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Anxiety, Attention Problems, Hyperactivity, and the Aberrant Behavior Checklist in Fragile X Syndrome

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Behavior problems are a common challenge for individuals with fragile X syndrome (FXS) and constitute the primary clinical outcome domain in trials testing new FXS medications. However, little is known about the relationship between caregiver-reported behavior problems and co-occurring conditions such as anxiety and attention problems. In this study, 350 caregivers, each with at least one son or daughter with full-mutation FXS, rated one of their children with FXS using the Aberrant Behavior Checklist—Community Version (ABC-C); the Anxiety subscale of the Anxiety, Depression, and Mood Scale; and the Attention/Hyperactivity Items from the Symptom Inventories. In addition to examining family consequences of these behaviors, this study also sought to replicate psychometric findings for the ABC-C in FXS, to provide greater confidence for its use in clinical trials with this population. Psychometric properties and baseline ratings of problem behavior were consistent with other recent studies, further establishing the profile of problem behavior in FXS. Cross-sectional analyses suggest that selected dimensions of problem behavior, anxiety, and hyperactivity are age related; thus, age should serve as an important control in any studies of problem behavior in FXS. Measures of anxiety, attention, and hyperactivity were highly associated with behavior problems, suggesting that these factors at least coincide with problem behavior. However, these problems generally did not add substantially to variance in caregiver burden predicted by elevated behavior problems. The results provide further evidence of the incidence of problem behaviors and co-occurring conditions in FXS and the impact of these behaviors on the family.

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INTRODUCTION

Fragile X syndrome (FXS), the leading known hereditary form of intellectual disability (ID), results from a trinucleotide (CGG) repeat expansion in the *FMR1* gene and the subsequent loss of function of the fragile X mental retardation protein (FMRP) [Gross et al., 2012]. Cognitive and social impairments are almost universally seen in males and commonly observed in affected females. Challenging behavior problems, including tactile defensiveness, hand flapping, poor eye contact, hyperactivity, tantrums, perseveration, hyperarousal to sensory stimuli, impulsivity, self-injury, and aggression, are also frequently reported [Hatton et al., 2002; Hagerman et al., 2009; Symons et al., 2010], especially in males.

For many individuals, behavior problems and mood instability constitute the most debilitating aspects of FXS, and treatments for anger, aggression, and mood volatility are commonly needed across the lifespan [Bailey et al., 2012a,b]. Behavior problems are often the most significant concern reported by parents, and high levels of stress and depression and low levels of quality of life for parents are commonly associated with elevated problem behaviors in children [McCarthy et al., 2006; Hall et al., 2007; Wheeler et al., 2008; Bailey et al., 2008a]. As a result, reduction in behavior problems is a primary focus of ongoing clinical trials testing the efficacy of new

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medications for FXS [Sansone et al., 2012]. Confidence in the ways that behavior problems are measured and an understanding of the relationship between behavior problems and other constructs such as anxiety and attention problems, two areas of high co-morbidity in FXS, however, are limited. This article reports the results of a study designed to test the factor structure of a parent rating scale used in almost all clinical trials for FXS; explores the interrelationships among anxiety, attention, and problem behaviors in FXS; and assesses the extent to which measures of anxiety and attention add to the predictive value of problem behavior assessment with regard to individual and caregiver outcomes in FXS.

Measurement of Behavior Problems

The measurement of behavior problems in individuals with intellectual disabilities (IDs) has been a challenge for both researchers and clinicians [Dekker et al., 2002]. Ideally, behavior problems should be documented by direct and systematic observation. But because most problem behavior occurs infrequently or in response to particular environmental stressors, direct observation can be expensive and time consuming, and instances of problem behavior could be missed. Rating scales by knowledgeable observers (e.g., parents, teachers, caregivers) are frequently used in lieu of direct observation, with generally good results. One of the most commonly used measures, the Aberrant Behavior Checklist (ABC) [Aman and Singh, 1986] was developed to address the need for a behavior scale for individuals with IDs. The original ABC was designed to assess behavioral concerns of adults within institutional settings. In order to better address the behavioral concerns of children and individuals not in institutional placements, the wording of the original ABC was changed on some items in a subsequent version—the ABC-Community (ABC-C) [Aman and Singh, 1994]. Examples of changes made from the original ABC to the ABC-C included revising "excessively active on the *ward*" to "excessively active *at home, school, work or elsewhere*." Several studies have supported the original factor structure for the newer version [Aman and Singh, 1994; Aman et al., 1995] and the psychometrics of both versions have been reported to be equally sound [Paclawskyj et al., 1997; Brown et al., 2002; Aman, 2010].

The ABC-C is a parent or caregiver rating scale assessing several clusters of problematic behavior—irritability, hyperactivity, lethargy/social withdrawal, stereotypy, and inappropriate speech. Over the last several decades, the ABC-C has been used extensively in descriptive and intervention studies [Van Bellinghen and de Troch, 2001; Aman et al., 2002]. Because of its strong psychometric properties and demonstrated sensitivity in double-blind placebo controlled trials, the ABC-C is frequently used as an outcome measure for medication and other intervention studies targeting challenging behaviors in individuals with a variety of diagnoses [McCracken et al., 2002; Arnold et al., 2003; Shea et al., 2004; Gerber et al., 2011; Ching and Pringsheim, 2012], including a number of studies of individuals with FXS [Paribello et al., 2010; Erickson et al., 2011; Jacquemont et al., 2011; Berry-Kravis et al., 2012].

Because of the widespread use of the ABC-C in clinical trials, several studies have examined its psychometric properties for specific populations [Brinkley et al., 2007; Ji et al., 2011]. A recent study investigating the application of the ABC-C for individuals with FXS concluded that a fragile X-specific factor structure is warranted [Sansone et al., 2012]. The original five factors were reorganized and a sixth factor emerged, Social Avoidance. Studies of children and adults with FXS, using both the original and the new factor structures have found that behaviors related to the Irritability and Hyperactivity subscales are the most concerning [Baumgardner et al., 1995; Gothelf et al., 2007; Sansone et al., 2012]. In a recent study we found that the Irritability subscale, in particular, was highly associated with several dimensions of caregiver burden, including number of specialist visits needed by an individual with FXS, medication use by individuals with FXS, economic burden due to FXS, caregiver injuries, and caregiver mental health [Bailey et al., 2012b]. The Irritability and Hyperactivity subscales capture aggressive and disruptive behaviors, as well as activity level, impulsivity, and distractibility. Compared with other samples of individuals with ID, males with FXS have been reported to have higher levels of stereotypic movements and unusual/inappropriate speech captured on other subscales of the ABC-C [Baumgardner et al., 1995; Sansone et al., 2012]. Given the use of the ABC-C as an outcome measure for clinical drug trials in FXS, as well as the use of the ABC-C in predicting outcomes for caregivers, further confirmation of the proposed FXS-specific factor structure of the ABC-C is needed.

Problem behavior in children with FXS and associated developmental disabilities, such as autism, have generally been reported as stable across different age groups [Hatton et al., 2002; Matson et al., 2010], suggesting that, at least in childhood, difficult behaviors do not change over time. However, studies exploring specific behaviors (Irritability and Hyperactivity) as measured by the ABC-C suggest these clusters of problems may decrease over time in children and adults with developmental disabilities [Brown et al., 2002]. Both cross-sectional and longitudinal studies are needed to provide more definitive answers to age-related aspects of the FXS phenotype and to determine the extent to which age should be a factor in interpreting outcomes in clinical trials.

Anxiety and Attention Problems in FXS

Several studies have shown that elevated behavior problems in FXS may be associated with factors such as increased cortisol [Hessl et al., 2002], atypical autonomic regulation [Heilman et al., 2011], inadequate levels of oxytocin [Hall et al., 2012], secondary genes [Hessl et al., 2008], or neuroanatomical abnormalities and reduced levels of FMRP (the protein disrupted by FXS) [Gothelf et al., 2007]. The pathways by which alterations in the *FMR1* gene lead to arousal and problem behaviors are not yet fully understood; however, clinical reports and research studies almost always mention anxiety and attention problems as fundamental characteristics of individuals with FXS [Bailey et al., 2008a; Cordeiro et al., 2011; Tranfaglia, 2011]. In a large study, we found that 84% of males and 67% of females with FXS had been diagnosed or treated for attention problems and 70% of males and 56% of females had been diagnosed or treated for anxiety problems [Bailey et al., 2008b]. Of interest is the extent to which anxiety or attention problems are associated with problem behaviors and whether measuring those constructs can help explain variation in other child and family outcomes over and above the variance explained by instruments such as the ABC-C.

Anxiety appears to be a pervasive concern for both males and females with FXS. Studies using parent questionnaires as well as DSM-IV checklists and interviews have documented significantly higher rates of anxiety disorders relative to the general population, as well as to other groups with IDs [Cordeiro et al., 2011]. A recent comprehensive study of anxiety symptoms in both males and females found 86% of males and 77% of females met criteria for at least one anxiety disorder [Cordeiro et al., 2011]. No differences were found based on IQ, age, or autism status.

In addition to anxiety, attention problems are a noted clinical concern in FXS. Attention Deficit/Hyperactivity Disorder (ADHD) is the one of the most commonly diagnosed co-morbid conditions [Tranfaglia, 2011], with up to 74% of males meeting diagnostic criteria at some point in their lives [Backes et al., 2000]. Hyperactivity is often described as the most intense and pervasive symptom of ADHD, especially in young children with FXS, and difficulty with attention regulation and impulse control are also frequently reported [Tranfaglia, 2011]. Attention problems have been hypothesized to be a predictor of challenging behavioral outcomes; early difficulties in visual attention have been shown to be related to later hyperactive behaviors in children with FXS [Scerif et al., 2012]. Furthermore, a global dysregulation of autonomic nervous system functioning, noted in individuals with FXS [Hall et al., 2009], may drive not only difficulties with attention regulation, hyperactivity, and impulsivity, but also may contribute to the sensory sensitivity and tactile defensiveness often described [Tranfaglia, 2011]. ADHD symptomology, therefore, is an important factor in considering the impact of behavioral outcomes for individuals with FXS and their caregivers.

Research Questions

Although profiles of behavior, anxiety, and attention problems in FXS have previously been reported, most studies have used questionnaires or rating scales normed for individuals without IDs and were conducted with relatively small samples. Further, despite the potential overlap of behavioral challenges with anxiety and attention regulation, no study to date has examined the interrelationships among anxiety, attention, and problem behaviors, nor has research examined the cumulative impact of these characteristics on functional outcomes for families. Accordingly, the present study extends research on behavior profiles of individuals with FXS to answer three questions:

1. *Can the findings of a recent study suggesting a new FXS-specific factor structure for the Aberrant Behavior Checklist—Community Version be replicated?*
   The original factor structure of the ABC-C has been used in literally hundreds of studies. A replication of the Sansone et al. [2012] report of a new six-factor structure for the ABC-C would provide greater confidence in its application in clinical trials for medications or other interventions that address behavior problems in FXS.

2. *To what extent are symptoms of general anxiety, ADHD, and problem behaviors evident in individuals with FXS and what are the interrelationships among these variables?*
   Using measures designed to assess behavioral and psychiatric outcomes in individuals with IDs, we examine in greater detail how these symptoms manifest in individuals with FXS and how they relate to one another. We hypothesized that many individuals with FXS would have clinically significant levels of anxiety and ADHD symptoms relative to norming samples. We also wanted to determine whether the mean subscale scores for males in our sample were comparable to the scores reported by Sansone et al. [2012]. Finally, we predicted that individuals scoring high on measures of ADHD and anxiety would be more likely to also experience higher levels of problem behaviors.

3. *Do measures of anxiety and ADHD symptoms explain additional variance in caregiver and family outcomes, beyond that explained by problem behaviors as measured by the ABC-C?*
   Irritability, as measured by the ABC-C, has previously been reported to be highly predictive of more negative outcomes for caregivers [Bailey et al., 2012b]. The current study extends this work by examining the relative contribution of anxiety and ADHD symptoms in predicting family outcomes. We hypothesized that measures of anxiety and ADHD would explain a significant portion of variance in caregiver outcomes, even when Irritability scores on the ABC-C are considered.

MATERIALS AND METHODS

Design

This study was a nonrepresentative survey of families affected by FXS. Survey items targeting behavior, attention, and anxiety problems were taken directly from the standardized instruments described below. The majority of participants (93%) completed the survey online. A telephone option was also available (7%).

Participants

Building on a previously successful model of survey research in FXS [Bailey et al., 2010], we invited 508 caregivers enrolled in a research registry who self-reported having a child with the full-mutation FXS age 5 and older to complete a new survey. A total of 350 families (69%) participated. The respondents were primarily female (91%), white (92%), married (84%), and well educated (61% with at least a 4-year college degree), with an average age of 49.8 years. Respondents provided information on 292 males (average age = 19.7, range = 5–66) and 58 females (average age = 17.1, range 6–44). For respondents who had more than one family member with FXS, the research team selected one using a predetermined algorithm based on gender and age. The term "child" or "children" is used for convenience to describe both children and adults for whom the respondents reported.

Measures

Parents rated their son or daughter on selected items from three standardized questionnaires and on a number of other items (described below) developed by the authors to assess caregiver burden [Bailey et al., 2012b].

Behavior problems. Caregivers completed the 58-item ABC-C. Each item was scored based on the respondent's perception of their child's behavior in the previous 4 weeks. The items, all rated on a 4-point scale ranging from 0 (*Not a problem*) to 3 (*Problem is severe*

in degree), are used to calculate raw subscale scores. Multiple studies have been published supporting reliability and validity of the ABC-C with adult [Aman and Singh, 1994; Aman et al., 1995] and child [Brown et al., 2002; Brinkley et al., 2007] populations with IDs.

Anxiety. Anxiety symptoms were assessed using items from the Anxiety, Depression, and Mood Scale (ADAMS) [Esbensen et al., 2003], a questionnaire developed to screen for psychiatric disorders in individuals with IDs. The full 28-item scale measures a range of psychopathology including manic/hyperactive behavior, depressed mood, social avoidance, general anxiety, and obsessive/compulsive behavior. Studies from Esbensen and Benson [2006] and Rojahn et al. [2011] suggest that the ADAMS has reasonable internal consistency within subscales, good convergence on factors, and generally correlates with other measures designed to assess similar constructs. Cordeiro et al. [2011] used the ADAMS as part of a larger study of 98 individuals with FXS and found that the General Anxiety subscale correlated significantly with several clinical diagnoses of anxiety, suggesting that it provided accurate information regarding the severity of anxiety symptoms in FXS. For this study, only the seven items assessing General Anxiety symptoms were used. Respondents rated the severity of each anxiety symptom in the previous 6 months on a scale from 0 (*Not a problem*) to 3 (*Severe problem*).

Attention and hyperactivity. Items from age-relevant versions of the Symptom Inventories—the *Child and Adolescent Symptom Inventory* (CASI) [Gadow and Sprafkin, 2010] or the *Adult Inventories* (AI) [Gadow et al., 2004]—were used to assess DSM-IV symptoms of ADHD. The Symptom Inventories provide several ways of measuring symptoms of ADHD, including severity scores as well as diagnostic cutoff scores. These inventories, which include age-specific caregiver rating scales, measure several different areas of psychopathology. They have been used extensively to characterize psychiatric diagnoses in a variety of populations including autism [Lecavalier et al., 2011; Gadow and DeVincent, 2012; Gadow et al., 2012] and FXS [Sullivan et al., 2006; Gabis et al., 2011]. The ADHD items on the CASI (19 items) and AI (18 items) are rated on a 4-point scale ranging from 0 (*Never*) to 3 (*Very often*) and reflect current behaviors. Responses provide two scores—a categorical symptom count (raw score) and a dimensional symptom severity score (T-score)—for three different ADHD diagnoses: ADHD Inattentive type, ADHD Hyperactive/Impulsive type, and ADHD combined type.

Caregiver burden. In addition to the standardized measures, survey respondents were asked to provide information regarding several areas of caregiving burden [Bailey et al., 2012b]. Many of these items were replicated from a previous survey of caregivers of individuals with FXS [Bailey et al., 2010]. Prior to data collection, we conducted cognitive testing to make sure the items were written clearly, the response options were not too broad or narrow, and the overall format of the survey was understandable. For this paper, we selected six items measuring caregiver burden: (a) daily hours of specialized caregiving provided by family members (i.e., *During a typical day, how many hours of care or special support do you and other family members provide for [CHILD]'s needs related to having fragile X?*), (b) the number of visits to medical specialists their son or daughter required, (c) the number of medications their son or daughter was taking specifically for FXS, (d) how much mental health counseling was sought for the caregiver, (e) how many times the caregiver had been injured by their son or daughter, and (f) the economic impact/financial burden of having a child with FXS.

Numbers provided by respondents for each of these variables were closely examined and transformed into dichotomous variables for the regression models. Specifically, the variables were coded as follows, with the percentage of caregivers in each group indicated as well: (1) family caregiving was dichotomized into families reporting 8 or fewer hours of care by family member (64%) versus those reporting more than 8 hr (34%), on the assumption that 8 hr constitutes a work day. Caregiver injuries were dichotomized into families reporting no injuries (71%) versus those reporting one or more injuries (29%), on the assumption that the presence or absence of caregiver injury was a salient distinction for severe family impact. Similarly, mental health counseling was dichotomized into families reporting no use of counseling (65%) versus those who had used a counselor (35%). Financial burden, number of specialist visits, and number of medications used were dichotomized to create a relatively even split in the groups: specialist visits less than five (55%) versus five or more (45%); number of medications: 0 or 1 (55%) versus 2 or more (45%); and financial burden: not at all or a little bit (44%) versus somewhat or a great deal (56%).

Logistic regression models were run separately using continuous and then dichotomized versions and the results showed no meaningful differences. Generalized linear models using continuous outcome variables were also run. Because of outliers, better-fitting models were created using the logistic regression models with recoded dichotomized outcomes.

Statistical Analysis

A confirmatory factor analysis for structure for FXS was conducted with males only to determine the best model fit. A good model fit would be indicated if the comparative fit index (CFI) and Tucker–Lewis Index (TLI) had values of 0.90 or higher and the root mean square error of approximation (RMSEA) had a value of 0.08 or less. In addition, factor loadings for each item should have values of 0.40 or higher. Descriptive statistics were used to characterize the nature and extent of aberrant behaviors, anxiety, and ADHD symptoms. Spearman correlation coefficients were calculated to examine the interrelationships among the child measures. Spearman correlation is more appropriate for measurements with an ordinal scale such as age categories. However, Pearson correlations were also calculated for the measurements that did not include any ordinal scales. There were no significant differences in the results, so only the Spearman correlation results are reported. Bonferroni-adjusted P values were calculated and are reported for all correlations.

Finally, regression analyses were used to test the relative contribution of problem behaviors, anxiety, and ADHD symptoms on different measures of caregiver burden. To account for missing data, only cases with complete data are used in each analysis; therefore, sample sizes vary somewhat across analyses.

RESULTS

Behavior Problems

Both the 5-factor and the 6-factor solutions for the ABC-C were appropriate based on the fit indices. For the original 5-factor

solution, we found a CFI of 0.91, TLI of 0.90, and a RMSEA of 0.06. The 6-factor solution proposed by Sansone et al. [2012] provided a marginally better fit with our sample, with a CFI of 0.94, TLI of 0.93, and RMSEA of 0.05. Each of the six subscales demonstrated very strong internal consistency. Cronbach's alphas by subscale were Irritability (0.93), Hyperactivity (0.91), Lethargy/Social Withdrawal (0.86), Social Avoidance (0.92), Stereotypy (0.84), and Inappropriate Speech (0.80). Although the 6-factor solution was not substantially superior to the original 5-factor structure, we used the 6-factor solution in subsequent analyses to compare our other findings with those reported by Sansone et al. [2012]. Factor loadings for both the 5- and 6-factor solutions for this sample are provided in Tables I and II.

Mean scores for males and females on the six subscales are provided in Table III. Figure 1 illustrates trends in ABC-C scores across age groups for both our sample and the Sansone et al. data. For males, age was negatively correlated with Irritability ($r = -0.30$, $P < 0.0001$), Hyperactivity ($r = -0.52$, $P < 0.0001$), and Stereotypy ($r = -0.18$, $P = 0.005$) and positively correlated with Social Avoidance ($r = 0.24$, $P < 0.001$). For females, age was negatively correlated with Hyperactivity ($r = -0.54$, $P < 0.001$). A comparison of our findings with the Sansone et al. sample by subscale and age group for males is displayed in Table IV. For the six age groups between ages 6 and 17, in 24 of 36 comparisons, our sample means were lower than those reported by Sansone et al. However, using *t*-tests to examine differences between our means and those reported by Sansone et al., only three comparisons were statistically significant: Inappropriate Speech, age group 10–11 ($t = -2.00$, $P = 0.05$); Hyperactivity, age group 12–13 ($t = -2.65$, $P = 0.01$); and Lethargy, age group 14–15 ($t = 3.30$, $P = 0.001$).

Sansone et al. combined all individuals ages 18–25 into one age group and did not include individuals over 25. In Table V, we provide means for adult males in our sample for two age groups: 18–25, and >25 years. Significant differences between our means and those reported by Sansone et al. were found for the 18- to 25-year old group on the Hyperactivity ($t = -3.20$, $P = 0.001$) and Stereotypy ($t = -2.07$, $P = 0.05$) subscales.

Anxiety

Mean scores for males and females on the Generalized Anxiety subscale of the ADAMS are reported in Table III. The mean scores for males fell in the 50th to 75th percentile based on the Rojahn et al. [2011] sample of adults with mild to profound ID, suggesting an elevated level of clinically significant anxiety symptoms in FXS. Anxiety scores for males remained stable across the age groups, as illustrated in Figure 2.

Attention

Mean T-scores for males and females on the CASI/AI are provided in Table III. Also reported are the number and percentage of males and females who exceeded clinical cutoffs for ADHD Inattentive and ADHD Hyperactive/Impulsive. Mean T-scores suggest moderate severity (T-scores in the range of 60–69 according to the CASI/AI manual) for males on both the Inattentive ($M = 62.2$) and Hyperactive/Impulsive ($M = 60.1$) subscales and for females on the Inattentive subscale ($M = 60.9$). Seventy-three (25%) males and 13 (22%) females had Inattention T-scores in the high severity range, and 76 (26%) males and 10 (17%) females met the clinical cutoff for ADHD Inattentive type. Sixty-eight (23%) males and 8 (14%) females had Hyperactive/Impulsive T-scores in the high severity range, and 44 (15%) males and 4 (7%) females met the clinical cutoff for ADHD Hyperactive/Impulsive type.

Age was negatively correlated with Hyperactive/Impulsive T-scores for both males ($r = -0.30$, $P < 0.001$) and females ($r = -0.49$, $P = 0.001$) and for Inattention T-scores for females ($r = -0.37$, $P = 0.01$). Figures 3 and 4 illustrate age trends for males in the mean T-scores as well as the percentage of males meeting the clinical cutoff for ADHD Inattention or Hyperactivity.

Correlations Among Child Measures

As shown in Tables V and VI, the ADAMS, T-scores for Inattention and Hyperactivity on the CASI/AI, and most of the subscales on the ABC-C were significantly correlated with one another for both males and females, suggesting individuals with FXS who experienced problem behaviors are also highly likely to have significant comorbid symptoms of anxiety and ADHD. The strength of these correlations varied however, suggesting some subscales of the ABC-C were more or less related to symptoms of anxiety and ADHD. For example, for males the Irritability subscale was moderately correlated with anxiety ($r = 0.56$) and both ADHD scales ($r = 0.51$ for Inattention and $r = 0.62$ for Hyperactivity), whereas the correlations between the Social Avoidance subscale of the ABC-C and anxiety and ADHD were lower ($r = 0.25$ for anxiety; $r = 0.25$ for Inattention).

Given the overlap of constructs on these measures, these correlations were run with and without similarly worded items on the CASI/AI and ABC measures, with inconsequential differences in findings. Therefore, in order to maintain the integrity of the measures, we kept all items intact for use in the correlation and regression analyses.

Associations With Caregiver Burden

The relative contribution of anxiety, ADHD symptoms, and problem behavior in males was examined for the six outcomes associated with caregiver burden: (1) number of hours the family spent in direct caregiving, (2) number of specialists the individual with FXS had visited in the past year, (3) number of prescription medications used by the individual with FXS, (4) caregiver/respondent's use of mental health counseling (5) injuries to the caregiver by the individual with FXS, and (6) financial burden of FXS on the family. Descriptive outcomes of the survey for these variables are described elsewhere [Bailey et al., 2012a]. Annual family income, child age, the Symptom Count raw scores for the Inattentive and Hyperactive/Impulsive scales of the CASI/AI, and the General Anxiety subscale from the ADAMS were included as predictor variables in all regression analysis. Given the high correlations between the scales of the ABC-C (see Tables V and VI), only those ABC-C subscales previously found [Bailey et al., 2012b] to be highly correlated with each of the individual outcome variables were included (See Table VII for a list of variables used in each model and a summary

TABLE I. Confirmatory Factor Analysis of Original 5-Factor Solution for the ABC (n = 292)

		Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
#	Item	Irritability	Lethargy	Stereotypy	Hyperactivity	Speech
2	Injures self	0.53				
4	Aggressive toward others	0.70				
8	Screams inappropriately	0.79				
10	Has temper tantrums	0.85				
14	Irritable	0.77				
19	Yells at inappropriate times	0.79				
25	Depressed mood	0.34				
29	Demands must be met	0.82				
34	Cries over minor annoyances	0.59				
36	Mood changes quickly	0.80				
41	Cries inappropriately	0.82				
47	Stamps feet	0.68				
50	Deliberately hurts self	0.56				
52	Physically violent to self	0.54				
57	Temper tantrums when does not get way	0.90				
3	Listless		0.39			
5	Seeks isolation		0.86			
12	Preoccupied		0.62			
16	Withdrawn		0.84			
20	Fixed facial expression		0.67			
23	Sits still and watches others		0.59			
26	Resists physical contact		0.63			
30	Isolates self		0.90			
32	Sits or stands in one position for long time		0.54			
37	Unresponsive to activities		0.76			
40	Is difficult to reach or contact		0.91			
42	Prefers to be alone		0.82			
43	Does not try to communicate		0.59			
53	Inactive		0.60			
55	Responds negatively to affection		0.64			
58	Shows few social reactions		0.82			
6	Recurring body movements			0.83		
11	Stereotyped, repetitive movements			0.90		
17	Odd or bizarre behavior			0.83		
27	Moves head repetitively			0.75		
35	Repetitive hand, body, or head movements			0.86		
45	Waves or shakes extremities			0.73		
49	Rocks back and forth			0.55		
1	Excessively active				0.80	
7	Boisterous				0.76	
13	Impulsive				0.72	
15	Restless				0.84	
18	Disobedient				0.89	
21	Disturbs others				0.78	
24	Uncooperative				0.87	
28	Does not pay attention				0.78	
31	Disrupts group activities				0.78	
38	Does not stay in seat				0.82	
39	Will not sit still				0.85	
44	Easily distractible				0.65	
48	Constantly runs or jumps				0.63	
51	Pays no attention when spoken to				0.73	
54	Excessively active				0.83	
56	Deliberately ignores direction				0.69	

TABLE I. (*Continued*)

#	Item	Factor 1 Irritability	Factor 2 Lethargy	Factor 3 Stereotypy	Factor 4 Hyperactivity	Factor 5 Speech
9	Talks excessively					0.68
22	Repetitive speech					0.88
33	Talks to self-loudly					0.71
46	Repeats words or phrases					0.92

ABC, Aberrant Behavior Checklist.
Model fit indices: Comparative fit index (CFI) = 0.91, Tucker–Lewis Index (TLI) = 0.90, and RMSEA = 0.06.

of regression results). Regression models for females were not estimated because of the small sample size.

Caregiving hours. The ABC-C Irritability subscale was the only measure significantly associated with caregiving hours, Wald $F(1,292) = 8.774$, $P = 0.003$. Higher Irritability scores were associated with greater caregiving hours.

Specialist visits. The ABC-C Irritability subscale Wald $F(1,292) = 6.164$, $P = 0.014$, was also significantly associated with the number of specialist visits for the child in the past year. The Hyperactive/Impulsive raw score from the CASI/AI was also significantly associated with specialist visits (Wald $F(1,292) = 5.601$, $P = 0.019$), accounting for significant variance over and above that explained by the Irritability subscale.

Medication use. The Irritability subscale (Wald $F(1,292) = 5.977$, $P = 0.015$) and age (Wald $F(1,292) = 7.081$, $P = 0.008$) were significantly associated with medication use, with increased age and higher Irritability scores associated with higher rates of medication use.

Mental health counseling. Family income was the only variable significantly associated with mental health counseling, (Wald $F(1,292) = 5.093$, $P = 0.007$); individuals with lower income reported more mental health counseling services in the previous 12 months.

Caregiver injuries. The Irritability subscale (Wald $F(1,292) = 22.606$, $P < 0.001$) and age (Wald $F(1,292) = 8.079$, $P = 0.005$) were significantly associated with caregiver injuries. The model suggests that younger males and males with high levels of Irritability were more likely to have caused injury to their caregivers.

Financial burden. The Irritability subscale (Wald $F(1,292) = 5.001$, $P = 0.022$), raw scores on the Inattentive subscale of the CASI/AI (Wald $F(1,292) = 4.002$, $P = 0.046$), and family income (Wald $F(1,292) = 3.867$, $P < 0.022$) were significantly associated with perceived financial burden.

DISCUSSION

Problem behaviors have frequently been reported in descriptions of individuals with FXS. However, many of these studies used behavior rating scales not designed for individuals with IDs. The ABC-C is one of the few exceptions, thereby making it one of the more widely used measures in clinical trials for individuals with IDs. In this paper we sought to extend current understanding of patterns of performance on the ABC-C for individuals with FXS and determine whether measures of anxiety and attention problems could be useful in accounting for variance in selected dimensions of caregiver burden in FXS.

We found that the newly proposed 6-factor structure of the ABC-C for individuals with FXS had slightly better fit statistics than the 5-factor structure, further confirming the findings reported by Sansone et al. [2012]. However, the difference in fit statistics was relatively small, and although our findings support the use of the new factor structure, the ultimate test will be whether restructuring the behavior items provides clearer insight into the unique challenges faced by individuals with FXS and whether use of the new factor structure provides a more differentiated indicator of intervention or treatment efficacy, data that are currently not available. Of particular interest will be whether scores on the newly proposed subscale for FXS—social avoidance—are clinically meaningful and should be a primary focus of intervention efficacy, data which are currently unknown.

The pattern of mean scores on all of the subscales of the ABC-C for both males and females was similar to scores reported in the Sansone et al. sample, although males in our sample scored lower on most of the subscales, a difference that was statistically significant for a few of the age group comparisons. Although not large, this discrepancy could be explained in part by the fact that many of the children in the Sansone et al. sample came from specialty FXS clinic populations. Children whose families bring them to such clinics may be experiencing greater developmental or behavioral challenges and, thus, are in greater need of the specialized evaluations available in these clinics. Further studies are necessary to understand these differences better, but neither study is likely to fully represent the FXS population.

The Irritability subscale of the ABC-C was the greatest contributor to multiple areas of caregiver burden, even when anxiety and ADHD symptoms were considered. This finding supports previous research suggesting that aggressive and disruptive behaviors are the most significant for child and family outcomes in FXS [McCarthy et al., 2006; Wheeler et al., 2008; Bailey et al., 2008a, 2012b]. Approximately 36% of this sample had mean Irritability scores above 10, while 12% had scores above 20. These individuals with significantly elevated scores on the Irritability subscales are most likely to need targeted interventions for reducing problem behaviors.

Anxiety has been considered to be especially problematic for individuals with FXS, with a significant percentage (86% of males and 77% of females) meeting criteria for one or more anxiety disorders in previous studies using DSM-IV diagnostic criteria

TABLE II. Confirmatory Factor Analysis of New 6-Factor Solution for the ABC (n = 292)

		Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Factor 6
#	Item	Irritability	Hyper.	Lethargy/withdraw	Social Avoid.	Stereo.	Speech
2	Injures self	0.52					
4	Aggressive toward others	0.68					
7	Boisterous	0.77					
8	Screams inappropriately	0.77					
10	Has temper tantrums	0.83					
14	Irritable	0.75					
18	Disobedient	0.88					
19	Yells at inappropriate times	0.77					
21	Disturbs others	0.80					
24	Uncooperative	0.87					
29	Demands must be met	0.80					
34	Cries over minor annoyances	0.58					
36	Mood changes quickly	0.77					
41	Cries inappropriately	0.80					
47	Stamps feet	0.67					
50	Deliberately hurts self	0.55					
52	Physically violent to self	0.53					
57	Temper tantrums when does not get way	0.88					
1	Excessively active		0.85				
13	Impulsive		0.79				
15	Restless		0.88				
31	Disrupts group activities		0.86				
38	Does not stay in seat		0.87				
39	Will not sit still		0.89				
44	Easily distractible		0.70				
48	Constantly runs or jumps		0.69				
54	Excessively active		0.88				
12	Preoccupied			0.55			
20	Fixed facial expression			0.60			
23	Sits still and watches others			0.51			
25	Depressed mood			0.38			
28	Does not pay attention			0.88			
32	Sits or stands in one position for long time			0.44			
37	Unresponsive to activities			0.71			
40	Is difficult to reach or contact			0.83			
43	Does not try to communicate			0.53			
51	Pays no attention when spoken to			0.81			
53	Inactive			0.48			
55	Responds negatively to affection			0.53			
56	Deliberately ignores direction			0.77			
58	Shows few social reactions			0.76			
5	Seeks isolation				0.91		
16	Withdrawn				0.90		
30	Isolates self				0.96		
42	Prefers to be alone				0.89		
6	Recurring body movements					0.83	
11	Stereotyped, repetitive movements					0.90	
17	Odd or bizarre behavior					0.82	
35	Repetitive hand, body, or head movements					0.86	
45	Waves or shakes extremities					0.73	
49	Rocks back and forth					0.53	
	Excessively active						
	Excessively active						
9	Talks excessively						0.68
22	Repetitive speech						0.88
33	Talks to self-loudly						0.71
46	Repeats words or phrases						0.92

ABC, Aberrant Behavior Checklist; Hyper., hyperactivity; Social Avoid., social avoidance; Stereo., stereotypy.
Model fit indices: Comparative fit index (CFI) = 0.94, Tucker–Lewis Index (TLI) = 0.93, and RMSEA = 0.05.

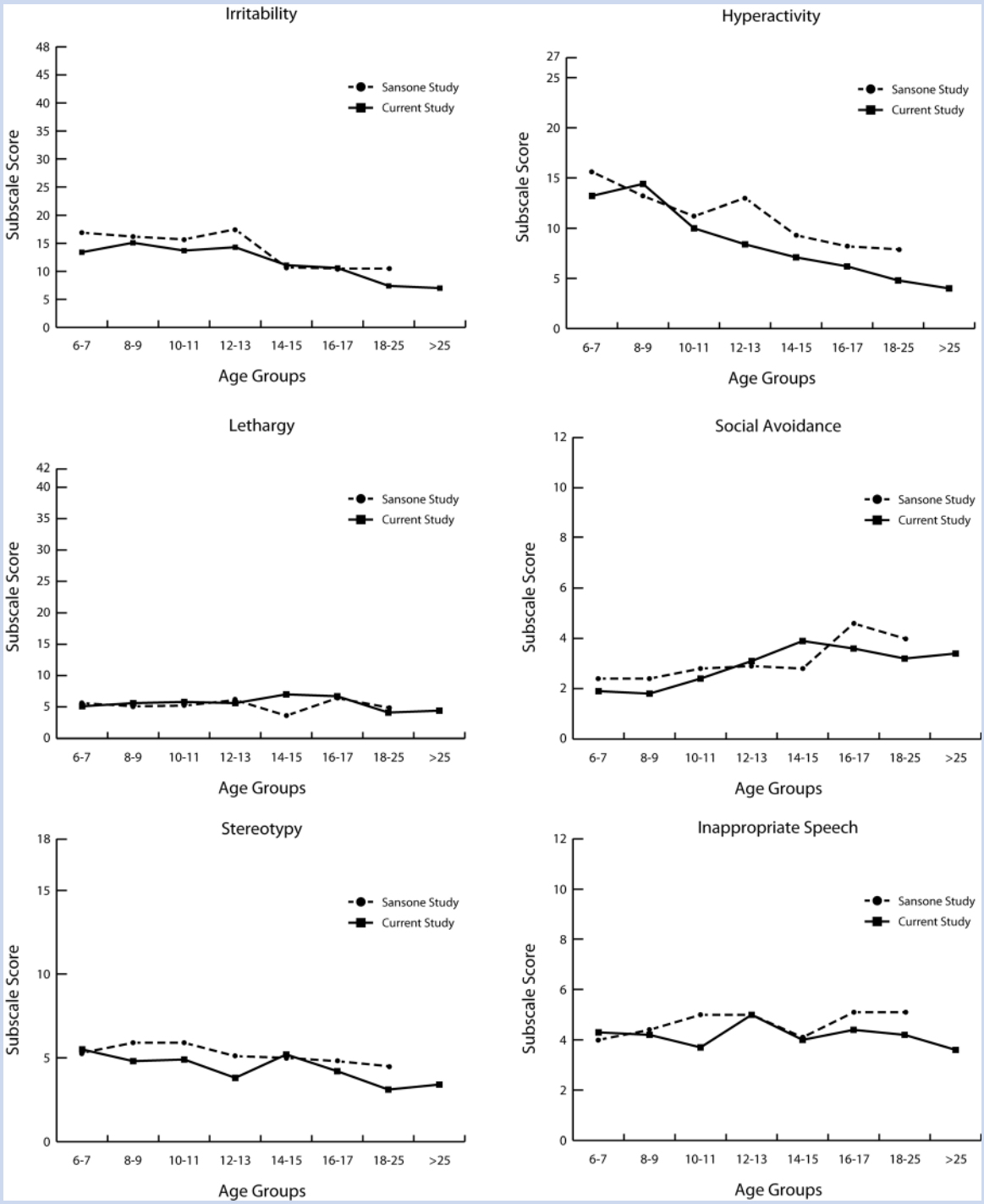

FIG. 1. Scores across age groups on the ABC-C subscales, current sample of males compared with Sansone et al. [2012] sample of males with FXS.

[Cordeiro et al., 2011]. Many of the challenging behaviors often described in FXS, including poor eye contact, gaze aversion, excessive shyness, as well as hand flapping, hand biting, aggression, and autistic symptoms, have been hypothesized to be anxiety driven [Boyle and Kaufmann, 2010; Tranfaglia, 2011]. Several neurobiological theories have been proposed to underlie the behavioral manifestations of anxiety dysregulation in FXS, including atypical physiological regulation [Heilman et al., 2011] and a dysfunction in inhibitory GABAergic circuits [Gothelf et al., 2007]. These theories have resulted in an expanding focus

TABLE III. Mean (SD) Scores for ABC-C,* ADAMS, and CASI/AI for Males and Females With FXS

	Males (n = 292)	Females (n = 58)
ABC-C irritability	10.30 (9.33)	8.38 (8.57)
ABC-C unresponsive/lethargy	5.25 (4.91)	5.00 (4.73)
ABC-C hyperactivity	7.25 (6.13)	4.07 (1.77)
ABC-C inappropriate speech	4.06 (2.86)	2.18 (2.59)
ABC-C social avoidance	3.05 (2.83)	2.70 (3.06)
ABC-C stereotypy	4.04 (3.36)	1.51 (2.11)
ADAMS generalized anxiety	5.95 (4.45)	5.12 (3.71)
CASI/AI inattention T-score	62.22 (12.54)	60.89 (13.96)
CASI/AI hyperactivity/impulsive T-score	60.11 (14.66)	52.94 (13.59)
CASI/AI inattention	26.00 (76)	17.20 (10)
% (n) meeting clinical cutoff		
CASI/AI Hyperactive/Impulsive	15.1 (44)	6.9 (4)
% (n) meeting clinical cutoff		

ABC-C, Aberrant Behavior Checklist—Community Version; ADAMS, Anxiety, Depression, And Mood Scale; CASI, children and adolescent symptom inventory; AI, adult inventory.
*Based on Sansone et al. [2012] 6-factor structure for FXS.

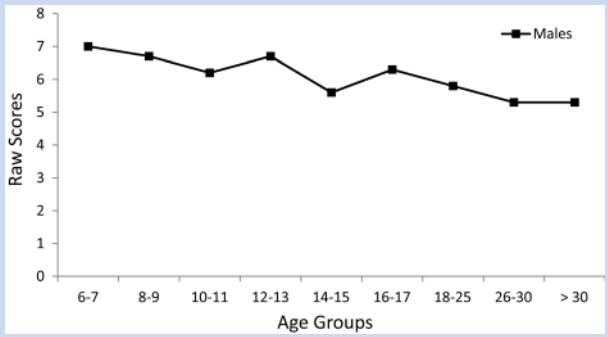

FIG. 2. Mean raw scores for general anxiety on the ADAMS across age groups.

on medication as treatment for many of the behavioral manifestations believed to be anxiety driven. Indeed, medication use for anxiety is reportedly high for this population (45% of males and 30% of females [Bailey et al., 2012a,b])—selective serotonin reuptake inhibitors are the most prevalent treatment [Berry-Kravis and Potanos, 2004].

Despite clinically significant levels of anxiety in our sample, anxiety did not contribute to caregiver burden variables above and beyond the variance accounted for by Irritability. Although anxiety symptoms are associated with increased arousal and behavioral dysregulation [Roberts et al., 2001; Hessl et al., 2002; Heilman et al., 2011] and may contribute to emotional reactivity, anxiety symptoms per se may not be as problematic for caregivers when compared with the more externalizing aggressive and disruptive behaviors. Of course, it is possible that because of the high association between anxiety scores and problem behaviors, our findings simply mean that the ABC-C captures both dimensions.

TABLE IV. Mean and (SD) of ABC-C Subscale Scores, Comparing the Current Study of Males With Data Reported by Sansone et al. [2012]

			Irritability		Unresponsive/lethargy		Hyperactivity	
Age group	Current, N	Sansone, N	Current	Sansone	Current	Sansone	Current	Sansone
6–7	21	74	13.4 (9.4)	16.9 (11.2)	5.1 (4.6)	5.6 (5.4)	13.2 (5.6)	15.6 (7.1)
8–9	26	58	15.1 (10.6)	16.2 (11.8)	5.6 (5.3)	5.1 (4.5)	14.4 (5.5)	13.2 (6.7)
10–11	28	66	13.7 (11.1)	15.7 (11.0)	5.8 (6.0)	5.2 (4.4)	10.0 (6.7)	11.2 (5.9)
12–13	23	49	14.3 (8.8)	17.5 (12.9)	5.6 (5.8)	6.1 (6.2)	8.4 (5.8)	13.0 (7.3)
14–15	27	51	11.1 (10.0)	10.7 (10.2)	7.0 (4.9)	3.6 (4.0)	7.1 (5.2)	9.3 (6.6)
16–17	28	21	10.6 (10.4)	10.5 (11.6)	6.7 (4.5)	6.4 (7.2)	6.2 (4.8)	8.2 (7.4)
18–25	64	69	7.4 (7.2)	10.5 (11.7)	4.1 (4.6)	4.9 (5.6)	4.8 (4.7)	7.9 (6.4)
>25	73	NA*	7.0 (7.1)		4.4 (4.1)		4.0 (3.9)	

			Inappropriate speech		Social avoidance		Stereotypy	
Age group	Current, N	Sansone, N	Current	Sansone	Current	Sansone	Current	Sansone
6–7	21	74	4.3 (3.4)	4.0 (2.9)	1.9 (2.5)	2.4 (2.7)	5.5 (3.7)	5.3 (4.8)
8–9	26	58	4.2 (3.4)	4.4 (2.8)	1.8 (2.5)	2.4 (2.9)	4.8 (3.6)	5.9 (4.7)
10–11	28	66	3.7 (2.8)	5.0 (2.9)	2.4 (3.3)	2.8 (2.9)	4.9 (3.3)	5.9 (4.7)
12–13	23	49	5.0 (2.5)	5.0 (3.0)	3.1 (3.5)	2.9 (3.1)	3.8 (3.3)	5.1 (4.9)
14–15	27	51	4.0 (2.5)	4.1 (3.3)	3.9 (2.7)	2.8 (3.0)	5.2 (3.2)	5.0 (4.8)
16–17	28	21	4.4 (2.4)	5.1 (3.6)	3.6 (3.3)	4.6 (3.9)	4.2 (3.5)	4.8 (4.5)
18–25	64	69	4.2 (3.2)	5.1 (3.4)	3.2 (2.7)	4.0 (3.2)	3.1 (2.8)	4.5 (4.8)
>25	73		3.6 (2.6)		3.4 (2.3)		3.4 (3.3)	

ABC-C, Aberrant Behavior Checklist—Community Version; SD, standard deviation.
*Sansone et al. did not test participants over the age of 25.

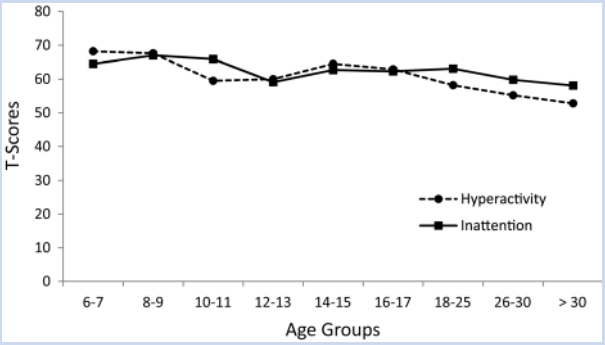

FIG. 3. Mean T-scores (severity) for inattention and hyperactivity scores on the CASI/AI across age groups.

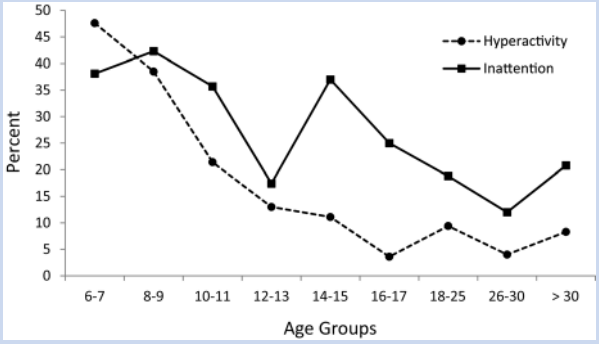

FIG. 4. Percentage of participants meeting clinical cutoff for ADHD inattention or hyperactivity across age groups.

Difficulties with attention regulation and comorbid diagnoses of ADHD are also commonly reported in individuals with FXS [Tranfaglia, 2011], with up to 74% of males reported to meet diagnostic criteria at some point in their lives [Backes et al., 2000]. Attention problems have been hypothesized to be a predictor of challenging behavioral outcomes, with early difficulties in visual attention related to later hyperactive behaviors in children with FXS [Scerif et al., 2012]. Furthermore, a global dysregulation of autonomic nervous system functioning, noted in individuals with FXS [Hall et al., 2009], may drive not only difficulties with attention regulation, hyperactivity, and impulsivity, but also may contribute to the sensory sensitivity and tactile defensiveness often described [Tranfaglia, 2011].

Our study supports previous findings of significantly elevated ADHD symptoms, with average T-scores in the moderate severity range for both males and females on the Inattention subscale and for males on the Hyperactive/Impulsive subscale of the CASI/AI. We found roughly a quarter of males and 17% of females met the clinical cutoff for ADHD Inattention, and just 15% of males and 7% of females met the clinical cutoff for ADHD Hyperactive/Impulsive. These findings differ from results found by Sullivan et al. [2006], who found 47.2% of boys met criteria for ADHD Inattentive type and 22% met criteria for ADHD Hyperactive/Impulsive type. These differences are almost certainly due to the different ages of the two samples, because the Sullivan sample included only young boys (ages 8–12), whereas our sample extended into adulthood. We found a moderate negative correlation with age for both inattention and hyperactivity, suggesting these symptoms do improve with age.

Although medication use for ADHD symptoms has previously been reported to be high in FXS [Sullivan et al., 2006], emerging evidence suggests variable outcomes of medication trials to treat ADHD symptoms, with results ranging from moderate benefit of specific nonstimulant medications [Torrioli et al., 2010] to significant psychiatric side effects in some subjects on stimulant medications [Berry-Kravis and Potanos, 2004]. Additional systematic

TABLE V. Spearman Correlations—Males With Full-Mutation FXS (n = 259)

	ADAMS	ADHD I	ADHD H	ABC-I	ABC-H	ABC-L	ABC-SA	ABC-ST	ABC-SP
ADAMS	1.00	0.51***	0.60***	0.56***	0.53***	0.51***	0.25***	0.33***	0.50***
ADHD I			0.65***	0.51***	0.59***	0.59***	0.25***	0.39***	0.35***
ADHD H				0.63***	0.80***	0.50***	0.17**	0.47***	0.53***
ABC-I					0.69***	0.61***	0.21***	0.48***	0.46***
ABC-H						0.50***	0.10	0.49***	0.46***
ABC-L							0.50***	0.48***	0.37***
ABC-SA								0.24***	0.23***
ABC-ST									0.36***
ABC-SP									1.00

ADAMS, generalized anxiety subscale from the Anxiety, Depression, and Mood Scale; ADHD-I, inattention T-score from child and adolescent symptom inventory or the adult inventories; ADHD-H, Hyperactive/Impulsive T-score from child and adolescent symptom inventory or the adult inventories; ABC-I, Aberrant Behavior Checklist, Irritability; ABC-H, Aberrant Behavior Checklist, Hyperactivity; ABC-L, Aberrant Behavior Checklist, Lethargy; ABC-SA, Aberrant Behavior Checklist, Social Avoidance; ABC-ST, Aberrant Behavior Checklist, Stereotypy; ABC-SP, Aberrant Behavior Checklist, Inappropriate Speech; FXS, fragile X syndrome.

*$P < 0.05$.

**$P < 0.01$.

***$P < 0.001$.

TABLE VI. Spearman Correlations—Females With Full-Mutation FXS (n = 50)

	ADAMS	ADHD I	ADHD H	ABC-I	ABC-H	ABC-L	ABC-SA	ABC-ST	ABC-SP
ADAMS	1.00	0.46***	0.51***	0.40**	0.38**	0.51***	0.23	0.25	0.39**
ADHD I			0.59***	0.44**	0.68***	0.50***	−0.04	0.27	0.54**
ADHD H				0.60***	0.80***	0.50***	0.12	0.29*	0.49***
ABC-I					0.58***	0.65***	0.15	0.42**	0.40**
ABC-H						0.43*	−0.10	0.29*	0.46***
ABC-L							0.45**	0.48***	0.56***
ABC-SA								0.20	0.34*
ABC-ST									0.32*
ABC-SP									1.00

ADAMS, generalized anxiety subscale from the Anxiety Depression and Mood Scale; ADHD-I, inattention T-score from child and adolescent symptom inventory or the adult inventories; ADHD-H, Hyperactive/Impulsive T-score from child and adolescent symptom inventory or the adult inventories; ABC-I, Aberrant Behavior Checklist, Irritability; ABC-H, Aberrant Behavior Checklist, Hyperactivity; ABC-L, Aberrant Behavior Checklist, Lethargy; ABC-SA, Aberrant Behavior Checklist, Social Avoidance; ABC-ST, Aberrant Behavior Checklist, Stereotypy; ABC-SP, Aberrant Behavior Checklist, Inappropriate Speech; FXS, fragile X syndrome.
*$P < 0.05$.
**$P < 0.01$.
***$P < 0.001$.

TABLE VII. Factors Associated With Caregiver Burden, Males (n = 292)

	Family caregiving hours[a]			Financial burden[b]			Caregiver injury[c]		
	B (SE)	*P*-value[d]	OR	B (SE)	*P*-value	OR	B (SE)	*P*-value	OR
ABC subscale									
Irritability	0.062 (0.021)	0.003	1.06	0.051 (0.023)	0.026	1.05	0.132 (0.028)	<0.0001	1.14
Lethargy	—	—	—	—	—	—	—	—	—
CASI/AI inattention	−0.001 (0.034)	0.974	1.00	0.074 (0.037)	0.046	1.08	−0.066 (0.037)	0.073	0.94
CASI/AI Hyper/Imp	0.040 (0.036)	0.258	1.04	−0.053 (0.039)	0.178	0.95	0.078 (0.040)	0.055	1.08
ADAMS	−0.000 (0.044)	0.993	1.00	0.084 (0.046)	0.072	1.09	−0.010 (0.053)	0.858	0.99
Age	−0.007 (0.014)	0.632	0.99	0.005 (0.014)	0.742	1.00	−0.048 (0.017)	0.005	0.95
Income[e]									
$50,001–$100,000	−0.190 (0.379)	0.616	0.83	−0.866 (0.392)	0.028	0.42	−0.253 (0.447)	0.572	0.78
More than $100,000	−0.269 (0.375)	0.473	0.76	−1.068 (0.393)	0.007	0.34	−0.098 (0.456)	0.829	0.91
	Mental health visits[f]			**Specialist visits[g]**			**Medication use[h]**		
	B (SE)	*P*-value	OR	B (SE)	*P*-value	OR	B (SE)	*P*-value	OR
ABC Subscale									
Irritability	0.021 (0.020)	0.292	1.02	0.054 (0.022)	0.014	1.06	0.062 (0.026)	0.015	1.06
Lethargy	NA	NA	NA	NA	NA	NA	0.007 (0.044)	0.880	1.01
CASI/AI inattention	0.022 (0.034)	0.521	1.02	−0.017 (0.032)	0.595	0.98	0.031 (0.036)	0.387	1.03
CASI/AI Hyper/Imp	0.014 (0.037)	0.712	1.01	0.083 (0.035)	0.019	1.09	0.015 (0.037)	0.687	1.02
ADAMS	0.072 (0.044)	0.097	1.08	−0.002 (0.044)	0.958	1.00	0.067 (0.046)	0.143	1.07
Age	−0.017 (0.016)	0.283	0.98	−0.011 (0.015)	0.448	0.99	0.038 (0.014)	0.008	1.04
Income[e]									
$50,001–$100,000	−0.946 (0.362)	0.010	0.39	−0.592 (0.369)	0.110	0.55	−0.084 (0.381)	0.826	0.92
More than $100,000	−1.104 (0.378)	0.004	0.33	−0.226 (0.380)	0.552	0.80	0.315 (0.373)	0.399	1.37

ABC, Aberrant Behavior Checklist; ADAMS, generalized anxiety subscale from the Anxiety, Depression, and Mood Scale; CASI/AI, child and adolescent symptom inventory/adult inventories.
[a]Family caregiving, binary recode: 0 if 8 or less hours of care by family member, 1 if more than 8 hr.
[b]Financial burden, binary recode: 0 if not at all or a little bit, 1 if somewhat or a great deal.
[c]Caregiver Injury, binary recode: 0 if no injury, 1 if one or more injury.
[d]*P*-value from *t*-test of B = 0.
[e]Income reference category is less than $50,000.
[f]Caregiver Health, binary recode: 0 if no mental health counseling, 1 if one or more mental health counseling.
[g]Specialist visits, binary recode: 0 if <5 visits, 1 if 5 or more visits.
[h]Medications, binary recode: 0 if taking 0 or 1 prescription medication, 1 if taking more than one prescription medications.

studies of medication trials that specifically focus on alleviating ADHD symptoms are still needed [Tranfaglia, 2011].

Age trends across all measures suggest that behaviors associated with anxiety and social interactions, including the ADAMS Generalized Anxiety scale and the ABC-C Social Avoidance and Inappropriate Speech subscales, appear to stay relatively stable across age, with a trend toward a slight increase in social avoidance. In contrast, ADHD symptoms, especially hyperactivity and irritability, appear to decrease with age in FXS. This finding is especially salient given the impact these externalizing behaviors appear to have on caregiver burden. This decrease in challenging externalizing behaviors in the older age groups is also in contrast to studies of individuals with autism and other developmental disabilities, where these behaviors have been noted to be chronic and stable across age [Murphy et al., 2009; Matson et al., 2010]. More research is needed to determine how challenging behaviors may manifest across the lifespan in FXS.

Limitations and Future Directions

This study used survey methodology to refine understanding of problem behaviors and comorbid psychiatric diagnoses in FXS. However, several limitations, some of which are inherent to survey studies, are noteworthy. First, a genetic diagnosis of FXS was not verified. Although it is highly unlikely that a parent would incorrectly describe their son or daughter as having FXS, a diagnostic report would have added confidence to our characterization of the sample. Second, the sample was relatively homogenous, with the majority being white, married, and well educated. In this study, income level was negatively associated with mental health counseling, suggesting a greater need for lower income families. But given the relatively high average income level of this sample, the relative impact of behavior problems on family outcomes is likely to be higher in a more demographically diverse group of families. Clearly this sample is not representative of the diverse U.S. or global population, and the study's conclusions should not be generalized to other racial or ethnic groups or to other country contexts. Third, the time span for symptoms reported on the three standardized scales was not exactly the same (e.g., past 6 months for the ADAMS, past month for the ABC-C), potentially reducing the strength of the associations between the variables. Fourth, we do not know the specific medications being taken for behavior problems or their efficacy in individual cases, which certainly could have affected parents' ratings. Finally, it is likely that some of our respondents were among those included in the Sansone et al. [2012] study, limiting our ability to characterize this study as a completely independent sample.

Despite these limitations, we found a consistent pattern of high levels of aggressive and disruptive behaviors as well as significant levels of comorbid ADHD, which were strongly predictive of many areas of caregiver burden (including number of injuries, financial burden, need for specialist visits, and caregiving hours). Further, we found high levels of anxiety symptoms, which although not directly predictive of caregiver burden, likely contribute to the dysregulation seen in individuals with the most problematic behaviors. These results highlight the severity of problem behaviors in a subset of individuals with FXS and indicate a significant need for studies that link treatment interventions to positive outcomes that are clinically meaningful for these individuals and their caregivers. Further research is also needed to determine thresholds for clinical significance on instruments such as the ABC-C and the ADAMS so that clinical trials can determine whether a statistically significant change in scores on these measures also corresponds to meaningful changes in function.

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