Review article

How ~~Common are Challenging Behaviours Amongst I~~common are challenging behaviours amongst individuals with Fragile X Syndrome? A ~~Systematic R~~systematic review

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Abstract

Fragile X Syndrome (FXS) appears to be associated with an increased risk for engaging in challenging behaviour, particularly self-injury, relative to those with mixed aetiology learning disabilities. Such behavioural issues are reported to be of high concern for those providing support. As such, this systematic review aimed to gain further epidemiological data regarding challenging behaviours in individuals with FXS, including: self-injurious behaviour (SIB), hand-biting as a specific topography of SIB, aggression and property destruction. Twenty eight manuscripts were identified which reported the prevalence of a relevant topography of behaviour, with widely varying prevalence estimates. Weighted averages of the prevalence of behaviours were calculated across studies. Comparison of proportions revealed significant gender differences and differences in the prevalence of types of behaviour. It is hoped that this comprehensive overview of data on this clinically significant topic will help to inform and drive future investigation to understand and provide effective intervention for the benefit of those with FXS.

Keywords: Fragile X Syndrome; Self ~~Injurious B~~injurious behaviour; Aggression; Property ~~D~~destruction; Problem ~~B~~behaviour; Challenging ~~B~~behaviour; Intellectual disability; Learning disability; Genetic syndromes; Behavioural phenotypes

What this paper adds?

This paper adds a systematic and comprehensive overview of the prevalence of challenging behaviours in individuals with Fragile X Syndrome. These behaviours are likely to have a negative impact upon the individuals themselves and those who support them. As such a deeper knowledge of the frequency of these behaviours is required in order to assist with the assessment of risk at the population level, to help to facilitate planning of service provision for these individuals and to contribute towards understanding of these behaviours, with an aim of developing effective support and intervention.

~~2~~1 Introduction

Some individuals ~~-~~with intellectual disabilities engage in behaviour which challenges those around them. Between 10–20% of individuals with intellectual disabilities have been described to engage in such behaviours (Jacobson 1982; Kiernan & Kiernan, 1994~~; Jacobson 1982~~), which most commonly include self-injurious behaviour, aggression and property destruction (Emerson et al., 2001). A number of risk markers have been identified for engagement in challenging behaviours, including: expressive communication deficits (McClintock, Hall, & Oliver, 2003), as well as co-morbid conditions, such as autism and epilepsy (Smith & Matson, 2010). In addition, an increasing body of evidence demonstrates that the likelihood of engaging in challenging behaviour relates to the genetic aetiology of an individual's intellectual disability (for instance: Arron, Oliver, Moss, Berg, & Burbidge, 2011).

Fragile X Syndrome (FXS) is the most common inherited cause of intellectual disability (Mazzocco, 2000) and a genetic condition in which challenging behaviours are frequently reported (for instance: Hessl et al., 2008). The condition is caused by a CGG triplet expansion on the FMR1 gene, located on the long arm of the X chromosome. As a result of this expansion, the gene typically becomes methylated, resulting in cessation or suppression of its protein product FMRP, which is important in many aspects of development and brain function (Santoro, Bray, & Warren, 2012; Verkerk et al., 1991). As a result of the X-linked nature of the condition, females show more variable effects and, on average, show less clear effects. The widespread effects of the genetic mutation are associated with a phenotype including varying degrees of intellectual disability, anxiety, attention deficits and autistic-like behaviour (Bailey, Raspa, Olmsted, & Holiday, 2008; Cordeiro, Ballinger, Hagerman, & Hessl, 2010).

Self-injurious behaviour, aggression and destructive behaviour have all been described in individuals with this condition (for example: Hessl et al., 2008). Indeed, hand-biting has been described as part of the behavioural phenotype (~~Hagerman et al., 1991~~Hagerman et al., 1992). It is reported by clinicians and parents that SIB and aggressive outbursts in FXS are often associated with sensory stimulation or unexpected change, which leads to the individual feeling overwhelmed and, in turn, hyperaroused (Miller et al., 1999) and stressed (~~Hessl et al., 2006~~Hessl et al., 2008). This has led to a suggestion that changes to the physiology of the stress response may be associated with the operant conditioning of challenging behaviours with an escape function, within this group (~~,~~ Hardiman & McGill, 2017; Langthorne et al., 2011; ~~Langthorne et al., 2012~~ Langthorne & McGill, 2012). In addition, a number of characteristics commonly associated with FXS have been identified as risk factors for engagement in challenging behaviour, for people with intellectual disabilities (McClintock et al., 2003). These characteristics include: autism (Oliver, Berg, Moss, Arron, & Burbidge, 2011), over-activity and impulsivity (Baumgardner, Reiss, & Freund, 1995). The heightened presence of these risk factors in FXS, as well as the syndrome-specific factors discussed, highlights several possible associations between FXS and challenging behaviours.

Parents and carers report that the problem behaviour of their children with FXS (such as, aggressive behaviours) create a significant caregiving burden: physically, emotionally and financially (Bailey et al., 2012). Accordingly, in interviews with parents, behavioural problems are rated as being of greater concern than cognitive delays (Hatton et al., 2000). Furthermore, for adults with FXS, the presence of mental health problems, including SIB and aggressiveness, is associated with lower independence, poorer employment outcomes, fewer friendships (for women) and greater assistance required in everyday life (Hartley et al., 2011). Given the significance of such behaviours, for both individuals with FXS and their families, it is important to gain an in-depth understanding regarding these behaviours, including epidemiology, risk factors and interventions. Although there have been a number of studies investigating the prevalence of challenging behaviours in FXS, the results of individual studies vary widely, making them difficult to interpret. Understanding the prevalence of challenging behaviours across individuals with FXS aids with understanding the needs of, and planning services for, these individuals. As such, a systematic review of the literature was warranted in order to collate the findings on this important topic, allowing better description of the prevalence of such challenges in FXS, and to inform future discussion and research. Therefore, the aims of this review were to address the following questions:

1. What proportion of individuals with FXS engage in self-injurious behaviour, physical aggression or destructive behaviours?
2. Are there gender differences in the prevalence of each of these types of behaviours?

~~3Methods3~~2 Methods

2.1 Inclusion criteria

For the purposes of this review, the challenging behaviour types were defined broadly as follows:

- Self-injurious behaviour (SIB): behaviour towards the self that has caused, or may cause, physical harm. Hand-biting was included as a specific topography where assessed in isolation in a study, given its association with FXS. This was defined as pressure being applied between the teeth to any part of the individual's own hands or fingers.
- Aggression: physically aggressive behaviour directed towards another person.
- Destructive behaviour: aggressive or damaging behaviour directed towards an individual's environment, such as objects or furniture.

Published data with sample sizes of 10 or more individuals reported to have FXS were included; where more detailed information about genetic status was provided, both full-mutation and mosaic cases were included. In addition, in order to be included, the studies were required to have sufficient data to calculate a percentage prevalence of either SIB (including hand-biting), aggression or property destruction. The presence of challenging behaviour was rated according to the data available in the article: both ratings on single items of questionnaires or interviews, and borderline or clinically significant scores on relevant subscales were included (see Table 1 for assessment measures). If the use of a measure which may have generated data relevant for this review was listed, but the results not provided in sufficient detail for inclusion, authors were contacted to request further details (where data were obtained in this fashion, this is noted in Table 1). There were no limits on the dates of publication for inclusion.

Table 1 Studies assessing the prevalence of challenging behaviour in FXS.

alt-text: Table 1

Study	Relevant Measure(s)	FXS[a] Participants			Recruitment*	Time-frame of measure	Prevalence SIB[b]	Prevalence Aggression	Prevalence Destructive Behaviour

		Number	% Male	Age (Years)					
Arron et al. (2011)	CBQ (Hyman et al., 2002)[c]	191	100	Mean 16.57 (SD[d] 8.81)	Fragile X support charity	Point	51.3%	52.1%	–
Bailey et al. (2012)	Specially developed items to measure proportion of caregivers who have sustained at least one injury inflicted by child.	350	83.4	Mean 19.5 (Range 5–66)	National Fragile X research database	Point	–	31% Males, 17% Females	–
Bailey et al. (2008)	"Has ___ ever been treated by a professional for…?"	1235	79.02	6+	National Fragile X research database	Long-term	Males 41%; females 10%; total 34.5%.	Males 38%; females 14%; total 32.96%.	–
Cronister et al. (1991)	Parent interview	Hand-Biting data available for 100/105 total participants	0	Mean 32.02	Not specified	Long-term	Hand biting: 9%	–	–
Dykens et al. (1989)	VABS[e] (Sparrow et al., 1989) "too physically aggressive" item.	27	100	Mean 27.4 (Range 3–51)	Not specified	Unclear	–	33.3%.	
Eden et al. (2014)	CBQ	112	100	Mean 10.88 (SD 2.58)	Fragile X Support Charity & University research database	Point	54.5%	60.9%	–
~~Fryns (1984)~~Fryns et al. (1984)	'Systematic extensive psychological and socio-familial investigation'	21	100	Mean 9.24 (Range 2–21)	Not specified	Unclear	Hand-biting 38.1%[f]	–	–
Gillberg et al. (1986)	"meticulously examined clinically by a child physician"	10	100	Range 2–17	Clinical setting	Unclear	50%	–	–
Gray et al. (2005)[g]	Clinically significant scores of Aggression subscales of ABC[h]: Aman et al., 1985) & CBCL[i] (Achenbach, 1991) combined.	57	100	Mean 4.7	Not specified	Point	31%	13%	–
Hagerman, (2002)[j]	Parent interview	306	78.1	N/A[k]	Clinical setting	Unclear	Hand-Biting. Males 50.21%; females 20.9%; total 43.79%.	Males 43.5%; females 22.4%; total 38.8%	–
Hagerman et al. (1992)	Parent interview	Hand biting data available for 30/32 total participants	0	Mean 8 (range 1–18)	Clinical setting	Long-term	Hand-biting 23.3%[l]	–	–
Hall et al. (2006)	Observation of hand-biting during a social demand task	114	64.9	Range 6–17. Male mean: 11.06 (SD 2.68), Female Mean: 10.42 (SD 3.10)	Fragile X Support charity, research database, university flyers contact and website	Point	25.68% males; 15% females; 21.93% total.	–	–
Hall et al. (2008)	Self-injury checklist (Bodfish et al., 1995).	60	51.7	Mean 13. 14	Fragile X Support charity, research database,	Point	58.1% males; 17.2% females; 38.3% total.	–	–

					university flyers contact and website				
Hartley et al. (2011)	Parents asked if child ever diagnosed with or treated for behavioural issue	328	72.9	Mean 31.14	Ongoing, national, longitudinal study	Long-term	47.26% males; 16.67% females; 38.41% total.	43.04% males; 12.79% females; 34.45% total.	–
Hartley et al. (2012)	Telephone interview based on Scales of Independent Behaviors (revised). Rate presence/absence behaviour each day during 8-day diary study	76	82.9	Mean 21.4 (12+)	Ongoing, national, longitudinal study	Point	16.9%	15.6%	14.3%
Hatton et al. (2002)	Clinically significant scores on aggression subscale of CBCL	59	100	Mean 7.22 (SD 2.03)	Genetic centres and clinical settings	Point	–	17.6%(+8% borderline)	–
Hessl et al. (2001)	Clinically significant scores on aggression subscale of CBCL	119	66.4	Mean 10.76 (SD 2.83)	Fragile X Support charity, research database, university flyers contact and website	Point		12.7% males; 12.5% females; 12.61% total.	
Hessl et al. (2008)[m]	BPI[n]	50	100	Mean 15.6 (SD 4.3)	Clinical setting	Point	79%	75%	36.17%[o]
Lachiewicz, (1992)	Clinically significant scores on aggression subscale of CBCL	38	0	Mean 7.43 (Range 4.5–11.9)	Fragile X Support Charity	Point	–	18%	–
Largo and Schinzel (1985)	Non-specified parent interview	13	100	Mean 6.5 (Range 2.6–12.5)	Clinical setting	Unclear	38.5%	53.8%	–
Newman et al. (2015)	BPI-S[p]	47	75	Mean 7.84 (SD 4.19, Range 2–17)	Fragile X Support charity and online forums	Point	80.9%	85.1%	
Pegoraro et al. (2014)	Examination of medical charts: data gathered from parent interview	13	92.3	Mean 12 (SD 3)	Clinical setting	Unclear	23%	53%	
Reilly et al. (2015)	Parents rate presence of “challenging aspects” including physical aggression	115	81.7	Mean 11.58	Fragile X Support charity	Unclear		41%	
Richards et al. (2012)	CBQ: SIB items.	212	100	Mean 15.3 (Range 6–47)	Fragile X Support Charity & research registry	Point	54.5%	–	–
Symons et al. (2003)	Self-injury questionnaire (occurrence, age of onset, forms, function (modified from O'Neill et al. (1990))	55	100	Mean 6.6 (Range 1.7–12)	Ongoing longitudinal study	Long-term and point	58% long-term prevalence (81% of which had continued in past month)	–	–
Symons et al. (2010)	SIB: Questionnaire based, in part, on the Self-Injury domain from the RBS-R[q] and a previous SIB and FXS survey (Symons et al., 2003). Aggression: sub-set parents asked one question on historical presence or absence of aggression.	1394;	Overall 78.2; Long-term = 78.06; past 30 days unclear	N/A	Fragile X Support charities, researcher, clinicians	Long-term and point	Long-term[r]: 41% males; 16.7% females; 35.7% total. Past 30-days[s]: males 32%, females 11.4%, total N/A[t]	Long-term: 39.75% males (N = 516); 18.6% females (N = 96); 36.4% total (N	–

								=612)[u]	
Wheeler et al. (2015)	Parents rated whether child had displayed at least one physically aggressive act in past 12 months	774	82.9	Male Mean 19.80 (SD = 11.41; range = 3-67); Female mean 16.33 (SD = 9.85; range = 3-48)	Research registry (ongoing national survey)	Point	–	92% males; 83% females; 90.4% total.	–
	Parents rated whether diagnosed or treated for aggression[v]	"	"	"		Long-term	–	38% males; 18% females	–
	Proportion of parents sustaining injuries from child.[w]	"	"	"		Point	–	31% males; 13% females	–
Valdovinos et al. (2009)	"Has the individual had problems with any of the following behaviours?" Options including: Aggression; Self-injurious behaviour (SIB) (hand biting, skin picking, head hitting, etc.)	392	N/A	N/A	National survey	Long-term	42.9%	36.0%	21.1%

[a]FXS: Fragile X Syndrome.

[b]SIB: Self-Injurious Behaviour.

[c]CBQ: Challenging Behaviour Questionnaire.

[d]SD: Standard Deviation.

[*].

[e]VABS: Vineland Adaptive Behavior Scales.

[f]Overall SIB data excluded due to discrepancy in data between table and text.

[g]Conference Abstract.

[h]ABC: Aberrant Behavior Checklist.

[i]Child Behavior Checklist.

[j]Updated data from Merenstein et al. (1996).

[k]N/A: Not Available.

[m]Additional unpublished data supplied by author.

[o]Data available for 47/50 participants.

[p]Behavior Problems Inventory-Short Form (~~Rojahn et al., 2012~~Rojahn et al., 2001).

[q]Repetitive Behavior Scales–Revised (Bodfish et al., 2000).

[r]SIB long-term prevalence data available for 1363/1394 participants.

[s]SIB data for past 30 days available for 1293/1394 participants.

[u]Data from matched pairs of FXS participants with and without SIB. Matched on gender, age, mutation status and family income.

[t]Note: Total cannot be calculated as the proportion of males and females are unclear for the sample for which point prevalence data is available.

[v]These data were the figures used from Wheeler et al. (2015) in the total calculations across studies.

[w]Further measures of aggression were collected, including peer injuries.

~~3~~2.2 Literature search

An electronic search of four databases (PsychINFO, PubMed, Web of Science, and SCOPUS) using a string including the terms "Fragile X Syndrome" (including variants, plus Medical Subject Headings (MeSH): Martin Bell or

Escalante) and “Challenging Behaviour” (including variants, plus MeSH: problem behaviour, behaviour problems, maladaptive behaviour, aberrant behaviour, self-injurious behaviour, self-injury, self-harm, aggression, aggressive behaviour, disruptive behaviour, destructive behaviour, destruction of property) was conducted, in January 2016. The initial search identified 824 records which consisted of 597 unique papers. Based on the inclusion criteria, 190 were reviewed at the full-text stage. After full-text review, 27 papers were identified for inclusion in the review (Fig. 1)

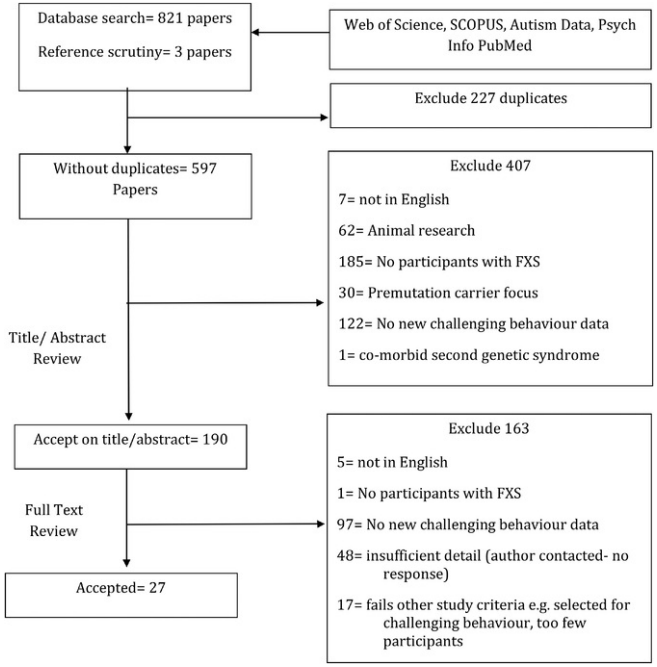

Fig. 1 Inclusion and exclusion process of the systematic review.

alt-text: Fig. 1

Initial data extraction was conducted by the first author. The reliability of the decisions about inclusion was checked for 20% of papers (100% agreement), and the reliability of data extraction was checked for 50% of individual extracted data items (98% agreement) by a doctoral student at the Tizard Centre with expertise in challenging behaviour. Where extracted data did not match, a collaborative decision was reached between the study authors.

~~3.3Data A~~2.3 Data analysis

Due to the gender dimorphic severity of presentation of FXS, the prevalence of the three target classes of challenging behaviours was investigated with regards to this variable. The measures used to assess prevalence were also classified into either point (presence of behaviour evaluated during a period of the past year) or long-term (evaluation of behaviour over a time longer than the previous year) prevalence estimates. In addition, a ‘total’ summary prevalence statistic was calculated using the results across studies, weighted by study sample size. Where both point and long-term estimates were available, long-term estimates were used for total calculations.

The significance of differences in prevalence of different types of challenging behaviours within and between genders were evaluated. In addition, exploratory analyses were conducted to investigate the influence of study variables, such as measure used and method of recruitment (i.e. clinical or non-clinical populations such as a national survey). Destructive behaviour was not analysed due to the small number of studies addressing the subject. Due to the partially-overlapping sample groups and non-independent behaviour categories, the ‘Comparisons of the Difference between Proportions Test’ (Clarke & Cooke, 2004) was used. This test was selected following consultation with a Statistician at the University [to insert after review], who created a spreadsheet to conduct the calculations. The following formulae were inputted into Microsoft Excel 2013 (where: n_1 = total number assessed in sample 1, n_2 = total number assessed in sample 2; p_1 = decimal proportion of individuals assessed who exhibit behaviour of interest in sample 1; p_2 = decimal proportion of individuals assessed who exhibit behaviour of interest in sample 2). A p-value was calculated in order to evaluate the significance of W using the Excel formula: = 1-NORMDIST((cell),0,1,TRUE). A p-value which reached a chosen level of significance ($p = 0.05$) indicates that there is a statistically significant difference between the percentage prevalence of the two behaviours.

$$W = \frac{p_1 - p_2}{\sqrt{\frac{p(1-p)}{n_1} + \frac{p(1-p)}{n_2}}} p = \frac{n_1 p_1 + n_2 p_2}{n_1 + n_2}$$

~~4Results43~~ Results

3.1 Studies

The individual results of included studies are summarized in Table 1. Sixteen studies assessed the prevalence of SIBs, eight of which included male-only samples; the remainder included both male and female participants (four presented compound results, four separated). The prevalence of SIBs were assessed using a variety of measures: the Self Injury Checklist (SIC: Bodfish, Crawford, Powell, & Parker, 1995. Used by: Hall, Lightbody, & Reiss, 2008) the Challenging Behaviour Questionnaire (CBQ: Hyman, Oliver, & Hall, 2002. Used by: Arron et al., 2011; Eden, de Vries, Moss, Richards, & Oliver, 2014; Richards, Oliver, Nelson, & Moss, 2012), Self-Injury Questionnaire (SIQ: O'Neill et al., 1990. Used by: Symons, Byiers, Raspa, Bishop, & Bailey, 2010) Child Behaviour Checklist (CBCL: Achenbach, 1991. Used by Gray et al., 2005 in conjunction with the Aberrant Behaviour Checklist: ABC (Aman, Singh, Stewart, & Field, 1985); Behaviour Problems Inventory (BPI: Rojahn, Matson, Lott, Esbensen, & Smalls, 2001. Used by: Hessl et al., 2008; Newman, Leader, Chen, & Mannion, 2015), the Repetitive Behaviour Scales- Revised (RBS-R: Bodfish et al., 2000. Adapted version used by Symons et al., 2010: see Table 1), Scales of Independent Behaviors- Revised (SIB-R: Bruininks, Woodcock, Weatherman, & Hill, 1996. Used by Hartley et al., 2012) non-validated survey item(s) (Bailey et al., 2008; Hartley et al., 2011; Valdovinos, Parsa, & Alexander, 2009) and non-specified clinical evaluation or parent interview (Fryns, Jacobs, Kleczkowska, & Berghe, 1984; Gillberg, Persson, & Wahlström, 1986; Pegoraro, Steiner, Celeri, Banzato, & Dalgalarrondo, 2014). In addition to the aforementioned investigations including a variety of topographies of SIB, five studies were identified which assessed hand-biting as a specific form of SIB (two assessed both males and females, two evaluated only females, and one assessed males). Hand biting was assessed through direct observation (Hall et al., 2008) and non-specified clinical evaluation or parent interview (Cronister et al., 1991; Fryns et al., 1984; Hagerman, 2002; Hagerman et al., 1992).

Aggressive behaviour was assessed in 20 studies: eight studies had male-only samples, one had a female-only sample and the remaining eleven included participants of both genders (6 presented separated results, 5 presented compound results). Aggression was measured in a variety of ways: CBQ (Arron et al., 2011; Eden et al., 2014), Vineland Adaptive Behaviour Scales (VABS: Sparrow, Cicchetti, & Balla, 1989. Used by: Dykens, Hodapp, & Leckman, 1989), CBCL (Gray et al., 2005 (as above); Hatton et al., 2002; Hessl et al., 2001; Lachiewicz, Spiridigliozzi, Gullion, Ransford, & Rao, 1994), BPI (Hessl et al., 2008; Newman et al., 2015), SIB-R (Hartley et al., 2012), non-validated questionnaire item(s) (Bailey et al., 2012; Bailey et al., 2008, Hartley et al., 2011; Reilly, Senior, & Murtagh, 2015; Symons et al., 2010; Wheeler, Raspa, Bishop, & Bailey, 2015; Valdovinos et al., 2009) and non-specified clinical evaluation or parent interviews (Hagerman, 2002; Largo & Schinzel, 1985; Pegoraro et al., 2014).

Destructive behaviour was assessed less frequently: one study included male samples and the other two provided compound results from mixed gender samples. Destructive behaviour was assessed using: SIB-R (Hartley et al., 2012), BPI (Hessl et al., 2008), non-validated survey item (Valdovinos et al., 2009).

The mean ages of participants were reported in 22 (81.5%) of the included studies and ranged from 4.7 years to 32.0 years (median 11.3, interquartile range 8.7). As such, participants in the studies were predominantly children or young adults, with older adults being under-represented.

~~4~~3.2 What proportion of individuals with FXS engage in self-injurious behaviour, physical aggression or destructive behaviours?

The ranges and total estimates, across all included studies, of the prevalence of each type of challenging behaviour are presented in Table 2. Across all studies and both genders, the total prevalence estimates across studies were 48.8% for self-injurious behaviour (32% for hand-biting), 35.8% for aggression and 24.5% for destruction (noting that a much smaller total group was studied for this behaviour type).

Table 2 *Summarised* prevalence estimates of challenging behaviours in individuals with FXS.

alt-text: Table 2

Topography	Study Estimate Range (%)		Entire sample estimate and size					
	Male	Female	Male		Female		Total	
			%	N	%	N	%	N
SIB	31~~-7910-~~–79	10–17.2	44.6	3010	14.2	676	48.8	4245
Hand Biting	25.7~~-50.29-~~–50.2	9–23.3	44	334	15.2	237	32	571

Aggression	12.7~~-85.112.5.~~–85.1	12.5–22.4	40.2	3539	13.9	779	35.81	4140
Destruction	36.2	–	36.2	47	–	–	24.5	515

43.3 Measured time period

Total prevalence estimates were calculated for studies utilising point- and long-term prevalence estimates separately, in order to investigate whether this methodological difference had a clear effect on the results. This exploratory analysis was conducted with the male results due to the larger sample size. Interestingly, the results in both time frames were similar for both SIB (point: 31.96%, 2193 participants; long-term: 35.56%, 2926 participants) and aggression (point, 36.88%, 1351 participants; long-term: 33.37%, 1923 participants).

43.4 Participant age

There was no association between mean participant age in a study and male prevalence estimates from the study, for either SIB (r_s ~~-.26, p-.52) or aggression (rs-.23, p-.55).5~~ $= 0.26$, $p = 0.52$) or aggression ($r_s = -0.23$, $p = 0.55$).

4 Are there gender differences in the prevalence of each of these types of behaviours?

54.1 Gender comparisons of prevalence

Using the total estimate figures calculated across studies, males were significantly more likely than females with FXS to engage in all types of challenging behaviour studied: SIB (W~~-18.43, n-3686, p <~~ $= 18.43$, $n = 3686$, $p < 0$.0001; including hand-biting: W~~-8.75, n-571, p <~~ $= 8.75$, $n = 571$, $p < 0$.0001) and aggression (W~~-17.15, n-4318, p <~~ $= 17.15$, $n = 4318$, $p < 0$.0001). This finding of increased behavioural challenges in males was consistent across all individual studies which compared male and female samples, for all behaviour types studied (Bailey et al., 20~~12, Bailey et al., 2008~~08, 2012; Hagerman, 2002; Hall, DeBernardis, & Reiss, 2006; Hall et al., 2008; Hartley et al., 2011; Hessl et al., 2001; Symons et al., 2010).

54.2 Comparing the prevalence of types of challenging behaviours

A significantly greater proportion of males, in the total sample from across all studies, engaged in SIB, compared to aggression (W~~-4.57 n-6549, p <~~ $= 4.57$ $n = 6549$, $p < 0$.0001). In comparison, there was no significant difference between the prevalence of these behaviour types in the smaller total sample of females with FXS studied, across the papers (W~~-.15, n-1455, p-~~ $= 0.15$, $n = 1455$, $p = 0$.88). This suggests that the types of behaviours exhibited by males and females with FXS differ in their relative frequency.

65 Discussion

The findings from across the studies reviewed, support the assertion that challenging behaviours are a common issue for individuals with FXS, particularly for males. In fact, between-group comparisons conducted within individual studies suggest that people with FXS may be at higher risk of exhibiting SIB than other groups, such as individuals with Down syndrome and mixed aetiology intellectual disabilities (~~Richards et al., 2012, Arron et al., 2011~~Arron et al., 2011; Richards et al., 2012). Although difficult to identify comparable research, this is further supported by comparing the results of this review on FXS, with the findings of research involving individuals with mixed aetiology intellectual disabilities. The range of SIB prevalence estimates for FXS, identified in this review, varied between 10% to 81%, which is higher than general estimates for intellectual disability, which typically range from 4% (Emerson et al., 2001: total population study) to 24% (Deb, Thomas, & Bright, 2001: research with adults in the community). However, the conclusions which can be drawn from such comparisons are limited, due to varying participant characteristics, sampling and study methodology. In addition, the prevalence of hand-biting across included studies was high, which is consistent with the notion that hand-biting is a prominent form of SIB exhibited by individuals with FXS, and is characteristic of the syndrome (~~Hagerman et al., 1991~~Hagerman et al., 1992).

This review also found prevalence estimates for aggression in FXS (12.5-~~-~~60.9%) which are higher than those relating to intellectual disabilities more broadly (2-~~-~~20%: Allen, 2000). This estimated prevalence range for individuals with intellectual disabilities (Allen, 2000) was derived through a non-systematic review of the literature, and, similar to this review, the authors highlighted that varying study methodology and populations likely contributed to the variance in estimates. As highlighted above, these non-direct comparisons are limited by the varying methodologies of studies. In a direct comparison, Arron and colleagues (Arron et al., 2011) found that boys with FXS were not more likely to exhibit aggressive behaviour compared to a group of individuals with intellectual disabilities of mixed aetiology. Interestingly, in Arron and colleagues' study, the individuals with FXS were significantly less likely to engage in aggressive behaviour when compared to individuals with other genetic conditions, suggesting a link between aggression and genetic variables. It seems that factors such as impulsivity and repetitive behaviour, and the extent to which they are expressed in the different genetic conditions, may underlie at least some of this variation (McClintock et al., 2003; Moss, Oliver, Arron, Burbidge, & Berg, 2009). Finally, the review highlighted that destructive

behaviour (such as destruction of items or property), despite being a common topography of behaviour in others with intellectual disability, has received little attention in FXS research.

If the prevalence of challenging behaviours such as SIB and aggression do vary between FXS and other genetic conditions (Arron et al., 2011), further research should be conducted in order to understand which characteristics may predispose individuals with FXS to developing these behaviours. In addition, it would be of value to identify whether these risk factors are syndrome-specific, or similar to risk factors which have been identified for the broader population of people with intellectual disabilities. Research has already demonstrated a number of factors which may make individuals with FXS more sensitive or vulnerable to developing behaviour described as challenging. For instance, within the studies included in this review, several factors associated with their occurrence were identified. Although not a comprehensive review of all of the literature on risk factors for challenging behaviours in individuals with FXS, which was not addressed in the review aims, these findings provide some illustrative examples. FXS is associated with an increased risk for anxiety (Cordeiro et al., 2010) and autistic behaviour (Oliver et al., 2011): positive correlations between these characteristics and challenging behaviour have been identified. Specifically, both males and females with FXS who experience greater severity of autism symptomatology and anxiety are at a greater risk for engagement in SIB (Arron et al., 2011, Symons et al., 2010). Similarly, over-activity and impulsivity are characteristic features of FXS, and in males increased severity has been associated with an increased likelihood of engaging in aggression (Arron et al., 2011).

In addition to these cognitive and behavioural characteristics, there may be factors at the biological level which influence the likelihood of engagement in challenging behaviours, for individuals with FXS. Lower levels of FMRP (the protein whose production is impaired or ceased in FXS), although not found to correlate with the prevalence or number of forms of SIB displayed (Hall et al., 2008; Symons, Clark, Hatton, Skinner, & Bailey, 2003~~; Hall et al., 2008~~), was found to be associated with both earlier onset of the behaviour and increased surface area being targeted (Symons et al., 2003). Although the pathways of this association are not fully understood, this suggests that there may be biological predictors which allow for stratification of risk within individuals with FXS. Furthermore, secondary genetic factors may also play a role in the risk for engaging in challenging behaviour; Hall et al.~~2008Hall et al. (2008)~~ (2008) identified the status of the 5HTTLPR gene (which has been associated with risk for antisocial behaviour and aggression in the general population: Ficks & Waldman, 2014) as a mediating factor for aggression in males with FXS. In order to inform strategies for intervention and prevention, future research should focus on a range of factors which may act as risk factors, such as co-morbidities, cognitive characteristics, genetic characteristics and environmental factors.

Age appears to be an important factor in the relative risk for engagement in challenging behaviours for individuals with intellectual disabilities. A review of the literature suggests a significant increase in the prevalence of aggression with age, from childhood and teenage years into adulthood (though due to a lack of research it is unclear whether this increase applies beyond the age of 45 years; Davies & Oliver, 2013). In contrast, the relative risk of SIB increases until around 30~~ to~~ 40 years, then begins to decrease. The data collected on age in this review (i.e. reported study means) is a crude way of assessing age, and there was no association between age and study prevalence. However, results may have been masked by variance and overlap in ages of participants across the studies. Given that there has been a lack of research with older adults with FXS, and that the participants in this review are relatively young, it is uncertain to what extent the findings are applicable across age ranges. Further research with older adults, as well as longitudinal research, is required to investigate the presentation of challenging behaviour in FXS across the lifespan.

There are several limitations to this review, the principal being that, in order to combine the results of studies employing heterogeneous measures and calculate the 'total' statistic, the assumption was implicitly made that the different assessments corresponded highly to one another. However, measures define behaviours in different ways and assess over different time periods, so are likely to yield varying results. In addition, the included results were derived from single items as well as questionnaire clinical cut-offs, which again are likely to yield differing results. The calculated estimates are intended to provide a broad overview of existing data on the prevalence of challenging behaviours within this syndrome, as such an overview has never before been collated, rather than an attempt to identify a 'true' estimate of prevalence.

Furthermore, many of the reported estimates of prevalence are likely to exaggerate the frequency of challenging behaviours within individuals with FXS. Due to the variable severity of the presentation of the FXS phenotype, it is likely that there are individuals with FXS, particularly females, who remain undiagnosed or who are not in contact with clinical services or support groups. A further limitation is that the gender-combined 'total' estimate is heavily weighted by male participants and therefore, given the aforementioned gender differences, is likely to exaggerate the total group prevalence of both classes of behaviour.

Finally, the methods of recruitment used across the different studies are also likely to have had an effect on the findings, and may contribute to the overall exaggeration of prevalence estimates. Of note, many studies recruited their participants from FXS support organizations (see Table 1). It is known that child characteristics, such as the presence of SIB, can influence the likelihood of parents seeking support (Mandell & Salzer, 2007), meaning that samples recruited in this way may be biased towards elevating the estimated prevalence. Similarly, many were recruited from clinical settings where individuals would be likely to be experiencing greater clinically-significant symptomatology, such as behavioural challenges. In addition, it is likely that there are individuals and families which are represented in more than one of the studies, though it is not possible to determine the extent to which this occurred. However, it may be that the likelihood for participating in multiple studies differs according to engagement in challenging behaviour, and as such may introduce additional bias. Specifically, individuals with high levels of behavioural challenges may be more likely to be represented in multiple studies, when compared to those with low levels of challenging behaviour. Those with challenging behaviours can be recruited both into exclusively clinic-based research and non-clinical research, thus exposing this group to a wide range of study participation opportunities. However, those with no challenging behaviour are less likely to be made aware of research in a clinical setting, as they are presumably

less likely to require this clinical input. As such, those with low levels of behavioural challenges may have fewer research participation opportunities. Therefore, this could create further bias towards the over-representation of those with behavioural challenges, across this research. Of note, many studies recruited from multiple sources, which makes the delineation of studies with differing recruitment types, and statistical investigation of the resultant effect, challenging. However, visual comparison of the spread of the prevalence estimates between the results of studies recruiting from clinical and non-clinical (e.g. support charities, research registries) settings did not suggest a clear pattern of difference between prevalence estimates from different recruitment strategies. Direct comparisons using same measures would be required to clarify the impact of recruitment methodologies on challenging behaviour prevalence estimates. Nevertheless, it is important to note the potential bias exerted through differing approaches to participant recruitment.

Despite these limitations, this review adds value to our understanding of socially and clinically significant behaviours in FXS. This review is the first to systematically collate data on challenging behaviours in this group. It is hoped that these data will help to enable increased understanding and improve intervention for the benefit of individuals and families living with FXS, through informing and influencing further research as well as planning for services to address the needs of this group.

~~Uncited reference~~

~~Holden and Gitlesen (2006).~~

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