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Aggression in fragile X syndrome

A. C. Wheeler, M. Raspa, E. Bishop & D. B. Bailey Jr.

RTI International, Research Triangle Park, NC, USA

Abstract

Background Individuals with fragile X syndrome (FXS), especially men, have long been described as presenting with significant behavioural challenges. Despite this known aspect of the phenotype, there has been little research exploring the prevalence, frequency, nature or consequences of aggressive behaviour in FXS.

Methods This study used survey methodology to gather caregiver reports on the types, frequency and severity of aggressive behaviour in 774 individuals with FXS.

Results Based on caregiver report, nearly all (>90%) male and female individuals were reported to have engaged in some aggression over the previous 12 months, with a third of male cases and slightly fewer than 20% of female cases being described as engaging in moderate to severe aggression or being diagnosed or treated for aggression. Further, aggressive behaviours in male individuals were serious enough that 30% had caused injuries to caregivers and 22% had caused injuries to peers or friends. Sensory issues and hyperactivity were significant predictors of the *frequency* of aggressive acts, while sensory issues and anxiety were predictive of the *severity* of aggression. Traditional behaviour management techniques as well as medication was described as the most common and successful treatment options.

Conclusions Aggressive behaviours are a significant concern for a subsample of both male and female individuals with FXS. Given that sensory concerns were predictive of both the frequency and the severity of aggression suggests these behaviours may be a reactive means of escaping uncomfortable situations.

Keywords aggression, fragile X syndrome

Introduction

The phenotype of fragile X syndrome (FXS) has long been characterised in part by behaviours such as aggression, self-injurious behaviour, hyperactivity, inattention and stereotypy (Hatton *et al.* 2002). However, of the many different forms of problem behaviour, none is more disturbing or more limiting than *aggression*, behaviours that result in emotional or physical harm to others or destruction of property. Several studies have suggested a prevalence of approximately a third of male individuals with FXS who present with a severe behavioural phenotype characterised by aggressive behaviour (Bailey *et al.* 2008; Arron *et al.* 2011; Powis & Oliver 2014). Despite these consistent findings, as well as decades of research describing general behaviour challenges in FXS, it remains unclear as to why a third of male individuals and nearly a fifth of female individuals with FXS present with increased aggression (Bailey *et al.* 2008), while many others exhibit a milder behavioural phenotype. The goals of the current study were to examine the frequency, severity, consequences, potential contributors and treatment

Correspondence: Dr Anne C. Wheeler, RTI International, 3040 Cornwallis Rd., Research Triangle Park, NC 27709, USA (e-mail: acwheeler@rti.org).

options for aggressive behaviours in individuals with FXS. A better understanding of the nature of aggressive behaviours and the factors that contribute to these more extreme behaviours is critical for developing appropriate treatments.

Possible predictors of aggressive behaviour

Multiple triggers and functions have been implicated in the expression of aggression in FXS, including both biological and environmental mechanisms. For example, FXS results from an expansion of repetitions of the trinucleotide sequence of cytosine and guanine (CGG) on the *FMR1* gene, which leads to reduced production of the fragile X mental retardation protein (FMRP). Reduction of FMRP leads to changes in expression of other proteins that may promote aggression, such as increased levels of amyloid precursor protein (Ray *et al.* 2011). FMRP-independent biological variation such as in the serotonin transporter 5-HTTLPR (Sokol *et al.* 2006; Hessl *et al.* 2008; May *et al.* 2010) has been associated with elevated aggression in FXS. Further, individuals with FXS may have abnormal autonomic response profiles that result in difficulty with self-calming and thus contribute to aggression and atypical social behaviour (Heilman *et al.* 2011). Additional evidence of biological underpinnings is suggested when comparing aggression in different genetic syndromes. For example, one study reported that aggression was significantly higher in Angelman and Smith–Magenis syndromes than in Cornelia de Lange, Cri du Chat, FXS or Prader–Willi syndrome (Arron *et al.* 2011). These differences may be due to genetic changes that result in skewed biological mechanisms resulting in traits that increase the likelihood of aggression. Indeed, several behavioural traits have been associated with aggression, including repetitive or ritualistic behaviours (Oliver *et al.* 2012), impulsivity and hyperactivity (Arron *et al.* 2011), deficits in social information processing (van Nieuwenhuijzen *et al.* 2011), problems regulating emotions and behavioural state (Bal *et al.* 2010), irritability (Bailey *et al.* 2012) and poor impulse control (Tsiouris *et al.* 2011).

However, environmental factors also clearly play a role in aggression. Negative interactions with others, challenging or boring tasks, social reinforcement, attention seeking and escape mechanisms have all been associated with increased aggression in both typically developing individuals and those with intellectual and developmental disabilities (IDD) (Embregts *et al.* 2009; Matson *et al.* 2011; May 2011).

In reality, there is probably no single factor contributing to these severe behaviours, which more likely result from the interaction between biological predisposition and environmental factors. However, increased knowledge of variables that are more or less associated with severe behaviours in FXS can help with awareness of risk factors and the development of interventions to prevent or reduce negative consequences associated with aggressive acts.

Consequences of aggressive behaviour

Aggressive behaviour can have both immediate and long-term negative consequences for the quality of life of individuals with FXS. Increased aggressive behaviour can result in reduced exposure to education, reduced quantity and quality of social interactions (Duncan *et al.* 1999) and increased likelihood of more restrictive learning and living environments (Jacobson & Ackerman 1993). Individuals with IDD and co-morbid aggression are more likely to be placed in residential treatment facilities (Jacobson & Ackerman 1993) and to be placed on antipsychotic medications (Tsakanikos *et al.* 2007). Further, aggressive behaviour has significant consequences for caregivers. In a recent study of caregiver burden in FXS, Bailey *et al.* (2012) asked 350 families whether they had been injured in the past year (e.g. knocked down or hit) by their son or daughter with FXS, how often, and the number of injuries requiring medical care. Approximately 31% of caregivers of male persons with FXS and 17% of caregivers of female persons reported at least one injury. The 89 parents of male individuals reporting injuries had a mean of 14.7 per year; on average, 2.7 of those injuries were serious enough to require medical care. While management of these behaviours is stressful for any parent, recent evidence suggesting a differential susceptibility to stress for *FMR1 premutation* carriers (Hartley *et al.* 2012; Seltzer *et al.* 2012) indicates a possible increased risk for some carrier mothers caring for severely aggressive children. More research is needed to determine the relative impact of this potential genetic risk; however, these results highlight the importance of studying the outcomes for families affected by FXS. Regardless of

the genetic impact, the more highly stressed parents are, the more likely they are to experience mental and physical health problems and subsequently have reduced ability to manage difficult behaviours in their children, leading to an increased need for intervention at the family level.

Treatment of aggressive behaviour

Currently, medication and behavioural interventions are often used in combination to help reduce aggression in FXS. Mood stabilisers (e.g. lithium) and antipsychotics (e.g. risperidone) have been shown to have moderate effects on some forms of aggression (Jones *et al*. 2011; McPheeters *et al*. 2011; Dove *et al*. 2012; Loy *et al*. 2012). The most common psychoeducational treatment approach is applied behaviour analysis (ABA), a systematic assessment of the antecedents and consequences that appear to control aggression, followed by individualised interventions in which those factors are systematically manipulated to reduce aggressive behaviour (Brosnan & Healy 2011). A recent study using parent-reported functions of behaviour in 34 individuals with FXS suggested that *escape* may be a primary function of aggressive behaviours in FXS (Langthorne & McGill 2012). However, the functions of aggression are likely to be highly specific to each child, as suggested by a study of behavioural interventions in three children with FXS (Moskowitz *et al.* 2011). Although the behavioural interventions were successful, the functions of the behaviours were noted to be different for each child, thereby requiring considerable individualised assessment prior to intervention development. Guidelines for treating aggression in youth have been described and argue for a multistep approach in which psychosocial interventions, including ABA, are the first line of treatment, followed by the systematic selection of medications and careful monitoring of treatment response (Scotto Rosato *et al*. 2012). However, little is known regarding the most common approaches used by parents and caregivers of individuals with FXS for managing aggressive behaviours on a daily basis.

Based on gaps in the knowledge base about aggressive behaviour in FXS, four questions guided the current study:

1 *What is the prevalence, frequency and nature of aggressive acts in male and female individuals with FXS across the life span?* Specifically, we were interested in better characterising the types of aggressive acts (e.g. hitting and biting) generally engaged in by individuals with FXS and examining these behaviours in a large sample of individuals with FXS to better understand the prevalence of severe behaviours.
2 *What individual and family variables are associated with aggression in FXS?* We were especially interested in determining if aggression was more common among individuals with co-occurring diagnoses such as autism or anxiety. Sensory issues, communication and hyperactivity were also considered to be likely contributors to aggressive behaviours. Family income was included as a family-level variable owing to previous studies indicating it was a significant predictor of challenging behaviour in typically developing children (Nagin & Tremblay 2001; Tremblay *et al*. 2004) as well as those with autism spectrum disorder (Kanne & Mazurek 2011) and young children at risk for IDD (Schroeder *et al*. 2014).
3 *What is the nature and consequences of aggression in FXS?* Specifically, we were interested in parental perceptions of severity and consequences of these behaviours for the individuals and their families.
4 *What are the most commonly reported interventions used by parents or caregivers for reducing aggressive behaviours?* In addition to understanding more about the common treatments used for aggressive behaviour in FXS, such as medication use and formal behaviour management plans, we were also interested in the types and efficacy of daily management techniques used by parents to reduce aggressive behaviours in their family members with FXS.

Materials and methods

Design

This study used survey methodology to describe caregiver-reported aggressive behaviours in male and female individuals with FXS. The questions asked were part of a large family survey in 2012 funded by the US Centers for Disease Control and Prevention. The survey included multiple modules covering a range of topics including, but not limited to, family adaptation, health care, leisure skills and autism

symptoms. The information gathered is all caregiver report, and genetic confirmation of FXS was not externally validated. The number of participants included in individual analyses varies slightly because of missing responses and skipped items. The majority of participants completed the survey online. A telephone option was also available but used by only 5.6% of the participants.

Participants

Participants were the primary caregivers of 642 male and 132 female individuals with full-mutation FXS aged 3 or older who had enrolled in a survey research registry. Recruitment for the registry occurred through announcements on the websites of the National Fragile X Foundation (www.nfxf.org) and FRAXA Research Foundation (www.fraxa.org). Of the 1113 eligible children whose families enrolled in the registry, the behaviour module was completed on 68%. 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. Family income was also generally high; 38% reported incomes over $100 000 a year. The average age of male individuals with FXS was 19.80 (SD = 11.41; range = 3–67) and female individuals were 16.33 years on average (SD = 9.85; range = 3–48). Female individuals with FXS over the age of 18 were only included if the respondent was their legal guardian; therefore, the sample of adult female individuals in this study is likely a lower-functioning subsample of women with FXS. The term 'child' or 'children' is used for convenience to describe both children and adults for whom the respondents reported. Almost all male (87%) and female individuals (90%) lived in the same household with the respondent. See Table 1 for more demographic information on the sample.

Measures

Caregivers rated their child with FXS on selected items developed by the authors to assess specific aggressive behaviours. Respondents were also asked to report on their child's sensory issues, ability to interact and any co-occurring diagnoses (including autism, anxiety and hyperactivity) their child had been given. Descriptive data on these items are provided in Table 1.

Aggressive behaviours

Caregivers were asked to endorse whether their child with FXS had engaged in any aggressive acts in the previous 12 months. They were also asked if their child had ever been 'diagnosed or treated' for aggression. In addition, multiple items were asked regarding the frequency and severity of aggressive behaviours. These items were developed based on a review of the literature regarding types of aggressive behaviours exhibited by individuals with IDD and a review of existing measures of global problem behaviours. Respondents were asked 'In the past 12 months, how often has (child) engaged in the following aggressive behaviours?' They were then provided a list of common behaviours (has temper tantrums; hits, pushes or kicks others; bites others; throws objects at others; argues; destroys own or other's property; is defiant; threatens others; bullies or teases others; verbally insults others; is sexually inappropriate) and asked to rate each behaviour on a 4-point scale from 0 (*never*) to 3 (*very often*). In addition, respondents were asked about their perception regarding the severity of the individual's aggression ('In the past 12 months, how severe were (child)'s aggressive behaviours?' [mild, moderate or severe]) and the amount of stress the individual's aggression has caused them ('How much stress as (child)'s aggressive behaviour caused for you?' [none at all, a little, some or a lot]).

Consequences of aggressive behaviour

In order to assess the individual and family consequences of aggressive behaviour, several questions were asked. To understand injuries to others, respondents were asked two sets of questions: one about injuries to them ('In the past 12 months, have you ever been injured by (child); e.g. knocked down, hit, slapped') and one about injuries to the child's peers or friends ('In the past 12 months, has (child) ever injured a peer or friend; e.g. knocked down, hit, slapped'). If respondents answered either of these items in the affirmative, they were asked follow-up questions: 'How many times during the past 12 months were you/peer/friend injured by (child)?' and 'How many of these

Table 1 Descriptive data for male and female samples

	Males	Females
Age	19.80 (SD = 11.41; range = 3–67)	16.33 (SD = 9.85; range = 3–48)
% Live at home (*n* = 641 male; 132 female)	87.4% (560)	90.2% (119)
% Any aggression in previous 12 months (*n* = 623 male; 119 female)	91.5% (570)	82.1% (92)
% Dx or Tx for aggression (*n* = 601 male; 119 female)	37.9% (228)	17.7% (21)
Frequency of aggressive acts (*n* = 620 male; 120 female)	5.23 (SD = 4.25, range = 0–24)	3.95 (SD = 4.30; range = 0–20)
Severity of aggression (*n* = 620 male; 119 female)	Mild = 69.8% (395) Moderate = 23.1% (131) Severe = 7.1% (40)	Mild = 79.2% (76) Moderate = 18.8% (17) Severe = 2.1% (2)
% Dx or Tx for hyperactivity (*n* = 614 male; 120 female)	60.91% (374)	28.33% (34)
% Dx or Tx for anxiety (*n* = 615 male; 119 female)	71.54% (440)	52.94% (63)
% Meeting DSM-IV criteria for autism (*n* = 603 male, 97 female)	39.1% (236)	24.7% (24)
Ability to interact (*n* = 627 male; 122 female)	36.04% (226), poor 42.26% (265), fair 18.50% (116), good 3.19% (20), very good	21.31% (26), poor 40.16% (49), fair 28.69% (35), good 9.84% (12), very good
Sensory Issues		
Responded strongly to sensory information in the environment (*n* = 572 male; 93 female)	Never = 24.3% (139) Sometimes = 44% (252) Often = 16.1% (92) Very often = 15.7% (90)	Never = 44.1% (41) Sometimes = 33.3% (31) Often = 10.8% (10) Very often = 11.8% (11)
Showed signs of hyperarousal (*n* = 573 male; 93 female)	Never = 9.4% (54) Sometimes = 44.4% (255) Often = 24% (138) Very often = 22.1% (127)	Never = 17.2% (16) Sometimes = 43% (40) Often = 16.1% (15) Very often = 23.7% (22)
Sought sensory input (*n* = 574 male; 93 female)	Never = 18.4% (106) Sometimes = 29.7% (171) Often = 22.1% (127) Very often = 29.7% (171)	Never = 49.5% (46) Sometimes = 23.7% (22) Often = 10.8% (10) Very often = 16.1% (15)
Sensory composite	4.45 (SD = 2.47; range = 0–9)	3.30 (SD = 2.53; range = 0–9)

injuries during the past 12 months resulted in a visit to a doctor, urgent care, or hospital emergency/department for care?' Respondents were also asked 'In the past 12 months, as a result of (child)'s aggressive behaviour, have any of the following consequences occurred? (child received detention or other in-school punishment, was suspended from school, was expelled from school, lost a job, was placed in a residential facility, was hospitalized, was arrested, made it difficult to find a babysitter/respite provider)?' Options for 'other' and 'none of the above' were also available. Because parents were asked to recall the number of injuries over the previous 12 months, the number of injuries should be considered broad estimates rather than the true incidence of injuries.

Strategies to reduce aggressive behaviours

Respondents were asked to indicate 'when (child) is acting aggressively, how long does it usually take them to calm down?' (1–2 min, 3–5 min, 5–10 min or more than 10 min). They were then asked 'in the past 12 months, which of the following have been

successful in helping you with (child)'s aggression?' followed by a series of intervention strategies (ignoring/walking away, time out or removal, loss of privileges/preferred item, earned privileges for not acting aggressively, re-direction, calming activities, medication, use of a behaviour therapist or other), each rated as 'not tried, not successful, somewhat successful or very successful'.

Sensory issues

Respondents rated their children on how often they demonstrated sensory sensitivity ('Respond strongly to sensory information in environment; e.g., getting very upset by fire alarms, bright lights, light touch, certain clothing textures, or certain foods'), hyperarousal ('show signs of hyperarousal; e.g., get easily overloaded or overwhelmed, is unable to cope or regulate emotions, easily upset, becomes withdrawn, socially anxious or avoidant') and sensory-seeking behaviours ('seek sensory input; e.g., rocking, flapping hands, biting hands, jumping, bouncing, walking on toes'). These three sets of behaviours were rated on a scale from 1 (*never*) to 4 (*very often*). A summary score was derived from these three items to assess overall sensory issues.

Ability to interact and co-occurring diagnoses

During enrolment, respondents reported whether their child had ever received a diagnosis or treatment for anxiety or hyperactivity and also rated their son's or daughter's overall 'ability to interact with others his or her age' on a scale from 1 (*very good*) to 4 (*poor*). Although not an ideal way to assess communication and social function, we needed a simple indicator of parent perceptions of these impairments to determine the extent to which variation in behavioural measures is associated with severity of communication or social interactions. Finally, caregivers completed a module specifically assessing autism symptoms, which was used to determine the likelihood of co-morbid autism diagnoses based on DSM-IV criteria for autistic disorder (see Wheeler *et al.* 2014 for details).

Statistical analysis

For both male and female individuals, descriptive statistics were used to characterise the prevalence of those who had been diagnosed or treated for aggression, the frequency of specific aggressive acts and overall severity of aggressive behaviours. Aggression was measured in two ways: (1) through a summary score of the frequency of specific aggressive acts (frequency of aggression) and (2) parent report of the severity of the child's aggression (severity of aggression). Because some of the aggressive acts ('argues', 'defiant', 'temper tantrums' and 'is sexually inappropriate') were not as well aligned with our definition of aggression as 'behaviour that causes physical or emotional harm to others or destruction of property', we ran the regressions both with and without these items. Spearman correlation coefficients were calculated to examine the interrelationships among the aggression variables and other child and family measures. Finally, regression analyses were used to test the relative contribution of age, co-occurring conditions, ability to interact and family income on the two different measures of aggression in male individuals only (because of the small *n* for the female sample). To account for missing data, only cases with complete data were used in each analysis; therefore, sample sizes varied somewhat across analyses.

Results

Frequency and severity of aggression

Most individuals with FXS (90%) were reported to have engaged in at least one aggressive act in the previous 12 months. This was true for both male and female individuals (92% for male and 83% for female individuals). Although nearly all participants were noted to have engaged in some aggressive acts, just over a third of male individual (38%) and 18% of female individuals were reported to have more severe aggression, enough to have been diagnosed or treated for aggressive behaviour. The frequency and severity of aggression for male and female individuals as a whole and across age are presented in Figs 1–4. Temper tantrums, defiance and arguing were the most commonly endorsed behaviours for both male and female individuals. Similarly, for both male and female individuals, the most common form of physical aggression was acts of hitting, pushing or kicking (54% of male and 31% of female individuals). Fewer male and female individuals were reported to engage in proactive aggressive behaviours such as

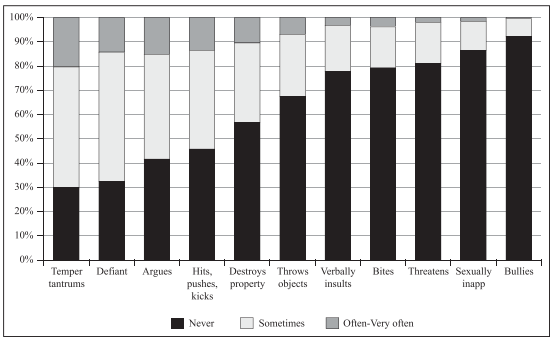

Figure 1 Frequency of aggressive behaviours for male individuals.

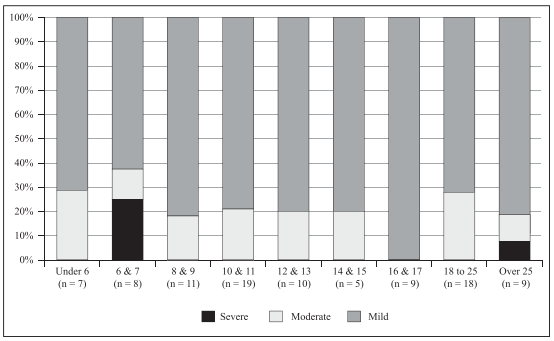

Figure 4 Severity of aggression across age groups for female individuals with fragile X syndrome.

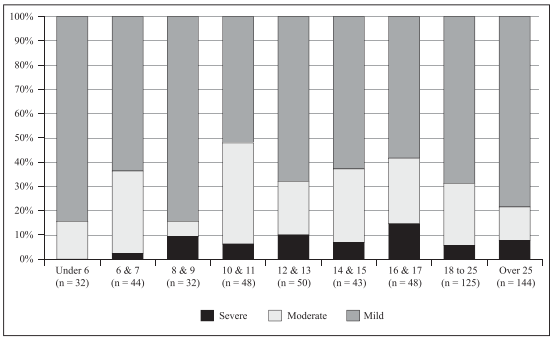

Figure 2 Severity of aggression across age groups for male individuals with fragile X syndrome.

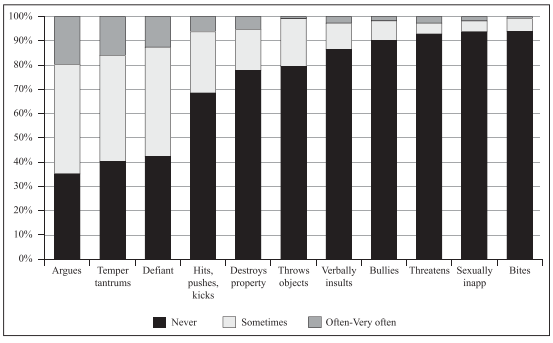

Figure 3 Frequency of aggressive acts for female individuals.

bullying (8% of male and 10% of female individuals) or threatening others (19% of male and 7% of female individuals).

Figures 2 and 4 present data on the severity of aggressive acts for male and female individuals across age groups, respectively. For all male individuals, 7% were rated as having 'severe' aggression, and 23% were rated as having 'moderate' aggression. Two per cent of female individuals were rated as having 'severe' aggression, while 19% were rated as having 'moderate' aggression. Although age was not a significant predictor of the frequency or severity of aggression, most aggressive acts were reported more frequently among younger children and adolescents than among adults. However, the frequency of some behaviours (temper tantrums, defiance and arguing) remained above 50% through adulthood for male and female individuals.

Predictors of frequency and severity of aggression

Results from the regression analyses (reported in Table 2) suggest that for male individuals the ability to interact ($\beta = -1.22$; $P < 0.01$), sensory challenges ($\beta = 0.55$; $P < 0.01$), presence of hyperactivity ($\beta = 0.79$; $P = 0.03$) and family income ($\beta = 2.71$; $P < 0.01$) were most predictive of the *frequency* of aggressive acts. A model run exploring predictors of more restricted definition of aggressive acts (excluding arguing, temper tantrums, defiant and sexual inappropriate) resulted in very similar findings, with the exception of 'ability to interact' no longer being a significant predictor (Table 2).

The *severity* of aggression was predicted by reported previous diagnoses of anxiety ($\beta = -0.52$; $P = 0.03$), sensory challenges ($\beta = -0.26$; $P < 0.01$) and family income ($\beta = -1.01$; $P < 0.01$). The presence of co-morbid autism and age were not predictive of any of the aggression variables.

Table 2 Factors associated with the frequency and severity of aggression in male individuals ($n = 633$)

	Frequency of aggressive acts*			Modified frequency of aggressive acts†					
	$R^2 = 0.19$			$R^2 = 0.17$			Severity of aggression‡		
	B	95% CI	*P*	*B*	95% CI	*P*	*B*	95% CI	*P*
Age	−0.02	−0.05, 0.01	0.22	−0.01	−0.03, 0.01	0.23	0.00	−0.02, 0.02	0.86
Autism§	−0.09	−0.86, 0.68	0.81	−0.10	−0.60, 0.39	0.69	−0.04	−0.46, 0.38	0.84
Hyperactivity¶	**0.79**	**0.07, 1.50**	**0.03**	**0.53**	**0.10, 0.97**	**0.02**	−0.34	−0.80, 0.12	0.15
Anxiety**	−0.03	−0.81, 0.75	0.95	−0.05	−0.56, 0.46	0.85	**−0.57**	**−1.00, 0.05**	**0.02**
Ability to Interact††									
Fair	−0.05	−0.89, 0.79	0.91	0.010	−0.44, 0.63	0.73	−0.01	−0.47, 0.44	0.95
Good/Very Good	**−1.22**	**−2.15, 0.30**	**<0.01**	−0.49	−1.12, 0.13	0.12	0.13	−0.51, 0.77	0.69
Sensory Composite‡‡	**0.55**	**0.37, 0.72**	**<0.01**	0.33	**0.22, 0.45**	**<0.01**	**−0.26**	**−0.35, 0.17**	**<0.01**
Family Income									
<$25,000	**2.71**	**0.84, 4.59**	**<0.01**	**1.83**	**0.62, 3.03**	**<0.01**	**−1.01**	**−1.67, 0.35**	**<0.01**
$25,000-$50,000	0.39	−0.54, 1.32	0.41	0.16	−0.44, 0.75	0.60	−0.04	−0.61, 0.53	0.88
$50,001-$75,000	−0.09	−0.98, 0.80	0.84	−0.02	−0.60, 0.57	0.95	0.25	−0.42, 0.93	0.46
$75,001-$100,000	0.50	−0.46, 1.46	0.31	0.15	−0.48, 0.78	0.63	−0.37	−0.94, 0.20	0.20

*Composite of frequency of 11 aggressive acts, each coded 0 = never; 1 = sometimes; 2 = often; 3 = very often; range of possible scores = 0–33.

†Modified composite of frequency of seven aggressive acts (excluding 'argues', 'temper tantrums', 'defiant' and 'sexually inappropriate' each coded 0 = never; 1 = sometimes; 2 = often; 3 = very often; range of possible scores = 0–21.

‡Severity of aggression: 'In past 12 months, how severe were [CHILD]'s aggressive behaviours': 1 = mild; 2 = moderate; 3 = severe.

§Met behavioural criteria for DSM-IV autistic disorder per parent report of symptoms: 1 = no; 2 = yes.

¶Ever diagnosed or treated for hyperactivity: 1 = no; 2 = yes.

**Ever diagnosed or treated for anxiety: 1 = no; 2 = yes.

††How would you describe [CHILD]'s ability to interact appropriately with others (his or her) own age? 1 = very good; 2 = good; 3 = fair; 4 = poor.

‡‡Composite score of three sensory items: sensory sensitivity (respond strongly to sensory information in environment; e.g. getting very upset by fire alarms, bright lights, light touch, certain clothing textures or certain foods), hyperarousal (show signs of hyperarousal; e.g. get easily overloaded or overwhelmed, is unable to cope or regulate emotions, easily upset, becomes withdrawn, socially anxious or avoidant) and sensory-seeking behaviours (seek sensory input; e.g. rocking, flapping hands, biting hands, jumping, bouncing and walking on toes), each rated: 1 = never; 2 = sometimes; 3 = often; 4 = very often. Range of scores = 3–12.

Consequences of aggression

Almost one-third (31%) of caregivers of male and 13% of female individuals reported having been injured (e.g. knocked down, hit or slapped) by the individual with FXS in the previous 12 months. In addition, caregivers also reported that 22% of male and 14% of female individuals had caused injury to a peer or friend in the previous 12 months. Those male individuals who caused injury to their caregivers did so an average of 17.32 (SD 44.32) times over the year with up to six of those injuries requiring a visit to the hospital or other healthcare setting. Female individuals were reported to cause, on average, 6.61 (SD 5.92) injuries over the year, with none requiring hospital or other healthcare visits.

About a quarter (25%) of caregivers of male individuals and 12% of caregivers of female individuals reported 'a lot' of stress related to their family member's aggression. An additional third (30%) of male individuals and 18% of female individuals were reported to have aggressive behaviour that caused 'some' stress to their caregivers. Related to stress, the most common individual or family consequence of aggression besides injury to others was difficulty finding respite, reported by caregivers of 6% of male and 4% of female individuals.

Treatment for aggression

Once acting aggressively, caregivers reported variability in the amount of time it takes their son to

calm. Nearly 20% were reported to take over 10 min to become calm, 25% take 5–10 min, 25% take 3–5 min and 30% were able to calm in 1–2 min. Similar trends were reported for female individuals: 26% take over 10 min to calm, 18% take 5–10 min, 14% take 3–5 min and 42% were able to calm in 1–2 min.

Redirection was the most commonly reported intervention tried for both male (95%) and female individuals (88%). Redirection was also rated as the most successful of all interventions tried for male individuals. This intervention was common and successful across most age ranges; only calming activities and medication were more successful, especially for adolescents. Other commonly reported intervention strategies for male individuals included *ignoring* (90% tried, 80% successful), *time out/removal* (85% tried, 79% successful) and *loss of privileges* (83% tried, 72% successful). A little over half of the male individuals (51%) had tried medication for aggression, and most caregivers (89%) reported medication to be somewhat or very successful. Thirty per cent had used a behaviour therapist for assistance with aggression, and 71% reported success with this approach. For all of these interventions, only around a quarter of respondents reported that the strategy was 'very successful', and an additional 10–28% rated each intervention as not successful (Fig. 5).

Commonly reported intervention strategies for aggression in female individuals included *loss of privileges* (81% tried, 89% successful), *calming activities* (78% tried, 90% successful), *ignoring* (76% tried, 79% successful) and *time out/removal* (72% tried, 86% successful). One-third (33%) of female individuals had tried medication for aggression, and most caregivers (86%) reported some success (Fig. 6).

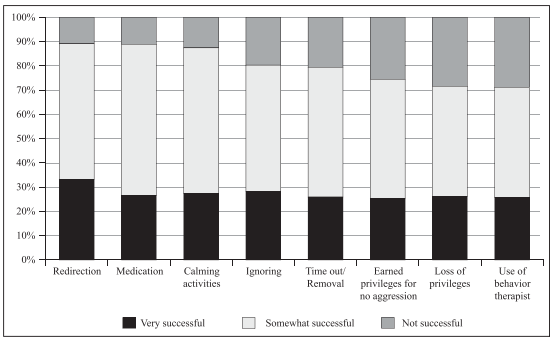

Figure 5 Interventions used to reduce aggression in male individuals.

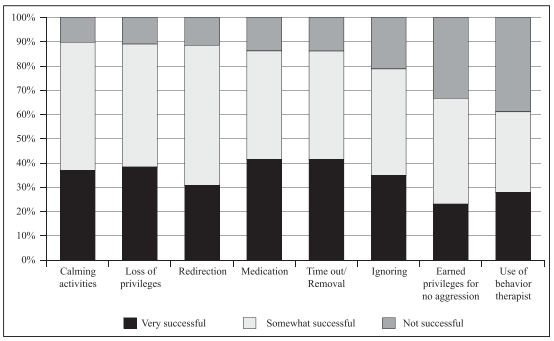

Figure 6 Interventions used to reduce aggression in female individuals.

Discussion

Aggression is not an uncommon behaviour challenge among individuals with IDs (Cooper *et al.* 2009; Poppes *et al.* 2010; Arron *et al.* 2011) and has been reported to be associated with negative life outcomes for the individuals (Bromley & Blacher 1991) and for family members (McIntyre *et al.* 2002; Lecavalier *et al.* 2006). However, despite strong evidence that a subset of male individuals with FXS presenting with a more severe behavioural phenotype, aggressive behaviours have not yet been well described in this population.

Results from this large survey of caregivers confirm previous findings that aggression is a significant concern for a subset of individuals with FXS; approximately a third of male individuals were reported to have been diagnosed or treated for aggressive behaviour. Further, aggressive behaviours in male individuals were serious enough that 30% had caused injuries to caregivers and 22% had caused injuries to peers or friends. Similar to previous findings (Bailey *et al.* 2012), several of these injuries were severe enough to require a hospital or clinic visit.

Although age was not a significant predictor in the regression models, aggressive behaviours in male individuals tended to start early and be more common among younger individuals, and less severity, fewer aggressive acts and fewer injuries were reported for adolescents and adults. This finding is similar to previous reports (Bailey *et al.* 2012; Sansone *et al.* 2012; Wheeler *et al.* 2014). However, some behaviours, specifically temper tantrums, defiance and arguing, were reported to occur in almost all age groups at a rate of approximately 50% for male and

female individuals. This rate suggests that although physical aggression may decrease as individuals become older, verbal aggression and difficulties regulating emotions may continue well into adulthood. It is important to note that for female individuals the adult population included only women for whom the respondent was the legal guardian; therefore, we do not have information on severe behaviours in higher-functioning, more independent women with FXS.

Most of the aggressive acts reported were physical in nature (e.g. hitting, pushing or kicking); fewer male and female individuals engaged in behaviours that could be thought of as pre-emptive or covert (e.g. bullying). This is not surprising given most studies assessing the nature of aggression in individuals with IDD or autism spectrum disorder report that aggressive acts are generally more reactive than proactive in these populations (Farmer & Aman 2011). Further supporting this idea, sensory issues were significant predictors of the severity and the frequency of aggression for male individuals and were strongly associated with aggression in female individuals. These results suggest that these severe behaviours in individuals with FXS, who have frequently been reported to experience increased sensory sensitivity and hyperarousal (Roberts *et al.* 2001; Heilman *et al.* 2011), may be a reactive attempt to reduce or escape from unpleasant sensory input. This hypothesis would support previous findings that the most common *function* of aggressive behaviours for individuals with FXS is escape (Langthorne *et al.* 2011).

In addition to sensory issues, the ability to interact was a significant predictor of the *frequency* of aggressive acts in male individuals when the full range of behaviours were included. When we removed 'defiant', 'argues', 'temper tantrums' and 'sexually inappropriate' from the composite score for frequency of aggressive acts, the ability to interact was no longer a significant predictor. This is not surprising given the more verbal nature of some of these items and that 'temper tantrums' and 'defiant' were the most frequently endorsed items for male individuals. The extent to which an individual struggles to understand language and communicate with others may increase frustration and ultimately lead to temper tantrums and other aggressive behaviours. Indeed, studies that have been carried out on augmentative communication suggest that when an individual with impaired communication is provided alternative methods to convey their wants and needs, challenging behaviours decrease (Ganz *et al.* 2012). Alternatively, individuals with greater challenges with emotion regulation, sensory sensitivities and subsequent challenging behaviours may be less likely to develop and maintain appropriate communication strategies and therefore have a lower ability to interact with others. It may be that the combination of difficulty with communication and behaviour modulation leads to increased aggressive acts, which result in fewer positive social communication opportunities, which further contributes to frustration and increases in aggression.

Interestingly, the ability to interact was not predictive of the *severity* of aggression, which may reflect parental perceptions of aggressive acts as a means to communicate rather than as a significant problem behaviour. However, a co-morbid diagnosis of anxiety was a significant predictor of the severity of aggression. These results may suggest that although most individuals with FXS engage in some aggressive acts, likely as a result of reactivity to sensory input or frustration with communication challenges, individuals who experience high levels of anxiety also may exhibit the most challenging behaviours. Anxiety has been associated with challenging behaviours in individuals with IDs in several studies (see Pruijssers *et al.* 2014 for a review), suggesting an important area of consideration for research and treatment. However, the relationship between anxiety and challenging behaviours is complex, and the direction of this relationship, as well as the role of additional variables such as arousal or coping, remains unclear at best. More research is needed to examine these relationships and the role they may have in intervention development.

Regarding treatment options, most respondents reported having success with some type of intervention strategies to reduce aggressive behaviour. Behavioural strategies most commonly reported to be successful for reducing aggression included redirection, calming activities and ignoring – all of which are components of many behaviour management plans (Stormont 2002). These strategies are also in line with empirical treatments that have effectively decreased aggression in studies of individuals with IDD (Brosnan & Healy 2011). Medication was also used to reduce aggressive

behaviours in about half of the male and a third of female individuals, with high success rates reported.

This study has several important limitations. All of the results are based solely on parent report. While the items were designed in consultation with experts and using standardised measures as a guide, they are not based on validated tools to measure aggressive behaviours. Genetic confirmation of FXS and specific genetic variables that may be predictive of severe behaviours could not be obtained for this study. Similarly, we do not have quality information on health, level of severity of ID, impulsivity or experiences of pain, all of which have been associated with aggression in other samples of individuals with IDD. We also do not have information regarding the contexts in which the behaviours occurred, specific medications used or hyperactivity or anxiety symptoms. Additional verification of these factors, as well as the impact of these variables, would have strengthened our findings. In addition, this was not a representative sample of families; a large majority were White, married, well educated and relatively wealthy. Lower income was associated with the severity and frequency of aggression, suggesting family resources may be an important factor with regard to behavioural outcomes. Additional research is needed to characterise severe behaviours across a more economic and racially or ethnically diverse sample of families. Given the comparatively high average income level of this sample, the relative impact of behaviour problems on family outcomes could potentially be higher in a more demographically diverse group of families.

Despite these limitations, these results highlight an important, but not yet well-studied, subset of behavioural phenotypes in FXS. Understanding the risks associated with more or less aggressive behaviour can help with prevention and treatment options that are more focused and efficacious for the individual and family. The frequency and severity of aggression in a subset of individuals with FXS are considerable and deserve focused attention by researchers and service providers who work with individuals with FXS and their families.

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Conflict of Interest

None

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