		
FMRP	– .54	2.46	– .04	– .03
Nonverbal IQ	– .08	.04	– .42*	– .32

^a $R^2 = .15$ for Step 1, $\Delta R^2 = .08$ for Step 2. ^b $R^2 = .10$ for Step 1, $\Delta R^2 = .14$ for Step 2. ^c $R^2 = .10$ for Step 1, $\Delta R^2 = .10$ for Step 2.

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

Communication domain after controlling for nonverbal IQ. Three of these items involve the production of communicative gestures (pointing to express interest, nodding, head shaking), 2 involve imitation (imitation of actions and imitative social play), and 1 involves the use of stereotyped utterances or delayed echolalia. Of the 6 items that differed between the groups for lifetime ratings, however, only the use of stereotyped utterances and delayed echolalia distinguished between the groups in current ratings, after controlling for nonverbal IQ. One additional item, the ability to engage in reciprocal conversations, that did not differ for the lifetime rating differed significantly for the current rating. Further, the two lifetime algorithm items that were focused on imitation were not included in the current rating.

The use of stereotyped utterances and delayed echolalia is not unexpected for individuals with fragile X syndrome, even without autism, because the fragile X syndrome phenotype is associated with pragmatic difficulties, including repetitive language, tangential talk, and topic perseveration (Murphy & Abbeduto, 2007; Roberts et al., 2007; Sudhalter & Belser, 2001). That the ability to engage in reciprocal conversations emerged as significantly different between the groups in the current, but not the lifetime, rating is particularly interesting given the lack of group differences in the Reciprocal Social Interaction domain. One possibility is that for participants with fragile X/autism, difficulties in reciprocal conversation reflect limitations in lexical and syntactic knowledge or in the specific pragmatic skills needed to engage in such conversations rather than a lack of

motivation to communicate with others. Neither of the communication items for which we observed significant between-group differences in the current ratings was included in the analyses of Hernandez et al. (2009) because these items were not used with nonverbal participants.

Three lifetime symptoms in the Restricted Interests and Repetitive Behaviors domain differed significantly between the groups. These symptoms reflect repetitive object use, compulsions and rituals, and circumscribed interests. Compulsions and rituals as well as circumscribed interests also showed between-group differences in the current ratings. Finally, although the group difference in unusual preoccupations failed to reach significance for the lifetime rating, this item did emerge as significantly different for the current rating.

In a recent study examining the presence and types of repetitive behaviors in genetic syndromes, Moss, Oliver, Arron, Burbidge, and Berg (2009) found that a large sample of participants with fragile X syndrome, who ranged in age from 4 to 47 years, demonstrated the highest frequency and greatest number of types of repetitive behaviors relative to any other syndrome group examined. The fragile X syndrome sample was especially elevated relative to the other genetic conditions in items reflecting hand stereotypies, lining up objects, preference for routines, echolalia, and restricted conversations. In the Moss et al. study, lining up objects and preference for routines were categorized together in the subdomain of Compulsions, a symptom of autism that was significantly different for our participants for both lifetime and current ratings. Participants with fragile X/autism in the current study also demonstrated relatively higher levels of stereotyped utterances and delayed echolalia. Although these two characteristics are queried in the Communication domain of the ADI-R, they correspond in topography to restricted conversation and echolalia observed for verbal participants in the Moss et al. study. Importantly, Moss et al. reported that none of the repetitive behaviors identified as having high specificity for individuals with fragile X syndrome was correlated with total scores on the Autism Screening Questionnaire (Berument, Rutter, Lord, Pickles, & Bailey, 1999), suggesting that some language characteristics and repetitive behaviors observed in fragile X syndrome may not be associated with diagnosis of autism.

In part because relative increases in cognitive impairment over time have been reported for fragile X syndrome (Hall et al., 2008; Skinner et al., 2005), an additional focus we had in the current study was whether participants would show lessening or worsening of autism symptoms over time within each ADI-R domain. Hatton et al. (2006) found that symptom severity did increase slightly over time as indexed by CARS scores in children who were younger, on average, than participants in the current study. In another sample of young boys with fragile X syndrome, Hernandez et al. (2009) found a general trend of worsening symptoms for young boys with fragile X syndrome only and improvement of symptoms for young boys with comorbid fragile X syndrome and autism spectrum disorders. In the current study, all participants in both groups showed improvement in autism symptoms from lifetime to current ratings.

Within the Reciprocal Social Interaction domain, offering to share and quality of social overtures improved with age for participants with fragile X syndrome only as reflected by differences between the lifetime and current ratings. In the same domain, seven symptoms of autism showed age-related improvement for participants with fragile X/autism. Use of other's body to communicate and the 2 items related to facial expressions did not show improvement from lifetime to current ratings for participants with fragile X/autism, but these 3 items had adjusted mean scores that were less than 1 for the lifetime rating. It is important that only 2 items, appropriateness of social responses and friendships, had adjusted current mean scores of greater than 1 for participants with fragile X/autism.

Within the Communication domain, we found that skills such as the use of gestures did improve with age for participants with comorbid fragile X syndrome and autism. However, the use of stereotyped speech and delayed echolalia did not improve for either group, with scores for this symptom of autism remaining stable between lifetime and current ratings and differing significantly between the groups for the current rating. Although participants with fragile X syndrome only improved significantly in the ability to engage in reciprocal conversations between the lifetime and current rating, this pattern of improvement was not evident for participants with fragile X/autism. Thus, despite age-related improvements in the use of gestural means of

communication, the ability to engage reciprocally in conversational turn-taking remained especially challenging for participants with fragile X/autism.

In contrast to the other two symptom domains, little improvement between lifetime and current ratings was noted for the Restricted Interests and Repetitive Behaviors domain, although none of the items evidenced a worsening of symptoms. The only improvements were observed for the group with comorbid fragile X syndrome and autism. Repetitive use of objects as well as hand and finger mannerisms improved significantly for participants with fragile X/autism across the two sets of ratings. In fact, repetitive object use was no longer significantly different between the groups in the current rating, with the groups not differing in hand and finger mannerisms for either set of ratings.

It is interesting to compare patterns of change in autism symptoms detected in the current study with those reported by Shattuck et al. (2007) for a large group of older children, adolescents, and young adults with idiopathic autism. Overall, Shattuck et al. observed longitudinal improvements in social reciprocity and verbal communication as well as restricted interests and repetitive behaviors. As was the case for the current study, none of the individual ADI-R items used by Shattuck et al. significantly worsened over time. Unlike participants with fragile X/autism in the current study, however, participants with idiopathic autism did not improve in nonverbal communication behaviors over the 4.5-year study period.

When examining age-related symptom change in the current study, we found that that the nonverbal IQ-adjusted mean item scores for the fragile X syndrome only group hovered around 1 for all three ADI-R domains, indicating impairments that were, on average, not marked enough to be scored as clear characteristics of autism. There were, however, two exceptions to this pattern. First, both fragile X syndrome only and fragile X/autism participants had scores exceeding 1 for friendships, and this item did not differ significantly or improve from lifetime to current ratings for either group. In fact, for the group with fragile X syndrome only, this item received the highest (i.e., most impaired) rating in the Reciprocal Social Interaction domain for both ratings. Second, participants with fragile X syndrome only had a lifetime mean score of 1.4 ($SD = .15$) for the diagnostic item tapping the ability

to engage in reciprocal conversation. Although the two participant groups in the current study did not differ on this Communication domain item for the lifetime rating, the group with fragile X syndrome only showed age-related improvement such that this item distinguished the groups in the current rating.

It is interesting that Shattuck et al. (2007) reported that these same two items, impairments in friendships and impairments in reciprocal conversation, were the most prevalent autism symptoms observed for individuals with idiopathic autism over the age of 10 years. Our results suggest that impairments in reciprocal conversation are present to a significant degree in individuals with fragile X/autism, with between-group differences increasing with age, whereas impairments in friendship are symptomatic of all individuals with fragile X syndrome regardless of autism status. It seems likely that delays in language learning and impairments in the ability to engage in back-and-forth conversational turn-taking could have a cumulative and negative impact on the ability to establish and maintain friendships with peers, regardless of an individual's motivation to interact with others. Indeed, it is also possible that hyperarousal and anxiety experienced by males with fragile X syndrome in social contexts contributes to deficits in peer relationships and friendships throughout development (Sudhalter & Belser, 2004). Of course, individuals with fragile X syndrome also may experience a lack of opportunity to establish friendships in addition to any possible lack of motivation to engage in reciprocal social interaction. Further, the ADI-R scoring for friendships includes the ability to interact reciprocally around nonstereotyped activities. Thus, the presence of circumscribed interests could also interfere with the ability to establish friendships. Regardless of the source, the establishment of reciprocal peer relationships should be targeted for treatment for all children and adolescents with fragile X syndrome.

In addition to using multivariate analysis of variance to identify algorithm items that differed significantly between fragile X syndrome only and fragile X/autism, we used a discriminant function analysis to identify the items within each ADI-R domain that maximally discriminated between the groups at the diagnostic time point (Bray & Maxwell, 1985). For the Reciprocal Social Interaction domain, item scores for group play with

peers, social smiling, as well as nonverbal IQ resulted in the highest number of participants who were classified into the correct diagnostic group. For the Communication domain, algorithm scores for stereotyped utterances, pointing to express interest, nodding as well as nonverbal IQ best discriminated between the groups. Finally, for the Restricted Interests and Repetitive Behaviors domain, repetitive object use, circumscribed interests, and verbal rituals best discriminated between the groups. It is interesting that nonverbal IQ did not contribute to group discrimination for the Restricted Interests/Repetitive Behaviors domain. Taken together, results of the discriminant analyses support the proposal that behavioral symptoms of autism in the areas of reciprocal social interaction and communication may be secondary to cognitive impairments in individuals with fragile X syndrome. However, cognitive impairments seem to influence the expression of repetitive and restricted behaviors equally in all individuals with fragile X syndrome. As other authors have suggested, it is possible that a psychological mechanism such as arousal might better describe the relationship between fragile X syndrome and autism symptoms in the domain of Restricted Interests and Repetitive Behaviors (Miller et al., 1999; Roberts, Boccia, Bailey, Hatton, & Skinner, 2001).

Finally, we found that FMRP was not related to ADI-R domain scores after controlling for nonverbal IQ. In contrast, Hatton et al. (2006) found that FMRP was significantly and negatively predictive of scores on the CARS for children with fragile X syndrome, whereas Loesch et al. (2007) found a similar relationship using the ADOS for individuals with fragile X syndrome ranging from childhood to adulthood. Hatton et al., however, did not control for nonverbal IQ. In the Loesch et al. study, although both FMRP and FSIQ were significant predictors of the ADOS Communication algorithm score, only FSIQ accounted for unique variance in the ADOS algorithm score for Reciprocal Social Interaction or the aggregated variable representing the sum of the Communication and Reciprocal Social Interaction algorithm scores. Taken together, the data suggest that FMRP levels have a largely indirect effect on symptoms of autism and that this effect is likely mediated through IQ.

One issue that we could not address in the current study concerns changes in diagnostic

classification over time. When used as intended by the developers, the ADI-R does not provide a diagnostic algorithm that can be used with current scores (i.e., an ADI-R diagnosis of autism is computed with an algorithm using behaviors reported for lifetime rating), preventing us from examining the stability of the autism diagnosis with age, as Hatton et al. (2006) did by examining CARS cutoff scores. By scoring the ADI-R according to the conventions provided in the manual, we were limited to examining changes in those individual ADI-R items that were used at both lifetime and current time points.

The present study was also limited by the use of only one measure of autism symptoms. Hernandez et al. (2009) assigned diagnostic status to young boys with fragile X syndrome by using *DSM-IV* criteria, the ADI-R, and the ADOS. According to these authors, the ADOS resulted in overidentification of participants as having autism, whereas complete agreement was obtained between the ADI-R and *DSM-IV* diagnoses. Harris and colleagues (2008) utilized the ADOS, ADI-R, and *DSM-IV* to determine autism status for a group of males with fragile X syndrome and concluded that it was the ADI-R that overidentified autism in fragile X syndrome. As researchers do not know the “true” prevalence of autism in fragile X syndrome, it is difficult to determine how well any of these instruments is performing when used with individuals who have the syndrome. This dilemma reinforces the importance of understanding whether autism symptoms in fragile X syndrome actually reflect the operation of the same underlying pathology as in idiopathic autism.

Results of the current study also are limited by the absence of a comparison group of nonverbal IQ-matched individuals with idiopathic autism. We plan to add such a comparison group in future studies. Results also are limited by reliance on retrospective rather than longitudinal measures of change, although there is evidence from idiopathic cases of autism that the two approaches yield much the same results. Nevertheless, replication with a longitudinal design is necessary. An additional limitation involves our sample of participants, all of whom had achieved phrase speech, resulting in use of the verbal algorithm for the Communication domain of the ADI-R. Results of the current study might have differed if the participant sample had included individuals considered nonverbal according to the

ADI-R scoring conventions. It is possible that nonverbal individuals with fragile X syndrome differ systematically from verbal individuals with fragile X syndrome, not only on items included in the Reciprocal Social Interaction domain but also in ways that affect the acquisition of spoken language; that is, children with fragile X syndrome who more readily demonstrate social reciprocity may also achieve more proficient spoken language status. This is an interesting issue given that most factor analytic examinations of the ADI-R have yielded a two factor structure consisting of a social–communication factor and a stereotyped language and repetitive behavior factor (Frazier, Youngstrom, Kubu, Sinclair, & Rezai, 2008; Snow, Lecavalier, & Houts, 2009). Finally, few studies on autism in fragile X syndrome have included females. Of the 15 females in the current sample of older children and adolescents with fragile X syndrome, 8 had nonverbal IQs less than or equal to 70. Of those 8 females, 2 met criteria for fragile X/autism. This proportion is in general agreement with Hatton et al. (2006), in which 2 of 32 females met the CARS autism cutoff. Future studies of autism symptoms in larger samples of females with fragile X syndrome will be particularly helpful given the wide range of nonverbal cognitive abilities and variability in FMRP expression in females with fragile X syndrome.

In summary, findings of the current study suggest that differences in social reciprocity, the defining feature of idiopathic autism, are not observed in individuals with fragile X syndrome relative to autism status when cognitive impairment is taken into account. This finding was observed for both lifetime (i.e., diagnostic) and current ratings obtained for the ADI-R. We observed differences in communication as well as restricted interests and repetitive behaviors, however, even after controlling for nonverbal IQ. Symptoms of autism improved over time for individuals with fragile X syndrome, regardless of autism status. Controlling for intercorrelations between the ADI-R items within each domain, we found that nonverbal IQ added to group separation for the Reciprocal Social Interaction and Communication domains, but not for the Restricted Interests and Repetitive Behaviors domain. Finally, although significant and negative associations with ADI-R domain scores were detected for both FMRP and nonverbal IQ, FMRP did not account for unique variance in

predicting domain scores once nonverbal IQ was added to the regression model.

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