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Autism Symptoms across Adulthood in Men with Fragile X Syndrome: A Cross-sectional Analysis

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Abstract

A cross-sectional analysis was used to examine age-related differences in ASD symptoms and corresponding differences in disruptive behavior and social skills in 281 adult men with Fragile X syndrome (FXS). Four age groups were created: 18–21 years, 22–29 years, 30–39 years, and 40–49 years. The 18–21 year-old group was reported to have more impairments in verbal communication than the 22–29 year-old group and more restricted and repetitive behaviors than the 40–49 year-old group. There was not an age-group difference in the percentage of men who met criteria for an ASD diagnosis based on respondent-reported, current symptoms. There was a trend for an age-related difference in disruptive behavior. Findings add to understanding of the developmental trajectory of ASD symptoms in adulthood.

Keywords

Fragile X syndrome; autism; DSM; adult; aging

Fragile X syndrome (FXS) is a neurodevelopmental disorder involving an unstable expansion of a CGG polymorphism within the 5’ untranslated region of the *FMR1* gene, located on the X chromosome (Kaufmann & Reiss, 1999). FXS is twice as common in males

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as in females, with an estimated prevalence of 1 in 4,000 males in the general population (Crawford, Acuna, & Sherman, 2001). In males, FXS is associated with a host of physical (e.g., large ears, long face, macroorchidism, and hyper-flexible joints), cognitive (e.g., intellectual disability and communication impairments), and behavioral (e.g., attention problems, hyperactivity, and anxiety) characteristics (e.g., Bailey, Raspa, Olmsted, & Holiday, 2008; Cornish, Turk, & Hagerman, 2008; Hagerman P& Hagerman, 2002). FXS is also associated with an increased prevalence of symptoms of autism spectrum disorder (ASD), consisting of impairments in social reciprocity, impairments in communication, and restricted and repetitive behaviors. Studies suggest that 15 to 42% of male children with FXS meet criteria for a diagnosis of ASD (Demark, Feldman, & Holden, 2003; Kaufmann et al., 2004; Rogers, Wehner, & Hagerman, 2001; Turk & Graham, 1997), and 60 to 90% exhibit ASD symptoms to some degree (Bailey, Hatton, Skinner, & Mesibov, 2001; Hagerman, 2002; Hatton et al., 2006). Although FXS is a lifelong disability, research has almost exclusively focused on the profile of ASD symptoms during childhood and adolescence. Little is known about the constellation of ASD symptoms in adult men with FXS or whether these symptoms change across adulthood. The purpose of the present study is to examine age-related differences in the number of ASD symptoms and in the likelihood of meeting criteria for a diagnosis of ASD based on respondent-reported current symptoms in a community sample of 281 adult men with FXS aged 18–49 years. An additional goal is to determine if age-related differences in ASD symptoms correspond to improvements in disruptive behavior and social skills across adulthood.

Among individuals with idiopathic ASD, several studies have documented a trajectory of improvement in ASD symptoms across adolescence and adulthood (Fecteau, Mottron, Berthiaume, & Burack, 2003; Shattuck et al., 2007). For instance, in their sample of 241 adolescents and adults with ASD aged 10 to 52 years (M = 22.0 years), Shattuck et al. (2007) found a pattern of improvement in all domains of ASD symptoms across a 4.5 year period using the Autism Diagnostic Interview-Revised (ADI-R; Lord, Rutter, & Le Couteur, 1994). In a subsequent analysis using this same sample but extending the time period to 8.5 years, the pattern of improvement in all domains of ASD symptoms remained significant (Woodman, Smith, Greenberg, & Mailick, 2014). Improvement was most pronounced in impairments in verbal communication and restricted and repetitive behaviors and least evident in impairments in social reciprocity.

Only a handful of studies have examined age-related change in ASD symptoms in individuals with FXS and these studies have focused on childhood (Hatton et al., 2006; McDuffy, Kover, Abbeduto, Lewis, & Brown, 2012). Findings from these studies are mixed. Hatton et al. (2006) examined differences in the severity of ASD symptoms using the Childhood Autism Rating Scale (CARS: Schopler, Reicher, & Renner, 1988) in a sample of 116 preschool-aged boys and girls with FXS. On average, ASD symptom severity was positively associated with age. In contrast, McDuffie et al. (2010) examined change in ASD symptoms using the ADI-R in a cross-sectional study involving 51 boys with FXS aged 10–16 years. In order to evaluate age-related change, the ADI-R current scores for adolescents versus children with FXS were compared. In addition, within-individuals, current ADI-R scores were subtracted from lifetime ADI-R scores to estimate retrospective accounts of

age-related changes. Findings suggested slight improvement in impairments in social reciprocity and impairments in communication, with little to no change in restricted and repetitive behaviors. One interpretation of these varied findings is that ASD symptoms are increasingly apparent and severe across the preschool years in FXS, but this is followed by a decline in impairments in social reciprocity and impairments in communication across older childhood and adolescence.

Only two studies have examined age-related patterns in ASD symptoms in adults with FXS. Smith, Barker, Seltzer, Abbeduto, and Greenberg (2012) examined ASD symptoms on the ADI-R in a sample of 136 adolescents and adults with FXS aged 12 years and older (*M* = 26.13 years, *SD* =10.21 years). They found that age was negatively associated with restricted and repetitive behaviors but was not related to impairments in social reciprocity or impairments in verbal communication after controlling for intellectual disability status. In contrast, in a sample of 18 adult men with FXS (mean age at the beginning of the study of 36.1 years), Sabaratnam, Murthy, Wijeratne, Buckingham, and Payne (2003) examined change in ASD symptoms across a 10 year period using items from the Disability Assessment Schedule (DAS; Holmes, Shah, & Wing, 1982) and MRC schedule of Handicaps, Behaviors, and Skills (HBS; Wing, 1980). There was not a significant change in ASD symptoms. Additional studies using larger samples are needed given these conflicting findings. Moreover, additional research is needed to determine if ASD symptom improvement in adulthood is clinically relevant. One strategy for gauging clinical relevance is to determine if age-related differences in number of ASD symptoms translate into differences in the percentage of adults with FXS who would meet criteria for a diagnosis of ASD if based solely on respondent-reported current symptoms. This strategy offers an estimate of diagnostic status, but does not mirror actual clinical diagnosis which would also consider observational measures and historical symptoms.

The presence of ASD has been linked to poor behavioral and social outcomes in individuals with FXS. Children with FXS and ASD have been found to have more behavior problems than those with FXS ‘only’ (Kauffman et al., 2004; Rogers et al., 2001). Similarly, adolescents and adults with FXS and ASD have been shown to have more emotional and behavioral problems and lower levels of adaptive behavior (Smith et al., 2012) and less independent outcomes in daily life (Hartley et al., 2011) than do adolescents and adults with FXS without ASD. If there is an age-related improvement in ASD symptoms across adulthood for men with FXS, it is important to understand if this corresponds to an age-related improvement in behavioral and social outcomes. Indeed, in the Smith et al (2012) study, age was negatively associated with behavior problems and positively associated with adaptive functioning in their sample of adolescents and adults with FXS.

The objectives of the present study were to: 1) examine age-related differences in number of ASD symptoms in adults with FXS and in the percentage of adults with FXS who meet criteria for a diagnosis of ASD based on respondent-reported current ASD symptoms; and 2) determine if there are corresponding age-related differences in disruptive behaviors and social skills. In order to accomplish the study objectives, we analyzed cross-sectional data from a large national online survey of parents or caregivers of 281 adult men with FXS completed in 2012–2013. Four age groups were created to capture differences in daily life

(e.g., in school versus out of school) as well as in chronological age: 18–21 years, 22–29 years, 30–39 years, and 40–49 years. Respondents reported on the adult man with FXS's ASD symptoms and current level of disruptive behaviors and social skills. In line with Smith et al. (2012), we hypothesized that that age would only be negatively associated with restricted and repetitive behaviors, such that the oldest age groups would be reported to have fewer restricted and repetitive behaviors but a similar number of impairments in social reciprocity and impairments in verbal communication as the younger age groups. Moreover, we predicted that the older age groups would be less likely to meet criteria for a diagnosis of ASD than the youngest age groups. In line with the expected lower number of restricted and repetitive behaviors and lower likelihood of meeting criteria for an ASD diagnosis, we expected a negative association between age and disruptive behavior and a positive association between age and social skills such that the older age groups would evidence fewer disruptive behaviors and better social skills than the younger age groups.

Method

Participants

Data from a large national survey of families of children and adults with FXS was used in the present analyses (Wheeler et al., 2014). Families were recruited for a survey registry through FXS foundations (National Fragile X Foundation, FRAXA Research Foundation, and Conquer Fragile X Foundation), research registries, and clinics. A total of 972 families with 2,140 children or adults with an *FMR1* enrolled in the survey registry. Of these, a total of 730 families who had at least one child with FXS participated in the survey. The subset of 281 respondents of men aged 18 to 49 years with the full mutation of the *FMR1* gene was included in the present analyses.

We divided the sample into four age groups: 18–21 year-olds, 22–29 year-olds, 30–39 year-olds, and 40–49 year-olds. As shown in Table 1, chi-square statistics indicated that there was not a significant difference between the age groups in the percentage of adults with FXS who were White (vs. other), who could speak (vs. not speak), or who had seizures (vs. no seizures). One-way analyses of variance (ANOVA) indicated no age-group difference in a global rating of health. However, there was an age-group difference in level of functional skills; the 18–21 year-old group had a lower level of functional skills than the three other age groups. In part, this difference may reflect true age-related improvements in functional skills (e.g., ability to pay bills and take the bus improves with practice across adulthood). Indeed, within-person increases in daily functional skills were found during adolescence and early adulthood for individuals with ASD (Smith, Maenner & Seltzer, 2012). However, to ensure that this age group difference does not reflect sample bias, level of functional skill was controlled for in all analyses. Chi-square statistics indicated that adults with FXS in the 18–21 year-old and 22–29 year-old groups were significantly more likely to live with family (and co-reside with the survey respondent) and less likely to live in group homes than were the two older age groups. This pattern is in line with age-related changes in residential setting seen more broadly in adults with developmental disabilities (Seltzer, Krauss, Orsmond, & Vestal, 2000). However, co-residence of the survey respondent (1 = co-

residing, 0 = not co-residing) was controlled for in all analyses to control for the potential impact of time spent with the adult man with FXS on ratings of symptoms and behaviors.

Chi-square statistics indicated that there was not a significant difference between the age groups in the respondent's gender, relation (parent vs. other) to the adult man with FXS, residential location, education, or FXS status. A one-way ANOVA indicated that there was a significant difference in the age of the respondents by age group. Respondents of the 18–21 year old group and 22–29 year-old group were younger than respondents of the 40–49 year-old group. This difference reflects that the large majority of respondents were parents.

Procedures

Respondents completed the survey online (94.4%) or via telephone (5.6%), which took approximately 1.5 hours, and included a broad array of questions about their families' characteristics and needs and the symptoms and functioning of the adult man with FXS.

Measures

All survey items were developed based on a rigorous development process which included a review of the literature, a review of existing relevant measures, discussions with experts in the field, and testing of all items as well as the survey as a whole by several caregivers of children or young adults with FXS.

Socio-demographics—Respondents reported on the adult man with FXS's socio-demographic characteristics. Chronological age was coded in years and months. Ethnicity was coded as White (1) versus other (0). Health was coded through a single item inquiring about overall health and rated on a 5 point scale from 'poor' (1) to 'excellent' (5). The presence of seizures was coded through a single item asking if the adult man with FXS had ever been diagnosed or treated for seizures and was scored as 'yes' (1) or 'no' (0). Ability to speak was assessed through a single item in the ASD symptom survey inquiring if the adult man with FXS "does not speak" and scored as 'yes' (does not speak; 1) or 'no' (speaks).

Functional skills—Respondents rated the adult man with FXS's functional skills using a 37-item measure assessing financial (e.g., 'judges whether [he/she] has enough money to buy a particular item), arithmetic (e.g., 'identifies numbers from 1 to 10'), conceptual (e.g., 'demonstrates understanding of first and last'), and reading and writing skills (e.g., writes 5 or more words from memory). These items were developed based on review of the literature and other measures of functional skills (See Bailey, Raspa, Holiday, Bishop, & Olmsted, 2009 for items). Each item was rated as 'does not do this' (1), 'needs a lot of help' (2), 'needs a little help' (3), or 'does this without help' (4). The total score was used in analyses, which had adequate internal consistency in the present sample (Cronbach's $\alpha = .95$).

ASD symptoms—Respondents reported on the adult man with FXS's ASD symptoms using 25 items from an ASD symptom survey. Items were developed to reflect observable behaviors and adaptable for a caregiver survey format. Item selection was based on review of literature and validated measures of ASD symptoms (ADI-R, Social Communication Questionnaire [Rutter, Bailey, & Lord, 2005, and Social Responsiveness Scale [Constantino

& Gruber, 2005]), and Diagnostic and Statistical Manual (DSM) criteria for an ASD diagnosis. Each item was rated as “absent” (0) or “present” (1). Six items assessed impairments in social reciprocity, 5 items assessed verbal communication (nonverbal communication was not assessed), and 14 items assessed restricted and repetitive behaviors. Table 2 displays the specific items within each domain. Consistent with previous studies of ASD symptoms in adolescent or adult populations (McDuffy et al., 2012; Shattuck et al., 2007; Smith et al. 2012), items related to imitative or imaginative play were omitted from the analysis. The 34 adults with FXS rated ‘yes’ to the item “does not speak” were omitted from analyses of impairments in verbal communication.

ASD diagnosis—Although ASD is considered to be a lifelong disorder, with symptom improvements, an individual may no longer meet criteria for ASD at a later age if only considering *current* (as opposed to historical) symptoms. We examined the percentage of adults with FXS who met criteria for a diagnosis of ASD if based solely on respondent-report of *current* symptoms using DSM fourth edition, text revision (DSM-IV TR) and fifth edition (DSM-5). This approach provides a gauge of whether age-related differences in ASD symptoms translate into clinically meaningful differences; however, this approach does *not* mirror actual clinical practice in which historical symptoms and observational measures are used in addition to caregiver report (APA, 2013). The DSM-5 introduced several major changes to diagnostic criteria for ASD; the impact of these changes is still under investigation and debate (Maenner et al., 2014; Wheeler et al., 2014). Given the uncertainty of the impact of DSM-5, and lack of any information on adults with FXS, in order to gauge clinical significance of any age-related differences, we examined the percentage of adult men with FXS who met criteria for DSM-IV TR as well as DSM-5 diagnosis of ASD based on respondent-report of current ASD symptoms.

To determine if adults with FXS met criteria for an ASD diagnosis, items from ASD symptom survey described above, including the item ‘Does not Speak’, were mapped onto the DSM-IV TR criteria for Autistic Disorder and Asperger’s Disorder and DSM-5 criteria for ASD (see Wheeler et al., 2014). Table 2 also displays how each item on the ASD symptom survey mapped onto the DSM-IV TR and DSM-5 criteria. The initial mapping of items to DSM-IV TR and DSM-5 criteria was conducted by an expert ASD diagnostician with nearly 10 years of experience assessing ASD (and research reliable on the Autism Diagnostic and Observation Schedule [Lord et al., 2000]) who was not involved in the initial survey design. This mapping was then confirmed by a clinician-researcher who had been working with children with ASD, FXS, and other developmental disabilities for more than 15 years. Moreover, this mapping was supported through a factor analysis (see Wheeler et al., 2014) which indicated that good fit of items to domains Two additional project staff separately reviewed the information about whether each diagnostic criterion within each symptom domain was met (present vs. absent); consensus discussions were used in the one case in which a discrepancy arose. Only adults with FXS who were reported to exhibit delays or abnormal functioning prior to age 3 years were considered for the DSM-IV-TR diagnosis.

Disruptive behavior—An 11-item disruptive behavior measure, developed based on a review of the literature regarding types of disruptive behaviors exhibited by individuals with intellectual and developmental disabilities as well as review of existing measures of global problem behaviors, was used. Items were rated on a 4-point scale as occurring 'never' (1) to 'very often' (4). Examples of items include "verbally insults others," "is sexually inappropriate," "argues," and "hits, pushes, or kicks others." In the present sample, the disruptive behavior measure had adequate internal consistency (cronbach's $\alpha = .82$), and was positively correlated ($r = .34$, $p < .01$) with the respondent's rating ('no' [0] or 'yes' [1]) on the item "[Adult with FXS's] behavior issues limit [his/her] ability to live independently"

Social skills—Respondents rated the adult man with FXS's social skills using a 14-item measure developed based on review of literature and other measures of social skills. Items were rated on a 4-point scale as occurring 'never' (1) to 'very often' (4). Examples of items are "has a good sense of humor," "is patient/able to wait," "actively participates in activities," "appropriately controls anger," and "maintains friendships". In the present sample, the social skill measure had good internal consistency (Cronbach's $\alpha = .87$), and was positively correlated ($r = .44$, $p < .01$) with an item asking respondents to rate the adult with FXS's "Ability to Interact" from 'poor' (1) to 'very good' (4), and negatively correlated ($r = -.25$, $p < .01$) with the disruptive behavior score

Data Analysis Plan

Histograms of residuals as well as quantile-comparison plots were examined to assess whether data was normally distributed. On individual measures, 2–7% of items were missing. For analyses involving summary scores (i.e., functional skill total score, ASD domain scores, disruptive behavior total score, and social skill total score), mean imputation was used in place of missing items if the respondent had at least 80% of the items for that scale completed. Correlations were used to examine associations among socio-demographic variables and outcome variables (ASD symptoms, diagnosis of ASD, disruptive behavior, and social skills). Functional skills and co-residence status (co-residence vs. not co-residing) of the respondent were controlled for in all analyses. Adults with FXS who were rated as "does not speak" were excluded from analyses of impairments in verbal communication, as respondents did not rate items in this domain for these individuals.

The first study objective was to examine age-related differences in number of ASD symptoms and ASD diagnosis based on respondent-reported current symptoms. One-way ANCOVAs were also conducted to compare impairments in social reciprocity, impairments in verbal communication, and restricted and repetitive behaviors of the four age groups. Post-hoc Bonferroni comparisons were used to identify group differences. These analytic approaches were also used to examine age group differences in prevalence of DSM-IV TR and DSM-5 diagnosis. The second study objective was to examine age-related differences in disruptive behavior and social skills. One-way ANCOVAs and post-hoc Bonferroni comparisons were separately conducted to compare the disruptive behavior and social skill total scores of the four age groups.

Results

Age and ASD symptoms and Diagnosis of ASD

Study variables had data with normal distributions without skew. Pearson's correlations, presented in Table 3, were conducted to examine associations among socio-demographic characteristics, ASD symptoms and diagnosis of ASD based on respondent-reported current symptoms. Ethnicity (White vs. other), health, and seizures were not associated with age or any of the ASD variables. Level of functional skills was significantly negatively associated with impairments in social reciprocity, impairments in verbal communication, and restricted and repetitive behaviors and DSM-IV TR and DSM-5 diagnosis of ASD. Ability to speak was significantly positively associated with impairments in social reciprocity, disruptive behavior, and restricted and repetitive behaviors. Co-residence of respondent was significantly related to disruptive behavior. Disruptive behavior was significantly positively associated with impairments in social reciprocity, impairments in verbal communication, restricted and repetitive behaviors, and DSM-IV TR and DSM-5 diagnosis of ASD. Social skills was significantly negatively associated with disruptive behavior, impairments in social reciprocity, impairments in verbal communication, restricted and repetitive behaviors, and DSM-IV TR and DSM-5 diagnosis of ASD.

Table 4 displays the unadjusted and adjusted means and standard errors for impairments in social reciprocity, impairments in verbal communication, and restricted and repetitive behaviors. The one-way ANCOVA comparing level of impairments in social reciprocity across the four age groups, controlling for functional skills and co-residence of respondent, was not significant (F (3, 281) = 0.05, p = .99), indicating that there was not a significant difference between the four age groups. In contrast, the one-way ANCOVA comparing impairments in verbal communication across the four age groups, controlling for functional skills and co-residence of respondent, was significant (F (3, 238) = 3.92, p = .01). Bonferroni post-hoc comparisons indicated that the 18–21 year-old group had a higher number of impairments in verbal communication than the 22–29 year-old group. There were no other significant age group differences. In the one-way ANCOVA comparing restricted and repetitive behaviors across the four age groups, controlling for functional skills and co-residence of respondent, was significant (F (3, 272) = 4.36, p = .01). Bonferroni post-hoc tests indicated that the 40–49 year-old group had fewer restricted and repetitive behaviors than the 18–21 year-old group. There were no other significant age group differences. Table 2 displays the endorsement of each ASD symptom item by age group.

One-way ANCOVAs were separately conducted to compare DSM-IV TR and DSM-5 diagnosis of ASD based on respondent-reported current symptoms across age groups, controlling for functional skills and co-residence of respondent. Table 5 displays the unadjusted and adjusted means and standard errors for DSM-IV TR and DSM-5 diagnosis of ASD by age group. The ANCOVAs for DSM-IV TR (F (3, 269) = 0.22, p = .66) and for DSM-5 (F (3, 290) = 0.27, p = .85) diagnosis of ASD were not significant. Across all age groups, the prevalence of ASD diagnosis based on respondent-reported current symptoms was higher using the DSM-IV TR as compared to the DSM-5 criteria. However, the discrepancy in ASD prevalence between the DSM-IV TR and DSM-5 for the 40–49 year-old

group (4.4% difference) was much lower than for the 18–21 year-old group (19.9% difference), 22–29 year-old group (17.1%), and 30–39 year-old group (16.4%). Review of item endorsement (Table 2) indicates that the younger age groups were more likely than the 40–49 year-old group to endorse items in the DSM-IV TR domain of impairments in communication. This domain is not included in the DSM-5; some items are no longer considered and others are now in the social communication or restricted and repetitive behavior domains. As a result, the changes to ASD diagnostic criteria in the DSM-5 would have impacted adult men aged 18 to 39 years-old more than adult men with FXS in their 40s, if diagnosis would be made solely on the basis of respondent-reported current symptoms.

Age, Disruptive Behavior, and Social Skills

Table 6 displays the unadjusted and adjusted means and standard errors for disruptive behavior and social skills by age group. The one-way ANCOVA comparing disruptive behavior across the four age groups, controlling for functional skills and co-residence of respondent, was at a trend level (F (3, 279) = 2.10, p = .10). Similarly, the one-way ANCOVA comparing social skills across the age groups, controlling for functional skills, was not significant (F (3, 288) = 0.10, p = .96).

Discussion

The present study adds to the small body of research on ASD symptoms in adulthood for men with FXS. Overall, findings suggest that there is a pattern of age-related improvement in some but not all ASD symptoms across adulthood for men with FXS. Specifically, the youngest age group (18–21 year-olds) had more impairments in verbal communication than the 22–29 year-olds and had more restricted and repetitive behaviors than the 40–49 year-olds. In contrast, there was not an age-group difference in number of impairments in social reciprocity. Smith et al. (2012) similarly found that age was negatively associated with restricted and repetitive behaviors but was not associated with impairments in social reciprocity in their sample of 136 adolescents and adults with FXS. Unlike in the present study, however, Smith et al. (2012) did not find a significant association between age and impairments in *nonverbal* communication (e.g., head nodding and pointing). Thus, it may be that improvement in communication is limited to a reduction of impairments in *verbal* communication and/or is restricted to adult men with FXS who can speak. This pattern of improvement is similar to that of adults with idiopathic ASD (Woodman et al., 2014), underscoring similarity in the developmental trajectory of symptoms across these populations. The present study's age-related pattern of improvement in ASD symptoms is in contrast to patterns seen across childhood and adolescence in FXS (McDuffie et al., 2010), highlighting how the trajectory of ASD symptoms differ across the life course. Future longitudinal research is needed to confirm these patterns using observational measures of within-person change.

In the domain of impairments in verbal communication, the greatest age-related differences were in 'speech is a mixture of meaningful and peculiar speech' and 'excessive questioning or preoccupation with particular topics.' Thus, among adult men with FXS who speak,

communication may become more meaningful and flexible and less unusual and repetitive with age. In the domain of restricted and repetitive behavior, the greatest age-related differences were in 'flaps hands,' 'rocking, spinning, finger wiggling, and toe walking,' and 'fascinated with light reflecting off object or moving only one part of toy/item', suggesting that repetitive behaviors and visual fixations may improve more than complicated routines and rituals and preoccupations across adulthood.

In our sample, there was not an age-group difference in the percentage of adult men with FXS who would meet criteria for a diagnosis of ASD using the DSM-IV TR or the DSM-5 criteria. Thus, although ASD symptoms decrease, these symptoms may not indicate clinically meaningful declines as symptoms continue to be sufficient in number to warrant an ASD diagnosis. DSM-IV TR criteria resulted in a higher prevalence of ASD diagnosis than did DSM-5 criteria, which is consistent with previous reports (Maenner et al., 2014; Wheeler et al., 2014). It is interesting to note that there was less of a discrepancy in the prevalence of ASD diagnosis based on current symptoms between the DSM-IV TR versus DSM-5 criteria for the 40–49 year-old group as compared to the younger age groups. This age-group difference appears to reflect differences in the constellation of symptoms endorsed. Specifically, the 18–21 year-old group had a higher endorsement of symptoms in the domain of impairments in communication for the DSM-IV TR than the 40- year-old group. This domain is not included in the DSM-5 (symptoms are either not considered or are in other domains), and thus the 18–22 year-old age group was more affected by changes in the DSM-5 than the oldest age group, when only considering current respondent-reported symptoms. Overall, this finding suggests that changes in the DSM-5 may have a greater impact on ASD diagnostic rates in young adults than in middle-aged adults with FXS. However, in actual clinical practice, *historical* symptoms are considered in addition to current symptoms in diagnostic decisions (APA, 2013). Consideration of historical symptoms has traditionally been used to capture symptoms in childhood. It is not clear if historical considerations also apply to adulthood in actual clinical practice; it is not clear if symptoms evident in young adulthood would influence diagnostic decisions for a middle-aged adult.

Impairments in social reciprocity are often considered to be the essential underlying feature of ASD (Volkmar & Klin, 2005). Across all age groups, 'avoids looking adults in eye' was the most frequently endorsed impairment in social reciprocity. Avoiding eye contact has been described as a hallmark feature of FXS in children and adolescents (Hagerman et al., 1986). Our findings suggest that avoiding eye contact continues to be a hallmark feature of FXS across adulthood. Given the lack of age-related differences in impairments in social reciprocity, it is not surprising that there was not an age-related difference in social skills in the present sample. Overall, these findings suggest that challenges with social interactions occur at a similar level in young adulthood as they did in middle adulthood for men with FXS.

There was some evidence of an age group difference in disruptive behavior in our sample of adult men with FXS; there was a trend for the 18–21 year-olds to have a higher level of disruptive behavior than the 30–39 year-olds and 40–49 year-olds. Smith et al. (2012) similarly found a negative association between age and behavior problems in their cross-

sectional sample of adolescents and adults with FXS. The improvement in verbal communication and restricted and repetitive behaviors may contribute to better behavioral regulation and smoother communication with others. Alternatively, the developmental mechanisms driving the improvement in ASD symptoms may similarly contribute more generally to a better ability to regulate emotions and behaviors.

Limitations and Future Study Directions

There are several strengths and weaknesses to the present study. We utilized data from a large national survey, the largest sample to date examining ASD symptoms in adult men with FXS. This was also the first study to assess clinical relevance of age-related improvements in ASD symptoms by comparing the ASD diagnostic status of our age-groups, if based solely on respondent-reported current symptoms using both DSM-IV TR and DSM-5 criteria. This approach estimates if age-differences may be clinically relevant but does *not* mirror clinical practice of ASD diagnosis (APA, 2013) which also considers observational measures and historical symptoms. Moreover, DSM-IV TR Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS) was not considered because it is not associated with specific symptom criteria. Thus, the current study is not equipped to provide insight into population-level prevalence of ASD diagnosis in adult men with FXS. A cross-sectional methodology was used in the present study. The socio-demographics of our four age groups were closely compared to identify potential differences, and functional skills and co-residence with the survey respondent were controlled for in all analyses. However, it is possible that generational differences, or differences in sample characteristics not assessed, are driving group effects. In particular, our sample of adults with FXS aged 40–49 years-old was small; it is not clear to what extent our sample reflects a random sample of the population of adults with FXS. For example, our sample was largely White and respondents were predominately high SES; thus, findings may not reflect age-related patterns in other race/ethnic and SES groups. Moreover, information about the national survey was widely circulated to FXS listservs, clinics, and research databases, making information about responses rate unclear. Future longitudinal studies are needed to see if findings from this study are replicated at a within-person level and to better understand if age-related improvements occur at a steady rate across adulthood. For example, it is not clear if restricted and repetitive behaviors steadily decline (somewhat indicated by the mean scores across age groups) or not until adult men with FXS reach their 40s.

As noted above, ASD symptoms were assessed through a respondent report survey designed for the national survey as opposed to a standardized measure. However, this survey was based on items from standardized measures of ASD symptoms and inquired about observable behaviors. Unfortunately, this survey did not assess impairments in nonverbal communication appropriate for adults; thus this category of ASD impairments was not evaluated. In addition, the ASD symptom survey inquired about the presence versus absence of ASD symptoms and did not capture the severity of each symptom. We examined age as a categorical variable to better understand when age-related differences may occur. However, analyses were also conducted using age as a continuous variable. Findings similarly indicated that age was significantly associated with impairments in verbal communication and restricted and repetitive behaviors but not impairments in social reciprocity (data

available from first author). Finally, we did not collect genetic information to confirm FXS status, although mechanisms were in place to authenticate the sample (e.g., respondents confirmed that adult had genetic testing, reported year of testing, and indicated test result). This also meant that the present study was not able to identify genetic factors that may be related to ASD symptoms.

In summary, this study suggests that there is an age-related pattern of difference in impairments in verbal communication and restricted and repetitive behaviors in adulthood. There was a corresponding age-related pattern of difference in disruptive behavior. In contrast, impairments in social reciprocity, generally considered to be the essential feature of ASD, was not associated with age and did not differ among our age groups. Relatedly, there was not an age-related difference in social skills. Differences in ASD symptoms did not translate into differences in the percentage of adults who would currently meet criteria for a diagnosis of ASD among the age groups. Adults with FXS and a diagnosis of ASD had a higher number of ASD symptoms across all three symptom domains than adults with FXS ‘only’. Age-related difference in ASD symptoms did not translate into an age-related difference in the percentage of adults who met diagnostic criteria for ASD when diagnosis was based solely on respondent-reported current symptoms. Changes to ASD in the latest version of the DSM (DSM-5) may have a greater impact on younger adults than middle-aged adults with FXS.

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Table 1

Characteristics of Adult Men with Fragile X Syndrome (FXS) and Respondents by Age Group

	18–22yrs N = 70	23–29 yrs N = 116	30–39 yrs N = 70	40–49 yrs N = 34	F value/Chi-square	P-value
Men with FXS						
White (n, [%])	80 (92.0%)	93 (93.0%)	68 (97.1%)	34 (100%)	3.13	.22
Functional Skills (M, SD)	117.94(33.62)	129.10 (28.77)	134.43 (31.08)	131.15 (32.99)	4.08	.01
Does not speak (n, [%])	16 (18.60%)	10 (10.31%)	7 (10.61%)	2 (6.90%)	4.38	.22
Health (M,SD)	3.87 (0.54)	3.54 (0.87)	3.55 (0.67)	3.32 (0.88)	0.98	.68
Residence (n, [%])						
Alone/roommate	0 (0%)	5 (5.3%)	4 (6.2%)	12 (30.8%)		
Respondent	81 (92.0%)	72 (76.6%)	38 (59.4%)	8 (20.5%)		
Group home	4 (4.5%)	10 (10.6%)	16 (25.0%)	15 (38.5%)		
Treatment center	0 (0%)	1 (1.1%)	0 (0%)	2 (5.1%)		
Other	3 (3.4%)	6 (6.4%)	6 (9.4%)	2 (5.1%)	92.34	<.001
Respondent						
Gender (n, [%])						
Female	64 (91.4%)	107 (92.2%)	62 (88.6%)	30 (88.2%)	3.61	.80
Age in yrs (M, SD)	50.93 (7.83)	55.34 (5.65)	62.60 (4.63)	72.39 (8.99)	98.08	<.001
Education (n,[%])						
College degree	60 (68.2%)	68 (72.3%)	44 (67.7%)	23 (59.0%)	2.28	.52
Residential Location (n,[%])						
Northeast, U.S.	24 (27.3%)	15 (16.0%)	15(23.1%)	5 (12.8%)		
Midwest, U.S.	23 (26.1%)	30 (31.9%)	15 (23.1%)	14 (35.9%)		
South, U.S.	28 (31.8%)	27 (28.7%)	20 (30.8%)	13 (33.3%)		
West, U.S.	10 (11.4%)	19 (20.2%)	12 (18.5%)	4 (8.9%)		
Outside of U.S.	2 (2.1%)	2 (2.1%)	2 (3.1%)	0 (0%)		
Not reported	1 (1.1%)	1 (1.1%)	1 (1.5%)	3 (7.7%)	17.65	.28
Relation (n, [%])						
Parent	94 (98.1%)	99 (99%)	34 (100%)	34 (100%)		
Other relative or guardian	1 (1.0%)	1 (0.6%)	0 (0.0%)	0 (0.0%)		
Co-Reside with Adult with FXS (n,[%])	64 (91.4%)	106 (91.4%)	43(61.4%)	10 (29.4%)	73.10	<.001

	18–22yrs N = 70	23–29 yrs N = 116	30–39 yrs N = 70	40–49 yrs N = 34	F value/Chi-square	P-value
FXS status (n, [%])						
Premutation	64 (72.7%)	63 (67.0%)	46 (70.8%)	23 (59.0%)		
Full mutation	2 (2.3%)	0 (0%)	0 (0%)	0 (0%)		
Non-FX	2 (2.2%)	2 (2.2%)	2 (3.0%)	2 (5.1%)		
Not tested	19 (21.6%)	29 (30.8%)	17 (26.2%)	14 (35.9%)	8.88	.43

Table 2

Mean adjusted for functional skills and Co-Residence of Respondent and Standard errors in parenthesis for endorsement of items mapped onto the Diagnostic and Statistical Manual (DSM) IV TR diagnosis of Autistic Disorder (AD) and DSM-5 diagnosis of Autism Spectrum Disorder (ASD) by age group

Item	DSM-IV TR AD	DSM-5 ASD	18–21 yrs N = 88	22–29 yrs N = 94	30–39 yrs N = 65	40–49 yrs N = 34
Impairments in Social Reciprocity						
Avoids looking adults in the eye	Social	Soc/Com	.85 (.05)	.87 (.04)	.73 (.07)	.75 (.11)
Looks through people	Social	Soc/Com	.36 (.06)	.29 (.05)	.23 (.08)	.18 (.13)
Has not developed any friendships with peers	Social	Soc/Com	.52 (.07)	.41 (.05)	.31 (.09)	.27 (.14)
Does not initiate sharing information about events with others unless prompted	Social	Soc/Com	.52 (.07)	.55 (.05)	.69 (.09)	.81 (.14)
Not responsive to others' facial expressions or emotional expressions	Social	Soc/Com	.21 (.05)	.16 (.04)	.22 (.07)	.28 (.11)
Displays inappropriate type/degree of emotional reaction	Social	Soc/Com	.53 (.07)	.27 (.05)	.47 (.09)	.38 (.14)
Does not Speak	Com	-------	.18 (.07)	.12 (.03)	.11 (.05)	−.08 (.08)
Impairments in Verbal Communication						
Speech is a mixture of meaningful and peculiar speech	Com	RRB	.64 (.07)	.49 (.05)	.45 (.09)	.29 (.14)
Echoes questions or statements made by others	Com	RRB	.65 (.06)	.62 (.05)	.80 (.08)	.58 (.13)
Excessive questioning or preoccupation with particular topics	Com	RRB	.79 (.06)	.63 (.05)	.66 (.08)	.72 (.13)
Repeats phrases over and over	Com	RRB	.73 (.06)	.72 (.05)	.83 (.08)	.71 (.12)
Repeats sounds or words	Com	RRB	.59 (.06)	.52 (.05)	.50 (.08)	.39 (.14)
Restricted and Repetitive Behaviors						
Strange finger movements, peculiar finger or body posturing	RRB	RRB	.33 (.06)	.29 (.05)	.38 (.08)	.15 (.13)
Rocking, spinning, finger wiggling, toe walking	RRB	RRB	.41 (.06)	.24 (.05)	.34 (.08)	.29 (.13)
Flaps hands	RRB	RRB	.52 (.06)	.50 (.05)	.46 (.08)	.33 (.13)
Plays with one object exclusively	-------	RRB	.35 (.06)	.28 (.05)	.28 (.08)	.03 (.12)
Preoccupied with using toy/item in unusual way	-------	RRB	.26 (.05)	.20 (.04)	.26 (.07)	−.03 (.11)
Focuses on one part of toy/item	RRB	RRB	.38 (.05)	.24 (.04)	.24 (.07)	−.05 (.11)
Fascinated with light reflecting off object or moving only one part of object	RRB	RRB	.30 (.05)	.20 (.04)	.17 (.07)	.09 (.11)
Looks at object from unusual angle	-------	RRB	.25 (.05)	.18 (.04)	.27 (.07)	−.05 (.11)
Insists on having object with him/her	-------	RRB	.42 (.06)	.34 (.05)	.26 (.08)	.17 (.13)
Gets involved with complicated rituals	RRB	RRB	.27 (.05)	.14 (.04)	.18 (.07)	−.03 (.11)
Becomes angry or upset when established routines altered	RRB	RRB	.61 (.07)	.64 (.05)	.60 (.09)	.54 (.14)

Item	DSM-IV TR AD	DSM-5 ASD	18–21 yrs N = 88	22–29 yrs N = 94	30–39 yrs N = 65	40–49 yrs N = 34
When adult tries to change routine, continues with same activity	RRB	RRB	.41 (.06)	.38 (.05)	.42 (.08)	.20 (.13)
When adult tries to change routine, he/she activity refuses	-------	RRB	.42 (.06)	.31 (.05)	.28 (.08)	.28 (.13)
Stiffens to touch or hard to hold	-------	RRB	.44 (.07)	.44 (.05)	.59 (.09)	.76 (.14)

Note. Soc/Com = Impairments in social communication and interaction. Com = impairments in communication. RRB = Restricted and repetitive behaviors. We also examined unadjusted means and standard errors and the overall pattern of endorsement remained the sam

Table 3

Correlations among Socio-demographics of Adult Men with FXS and Key Study Variables

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1. White	--													
2. Chronological Age	.11	--												
3. Health	−.02	.11	--											
4. Seizures	.09	.01	−.18**	--										
5. Functional Skills	−.02	.05	−.14*	.15*	--									
6. Ability to Speak	−.01	−.05	.07	−.05	−.31**	--								
7. Co-Residence with Respondent	.13*	.49**	.03	−.06	−.07	.03			.					
8. Social Skills	−.03	.02	.17**	.06	.45**	−.19**	.04	--						
9. Disruptive Behavior	.01	−.21**	.15**	−.03	−.17**	−.02	−.15*	−.25**	--					
10. Social Reciprocity	−.01	−.01	−.03	.002	−.25**	.25**	.06	−.43**	.31**	--				
11. Verbal Communication	−.01	−.14*	.09	−.11	−.22**	−.11	.−.03	−.14*	.17**	.28**	--			
12. Restricted and Repetitive Behaviors	.08	−.21**	.06	−.10	−.40**	.14*	.02	−.39**	.26**	.55**	.46**	--		
13. DSM-IV TR ASD	.09	−.05	.001	−.10	−.24**	.02	.08	−.26**	.22**	.39**	.29**	.39**	--	
14. DSM-5 ASD	.08	−.02	.02	−.06	−.19**	.20**	−.01	−.35**	.09	.49**	.06	.32**	.27**	--

Note. DSM-IV TR ASD = Diagnostic and Statistical Manual fourth edition, text revision diagnosis of Autistic Disorder; DSM-5 ASD = Diagnostic and Statistical Manual Fifth edition diagnosis of Autism Spectrum Disorder.

*P <.05,

**P <.01.

Table 4

Unadjusted Mean and Standard Error in parenthesis for Autism Symptom Domain Scores by Age group and then adjusted for Functional Skills and Co-Residence with Respondent

	Unadjusted				Adjusted for Functional Skills and Co-Residence with Respondent			
	18–21 yrs (n = 70)	**22–29 yrs (n =114)**	**30–39 yrs (n = 65)**	**40–49 yrs (n = 33)**	**18–22 yrs (n = 70)**	**23–29 yrs (n = 114)**	**30–39 yrs (n = 65)**	**40–49 yrs (n = 33)**
Social Reciprocity	2.79 (0.15)	2.58 (0.16)	2.50 (0.20)	2.71 (0.25)	2.67 (0.18)	2.61 (0.14)	2.61 (0.19)	2.69 (0.29)
* Verbal Communication	3.53 (0.19)	2.71 (0.17)[a]	2.77 (0.23)	2.46 (0.29)	3.48 (0.20)	2.68 (0.16)[a]	2.89 (0.20)	2.42 (0.33)
Restricted/ Repetitive Behavior	5.12 (0.36)	4.04 (0.35)	3.70 (0.45)	2.71 (0.58)[a]	5.05 (0.38)	4.14 (0.29)	4.07 (0.40)	2.27 (0.65)[a]

Note.

*analyses with subsample of men with FXS in 18–21 years (n = 72), 22–29 years (n = 81), 30–39 years (n = 55), and 40–49 years groups reported to speak.

[a]lower than 18–21 year-old group

Table 5

Unadjusted Mean and Standard Error in parenthesis for Percentage of Adult Men within each Age Group who met Diagnostic and Statistical Manual Fourth Edition Text Revision (DSM- IV TR) criteria for Autistic Disorder (AD) and Fifth Edition (DSM-5) criteria for Autism Spectrum Disorder based on current symptoms and then adjusted for functional skills and co-residence with respondent

	Unadjusted				Adjusted for Functional Skills			
	18–21 yrs (n = 70)	**22–29 yrs (n = 116)**	**30–39 yrs (n = 70)**	**40–49 yrs (n = 34)**	**18–21 yrs (n = 70)**	**22–29 yrs (n = 116)**	**30–39 yrs (n = 70)**	**40–49 yrs (n = 34)**
DSM-IV	45.6 (5.9)	35.8 (4.7)	34.9 (6.1)	33.3 (8.9)	43.6 (5.3)	37.5 (5.0)	35.8 (6.2)	29.8 (7.9)
TR DSM-5	25.7 (4.9)	21.4 (3.8)	17.1 (4.9)	23.5 (7.1)	23.7 (5.1)	21.1 (3.9)	18.7 (5.1)	25.4 (7.8)

Table 6

Unadjusted Mean and Standard Errors in parenthesis for Disruptive Behavior and Social Skills Total Scores by Age group and then adjusted for Functional Skills and Co-Residence with Respondent

	Unadjusted				Adjusted for Functional Skills			
	18–21yrs (n = 69)	**22–29 yrs (n = 115)**	**30–39yrs (n = 69)**	**40–49 yrs (n = 34)**	**18–21yrs (n = 69)**	**22–29 yrs (n = 115)**	**30–39yrs (n = 69)**	**40–49 yrs (n = 34)**
Disruptive Behavior	16.22 (0.39)	15.55 (0.38)	14.58 (0.46)	13.53 (.59)	15.95 (0.45)	15.46 (0.35)	14.82 (0.45)	13.93 (0.68)
Social Skills	35.39 (0.86)	35.77 (0.84)	27.20 (1.00)	36.00 (1.28)	36.02 (0.78)	35.40 (0.91)	36.97 (0.91)	35.86 (1.16)