School of Psychology
Ysgol Seicoleg

Care provision for people with Fragile X Syndrome: Should it be need or diagnosis driven?

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Cardiff University

Jennifer Daffin

Supervised by Dr John Fox (formerly by Dr Dougal Hare)

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Declaration

This work has not been submitted in substance for any other degree or award at this or any other university or place of learning, nor is being submitted concurrently in candidature for any degree or other award.

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Abstract

Initially, researchers proposed that Fragile X syndrome (FXS) should be called AFRAX syndrome because it was thought to be caused by an autism gene (Gillberg, Persson, & Wahlström, 1986). However, as research into FXS has progressed and an exploration of the behavioural phenotype has taken place important differences have emerged.

The systematic review (Paper 1) aims to delineate a behavioural phenotype for Fragile X Syndrome (FXS). Ten papers were included in the review. All papers were of a standard to demonstrate a behavioural phenotype for FXS. There are attributes of the FXS behavioural phenotype that meet the criteria for both Attention Deficit Hyperactive Disorder (ADHD) and/or Autism Spectrum Condition (ASC). However, there is robust evidence to support a broad FXS behavioural phenotype comprising: 1) social behavioural and communication difficulties, 2) emotional regulation difficulties, 3) repetitive and restrictive behaviour and speech. Several recommendations for research and clinical practice are discussed.

The aim of the empirical study (paper 2) was to examine if there are differences between the behaviour phenotype profiles of those with FXS who have a diagnosis of ASC and those that do not. Parents were asked to complete an online questionnaire that included the Social Responsiveness Scale (SRS), the Wessex Questionnaire, and standard demographic information. The findings of the 38 parents who completed the questionnaire are discussed below.

Finally, the research review (Paper3) will explore the author's research process. This includes a discussion about the decisions to undertake the research, as well as a review of the methodological limitations, implications for policy direction, further research and clinical implications.

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Part 1

The Fragile X Syndrome Behavioural Phenotype:

A Systematic Review

The following paper has been prepared for submission to the Journal of Intellectual Disability Research (Word Count – 7,679; journal word count 4,500)

Abstract

Background Fragile X Syndrome (FXS) is the most commonly known inherited cause of intellectual disability (ID). People with FXS often display behaviours akin to Autism Spectrum Condition (ASC) but the behaviour phenotype for FXS is yet to be delineated. This review aims to delineate the behavioural phenotype for FXS.

Materials and Methods Psychinfo and MEDLINE were searched (Nov 2017) alongside manual screening to identify relevant literature. Papers were included in the review if they were published in a peer-reviewed journal and if they conducted empirical research into the behavioural phenotype of FXS.

Results Ten articles met the inclusion criteria and were quality assessed. All papers were of a standard to demonstrate a behavioural phenotype for FXS. There are behavioural attributes of the FXS behavioural phenotype that meet the criteria for both Attention Deficit Hyperactive Disorder (ADHD) and/or ASC. There is initial evidence to support a broad FXS behavioural phenotype for males with FXS comprising 1) social behavioural and communication difficulties, 2) emotional regulation difficulties 3) repetitive and restrictive behaviour and speech.

Conclusion There is some evidence to begin to delineate a behavioural phenotype for FXS for males. However, not enough papers were found to delineate the behavioural phenotype for females with FXS. Several recommendations for research and clinical practice are discussed.

Keywords: Fragile X Syndrome, FXS, Autistic Spectrum Condition, ASC, autism, autism traits, Attention Deficit Hyperactivity Disorders, ADHD, behavioural phenotype

Conflict of interest statement: None to declare

Introduction

Fragile X Syndrome (FXS) is the most commonly known inherited cause of intellectual disability (ID; Crawford, Acuña, & Sherman, 2001) and is the second most prevalent genetic cause of ID (Thurman, et al., 2014). The genetic basis of FXS was identified over 25 years ago (Verkerk, et al., 1991) and FXS is now known to be part of a group of Fragile X Mental Retardation 1 (FMR1) mutation-related disorders termed Fragile X-associated Disorders (FXD). These include Fragile X-associated tremor/ataxia syndrome (FXTAS) and Fragile X-associated primary ovarian insufficiency syndrome (FXPOI; Boyle & Kaufmann, 2010). Of the people who have FXS, nearly all males will have an ID but only a third of females will. Whilst the exact number of people with FXS is unknown, it is estimated that it affects approximately 1 in 5000 males (Coffee et al., 2009). Females with FXS have a much milder expression because they will have one unaffected X chromosome and in most cases females with FXS will present with a lower intelligence quotient (IQ) or borderline ID (Hagerman et al., 2009).

Many people with FXS and ID also show behavioural characteristics including short attention span, distractibility, impulsiveness, restlessness, over-activity, sensory problems and anxiety as well as difficulties with eye contact, anxiety in social situations, insistence on familiar routines and hand flapping or hand biting. It is these behavioural features, which are phenomenologically like Autism Spectrum Condition (ASC). This has resulted in some people with FXS being diagnosed with co-morbid ASC (Boyle & Kaufmann, 2010; Hall, et al., 2009).

FXS was initially referred to as Autism-Fragile-X (AFRAX) syndrome and was considered to be genetically congruent with ASC (Gillberg, Persson, & Wahlström, 1986) but more recent research on the genotype and phenotype of FXS suggests FXS is a distinct disorder, which

raises questions about interplay between ASC and FXS and the co-morbidity of the two disorders.

ASC is the term for a group of behaviourally-defined neurodevelopmental disorders (Happé, Ronald, & Plomin, 2006) that historically includes Autism Spectrum Disorder (ASD) autistic disorder, childhood ASC, Pervasive Developmental Disorder – not otherwise specified (PDD-NOS), and Asperger's syndrome (World Health Organization, 1992). Whilst ASC is thought to have a genetic basis with 90% heritability, the specific genotype is currently unknown (Awenat et al., 2013; Gupta & State, 2007; Richards, et al., 2015). ASC is characterised by difficulties in communication, reciprocal social interaction and the presence of restrictive and repetitive behaviours (RRB; American Psychiatric Association, 2013). In the UK, approximately 1 in 100 people have ASC (Baird et al., 2006). Males are three times more likely to have ASC than females (Loomes & Mandy, 2017). There are thought to be two variants of ASC. Syndromic ASC which is autism that occurs in conjunction with a known ID developmental syndrome (IDDS; 10-20% of all cases, Geschwind, 2011) and idiopathic ASC (iASC) which is autism that occurs in the absence of a known IDDS. As research into ASC in specific syndromes has developed, evidence has emerged that individuals with certain genetic and metabolic syndromes could have an atypical profile of ASC. This supports the idea that there is a distinction between syndromic variants of ASC and iASC (Hall, et al., 2010; Richards et al., 2015).

There has long been recognition of the limitations of this approach including its creation of an arbitrary cut off for classification. Advances in technology mean that to date over 2000 IDDS have been identified. This means that an estimated 80% of the causes of ID have been identified (Ellison, Rosenfeld & Shaffer, 2013).

In 1940, Waddington proposed the idea of the epigenetic landscape, which is a metaphor for how gene regulation modulates development. This idea describes how intrinsic developmental variation occurs and states that although there can be the same genotype starting point, developmental trajectory results in different phenotypic endpoints (Waddington, 1940). Also known also as behavioural phenotypes, these are patterns of behaviour that present in syndromes caused by genetic and environmental interactions. A behavioural phenotype is characterised by patterns of social, linguistic, cognitive and motor observations, which are associated consistently with a particular biological or genetic disorder (O'Brien, 2006).

This concept developed as the neuro-constructivist approach; the idea that the brain does not have innate modularity rather it develops through interactions between genes, the environment and ontogeny (Karmiloff-Smith, 2006). Consequently, a phenotype might have a phenotype might have multiple genotypes or share a genotype with another phenotype. For example, Prader-Willi syndrome and Angelman's syndrome have essentially the same genotype (Cassidy, Dykens, & Williams, 2000). There is a high level of co-morbid ASC in people with FXS. It is known that Fragile X Mental Retardation Protein (FMRP) influences both ID and ASC in FXS. This lead researchers to propose that ASC in FXS may be a part of its distinct behavioural phenotype, rather than occurring co-morbidity specifically because of the reduced impairments in communication and reciprocal social interaction associated with FXS (Hall et al., 2010)

It is therefore important to delineate syndrome behavioural phenotypes to clarify the mechanisms behind genotype expression. A better understanding of developmental delay

experiences, social communication, sensory differences, emotional dysregulation and repetitive behaviours could lead to better outcomes for people with FXS (Waite et al., 2014).

Understanding the behavioural phenotype of FXS is an important step in ensuring that people with FXS and their families receive appropriate behavioural and educational support and intervention (Moss & Howlin, 2009). Determining whether the often reported autistic-traits in FXS represent a form of co-morbid syndromic ASC or are in fact part of the behavioural phenotype of FXS has implication for service provision. Additionally, how syndromic ASC may differ from idiopathic ASC has important implications for understanding the basis of ASC *per se* (Richards et al., 2015).

The purpose of the current systematic review is to collate research relating to the FXS behavioural phenotype to develop a provisional behavioural phenotype for FXS.

Methodology

Search Strategy

Medline, Psychinfo, and PubMed (1991 to August 2019) databases were searched for relevant articles. The search was limited to empirical research with human participants published in English language peer-reviewed journals. A cut-off date of 1991 was used to correspond to the discovery of the FMR1 gene so as to frame and retain the context of research to those with a diagnosis of Fragile X syndrome (Rousseau, et al., 2011). The search terms were agreed through consensus within the research team and reflect the common terms found in the literature.

Inclusion Criteria: Only peer-reviewed papers that had examined the behavioural phenotype for FXS were included (including systematic reviews) that were written in the English

language, involved human participants and were empirical research papers in peer-reviewed papers from 1991 onwards.

Exclusion Criteria: All non-peer reviewed papers including dissertations, conference abstracts, books, letters, and commentary papers were excluded.

Search string: *"Fragile X syndrome"* AND *"behavio?r* phenoty*".* The fields 'title', 'abstract' and 'keywords' were searched.

Search Results The search returned 147 papers. After excluding those that did not meet the criteria, a total of ten papers were included in the current review (figure 1).

Quality Assessment

There are limited tools for assessing the methodological quality of research on behavioural phenotypes and the current review used an adapted version of a tool developed by Cross & Hare (2013) that assesses the following aspects of behavioural phenotyping studies. The element adapted was syndrome diagnoses. This point was amended to reflect how FXS gets diagnosed.

1. **Control group** (Flint & Yule, 1994; Hodapp & Dyken, 2001) Papers will score: 0 = no control group, 1 = comparisons between non-genetically distinct groups or utilise standardised assessment tool, 2 = genetically distinct control group.
2. **Sample size** Papers will score: 0 = fewer than 15 participants, 1 = 15-30 participants, 2 = 30+ participants.
3. **Recruitment** (O'Brien & Yule, 1995). Papers will score: 0 = participants selected by clinicians or unclear how selected, 1 = participants recruited either through charity or

medical clinics, 2= multiple methods, multiple clinics or multiple charities are used for recruitment.

4. **Syndrome Diagnosis** (Lloyd & Valles, 2010). Papers will score: 0 = syndrome diagnosis based on self-report, or it is unclear how it was obtained, 1 = diagnosis based on physical features or sibling diagnosis, 2 = diagnosis based on appropriate genetic/enzyme testing.
5. **Methodology** (Lloyd & Walles, 2010; Flint & Yule, 1994; Einfeld & Hall, 1994). Papers will score: 0 = no validated measures are used or unclear, 1= used validated and/or standardised measure, 2 = validated and/or standardised measures are used alongside new measures, observations or other methodology.
6. **Considerations for development** (a trajectory over time is included; Hodapp & Dyken, 2001; Karmiloff-Smith, 1998). Papers will score: 0 = participants are compared 'en mass', 1 = the study considers age overtime as a variable for at least one aspect of development or behaviour, 2 = age is considered overtime as a variable in relation to development or behaviour (or all areas investigated).
7. **Appropriate statistics/comparisons.** Paper will score: 0 = data not analysed or unclear, 1 = descriptive statistics are used, 2 = appropriate comparative/correlative statistics are reported.

Scoring

Papers that scored 9 or above (≥ 9) were deemed to be of reasonable methodological quality and thus likely to contribute to the understanding of any given behavioural phenotype (Cross & Hare, 2012). All ten papers in the current review scored ≥ 9 and were therefore considered to be of reasonable methodological quality (see table 1 for results).

Data selection process

Paper selection was made independently by two reviewers based on title and abstract according to the inclusion criteria. The final selection was made by the same two independent reviewers based on the full text. When the reviewers were not certain of classifications a third opinion would have been obtained from within the research team. This was not necessary on this occasion.

Data-extraction analysis

The data from each paper was extracted by two reviewers. The prevalence of each phenotype was extracted where statistical significance was observed.

Identification of behavioural phenotypes

In this systematic review, a tailored data analysis process was used in order to synthesise the FXS behavioural phenotype. Key variables for each phenotype reported in the included papers were extracted as per Dell'Isola and colleague's phenotype analysis procedure (2016). Using the theory and previous evidence, each key variable was assigned to a category (e.g. emotional regulation, sensory needs, repetitive and restrictive behaviour) indicating the underlying mechanism represented by that specific variable. Variables (e.g. withdrawn, strict routine) were considered to suggest similar mechanisms and classified in the same category if it was specifically stated by the author of the paper (e.g. two subgroups extracted from two different studies were reported by the respective authors as representing the same phenotype). Each phenotype was then classified in the category indicated by the variable that characterized it. A phenotype was considered supported by evidence when at least two studies identified a phenotype under the same category. If a phenotype was reported in only

a single study this was not considered robust enough evidence to be included in the final list of phenotypes identified in this review (see table 2 for results).

Results

The ten papers included in the current review are summarised in Table 1. There are five papers that review the behavioural phenotype for males with FXS and one paper that included females within its study. There were therefore not enough papers to explore the behavioural phenotype for females with FXS. In addition to describing the findings for males with FXS, four papers explored autism in the context of the behavioural phenotype of FXS. These papers will be reported on separately.

Critical Item Ratings

Critical item overall scores were given based on item priority as determined by the tool's original item inclusion criteria as used by the author. The following priority ranking were therefore given; 1) methodology, 2) statistics, 3) sample size, 4) control group, 5) recruitment method, 6) diagnosis, 7) developmental trajectory (see table 2). Critical items were ranked based on the literature in the field used in the construction of the original tool. 'Methodology' was considered to be the most substantive critical item and useful in determining the overall quality of the studies included. It can be seen below that whilst analysis method and sample size are also important items there is little variability in the scoring. This is explored further in the limitations section. Internal rating of the critical ranking process separated the papers into three categories based on total scores; 9-10 low, 11-12 medium and 13-14 high ranking. Nine is the cut off point for inclusion in the original tool. No high-ranking papers were found in this review. Weighting the papers by this method indicated that papers 1-3 are perhaps of greater

value than 4-6. The top three include; Reiss & Freund, 1992, Baumgarder, et al., 1995 and Backes, et al., 2000 Germany.

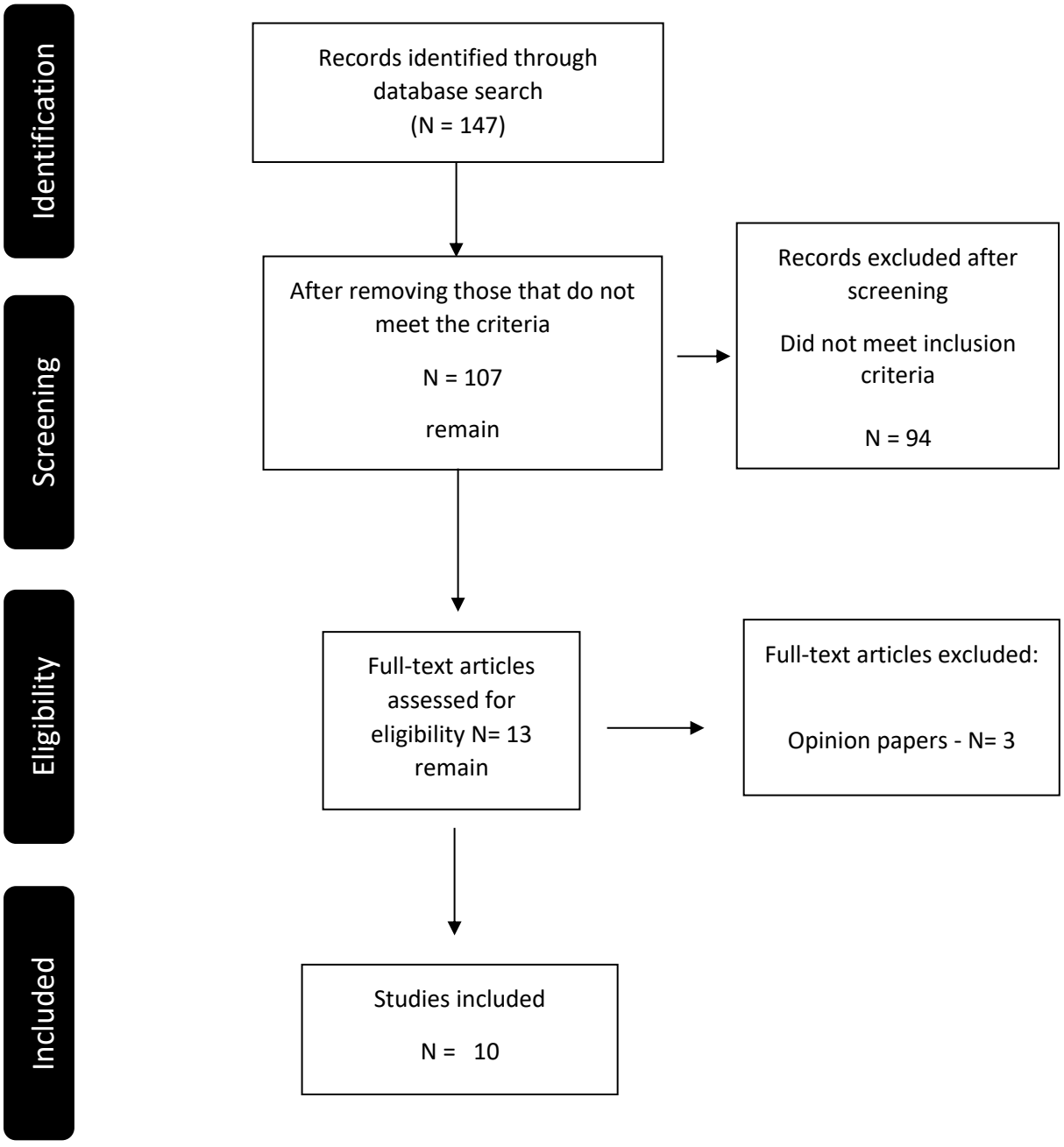

Figure 1. PRISMA Flow Chart

NB: All dissertations, conference abstracts, books, letters, and commentary papers were excluded. García-Perdomo's (2016) patient or population, intervention, comparison and outcome (PICO) strategy was used to support definition of the criteria.

Table 1: Summary of Papers Investigating Behavioural Phenotype of FXS.

Author/ Year/ Country	Study Aims	Methodology	Analysis Method	Sample Size (age range)	Control Group	Recruitment	Diagnosis	Dev. Factors	Findings
Reiss & Freund, 1992, USA	To test the hypothesis that boys with FXS syndrome would show a particular pattern of behavioural dysfunction from the autistic spectrum when compared to a cognitive and developmental-matched non-FXS control group.	Standardised Validated measures	Descriptive statistics/percentages. Comparative statistics within syndrome	33 male children with cytogenetically confirmed FXS (3-18 years)	Yes	Multiple clinics	Genetic testing	No	The investigation supports the contention that FXS males manifest a specific subset of behaviours from the autistic spectrum.
Score (12)		2	2	2	2	2	2	0	
Baumgarder, et al., 1995; USA	Identify the neuro-behavioural profile for males with FXS.	Standardised Validated measures	Descriptive statistics/percentages. Comparative statistics between syndrome and genetically distinct control group.	31 Males with FXS and 30 males with DD (3-12 years)	Yes	Multiple clinics	Genetic testing	Age equivalent scores	Etiological differences found between the two groups but no FXS specific profile found in terms of ABC measure.
Score (12)		2	2	2	2	2	2	0	
Backes, et al., 2000; Germany	To determine the cognitive, behavioural phenotype of FXS.	Standardised Validated measures Clinical interview idiosyncratic questionnaire	Descriptive statistics/percentages. Comparative statistics within and between syndrome and genetically distinct control group.	49 males with FXS and 19 control males w/ TS (Age not specified)	Yes	Multiple clinics Multiple Charites	Genetic testing	No	Behavioural Phenotype for boys is characterised by strengths in acquiring knowledge and simultaneous processing. Limited by high levels of hyperactivity, oppositional defiant disorder.
Score (12)		2	2	2	2	2	2	0	
Smith, et al., 2012; USA	Comparing FXS and ASC through adolescence to adulthood (Behavioural Phenotype)	Standardised Validated measures	Descriptive statistics/percentages Within syndrome. Comparative statistics	136 children with FXS (12-18 years old) compared with 133 mothers of children with ASC.	Yes	Not clearly specified in text	Genetic testing	No	Those diagnosed with FXS and ASC have greater communication and social reciprocity impairments than those with FXS only. Dual diagnosis exhibited higher repetitive and restricted behaviours.
Score (11)		1	2	2	2	2	2	0	
Steinhausen, et al., 2002; EU	Behavioural phenotypes were studied in four ID syndromes using the Developmental Behaviour Checklist (DBC). The four samples comprised foetal alcohol syndrome (FAS), Prader-Willi syndrome (PWS), fragile X syndrome (FRAX), and tuberoses sclerosis complex (TSC).	Standardised Validated measures	Descriptive statistics with comparative statistics within syndrome were used for analysis.	Sample 49 males (age 5-16 years) with FXS	Yes	Single clinic or diagnostic centre Multiple Charities	Not specified in text	None	FAS and FRAX proved to be most clearly differentiated from the other two samples, with PWS and TSC showing lower scores and less abnormal behaviour profiles. Neither IQ score nor gender nor age contributed to variations in numbers of behaviour abnormalities. DBC as a quantitative approach contributes significantly to the differentiation of behavioural phenotypes in various ID.
Score (9)		1	2	2	2	2	0	0	

Hull & Hagerman, 1993; USA	To compare the physical and behavioural phenotype of controls, permutation and full mutation FXS in females without developmental delay.	Clinical interview. Idiosyncratic questionnaire.	Descriptive statistics/percentages and comparison tests.	139 participants all female (age not specified)	Yes	Single clinic or diagnostic centre	Genetic testing	no	Women with partial mutation presented with poor eye contact. Women in the FXS category presented with high rates of hyperactivity, anxiety, hand flapping and hand biting but not at a significantly different rate to the control group.
Score (9)		1	1	2	2	1	2	0	

Table 2 Critical Item *Summary of Papers Investigating Behavioural Phenotype of FXS.*

Author/ Year/ Country	1.Methodology	2.Analysis Method	3. Sample Size (age range)	4.Control Group	5.Recruitment	6.Diagnosis	7.Dev. Factors	Total score	Critical Factor Weight
1. Reiss & Freund, 1992, USA	2	2	2	2	2	2	0	12	**Medium**
2. Baumgarder, et al., 1995; USA	2	2	2	2	2	2	0	12	**Medium**
3. Backes, et al., 2000, Germany	2	2	2	2	2	2	0	12	**Medium**
4. Smith, et al., 2012; USA	1	2	2	2	2	2	0	11	**Medium**
5. Steinhausen, et al., 2002; EU	1	2	2	2	2	0	0	9	**Low**
6. Hull & Hagerman, 1993, USA	1	1	2	2	1	2	0	9	**Low**

Table 3: Summary of Papers Investigating Autism in the Behavioural Phenotype of FXS.

Author/ Year/ Country	Study Aims	Methodology	Analysis Method	Sample Size (age range)	Control Group	Recruitment	Diagnosis	Dev. Factors	Findings
Lee et al., 2016; USA	To characterise ASD phenotypes in boys and girls with FXS across development and compare it to boys and girls with idiopathic ASD over time	Standardised/ Validated measures	Descriptive statistics with between syndrome comparative statistics and between syndrome correlations were used	34 females and 31 males with FXS and 19 boys with autism only (age not specified)	Yes	Clinics, advocacy groups and participant registries	Not stated		ASD traits increased in those with FXS over time. Indicating a positive correlation between time and ASD. This was more so in boys than girls and specifically related to social communication.
Score (11)		1	2	2	2	2	0	2	
	To explore the behavioural phenotype	Standardised/	Descriptive statistics with between	23 males with FXS and ASC	Yes	Multiple clinics	Genetic testing	No	FSX + ASC and iASC are similar in RRB and social approach but differ

Wolff, et. al., 2012; USA	expression (through Autism) in FXS	Validated measures	syndrome comparative statistics and between syndrome correlations were used	and 38 with iASC (age not specified)		Multiple Charites			in more complex forms of RRB and social responses. Indication of unique etiological presentation.
Score (12)		2	2	2	2	2	2	0	
Disanayake et al., 2009; Australia	To investigate the cognitive and behavioural phenotype associated with idiopathic ASC and comorbid ASC.	Standardised/ Validated measures	Descriptive statistics with between syndrome comparative statistics and between syndrome correlations were used.	49 boys with ASD, 48 boys with ASD and FXS and their parents (age, M 45, 34; F 32, 30) (5-36 years)	Yes	Register	DNA	none	Those with FXS and ASD scored higher on social communication. Those with FXS and ASD had overall lower scores a part from comprehension. No FXS/ASD parental effect was found. Suggestion that FXS may be primarily cognitively related rather than behavioural made.
Score (10)		1	2	2	2	1	2	0	
Rogers, et al., 2001; USA	To explore the behavioural phenotype of ASC in FXS	Standardised/ Validated measures	Descriptive statistics/percentages Within and between syndrome comparative statistics	27 children with AD, 24 with FXS and 23 with DD (age 21-48 months). Sex not specified.	Yes	Multiple clinics Multiple Charites	Genetic testing	No	Findings suggest there is genetic influence in FXS & autism presentation.
Score (10)		1	2	2	2	2	2	0	

Table 4 Critical Item Summary of Papers Investigating Autism in the Behavioural Phenotype of FXS.

Author/ Year/ Country	1.Methodology	2.Analysis Method	3. Sample Size (age range)	4.Control Group	5.Recruitment	6.Diagnosis	7.Dev. Factors	Total score	Critical Factor Weight
Wolff, et. al., 2012; USA	2	2	2	2	2	2	0	12	**Medium**
Lee et al., 2016; USA	1	2	2	2	2	0	2	11	**Medium**
Rogers, et al., 2001; USA	1	2	2	2	2	2	0	10	**Low**
Disanayake et al., 2009; Australia	1	2	2	2	1	2	0	10	**Low**

Of the ten papers included in the current review, all scored above the cut-off point (≥ 9). All papers reported statistically significant results and therefore were included to contribute to the concept of a distinct FXS behavioural phenotype. In order to further delineate the quality of the papers, items were ranked into their critical worth. Information from the top-scoring papers potentially carry more weight than those from lower-scoring categories. This should be considered when interpreting any discrepancies or anomalies in findings. The additional critical item ratings largely reflect the total scores generated by the tool. Where discrepancies occur most often this was due to missing or ambiguous information in papers.

Behavioural Phenotype in FXS

The following section describes the six papers that explored the behavioural phenotype in FXS. This included four papers that reviewed the behavioural phenotype in males, one in females and one combined males and females together.

Summary of Medium Scoring Papers

Papers within the medium category include;

1) **Reiss, A., & Freund, L. (1992)** Behavioural Phenotype of Fragile X Syndrome: DSM-III-R Autistic Behavioural in Male Children. American Journal of Medical Genetics. (USA; scored 12/14)
2) **Baumgarder, T., Reiss, L., Freund, L., & Abrams, M. (1995)** Specification of the Neuro Behavioural Phenotype in Males with Fragile X Syndrome. Peadiatrics. (USA; scored 12/14)

3) **Backes, M., Genc, B., Schreck, J., Doerfler, W., Lehmkuhl, G., & von Gontard, A. (2000).** Cognitive and behavioral profile of fragile X boys: correlations to molecular data. American Journal of Medical Genetics. (Germany; scored 12/14)
4) **Smith, L.E., Barker, E. T., Seltzer, M. M., Abbeduto, L., Greenberg, J. S., Smith, L. E., & Greenberg, J. S. (2012).** Behavioral phenotype of fragile X syndrome in adolescence and adulthood. American Journal on Intellectual & Developmental Disabilities (USA; scored 11/14)

Review of Medium Scoring Papers

1. Reiss & Freund (1992) tested the hypothesis that boys with FXS syndrome would show a pattern of behavioural dysfunction distinct from ASC, when compared to a cognitive and developmental-matched non-FXS control group. A total of 33 male children with cytogenetically confirmed FXS aged 3-18 years were included. The study identified a number of significant areas associated with the FXS behavioural phenotype. These relate to: 1) social communication; gaze aversion, absent or abnormal gestural language, 2) language use; unusual rate, volume and tonal quality of speech, echolalia, and 3) perseveration for word, phrase or topic and lack of fantasy and pretend play. Those with FXS specifically exhibit repetitive and restrictive behaviour (e.g. hand flapping, rocking and hand biting), and unusual responses to sensory stimuli (e.g. oversensitivity to sounds and touch, mouthing and smelling objects inappropriately and a resistance to change in routine). Descriptive statistics along with comparative statistics between syndrome and a genetically distinct control group were used for analysis. The Autism diagnosis interview (ADI-R), Autism Diagnostic Observation Schedule (ADOS-G) and Wechsler intelligence tests (WPPSI-R/WPPSI-III) measures were used. The limitations relate to there being ascertainment bias in the recruitment of participants.

Participants were recruited based on their involvement with service provision rather than randomly recruited and no measures of developmental trajectory was used.

2. Baumgarder, Reiss, Freund & Abrams (1995) examined the neuro-behavioural profile of FXS. Despite some methodological limitations relating to recruitment and measures, the paper reported significant results indicating a distinct FXS behavioural phenotype. A total of 31 males with FXS and 30 males with developmental delay aged between 3-12 years were included. The authors found high rates of ADHD diagnosis in people with FXS, with 73% meeting criteria for attention deficit hyperactivity disorder (ADHD) and 38% for ASC. The results indicated that people with FXS display high levels of hyperactivity, have repetitive speech and repetitive behaviours. Specifically, they displayed more excessive activity, restlessness, impulsivity and distractibility and this has consequences for processing complex internal and external stimuli for social functioning. The authors suggested this causes rather than is the cause of attachment and empathy issues. However, the control group was made up of people with developmental disorders and not those with ASC traits. There was no correlation between FXS amplification and phenotypic profile. Descriptive statistics along with comparative statistics between syndrome and a genetically distinct control group were used for analysis. The Vineland Adaptive Behavioural Scale and Aberrant Behaviour Check List (ABC) measures were used. Measure of developmental trajectory was also used.

3. Backes, Genc, Schreck, Doerfler, Lehmkuhl, & von Gontard (2000) compared boys with FXS to those with tuberous sclerosis complex (TSC). They found a positive correlation between IQ score and degree of developmental delay. In boys with FXS there are higher rates of ADHD and opposition defiance disorder diagnosis as well as functional enuresis and encopresis. It indicated that hyperactivity is the most common reported diagnosis across the group and that

it is more common amongst children with FXS than other developmental disorders. Behavioural problems were six times higher in males with FXS than in the general population. No significant correlation was found between the behavioural phenotype and genotype for FXS. A total of 49 males with FXS and 19 control males with TSC were included. Age was not specified in the text. Descriptive statistics along with comparative statistics were used. The Kaufman Assessment Battery for Children (K-ABC) and Wechsler tests (HAWIK-R and HAWIE) measures were used. In this study only measures of cognitive ability were included. Specific behaviour related measures were not included. Children's diagnostic Interview for psychiatric symptoms (DIPS) does not assess for ASC.

4. Smith, Barker, Seltzer, Abbeduto, Greenberg, Smith & Greenberg (2012) compared FXS and ASC behavioural phenotypes across adolescence to adulthood. The results showed that those with FXS only, were less socially impaired than the group with ASC or FXS and ASC. However, the rates of RRB in adolescents and adults were the same for those with FXS only and ASC only. Those with FXS and ASC had the highest levels of behavioural problems and psychological symptoms (social offensive behaviour, withdrawn behaviour and uncooperative behaviour, intrusive behaviour and inattention). The researchers identified a pattern of externalizing behavioural problems that were not necessarily autism-specific symptoms, but which were associated with an additional co-morbid diagnosis of autism. Those with FXS and ACS were more impaired in social reciprocity and communication. Some of the difficulties with RRB, adaptive function and behavioural problems were shown to decrease in older children with FXS. The Autism diagnosis interview (ADI-R) and the social communication questionnaire (SCQ) were used. Whilst a wide age range means specific points in time could not be compared the ASC only group were considerably older than FXS group which impacts on the ability to compare groups.

Summary of Low Scoring Papers

Papers in the low-range of scoring include;

1) **Steinhausen, H.-C., von Gontard, A., Spohr, H.-L., Hauffa, B. P., Eiholzer, U., Backes, M., & Malin, Z. (2002).** Behavioral phenotypes in four mental retardation syndromes: Fetal alcohol syndrome, Prader-Willi syndrome, fragile X syndrome, and tuberosis sclerosis. American Journal of Medical Genetics, (EU; scored 9/14)
2) **Hull, C., & Hagerman, R. J. (1993).** A study of the physical, behavioral, and medical phenotype, including anthropometric measures, of females with fragile X syndrome. American Journal of Diseases of Children (USA; scored 9/14).

Review of Low Scoring Papers

1. Steinhausen, von Gontard, Spohr, Hauffa, Eiholzer, Backes, & Malin, (2002) found differences between those diagnosed with foetal alcohol syndrome (FAS), Prader-Willi syndrome (PWS), TSC and FXS are explored in this paper. A sample of 49 males (age 5-16 years) with FXS were included. The authors found children with FXS were less likely to chew or mouth objects or body parts, hit or bite self, hum, and were much more likely to present with overactive behaviour and flicks, taps, and twist object compared to the other groups. The group of children with FXS were more likely to engage in repetitive speech, be shy, avoid eye contact, laugh and giggle for no obvious reasons, and repeat movements of various body parts. The group also disproportionately lacked self-confidence and self-esteem. The FXS sample showed the most complex behavioural pattern among all four syndromes studied, with the presence of autistic traits being a significant discriminator between FXS and FAS. FXS

was the most closely aligned to FAS in terms of presentation. Both FAS and FXS were associated with elevated levels of behavioural difficulties, with higher scores on measures of overexcitement/impulsivity, being verbally abusive or swearing, irritability and attention-seeking. Descriptive statistics with inferential statistics within syndrome were used for analysis. The Developmental Behaviour Checklist and Kaufman Assessment Battery for Children were used. This study is limited by the young age range of participants, which meant it was difficult to distinguish what was part of usual development.

2. Hull and Hagerman (1993) compared females with FXS to their female siblings without FXS against a control group. A total of 139 participants, all female, were included. Age was not specified in the text. It explored the physical, behavioural, and medical phenotype of females with FXS. The findings relating to behavioural phenotype characterised females with FXS as having difficulties with poor eye contact, and additional educational needs including additional support with mathematics. The paper also found a difference in attention and hyperactivity, impulsivity, panic attacks, hand flapping, and hand biting. However these were not significantly different across the three groups. Descriptive statistics along with comparison tests were used for analysis. A physical examination, questions about education, interventions accessed, and speech and language issues were asked. Formal measures were not used.

Summary of the Autism in the Behavioural Phenotype for FXS papers

1) **Wolff, J. J., Bodfish, J. W., Hazlett, H. C., Lightbody, A. A., Reiss, A. L., & Piven, J. (2012).** Evidence of a distinct behavioral phenotype in young boys with fragile X syndrome and autism. *Journal of the American Academy of Child and Adolescent Psychiatry*, *51*(12), 1324–1332; scored 12
2) **Lee, M., Martin, G. E., Berry-Kravis, E., & Losh, M. (2016).** A developmental, longitudinal investigation of autism phenotypic profiles in fragile X syndrome. Journal of neurodevelopmental disorders, 8, 47; scored 11
3) **Rogers, S. J., Wehner, E. A., & Hagerman, R. (2001).** The behavioral phenotype in fragile X: Symptoms of autism in very young children with fragile X syndrome, idiopathic autism, and other developmental disorders. Journal of Developmental and Behavioral Pediatrics, 22(6), 409–41
4) **Dissanayake C., Bui Q., Bulhak-Paterson D., Huggins R. & Loesch D. (2009).** Behavioural and cognitive phenotypes in idiopathic autism versus autism associated with fragile X syndrome. Journal of Child and Adolescent Psychology and Psychiatry 50, 290–9; scored 10

Review of papers with a focus on Autism in the Behavioural Phenotype for FXS

1. Wolff, J. J., Bodfish, J. W., Hazlett, H. C., Lightbody, A., Reiss, A. L., & Piven, J. (2012) aimed to explore the autism expression within the behavioural phenotype in FXS. The study was made up of 34 females and 31 males with FXS and 19 boys with autism only (age not specified). It makes comparisons between those with FXS and an autism diagnosis and those with idiopathic autism. Findings demonstrate differences in the more complex forms of RRB

and in some social response behaviours between people with FXS and those with both FXS and ASC. In lower order RRB (e.g. stereotypy and self-injury) and social approaches the paper found similarities between the two groups. This is important because RRB has been linked to developmental disability and is not specific to ASC. However, no overall differences between FXS only and the FXS with autism group were found. Descriptive statistics along with between syndrome comparative statistics and between syndrome correlations were used. The Autism Diagnostic Observation Schedule (ADOS-G), Repetitive Behavioural Scale (RBS) and Mullen Early Learning Composite (ELC) were used. The study would have benefited from a standard measure of social communication. No comparisons to those with FXS only were presented.

2. Lee, M., Martin, G. E., Berry-Kravis, E., & Losh, M. (2016) aimed to characterise ASD phenotypes in boys and girls with FXS across their development and compared it to boys and girls with idiopathic ASD over time. The study was made up of 23 males with FXS and ASC and 38 with idiopathic ASC (age not specified). Some differences between FXS and ASC groups across time were reported. The paper found that over time there was a greater difference in profiles for the ASC group in relation to restrictive behaviour. This indicates that respective and restrictive behaviour may not be the same in FXS and ASC. This finding indicates that developmental trajectories should be given greater consideration in future studies. Social communication issues and behaviour problems are predictive of a later FXS ASC diagnosis. Descriptive statistics along with between syndrome comparative statistics and between syndrome correlations were used. The Autism Diagnostic Observation Schedule (ADOS-G) and Autism diagnosis inter (ADI-R) measures were used. The study is limited by the fact that only autism measures were used rather than behaviour specific ones.

3. Rogers, S. J., Wehner, E. A., & Hagerman, R. (2001) explored the behavioural phenotype of ASC in FXS. A total of 27 participants with a diagnosis of ASC (24 with FXS and 23 with developmental delay) aged 21-48 months were included. Sex of the children was not defined in the text. The purpose of this study was to compare the symptoms of autism in very young children with fragile X syndrome (FXS) to those with idiopathic autism and with other developmental disorders. The hypotheses were that the children with FXS would demonstrate a unique pattern of behaviour compared with the other two groups. It was thought they would display more symptoms of autism than the developmentally delayed group. However, this would be a unique pattern compared to the group with idiopathic autism. These hypotheses were not supported by the findings and differences were not found, other than between those with developmental delay and FXS. Differences in the severity of developmental delay across the two groups were not held. The authors reflect on the limitations of the young age of the sample (chronologically 2-3 years, developmentally 12-24 months) and that those in the study with developmental disability and ASC also had lower IQ scores. This may have impacted the results. Descriptive statistics along with within and between syndromes comparative statistics were used for analysis. The Autism Diagnostic Interview-Revised (ADI-R), the Autism Diagnostic Observation Schedule-Generic (ADOS-G), The Mullen Scales of Early Learning (MSEL) and the Vineland Adaptive Behaviour Scales, Interview Edition were used. The participants used in this study were very young, making it difficult to generalise or conclude findings.

4. **Dissanayake C., Bui Q., Bulhak-Paterson D., Huggins R. & Loesch D. (2009)** aimed to investigate the cognitive and behavioural phenotype associated with idiopathic ASC and comorbid ASC. The study was made up of 49 boys with ASD, 48 boys with ASD and FXS and their parents. The participants were aged 5-36 years. It found that while individuals with FXS

and ASC demonstrate a similar profile of scores on the Autism Diagnostic Observation Schedule (ADOS) to individuals with idiopathic ASC, those with FXS score significantly lower on tests of performance and verbal communication. The authors suggest that the common pathway underlying the shared characteristics of FXS and ASD is likely to be neural rather than genetic, whereby different biological pathways may lead to a common cognitive and behavioural outcome. Further work is required to understand where the similarities come from. Descriptive statistics along with between syndrome comparative statistics and between syndrome correlations were used. Autism Diagnostic Observation Schedule-Generic (ADOS-G), and Wechsler intelligence tests (WPPSI-R) were used. The study is limited by the fact that only ASC specific measures were used. The age range is broad (5- 36 years of age) meaning a thin spread of individuals across ages, which is not controlled for in the results.

Summary of the findings from the Autism specific behavioural phenotype papers reviewed

In the case of FXS and syndromic ASC compared to idiopathic ASC, there appear to be lower levels of compulsive and ritualistic behaviour and fewer social communication difficulties. When comparing FXS and syndromic ASC with idiopathic ASC and ID, there are reported differences in both gross and fine motor skills and in expressive language skills. Those with FXS and ASC had lower ability in these areas. Those with FXS and ASC also had the highest levels of behavioural and psychological difficulties. Overall, those with FXS only were less impaired than those with FXS and ASC. Wolff, et. al., 2012, Rogers, et al., 2001 and Disanayake et al., 2009 did not find significant difference to describe a distinct autism-specific behavioural phenotype in FXS. Lee et al., 2016 found significant differences across time suggesting that

ASC behaviours in FXS worsen over time. Further research would be required to support these findings.

Data synthesis for the development of the FXS Behavioural Phenotype

The findings from the behavioural phenotype papers are synthesised across tables 5 and 6 using the Dell'Isola and colleague's phenotype analysis procedure (2016).

FXS Behavioural Phenotype Data Synthesis

There were six papers eligible for data synthesis. However, only one paper, Hull & Hagerman, (1993), clearly identified the behavioural phenotype characteristics for females. It was not possible to identify from Smith, et al., (2012) which items specifically related to females. The Dell'Isola procedure requires a minimum of two papers to identify a characteristic for it to qualify, therefore the female FXS behavioural phenotype is not described within the findings in table 5. Therefore, the below table synthesises the data from the five remaining eligible papers (see table 1 for details).

Table 5. Summary of the Significant Findings from the Male Behavioural Phenotype Papers Reviewed

FXS Behavioural Phenotype Characteristic	FXS in Males
Social, Behavioural and Communication Difficulties	
Gaze aversion/poor eye contact	Reiss & Freund, 1992
	Steinhausen, et al., 2002
Shyness/withdrawn	Steinhausen, et al., 2002
	Baumgarder, et al., 1995
	Reiss & Freund, 1992
Social communication difficulties	Backes, et al., 2000
	Reiss & Freund, 1992
Uncooperative	Steinhausen, et al., 2002
	Backes, et al., 2000
Socially disruptive behaviour	Backes, et al., 2000
	Steinhausen, et al., 2002
Emotional Regulation Difficulties	
Restlessness/Hyperactive	Baumgarder, et al., 1995
	Steinhausen, et. al., 2002
	Backes, et al., 2000
Impulsivity	Baumgarder, et al., 1995
	Steinhausen, et al., 2002
	Backes, et al., 2000
Distractibility	Baumgarder, et al., 1995
	Steinhausen, et al., 2002
	Backes, et al., 2000
Attention	Steinhausen, et al., 2002
	Baumgarder, et al., 1995
	Backes, et al., 2000
Irritable	Steinhausen, et al., 2002
	Baumgarder, et al., 1995
	Backes, et al., 2000
Self-injurious behaviour	Baumgarder, et. al., 1995
Repetitive and Restrictive Behaviour	
Repetitive and excessive speech with unusual tone/quality	Reiss & Freund, 1992
	Baumgarder, et al., 1995
	Steinhausen, et al., 2002
Repetitive stereotyped movements (hand arm and body)	Reiss & Freund, 1992
	Baumgarder, et al., 1995
	Steinhausen, et al., 2002
Resistance to change in routine	Reiss & Freund, 1992
	Steinhausen, et al., 2002
Sensory Needs	
Oversensitively to sounds and touch	Reiss & Freund, 1992
Mouthing and Smelling objects	Reiss & Freund, 1992

FXS Behavioural Phenotype for the Males with FXS

Summarising the above table, the behavioural phenotype in males with FXS the following characteristics were identified;

- Social, behavioural and communication difficulties
- Emotional regulation difficulties
- Repetitive and restrictive behaviour

FXS Behavioural Phenotype and Autism Data Synthesis

There were four papers eligible for data synthesis for this section. It was however not possible to delignate males from females across all the papers and therefore findings have been reviewed collectively in order to apply the Dell'Isola phenotype analysis procedure (2016).

Table 6. Summary of the Significant Findings from the Autism in the FXS Behavioural Phenotype Papers Reviewed

FXS Behavioural Phenotype Characteristic	Supporting Study	Findings Description
Social, Behavioural and Communication Difficulties		
Gaze Integration	Wolff et al., 2012	Lower ability in those with FXS with autism compared to idiopathic autism. No significant differences between FXS and autism against those with FXS only were reported.
Quality of Social Interaction	Lee et al., 2016	Higher prevalence of difficulty for those with FXS with autism compared to those with FXS only
	Wolff et al., 2012	Lower ability in those with FXS and autism compared to idiopathic autism. No significant differences between FXS and autism against those with FXS only were reported.
	Lee et al., 2016	Higher prevalence of difficulty for those with FXS with autism compared to those with FXS only
Social Expressions	Wolff et al., 2012	Lower ability in those with idiopathic autism compared to those with FXS with autism. No

		significant differences between FXS with autism against those with FXS only were reported.
Reciprocal social interaction	Rogers et al., 2001	Higher prevalence of difficulty for those with FXS with autism compared to those with FXS only.
	Dissanayake et al., 2009	Higher prevalence of difficulty for those with FXS and autism compared to those with idiopathic autism
Communication	Rogers et al., 2001	Higher prevalence of difficulty for those with FXS with autism compared to those with FXS only
	Dissanayake et al., 2009	Higher prevalence of difficulty for those with FXS with autism compared to those with idiopathic autism
	Lee et al., 2016	Higher prevalence of difficulty for those with FXS with autism compared to those with FXS only
Shared enjoyment	Lee et al., 2016	Higher prevalence of difficulty for those with FXS and autism compared to those with FXS only
Repetitive and Restrictive Behaviour		
Compulsive and ritual behaviour	Wolff et al., 2012	Higher prevalence of difficulty for those with idiopathic autism compared to those with FXS with autism. No significant differences between FXS and autism against those with FXS only were reported.
	Lee et al., 2016	Those with idiopathic autism had higher prevalence of difficulty compared to both FXS only and FXS with autism.
Restricted and repetitive behaviours (not specified)	Rogers et al., 2001	Higher prevalence of difficulty for those with FXS and autism compared to those with FXS only
		Those with idiopathic autism had higher prevalence of difficulty compared to both FXS only and FXS with autism.
	Lee et al., 2016	
Developmental trajectory		
Overall severity of symptoms	Lee et al., 2016	Those with FXS and autism showed less severity of symptom increase overtime compared to those with idiopathic autism.
Social impairments	Lee et al., 2016	Those with FXS only were less socially impaired at second time measure compared to both FXS with autism and idiopathic autism groups.

FXS Behavioural Phenotype and Autism

Summarising the above table, the following characteristics were identified as demonstrating differences;

- Social, behavioural and communication difficulties
- Restricted and repetitive behaviours

People with FXS and ASC were found to have more social behaviour and communication difficulties in comparison to people with either FXS alone or idiopathic ASC. Specifically, there appear to be key differences in communication ability across the three groups. This difficulty appears to impact those with a diagnosis of FXS with and without a diagnosis of autism differently to those with idiopathic autism. Those with FXS with autism have less difficulty with restricted and repetitive behaviours compared to those with idiopathic autism.

Overall Summary of Behavioural Phenotype Data

The broad FXS behavioural phenotype is emerging along a continuum with repetitive behaviours, social communication difficulties and emotional regulation difficulties. Across the studies included in this review similarities and differences in the behavioural phenotype patterns are explored below.

FXS Behaviour Phenotype Studies

Social, behavioural and communication difficulties were found consistently across all four studies. Emotional Regulation Difficulties were found consistently across three studies. Reiss & Freund (1992) did not use measures to explore emotional regulation difficulties. Their paper focused on the DSM-III ASC criteria to explore the FXS behavioural phenotype, which does not account for emotional regulation difficulties. This limited their ability to comment

on these aspects. Repetitive and restrictive behaviour were found consistently across three studies. Back and colleague's (2000) use of the Children's DIPS assessment limited their ability to explore ASC across their sample, as it does not measure these characteristics.

Whilst Smith and colleagues (2012) found significant findings across all three domains, the study is unable to contribute to the FXS behavioural phenotype in accordance with the Dell'Isola phenotype analysis procedure (2016).

Therefore, based on the current review, there is evidence to tentatively support a broad FXS behavioural phenotype for males comprising; 1) social behavioural and communication difficulties, 2) emotional regulation difficulties 3) repetitive and restrictive behaviour.

FXS Behavioural Phenotype and Autism

Social, behavioural and communication difficulties were found consistently across all four studies. Repetitive and restrictive behaviour were found consistently across three studies. Dissanayake et al., 2009 did not find significant differences across its repetitive behaviour domains assessed by the ADOS. It is possible the broad range of age (5-36 years) in this study may have impacted the findings. Emerging data on the impact of development over time has demonstrated differences in severity.

Based on the current review, there is evidence to tentatively support a broad FXS behavioural phenotype in relation to autism comprising differences between; 1) social behavioural and communication difficulties, and 2) repetitive and restrictive behaviour and speech difficulties.

Discussion

The current review included ten papers examining the behavioural phenotype of FXS. All papers were rated as methodologically sound. Papers were explored in two parts; an overall behavioural phenotype for FXS and a behavioural phenotype for autism and FXS. For the overall behavioural phenotype, it was only possible to delineate the behavioural phenotype for males with FXS because there were not enough papers identified that explored females with FXS. Four papers explored the behavioural phenotype in the context of autism. Caution should be used went interpreting these findings as a low number of papers were identified to explore the behavioural phenotypes in each instance. The studies included in this review have shown that there are behaviours that are reported across the FXS continuum including emotional regulation difficulties, repetitive and restrictive behaviour and social communication problems. These are further compounded by the presence of increased intellectual disability. Communication appears to play a distinct role within FXS, which was observed across those with and without an autism diagnosis.

Review Limitations

Limitations in the Reviewing Tool's Quality

This review was conducted using an adapted version of a tool developed by Cross & Hare (2012) to review the disorders of mucopolysaccharide. Given the adaptations have not been validated, caution should be used when interpreting the results of this review. The scoring system was based on the existent literature for methodology in behavioural phenotype research. However validation of the tool could yield greater utility. It has not been robustly tested for its use with FXS. The tool would benefit from an exploration of the pros and cons of its application. This study did not explore the differences between mucopolysaccharide

and FXS or consider in depth what impact this could have on the tool. Mucopolysaccharide occurs in one in 25,000 births whereas FXS occurs in 1 in 5000 males (Moore, et al., 2008). This difference in prevalence was potentially not adequately considered in the adaptation of the tool in relation to the sample size measure. Future uses should ensure this measure reflects prevalence rates.

Across the studies diagnosis of ASC is an area requiring further exploration. Since ASC is diagnosed from behavioural interpretations rather than biomarkers this leaves room for some interpretation by individual researchers and clinicians. The subjective nature of diagnosis and variety of tools used within the studies limits the validity of this reviews ability to categorically define the behavioural phenotype for FXS. Diagnostic rating scales for ASC can vary depending on which and how many are used. This can lead to subtle but significant differences in criteria for inclusion or interpretation of results. This can make the comparison of studies difficult and limit generalisability. Additionally, changes made to the Diagnosis Statistics Manual (DSM) criteria over time mean research is difficult to compare as the concepts measured have changed. Most notably in the DSM-5 edition (Volkmar, 2013).

All of the papers selected for inclusion scored above the cut-off point for inclusion. This provides some reassurance to the field that the area of FXS and behavioural phenotype is producing good quality studies, which are therefore able to be unified to begin to construct a FXS behavioural phenotype.

Limitations of a Behavioural Phenotype Approach

This paper reviewed studies using a narrow definition of behavioural phenotype to establish a baseline of the concept within the literature. By restricting the exploration of FXS to its characterisation as a behavioural phenotype there are a number of aspects of FXS that are

excluded from consideration. Tabolacci and Chiurazzi (2013) identified that there are known rare unaffected males carrying unmethylated full mutations, which would not necessarily be identified through a behavioural phenotype approach but which contribute important understanding of FXS. By exploring behavioural elements in isolation from, for example, cognitive and epigenetic characteristics a holistic overview of FXS is missed. This decision was made in this instance in order to explore what work had been carried out to date under the direct concept of 'behavioural phenotype' and to explore what work was contained under this. It is evident from the review that papers are not focusing on the breath of the behavioural phenotype and important characteristics have been missed.

Limitations to the Search Criteria

By limiting the search criteria to behaviour only a rounded view of FXS is not able to have been captured in this review. In doing this the review does not also accurately reflect those characteristics associated with ADHD and emotional regulation. These elements are cognitive aspects, which would not be accurately assessed through a behavioural lens (Gross & Thompson, 2007). These ideas were not conceptualised as independent mechanisms in the questionnaires.

As the field of behavioural phenotype is relatively new there is some discrepancy in the consistency of terms used to describe this work. No other FXS behavioural phenotype systematic reviews were identified in the literature and therefore this review has restricted its use of search terms to papers that explored the FXS behavioural phenotype in the broad sense in order to establish this concept in the first instance. However, it is known that not all research examining behavioural phenotypes is done within this paradigm. Terms such as

'neuro-behavioural', 'profile', 'social behaviour' and 'autistic behaviour' were not included in order to retain a clear and concise review question with a robust reproducible search strategy (García-Perdomo, 2016). Including the above search terms would broaden out the definition of the search beyond that intended by behavioural phenotype. It is hoped this issue diminishes with time as researchers begin to use similar terminology to describe this work.

Research Implications

Future research should take the following considerations into account in order to support the development of the FXS behavioural phenotype;

1) There is a need for additional attention to be given to the study of the behavioural phenotype for females with FXS. There may be important lessons that could be extrapolated from these studies that would broaden understanding of the FXS behavioural phenotype.
2) It is important the research base moves away from relying on autism specific rating-scales to explore differences in FXS. Similarly, there was a large focus on autistic trait behaviours in the papers reviewed. It would be of benefit to include rating-scales that also capture behaviours such as hyperactivity. Interpreting behaviour within an autism pretext given the limitations to the aetiology already described could limit understanding and development of the FXS behavioural phenotype.
3) Standardisation of terminology would support the development of a coherent paradigm for the FXS behavioural phenotype.

Clinical Implications

It has been demonstrated that phenotypic behaviour can be mediated by physical and social intervention (Hanley, Iwata, & McCord, 2003). Therefore, clinicians should use the knowledge of behavioural phenotypes to plan and develop early and ongoing interventions for people with FXS. Routine assessment of FXS behavioural phenotypic features should be carried out. In respect of the behavioural phenotype delineated from this review co-morbid diagnosis of ASC and/or ADHD should also be considered.

This review would suggest behavioural interventions should be targeted to the specific needs of the child with FXS and that particular attention is given to communication and social skills training. It may be necessary to develop a specific FXS centre of excellence to advance this research and to meet the requirements of people with FXS's unique needs.

Further Research

Additional reviews are required in order to further delineate the findings in this review. The specific differences within each domain require further exploration. This will allow for greater clarity on the emerging difference. This review also demonstrates that further delineation of the genetic, social and environmental influences is required in order to understand how each domain is being influenced. Most papers did not include developmental trajectory. Beyond the above delineations introducing developmental trajectory measures over time would support this work further.

Conclusion

The current review has begun to identify the behavioural phenotype for males with FXS. In doing so it has highlighted further areas of development for research and clinical practice.

This review demonstrates that key elements of the FXS experience are screened out when a narrow approach such as behaviour phenotype is used. Observing autistic traits, hyperactivity and over-arousal collectively in the delineation of the behavioural phenotype for FXS will allow for greater understanding of their interplay. However a more detailed and holistic approach should be considered in further studies. These are often explored separately and therefore understanding of their interconnectivity may not have been fully acknowledged.

Access to accurate behavioural phenotype information for a given condition such as FXS enables service providers to explore better provision. It could also aid clinicians to develop a more sensitive understanding of the needs of people with FXS and their families and carers.

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Part 2

Care provision for people with Fragile X Syndrome: Should it be need or diagnosis driven?

The following paper has been prepared for submission to the Journal of Intellectual Disability Research (Word Count – 3659; Journal Limit 4500)

Abstract

Background Fragile X Syndrome (FXS) is the most common inherited cause of intellectual disability. People with FXS are often diagnosed with an Autism Spectrum Condition (ASC). Initially researchers thought that FXS was caused by an autism gene. However, as research into FXS has progressed and an exploration of the behavioural phenotype has taken place important differences have emerged.

Aims The aim of the study was to examine if there are differences between the behaviour phenotype profiles of those with FXS who have a diagnosis of ASC and those that do not.

Method An online battery of questionnaires, comprising of the Social Responsiveness Scale 2 (SRS-2), the Wessex Questionnaire, and a standard demographic information were completed. Participants were grouped by FXS and ASC (FXS+), high scoring on the SRS with no ASC diagnosis (FXS-Hi) and low scoring on the SRS with no ASC diagnosis (FXS-Lo). A total of 38 responses were included which were completed by parents, representing N=29 (76%) males and N=9 (24%) females aged 6-15 years old.

Results Differences were observed between the FXS+low and the other two categories, FXS+Hi and FXS+ASC. No significant difference was found between the FXS+Hi and the FXS+ASC groups.

Conclusions The findings inform understanding of how a behavioural phenotype approach is expressed across FXS. Limitation of this study and approach are discussed.

Keywords: Fragile X Syndrome, FXS, Autistic Spectrum Condition, ASC, autism, autism traits, unmet need, behavioural phenotype, diagnosis, ASD, Autism Spectrum Disorder

Conflict of interest statement: None to declare

Introduction

Fragile X Syndrome (FXS) is the most common inherited cause of intellectual disability (ID; Crawford, Acuña, & Sherman, 2001) and its prevalence is second only to Down syndrome as a genetic cause of intellectual disability (Thurman, et. at., 2014). The Fragile X Mutation Retardation one (FMR1) gene responsible for FXS was discovered over 25 years ago (Verkerk et. al., 1991). FXS is part of a group of FMR1 mutation-related disorders, termed Fragile X-associated disorders (FXD), including Fragile X-associated tremor/ataxia syndrome (FXTAS) and Fragile X-associated primary ovarian insufficiency syndrome (FXPOI; Boyle & Kaufmann, 2010). Of the people who have FXS, nearly all males will have an intellectual disability (ID) but only a third of females will (Riley, et. al., 2017). The exact number of people who have FXS is unknown, but it has been estimated that approximately 1 in 5,000 males are born with the disorder (Coffee et. al., 2009). Females will have a much milder expression because they will have one unaffected X chromosome and usually present with a low to borderline intellectual disability (Hagerman et. al., 2009).

Many people with FXS show behavioural features including; short attention span, distractibility, impulsiveness, restlessness, over-activity, sensory problems and anxiety as well as difficulties with eye contact, anxiety in social situations, insistence on familiar routines and hand flapping or hand biting. The difficulties associated with FXS mean people with FXS usually have input from the local learning disability teams to support the management of their difficulties (Wadell, Hagerman, & Hessl, 2013).

Such behavioural features appear very similar to ASC and dual diagnosis of FXS and ASC is common (Boyle & Kaufmann, 2010; Hall, et. al., 2009). FXS was initially termed AFRAX

syndrome because it was thought that it was caused by an autism gene (Gillberg, Persson, & Wahlström, 1986) but important differences have subsequently become apparent.

Whilst ASC is thought to have a genetic basis with 90% heritability, the specific genotype is currently unknown (Richards, et. al., 2015). ASC is characterised by difficulties in communication, reciprocal social interaction and the presence of restrictive and repetitive stereotyped behaviours (RRB); (American Psychiatric Association, 2013). As research into ASC in specific syndromes has developed, evidence has emerged that individuals with certain genetic and metabolic syndromes could have an atypical profile of ASC phenomenology (Backes et. al., 2000). This supports the notion of a distinction between syndromic variants of ASC and idiopathic ASC (Hall, et. al., 2010; Richards et. al., 2015).

It is also known that autistic traits in FXS may be associated with lower levels of ID (Einfeld, Molony, & Hall, 1989). This has led researchers to propose that ASC in FXS may be a part of its distinct behavioural phenotype rather than occurring co-morbidly because of the reduced impairments in communication and reciprocal social interaction associated with FXS (Hall et. al., 2010; Daffin, et. *al., in preparation).*

More recent conceptualisations of ASC have advanced the notion that rather than being a single entity, ASC can be thought of as two genetically independent traits that tend to occur together, namely social communication dysfunction (SCD) and repetitive, restrictive and ritualistic behaviour (RRRB); (Happé, Ronald, & Plomin, 2006). This could explain why there has not been a specific gene identified for ASC. It is possible the answer may appear as specific genes for these two separate genetic traits. Social communication is the central cultural mechanism that coordinates behaviour, conceptions and thinking (Ratner, 2012). Ability to engage in social communication appears to occur on a continuum, with differences apparent

even in the neurotypical population. Beyond a certain point on this continuum, impaired social communication ability becomes an impediment on function and a person can be said to have an ASC (Ousley & Cermak, 2014). RRRB, on the other hand, does not appear to have an evolutionary purpose to functional human behaviour and is essentially automatic 'stimulus bound' behaviour. What is impaired in the case of this trait is the fundamental human ability to over-ride this automatic behavior; a function located in the frontal and pre-frontal ('executive function') areas of the brain (Happe & Frith, 1996). When this ability to over-ride is sufficiently impaired beyond a certain point, a person can be said to have an ASC.

Both traits can be readily measured. Social communication functioning via the Social Responsiveness Scale 2 (SRS-2; Constantino & Gruber, 2005) and repetitive behaviour using the Repetitive Behavioural Questionnaire 2 (RBQ-2); (Barrett, et. al., 2015). Scores on the RBQ2 correlate with 'gold standard' autism assessments (ADI/ADOS/DISCO; Carrington et. al., 2015). Scores on the SRS and RBQ2 are not necessarily correlated themselves indicating a degree of independence (Wolfenden, et. at., 2019).

Generic learning disability services have struggled to meet the needs of individuals with ASC with a reliance on responding to ASC diagnoses rather than the actual level of need and/or ASC behaviour (Dittrich & Burgess, 2012). Several recent studies have found clinically important differences between FXS and non-syndromic ASC that are masked by reliance on the categorical diagnosis of ASC (Abbeduto, McDuffie, & Thurman, 2014). This suggests interventions should account for these differences and be developed specifically for people with FXS. This could mean services recognise FXS in its own entity in addition to recognizing ASC (Hall et. al., 2010). It could also mean services that are needs-led rather than diagnosis driven would better accommodate these specific syndrome variations. An example of this

approach is the Integrated Service for Children with Additional Needs (ISCAN) in Aneurin Bevan University Health Board, South Wales.

The aim of the study was to examine if there are differences between the behaviour phenotype profiles of those with FXS with a diagnosis of ASC, compared to those without. If ASC in FXS is more accurately understood as a part of a distinct behavioural phenotype rather than occurring co-morbidly, similarities between those with high and low social communication needs should emerge. By comparing those with ASC, those with high and those with low social communication skills the study aims to demonstrate the FXS behavioural phenotype across a continuum of ability. On this basis it tested the following hypothesis: those in the FXS+Low group would have the least severity of scores on the SRS-2 total scores and sub-categories scores compared to those in both the FXS+Hi and FXS+ASC groups. Mann-Whitney U tests were employed to ascertain these differences.

Methodology

Design and Participants

The current study utilised a within-group design and was conducted online using Qualtrics software to collect questionnaire data from parents of children aged 6-15 years with a diagnosis of FXS from across the UK. Therefore 38 parent completed responses were included, representing N=29 (76%) males and N=9 (24%) females. There were 34 participants (89.5%) identifying as white, N=1 (1.9%) as mixed/multiple ethnicity, N=1 (1.9%) Asian/Asian British and N=3 (6.2%) as 'other ethnic group' (see table 1 below).

Table 1. Children with FXS by Sex, Age and Ethnicity Included in the Study

Sex		Age		Ethnicity		
Females	Males	6-10 age	11-15 age	White	Mixed/multiple ethnicity	Asian/Asian British
9 (24%)	29 (76%)	19 (50%)	19 (50%)	34 (89.5%)	1 (1.9%)	3 (6.2%)

Measures

Social Responsiveness Scale

The Social Responsiveness Scale 2 (SRS-2) is a 65-item questionnaire measuring social ability of children from 2 - 18 years old (Constantino, 2013; see appendix 9D). It provides a continuous measure of social ability (from impaired to above average) across 5 subcategories (social awareness, social cognition, social communication, and social motivation). Restricted interests and repetitive behaviour items are scored on a 4-point Likert-type scale, ranging from not true = 1, sometimes true = 2, often true = 3, to almost always true = 4 (a high score indicates a high difficulty). These are converted following the manual coding into 0-3. There are 16 items which are reverse scored. Using the manual tables these are then converted to T-scores. Rating scales are provided for males and for females.

The SRS-2 has been shown to have good internal and re-test reliability and good construct validity (Bruni, 2014). . Cronbach's alpha scores indicate that the overall SRS scale has good internal consistency (a = .94 in males; a = .93 in females, parent rated; Constantino & Gruber, 2005). A single underlying factor structure has been identified by USA studies in both clinical and general population samples (Constantino et al., 2000; Constantino, Hudziak, et al., 2003; Constantino et al., 2004). For this reason, although the SRS theoretical subscales

have also been reported to show good internal consistency (Constantino & Gruber, 2005), the authors recommend they should only be used for the purpose of clinical description.

Wessex Scale

The Wessex Scale (Kushlick, et. al., 1973; see appendix 9E) was used as a measure of adaptive functioning and comprises five subscales: continence, mobility, self-help skills, speech and literacy which are scored using a 4-point Likert scale; daily=1, weekly=2, monthly=3, and never=4. It has been demonstrated to be an effective tool for large-scale questionnaire studies (Richards, Oliver, Nelson, & Moss, 2012) and has good inter-rater reliability and validity (May, Hallett, & Crowhurst, 1982). Cronbach alpha details were not available. The Wessex is used for children aged six years plus (Burbidge, et. al., 2010).

Recruitment

An online link for the Qualtrics application was distributed by the UK FXS Society between December 2018 and March 2019 via the Fragile X Society database of consenting research participants, mailing lists and online media outlets (e.g. Facebook). Participants were informed that printed and accessible versions were also available and were given details of how to contact the researchers to obtain these. The online questionnaire took an estimated 33 minutes to complete.

Ethical Approval and Consent

Ethical approval for the project was obtained from the FXS Society as well as from Cardiff University School of Psychology Ethics Committee (copies of the ethical approval as well as participation information and consent procedures can be found in appendices 7 & 8).

Results

The SRS-2 and Wessex data (adaptive functioning) were examined to ascertain whether they met parameters for the normal distribution. Tests of normality, skewness, and kurtosis as well as uneven sample sizing indicated that the data was skewed the kurtosis was non symmetrical. Therefore, the assumptions for the use of parametric statistical tests were not met as assessed by the Kolmogorov-Smirnov tests ($p<.05$). Therefore, non-parametric tests were used (appendix 14; Howitt & Cramer, 2017).

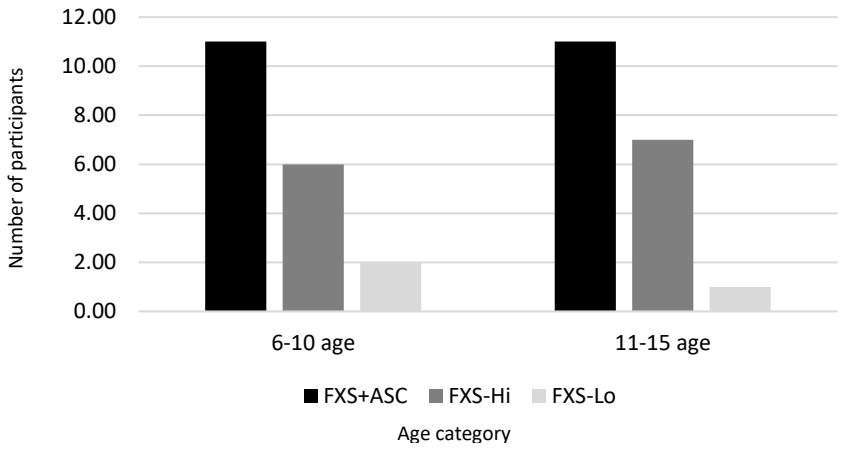
Kruskal-Wallis H tests were employed to test for between-group differences on SRS-2 between the three groups. Participants were assigned to one of three groups (FXS-ASC; FXS+Hi; FXS+Low), which also supports a control group for exploratory analysis. Associations between adaptive functioning and behaviour traits were explored using Spearman's Rank order correlations whilst controlling for age.

Descriptive Data

Participants were grouped by those that had FXS and a diagnosis of ASC (FXS+ASC). Those that scored above the mean (M=70.25) were defined as FXS+Hi on the SRS-2 and those below it as FXS+Low. This was calculated using the mean score of the FXS only participants in the study. The SRS-2 was used to create categories because it measures ability across a number of domains (with the exception of emotional regulation difficulties) associated with the FXS behavioural phenotype (Constantino, 2013) and a useful measure for comparisons that was not also a diagnostic tool.

Table 2. Category Grouping of Children by Sex and Age Group Represented in the Data

Group	Sex		Age	
	Females	Males	6-10 age	11-15 age
FXS+ASC	3 (7.89%)	19 (50%)	11 (28.94%)	11 (28.94%)
FXS-Hi	2 (5.26%)	5 (13.15%)	1 (2.6%)	5 (13.15%)
FXS-Lo	4 (10.52%)	5 (13.15%)	7 (18.2%)	3 (7.89%)



Graph 1. FXS Group by Age Category

Age and Group Category

A chi-squared ($\chi 2$) test of association revealed that there was not a significant difference between age groups of participants and FXS grouping $\chi 2 = 6.34$, $p = 0.042$. As can be seen in graph 1 the distribution of 6-10 years and 11-15-years across the FXS groups is roughly the same. This analysis is important because diagnosis should be considered in the context of adaptive functioning and developmentally expected behaviours. Additionally, severity in traits within FXS have been shown to differ over developmental trajectory and decrease into adulthood and therefore could impact upon findings (Baumgarder, et al., 1995).

Sex and Group Category

A chi-squared ($\chi 2$) test of association revealed that there was not a significant difference between sex of participants and FXS grouping $\chi 2 = 3.46$, $p = .177$. There is a near significant different at a linear by linear level, p=0.066. Overall, there were only nine females compared to 29 males in this study and some of the counts were below five and were close to the minimum expected count of 1.66. The ratio for males to females with FXS is 1.4:0.9. The spread of sex within this study does not reflect the distribution across the general population.

Adaptive Functioning and Group Category

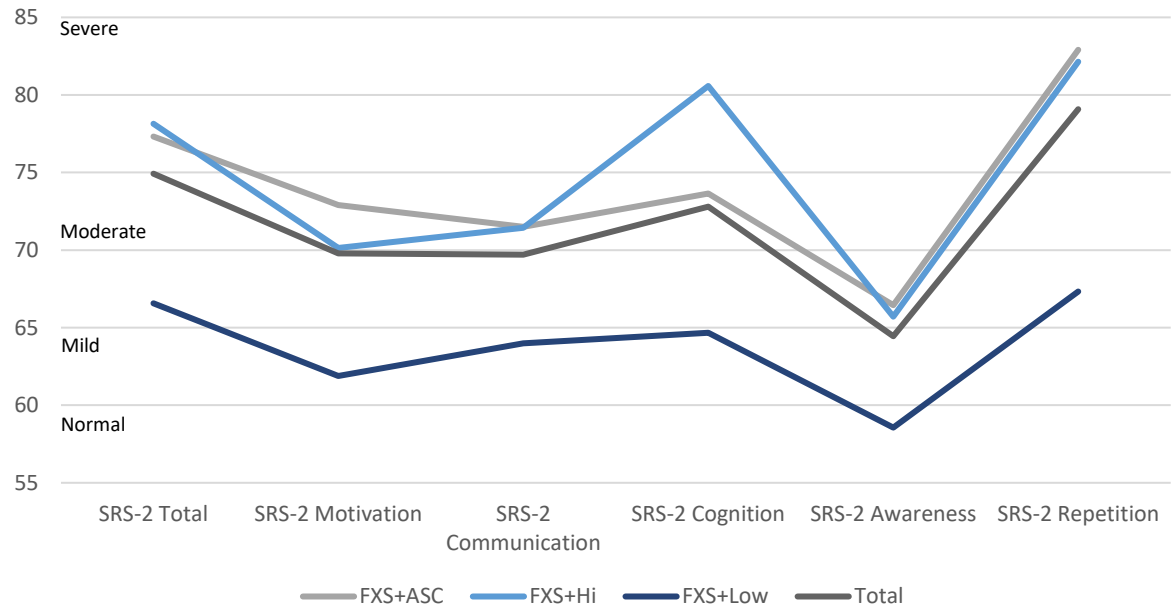
The three groups (FXS+ASC, FXS+Hi and FXS+Low) were matched group-wise against social and physical ability scores from the Wessex. There were no significant group differences in

these scores (FXS+ASC M=37.5, IQR=30; FSX+Hi M=43.87, IQR=9; FXS+Low M=32.88 IQR=25; H=3.02, df= 2, p=.221). This indicates they were similar in their adaptive functioning skills.

Inferential Statistics

The hypothesis that those in the FXS+Low group would have the least severity of scores on the SRS-2 total and sub-category scores compared to those in both the FXS+Hi and FXS+ASC groups was partly upheld. Table 3 provides means, standard deviations and ranges of measures for all participants and participant groups. Between-group differences on the SRS-2 measure categories are presented using Kruskal-Wallis H tests. There were significant differences found across the SRS-2 categories but not the total SRS-2 scores. Therefore, the hypothesis is only partially upheld.

The FXS+ASC group scored on average as severe however they scored within the moderate range for all but the repetition category in which they scored as severe. Scores in the moderate range indicate difficulties that are clinically significant which are related to reciprocal social behavior. The FXS+Hi group on average scored in the severe range but have a more varied profile ranging from mild-severe. The SRS 2 scoring criteria would indicate that a score in the range of moderate to severe, made by separate two raters would indicate a diagnosable ASC. The FXS+Low group also scored on average within the moderate range.



Graph 1. FXS group by SRS-2 category scores

The category least impaired across all three groups was awareness. The FXS+Low group scored within the 'normal' range for this category whilst the FXS+Hi scored within the mild range. The FXS+ASC group scored within the moderate range. The category most impaired was repetition. This was followed by cognition. The FXS+Hi group were most impaired in this category whilst the FXS+ASC group were most impaired for repetition. FXS+Hi were far more impaired in the category of cognition compared to FXS+ASC. This is unlike the other categories where scores are more closely aligned.

Mann-Whitney U tests revealed that there were no significant differences between the FXS+Hi and FXS+ASC groups across the categories or total scores. There were significant differences across the FXS+Low and FXS+Hi groups for each of the categories but not across the total scores. There were significant differences between the FXS+low and FXS+Hi groups in the cognitive, awareness and repetitive behaviour sub-categories but not across the motivation, communication or total scores (see table 4 below).

Table 3 *Descriptive statistics for the SRS 2 by FXS category*

Categories	**FXS+ASC Raw Mean**	**T Score Mean**	**(SD)**	**Range**	**Ranking**	**FXS+Hi Raw Mean**	**T Score Mean**	**(SD)**	**Range**	**Ranking**
SRS-2 Total	101.05	77.32	8.27	36	Severe	101.43	78.14	7.56	22	Severe
SRS-2 Motivation	16.91	72.91	10.291	41	Moderate	15.29	70.14	5.699	18	Moderate
SRS-2 Communication	30.45	71.50	6.390	24	Moderate	30.29	71.43	5.968	14	Moderate
SRS-2 Cognition	19.14	73.64	8.341	35	Moderate	22.14	80.57	8.284	24	Severe
SRS-2 Awareness	11.22	66.45	6.390	28	Moderate	11.57	65.71	7.499	22	Mild
SRS-2 Repetition	23.33	82.91	11.629	42	Severe	22.14	82.14	8.009	26	Severe

P < 0.05

Table 3 Cont. *Descriptive statistics for the SRS 2 by FXS category*

Categories	**FXS+Low Raw Mean**	**T Score Mean**	**(SD)**	**Range**	**Ranking**	**Total Raw Mean**	**T Score Mean**	**(SD)**	**Range**	**Ranking**	**H**	**P**
SRS-2 Total	72.00	66.56	5.69	31	Moderate	93.71	74.92	8.35	41	Moderate	1.01	0.60
SRS-2 Motivation	11.23	61.89	8.115	20	Mild	15.26	69.79	10.03	49	Moderate	4.79	**0.09**
SRS-2 Communication	23.33	64.00	6.442	20	Mild	28.21	69.71	6.95	34	Moderate	5.23	**0.07**
SRS-2 Cognition	14.22	64.67	5.172	15	Mild	18.52	72.79	9.18	40	Moderate	6.17	**0.05**
SRS-2 Awareness	9.44	58.56	4.362	14	Normal	10.86	64.45	6.90	30	Mild	6.01	**0.05**
SRS-2 Repetition	13.78	67.33	5.937	21	Moderate	20.86	79.08	11.78	47	Severe	7.67	**0.02**

P < 0.05

Table 4. *Mann-Whitney U test results for the SRS 2 by FXS category*

Group	**SRS Categories**					
	Motivation	Communication	Cognitive	Aware	Repetitive	Total
FXS+Low & FXS+Hi						
Mann-Whitney U	15.5	14	0	11.5	3.5	21
P	0.09	0.06	**0.00**	**0.03**	**0.00**	0.27
FXS+Low & FXS+ASC						
Mann-Whitney U	42	41	35.5	24.5	28.5	95
P	**0.01**	**0.01**	**0.01**	**0.00**	**0.00**	0.86
FXS+Hi & FXS+ASC						
Mann-Whitney U	68.5	77	44	61.5	70.5	50.5
P	0.66	1	0.09	0.43	0.74	0.17

P < 0.05

Discussion

The aim of this study was to explore if those in the FXS+Low group would have the least severity of scores on the SRS-2 compared to those in both the FXS+Hi and FXS+ASC groups. At a total score level, no significant differences were found. It therefore appears at a surface level that all three of these groups are similar. This however is not the case when their respective sub category profiles are explored. Therefore, the hypothesis was partially upheld. There was difference between the FXS+Low and FXS+ASC groups with significant difference across all of the categories. There was difference between the FXS+Low and the FXS+Hi across three sub-categories; cognitive, awareness and repetitive behavior.

This suggests that there are different profiles across the groups and warrants additional exploration. The FXS+Low group does however have a much higher percentage of females (44%), compared to the FXS+Hi group (28%) and the FXS+ASC group (14%). These differences might explain some of the variance and should be explored by future studies. The FXS+Hi group has twice as many females as the FXS+ASC group and it is known that FXS presents differently in females compared to males at a biological level. The over representation of females in the FXS+Low and FXS+Hi groups does not match population prevalence

expectations and raises a question about potential sampling bias. A single underlying factor structure has been identified by USA studies in both clinical and general population samples (Constantino et al., 2000; Constantino, Hudziak, et al., 2003; Constantino et al., 2004). For this reason, although the SRS theoretical subscales have also been reported to show good internal consistency (Constantino & Gruber, 2005) research should be conducted to explore the sub-categories application further. Caution should therefore be used when interpreting these results.

There were significant differences between the FXS+low and FXS+Hi groups in the cognitive, awareness and repetitive behaviour sub-categories but not across the motivation, communication. It is unclear why this is the case. However, it is known that people with FXS differ compared to those with iASC on measures of communication (Hall et. al., 2010). The sub category differences found by this study suggest further exploration of this should be carried out. It is possible this study would have benefited from exploring differences at the level of sex in order to better understand how this and ID might be contributing specifically.

It is known that children with high anxiety can have more repetitive and restrictive behaviour (Rodgers, et, al., 2012) and that those with 'ADHD' traits are prone to also experience anxiety (Schatz & Rostain, 2006). It could be that the expressed differences between the groups are underpinned by social behavior and communication difficulties that are observed as increased levels of repetitive and restrictive behavior. Significant differences in the profile of social and communicative difficulty in FXS compared with individuals diagnosed with idiopathic autism has been previously demonstrated (Hall, et. al., 2010). It is possible that the homogeneity of the experience of the FXS+ASC group and the severity of their repetitive

behavior may mean they are over-represented within the ASC diagnosis group. It could be that those with FXS+Hi are more significantly impacted by their FXS at a cognitive level which makes their presentation appear less like ASC and more like an ID issue. Studies are beginning to discover more specific differences between those with FXS and those with idiopathic autism in relation to social communication and language abilities (Sterling, 2018; Friedman, L., Sterling, A., Barton-Hulsey, A., 2018). This would suggest that standard autism interventions for individuals with FXS are not optimal (Hall, et. al., 2010). Given these emerging differences, use of ASC diagnosis tools with people with FXS warrants further exploration to ensure clinicians are considering the full range of domains in ASC diagnosis and not relying predominantly on the social communication, cognition and repetitive behaviour categories where an individual is known to have a diagnosis of FXS.

Research Limitations

There was no assessment of hyper-activity or inattention in this study, which appears to be part of the FXS behavioural phenotype. The SRS-2 does not have a domain for emotional regulation. Further studies would benefit from including measures that cover all aspects of the proposed FXS behavioral phenotype, which includes difficulties associated with; social behavior and communication, emotional regulation and repetitive and restricted behavior. The SRS-2 interpretation is based on the DSM-5 and it designed to be a measure of ASC. It would benefit from focusing on social communication as distinct from diagnostic criteria. Especially given the criticism of the validity of the DSM-5 (Kraemer, Kupfer, & Clarke, (2012). Additionally, the measures applicability could benefit from further exploration into non-homogenous profiles. When examining at the total score level no differences were found

across the three groups. It was only when further exploration at the category level was explored that distinct differences emerged.

In determining a participant's child's diagnosis of ASC, it was not specified if a participant had been assessed but then determined not to have a diagnosis or if they had not yet been assessed. Those without ASC may have undiagnosed ASC as well as not having ASC.

It should be noted that the Wessex scale is not as in-depth or sensitive in its measure of the level of adaptive functioning as other measures are. This study would have benefited from using more sensitive and standardized measures such as the Vineland Adaptive Behavior scales.

There are emerging differences in the make-up of service provision for CAMHS and CLDT across England, Scotland, Wales and Northern Ireland (Welsh Government, 2018). These differences in available provision and service structure were not reflected in the questions asked.

The questions about use of services did not take into consideration provision beyond that of CMHT and CLDT. It did not consider provision that already caters for a need-led basis, which are organized outside of a CMHT and CLDT model. It did not, for example, make reference to provision such as the Integrated Service for Children with Additional Needs in Aneurin Bevan University Health Board, South Wales. Parents may therefore not have reported services received from such provisions. This has not been accounted for in the study design. Further research would benefit from taking these differences in service provision into account.

Finally, a larger sample of participants would have provided the study with greater statistical power and may have yielded more substantive results.

Research Implications

Further research should explore how the domains of the behavioural phenotype for FXS present in comparison to ASC. This could support a better understanding of the differences in RRB across the groups which appears not to be associated with ID levels but may be more aligned with difficulties in socially orientated cognitive abilities. Additional exploration should be given to understand if increased levels of RRB play a significant part in ASC diagnosis. Consideration should also be given to explore if a decrease in ability in social understanding and relating to/communicating with others leads to increased levels of anxiety within people with FXS. This could account for the larger differences in 'rigidity of routine' and 'restricted patterns of behavior' compared to lower expression of 'sensory needs' and 'repetitive motor movement'.

The SRS-2 may be a better tool for understanding an individual's FXS related difficulties in the context of potential underlying anxiety. Further exploration should be given to the differences between FXS RRRB and those with ASC only to better understand where anxiety derived behaviours may be contributing to observed behaviour.

Exploration into specific interventions for people with FXS should be explored with these domains in mind. Consideration of the concept of a genetic basis of idiopathic autism should be given as well as exploration into the role attachment and resilience theory in FXS.

Policy and Clinical Implications

Clinicians should consider the knowledge of behavioural phenotypes in planning and developing early and ongoing interventions for people with FXS. Children with FXS require

clinical services to support their ongoing needs. This input is likely to span their lifetime as the difficulties may change and/or emerge over time. A diagnosis of ASC may prove clinically useful given that service provision in Wales is organized around the All Wales Autism Strategy. Consideration to FXS should be given within this existing pathway and should also be given to services that organize around a needs-led model, such as the integrated service for children with additional needs (ISCAN) in Aneurin Bevan University Health Board, South Wales. Services that are needs-led may overcome many of the barriers faced by people with FXS in other services. Under these approaches blank 'one-size fits all' autism interventions would not be applied indiscriminately to people with FXS.

Conclusions

There have been many advances in services provided for individuals with FXS and ASC over the past few decades driven by advances in research (Rutter et. al., 1999). The current study provides some direction for further research that could support the development of how the behavioural phenotype in FXS might be clinically beneficial as well as identifies some limitations in its use.

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Part 3

Critical Evaluation of the Fragile X Syndrome Behavioural Phenotype Project

(Word count: 4353)

NB *Following a formal complaint post viva about the supervision and oversight provided for this project and a July 2019 – April 2020 period of rewriting the below does not reflect the processes association with the above two papers and should be disregarded.*

Research Process

Research, like the theoretical ideas for this project is not categorical and certain. There is debate and discussion about 'how to do research' and what constitutes good research. This lack of clarity can breed uncertainty and anxiety for those new to research. It can also deter people less familiar with the praxis and cause them to disengage from research.

There is a belief that research is like detective work, but it is more like an adventure (Barker et al., 2012). Often the conclusions do not bring solutions. Only additional questions and this is undoubtably true of this project. This project's ideas are part of a much larger explorative journey beyond the scope of this research team and the discipline of psychology.

Similarly, research is not immune from systemic influence. Just like formulation needs to consider the wider social and political context, so too does research (Rosa & Tudge, 2013). The impact of politics on research can be observed through which papers get published. Although it's much harder to observe which ideas are not being privileged, research methods have attempted to go some way to address this using meta-analysis. Meta-analysis is the statistical procedure for combining data from multiple studies. This process is used to, for example, examine publication bias. Journals have been criticised for not publishing data that lack statistical significance (Sedgwick, 2015). It is important to be mindful of this throughout the research process; from idea conception to publication and beyond in clinical and policy application. This is often a barrier to bringing about timely change. The implications of this will be discussed in relation to this project.

FXS Project Rationale

This project is part of a larger research team that is working towards the development of a better understanding of Fragile X Syndrome (FXS). There will be several research projects that will utilise the data collected as part of this project.

The purpose of the systematic review was to further delineate the behavioural phenotype for FXS. The purpose of the empirical project was to ascertain the level of unmet need in the FXS population. It is hypothesised that this unmet need is perpetuated by the lack of clarity around the FXS behavioural phenotype and therefore underlying mechanisms of difficulty. This means that often interventions for people with FXS are blunt because their primary function and validity is for people with autism. Research has demonstrated that there are subtle but key differences between the two populations as well as some interesting overlaps that warrant further exploration (Daffin, et. al., *in preparation*). Therefore, the second aim of this project was to delineate the FXS behavioural phenotype using tools not specifically designed to diagnose autism. Previous research outlines the FXS behavioural phenotype using autism diagnosis tools. These tools carry several limitations outlined later in this evaluation paper. This project therefore sought a novel way of distinguishing the behavioural phenotype, which did not rely upon assumptions made for categorising people with autism.

Participation and Recruitment

It was envisaged that the FXS Society participant's database would yield a much greater response rate. This project therefore had to be taken as a pilot project. Relying on an external

organisation for participants brought several challenges. It was not possible to have control over dissemination of the questionnaire or contribute to the methods through which it was shared. Whilst it was appreciated that this was done to safeguard participants it made it hard to review and amend independently and in a timely manner where recruitment issues were occurring.

Research Governance

The UK policy framework for health and social care research sets out principles of good practice in the conduct and management of health and social care research in the UK. These principles protect and promote the interests of people who have used services and the public. They do this by outlining ethical conduct and research management standards for health and social care research. The purpose of this framework is to support and facilitate high-quality research in the UK that also has the confidence of the public. Although health policy is devolved to the four UK nations, as a commitment to maintaining compatible standards for research ethics this framework replaces former individual nation policies and is overseen by UK Ethics Committee Authority (UKECA; NHS Health Research Authority, 2017).

In order to operate within the framework this research project sought the opinion of parents of children with FXS and a third sector organisation in its conception. It received ethical approval from the Cardiff University School of Psychology y as well as from the Fragile X Society's research board. Due to the time constraints of the project it was not possible to consult the population more widely. It was however hoped that the Fragile X Society research board panel, made up of people who have used services and their family or support, as well as researchers and professionals, would go some way to mitigate here.

Additionally, due to the constraints of the project it was not possible to involve members of the public in the research process. The project was not able to meet the additional needs of people with FXS in order to effectively involve them in this way either. Parents of children with FXS were however offered the opportunity to be involved in the dissemination of the research questionnaire as well as in the dissemination of the results. This was done through the support of the Fragile X Society.

Members of the Public, Support Workers and/or Family Involvement

Local members of the Fragile X Society were consulted in the initial stages of the research project. They inputted into the formation of ideas, as well as about how the project should choose respondents. The project would have benefited from improved relations with the local Fragile X society. This project was the first time the groups had worked together, and future projects will benefit from the establishment of this relationship. It is hoped that by disseminating the findings from this project and inviting members of the Fragile X society and public to comment on and discuss it, there will be greater trust between the department and the Fragile X society. It is hoped this would improve participants response rates as respondents observe there is value in working with Cardiff University and that the partnership is an opportunity for them to effect change.

Review of Methodology

The Social Responsiveness Scale (SRS; Constantino & Gruber, 2005), Repetitive Behavioural Questionnaire 2 (RBQ2; Barrett, et. al., 2015), Wessex Questionnaire (Kushlick, Blunden, &

Cox, 1973) and a needs assessment along with questions regarding service provision and basic demographic information were collected.

Strengths of Methodology

The SRS measures social ability of children from 4 years to 18 years old (Constantino & Gruber, 2005). It provides a continuous measure of social ability (from impaired to above average). In contrast to a dichotomous approach (i.e., yes or no) to establishing diagnostic criteria, the SRS was designed using a continuous scaling approach (i.e., 1 to 4) to assess the degree of social impairment deficits. It was for this reason that the SRS was chosen for this project. Previous findings have shown that the SRS factors are predictive of autism traits and behavioural measures (Chan, Smith, Hong, Greenberg, & Mailick, 2017).

The RBQ2 measures restricted and repetitive behaviours, which forms one of the core diagnostic criteria for autism spectrum disorder (World Health Organization, 1992). It was developed at the Wales Autism Research Centre, Cardiff University. It is a set of questionnaires based on items from the Diagnostic Interview for Social and Communication Disorders (DISCO: Barret, et. al., 2015). It is known to measure to components; Repetitive Motor Behaviours and Insistence on Sameness (Barrett, Baker, Jones & Leekam, 2015).

The Wessex questionnaire is used to assess ability in children and adults with intellectual disabilities (Kushlick et al., 1973). It comprises five subscales including: continence, mobility, self-help skills, speech and literacy. It has good interrater reliability and has been shown to be an effective tool for large-scale questionnaire studies (Richards, Oliver, Nelson, & Moss, 2012).

An assessment of unmet needs (Bromley, Hare, Davison, & Emerson, 2004) [derived from (Chamba & Joseph Rowntree Foundation., 1999)] and a bespoke questionnaire (adapted from Bromley et al., 2004) covering received educational and other service provision and standard demographic information were also collected.

Strengths of Questionnaires

Using questionnaires means that responses are gathered in a standardised way, so questionnaires are more objective when compared to interviews. It is relatively quick to collect information using a questionnaire and it means mixed methods of collection as well as digital collection can be used (Popper, 2004). This is important when considering a population that is dispersed geographically and would otherwise be hard to reach.

Limitations of Methodology

Both the SRS and BRB2 are relatively new in their use and therefore their application in research has not yet had the extensive rigour of some measures tested over much longer periods of time. Both have recent validity with in the past 5 years. This means that their use within larger scale projects is yet to emerge and be robustly examined.

In determining a participant's child's diagnosis of ASC, it was not specified if a participant had been assessed but been excluded from a diagnosis or if they had not yet been assessed. This places a limitation on interpreting the SRS, BRB2 and Wessex beyond an ASC or not ASC presentation.

Limitations of Questionnaires

Questionnaires are standardised so it is not possible to explain any points in the questions that participants might misinterpret. This could be partially solved by piloting the questions

on a small group of students or at least friends and colleagues (Popper, 2004). We were not able to pilot this questionnaire before its dissemination. The sensitive and complex nature of the topic (children's unmet needs) may mean participants do not want to disclose or are unable to disclose issues to a questionnaire. Richer information may have been obtained through interviews where there is a relational element to the process. A limitation to this project may have been the length of time required to complete the questionnaire. It took approximately 30 minutes to complete and no reward was offered for participation. This may have deterred people from participation. Of the 91 people who began or partially completed the survey, one person was removed for duplication and only 48 completed the survey to a 95% or above completion rate. A different set of needs questions many have revealed additional differences. Further exploration should be carried out as per work by Chamba and colleagues (1999).

The SRS-2 is not an open access measure and the researchers used the research budget plus additional psychology departments' funds to obtain access to the measure. Were this not a project with multiple research budgets attached the manual would not have been accessible. The manual costs £100. From the sub-group categories of the measures it can be seen that subtle but key difference emerge. This is an important ethical consideration for the research team. It raises many questions about the limitations of closed access research. Transparency, openness, and reproducibility are readily recognized as vital features of science (McNutt, 2014). Open access and open source research and measures more readily allow scientific norms and values to be furthered and translated into concrete actions and change (Miguel, et. al., 2014).

Theoretical Considerations

Theoretical Limitations

There are several different terms used to describe the behaviour associated with FXS. These include behavioural phenotype, social behavioural profile and neuro-behavioural phenotype. This indicates a lack of consistency in terminology within the research field but also a lack of agreement. This made it difficult to find papers and ensure that all appropriate papers were included in the review.

There is also a lack of clarity around the aetiology of autism, which means that there is scope for interpretation by individual researchers. This difficulty is expressed via diagnostic rating scales for autism that vary depending on which and how many are used. This can lead to subtle but significant differences in criteria for inclusion or interpretation of results. This makes comparison of studies difficult and limits their generalisability. Additionally, changes made to the Diagnosis Statistics Manual (DSM) criteria over time mean research over time is difficult to compare as the concepts measured change.

Implications for theoretical consideration

The findings from the study would indicate that there is merit in the notion that ASC is something to be measured rather than a disorder to be diagnosed. This would suggest that there is a need for ASC to be redefined as something more akin to cognitive impairment rather than a discrete disorder. It would therefore be more appropriate to ask 'how autistic someone is' rather than whether they have ASC. This is an inverse parallel with ID, which we can now diagnose in terms of genetic syndromes rather than measuring IQ. On this basis it would now appear prudent that researchers ask the following questions; why does sensory dysfunction

and the elevated risk of seizures co-occur? Are these aspects reflecting a secondary 'shotgun' neurological dysfunction in the brain circuits near to those underpinning autistic traits (Goodman, 1989)? Where do other psychological features of ASC, such as anxiety, special interests and savant abilities interplay? Would this reflect an individual secondary adaptation to each person's ASC 'developmental trajectory', which is necessarily constrained within the parameters of the two autistic traits and range of secondary organic dysfunction? Does this imply a genetic basis of idiopathic autism? Finally, how does attachment theory interact?

Suggestions for Further Research

The use of dichotomous phenomenologically defined diagnoses may crudely categorise behaviours that naturally exist as continuous variables. For this reason, it is important the research base moves away from relying on autism specific rating scales to explore differences in FXS. Additionally, the exclusion of those with other autism spectrum conditions may skew and/or narrow the results. In the review paper, only the Baumgarder, et al., 1995 paper included measures of behaviour that were not examined through an autism lens. Whilst other papers include measures of behaviour not associated with autism they are analysed and compared to groups with autism and developmental delay or developmental delay only. It would be of benefit to make broader comparisons since rates of behaviour associated hyperactivity are present in higher rates. Interpreting behaviour within an autism context, given the limitations to its aetiology as already described above, is limiting understanding and development of the FXS behavioural phenotype and ASC.

The factors that lead to a person receiving a diagnosis of autism appeared to cluster around particular attributes. Most often those associated with repetitive and restriction behaviour. It is already known that repetitive and restrictive behaviours are strongly associated with

ADHD. This is because of the inability to switch attention. This finding has also been demonstrated for social communication, however not as strongly (Polderman, et. al., 2014). Expanding the focus of the behavioural phenotype away from autism may shed new light on the mechanisms behind these behaviours in FXS. Further research (including this empirical paper) would benefit from including in assessment all three of the areas associated with the FXS behavioural phenotype identified in the review paper.

Significant differences were found between environmental influences and behaviour outcomes. This should be taken into consideration when delineating the behavioural phenotype for FXS. There are known vulnerabilities within the pre-mutation population that may influence parenting style and wellbeing (Farzin et al., 2006). This could mean there is a multi-factor impact upon the person with FXS's development. Firstly, there are the difficulties associated with the genetic mutation. Then there are the direct environmental impacts from parenting styles and wellbeing. Finally, there is the wider impact from society, which determines how much social support is provided to the child with FXS and to their family. This could include things such as sigma and isolation as well as being able to access good service provision and support networks.

Additionally, consideration should be given to the attachment relationship the parents are able to form with the child with FXS. It is known that the presentation of autism is difficult to delineate from that of attachment difficulties and so consideration to these factors should be given (Davidson et al., 2015). It is also known that these difficulties can develop when a child and/or a parent find it difficult to form interpersonal connections with one another. The evidence base indicates that for children with FXS both instances are present and therefore likely to impact their attachment development.

Although it was recognised that the inclusion of females because of the different chromosome expression may bias research results there were no studies found in the search using the designated search terms that explored the behavioural phenotype for females with FXS. There may be important lessons that could be extrapolated from these studies that would broaden the understanding of the FXS behavioural phenotype.

Implications for Clinical Practice and Service Development

Clinical Implications

It has been demonstrated that phenotypic behaviour can be mediated by physical and social intervention (Hanley et al., 2003). Therefore, clinicians should use the knowledge of behavioural phenotypes to plan and develop early and ongoing interventions for people with FXS.

Children with FXS require clinical services to support their development. This input is likely to span the lifetime as the difficulties the child faces develop and change over time. This review recommends that the behavioural interventions should be targeted to the specific needs a child with FXS presents with. Although there is recognition of cross over there are also specific FXS needs and these are unique from other diagnosis and presentations, such as autism. There should therefore be a focus on communication and social skills training for people with FXS.

There is also a rational for developing family interventions to help support the vulnerabilities of parents with children with FXS. These interventions should consider parental interaction, and stress management. It is thought that this will improve the quality of life of the whole family.

Implications for Local and National Policy, Priorities and Services

The Government of Wales Act 1998 means that Wales has several devolved powers. These include the powers for health and social care provision in Wales.

Implications for Welsh Government Policy

Wales Autism Research Centre (WARC) was formally established in 2010 as the first national autism research centre in the UK. It plays a key role in the autism community with a strong reputation for translation of research into policy and practice. They should be made aware of these findings and recommendations to ensure best practice in policy and practice.

The National Autism Team is funded by Welsh Government and hosted by the Welsh Local Government Association, working in close partnership with Public Health Wales. The team works closely with the Welsh Government, local ASC leads within local authorities and health boards, key stakeholders and advisory groups. The newly establish National IAS Leads Network has responsibility for ensuring the delivery of training. Ensuring the National IAS Leads Network are aware of these findings and that they are considered in the 2019/2020 work plan is essential.

Implications at a UK level

As WARC is the UK National Centre for Autism, disseminating the findings with them will hopefully influence Wales and the UK policy development. In April 2014 the UK government published 'Think Autism', a strategy for meeting the needs of autistic adults in England. The

strategy supports the Autism Act 2009. This year the Department of Health and Social Care, working with the Department for Education, will review the strategy and extend it to cover children as well as adults. They are currently consulting on people's experiences of care and support. Whilst it is not possible to share the findings because they are a mixture of experiences across the UK and the consultation is only interested in England, ensuring these findings can contribute to this thinking would be important.

Political and Social Implications

The history of the autism diagnosis is fraught with political intrigue and conflict (Siegel, 2018). Since Kanner's 'refrigerator mothers' theory of the 1940's cross over between what is 'autism-related' from what is 'attachment-related' has existed (Williams, et. al., 2002). The severity of autism varies, leaving some individuals high-functioning and others unable to care for themselves but diagnosing autism often relies more on financial pressures from schools and parents rather than on medical evidence. There have been calls for conceptual clarity and this project is part of that process. The reaction to Kanner's work is important to observe and is an example of how the media influences public opinion but also how research intentions and results can be misrepresented. The consequence of misrepresentation can impact progress over many generations. The same phenomenon has been observed many times including in childhood immunisations, and attachment research. What underlies all three mentioned instances is not a knowledge deficit but our ideologies (Baumgaertner, Carlisle, & Justwan, 2018). Where research in ASC and attachment have stumbled is in ideological associated with gender and political conservatism. It is not possible to separate a researcher from their ideologies and so when interpreting research, one must also consider the lenses through which ideas are constructed and how those ideas may be limited by the ideological views of

their constructors. Equally no matter what a researcher's intentions (if they even had known intentions) how the establishments of our time use findings to support their own gain is beyond a researchers individual control (Duschinsky, Greco, & Solomon, 2015). The process highlights the importance of engagement with democracy at a societal level but also the importance of cascading the values of democracy down into the research domain. Democracy intrinsically requires that persons be treated equally. However, it requires persons to come forward and be engaged. Marginalised groups are disadvantaged in this process and therefore researchers and research institutes have a duty to recognise and compensate those that lack political power in order to ascertain a balanced view (Post, 2005). A potential solution to this is to examine the system by which research is reviewed. There are many criticisms of the peer review system, one being that it creates substantial bias (R. Smith, 2006). Reform of this process and setting clearer protocols and standards could benefit the research process greatly (Ahmed & Garparyan, 2013).

Implications for Service Development

It appears that it would be efficacious to formulate an FXS strategy based on meeting individual needs of people with FXS within education and health services. A first step towards this would be to audit the current training programmes offered within health and education services. It has been demonstrated that phenotypic behaviour can be mediated by physical and social intervention (Hanley et al., 2003). Therefore, clinicians should use the knowledge of behavioural phenotypes to plan and develop early and ongoing interventions for people with FXS. This could be undertaken to clarify whether those receiving the training are implementing FXS informed recommendations effectively.

Children with FXS require clinical services to support the development of their ongoing needs. This input is likely to span the lifetime as the difficulties the child faces develop and change over time. The results indicate that behavioural interventions should be targeted to the specific needs a child with FXS has. Although there is recognition of cross over there are also specific FXS needs and these are unique from other diagnosis and presentations, such as ASC. There should therefore be a focus on communication and social skills training for people with FXS.

Dissemination

The research conducted as part of this project will be shared with the UK Fragile X Society and will be presented at their annual UK Fragile X Conference. It will also be disseminated at the European Conference on Intellectual and Developmental Disabilities conference and the UK Annual Seattle Club Conference.

The results will also be disseminated within the School of Psychology at Cardiff University and the Department of Clinical Psychology. The researcher will also seek to share the findings at the NHS Wales Learning Disability Directorate Special Interest Group (SIG) at which there is representation from all the Welsh Health Boards.

Findings will be disseminated in a user friendly and accessible way via the Fragile X Society and its social media outlets. This will involve the creation of a short video articulating the research results and implications and a one-page leaflet. For service level engagement an SBAR format will also be created. It will also invite members of the public to comment on the findings. These will then inform future research and further dissemination.

In the interest of public accessibility, the researcher will make the papers available on Research Gate. The findings will also be shared with relevant policy bodies in Wales and the UK as described above. See appendix 12, and 13 for copies of the poster presentations and SBAR.

Conclusion

The review identified that the behavioural phenotype for FXS includes 1) social behavioural and communication difficulties, 2) emotional regulation difficulties 3) repetitive and restrictive behaviour and speech. In doing so it has identified further areas of development for research and clinical practice. Observing these traits collectively in the delineation of the behavioural phenotype for FXS will allow for greater understanding of their interplay. These are often explored separately and therefore understanding of their interconnectivity has not been fully acknowledged.

Access to accurate behavioural phenotype information for a given condition such as FXS enables better service provision. It also aids clinicians to develop a more sensitive understanding of the needs of people with FXS and their families and carers. Therefore, further training should be provided to staff to support their understanding of FXS.

There have been many advances in services provided for individuals with FXS and ASC over the past few decades driven by advances in research (Rutter et al., 1999). The study demonstrated that despite the heterogeneity of needs of individuals with FXS current health and education provision appear to provide a satisfactory service to the majority but there is

some way to go in ensuring the individual needs of people with FXS are acknowledged separately.

The findings of the research project will help inform ways of best supporting families by tailoring psychological interventions to reduce distress and promote wellbeing and resilience for those with FXS and their families. The delineation of a FXS behavioural phenotype raises more questions than it answers but in doing so creates a new pathway for additional exploration of the underlying causes of not only FXS but also ASC.

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Appendix 1 Consent Form

Participant ID:_____

Title of Project: Children and young people with Fragile X Syndrome: Behavioural phenotype and support needs.

Name of Researcher: Jen Daffin

Cardiff University in collaboration with the Fragile X Society

Please tick as appropriate

1	I confirm that I have read the information sheet dated..... (version.....) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2	I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected, up until the research data has been analysed.	
3	I understand that data collected during the study may be looked at by individuals from Cardiff University where it is relevant to my taking part in this research. I give permission for these individuals to have access to my data.	
4	I understand my participation is anonymous and my confidentiality will be upheld at all time.	

5	I agree to take part in the above study.	

Name of child _____

Name of Participant (Parent) _____ Participant Signature

_____

Date _____

Appendix 2 Cover Sheet

22nd January 2018

Dear Parents and Carers,

My name is Jen Daffin and I am a third year student on the doctorate of Clinical Psychology at Cardiff University. As part of my training I am undertaking a research thesis project entitled: Children and young people with Fragile X Syndrome: Behavioural phenotype and support needs.

We plan to gather information from parents and carers to explore how families are finding the support they receive from services. Using this information we also want to explore how different people's FXS difficulties get assessed and supported by services. The findings from this work will then be used to inform how to better design and/or deliver services to meet the needs of people with FXS and their families.

We understand your time is precious and so have tried to ask as few questions as possible. Thank you for your time and if you have any questions please feel free to contact me and the research team on the details below.

Yours faithfully,

Jen Daffin
Clinical Psychologist in Training
Cardiff University

Contact details:

11th Floor, Psychology Department, Tower Building
70 Park Place
Cardiff
CF10 3AT
Tel. 029 208 70582 Email: daffinj@cardiff.ac.uk

Appendix 3 Participant Information Sheet

Participant Information Sheet

Children and young people with Fragile X Syndrome: Behavioural phenotype and support needs

Research Team: Jen Daffin, and Dr Dougal Hare (Cardiff University).

We would like to invite you to take part in our research study. Joining the study is entirely up to you. Before you decide to take part we would like you to understand why the research is being done and what it would involve.

What is the purpose of the study?

Lots of people with Fragile X Syndrome (FXS) also get a diagnosis Autistic Spectrum Condition (ASC). However, there is some research to suggest that these are separate presentations and need to be explored more to understand how they are similar but importantly how they differ. There is little research into what the behavioural patterns (phenotype) of people with FXS are and how these differ from the patterns of people who have ASC. We would like to explore this in this study.

Lots of people say that they seek a diagnosis if ACS for their child with FXS because it means they get access to some services that they wouldn't without the diagnosis of ASC. We would like to explore how people with FXS are getting their needs met and if specific FXS services are needed so that their needs can be better met.

Why have I been invited to take part in this study?

You have been invited to take part because you are part of the Fragile X Society research list and have previously given your permission to be contacted to take part in research related to FXS. By being on this list we have assumed that you are a parent of a child with FXS. We are looking for parents whose children are under the age of 16 and have a confirmed diagnosis of FXS who live in the UK.

Do I have to take part?

No, you do not have to take part in the study if you do not want to. Taking part in the research is voluntary; this means it is completely up to you to take part. Your decision to participate in this study will not be connected to the care you and your family are receiving now or in the future. If you decide to take part and sign the consent form but change your mind later, you are free to Stop taking part at any point and do not need to give us a reason. There will not be any consequences to your current or future treatment if you decide to do this.

What will participation involve?

- Parents/ carers will complete a set of questionnaires, which ask about their demographic details, your childs FXS presentation, if you feel you are receiving the right (or enough) support, and if you feel you are receiving the right (or enough) support for your child's education and health needs. Together, these questionnaires will take about 30 minutes to complete.
- If you are completing paper copies you will be provided with a pre-paid envelope to return the questionnaires.

What are the possible disadvantages and risks of taking part?

It is possible that the questionnaires might raise issues that could be distressing to think about. A list of agencies and people you can contact is provided should you need any additional information/support.

What are the possible benefits of taking part?

The information gained will help services to better understand the needs of a child with FXS and identify ways services can help better meet those needs. This will help clinicians to develop appropriate support packages, which may help other families in the future.

Will my taking part in the study be kept confidential?

Yes. We will handle data sensitively and in confidence, and follow legal and ethical guidelines.

- All data collected about you and your child will be kept strictly confidential and only viewed by members of the research team. It will be stored securely in a locked filing cabinet at the University.
- Data will be entered onto a computer database which will be password protected and encrypted. Each participant will be assigned a number, thus names will not be entered onto the database.
- We plan to publish the research and names of participants will not be used. All published data will be anonymous.

What if there is a problem?

It is unlikely that anything would go wrong, but if you have a concern about any aspect of the study, you should contact one of the researchers. If you are not satisfied and wish to make a formal complaint, you can do so through the Cardiff University School Research Ethics Committee complaints procedure. Details can be obtained from the University by calling 029 2087 4000.

In the event that something does go wrong and you are harmed during the study and this is due to somebody's negligence, then you may have grounds for a legal action for compensation against Cardiff University, but you might have to pay your legal costs.

Will I receive any payment for taking part in the study?

Participants will not receive any payment for taking part.

Who is organising the research?

This research is being conducted as part of the Doctorate in Clinical Psychology at Cardiff University for Trainee Clinical Psychologist/postgraduate student Jen Daffin. This study will be carried out under the guidance of Dr Dougal Hare (Academic Supervisor). It is funded by Cardiff University.

Where will the findings be published?

- We intend to publish the results in peer-reviewed journals
- We intend to present the results at scientific and other relevant conferences
- We may put a summary of the findings in the Fragile X Society newsletter.
- We will provide participants with a summary of the findings if they would like this.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee who protect the rights, safety, dignity and wellbeing of participants. This study has been reviewed and given a favourable opinion by the Cardiff University School of Psychology Research Ethics Committee.

Who can I contact for further information?

If you would like to discuss the study or have any questions or concerns, please do not hesitate to contact Jen Daffin at daffinj@cardiff.ac.uk or tel. 02920 870582. Alternatively, you can contact Dr Dougal Hare, Department of Clinical Psychology, 11th Floor Tower Building, Park Place, Cardiff University, Cardiff CF10 3AT.

You can keep this copy of the information sheet.

Appendix 4 Debrief Letter

Dear

Children and young people with Fragile X Syndrome: Behavioural phenotype and support needs.

This study aimed to better understand what the behavioural presentation (phenotypes) of people with Fragile X Syndrome (FXS) looks like and how that differs from Autistic Spectrum Condition (ASC). We were also interested in examining service provision patterns in order to understand if people with FXS are having their support needs met as well as if a 'co-morbid diagnosis of ASC' supports the meeting of those needs.

The findings from this research may help inform ways of better supporting people with FXS and their families in the future, for example, by tailoring psychological interventions to better met their needs.

You were asked to complete some questionnaires which measured:

- Your child's FXS related behaviours
- Your perception of unmet needs
- Your perception of the educational and other service provision you receive for your child
- Your socio-demographic information

All the data we collected for this study is confidential, all personal and identifiable information will be kept anonymous and only the researcher relevant members of the research team can access it.

If you have any questions or queries about this project, please phone me on 02920870582 or email me at daffinj@cardiff.ac.uk. Alternatively, you can contact my supervisor, Dr Dougal Hare on the above telephone number or email address hared@cardiff.ac.uk .

If you would like to make a complaint please contact Cardiff university School Research Ethics Committee. Details can be obtained by contacting the university on 029 2087 4000.

Your participation in this study is greatly appreciated and thank-you again for your participation.

Yours sincerely, Jen Daffin **Trainee Clinical Psychologist**

Appendix 5 Research Protocol

Research Protocol

Project title: Children and young people with Fragile X Syndrome: Behavioural phenotype and support needs

Research Team

Jen Daffin, Trainee Clinical Psychologist, Doctorate of Clinical Psychology, Cardiff University

daffinj@cardiff.ac.uk

Dr Dougal Hare, Research Director, Doctorate of Clinical Psychology, Cardiff University hared@cardiff.ac.uk

Address: Department of the Doctorate in Clinical Psychology, 11th Floor, Tower Building, 70 Park Place, Cardiff, CF10 3TA

Telephone: 02920 870582

Project summary

Autistic-like traits have often been reported in children with Fragile X syndrome (FXS; Hagerman et al 1986) and parents of children with FXS increasingly seek a diagnosis of co-morbid autism spectrum condition (ASC) in order to access additional educational and other services for their child. However, the validity of such co-morbid ASC has been questioned (Hall et al 2010; Abbeduto, McDuffie & Thurman 2014) and the relationship between FXS and ASD remains unclear (Cornish, Turk & Levitas 2007), with obvious clinical and service implications.

The proposed study therefore aims to:

• To further delineate the autistic–like aspects of the FXS behavioural phenotype

• To examine the relationship between service provision and the presence of autistic-like features / 'co-morbid ASC' in children with FXS .

The findings from this research may help inform ways of better supporting families in the future, for example, by tailoring psychological interventions to reduce distress and promote wellbeing and resilience.

Rationale & background information

Fragile X Syndrome (FXS) is the most commonly known inherited cause of intellectual disability (Crawford, Acuña, & Sherman, 2001). It is second only to Down syndrome as a genetic cause of intellectual disability (Thurman, McDuffie, Hagerman, & Abbeduto, 2014). The gene responsible for FXS was discovered over 25 years ago (Verkerk et al., 1991). FXS is known to be part of a group of FMR1 mutation-related disorders, termed fragile X-associated disorders (FXD), which also includes fragile X-associated tremor/ataxia syndrome (FXTAS) and fragile X-associated primary ovarian insufficiency syndrome (FXPOI; (Boyle & Kaufmann, 2010).Collectively these are known as FXS. Of the people who have FXS, nearly all males will have an intellectual disability (ID) but only a third of females will. The exact number of people who have FXS is unknown, but it has been estimated that about 1 in 5,000 males are born with the disorder (Coffee et al., 2009). Females will have a much milder expression because they will have one unaffected X chromosome. In most cases females will present with a low to borderline intellectual disability (O'Brien, 2006).

Fragile X syndrome (FXS) results from a cytosine-guanine-guanine (CGG) expansion that triggers hypermethylation and silencing of the FMR1 (fragile X mental retardation 1) gene on the X chromosome at Xq27.3 (O'Brien, 2006; Oostra & Willemsen, 2003). The expansion typically leads to a decrease or absence of FMRP (fragile X mental retardation protein) which is the protein produced by the FMR1 gene. This is essential for synaptic plasticity and experience-dependent learning (Bassell & Warren, 2008). As a consequence the brain in individuals with FXS is larger and approximately 10% heavier than brains that have developed at regular rates. There is also a direct correlation between the length of the repeat CGG sequence and the severity of the phenotypic expression in terms of physique, intellect and behaviour (O'Brien, 2006). Expansions in the 55–200 repeat status, termed premutation or ''carrier'' status, do not significantly affect the transcription of FMRP. It is expansions above 100 CGG repeats that most often lead to the full mutation, and therefore FXS, in their offspring. Relatively normal levels of FMRP, individuals with the FMR1 premutation mean that they do not generally have the same phenotype as those with FXS (Boyle & Kaufmann, 2010).

Many people with FXS, as well as ID, will also have behavioural features including short attention span, distractibility, impulsiveness, restlessness, over activity, sensory problems

and anxiety. People with FXS can also have difficulties with eye contact, anxiety in social situations, insistence on familiar routines and hand flapping or hand biting. It is these behavioural features, which on the surface appear very similar to ASC, that have lead clinicians to diagnose some people with FXS with idiopathic ASC (Hall, Lightbody, Huffman, Lazzeroni, & Reiss, 2009). The difficulties associated with FXS are prominent and as such often people with FXS have contact with local mental health community teams to support in the management of their difficulties (O'Brien, 2006).

Initially researchers proposed that the syndrome was called AFRAX syndrome (ASC-Fragile X) because it was thought that it was caused by an 'autism' gene (O'Brien, 2006). However, as research into FXS has progressed and an exploration of the behavioural phenotype is taking place important differences have emerged.

Autism Spectrum Condition and how it Differ from FXS

ASC spectrum Condition (ASC) is a broad term for a group of behaviourally defined neurodevelopmental disorders that historically includes ASC spectrum disorder (ASD) autistic disorder, childhood ASC, pervasive developmental disorder – not otherwise specified (PDD-NOS), and Asperger's syndrome (World Health Organization, 1992). This reflects the different diagnostic manuals and tools used, as well as the different ASC profiles individuals present with.

In line with the British Psychological Society guidelines on Language in Relation to Functional Psychiatric Diagnosis, of which ASC is not explicitly included but which it is accepted that ASC does not have a known aetiology and with respect to the lack of validity held by the Diagnostic Statistics Manual (DSM) and the International Classification of Disease (ICD) the term 'condition' rather than 'disorder' shall be used (Awenat et al., 2013; Caroline Richards, Jones, Groves, Moss, & Oliver, 2015).

ASC is characterised by difficulty found in communication, reciprocal social interaction and the presence of restrictive and repetitive stereotyped behaviours (American Psychiatric Association, 2013). It is described as a developmental disability that affects how people view the world and others around them. In the UK 1 in 100 people are said to have ASC (Baird et al., 2006). Males are five times more likely to have a diagnosis than females (Fombonne, 2009). However, it is thought that diagnostic criteria may under report the level of ASC within the female population (Gould & Ashton-Smith, 2011).

The cause of ASC is mostly unknown and therefore diagnosis is dependent upon behavioural criteria (Happé, Ronald, & Plomin, 2006). In the UK the diagnosis of ASC is made using the diagnostic statistics manual (DSM-IV) criteria and the use of standardised measures such as the ASC Diagnostics Observation Schedule (ADOS; Lord et al., 1989) or the Diagnostic Instrument for Social and Communication Disorders (DISCO; American Psychiatric Association, 2013; Wing, Leekam, Libby, Gould, & Larcombe, 2002).

As research into ASC in specific syndromes has developed evidence has emerging that individuals with certain genetic and metabolic syndromes could have an atypical profile of ASC phenomenology. This is providing support for the idea that there is a distinction

between syndromic variants of ASC and idiopathic ASC (Hall, Lightbody, Hirt, Rezvani, & Reiss, 2010; Caroline Richards et al., 2015).

Behavioural Phenomenology

Behavioural Phenotypes are patterns of behaviour that present in syndromes caused by chromosomal or genetic differences. A behavioural phenotype is characterised by patterns of social, linguistic, cognitive and motor observations which are associated consistently with a particular biological or genetic disorder (O'Brien, 2006). The term 'endophenotype' describes unobservable characteristics such as thoughts, emotional and motivational states. Sometimes a distinction is therefore made between behavioural phenomenology and clinical phenomenology which can also include cognitive and emotional or motivational phenotypes (Waite et al., 2014).

The purpose of delineating syndrome behavioural phenotypes is to clarify the mechanisms behind genotype expression. It means to link together genes, brain and behaviour (Dykens, 2000). The aim of this is to inform intervention and care delivery and pathways. This is important in helping to understand the experience of people with specific syndromes. This includes better understanding of developmental delay experiences, self-injurious behaviour, social exploitation, social anxiety, social skill deficits, sensory differences, temper outbursts and repetitive behaviours (Waite et al., 2014). This can lead to better outcomes for people in terms of understanding how a person interacts with their environment and how to adapt it to their needs.

The Importance of Understanding the FXS Behavioural Phenotype

Understanding the differences in FXS is crucial in ensuring that individuals receive appropriate behavioural management and educational support and intervention (Moss & Howlin, 2009). It is known that the ASC phenomenology varies across different syndromes. The expression of ASC is however consistently more likely to be found in those with an identified syndrome than in the general population. Additionally, how ASC in genetic and metabolic syndromes differs from idiopathic ASC has important implications in understanding the mechanisms underlying ASC (Caroline Richards et al., 2015).

There have been a number of studies attempting to evaluate medications targeted to the specific underlying pathology. Developing an understanding of the FXS behavioural phenotype will allow for specific interventions to be developed. If these interventions are proven to be more successful than standard ACS interventions then they should be prioritized and services should recognise FXS in its own entity (Hall, et. al., 2010).

Previous studies of ASC in FXS have recruited participants who already have a diagnosis of ASC and FXS, or ASC or FXS only. This approach has meant that previous studies findings may have been masked by the use of categorical diagnosis. The use of the ADOS and ADI-R to make a diagnosis of ASC may not allow for the range required to understand individual difference in FXS. Although they are both gold standard measures there purpose and design was to capture ASC. They have therefore not been normed or calibrated for FXS and may not pick up specific syndrome differences (Abbeduto, McDuffie, & Thurman, 2014).

In order to allow for a finer distinction, the following study will use the Social Responsiveness Scale (SRS; Constantino & Gruber, 2005), Repetitive Behavioural Questionnaire 2 (RBQ2; Barrett, et. al., 2015), Wessex Questionnaire (Kushlick, Blunden, & Cox, 1973) in order to attempt to explore if there are distinctions between FXS and ASC that are not captured when the ADOS or other measure of ASC are used. The identification of a specific behavioural phenotype for FXS raises a question about levels of current unmet need in service provision for people with FXS. This study also seeks to assess parent's experience of their children's needs specific to FXS and whether they are being met by health and education service providers in the United Kingdom (UK).

Study goals and objectives

Specifically this project aims to:

• To further delineate the autistic–like aspects of the FXS behavioural phenotype

• To examine the relationship between service provision and the presence of autistic-like features / 'co-morbid ASC' in children with FXS .

The findings from this research may help inform ways of better supporting families in the future, for example, by tailoring psychological interventions to reduce distress and promote wellbeing and resilience.

Study Design

The study will be undertaken with the UK Fragile X Society (CEO, Becky Hardiman, based at the Tizard Centre, University of Kent) and a sample of N=1500 parents of children with a diagnosis of FXS can potentially be accessed via the Fragile X Society membership database and its associated media outlets.

The primary inclusion criteria will be being a parent of a child aged under 16 years with a confirmed diagnosis of Fragile X. The relevant questionnaires will be distributed online (and by post on request). No incentives or payment will be provided. It is intended that this will be the first of a series of studies looking at FXS, participants will be additionally asked (a) if they consent to be contacted at a later date to take part in both follow up studies and/or new studies (NB engagement in the current study will not be dependent on consent to be contacted for future studies and/or involvement in follow up studies) and (b) if they consent to their data from the current study being made available to other researchers working on FXS under the supervision of Dr Hare (NB engagement in the current study will not be dependent on consent for data to be made available to other researchers).

Measures

The following measures will be used:

The Social Responsiveness Scale (SRS; Constantino & Gruber, 2005), Repetitive Behavioural Questionnaire 2 (RBQ2; Barrett, et. al., 2015), Wessex Questionnaire (Kushlick et al., 1973) and a needs assessment along with questions regarding service provision and basic demographic information will be collected.

The SRS measures social ability of children from 4 years to 18 years old (Constantino & Gruber, 2005). It provides a continuous measure of social ability (from impaired to above average).

The RBQ2 measures restricted and repetitive behaviours which forms one of the core diagnostic criteria for autism spectrum disorder (World Health Organization, 1992). It was developed at the Wales Autism Research Centre, Cardiff University. It is a set of questionnaires based on items from the Diagnostic Interview for Social and Communication Disorders (DISCO: Barret, et. al., 2015).

The Wessex questionnaire is used to assess ability in children and adults with intellectual disabilities (Kushlick et al., 1973). It comprises five subscales including: continence, mobility, self-help skills, speech and literacy. It has good interrater reliability and has been as argued to be an effective tool for large-scale questionnaire studies (Richards, Oliver, Nelson, & Moss, 2012).

Additional information about support needs will be collected based on assessment was based on work by Bromley, Hare, Davison, and Emerson (2001) which was an assessment of health needs of families and / or carers of adults with children with autistic disorders.

Partial postcodes will be collected to map onto lower-layer super output areas (LOSA). Demographic information such as age, gender and diagnosis will also be collected.

Procedure

The university school of psychology is licenced to use the online data collection programme Qualtrics. Qualitrics is accessible both for computer and smartphone users. No financial incentives for participation were given.

The online link for the survey was distributed between for 3-4 months. It will be distributed via the Fragile X Society database of consenting research participants, the mailing list, online media outlets including, facebook, twitter and youtube. Participants will be made aware that alternative formats were available and were given details of how to contact the researchers to obtain these. The online questionnaire took an estimated 30 minutes to complete.

Ethical Approval and Consent

All participants will be recruited via the Fragile X Society and their related social media outlets as such ethical approval for the project was sort from the society as well as from Cardiff University, School of Psychology ethics committee.

Completing questionnaires for the study may highlight areas of need for individuals and their families potentially raising awareness/distress in them. Service support information will be provided to participants.

Copies of the ethical approval as well as participation information and consent procedures are attached.

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Online Questionnaire link: https://cardiffunipsych.eu.qualtrics.com/ControlPanel/

Appendix 6 List of Support Services

Children and young people with Fragile X Syndrome: Behavioural phenotype and support needs

Some of the questionnaires used in this study covered potentially sensitive material. If you feel affected by taking to this research and wish to seek additional support or advice, we recommend that you contact one of the following services:

- **'Contact a family: For parents of children with disabilities'**

  www.cafamily.org.uk

  Telephone support available Monday-Friday, 9.30am to 5.00pm on

  0800 808 3555 or email helpline@cafamily.org.uk

- **Fragile X Society**

  www.fragilex.org.uk

  Phone: 01371 875100

  Email: info@fragilex.org.uk

- **Dr Dougal Hare**, Clinical Psychologist in the field of Intellectual Disabilities:

  South Wales Doctoral Programme in Clinical Psychology

  11th Floor, Tower Building, 70 Park Place

  Cardiff, CF11 3AT

  Email: HareD@cardiff.ac.uk

  Telephone: 02920 870 582

Appendix 7 Ethical Approval from Cardiff University School of Psychology Committee

Ethics Feedback - EC.17.03.14.4865R

Dear Jennifer The Ethics Committee has considered your revised project proposal: Children and young people with Fragile X Syndrome: Behavioural phenotype and support needs (EC.17.03.14.4865R).

The project has now been approved.

Please note that if any changes are made to the above project then you must notify the Ethics Committee. Best wishes, Mark

Appendix 8 Ethical Approval from FXS Society Research Panel

Re: Cardiff University FXS research work Dear Dougal and Jennifer, Sorry, just a short email as on the road. Our advisor is happy with the plan outlined yesterday, if you could forward me the updated survey. Will email again later. Best wishes, Rachel Sent from my iPhone

On 15 Jan 2018, at 15:58, Dougal Hare wrote: Thank you ! Dougal Dr Dougal Julian Hare Reader in Clinical Psychology Research Director, South Wales DClinPsy Programme Cardiff University

From: Rachel Instone Sent: 15 January 2018 15:37:41 To: Dougal Hare Cc: Jennifer Daffin; Becky Hardiman; Lucia Elghali; Steve Harris Subject: Re: Cardiff University FXS research work Rachel Instone Tue 16/01/2018 10:58 To:Dougal Hare ; Cc:Jennifer Daffin ; Becky Hardiman ; Lucia Elghali ; Steve Harris ; 02/05/2019 Mail – DaffinJ@cardiff.ac.uk https://outlook.office.com/owa/?realm=cardiff.ac.uk&path=/mail/search 2/5

Dear Dougal, It was good to talk to you earlier and I am sure we can find a solution to this. As I said, we go through the same process with any research that is proposed to the society and this is to ensure that anything we ask our families to participate in is of a high standard. I spoke to Lucia earlier and she was very enthusiastic about the work that you are doing at Cardiff and that she'd enjoyed meeting with you and Jennifer last March. I understand that time is the main issue here, Jennifer needs to start collecting data as soon as possible. I have contacted our specialist advisor, they are away until tomorrow. I have suggested that Jennifer could make the amendments to the survey (address the typos, inconsistencies etc) so that we can disseminate it and that she could also send a bullet point list outlining how she will address the comments from our advisor. I will let you know what the response is as soon as I hear. As I have said, the committee is supportive of the questionnaire, but there were some typos etc that I think Jennifer has addressed now, is that right, Jennifer? I can have another look at it if you could send me the link.

Best wishes, Rachel Rachel Instone Voluntary Research Officer, Fragile X Society, UK

Appendix 9 Questionnaires

Fragile X Syndrome and Autism Needs Questionnaire -

Start of Block: Participants Information

Q160 The following questions relate to your consent to participate in this study.

	Yes (1)	No (2)
I confirm that I have read the information sheet for this above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. (1)	○	○
I understand that I can withdraw from the study at any time and have my data removed, without necessarily having to give reasons for this, and that there would not be any adverse consequences of doing so (2)	○	○
I understand that data collected during the study may be looked at by individuals from Cardiff University where it is relevant to my taking part in this research. I give permission for these individuals to have access to my data. (3)	○	○
I understand my participation is anonymous and my confidentiality will be upheld at all time. (4)	○	○
I agree to take part in the above study. (5)	○	○

Q158 Please sign in the box (with your mouse or on touch screen) below to confirm the answers above as your own.

End of Block: Consent to Participation

Start of Block: Demographics

Appendix 9a Demographic Questions

Q60 What is the first part of your postcode (e.g. CF10)?

_____

Q64 What is your relationship to the child you are answering this question about?
(If you have more than one child with FXS please complete two separate surveys, one for each child you wish to include.)

- ○ Parent (1)
- ○ Other family member (2)
- ○ Carer (3)
- ○ Residential/Hostel Staff (4)
- ○ Other (5)

Q61 Is your child:

- ○ a girl (1)
- ○ a boy (2)

Q62 How old is your child?

- 0-5 years old (1)
- 6-10 years old (2)
- 11-15 years old (3)

Q63 Does your child have a diagnosis of Autism Spectrum Condition / Autism?

- Yes (1)
- Currently under/awaiting Assessment (2)
- No (3)

Q65 What is your child's ethnicity?

- White (Inc. English/ Welsh/ Scottish/ N. Irish/ Irish / other white) (1)
- Mixed or multiple ethic group (2)
- Asian/Asian British (3)
- Black (African/Caribbean/Black British) (4)
- Other ethnic group (5)

Appendix 9b Services and Support Questions

Q165 The following questions relate to the support your child and/or your family receive from services.

84 Have you ever received support from the child and adolescent mental health services (CAMHS) for your child?

- ○ Yes (1)
- ○ No (2)

Q85 Have you ever received support from a Children's Learning Disability team?

- ○ Yes (1)
- ○ No (2)

Appendix 9c RBQ-2 Questions

Q164 The following questions relate to your child's behaviour.

Q2 Does your child arrange items in rows or patterns?

- ○ Never or rarely (1)
- ○ 1-15 bouts of this behaviour daily (2)
- ○ 15 -29 bouts of this behaviour daily (3)
- ○ 30 or more bouts of this behaviour daily (4)

Q57
Does your child repeatedly fiddle with items?

For example, do they spin, twiddle, bang, tap, twist, flick or wave anything repetitively?

- ○ Never or rarely (1)
- ○ 1-15 bouts of this behaviour daily (2)
- ○ 15 -29 bouts of this behaviour daily (3)
- ○ 30 or more bouts of this behaviour daily (4)

Q58 Does your child spin themselves around and around?

- Never or rarely (1)
- 1-15 bouts of this behaviour daily (2)
- 15 -29 bouts of this behaviour daily (3)
- 30 or more bouts of this behaviour daily (4)

Q59 Does your child rock backwards and forwards, or side to side, either when sitting or when standing?

- Never or rarely (1)
- 1-15 bouts of this behaviour daily (2)
- 15 -29 bouts of this behaviour daily (3)
- 30 or more bouts of this behaviour daily (4)

Q11
Does your child pace or move around repetitively?

For example, does your child walk to and fro across a room, or around the house or garden repetitively?

- ○ Never or rarely (1)
- ○ 1-15 bouts of this behaviour daily (2)
- ○ 15 -29 bouts of this behaviour daily (3)
- ○ 30 or more bouts of this behaviour daily (4)

Q12
Does your child make repetitive hand and/or finger movements?

For example, does your child repetitively wave, flick, flap or twiddle his/her hands or fingers repetitively?

- ○ Never or rarely (1)
- ○ 1-15 bouts of this behaviour daily (2)
- ○ 15 -29 bouts of this behaviour daily (3)
- ○ 30 or more bouts of this behaviour daily (4)

Q45
Does your child have a fascination with specific objects?

For example, trains, road signs or other things?

- ○ Never or rarely (1)
- ○ Mild or occasional (2)
- ○ Marked or notable (3)

Q37 Does your child like to look at objects from particular or unusual angles?

- ○ Never or rarely (1)
- ○ Mild or occasional (2)
- ○ Marked or notable (3)

Q38 Does your child have a special interest in the smell of people or objects?

- ○ Never or rarely (1)
- ○ Mild or occasional (2)
- ○ Marked or notable (3)

Q40 Does your child have a special interest in the feel of different surfaces?

- Never or rarely (1)
- Mild or occasional (2)
- Marked or notable (3)

Q41 Does your child have any special objects you like to carry around?

- Never or rarely (1)
- Mild or occasional (2)
- Marked or notable (3)

Q42 Does your child collect or hoard items of any sort?

- Never or rarely (1)
- Mild or occasional (2)
- Marked or notable (3)

Q43 Does your child insist on things at home remaining the same?

For example, furniture staying in the same place, things kept in certain places, or arranged in certain ways?

- ○ Never or rarely (1)
- ○ Mild or occasional (does not affect others) (2)
- ○ Marked or notable (occasionally affects others) (3)
- ○ Serious or severe (affects others on a regular basis) (4)

Q47 Does you child get upset about minor changes to objects? (e.g. flecks of dirt on your clothes, minor scratches on objects?)

- ○ Never or rarely (1)
- ○ Mild or occasional (does not affect others) (2)
- ○ Marked or notable (occasionally affects others) (3)
- ○ Serious or severe (affects others on a regular basis) (4)

Q46 Does your child insist that aspects of daily routine must remain the same?

- ○ Never or rarely (1)
- ○ Mild or occasional (does not affect others) (2)
- ○ Marked or notable (occasionally affects others) (3)
- ○ Serious or severe (affects others on a regular basis) (4)

Q48 Does your child insist on doing things in a certain way or re-doing things until they are “just right”?

- ○ Never or rarely (1)
- ○ Mild or occasional (does not affect others) (2)
- ○ Marked or notable (occasionally affects others) (3)
- ○ Serious or severe (affects others on a regular basis) (4)

Q49 Does your child play the same music, game or video, or read the same book repeatedly?

- ○ Never or rarely (1)
- ○ Mild or occasional (not entirely resistant to change or new things) (2)
- ○ Marked or notable (will tolerate changes when necessary) (3)
- ○ Serious or severe (will not tolerate any changes) (4)

Q52 Does your child insist on wearing the same clothes or refuse to wear new clothes?

- ○ Never or rarely (1)
- ○ Mild or occasional (not entirely resistant to change or new things) (2)
- ○ Marked or notable (will tolerate changes when necessary) (3)
- ○ Serious or severe (will not tolerate any changes) (4)

Q55 Does your child insist on eating the same foods, or a very small range of foods, at every meal?

- Never or rarely (1)
- Mild or occasional (not entirely resistant to change or new things) (2)
- Marked or notable (will tolerate changes when necessary) (3)
- Serious or severe (will not tolerate any changes) (4)

Q56 What sort of activity would your child choose if they are left to occupy themself?

- A range of different and flexible self-chosen activities (1)
- Some varied and flexible interests but commonly choose the same activities (2)
- Almost always choose from a restricted range of repetitive activities (3)

End of Block: Repetitive Behaviours

Appendix 9D SRS 2 Questions

Q163 The following questions relate to your child's social skills and responses.

88 Seems much more fidgety in social situation than when alone

- ○ Not true (1)
- ○ Sometimes true (2)
- ○ Often true (3)
- ○ Almost always true (4)

Q90 Expression on their face doesn't match what they are saying

- ○ Not true (1)
- ○ Sometimes true (2)
- ○ Often true (3)
- ○ Almost always true (4)

Q91 Seems self-confident when interacting with others

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q92 When under stress they show rigid or inflexible patterns of behaviour that seem odd

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q93 Doesn't recognise when others are trying to take advantage of them?

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q94 Would rather be alone then with others

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q95 Is aware of what others are thinking or feeling

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q96 Behaves in ways the seem strange or bizarre

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q97 Clings to adults, seems too dependent on them

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q98 Takes things literally and doesn't get the real meaning of a conversation

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q99 Has good self-confidence

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q100 Is able to communicate their feelings to others

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q101 Is awkward in turn-taking interactions with peers (for example, doesn't seem to understand the give-and-take of conversations)

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q102 Is not well coordinated

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q103 Is able to understand the meaning of other people's tone of voice and facial expressions

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q104 Avoids eye contact or has unusual eye contact

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q105 Recognizes when something is unfair

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q106 Has difficulty making friends, even when trying their best

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q107 Gets frustrated trying to get ideas across in conversations

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q108 Shows unusual sensory interests (for example, mouthing or spinning objects or strange ways of playing with toys

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q109 Is able to imitate others actions

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q110 Plays appropriately with children their age

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q111 Does not join group activities unless told to do so

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q112 Has more difficulty than other children with changes in their routine

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q113 Doesn't seem to mind being out of step with or "not the same wavelength" as others

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q114 Offers comfort to others when they are sad

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q115 Avoids starting social interactions with peers or adults

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q116 Thinks or talks about the same thing over and over

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q117 Is regarded by other children as 'odd' or 'weird'

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q118 Becomes upset in a situation with lots of things going on

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q119 Can't get their mind off something once they start thinking about it

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q120 Has good personal hygiene

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q121 Is socially awkward, even when they are trying to be polite

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q122 Avoids people who want to be emotionally close to them

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q123 Has trouble keeping up with the flow of a conversation

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q124 Has difficulty relating to adults

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q125 Has difficulty relating to peers

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q126 Responds appropriately to mood changes in others (for example, when a friend's or playmate's mood changes from happy to sad)

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q127 Has an unusually narrow range of interests

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q128 Is imaginative, good at presenting (without losing touch with reality)

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q129 Wanders aimlessly from one activity to another

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q130 Seems overly sensitive to sounds, textures, or smells

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q131 Separates easily from caregivers

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q132 Doesn't understand how events relate to one another (cause and effect) the way other children of their age do

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q133 Focuses their attention to where others are looking or listening

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q134 Has overly serious facial expressions

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q135 Is too silly or laughs inappropriately

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q136 Has a sense of humour, understands jokes

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q137 Does extremely well at a few tasks, but does not do as well at most other tasks

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q138 Has repetitive, odd behaviours such as hand flapping or rocking

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q139 Has difficulty answering questions directly and ends up talking around the subject

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q140 Knows when they are talking too loud or making too much noise

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q141 Talks to people with an unusual tone of voice (for example, talks like a robot or like they are giving a lecture)

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q142 Seems to react to people as if they are objects

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q143 Knows when they are too close to someone or are invading someone's space

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q144 Walks in between two people who are talking

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q145 Gets teased a lot

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q146 Concentrates too much on parts of things rather than seeing the whole picture (for example, if asked to describe what happened in a story, they may talk only about the kind of clothes the characters were wearing)

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q147 Is overly suspicious

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q148 Is emotionally distant, doesn't show their feelings

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q149 Is inflexible, has a hard time changing their mind

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q150 Gives unusual or illogical reasons for doing things

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q151 Touches others in an unusual way (for example, they may touch someone just to make contact and then walk away without saying anything)

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q152 Is often tense in social settings

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Q153 Stares or gazes off into space

- Not true (1)
- Sometimes true (2)
- Often true (3)
- Almost always true (4)

Page Break

Appendix 9E Wessex Questionnaire

Start of Block: Wessex Questionnaire

Q72 The following questions are about the kind of support your child might need.
If you child requires support in any of the following areas please indicate the frequency of need using the below table.

	Daily (1)	Weekly (2)	Monthly (3)	Never or occasionally (4)
Wetting at night (1)	○	○	○	○
Soiling in the night (2)	○	○	○	○
Wetting in the day (3)	○	○	○	○
Assistance with walking (4)	○	○	○	○
Assistance walking up stairs (5)	○	○	○	○
Eating and drinking (6)	○	○	○	○
Getting dresses (7)	○	○	○	○
Getting washed (8)	○	○	○	○

Q73 Does your child have difficulty with their vision?

- My child has very poor vision or is registered blind (1)
- My child has significant difficulty with their vision (2)
- My child wears corrective glasses (3)
- No problems with vision (4)

Q74 Does your child have difficulty with their hearing?

- My child has very poor hearing or is described as deaf (1)
- My child has significantly poor hearing (2)
- My child wears corrective aids to support hearing (3)
- My child has no problems with their hearing (4)
- Definitely not (5)

Q75 Does your child have difficulty with their speech?

- ○ My child does not use speech (1)
- ○ My child uses a few key words (2)
- ○ My child uses short sentences (3)
- ○ My child chooses not to speak (4)
- ○ My child does not have any speech issues (5)

Q76 If your child talks using sentences is their speech:

- ○ Difficult to understand even by acquaintances and impossible for strangers (1)
- ○ Easily understood for acquaintances, difficult for strangers (2)
- ○ Clear enough to be understood by anyone they speak with (3)

Q77 How well can your child do the following:

	Does not do this (1)	Can do this a little (2)	Can do this well (3)
Read (1)	○	○	○
Write (2)	○	○	○
Counting (3)	○	○	○

End of Block: Wessex Questionniare

Start of Block: Debrief

Q161 **This is the end of the survey. Thank you for taking time to complete it.**
Above this project:
Children and young people with Fragile X Syndrome: Behavioural phenotype and support needs. This study aimed to better understand what the behavioural presentation (phenotypes) of people with Fragile X Syndrome (FXS) looks like and how that differs from Autism Spectrum Condition (ASC). We were also interested in examining service provision patterns in order to understand if people with FXS are having their support needs met as well as if a 'co-occurring diagnosis of ASC' supports the meeting of those needs. The findings from this research may help inform ways of better supporting people with FXS and their families in the future, for example, by tailoring psychological interventions to better meet their needs. You were asked to complete some questionnaires which measured: · Your child's FXS related behaviours · Your perception of unmet needs · Your perception of the educational and other service provision you receive for your child · Your socio-demographic information All the data we collected for this study is confidential, all personal and identifiable information will be kept anonymous and only the researcher relevant members of the research team can access it. If you have any questions or queries about this project, please phone me on 02920870582 or email me at daffinj@cardiff.ac.uk. Alternatively, you can contact my supervisor, Dr Dougal Hare on the above telephone number or email address hared@cardiff.ac.uk .

If you would like to make a complaint please contact Cardiff University School Research Ethics Committee. Details can be obtained by contacting the university on 029 2087 4000. Your participation in this study is greatly appreciated and thank-you again for your time and participation.

Q162 **List of Support Services Children and young people with Fragile X Syndrome: Behavioural phenotype and support needs** Some of the questionnaires used in this study covered potentially sensitive material. If you feel affected by taking to this research and wish to seek additional support or advice, we recommend that you contact one of the following services:

'**Contact a family: For parents of children with disabilities'** www.cafamily.org.uk Telephone support available Monday-Friday, 9.30am to 5.00pm on 0800 808 3555 or email helpline@cafamily.org.uk

Fragile X Society www.fragilex.org.uk Phone: 01371 875100 Email: info@fragilex.org.uk **Dr Dougal Hare**, Clinical Psychologist in the field of Intellectual Disabilities: South Wales Doctoral Programme in Clinical Psychology 11th Floor, Tower Building, 70 Park Place Cardiff, CF11 3AT Email: HareD@cardiff.ac.uk Telephone: 02920 870 582

End of Block: Debrief

Appendix 10 LSRP Diary

Issues

Delay in funding for SRS – find information in emails

Delay in approval form FXS. 26th October 2017 FXS communicate new process. Documetnal sent 1/11/17 – 8/11/17 additional info requested by committee.

29 11 17 provisional approval sent. Two additional questions asked.

10/1/19 – data collection is slow and not hitting numbers

2/3/19 – access to SRS handbook to find out subscales

From FXS description:

Just an aside, this fits with Edelman's 'neural darwinism' mechanism that posits that typical human development is predicated on the experience-dependant pruning of initially over-developed neural networks, resulting in more efficient systems.

2/5/19 Inclusion of ADHD criteria in questionnaire

4/5/19 Can't work out if had ASC test and not given diagnosis vs not taken the test

Appendix 11 Journal of Intellectual Disability Research Author Guidelines

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Note that submission implies that the content has not been published or submitted for publication elsewhere except as a brief abstract in the proceedings of a scientific meeting or symposium.

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It is a requirement that all authors have been accredited as appropriate upon submission of the manuscript. Contributors who do not qualify as authors should be mentioned under Acknowledgements.

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