Movement disorders and catatonia-like presentations in rare genetic syndromes

A thesis submitted to the University of Manchester for the degree of Doctor of Clinical Psychology (ClinPsyD) in the Faculty of Biology, Medicine and Health

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Contents

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Thesis Abstract

This thesis forms part of the examination for the degree of Doctor of Clinical Psychology (ClinPsyD), in the Faculty of Medical and Human Sciences at the University of Manchester. The thesis was written by Louise Handley and submitted in June 2016 for examination in September 2016.

The prevalence of Autism Spectrum Disorder (ASD) and its defining features has been increasingly investigated in genetic syndromes associated with intellectual disability, with syndrome specific profiles reported. The experience of catatonia and other movement disorders in people with ASD has been increasing highlighted within both research and diagnostic guidelines. However, these issues have not typically been investigated alongside other features of ASD within research into genetic syndromes.

The first paper in this thesis provides a review of the literature on movement disorders in genetic syndromes associated with ASD, which focuses on the prevalence of reported movement disorders, the methods of assessment used, and the quality of research to date. An empirical study is reported in Paper 2. Within a cohort of individuals with Cornelia de Lange and Fragile X syndromes the prevalence of attenuated behaviour [autistic catatonia] is examined, based on parent/carer report, and the extent to which features of ASD predict later attenuated behaviour is investigated. Paper 3 provides a critical reflection on the first two papers as well as some wider considerations on undertaking research in this area.

The results of both the literature review and the empirical study indicated that across a number of genetic syndromes (Angelman syndrome, Cornelia de Lange syndrome, Fragile X syndrome and Rett syndrome) attenuated behaviour [autistic catatonia] and/or movement disorders affect a substantial proportion of individuals. Furthermore, repetitive behaviours, one of the characteristic features of ASD, appear to predict later attenuated behaviour in Cornelia de Lange and Fragile X syndromes

The results presented in this thesis have important implications for the way services support individuals with specific genetic syndromes. Paper 1 confirms the high prevalence of movement problems in Angelman and Rett syndromes, and Paper 2 provides a new insight into movement problems in Cornelia de Lange and Fragile X syndromes. Movement disorders are reported to impact negatively on wellbeing and quality of life in people with ASD, and are likely to have a similar impact on the lives of people with genetic syndromes. Greater awareness and recognition of movement problems in CdLS and FXS is required, and although specialist services may already be aware of some of the above issues, there should be an increased emphasis on ensuring that community services are aware of the needs of individuals with genetic syndromes, including the implications of movement problems for support needs and quality of life.

Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

Copyright Statement

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Finally, and in many ways most importantly, I would like to thank my soon to be husband, Dave. As you know this has been tough for me, and in many ways has been an even greater personal challenge than completing my PhD. There were times I felt like giving up, so thank you for being a constant support through the good and bad days of this doctorate, and for giving me the strength to keep going. Thank you for taking over at home on the days when there is just too much to do, and most importantly for showing me that whatever happens there are things in life so much more important than a doctorate.

Paper 1: Movement disorders in genetic syndromes: A systematic review

Word Count

Whole text: 8,781

Main text: 5,133 (excludes tables, figures and references)

Tables and figures word count: 1,455

References word count: 2,193

The following paper has been prepared for submission to *Journal of Applied Research in Intellectual Disabilities.* The guidelines for authors can be found in Appendix A. The formatting of the paper presented here has been altered in order to increase readability. Tables and Figures are presented within the main body of the text, and the line spacing has been set at 2.0.

Abstract

Background Movement disorders can restrict people's independence, particularly for those with additional support needs. No systematic review of movement disorders in genetic syndromes has yet been published. The aim of this review was to summarise and evaluate literature on the prevalence of movement disorders in genetic syndromes.

Method Medline, Embase, PsychINFO and CINAHL were systematically searched for papers published in the last 30 years in English in peer-reviewed journals. Only papers reporting the prevalence of a movement disorder in participants with a genetic syndrome confirmed by DNA analysis were included.

Results Sixteen papers were identified, all relating to Angelman or Rett syndrome. Ataxia was reported in the majority of Angelman syndrome participants. A variety of different movement disorders were identified in Rett syndrome. Methodological bias was common.

Conclusions Movement disorders affect substantial numbers of individuals with genetic syndromes. Services must provide appropriate support to reduce restrictions on quality of life.

Key words: movement disorder, Angelman syndrome, Rett syndrome, review.

1.1 Introduction

Movement disorders have been shown to have a negative impact on quality of life for adults in the general population (Dodel & Shrag 2010; López-Bastida *et al.* 2008). For those who are already limited in terms of their communication and adaptive or social functioning, such as individuals with intellectual disabilities (ID) and/or Autism Spectrum Disorder (ASD), the additional impact of a movement disorder is likely to place even greater restrictions on independence and quality of life. A number of first-hand reports highlight the difficulties experienced by individuals with ASD as a result of movement disorders in addition to other aspects of autism (e.g., Robeldo *et al.* 2012).

Movement disorders have been frequently identified in individuals with ASD, with ataxia reported in a number of studies (see Fatemi & Folsom 2013), as well as akinesia, dyskinesia, bradykinesia, Tourette syndrome, and catatonic-like symptoms among others (see Donnellan *et al.* 2013; Leary & Hill 1996), with cerebellum and basal ganglia dysfunction being implicated (see Nayate *et al.* 2005), resulting in some researchers proposing that ASD could be, at least in part, a disorder of movement (Nayate *et al.* 2005). However, the extent to which movement disorders may be linked to autistic traits *per se* in those without idiopathic autism is less clear. Features of ASD have been reported in various genetic neurodevelopmental syndromes (Moss & Howlin 2009). There are clear differences in the specific profile of such autistic traits across different genetic syndromes (e.g., Cochran *et al.* 2015; Moss *et al.* 2009, 2013), which may point to different underlying genetic and neurological mechanisms (e.g., Woodcock *et al.* 2010, 2011).

For some genetic syndromes associated with ASD, movement disorders form part of the consensus criteria for clinical diagnosis, such as in the case of ataxia in Angelman syndrome (Williams *et al.* 2006), whilst in others the clinical picture is less clear. To date, the description of movement disorders in genetic syndromes has traditionally taken the form of case reports (e.g., Fernandez *et al.* 2000; Holm 1985; Lawson-Yeun *et al.* 2006; Smith *et al.* 1998; Wright *et al.* 1992) but this does not permit estimation of prevalence, without which it is not possible to make comparisons across different genetic syndromes, and to examine whether different phenotypic profiles emerge. Similarly, case descriptions have typically been based on clinical observation and judgement (e.g., Bottani *et al.* 1994; Lawson-Yeun *et al.* 2006; Smith *et al.* 1998). However, the confidence with which any conclusions can be made regarding the prevalence of movement disorders is dependent in part on the reliability and validity of the method of assessment and the overall quality of the research. To date, there has been no systematic review of the extant literature on the prevalence of movement disorders in genetic syndromes.

1.1.1 Aims

The aims of this systematic review were to summarise data on the prevalence of movement disorders in a number of different genetic syndromes, to describe the range of assessment methods used in the diagnosis of movement disorders, and to evaluate the quality of research in this area. Selection of syndrome groups for inclusion was predicated on the known rates of ASD (Moss & Howlin 2009; Richards *et al.* 2015). On this basis, Angelman syndrome, CHARGE syndrome,

Cohen syndrome, Cornelia de Lange syndrome, Fragile X syndrome, Rett syndrome and Tuberous Sclerosis Complex were identified as the basis of the current review.

1.2 Method

The guidelines set out in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (Moher *et al.* 2009) were followed where possible (see Appendix B).

1.2.1 Search strategy

An electronic literature search was performed by the first author [LH] on 1st April 2016 to identify papers published between 1985 and 2015, across four separate databases: Medline, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and PsychINFO. Search terms relating to any one of the seven genetic syndromes were combined with terms relating to movement disorders, using the 'AND' function. MESH/subject headings were used where possible. Selection of search terms for each of the genetic syndromes was based on the synonyms provided by the National Organisation for Rare Disorders (2016). The full list of search terms is provided in Table 1. Searches across each database were limited to journal articles published in the English language that pertained to human participants. The reference lists of relevant papers were examined for other potentially relevant studies not identified through the database search.

Table 1: Summary of search terms	
Angelman syndrome	'angelman' OR 'happy puppet' OR Angelman Syndrome (MESH term) OR happy puppet syndrome (MESH term)
CHARGE syndrome	'charge syndrome' OR 'hall-hittner' OR 'hall hittner' OR CHARGE syndrome (MESH term)
Cohen syndrome	'cohen' OR 'pepper syndrome' OR Cohen Syndrome (MESH term)
Cornelia de Lange syndrome	'cornelia de lange' OR 'cornelia-de-lange' OR 'brachmann de lange' OR 'brachmann-de-lange' OR 'cdls' OR 'bdls' OR 'de lange' OR 'de-lange' OR 'amsterdam syndrome' OR Cornelia de Lange Syndrome (MESH term) OR De Lange Syndrome (MESH term)
Fragile X syndrome	'fragile x' OR 'fragile-x' OR 'fragile site' OR 'fxs' OR 'fra(X)' OR 'fraX' OR 'FMRP' OR 'marker x' OR 'martin-bell' OR 'martin bell' OR 'x-linked mental retardation' or Fragile X Syndrome (MESH term) OR Mental Retardation, X-Linked (MESH term)
Rett syndrome	'rett' OR 'rtt' OR Rett Syndrome (MESH term)
Tuberous Sclerosis Complex	'tuberous sclerosis' OR 'tuberose sclerosis' OR 'TSC' OR 'phakomatosis ts' OR 'bourneville pringle' OR Tuberous Sclerosis (MESH term)
Movement disorder	'movement' OR 'motor' OR 'movement disorder*' OR 'ataxi*' OR 'apraxi*' OR 'gait OR 'tremor' OR 'parkinson*' OR 'dyskinesia' OR 'akinesia' OR 'cataton*' OR Movement (MESH term) OR Motor Skills Disorder (MESH term) OR Movement Disorders (MESH term) OR Ataxia (MESH term) OR Apraxias (MESH term) OR Gait (MESH term) OR Gait Disorders (MESH term) OR Tremor (MESH term) OR Parkinsonian Disorders (MESH term) OR Dyskinesias (MESH term) OR Catatonia (MESH term)

1.2.2 Inclusion and exclusion criteria

Studies were required to meet the following inclusion criteria:

1. Written in the English language
2. Published as a full length report in a peer-reviewed journal
3. Provide a clear description regarding the recruitment/selection of participants
4. Provide information regarding the age/age range of participants
5. Specify individuals with Angelman syndrome, CHARGE syndrome, Cohen syndrome, Cornelia de Lange syndrome, Fragile X syndrome, Rett syndrome or Tuberous Sclerosis Complex syndrome as the main population being researched
6. Include participants whose genetic syndrome has been confirmed through DNA analysis
7. Provide a description of the assessment tool or procedure used
8. Report on identified movement disorder, defined as *a neurological condition resulting in abnormal or slowed movement*

If papers included participants both with and without genetic confirmation of the syndrome of interest, they were only included if data were presented separately for those with and without genetic confirmation by DNA analysis. Studies were excluded if they did not constitute a stand-alone paper/ full length report (e.g., letters to the editor, commentaries, published conference abstracts), if they related to developmental motor skills or to biomechanical aspects of movement (such as

scoliosis or hypotonia), if participants were selected on the basis of having an identified movement disorder, or if they provided insufficient detail to determine eligibility for inclusion in the review. Studies reporting on stereotyped movements were not included for the purposes of the current review, as the prevalence of repetitive and stereotyped behaviours in genetic syndromes has been described elsewhere (e.g., Moss *et al.* 2009), and stereotypy may sometimes be considered a functional behaviour (Cunningham & Schreibman 2008).

1.2.3 Data extraction

Data relating to the prevalence of any specified movement disorder were extracted from all included papers. In addition to prevalence data, authors, year of publication, sample size and characteristics, recruitment method, genetic mechanism and method of assessment were recorded for each study.

1.2.4 Quality assessment

Relatively few quality rating tools are available for the evaluation of studies of prevalence, and there is wide variability in the quality of those tools which are available (see Sanderson *et al.* 2007). For the current study the risk of bias assessment initially developed by LeBoeuf-Yde and Lauritsen (1995) and later revised by Hoy *et al.* (2012) was used (see Appendix C). Hoy and colleagues (2012) reported good inter-rater reliability for their risk of bias assessment as well as positive feedback regarding the ease of use of this measure. Studies are rated as 'High' versus 'Low' risk of bias across ten domains, which relate to the internal and external validity of

the findings. An overall summary rating of 'Low', 'Moderate' or 'High' risk was made, based on responses across the ten items. Hoy and colleagues do not provide specific guidelines for the summary ratings. Within the current review individual items were scored 0 ('Yes') or 1 ('No'). Item scores were summed to determine the overall summary rating, with scores of 0-2 being rated 'Low', 3-7 rated 'Moderate' and 8-10 rated 'High'. For the current review a second independent rater scored 50% of papers. A Kappa of .53 was obtained for the overall risk of bias rating, indicating fair reliability (Fleiss, 1981).

1.3 Results

The initial database search returned a total of 2,001 papers, of which 309 were duplicates. A further 26 papers were identified through the reference lists of papers identified in the initial search. After screening of titles and abstracts 93 potentially relevant papers were identified. Of these 93 papers 16 were identified as meeting the criteria for inclusion in the review. The PRISMA diagram (Moher *et al.* 2009) presented in Figure 1 provides a summary of the search results, including the reasons for exclusion of papers. All of the 16 papers meeting criteria for inclusion related to individuals with either Angelman syndrome or Rett syndrome. Of all 16 studies identified, only three focused explicitly on disorders of movement. In the remaining studies movement disorders were reported as part of a broader description of clinical characteristics. Results are reported separately by syndrome, and an overview of common methodological issues across all papers is also

provided. A summary of all 16 papers is provided in Table 2 and a full breakdown of quality ratings for each paper is provided in Table 3.

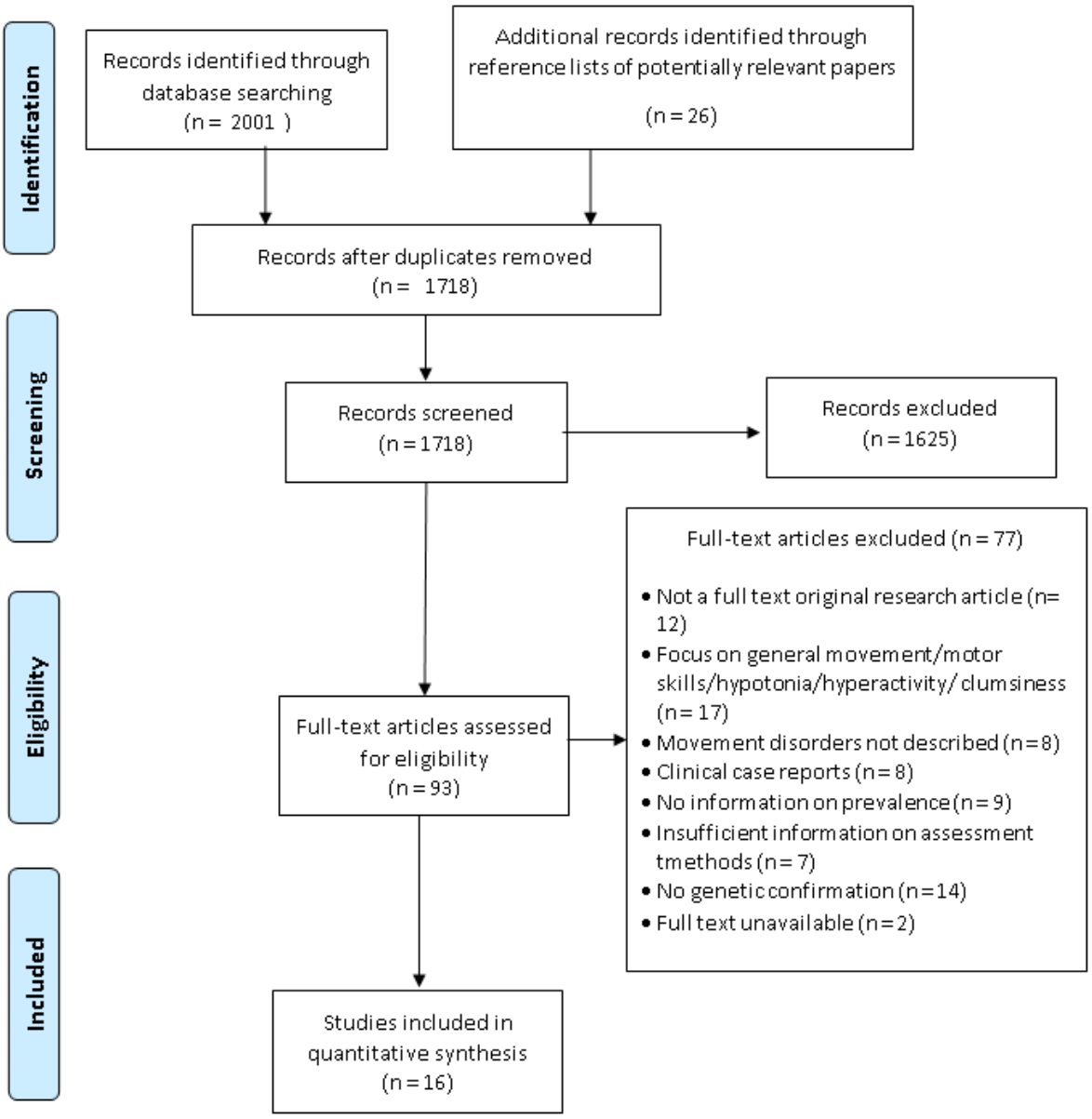

Figure 1: PRISMA diagram depicting selection procedure for papers

Table 2: Sample characteristics, methodology, and quality assessment for studies reporting the prevalence of movement disorders in Angelman syndrome and Rett syndrome

Authors	Syndrome	N	% Male	Age Range *(M, SD)*	Genetic mechanism	Recruitment information	Assessment method	Movement disorders identified	% prev. (*N*)	Risk of Bias
Bai et al. (2014)	Angelman	30	50.0	2.7-9.6 years at last observation (M 5.3yrs, SD 2.1yrs)	Deletion	Sample of children with Angelman syndrome in China – recruitment method not specified.	Purpose-made questionnaire based on clinical criteria	Ataxic movement	100% (24) of those able to walk	Moderate
Beckung *et al.* (2004)	Angelman	11	Unclear for subgroup with DNA confirmation	Unclear for subgroup with DNA confirmation	Not reported	Individuals referred to a Children's Hospital in Sweden for investigation of Angelman syndrome	Extensive clinical investigation – movement problems classified based on performance	Gait ataxia Tremor	72.7% (8) 27.3% (3)	Moderate
Buoni *et al.* (1999)	Angelman	11	54.5	1yr 6 months to 15 yrs at last observation (Not reported)	10 deletion 1 UPD	Genetic screening of 144 patients at Paediatric Institute	Medical records, history and clinical examination	Ataxia	100% (11)	Moderate
Clayton-Smith (2001)	Angelman	28	42.9	16-40 years (Not reported)	19 deletion 7 UBE3A mutation 1UPD 1 imprinting defect	Participated in a previous study or seen personally by the author	Medical notes, parent/carer-reported history and clinical examination	Ataxic gait Worsening Tremor	100% (28) 25.0% (7)	Moderate

Table 2 continued

Authors	Syndrome	N	% Male	Age Range *(M, SD)*	Genetic mechanism	Recruitment information	Assessment method	Movement disorders identified	% prev. (*N*)	Risk of Bias
Guerrini *et al.* (2006)	Angelman	11	45.5	3-28 years (Not reported)	8 deletion 2 UPD 1 microdeletion	Unclear	Rated scale score based on observation	Jerky, tremulous, dystonic movement	100% (11)	Moderate
Moncla *et al.* (1999)	Angelman	14	57.1	9 months – 33 years at diagnosis (Not reported)	All UBE3A mutation	Referred to the authors in Department of Genetic Medicine	Clinical history, anthropometric data and physical and neurological findings	Ataxia	100% (14) total 21.4% (3) typical 21.4% (3) mild 57.1% (8) extremely mild	Moderate
Saitoh *et al.* (1994)	Angelman	40	47.5	Unclear	37 deletion 3 sub-microscopic deletion	Large sample of individuals with Angelman syndrome in Japan – recruitment method not specified	Questionnaires completed by physicians	Ataxic movement	97.1% (34) of those for whom ataxic movement data reported	High
Sandanam *et al.* (1997)	Angelman	11	81.8	24-36 years at last review (M 31.5 yrs)	All deletion	Genetic screening of residents of 2 residential institutions	Review of records, history and clinical examination completed by 2 clinicians	Ataxic gait	100% (9) of those able to walk	Moderate

Table 2 continued

Authors	Syndrome	N	% Male	Age Range *(M, SD)*	Genetic mechanism	Recruitment information	Assessment method	Movement disorders identified	% prev. (*N*)	Risk of Bias
Smith *et al.* (1996)	Angelman	27	33.3	3-34 years at last review (M 11.2 yrs)	Deletion	Referrals for genetic testing from physicians across Australia and New Zealand as part of a research grant.	Data sheet based on clinical criteria plus medical records, parent interviews, photos and videos where available, and either correspondence with referrer or clinical examination by authors.	Ataxia – wide-based gait, unsteadiness with jerky movements or thumping heavy gait	100% (27)	Moderate
Smith *et al.* (1997)	Angelman	4	50.0	7-11 years (M 8 yrs)	Uniparental disormy	As above	Data sheet based on clinical criteria, plus medical records, parent interviews and correspondence with referrer.	Ataxia	100% (4) total 75% (3) mild and most evident when excited	High
Tan *et al.* (2011)	Angelman	92	54.3	5-60 months (Median 33.5 months)	68 deletion 13 UPD/ imprinting 11 UBE3A mutation	Part of a multi-centre study with enrolment through support groups and referral from professionals	Structured medical history and physical examination by a clinical geneticist	Ataxic gait	87.8% (36) of those able to walk 95.5% (21) deletion 72.7% (8) UPD/imprinting 87.5%(7) UBE3A	Moderate

Table 2 continued

Authors	Syndrome	N	% Male	Age Range *(M, SD)*	Genetic mechanism	Recruitment information	Assessment method	Movement disorders identified	% prev. (*N*)	Risk of Bias
Zori *et al.* (1992)	Angelman	16	Unclear	Unclear - children	Deletion	American families with a child with Angelman syndrome – recruitment method not specified for these families	Family questionnaire assessing clinical, cytogenetic and developmental variables, plus physical examination and lab data	Ataxic gait Jerky gait	81.3% (13) 93.8% (15)	Moderate
Bartholdi *et al*. (2006)	Rett	4	0	4-19 years at last observation (Not reported)	Exon 1 mutation/ genomic rearrangement in MECP2	Recruited from a larger cohort of individuals with Rett syndrome in Switzerland. No further details.	Medical records and clinical examination	Gait ataxia	25,% (1), 50% of those walking	Moderate
Einspieler *et al.* (2005)	Rett	12	0	0-6 months (Not reported)	6 truncating mutations, 3 missence mutations, 2 deletions, 1 substitution at 401	Videotapes donated by British families to the project	Videotapes analysed by two observers	Tremor Abnormal general movement	27.3% (3) 100% (9)	Moderate

Table 2 continued

Authors	Syndrome	N	% Male	Age Range *(M, SD)*	Genetic mechanism	Recruitment information	Assessment method	Movement disorders identified	% prev. (*N*)	Risk of Bias
Smeets *et al.* (2005)	Rett	10	0	3-54 years at diagnosis (Not reported)	Hotspot deletion in C-terminal segment of MECP2	Seen by first author clinically – Clinical Genetics Department in a University Hospital in Belgium	Observed and assessed by first author and parents/carers	'Awkward' walking pattern Short stiff steps as seen in Parkinson's disease	20.0% (2) 10.0% (1)	Moderate

Table 2 continued

Authors	Syndrome	N	% Male	Age Range *(M, SD)*	Genetic mechanism	Recruitment information	Assessment method	Movement disorders identified	% prev. (*N*)	Risk of Bias
Temudo *et al.* (2008)	Rett	60	Not reported. Not all female.	5-13.5 years (Median 7.0)	26 missence mutations, 34 truncating mutations	Referred to the project by any Paediatric Neurologist across Portugal	Motor-Behavioral Assessment Scale for Rett syndrome	Ataxia	35.0% (21) 46.2% (12) Missence (M) 26.5% (9) Truncating (T)	Moderate
								Ataxic/rigid gait	43.6% (unclear) 36.8% M 50.0% T	
								Dystonia	63.3% (38) 46.2% (12) M 76.5% (26) T	
								Rigidity	48.3% (29) 34.6% (10) M 58.8% (20) T	
								Pyramidal signs	28.3% (17) 23.1% (6) M 32.4% (11) T	
								Tremor	48.3% (29) 50.0% (13) M 47.1% (16) T	

Table 3: Summary of risk of bias ratings given to each paper

Author	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Summary rating
Angelman syndrome papers											
Bai *et al.* (2014)	High risk	High risk	High risk	High risk	High risk	High risk	High risk	Low risk	Low risk	Low risk	Moderate
Beckung *et al.* (2004)	High risk	High risk	High risk	High risk	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Moderate
Buoni *et al.* (1999)	High risk	High risk	High risk	High risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk	Moderate
Clayton-Smith (2001)	High risk	High risk	High risk	High risk	High risk	High risk	High risk	Low risk	Low risk	Low risk	Moderate
Guerrini *et al.* (1996)	High risk	High risk	High risk	High risk	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Moderate
Moncla *et al.* (1999)	High risk	High risk	High risk	High risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk	Moderate
Saitoh *et al.* (1994)	High risk	High risk	High risk	High risk	High risk	High risk	High risk	Low risk	High risk	High risk	High
Sandanam *et al*. (1997)	High risk	High risk	High risk	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk	Moderate
Smith *et al.* (1996)	Low risk	High risk	High risk	High risk	High risk	Low risk	High risk	High risk	High risk	Low risk	Moderate
Smith *et al.* (1997)	Low risk	High risk	High risk	High risk	High risk	High risk	High risk	Low risk	High risk	High risk	High
Tan *et al.* (2011)	High risk	Low risk	Low risk	High risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk	Moderate
Zori *et al.* (1992)	Low risk	High risk	High risk	High risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk	Moderate

Table 3 continued

Author	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Summary rating
Rett syndrome papers											
Bartholdi *et al.* (2006)	High risk	High risk	High risk	High risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk	Moderate
Einspieler *et al.* (2005)	High risk	High risk	High risk	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate
Smeets *et al.* (2005)	High risk	High risk	High risk	High risk	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Moderate
Temudo *et al.* (2008)	Low risk	Low risk	Low risk	High risk	Low risk	High risk	High risk	Low risk	Low risk	High risk	Moderate

1.3.1 Movement disorder in Angelman syndrome

Out of the 16 papers identified, 12 related to movement disorder in Angelman syndrome and could be broadly categorised into those based on clinical assessment (clinical examination, medical records and/or history taking) and those utilising idiosyncratic questionnaires. Several papers reported clinical characteristics across larger cohorts of individuals, some of whom were diagnosed based only on clinical criteria (Beckung *et al.* 2004; Buoni *et al.* 1999; Saitoh *et al.* 1994; Zori *et al.* 1992). In each case, results are only reported for the sub-group of individuals with genetic confirmation of Angelman syndrome.

Papers examining movement disorders in Angelman syndrome were focused almost exclusively upon the presence of ataxic/jerky movements, considered phenotypic of Angelman syndrome (Williams *et al.* 2006), with three exceptions (Beckung *et al.* 2004; Clayton-Smith 2001; Guerrini *et al.* 1996). The number of participants included in the studies ranged from four to 92, due in part to the underlying genetic mechanism, with the smallest sample (Smith *et al.* 1997) being made up exclusively of individuals with uniparental disomy (UPD), a less common mechanism in Angelman syndrome than maternal deletion (see Williams *et al*. 2010). The 12 papers covered a broad range of ages, with five studies focused exclusively on children (Bai *et al.* 2014; Buoni *et al.* 1999; Smith *et al.* 1997; Tan *et al.* 2011; Zori *et al.* 1992), two exclusively on adults (Clayton-Smith 2001; Sandanam *et al.* 1997), and three focused on children and adults (Guerrini *et al.* 1996; Moncla *et al.* 1999; Smith *et al.* 1996). For the remaining two studies (Beckung *et al.* 2004; Saitoh *et*

al. 1994) it was not possible to determine the age of the subgroup of individuals with genetically confirmed Angelman syndrome.

The risk of bias was variable across studies. Whilst the majority were considered to be at moderate risk of bias, there were two exceptions to this. Saitoh *et al.*'s (1994) and Smith *et al.*'s (1996) papers were both judged to be at high risk of bias. None of the 12 papers reported on the validity or reliability of the assessment method for movement disorders. Whilst clinical assessment may be considered most analogous to the means by which movement disorders are typically diagnosed in medical practice, none of the studies report evidence to support the reliability or validity of this method. One paper (Sandanam *et al.* 1997) did report using at least two clinicians for each assessment, which might be expected to increase the reliability of the clinical judgements made, but it was not possible to determine whether this was the case, and inter-rater reliability information was not provided. Whilst the use of a questionnaire or data sheet might ensure consistency in the information asked of each informant, the likely accuracy of this information was unclear, as none of the studies using questionnaire methods (Bai *et al.* 2014; Saitoh *et al.* 1994; Smith *et al.* 1996, 1997; Zori *et al.* 1992) reported on the psychometric properties of their purpose-made measures.

The reported prevalence of ataxic/jerky movements in Angelman syndrome ranged from 72.7% (Beckung *et al.* 2004; Tan *et al.* 2011) to 100% (Bai *et al.* 2014; Buoni *et al.* 1999; Clayton-Smith 2001; Moncla *et al.* 1999; Sandanam *et al.* 1997; Smith *et al.*, 1996, 1997), across the 11 studies that provided prevalence estimates. In those with a non-deletion mechanism, ataxic/jerky movement was often reported to be milder

or less prevalent (e.g., Moncla *et al.* 1999; Tan *et al.* 2011; Smith *et al.* 1997). Two studies also reported on the prevalence of tremor in individuals with Angelman syndrome. The prevalence estimates of 27.3% (Beckung *et al.* 2004) and 25.0% (Clayton-Smith 2001) appeared relatively consistent and indicated that around a quarter of individuals were affected by tremor, although Clayton-Smith did not elaborate on what is meant by 'worsening tremor'. Finally, one study reported that all participants presented with a jerky, tremulous, dystonic movement, which was determined to be a result of cortical myoclonus (Guerrini *et al.* 1996).

1.3.2 Movement disorder in Rett syndrome

Four papers relating to Rett Syndrome were identified and are summarised in Table 2. One of these papers (Einspieler *et al.* 2005) included participants with and without genetically confirmed Rett syndrome, therefore calculated prevalence rates were based only on those with an identified genetic mechanism. All studies were published in the last 11 years, which is probably due to the relatively recent progress in understanding the genetic basis of Rett syndrome (Amir *et al.* 1999), which was only fully defined clinically in the 1980s (Hagberg *et al*. 1985). The sample size of studies varied between four and 60 participants and, again, this was partly dependent on the underlying genetic mechanism. Bartholdi *et al.*'s (2006) study consisted of four girls with Rett syndrome, but the focus of their report was on describing the clinical findings in individuals with relatively uncommon underlying mechanisms, namely exon 1 mutations and genomic rearrangements in MECP2. Three of the four studies focused on children and adolescents (Bartholdi *et*

al. 2006; Einspieler *et al.* 2005; Temudo *et al.* 2008). Only one adult was identified (Smeets *et al.* 2005), which may reflect greater interest in the characteristic regression period that begins in childhood (see Hagberg 2002; Neul *et al.* 2010).

Recruitment methods differed across each of the studies, including self-selection (Einspieler *et al.* 2005), referral by relevant clinicians (Temudo *et al.* 2008), retrospective study of individuals seen by the author in clinical practice (Smeets *et al.* 2005) and recruitment of individuals from an existing cohort (Bartholdi *et al.* 2006). Similarly, the methods of assessment used varied, with two studies (Bartholdi *et al.* 2006; Smeets *et al.* 2005) reliant on clinical examination and/or medical records whilst the other researchers developed idiosyncratic assessment methods for the identification of movement disorders. In the case of the latter, Temudo *et al.* (2008) did not report the psychometric properties of their Motor-Behavioral Assessment Scale, whilst Einspieler *et al.* (2005) reported 94% agreement between raters and 92% test-retest agreement.

The risk of bias was moderate across each of the studies, with Bartholdi and colleagues' (2006) study methods and reporting being the most susceptible to bias. Across each of the studies, particular concerns were identified in relation to the lack of information on the representativeness of the sample and possible selection bias. However, relative strengths of each of the studies were that the same mode of data collection was applied for all participants, and participants were directly observed by the authors.

It was possible to obtain a prevalence estimate for seven different aspects of disordered movement within Rett syndrome. Two studies provided information on

ataxic gait (Bartholdi *et al.* 2006; Temudo *et al.* 2008), with prevalence estimates relatively consistent despite different underlying genetic mechanisms. Between 43.6%-50.0% of those able to walk were reported to show ataxic gait. Tremor was also examined across two separate studies, but the estimated prevalence varied from 27.3% in young infants (Einspieler *et al.* 2005) to 48.3% in older children (Temudo *et al.* 2008). Some form of abnormal general movement was recorded in 100% of 0-6-month-olds observed by Einspieler and colleagues. They describe this as an absence of normal fidgety movements, jerky or abnormally slow movements, or abrupt and disorganised movements, present in 30%, 35% and 35% of children, respectively.

In Temudo *et al.*'s (2008) study, various additional movement problems were identified. Ataxia was reported in 35.0% of children, dystonia in 63.3%, rigidity in 48.3% and pyramidal signs in 28.3%. There were some apparent differences in prevalence dependent on underlying genetic mechanisms, with ataxia reported in 46.2% and 26.5% of individuals with missense and truncating mutations, respectively, dystonia reported in 46.2% and 76.5%, respectively, rigidity reported in 34.6% and 58.8%, respectively, pyramidal signs reported in 23.1% and 32.4%, respectively, and ataxic gait reported in 36.8% and 50.0%, respectively. However, Temudo and colleagues did not report on the significance of these group differences.

1.3.3 Common themes in relation to quality of research

There were common issues in all 16 of the papers included in the current review. Regarding external validity of the research, nine of the studies did not describe recruitment methods in sufficient detail to allow judgements to be made regarding the representativeness of the sampling frame, possible selection bias within the sampling frame, or the likelihood of response bias (Bai *et al.* 2014; Bartholdi *et al.* 2014; Buoni *et* al. 1999; Clayton-Smith 2001; Guerrini *et al.* 1996; Moncla *et al.* 1999; Saitoh *et al.* 1994; Smeets *et al.* 2005; Zori *et al.* 1992). Whilst two studies referred to recruitment from a larger cohort or participants of a previous study, the recruitment of participants into these original cohorts was not described. A further three studies relied on a sampling frame that may not have been representative of the target population and did not use random selection or consensus sampling within their sampling frame (Beckung *et al.* 2004; Einspieler *et al.* 2005; Sandanam *et al.* 1997). For example, Sandanam and colleagues recruited their sample through institutional settings only and did not genetically screen all of the residents for possible Angelman syndrome. Issues of possible response bias were rarely discussed, possibly because information was collected through routine clinical assessment in many cases.

Regarding internal validity, only five studies provided any definition for the movement disorder in question (Beckung *et al.* 2004; Einspieler *et al.* 2005; Guerrini *et al.* 1996; Smeets *et al.* 2005; Smith *et al.* 1996) and the reliability of the assessment method was reported in only one study (Einspieler *et al.* 2005). In four studies (Bai *et al.* 2014; Saitoh *et al.* 1994; Smith *et al.* 1996, 1997) no direct observation of the

participants was conducted by the authors, increasing the risk of bias in these estimates. In one further study (Clayton-Smith 2001), it was unclear whether the entire sample had been examined clinically by the author.

In terms of the relative strengths of the research under review, all but one paper (Smith *et al.* 1996) applied the same methods to each of the study participants, and with two exceptions (Saitoh *et al.* 1994; Temudo *et al.* 2008), all of the studies provided an appropriate numerator and denominator for the calculation of prevalence.

1.4 Discussion

This was the first paper to systematically review and evaluate research on the prevalence of movement disorders in genetic syndromes associated with ASD, and to report on the range of assessment methods used for the identification of movement disorders within this population. More specifically, the review was designed to focus on movement disorders in Angelman syndrome, CHARGE syndrome, Cohen syndrome, Cornelia de Lange syndrome, Fragile X syndrome, Rett syndrome and Tuberous Sclerosis Complex. Of the 16 studies meeting the inclusion criteria, 12 related to Angelman syndrome and four to Rett syndrome. No studies relating to any of the other syndromes met the criteria for inclusion. The over-representation of Angelman and Rett syndrome among the results of the review may reflect the fact that movement disorders are considered part of the diagnostic criteria in these groups (Neul *et al.* 2010; Williams *et al.* 2006).

Assessment methods included clinical assessment (clinical examination, medical records and/or clinical history taking), questionnaires and assessment scales, and a video observation method used in one study (Einspieler *et al.* 2005). The majority of studies in relation to Angelman syndrome focused on ataxia or ataxic/jerky gait. Perhaps unsurprisingly, given that ataxia is considered to be a diagnostic characteristic of Angelman syndrome (Williams *et al.* 2006), a number of studies reported a 100% prevalence rate, with the lowest reported prevalence being 72.7% in those with uniparental disomy (UPD) or an unspecified underlying genetic mechanism (Beckung *et al.* 2004; Tan *et al.* 2011). Tremor was reported in around a quarter of individuals with Angelman syndrome (Beckung *et al.* 2004; Clayton-Smith 2001). Ataxic movements were reported less commonly in Rett syndrome, affecting 50% or fewer individuals (Bartholdi *et al.* 2006; Temudo *et al.* 2008). Other movement problems were reported in Rett syndrome, including dystonia in 63.3% and pyramidal signs in 28.3% (Temudo *et al.* 2008). The prevalence of tremor was estimated at 27.3% in young children (Einspieler *et al.* 2005), similar to the prevalence in Angelman syndrome, although for older children this rose to 48.3% (Temudo *et al.* 2008).

Across the majority of studies, moderate levels of bias were introduced into the findings, due to issues such as lack of detail in reporting recruitment methods, absence of reliability and validity information for the assessment methods used, and failure to provide a definition for the movement disorders reported.

1.4.1 Strengths and limitations

The results here have added to our overall understanding of the phenotypes of Angelman and Rett syndromes, as well as highlighting important gaps in the literature. Each study was evaluated for methodological bias, using an appropriate evaluation tool with relatively good reliability (Hoy *et al.* 2012).

The conclusions that can be reached about movement disorders in genetic syndromes are somewhat limited by the lack of available cohort studies in relation to CHARGE syndrome, Cohen syndrome, Cornelia de Lange syndrome, Fragile X syndrome and Tuberous Sclerosis Complex, as well as the level of methodological bias identified in those studies reporting on the prevalence of movement disorders in Angelman and Rett syndromes. In order to increase the level of confidence in reported prevalence data, future research should focus on developing valid and reliable assessment tools for identifying movement disorders in these groups, and these should be based on standardised definitions. Authors must also ensure that recruitment methods are reported in sufficient detail.

In terms of the review strategy presented here, it could be argued that the requirement for an underlying genetic mechanism to be identified would have led to the exclusion of a number of potentially relevant studies, as in some cases advances in our understanding of the underlying mechanisms have occurred only relatively recently (e.g., Amir *et al.* 1999; Kolehmainen *et al.* 2003; Krantz *et al.* 2004). All but one of the papers excluded based on the absence of DNA confirmation of the genetic syndrome related to Angelman or Rett syndrome. The other study excluded on this basis related to a small cohort of children with Cornelia de Lange

syndrome. In their sample of five children, Leroy *et al.* (1993) reported a wide-based unsteady gait in two out of the three children able to walk. Although the criterion for genetic confirmation led to the exclusion of a number of papers, it was deemed necessary to reduce the bias introduced by examining the prevalence of specific clinical characteristics in a clinically defined sample. This appears particularly important, given that 11 out of 12 studies in Angelman syndrome focused primarily on ataxic/jerky gait, which is one of the criteria for clinical diagnosis (Williams *et al.* 2006). Similarly, case reports were excluded from this review. Whilst they do not contribute to estimates of prevalence, such papers can provide valuable insights into movement disorders in individuals with genetic syndromes. For example, one notable paper described presentations of Gilles de la Tourette syndrome and tic disorder in five individuals with Fragile X syndrome (Schneider *et al.* 2008). Other case reports have described issues such as chorea in a woman with Tuberous Sclerosis Complex (Wright *et al.* 1992) and Parkinsonian symptoms in a man with probable Cornelia de Lange syndrome (Fernandez *et al.* 2000).

Although it is possible that the selected search terms did not capture each specific movement disorder that has been described in the population of interest, due to the vast number of possible movement disorders, it is also likely that the broader search terms such as 'movement disorder' captured the majority of relevant papers. For example, papers in relation to tics (Schneider *et al.* 2008) and extrapyramidal signs (Fitzgerald *et al*. 1990; Temudo *et al.* 2008) were identified, despite the fact that search terms specific to these disorders were not used.

1.4.2 Implications and future research

The results of this review indicate that the majority of individuals with Angelman syndrome and Rett syndrome experience some form of movement disorder, confirming clinical diagnostic criteria for these syndromes. However, the specific profile of movement disorders appeared to vary across syndrome, with ataxic/jerky gait being more prevalent in Angelman syndrome than Rett syndrome, and a conversely greater proportion of people with Rett syndrome experiencing tremor, at least in older children. Therefore, the specific difficulties experienced by individuals as a result of disordered movement, and the corresponding support needs of these individuals is likely to differ significantly across different genetic syndromes. In line with findings in relation to ASD (Fatemi & Folsom 2013) a substantial number of individuals with both Angelman and Rett syndrome exhibited ataxic gait. However, the finding of higher rates of ataxia in Angelman syndrome despite a lower prevalence of ASD than Rett syndrome (Richards *et al*. 2015) indicates that syndrome specific differences may be a more important factor than the presence of ASD *per se*. Future studies should examine directly the association between movement disorders and specific features of ASD in groups of individuals without idiopathic autism.

Interestingly, though the majority of individuals with Rett syndrome experienced some form of disordered movement, the findings of the review highlighted that no one movement problem was experienced by all individuals. Therefore, it is important that clinicians assess the idiosyncratic profile of difficulties in children with Rett syndrome. Furthermore, the papers included in the current

review almost exclusively reported on findings in children. High quality research into movement disorders in *adults* with Rett syndrome is therefore required.

As well as causing possible discomfort and distress, issues such as ataxia, tremor, dystonia and other involuntary movements are likely to pose serious limitations on the ability of people with Angelman and Rett syndrome to engage in a variety of activities without significant support. The results of this review confirm previous clinically derived diagnostic criteria. Whilst movement problems in these syndrome groups are already recognised by specialist services, it is important to increase awareness within community services, where syndrome specific needs and support have historically often not been emphasised (see Hare *et al.*, in press).

The overall lack of research into the prevalence of movement disorders in the majority of genetic syndromes investigated here may relate to the wider issue of diagnostic overshadowing (Reiss *et al.* 1982), whereby movement problems are seen as part and parcel of having either ASD or an intellectual disability and clinicians and researchers alike therefore fail to investigate and identify specific disorders of movement. Leary and Hill (1996) found evidence to suggest that the same movement disorders that might be attributed to neurological disorder in other individuals are more likely to be perceived as behavioural in people with ASD. Future research should build on clinical case reports to examine the prevalence of identified movement disorders within larger cohorts of individuals with a specific genetic syndrome. Consideration should also be given to possible differences according to the underlying genetic mechanism.

1.4.3 Conclusions

Sixteen papers met the criteria for inclusion within the current literature review and related to the prevalence of movement disorders in Angelman syndrome and Rett syndrome. The review highlighted that the majority of individuals with both Angelman and Rett syndrome were affected by some form of movement disorder, with up to 100% of people with Angelman syndrome displaying ataxia, and the majority of those with Rett syndrome exhibiting dystonia. However, issues with methodological bias were consistently identified across studies. These findings highlight the need for services to acknowledge and assess for movement disorders when supporting individuals with Angelman and Rett syndromes. The risks posed to the person's physical and emotional wellbeing must be considered and services must work to reduce the impact of movement disorders on the lives of people and their families. Future research should focus on expanding on the current literature, by examining movement disorders in other genetic syndromes, and by employing more robust methods of assessment.

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Paper 2: Attenuated behaviour in Cornelia de Lange and Fragile X syndromes: presence and association with features of autism

Word Count

Whole text: 7,270

Main text: 5,432 (excludes tables and references)

Tables word count: 315

References word count: 1,523

The following paper has been prepared for submission to the *Journal of Intellectual Disability Research*. The guidelines for authors can be found in Appendix D. The formatting of the paper presented here has been altered in order to increase readability. Tables and Figures are presented within the main body of the text, and the line spacing has been set at 2.0. Further detail has been added in places to provide contextual information for readers of the thesis.

Abstract

Background: Catatonia-like presentations in people with autism have been increasingly recognised within research and diagnostic guidelines. Breen and Hare (in preparation), who created the Attenuated Behaviour Questionnaire to examine catatonia-like presentations in people with Autism Spectrum Disorder (ASD), reported current attenuated behaviour [autistic catatonia] in 48.3% of participants. Attenuated behaviour was significantly related to repetitive behaviour. The current study aimed to investigate attenuated behaviour within genetic syndromes associated with ASD and to examine ASD and repetitive behaviour as longitudinal predictors of attenuated behaviour.

Method: The Attenuated Behaviour Questionnaire was completed by parents/carers of 33 individuals with Cornelia de Lange syndrome (CdLS) and 69 individuals with Fragile X syndrome (FXS). Information collected from the same informants four years previously was utilised to examine ASD and repetitive behaviour as predictors of later attenuated behaviour, controlling for age, gender, and ability.

Results: Catatonia-like attenuated behaviour was reported for a substantial minority of individuals with CdLS (30.3%) and FXS (11.6%). Phenotypic differences were not observed. Across the two groups repetitive behaviour predicted the presence of attenuated behaviour four years later, after controlling for age, gender and ability.

Conclusions: Attenuated behaviour appeared to affect a significant number of individuals with CdLS and FXS, and is likely to impact on access to services and

quality of life. Repetitive behaviours predicted subsequent risk across both groups, and should be assessed by services as part of a pro-active strategy of support. However, further research is required to identify additional markers.

Key words: genetic syndromes, autism, movement disorder, catatonia, predictor.

2.1 Background

The aetiology of intellectual disability (ID) is varied and includes environmental factors, neonatal sequalae, disease, genetic and idiopathic causes (e.g., Karam *et al.* 2015; Wellesley *et al.* 1991). Genetic causes account for between 30% and 50% of ID (Arvio & Sillanpää 2003; Wellesley *et al.* 1991). There is a national move to individualised person-centred support and care (e.g., National LD Professional Senate 2015; NHS England 2015), but potentially important information is lost by ignoring commonalities within specific genetic syndromes. As a result, services are at risk of limiting the potential advice and support they can offer to clients and those who support them. In a Q-methodology study of clinical psychologists' views about genetics and ID, Hare *et al. (*in press) identified two primary factors representing the views of the majority of participants. Whilst most trainees and newly qualified psychologists emphasised the need for integrated genetic and social models, more experienced psychologists emphasised a social model of disability. These results appear to reflect a tradition of adopting a predominantly social model of disability within clinical psychology. However, as newly qualified clinicians enter services, the importance of understanding behavioural phenotypes is likely to be accentuated.

Research into syndrome-specific phenotypes has revealed important information about common behaviours and health problems within different genetic syndromes, with implications for clinical practice. For example, research pointing to increased risk for thyroid dysfunction in Down syndrome (Pueschel & Pezzullo 1985; Šare *et al.* 1978) has resulted in greater awareness for professionals

and families, and regular blood screening for people with Down syndrome (British Thyroid Association 2006). The initiatives and pathways provided by many Community Learning Disability Teams (CLDTs) around screening for early indicators of dementia in people with Down syndrome (Cairns *et al.* 2010; Findlay & Fillingham 2014) are another key example of clinical practice and service planning influenced by research into syndrome-specific phenotypes. Similarly, research has also highlighted an increased risk for gastrointestinal problems in Cornelia de Lange syndrome (e.g., Bull *et al.* 1993; Cates *et al.* 1989), for specific sleep problems in various genetic syndromes (e.g., De Leersnyder *et al.* 2001; Didden *et al.* 2004) and for specific profiles of behaviour that challenges within particular genetic syndromes (e.g., Arron *et al.* 2011). Simultaneously, the identification of specific genetic syndromes underlying ID has become more effective with recent advances within clinical genetics (Allison *et al.* 2006), making such findings increasingly relevant as more and more people present to CLDTs with a diagnosed genetic syndrome.

Within a number of genetic syndromes, the nature of Autism Spectrum Disorder (ASD) presentations has been extensively studied (Moss & Howlin, 2009; Moss *et al.* 2009, 2013; Richards *et al.* 2015). Researchers have now begun to map the developmental trajectory of specific behavioural characteristics of ASD within genetic syndromes, reporting changes in repetitive behaviour and social behaviour over time (e.g., Adams *et al.* 2011; Cochran *et al.* 2015; Moss *et al.* under review). Whilst the specific profile of ASD characteristics varies across genetic syndromes (e.g., Moss *et al.* 2009, 2013), there is increasing evidence that particular ASD

characteristics consistently predict the presence of other behaviours across genetic syndrome groups. More specifically, there is evidence that repetitive and restricted behaviours (RRB), which are a core diagnostic feature of ASD, are associated with an increased risk of self-injurious behaviour (SIB) across various syndromes as well as within idiopathic autism and ID (Davies & Oliver 2016; Eden *et al.* 2014; Oliver *et al.* 2012; Richards *et al.* 2016), despite the differing profiles of SIB across these groups (Arron *et al.* 2011). Such studies are of particular relevance to the planning of long-term service provision and screening pathways, and highlight key characteristics, such as RRB, as markers of later risk across the whole population of people with ID.

Whilst previous studies into behavioural phenotypes have provided important information about the behavioural features of ASD across different genetic syndromes, researchers have not yet attempted to define the syndrome specific profile of other characteristics that appear related to ASD. For example, there is increasing evidence to suggest an overlap in presenting issues between ASD and other neurological conditions. Research has identified an increased prevalence of Parkinsonian features in adults over 39 years of age with ASD (Starkstein *et al.* 2015), with common brain regions possibly affected in the two disorders (Hollander *et al.* 2009). In addition to repetitive behaviours (Hollander *et al.* 2009), catatonic-like states have been reported in both disorders (Patterson 1986; Wing & Shah 2000), with the Diagnostic and Statistical Manual of Mental Disorders (DSM-5: American Psychiatric Association 2013) introducing an additional code to represent ASD with co-morbid catatonia. Whilst there are difficulties in diagnosing catatonia *per se* (Penland *et al.* 2006), it is clear that a significant number of individuals with ASD

experience difficulties characterised by increased slowness, difficulties in initiating and completing movements, increased passivity, and an increased reliance on prompting from others (Wing & Shah 2000)

In order to further understand and characterise these particular motor and behavioural manifestations in individuals with ASD, Breen and Hare (in preparation) developed the Attenuated Behaviour Questionnaire (ABQ), a third-party measure of catatonia-like features or 'attenuated behaviour' primarily derived from Wing and Shah's (2000) clinical studies. The authors reported that 85% of participants had displayed at least one core feature of attenuated behaviour within their lifetime, with 48.3% meeting their proposed clinical cut-off for autistic catatonia. Those who showed attenuated behaviour [autistic catatonia] also had significantly higher scores on a formal measure of RRB.

The current study expanded on Breen and Hare's initial work (in preparation) by examining the presence of attenuated behaviour [autistic catatonia] and disordered movement in two genetic syndromes in which ASD has been commonly reported and described, Cornelia de Lange syndrome and Fragile X syndrome (e.g., Moss *et al.* 2009, 2013, under review; Richards *et al.* 2015). The study also built on the previous findings of a relationship between RRB and attenuated behaviour in ASD, examining this relationship across both syndrome groups and investigating the longitudinal predictive value of ASD characteristics in highlighting later risk for attenuated behaviour, building on previous reports of RRB as a cross-syndrome risk marker for other behaviours of concern.

2.1.4 Aims and hypotheses

The first aim was to identify the prevalence and profile of attenuated behaviour [autistic catatonia] and disordered movement in Cornelia de Lange syndrome (CdLS) and Fragile X syndrome (FXS), using the ABQ (Breen & Hare in preparation). The second aim was to investigate the extent to which RRB and probable ASD at Time 1 (T1) were predictive of later attenuated behaviour at Time 2 (T2) across both syndromes, and the third aim was to investigate whether these relationships differed across the two syndrome groups. The final aim was to determine the influence of possible confounding variables (age, gender and ability level) on any significant predictive relationship between ASD or RRB and later attenuated behaviour. In line with Breen and Hare's (in preparation) findings in ASD and previous research into ASD characteristics as cross-syndrome risk markers, it was hypothesised that across the combined sample (CdLS and FXS): 1) RRB at T1 would be a significant predictor of the presence of attenuated behaviour at T2 and 2) the presence of probable ASD at T1 would be a significant predictor of the presence of attenuated behaviour at T2. No hypotheses were proposed in relation to differences between CdLS and FXS due to the lack of existing literature.

2.2 Method

2.2.1 Participants

Parents or carers of children and adults with either CdLS or FXS were recruited via an existing research database of people diagnosed with specific genetic syndromes and their parents or carers who have given consent to be contacted about relevant

research studies (e.g., Moss *et al.* 2009, 2013, under review). Only males with FXS were listed on the database, due to the absence of ID in at least half of females with FXS (de Vries *et al.* 1996). Eligibility criteria for the study were 1) parent/carer of an individual with either CdLS or FXS, 2) provided T1 data on the Social Communication Questionnaire and Repetitive Behaviour Questionnaire as part of a previous study (e.g. Moss *et al.* 2013, under review), 3) child's genetic diagnosis confirmed by an appropriate healthcare professional (GP, clinical geneticist or consultant paediatrician) and 4) residence in the UK or Republic of Ireland.

2.2.2 Recruitment

An initial letter was sent out to parents/carers regarding a follow up study that might be of potential interest to them (see Appendix E). A flyer for the study was also included (see Appendix F). Follow-up calls to discuss the research with parents/carers in more detail, answer any questions they might have, and invite them to take part were made up to 28 days after letters were sent, with at least three attempts at different times of day being made to contact potential participants.

2.2.3 Measures

Initial data at T1 were obtained from parents'/carers' responses on the following questionnaires, completed four years previously as part of an ongoing programme of research (e.g., Moss et al. 2009, 2013, under review):

The Repetitive Behaviour Questionnaire (RBQ; Moss & Oliver 2008 - Appendix G) is a 19-item-questionnaire that measures the frequency and severity of RRBs in adults and children with and without ID and comprises five subdomains of *stereotyped behaviour* (3 items), *compulsive behaviour* (8 items), *insistence on sameness* (2 items), *restricted preferences* (3 items), and *repetitive speech* (3 items). Items are scored on a 0 ('Never') to 4 ('More than once a day') scale of frequency, with higher scores indicating a greater frequency of RRB. According to Moss and colleagues (2009), the RBQ shows reasonable concurrent validity with the repetitive scale of the Autism Screening Questionnaire (Berument *et al*. 1999), the former version of the Social Communication Questionnaire, and internal consistency is good for the full scale measure.

The Wessex Scale (Kushlick *et al.* 1973 – Appendix H) is a 15-item-questionnaire that assesses several dimensions of ability in children and adults with intellectual disabilities and comprises five subscales relating to *continence* (4 items), *self-help skills* (3 items), *mobility* (2 items), *speech* (1 item) and *literacy* (3 items) with two additional items to assess vision and hearing impairments. Evidence supports the inter-rater reliability of the Wessex Scale for a large sample of children and adults (Palmer & Jenkins 1982). Items are scored on a scale from 1 to 3, with higher scores indicating a greater level of ability.

Historical information was also available for participants in relation to the following measure, but due to the design of the longitudinal research programme, the point of completion varied according to the point of initial enrollment:

The Social Communication Questionnaire (SCQ; Rutter *et al.* 2003 - Appendix I) is a 40-item informant-report screening questionnaire designed to identify individuals with ASD. It examines the severity of impairment across three domains of c*ommunication* (13 items), *reciprocal social interaction* (15 items), and *restricted, repetitive and stereotyped patterns* (8 items). Items are given a rating of 1 ('Yes') or 0 ('No'), with 24 items being reverse scored. There are an additional six items that are only completed for individuals who can communicate verbally. Higher scores indicate a greater number of ASD features and a cut-off score of 15 on the 'lifetime' version is recommended to screen for ASD (Berument *et al.* 1999). The SCQ showed concurrent validity with the Autism Diagnostic Interview (Le Courteur *et al.* 1989) when used in a sample of 200 participants with diagnoses including ASD, ID, and various genetic syndromes (Berument *et al.* 1999). In the current study, participants were categorised into those with and without possible ASD based on the cut-off score of 15.

Time 2 data were collected from participants using:

The Attenuated Behaviour Questionnaire (ABQ : Breen & Hare in preparation – Appendix J) is a 28-item-questionnaire developed for the assessment of catatonic-

like attenuated behaviour and other aspects of motor and repetitive behaviour in children and young people with ASD aged 12-25. The questionnaire assesses the presence, frequency and severity of symptoms across core and subsidiary *motor*, *affective* and *behavioural* domains. Within the current study, only the *core attenuated behaviour* domain (six items) and the *motor* domain (seven items) were included. An individual is classified as showing attenuated behaviour [autistic catatonia] based on the presence of at least three of the six characteristics in the core domain. Categorisation of individuals based on this criterion shows good sensitivity and specificity against diagnosed catatonia (Breen 2014; Breen & Hare in preparation).

Parents/carers also completed a number of additional items at Time 2 relating to demographics and other relevant information including health problems and medications.

2.2.4 Ethical approval

Ethical approval was granted for this study by Coventry and Warwickshire Research Ethics Committee as part of an amendment to larger project being undertaken by the research group (see Appendix K). Approval was also granted by the University of Manchester (UREC reference number 16032).

2.2.5 Procedure

Participants who expressed an interest in completing T2 measures were sent an email containing a brief reminder of the study and a link to an online survey, hosted

by LimeSurvey©. Participants were required to enter a unique identification number and password in order to complete the questionnaires. Parents/carers were presented with an initial information sheet (see Appendix L), based on the age of the person they would be answering the questionnaire in relation to (children under 16 or adults over 16). Based on their responses, parents were directed to one of three consent forms (Appendix M). In the case of adults with CdLS/FXS unable to provide consent parents/carers were asked to act as a personal consultee (see Appendix N). Following informed consent participants were directed to the survey where they were required to complete some background questions followed by the ABQ. A box was also available for parents to provide comments on any of their responses.

Participants were provided with the option to save their responses at any point and return to the survey at a later time. Throughout the online survey the contact details for the primary researcher were provided in case participants experienced any issues with the survey or wished to discuss anything further. Where parents/carers were not able to complete the study online all of the above information was posted to them in paper format, along with a pre-paid return envelope for the questionnaire and consent form.

Follow-up telephone calls were made three to four weeks after online/postal questionnaires were sent in order to remind parents/carers to complete the questionnaires, answer any questions, and clarify any unclear responses.

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2.2.6 Data analysis

Missing data were recorded for four participants in total. Two had missing data in relation to disordered movement and three in relation to whether the participant met the ASD cut-off on the SCQ. Where missing data were recorded, participants were excluded from relevant analyses.

When normality assumptions were not met for continuous variables, a non-parametric Mann-Whitney U Test was conducted to compare T1 scores of those with and without later attenuated behaviour at T2. In relation to dichotomous variables, where observed cell values were below five, a Fisher's Exact Test was used. For all other univariate analyses, Pearson's Chi-Squared and Independent Samples T-Tests were conducted for dichotomous and continuous T1 variables, respectively, to examine differences in T1 variables according to the presence of attenuated behaviour at T2. Based on the ratios in the current study (for those with versus without attenuated behaviour) a total sample of 92 was required (with 15 participants in the smallest group) in order to detect a large effect (0.8) with 80% power and an alpha criterion of .05.

A logistic regression analysis was conducted, with T2 attenuated behaviour as the outcome variable. To control for confounding variables, age, gender and ability level were entered at Step 1, with the predictors of interest (syndrome group, ASD cut-off status and RBQ score) entered at Step 2. A syndrome group x ASD cut-off interaction term was also added at Step 2, to examine any group differences in the relationship between meeting the ASD cut-off and having attenuated behaviour

at T2. Based on the commonly accepted rule of ten participants per predictor variable (e.g., Peduzzi *et al.* 1996) a sample size of 70 or more was required.

2.3 Results

Kolmogrov-Smirnov tests were conducted for each continuous variable. Neither age ($D(102) = .07$, $p = .20$) nor RBQ total scores ($D(102) = .06$, $p = .20$) differed significantly from a normal distribution, but ability level, as determined by Wessex self-help score, did not meet the assumption of normality ($D(102) = .18$, $p < .001$). A non-parametric Mann-Whitney U Test was therefore conducted to compare T1 ability scores for those with and without attenuated behaviour at T2.

2.3.1 Sample description

In total, 209 eligible participants were identified from the database, 140 (67.0%) of whom could be contacted. Of these 140 potential participants 132 (94.3%) initially agreed to take part. Completed questionnaires were received for33 participants with CdLS and 70 participants with FXS were recruited. The overall completion rate for parents/carers who expressed an interest in the study was 78.0% (103/132). One FXS participant was later excluded due to inconsistencies between T1 and T2 data[1], leaving a total of 102 participants. Demographic characteristics of the sample are presented in Table 1.

[1] The stated date of birth of the participant was not the same at T1 and T2, adding question to whether the parent/carer answered both sets of questionnaires about the same individual

Table 1: Demographics and characteristics of individuals recruited at T2

		Cornelia de Lange	Fragile X
	n	33	69
Gender	% male	30.3	100
	(n)	(10)	(69)
Age (years)	Mean	27.73	24.39
	(SD)	(11.20)	(9.78)
	Range	8-53	8-51
Possible ASD†	% meeting cut-off	75.0	86.6
	(n)	(24)	(58)
Prevalence of health problems	% prevalence	63.6	32.6
	(n)	(21)	(21)
Medication	% prevalence	87.9	46.4
	(n)	(29)	(32)

Note. †One CdLS participant and two FXS participants had missing data for ASD cut-off

In total, 19 respondents (18.6%) were parents/carers of children with CdLS or FXS aged under 16 years and 83 (81.4%) were parents/carers of adults with CdLS or FXS. The age range of participants was 8-53 years in the CdLS group and 8-51 years in the FXS group. Whilst there was no significant difference between the CdLS and FXS groups in terms of the average age of individuals with a genetic syndrome ($t(100) = 1.54$, $p = .13$), there was a significant difference in the gender distribution of participants across the two groups ($\chi^2 = 62.09$, $p < .001$). There was no significant difference between the two groups in the proportion of individuals meeting the ASD cut off ($\chi^2 = 2.04$, $p = .17$). Reported medications most commonly related to gastro-oesophageal problems and epilepsy in CdLS. Epilepsy, anti-psychotic, anti-

depressant and gastro-oesophageal medications were most commonly reported in FXS.

2.3.2 Specific movement problems

Using the movement domain of the ABQ, the prevalence of various movement problems in the CdLS and FXS groups was calculated (Table 2), in line with the first aim of the study. There were no significant differences between the CdLS and FXS groups in terms of the reported prevalence of any movement problems ($p>.05$ for all comparisons). One participant with FXS did not complete the items relating to specific movement problems and so was excluded from all analyses.

Table 2: Number of individuals with CdLS and FXS reported as showing specific movement problems

		Cornelia de Lange	Fragile X
	n	33	69
Any movement problem	% (n)	84.4 (27)	79.1 (53) †
Repetitive body movements (stereotypy)	% (n)	66.7 (22)	58.8 (40)†
Stiff poses	% (n)	18.2 (6)	16.2 (11)†
Tics	% (n)	31.3 (10)†	44.1 (30)†
Odd hand/ foot movements	% (n)	48.5 (16)	64.7 (44)†
Twisting/flicking of hands	% (n)	30.3 (10)	26.5 (18)†
Jerky movements	% (n)	21.2 (7)	32.4 (22) †
Unusual gait	% (n)	60.6 (20)	45.6 (31) †

Note. †One missing response for each of these items.

2.3.3 Core symptoms of attenuated behaviour in Cornelia de Lange and Fragile X syndromes

In line with the first aim of the study, the prevalence of attenuated behaviour symptoms, as assessed by the ABQ core domain, in both CdLS and FXS was delineated and compared (Table 3). There was a significant difference between slowness of movement ($\chi^2 = 7.32$; $p = .017$), which was significantly more prevalent in the CdLS group. Based on Breen and Hare's (in preparation) definition of attenuated behaviour [autistic catatonia], ten (30.3%) individuals with CdLS and eight (11.6%) individuals with FXS displayed attenuated behaviour. The difference

in prevalence between groups was significant ($\chi^2 = 5.38$; p = .028), reflecting a higher prevalence in the CdLS group.

Table 3: Percentage of individuals with CdLS and FXS reported to show core symptoms of attenuated behaviour at T2

		Cornelia de Lange	Fragile X
Total n		33	69
Periods of stiffness	% (n)	15.2 (5)	5.8 (4)
Periods of stuckness	% (n)	24.2 (8)	14.5 (10)
Movement perseveration	% (n)	39.4 13)	21.7 (10)
Difficulty initiating movement	% (n)	15.2 (5)	4.3 (3)
Slowness of movement	% (n)	24.2 (8)*	5.8 (4)
Requiring prompts	% (n)	42.4 (14)	34.8 (24)

Note. *p<.05.

2.3.4 Relationship between age, gender, ability and core attenuated behaviour symptoms

The relationship between attenuated behaviour and age, gender and ability was investigated (Table 4), with no significant difference in age at T1 for those with and without attenuated behaviour at T2 across the whole sample (t(100) = 1.26; p = .21). Similarly, those who did and did not display attenuated behaviour at T2 did not differ in terms of T1 ability level (U = 561.00; p = .08). There was a significant difference in gender for those with and without attenuated behaviour ($\chi^2 = 9.43$; p =

.004), with a higher proportion of females than males showing attenuated behaviour.

Table 4: T1 characteristics according to presence of attenuated behaviour at T2

		Attenuated behaviour	
		Present	**Absent**
Total n		18	84
T1 Wessex ability level	Median (IQR)	6.5 (5-7)	7 (6-9)
T1 Age	Mean (SD)	23.83 (9.03)	20.48 (10.53)
Repetitive behaviour score	Mean (SD)	33.82* (16.48)	25.32 (14.03)

Note. *p<.05.

2.3.5 Attenuated behaviour and features of ASD in the total sample

The relationships between both T1 RBQ scores and ASD cut-off status and T2 attenuated behaviour were investigated, in line with hypotheses one and two (Table 4). T1 RBQ scores differed significantly between individuals who did and did not display attenuated behaviour at T2 ($t(100) = 2.26$; $p = .026$), with higher scores for those who displayed attenuated behaviour at T2. The presence of attenuated behaviour at T2 did not differ significantly according to whether an individual met the cut-off for ASD on the SCQ ($\chi^2 = .44$; $p = .40$). The three participants with missing SCQ data were not included in the latter analysis.

It was not possible to examine syndrome group differences in the relationship between T1 RBQ score and T2 attenuated behaviour, as the size of the

CdLS sample was insufficient to detect even a large effect (0.8) with 80% power and an alpha level of 0.1.

2.3.5.1 Influence of confounding variables on the relationship between T1 repetitive behaviour and T2 attenuated behaviour

In line with the third and fourth aims of the study, a binary logistic regression was conducted, with presence/absence of attenuated behaviour at T2 as the dependent variable. Age, gender and ability score were entered at Step 1 in order to control for these potential confounds, with syndrome group, RBQ score, ASD cut-off status and syndrome group*ASD cut-off status entered at Step 2. In total, 98 of the participants had complete data and were included in the regression analysis. At Step 2, the overall model was significant ($\chi^2(7) = 19.01$; p = .008) with a significant predictive effect for RBQ score (OR = 1.07; 95% CI = 1.02-1.12; p = .003). Neither ASD cut-off status (OR = 1.20; 95% CI = .098-14.66; p = .89) nor syndrome * ASD cut-off status (OR = .33; 95% CI = .01-12.05; p = .54) contributed significantly to the model. Syndrome group was no longer a significant predictor of T2 attenuated behaviour after controlling for age, gender and ability level (OR = 1.16; 95% CI = .09-15.64; p = .91).

2.4 Discussion

The present study was designed with several specific aims and hypotheses, the first of which was to delineate the prevalence of attenuated behaviour [autistic catatonia] and related motor problems in CdLS and FXS, with a second aim of investigating

the predictive relationship between features of ASD, based upon ASD cut-off status and RBQ score, and subsequent attenuated behaviour. The third aim was to investigate any moderating effect of syndrome group on this relationship, and the final aim was to examine the influence of possible confounding variables on this relationship. Two hypotheses were developed and investigated, based on these aims. In line with the first aim of the study, varying prevalence rates were reported for the different signs of attenuated behaviour and disordered movement. Although the prevalence of attenuated behaviour appeared significantly higher in the CdLS group, this was not the case after controlling for confounding variables. With regards to the second and fourth aims, as well as the first hypothesis, T1 scores on the RBQ significantly predicted the presence of T2 attenuated behaviour across the combined sample, even after controlling for age, gender and ability level. Due to insufficient power it was not possible to investigate any moderating effect of syndrome group on this relationship, in line with the third aim. In relation to the second hypothesis no significant predictive relationship was found between meeting the ASD cut-off on the SCQ and the presence of T2 attenuated behaviour, and there was no significant moderating effect of syndrome group on this relationship.

The results indicated a relatively low prevalence of attenuated behaviour in individuals with CdLS and FXS, in comparison to those diagnosed with idiopathic ASD (Breen & Hare in preparation), with 30.3% and 11.6% of individuals with CdLS and FXS, respectively, showing attenuated behaviour. Within the current sample, 75.0% and 86.6% of CdLS and FXS participants, respectively, met the screening cut-

off for ASD. Therefore, the relative prevalence rate of attenuated behaviour was still lower than expected when compared to Breen and Hare's sample of 99 individuals with ASD, particularly for those with FXS. There was some evidence for a different profile of specific symptoms across the syndrome groups, in line with reports of differing profiles of ASD features in FXS and CdLS (e.g., Moss *et al.* 2009, 2013); however, this related only to slowness of movement. Whilst attenuated behaviour was seen only in the minority of participants, 84.4% of CdLS and 79.1% of FXS individuals, respectively, showed some form of disordered movement.

In line with the first hypothesis, as well as Breen and Hare's findings, the extent to which an individual showed RRB at T1 was predictive of the presence of attenuated behaviour at T2, after controlling for age, gender and ability level. As noted above, the prevalence of T2 attenuated behaviour did not differ significantly between those individuals identified as being more or less likely to have ASD. Interestingly, there were no age-related differences in the prevalence of attenuated behaviour, in contrast to previous findings of an age-related increase in RRB in CdLS (Moss *et al.* under review).

2.4.1 Strengths and limitations of the study

The current study was the first to explore the prevalence of attenuated behaviour in genetic syndromes associated with ASD and ID as well as being the first to examine aspects of disordered movement in a large cohort of individuals with either CdLS or FXS (see Paper 1). The results provided an important contribution to our understanding of the specific presentation of attenuated behaviour and related

movement problems in CdLS and FXS. Considering the prevalence rates of FXS of 1 in 4000 (Turner *et al.* 1996) and CdLS of around 1 in 45,000 (Barisic *et al*. 2007), the number of participants recruited was a strength of the current study, permitting further mapping of the behavioural phenotypes of both syndromes. Although the recruitment strategy is likely to have maximised the potential number of participants completing T2 questionnaire data, the study was limited by the inability to control for T1 attenuated behaviour as a predictor of subsequent attenuated behaviour. It was not possible within the limitations of the current study to collect both T1 and T2 data, and T1 variables were therefore assessed through data collected as part of a previous study. This previous study did not utilise the ABQ. The selection of other T1 measures was similarly limited by the reliance of historical data. Future research should assess a wider range of predictor variables, as well as controlling for the presence of attenuated behaviour at T1.

2.4.2 Clinical implications and directions for future research

The results of the current study suggest that episodes of catatonia-like attenuated behaviour are likely to be an issue for a substantial minority of individuals with CdLS and FXS. Without additional support, episodes of attenuated behaviour and disordered movement have the potential to restrict people's independence and quality of life, and to impact on their rights to partake in meaningful activities and to engage with their community (Equality Act 2010; O'Brien 1992). Furthermore, these difficulties are likely to add to the level of care and assistance that individuals require from their family/carers on a day-to-day basis. Service must ensure that

families receive appropriate support to enable them to provide the right level of care. Families are also unlikely to be familiar with catatonia-like presentations, and services should provide pro-active education to ensure attenuated behaviour is properly understood and not attributed to factors such as boredom, laziness, or low mood.

Within CLDTs, as well as statutory services more widely, reasonable adjustments (Equalities Act 2010) should be made to facilitate physical access and engagement (National LD Professional Senate 2015; Department of Health 2016) for individuals with CdLS and FXS experiencing attenuated behaviour and disordered movement. This is a particularly important concern given the level of need, with 63.6% and 32.6% of CdLS and FXS individuals, respectively, in the current study experiencing recent health problems. Routine screening for attenuated behaviour [autistic catatonia] should be considered in those with CdLS and FXS, particularly for those who exhibit high levels of RRB. Such initiatives would allow for a more pro-active approach in providing information and support to individuals, families and staff carers.

The current study provides a valuable initial insight into the prevalence of attenuated behaviour within CdLS and FXS, but further research using larger samples and participants with other genetic syndromes is required to confirm the status of RRB as a cross-syndrome risk marker. Meeting the ASD cut-off on the SCQ was not significantly associated with showing attenuated behaviour, but the SCQ is not a diagnostic assessment *per se.* Future studies should ideally utilise a diagnostic

instrument such as the Autism Diagnostic Observation Schedule- Second Edition (ADOS-2: Lord *et al.* 2012).

Across ASD, CdLS and FXS there is a need to elucidate the specific neurological and/or psychological mechanisms underlying attenuated behaviour. Such research will have implications for approaches to intervention and management. For example, attenuated behaviour in ASD has been termed catatonia by some (e.g., Wing & Shah 2000), but a number of clinicians have advocated electroconvulsive therapy for the treatment of catatonia in autism (see DeJong, Bunton & Hare 2014, for a review of treatment approaches), which would bring with it considerable ethical implications, particularly in relation to issues of capacity (Mental Capacity Act 2005).

2.4.3 Conclusions

The current study investigated the issue of ASD-related attenuated behaviour in people with CdLS and FXS, and the predictive value of other ASD characteristics in differentiating between those with and without later attenuated behaviour in each of these groups. The results indicated that attenuated behaviour was present in a significant minority of individuals with CdLS and FXS, with associated movement problems being seen in the majority of individuals. No phenotypic differences were observed in the profile of attenuated behaviour. Furthermore, across both groups RRB emerged as a significant predictor of attenuated behaviour four years on, highlighting the importance of RRB as a cross-syndrome risk marker for attenuated behaviour.

The results of the current study present a further challenge for clinicians to identify syndrome-specific needs that have a direct impact on community access and to prioritise preventative action and support for families, including the development of screening pathways. Further research is required to identify other characteristics that could be used to inform a preventative screening approach to attenuated behaviour. Research into the mechanisms underlying these difficulties is also required in order to provide effective interventions.

2.4.4 Acknowledgements

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Paper 3: Critical Reflection

Word Count

Whole text: 6,324

Main text: 5,147 (excludes references)

References word count: 1,177

3.1 Introduction

This paper provides a critical reflection on the thesis. It includes reflections on each stage of the research process and expands on previous discussions in Papers 1 and 2.

3.1.1 Choice of research area

The development of the research project began over the summer of 2014, building on the results of Breen and Hare's (in preparation) novel questionnaire study of catatonia-like presentations in ASD. The overall aims of the research were to investigate the prevalence of attenuated behaviour and associated movement disorders across a number of genetic syndromes and examine the relationship with features of ASD within these groups. Both theoretical and clinical influences shaped the research aims. From a theoretical perspective, there is increasing evidence that movement disorders affect a substantial number of individuals with ASD (Donnellan, Hill & Leary,2013; Fatemi & Folsom, 2013; Leary & Hill, 1996), and that the presence of attenuated behaviour is significantly related to the extent to which individuals exhibit particular diagnostic characteristics such as repetitive behaviour (Breen & Hare, in preparation). However, the applicability of these findings across clinically identifiable subgroups of people who are likely to have ASD required further investigation. From a clinical perspective, individuals with ASD have reported that movement disorders can affect their quality of life and wellbeing (Robeldo, Dennellan & Strandt-Conroy,2012). The field supervisor for the current project had noted a number of reports from parents and professionals

describing movement disorders in people with Cornelia de Lange syndrome (CdLS) and Fragile X syndrome (FXS). From each perspective, a lack of current knowledge on the prevalence of movement disorders and related factors within genetic syndromes was noted.

3.1.2 Development of the project

The ClinPsyD research sub-committee were extremely positive in their response to the original proposal, and commented specifically on the advantages of having access to details of potentially interested parents/carers through an existing research database. However, at this stage the difficulties of setting up a collaborative research project with an existing research team at another university were not fully anticipated. In the first instance, an initial project meeting between researchers from Manchester and Birmingham did not take place until March 2015. A number of further delays and modifications to the project occurred as a result of the collaboration. Namely, there was a lengthy delay in receiving the honorary research contract required to access the participant database, and the ethical amendment was delayed in order to tie in with the submission of another substantial amendment from the team at Birmingham. It was also necessary to co-ordinate the timing of recruitment with other projects within the broader programme of research, to ensure participants were not overburdened, and this also had an impact on the measures used (see Section 3.3.4). The ethical constraint that all participant data remain on site introduced a further challenge in terms of the extensive amount of travel required between Manchester and Birmingham and the associated costs.

Whilst a number of papers have commented on the challenges of research collaborations between academic and clinical or community organisations (McCann, 2007; Ross et al., 2010), the challenges of collaborations across academic institutions are not well documented. The reflections presented here may provide insights into some of the difficulties.

3.2 Paper 1: Literature review

3.2.1 Identification of papers

Overall, the search strategy was designed to be fairly comprehensive, and the four databases searched related to a range of different professional fields. However, a number of methodological dilemmas and challenges emerged throughout the process. The initial aim for the literature review was to report on movement problems in genetic syndromes as identified through standardised reliable assessment tools, but an initial scoping search highlighted the lack of studies using high quality assessment measures, and this criterion was dropped as a result. In terms of the other inclusion criteria, a brief discussion of some specific issues is provided in Paper 1. A number of ambiguities arose when attempting to assess whether papers reported on the prevalence of a specific movement disorder. Potentially ambiguous studies were excluded to ensure the validity of the results. Studies relating to hypotonia were not included, because hypotonia can have both neurological and non-neurological causes (NHS Choices, 2016). Similarly, studies reporting on hyperkinesis were excluded, because the term can also refer to hyperkinetic disorder as defined in ICD-10 (World Health Organisation, 1992),

which relates to issues of inattention, hyperactivity and impulsivity. It is therefore important to acknowledge that a small number of potentially informative studies may have been excluded due to the stringent inclusion and exclusion criteria used.

3.2.2 Terminology

As discussed briefly in Paper 1, the selection of specific search terms in relation to movement disorders posed a challenge, due to the broad range of possible disorders. Due to this being a clinical area with a more medical focus, the lack of familiarity with some of the medical terminology may have been a disadvantage. The selection of terms was based in part on an initial search of relevant journals, including *Movement Disorders, Journal of Movement Disorders and Journal of Clinical Movement Disorders*, for articles relating to the genetic syndromes of interest. Although these articles were often single case studies or articles where disorders in genetic syndromes were merely referenced, they provided a starting point in terms of potentially relevant disorders. Other more general terms such as 'movement' and 'motor' were included in an attempt to capture additional movement disorders not identified through relevant case studies. This led to an over-inclusive search, with 2,001 articles being returned. However, this was deemed a lesser concern than omitting potentially relevant articles.

3.2.3 Quality rating assessment

Consideration was given to a number of quality assessment tools. A number of more widely utilised tools, such as the Effective Public Health Practice Project (2008)

quality assessment tool, the STROBE (2007) checklist, or the Critical Appraisal Skills Programme (2013) checklist for diagnostic tests were considered but rejected on the basis that there was an assumption that studies included some form of group comparison, or on the basis that they constituted a checklist and not a rating scale. Specific assessment tools for prevalence studies were therefore sought. The Risk of Bias tool that was eventually selected (Hoy et al., 2012) was the only tool designed for general use across epidemiological research that had demonstrated reliability. However, within the current study, the inter-rater reliability was only 'fair'. Furthermore, whilst Hoy and colleagues reported that their assessment tool was easy to use, within the current literature review both raters found the tool difficult to use, due to difficulties interpreting the item descriptions and locating the relevant information in the papers. This may be a reflection on the applicability of the tool to research in this area, but the discrepancy may also highlight potential biases when authors evaluate their own measures. Whilst equal weighting was given to all items within the current review, the interpretation of papers could potentially be improved in future but giving more weighting to items relating to issues more pertinent to this area of research, such as the reliability and validity of assessments used, and the representativeness of the sample selected.

3.3 Paper 2: Empirical paper

3.3.1 Research topic

The selection of the research topic was based on a combination of clinical importance, previous research, researchers' personal interest and anecdotal

evidence (see Section 3.1.1). However, it should be acknowledged that this is a somewhat controversial area of research. Although the occurrence of catatonia-like presentations in a substantial number of individuals with ASD has now been well documented (e.g., Ghaziuddin, Quinlan & Ghaziuddin,2004; Ohta, Kano & Nagai,2006; Wing & Shah, 2000, 2006), not all academics or clinicians agree with the concept of catatonia in ASD, as introduced in the Diagnostic and Statistical Manual -5 (DSM-5; American Psychiatric Association, 2013), arguing instead that these presentations may differ from catatonia in important ways (e.g., Brasĭć et al., 2000). Understandably, there are reservations about the clinical utility of diagnosing catatonia *per se* in ASD, due to the lack of high quality evidence on specific interventions for catatonia (see De Jong, Bunton & Hare,2014). The debate around catatonia in ASD was discussed during the process of developing the research project. Regardless of whether such presentations were accepted as true catatonia, there was enough evidence to indicate that problems consisting of slowed or stiff movements, motor stereotypies and motor perseveration were present in a substantial number of individuals with ASD, and therefore might also affect other groups of individuals with neurodevelopmental disorders. The term 'attenuated behaviour' rather than 'catatonia' was used to acknowledge the lack of consensus in relation to the concept of autistic catatonia.

3.3.2 Recruitment

The procedure of making phone calls to potential participants before and after providing the questionnaire proved to be an effective strategy in maximising

recruitment, with the overall return rate of 78.0% comparing favourably with other questionnaire-based studies in people with genetic syndromes (e.g., Arron, Oliver, Moss, Berg & Burbidge, 2011; Moss, Oliver, Nelson, Richards & Hall,2013). The initial phone call allowed the researcher to anticipate and address possible issues that might lead to difficulties in completing the questionnaire (see Section 3.3.5). However, it should be noted that the participants for the current study had voluntarily signed up to have their details held on the participant database, and it is possible that they represent a somewhat biased sample. For example, it may be that the families of individuals with CdLS or FXS who have less complex needs are less motivated to engage with syndrome support groups and to take part in relevant research studies. It is also possible that certain families would be less likely to access support groups in the first place, due to lack of accessible information in other languages, lack of transport, or having particular beliefs that emphasise religious or spiritual approaches to support (see Fatimilehin & Nadirshaw, 1994). The challenge therefore is in how to involve these families in clinical research. Recruitment directly via clinical geneticists might provide access to a more representative group of parents/carers. However, due to significant advances in genetic testing in the last decade (Allison, Cui, Page & Sabripour, 2006), clinic referrals are increasingly likely to be for younger children, and accessing a representative adult population remains problematic.

3.3.3 Public and patient involvement

INVOLVE (2015) sets out a number of areas for public and patient involvement (PPI) in research, including as joint grant-holders, in identifying research priorities, as members of a project advisory group, in commenting on research materials, in undertaking interviews or carrying out research. As part of the development of the empirical study the University of Manchester's Community Liaison Group (CLG) was consulted. Two members of the group gave advice on the research proposal. This input was extremely useful in ensuring accessible language was used to describe the rationale for the study and what was involved. In line with the advice of the CLG, the formatting of the ABQ was changed to increase clarity and make it easier for respondents to navigate the questionnaire. However, it should be noted that there was a lack of PPI in the original discussion of research priorities and in the process of actually undertaking the research, although one parent did feed back to the research team that she was grateful that someone was finally looking at movement disorders in FXS, because she had felt for some time that this should be looked into.

Although the CLG members provided some very useful general feedback about the accessibility of the study, individuals with CdLS or FXS and their parents/carers were not consulted. In order to ensure that future studies have the most meaningful implications for the lives of people with CdLS and FXS and those around them, people with CdLS and FXS and relevant stakeholders should be consulted from an early stage so that they can play a key role in shaping the entire

research process. This might be achieved through consultation with families attending syndrome support group conferences.

3.3.4 Ethical considerations

When undertaking studies as part of a larger ongoing programme of research, different ethical considerations are raised when compared to a single standalone study. Primarily, the need to avoid over-burdening participants has to be balanced against the responsibility to engage in rigorous high quality research. In particular, when recruiting participants from a rare population, where there may only be a relatively small number of potential respondents available, the issue of over-researching the same group of people is raised, which brings with it the further risk of exhausting participants' motivation and good will, such that they may be less likely to engage in future research. This in itself may then impact on the quality of future research, leaving studies with smaller less representative samples. In relation to the current study, the decision was made to minimise the burden to participants. It became apparent that a number of potential participants had taken part in an intensive research project within the previous six to 18 months, involving a full day of observations and assessments. Ways of reducing participant burden were therefore considered, and only historical data were used for ASD-related measures. Although this meant that it was not possible to examine the cross-sectional relationship between attenuated behaviour, repetitive behaviour and ASD, it was considered to be the more ethical approach. Similarly, the original intention was to also recruit a group of individuals with Tuberous Sclerosis Complex (TSC), another

genetic syndrome associated with ASD. However, many of the potential TSC participants were still involved in another study at the time of recruitment. Being mindful of the long-term goals and priorities of the research team in Birmingham and ensuring that they were not put at risk by the current study helped to ensure a positive ongoing relationship with the University of Manchester that may foster other collaborative projects in the future.

The issue of capacity to consent (Mental Capacity Act: Department of Health, 2005) for adults with ID also poses significant challenges to the design of clinically relevant research and the ability to gain ethical approval through NHS Research Ethics Committees. The current study was conducted as part of an ongoing research programme that provided a clear process for parents/carers to make a decision about the person's capacity and allowed them to act as a nominated or personal consultee in cases of the person being unable to consent. Whilst this may be an acceptable approach in questionnaire studies, where the likely harm and burden to the person are minimal, in other cases people may be excluded from research if they are unable to consent. One parent in the current study spoke of his frustration that his daughter was recently unable to take part in a study of anxiety due to an inability to provide consent, despite the fact that he felt anxiety was impacting significantly on his daughter's life. There is a responsibility therefore for researchers to ensure that clear and ethical processes are developed to prevent individuals being excluded from research that has the potential to benefit them and their families.

3.3.5 Hypothesis selection

The design of the research questions and development of resulting hypotheses was based to some extent on the interests of the researchers and the potential contribution to the literature and clinical practice. However, the research questions were partly shaped by both the practical considerations in the design of the study, including the need to avoid over-burdening participants and the availability of existing data, as well as the expanding area of research examining developmental trajectories and longitudinal predictors of later behaviour in genetic syndromes (e.g., Cochran, Moss, Nelson & Oliver,2015; Moss et al., 2013; Richards, Moss, Nelson & Oliver,2016). Overall, the development of empirically and theoretically derived hypotheses was difficult, given the lack of existing knowledge relating to catatonia and disordered movement in genetic syndromes (see Paper 1). The study was therefore primarily exploratory, and the hypotheses that were developed were based on established relationships observed within individuals with ASD (Breen & Hare, in preparation). Had practical and ethical constraints been less influential, the study design would have ideally allowed for investigation of a hypothesised cross-sectional relationship between attenuated behaviour and repetitive behaviour, as well as allowing the researchers to test the hypothesis that T1 repetitive behaviour would remain a significant predictor of T2 attenutated behaviour, after controlling for the presence of attenuated behaviour at T1. This would have allowed for firmer conclusions to be drawn in relation to the status of repetitive behaviour as a risk marker for attenuated behaviour and provided stronger support for the

applicability of the findings to long term screening and prevention initiatives for attenuated behaviour within services.

3.3.6 Measures

The ABQ is a newly developed questionnaire, originally designed for completion by parents/carers of individuals with ASD. Whilst the initial psychometric data reported by the authors look promising, the feasibility of the ABQ for use in other groups has not yet been proven. However, as highlighted in Paper 1, there is a clear lack of standardised appropriate measures for the assessment of movement disorders in genetic syndromes, and to the author's knowledge no other informant-report measures of attenuated behaviour [autistic catatonia] exist.

Elements of the ABQ may be less appropriate for use in certain populations. For example, those more severely affected by CdLS often have under-developed limbs and/or fingers and may not be mobile (Jackson, Kline, Barr & Koch,1993; Leroy et al., 1993). Therefore, items referring to 'move their hands' or 'walk unusually' have the potential to cause distress to respondents by highlighting the things that the person they care for cannot do. Whilst in the current study it was possible to address and discuss this issue in a sensitive manner with all respondents prior to completion of the questionnaire, researchers should apply caution in using the ABQ with individuals with significant physical disabilities. Physical disabilities may also confound responses to certain items. For example, hip dislocation and leg length discrepancy are relatively common in CdLS (Kline et al., 2007). Within the online questionnaire space was given for respondents to leave comments on the

ABQ. Seven respondents commented that the person they care for walks unusually as a result of physical disabilities, such as flat or club foot, scoliosis, or dislocated hips. The most commonly endorsed item from the core domain related to the need to provide prompts to the individual. In groups such as CdLS and FXS where there is likely to be a broad range in the level of adaptive functioning (Kline et al., 2008; Hartley et al., 2011), prompts may be a necessary part of helping the individual to engage in tasks and might not always represent a symptom of attenuated behaviour. This issue was reflected in the comments of two of the respondents. Ideally, the authors of the ABQ would consider adapting a number of the items slightly to maximise its applicability across different groups.

Selection of T1 measures was restricted by the reliance on historical information. However, both the Social Communication Questionnaire (SCQ; Rutter, Bailey & Lord, 2003) and Repetitive Behaviour Questionnaire (RBQ; Moss & Oliver, 2008) are reported by the authors to be reliable measures. The SCQ is preferable to alternatives, such as the Social Responsiveness Scale- Second Edition (Constantino, 2012), because the same version can be used across the age range. The RBQ has been widely used to examine repetitive behaviour in individuals with a range of genetic syndromes (e.g., Arron et al., 2011; Moss, Oliver, Arron, Burbige & Berg,2009; Woodcock, Oliver & Humphreys,2009), and was used by Breen and Hare in their study. Its use in the current study was therefore consistent with other relevant research.

3.3.7 Data analysis strategy

Reducing missing data was particularly important in the current study given the relatively small number of CdLS participants. Follow up calls were used to collect information on missing data. However, four participants were excluded from the final analysis. Two participants could not be contacted regarding missing T2 data, and three had existing missing data from T1. Missing data were excluded because feedback from those who were contacted indicated that missed responses generally indicated specific nuances in the individual's behaviour that needed to be discussed further. It was felt that imputing scores based on the overall sample would not be appropriate to these more unique cases.

Due to insufficient numbers of participants (see Section 2.2.6) it was not possible to test for the moderating effect of syndrome on the relationship between repetitive behaviour and attenuated behaviour. In a 2x2 (syndrome group x attenuated behaviour) between-groups ANOVA, the interaction term was not significant ($F(1,98) = 1.11$; $p = .29$; eta-squared = .01). However, this result was not reported in the main paper, because it was possible that the study did not have sufficient power to detect a significant interaction. If possible, future studies with larger samples should examine possible moderating effects of syndrome group.

3.4 Resources

Undertaking a project such as the one described in this thesis within the constraints of a ClinPsyD poses various challenges. In comparison to the experience of undertaking research as part of a PhD qualification, both financial and human

resources are more restricted. Firstly, the research itself does not take place as part of a wider programme of research that has received specific funding, which in turn has an impact on the methodological design. Similarly, the time allocated to the project as part of the broader ClinPsyD programme is limited and must be balanced with a range of other responsibilities. Within the current project the collection of data under a research programme at a separate university was challenging, given the demands this posed in terms of travel time, availability to contact parents, and the practicalities of overseeing a research project based two hours away. Creative use of the available resources and good time management were therefore essential to completing a high quality piece of research.

To maximise recruitment the researcher spent weekends in Birmingham making calls to participants, and enlisted the help of a placement student in Birmingham to follow up parents/carers who could not be contacted on Fridays or at weekends. In terms of the measures used, the ABQ is a free resource and was available from one of the authors of the empirical study. Similarly, repetitive behaviour, ASD, and ability were assessed using historical data, which reduced the financial cost of assessments and made more efficient use of respondents' time.

The use of an online survey was intended to eliminate the resource costs of providing paper questionnaire packs to all potential participants. However, using a purely online method presented issues in terms of accessibility, as not all potential participants had the resources or the confidence to complete an online questionnaire, so it was necessary to send out postal questionnaires to 28% of participants who agreed to take part. Interestingly, the return rate for postal

questionnaires (83.8%) was higher than for the online survey (74.7%). A further issue was that the online survey had to be designed using the survey software covered by the original NHS ethics application. However, having no previous experience in using LimeSurvey©, the initial development of the online questionnaire by the primary researcher was extremely time-intensive. The reliance on technology also introduced further challenges, when a technical issue with the software delayed the activation of the survey by three weeks.

If more resources had been available it would have been possible to invest additional time in recruitment, to use more in depth assessments of ASD, such as the Autism Diagnostic Interview-Revised (Rutter, Le Couteur & Lord,2003) or Autism Diagnostic Observation Schedule-2 (Lord et al., 2012), and to co-ordinate the questionnaire assessments with a comprehensive clinical examination by a relevant professional to validate information collected from parents/carers in relation to health problems and disordered movement.

3.5 Anecdotal observations

One of the most salient observations whilst carrying out the research was the sense of gratitude that parents and carers expressed towards researchers who showed an interest in understanding more about CdLS or FXS, and providing more information and support for other families and professionals. Anecdotally, it seemed that a number of families sought help and advice through syndrome support groups rather than mainstream services, with the primary researcher having to signpost two parents to Community Learning Disability Teams (CLDTs)

because they had previously been unaware of these services. A number of those parents/carers who had received support through CLDTs and talked about their concerns that professionals often took a generalised approach to working with people with ID, and often did not appear to have any specialist knowledge in relation to the person's syndrome. From the researcher's perspective this often seemed to lead to a sense of frustration and helplessness on the part of the parent/carer. This is an important observation because it highlights a message from families to professionals within ID services to take interest in and account for genetics and personalised medicine in the way that they support people and their families.

A number of clinical issues arose during the process of recruitment and follow up. For example, two parents of people with FXS reported being particularly concerned about their son having been prescribed anti-psychotics in relation to difficult to manage behaviours. Several individuals with CdLS and FXS were also reported to have moved to a residential setting between T1 and T2, due to increasing complexity in their support needs. As described above, two parents were also signposted to CLDTs due to concerns about anxiety and communication problems. These issues highlight the complexities of caring for an individual with CdLS or FXS, and the importance of appropriate advice and support to be provided to these parents in a timely manner to reduce the long-term impact on people and their families. Finally, two individuals whose parents/ carers had taken part in the study at T1 had passed away when parents/ carers were contacted at T2. One notable difference between carrying out research in a clinical versus a purely academic

context is the ability of the researcher to engage with participants in a more therapeutic way, and to be able to more comfortably handle difficult conversations that arise and signpost appropriately.

3.6 Clinical implications

Specific implications of the literature review and empirical study are outlined in Papers 1 and 2, and key recommendations for services are made:

- Both papers highlight that movement disorders affected a substantial number of individuals with genetic syndromes. There is an important responsibility for professionals and services to increase the awareness of patients and their families regarding these issues, particularly within CdLS and FXS, where the relatively high prevalence of attenuated behaviour and disordered movement has not previously been recognised.
- The potential barriers that movement problems pose to the rights of an individual and their family to access services must be addressed. As the influence of genetics is increasingly recognised within CLDTs in line with the expectations of many parents (Section 3.5),these community services should acknowledge the impact of movement disorders on people's wellbeing and quality of life, and the additional challenges faced by parents and staff carers in the way they support people.
- Papers 1 and 2 highlight that in the majority of cases (with the exception of ataxia in Angelman syndrome) no one individual movement disorder affects every individual with a given syndrome, although within each group a large

majority do experience at least one movement problem. Therefore, the specific profile of movement issues should be assessed for each individual with a given syndrome, in order to provide individualised support.

- It is hoped that services will take a pro-active approach to attenuated behaviour within CdLS and FXS, providing information and advice to individuals, families and staff and using a screening approach to highlight those at risk..
- Community health services more widely must continue to ensure that reasonable adjustments (Equality Act, 2010) are made to the physical environment and to the way that appointments and assessments are carried out, to ensure that people with genetic syndromes are not excluded. This is a particularly significant point given the high prevalence of physical health problems in these groups (see Paper 2; Bull, Fitzgerald, Hiefetz & Brei,1993; Cates, Billmire, Bull & Grosfeld, 1989).

3.7 Dissemination

In line with the protocol of the research team at the University of Birmingham each parent/carer who took part in this project will receive a personalised feedback report, summarising their own responses and how these compare to the overall results. The first author will present the results at the next national CdLS Foundation family conference, and a similar opportunity to present at a conference organised by the Fragile X Society or write an article for their newsletter is being sought. It is hoped this strategy will maximise dissemination to individuals with

genetic syndromes and their parent/carers beyond the participants of the current study. The findings of the literature review and empirical study have been prepared for submission to academic journals in the field of ID, with the aim of disseminating the findings to the wider academic and professional community.

3.8 Personal reflections

The completion of the work presented within this doctoral thesis has taken place despite a number of challenges to the timescale of the project. In addition to delays to the start of the project (see Section 3.1.2), there was a change in the supervision arrangements prior to the start of recruitment for the empirical project, which introduced some interruption and uncertainty to the supervision process. Being able to accept and hold the anxiety created by these issues posed an additional challenge over and above the logistics of carrying out the work itself. As described in Section 3.4, the resources available as part of a ClinPsyD project also differed greatly to those that I had previously experienced when undertaking a funded PhD project, and the process of adjusting my expectations for scope of the research that can be carried out also took time. However, pulling together an interesting and clinically important piece of research despite these challenges has brought with it a great sense of achievement.

3.9 Conclusions

The broader aim of this thesis was to explore the prevalence of movement disorders and catatonia-like symptoms in genetic syndromes associated with ASD,

and to examine possible predictive factors. The literature review highlighted a lack of high quality prevalence studies, with much of the available research reporting only on disorders that have typically formed part of the clinical diagnosis, rather than broadening our knowledge of the range of movement problems experienced. The empirical paper provided a novel examination of attenuated behaviour and movement disorders within a large sample of individuals with CdLS and FXS, and indicated that significant minority of these experience disordered movement and/or catatonia-like attenuated behaviour, with repetitive behaviour being a significant predictor of later attenuated behaviour. Results across both papers highlight the need for services to recognise and account for movement problems that add to the complex set of difficulties experienced by individuals with CdLS and FXS and their families, and to provide appropriate pro-active support to allow the individual and their family to live fulfilled and meaningful lives.

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Appendices

Appendix A - Author guidelines for *Journal of Applied Research in Intellectual Disabilities*

1. GENERAL

The *Journal of Applied Research in Intellectual Disabilities* is an international, peer-reviewed journal which draws together findings derived from original applied research in intellectual disabilities. The journal is an important forum for the dissemination of ideas to promote valued lifestyles for people with intellectual disabilities. It reports on research from the UK and overseas by authors from all relevant professional disciplines. It is aimed at an international, multi-disciplinary readership.

The topics it covers include community living, quality of life, challenging behaviour, communication, sexuality, medication, ageing, supported employment, family issues, mental health, physical health, autism, economic issues, social networks, staff stress, staff training, epidemiology and service provision. Theoretical papers are also considered provided the implications for therapeutic action or enhancing quality of life are clear. Both quantitative and qualitative methodologies are welcomed. All original and review articles continue to undergo a rigorous, peer-refereeing process.

Please read the instructions below carefully for details on submission of manuscripts, the journal's requirements and standards as well as information concerning the procedure after a manuscript has been accepted for publication. Authors are encouraged to visit http://authorservices.wiley.com/bauthor/ for further information on the preparation and submission of articles.

All manuscripts must be submitted solely to this journal and not published, in press, or submitted elsewhere.

2. ETHICAL GUIDELINES

Acceptance of papers is based on the understanding that authors have treated research participants with respect and dignity throughout. Please see Section 2.2 below.

2.1 Authorship and Acknowledgements

Authorship: Authors submitting a paper do so on the understanding that the manuscript has been read and approved by all authors and that all authors agree to the submission of the manuscript to the journal. ALL named authors must have made an active contribution to the conception and design and/or analysis and interpretation of the data and/or the drafting of the paper and ALL authors must have critically reviewed its content and have approved the final version submitted for publication. Participation solely in the acquisition of funding or the collection of data does not justify authorship.

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

Acknowledgements: Under Acknowledgements please specify contributors to the article other than the authors accredited. Please also include specifications of the source of funding for the study and any potential conflict of interest if appropriate. Suppliers of materials should be named and their location (town, state/county, country) included.

2.2 Ethical Approvals

Research involving human participants will only be pubished if such research has been conducted in full accordance with ethical principles, including the World Medical Association Declaration of Helsinki (version, 2002 www.wma.net) and the additional requirements, if any, of the country where the research has been carried

out. Manuscripts must be accompanied by a statement that the research was undertaken with the understanding and written consent of each participant (or the participant's representative, if they lack capacity), and according to the above mentioned principles. A statement regarding the fact that the study has been independently reviewed and approved by an ethical board should also be included.
All studies using human participants should include an explicit statement in the Material and Methods section identifying the review and ethics committee approval for each study, if applicable. Editors reserve the right to reject papers if there is doubt as to whether appropriate procedures have been used.

Ethics of investigation: Papers not in agreement with the guidelines of the Helsinki Declaration as revised in 1975 will not be accepted for publication.

2.3 Clinical Trials

Clinical trials should be reported using the CONSORT guidelines available at www.consort-statement.org. A CONSORT checklist should also be included in the submission material (www.consort-statement.org).
The *Journal of Applied Research in Intellectual Disabilities* encourages authors submitting manuscripts reporting from a clinical trial to register the trials in any of the following free, public trials registries: www.clinicaltrials.org, www.isrctn.org. The clinical trial registration number and name of the trial register will then be published with the paper.

2.4 Conflict of Interest and Source of Funding

Conflict of Interest: Authors are required to disclose any possible conflict of interest. These include financial (for example patent ownership, stock ownership, consultancies, speaker's fee). Author's conflict of interest (or information specifying the absence of conflict of interest) will be published under a separate heading.
The *Journal of Applied Research in Intellectual Disabilities* requires that sources of institutional, private and corporate financial support for the work within the manuscript must be fully acknowledged, and any potential conflict of interest noted. As of 1st March 2007, this information is a requirement for all manuscripts submitted to the journal and will be published in a highlighted box on the title page of the article. Please include this information under the separate headings of 'Source of Funding' and 'Conflict of Interest' at the end of the manuscript.

If the author does not include a conflict of interest statement in the manuscript, then the following statement will be included by default: 'No conflict of interest has been declared'.

Source of Funding: Authors are required to specify the source of funding for their research when submitting a paper. Suppliers of materials should be named and their location (town, state/county, country) included. The information will be disclosed in the published article.

2.5 Permissions

If all or parts of previously published illustrations are used, permission must be obtained from the copyright holder concerned. It is the author's responsibility to obtain these in writing and provide copies to the Publishers.

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If your paper is accepted, the author identified as the formal corresponding author for the paper will receive an email prompting them to login into Author Services; where via the Wiley Author Licensing Service (WALS) they will be able to complete the license agreement on behalf of all authors on the paper.

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4. SUBMISSION OF MANUSCRIPTS

Submissions are now made online using ScholarOne Manuscripts (formerly Manuscript Central). To submit to the journal go to http:// mc.manuscriptcentral.com/jarid. If this is the first time you have used the system you will be asked to register by clicking on 'create an account'. Full instructions on making your submission are provided. You should receive an acknowledgement within a few minutes. Thereafter, the system will keep you informed of the process of your submission through refereeing, any revisions that are required and a final decision.

4.1 Manuscript Files Accepted

Manuscripts should be uploaded as Word (.doc) or Rich Text Format (.rft) files (not write-protected) plus separate figure files. GIF, JPEG, PICT or Bitmap files are acceptable for submission, but only high-resolution TIF or EPS files are suitable for printing.

To allow double-blinded review, please upload your manuscript and title page as **separate** files.

Please upload:

1. Your manuscript without title page under the file designation 'main document'.
2. Figure files under the file designation 'figures'.
3. Title page which should include title, authors (including corresponding author contact details), acknowledgements and conflict of interest statement where applicable, should be uploaded under the file designation 'title page'.

All documents uploaded under the file designation 'title page' will not be viewable in the HTML and PDF format you are asked to review at the end of the submission process. The files viewable in the HTML and PDF format are the files available to the reviewer in the review process.

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Original Articles, Review Articles, Brief Reports, Book Reviews and ***Letters to the Editor*** are accepted. ***Theoretical Papers*** are also considered provided the implications for therapeutic action or enhancing quality of life are clear. Both quantitative and qualitative methodologies are welcomed. Articles are accepted for publication only at the discretion of the Editor. Articles should not exceed 7000 words. Brief Reports should not normally exceed 2000 words. Submissions for the Letters to the Editor section should be no more than 750 words in length.

6. MANUSCRIPT FORMAT AND STRUCTURE

6.1 Format

Language: The language of publication is English. Authors for whom English is a second language must have their manuscript professionally edited by an English speaking person before submission to make sure the English is of high quality. It is preferred that manuscripts are professionally edited. A list of independent suppliers of editing services can be found at http://authorservices.wiley.com/bauthor/english_language.asp. All services are paid for and arranged by the author, and use of one of these services does not guarantee acceptance or preference for publication.

6.2 Structure

All manuscripts submitted to the *Journal of Applied Research in Intellectual Disabilities* should include:

Cover Page: A cover page should contain only the title, thereby facilitating anonymous reviewing. The authors' details should be supplied on a separate page and the author for correspondence should be identified clearly, along with full contact details, including e-mail address.

Running Title: A short title of not more than fifty characters, including spaces, should be provided. ***Keywords***: Up to six key words to aid indexing should also be provided.

Main Text: All papers should have a structured abstract (maximum 150 words) as follows: Background, Method, Results, and Conclusions. The abstract should provide an outline of the research questions, the design, essential findings and main conclusions of the study. Authors should make use of headings within the main paper as follows: Introduction, Method, Results and Discussion. Subheadings can be used as appropriate. All authors must clearly state their research questions, aims or hypotheses clearly at the end of the Introduction. Figures and Tables should be submitted as a separate file.

Style: Manuscripts should be formatted with a wide margin and double spaced. Include all parts of the text of the paper in a single file, but do not embed figures. Please note the following points which will help us to process your manuscript successfully:

-Include all figure legends, and tables with their legends if available.

-Do not use the carriage return (enter) at the end of lines within a paragraph.

-Turn the hyphenation option off.
-In the cover email, specify any special characters used to represent non-keyboard characters.
-Take care not to use l (ell) for 1 (one), O (capital o) for 0 (zero) or ß (German esszett) for (beta).
-Use a tab, not spaces, to separate data points in tables.
-If you use a table editor function, ensure that each data point is contained within a unique cell, i.e. do not use carriage returns within cells.

Spelling should conform to *The Concise Oxford Dictionary of Current English* and units of measurements, symbols and abbreviations with those in *Units, Symbols and Abbreviations* (1977) published and supplied by the Royal Society of Medicine, 1 Wimpole Street, London W1M 8AE. This specifies the use of S.I. units.

6.3 References

The reference list should be in alphabetic order thus:
-Emerson E. (1995) *Challenging Behaviour: Analysis and Intervention in People with Learning Disabilities*. Cambridge University Press, Cambridge.
-McGill P. & Toogood A. (1993) Organising community placements. In: *Severe Learning Disabilities and Challenging Behaviours: Designing High Quality Services* (Eds E. Emerson, P. McGill & J. Mansell), pp. 232-259. Chapman and Hall, London.
-Qureshi H. & Alborz A. (1992) Epidemiology of challenging behaviour. *Mental Handicap Research* 5, 130-145
Journal titles should be in full. References in text with more than two authors should be abbreviated to (Brown *et al*. 1977). Authors are responsible for the accuracy of their references.

We recommend the use of a tool such as EndNote or Reference Manager for reference management and formatting.
EndNote reference styles can be searched for here:
http://www.endnote.com/support/enstyles.asp
Reference Manager reference styles can be searched for here:
http://www.refman.com/support/rmstyles.asp
The Editor and Publisher recommend that citation of online published papers and other material should be done via a DOI (digital object identifier), which all reputable online published material should have – see www.doi.org/ for more information. If an author cites anything which does not have a DOI they run the risk of the cited material not being traceable.

6.4 Tables, Figures and Figure Legends

Tables should include only essential data. Each table must be typewritten on a separate sheet and should be numbered consecutively with Arabic numerals, e.g. Table 1, and given a short caption.

Figures should be referred to in the text as Figures using Arabic numbers, e.g. Fig.1, Fig.2 etc, in order of appearance. Figures should be clearly labelled with the name of the first author, and the appropriate number. Each figure should have a separate legend; these should be grouped on a separate page at the end of the manuscript. All symbols and abbreviations should be clearly explained. In the full-text online edition of the journal, figure legends may be truncated in abbreviated links to the full screen version. Therefore, the first 100 characters of any legend should inform the reader of key aspects of the figure.

Preparation of Electronic Figures for Publication

Although low quality images are adequate for review purposes, print publication requires high quality images to prevent the final product being blurred or fuzzy. Submit EPS (line art) or TIFF (halftone/photographs) files only.

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Appendix B – PRISMA checklist

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

Appendix C – Risk of bias assessment tool

Appendix 1: Risk of Bias Tool

Name of author(s):_____ Year of publication:_____

Name of paper/study:-

_____

This tool is designed to assess the risk of bias in population-based prevalence studies. Please read the additional notes for each item when initially using the tool. Note: If there is insufficient information in the article to permit a judgement for a particular item, please answer **No (HIGH RISK)** for that particular item.

Risk of bias item	Criteria for answers (please circle one option)	Additional notes and examples
External Validity		
1. Was the study's target population **a close representation** of the national population in relation to relevant variables, e.g. age, sex, occupation?	• **Yes (LOW RISK):** The study's target population was a close representation of the national population. • **No (HIGH RISK)**: The study's target population was clearly NOT representative of the national population.	The **target population** refers to the group of people or entities to which the results of the study will be generalised. Examples: • The study was a national health survey of people 15 years and over and the sample was drawn from a list that included all individuals in the population aged 15 years and over. The answer is: **Yes (LOW RISK).** • The study was conducted in one province only, and it is not clear if this was representative of the national population. The answer is: **No (HIGH RISK).** • The study was undertaken in one village only and it is clear this was not representative of the national population. The answer is: **No (HIGH RISK).**
2. Was the sampling frame a **true or close representation** of the target population?	• **Yes (LOW RISK):** The sampling frame was a **true or close** representation of the target population. • **No (HIGH RISK)**: The sampling frame was NOT a **true or close** representation of the target population.	The **sampling frame** is a list of the sampling units in the target population and the study sample is drawn from this list. Examples: • The sampling frame was a list of almost every individual within the target population. The answer is: **Yes (LOW RISK).** • The cluster sampling method was used and the sample of clusters/villages was drawn from a list of all villages in the target population. The answer is: **Yes (LOW RISK).** • The sampling frame was a list of just one particular ethnic group within the overall target population, which comprised many groups. The answer is: **No (HIGH RISK).**
3. Was some form of **random selection** used to select the sample, OR, was a census undertaken?	• **Yes (LOW RISK):** A census was undertaken, OR, some form of random selection was used to select the sample (e.g. simple random sampling, stratified random sampling, cluster sampling, systematic sampling). • **No (HIGH RISK)**: A census was NOT undertaken, AND some form of random selection was NOT used to select the sample.	A census collects information from every unit in the sampling frame. In a survey, only part of the sampling frame is sampled. In these instances, random selection of the sample helps minimise study bias. Examples: • The sample was selected using simple random sampling. The answer is: **Yes (LOW RISK).** • The target population was the village and every person in the village was sampled. The answer is: **Yes (LOW RISK).** • The nearest villages to the capital city were selected in order to save on the cost of fuel. The answer is: **No (HIGH RISK).**
4. Was the likelihood of **non-response bias minimal?**	• **Yes (LOW RISK):** The response rate for the study was >/=75%, OR, an analysis was performed that showed no significant difference in relevant demographic characteristics between responders and non-responders • **No (HIGH RISK)**: The response rate was <75%, and if any analysis comparing responders and non-responders was done, it showed a significant difference in relevant demographic characteristics between responders and non-responders.	Examples: • The response rate was 68%; however, the researchers did an analysis and found no significant difference between responders and non-responders in terms of age, sex, occupation and socio-economic status. The answer is: **Yes (LOW RISK).** • The response rate was 65% and the researchers did NOT carry out an analysis to compare relevant demographic characteristics between responders and non-responders. The answer is: **No (HIGH RISK).** • The response rate was 69% and the researchers did an analysis and found a significant difference in age, sex and socio-economic status between responders and non-responders. The answer is: **No (HIGH RISK).**

Internal Validity		
5. Were data collected **directly from the subjects** (as opposed to a proxy)?	• **Yes (LOW RISK):** All data were collected directly from the subjects. • **No (HIGH RISK)**: In some instances, data were collected from a proxy.	A proxy is a representative of the subject. Examples: • All eligible subjects in the household were interviewed separately. The answer is: **Yes (LOW RISK)**. • A representative of the household was interviewed and questioned about the presence of low back pain in each household member. The answer is: **No (HIGH RISK)**.
6. Was an acceptable case definition used in the study?	• **Yes (LOW RISK):** An acceptable case definition was used. • **No (HIGH RISK)**: An acceptable case definition was NOT used.	• For a study on low back pain, the following case definition was used: "Low back pain is defined as activity-limiting pain lasting more than one day in the area on the posterior aspect of the body from the bottom of the 12th rib to the lower gluteal folds." The answer is: **Yes (LOW RISK)**. • For a study on back pain, there was no description of the specific anatomical location 'back' referred to. The answer is: **No (HIGH RISK)**. • For a study on osteoarthritis, the following case definition was used: "Symptomatic osteoarthritis of the hip or knee, radiologically confirmed as Kellgren-Lawrence grade 2-4". The answer is: LOW RISK.
7. Was the study instrument that measured the parameter of interest (e.g. prevalence of low back pain) shown to have **reliability and validity (if necessary)**?	• **Yes (LOW RISK):** The study instrument had been shown to have reliability and validity (if this was necessary), e.g. test-re-test, piloting, validation in a previous study, etc. • **No (HIGH RISK)**: The study instrument had NOT been shown to have reliability or validity (if this was necessary).	• The authors used the COPCORD questionnaire, which had previously been validated. They also tested the inter-rater reliability of the questionnaire. The answer is: **Yes (LOW RISK)**. • The authors developed their own questionnaire and did not test this for validity or reliability. The answer is: **No (HIGH RISK)**.
8. Was the **same mode of data collection** used for all subjects?	• **Yes (LOW RISK):** The same mode of data collection was used for all subjects. • **No (HIGH RISK)**: The same mode of data collection was NOT used for all subjects.	The mode of data collection is the method used for collecting information from the subjects. The most common modes are face-to-face interviews, telephone interviews and self-administered questionnaires. Examples: • All eligible subjects had a face-to-face interview. The answer is: **Yes (LOW RISK)**. • Some subjects were interviewed over the telephone and some filled in postal questionnaires. The answer is: **No (HIGH RISK)**.
9. Was the **length of the shortest prevalence period** for the parameter of interest appropriate?	• **Yes (LOW RISK):** The shortest prevalence period for the parameter of interest was appropriate (e.g. point prevalence, one-week prevalence, one-year prevalence). • **No (HIGH RISK)**: The shortest prevalence period for the parameter of interest was not appropriate (e.g. lifetime prevalence)	The prevalence period is the period that the subject is asked about e.g. "Have you experienced low back pain over the previous year?" In this example, the prevalence period is one year. The longer the prevalence period, the greater the likelihood of the subject forgetting if they experienced the symptom of interest (e.g. low back pain). Examples: • Subjects were asked about pain over the past week. The answer is: **Yes (LOW RISK)**. • Subjects were only asked about pain over the past three years. The answer is: **No (HIGH RISK)**.
10. Were the **numerator(s) and denominator(s)** for the parameter of interest appropriate?	• **Yes (LOW RISK):** The paper presented appropriate numerator(s) AND denominator(s) for the parameter of interest (e.g. the prevalence of low back pain). • **No (HIGH RISK)**: The paper did present numerator(s) AND denominator(s) for the parameter of interest but one or more of these were inappropriate.	There may be errors in the calculation and/or reporting of the numerator and/or denominator. Examples: • There were no errors in the reporting of the numerator(s) AND denominator(s) for the prevalence of low back pain. The answer is: **Yes (LOW RISK)**. • In reporting the overall prevalence of low back pain (in both men and women), the authors accidentally used the population of women as the denominator rather than the combined population. The answer is: **No (HIGH RISK).**
11. Summary item on the overall risk of study bias		
• **LOW RISK OF BIAS:** Further research is very unlikely to change our confidence in the estimate. • **MODERATE RISK OF BIAS:** Further research is likely to have an important impact on our confidence in the estimate and may change the estimate.		

- **HIGH RISK OF BIAS:** Further research is very likely to have an important impact on our confidence in the estimate and is likely to change the estimate.
-

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Qualitative Studies are only considered if they have strong theoretical underpinnings and use an established method of data synthesis.

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R.Hastings@warwick.ac.uk

Brief Reports of up to 1,500 words are encouraged especially for replication studies, methodological research and technical contributions.

AnnotationArticles should be no more than 5,500 words long including tables and figures and should not have been previously published or currently under review with another journal. The normal instructions to authors apply. The date for submission of the article should be negotiated with the Editor in Chief. An honorarium of £400 in total shall be paid to the authors(s) when the article is accepted for publication.

Three main types of Annotations will be commissioned: 1. Authoritative reviews of empirical and theoretical literature. 2. Articles proposing a novel or modified theory or model. 3. Articles detailing a critical evaluation and summary of literature pertaining to the treatment of a specific disorder.

A Hypothesis Paper can be up to 2,500 words and no more than twenty key references. It aims to outline a significant advance in thinking that is testable and which challenges previously held concepts and theoretical

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5.1. Format

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A high proportion of papers are submitted with the term ‘behavior’ as opposed to ‘behaviour’; please use ‘behaviour’.

Where applicable the journal standard is to use words ending in –ise as opposed to –ize. For example, use ‘analyse’ ‘standardise’ as opposed to ‘analyze’ and ‘standardize’

5.2. Structure

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Title Page: Please remember that **peer-review is double-blind**, so that neither authors nor reviewers know each others' identity. Therefore, **no identifying details of the authors or their institutions must appear in the submitted manuscript; author details should be entered as part of the online submission process**. However, a 'Title Page' must be submitted as part of the submission process as a 'Supplementary File Not for Review'. This should contain the title of the paper, names and qualifications of all authors, their affiliations and full mailing address, including e-mail addresses and fax and telephone numbers.

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The reference list should be in alphabetical order thus:

- Giblett E.R. (1969) Genetic Markers in Human Blood.
- Blackwell Scientific Publications, Oxford.
- Moss T.J. & Austin G.E. (1980) Preatherosclerotic lesions in Down's syndrome. *Journal of Mental Deficiency Research* **24**, 137- 41.
- Seltzer M. M. & Krauss M.W. (1994) Aging parents with co-resident adult children: the impact of lifelong caregiving. In: *Life Course Perspectives on Adulthood and Old Age* (eds M. M. Seltzer, M.W. Krauss & M. P. Janicki), pp. 3–18. American Association on Mental Retardation, Washington, DC.

Where more than six authors are listed for a reference please use the first six then 'et al.'

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Tables and figures should be referred to in the text together with an indication of their approximate position recorded in the text margin.

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Appendix E – Initial letter to parents

UNIVERSITY OF BIRMINGHAM

Address

Date

Re: CHILD ; DOB: XXXXX

Dear Parent Name

You may remember that you have taken part in our research before by completing questionnaires about CHILD. We hope you found the feedback that we sent to you helpful.

We are now continuing this project by carrying out a follow-up study. This is the first study to follow up people with X syndrome over such a long period of time and the results of this study will be important for understanding how people with X syndrome develop and change as they grow older. The more people that take part in the research, then the more meaningful the results are. A good response at this follow up will provide new and valuable information.

We are contacting you because you have agreed for your personal details to be kept at the Cerebra Centre for Neurodevelopmental Disorders at the University of Birmingham, and to be contacted with information about future research at the centre. We would like to invite you and CHILD to continue to take part in this research by completing an online questionnaire. When we have analysed the information you send to us, we will provide personalised feedback about CHILD and we will report any changes from previous assessments.

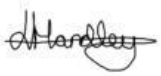
We have included some more information about the research we are doing with this letter. We will also try to contact you in the next couple of weeks to talk to you about the study and find out if you want to take part. After this you will be sent an email or letter with a link to the online questionnaire.

If you are unclear about any aspect of the study or have any questions then contact Dr Louise Handley at l.r.handley@bham.ac.uk or on 0121 414 7206.

Thank you for your time and we look forward to speaking to you.

Centre Director: Prof. Chris Oliver
The Cerebra Centre for Neurodevelopmental Disorders,
School of Psychology, University of Birmingham, Edgbaston, Birmingham, B15 2TT
Website: http://www.birmingham.ac.uk/cndd **FIND website:** www.findresources.co.uk
E-mail: cndd-enquiries@contacts.bham.ac.uk

Yours sincerely



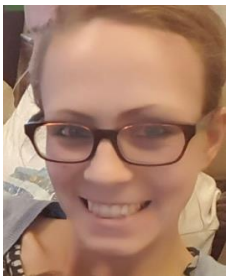
Louise Handley
Honorary Researcher

Chris Oliver
Professor of Neurodevelopmental Disorders

Centre Director: Prof. Chris Oliver
The Cerebra Centre for Neurodevelopmental Disorders,
School of Psychology, University of Birmingham, Edgbaston, Birmingham, B15 2TT
Website: http://www.birmingham.ac.uk/cndd **FIND website:** www.findresources.co.uk
E-mail: cndd-enquiries@contacts.bham.ac.uk

New Research –Movement in Neurodevelopmental Disorders

Prof. Chris Oliver at the Cerebra Centre for Neurodevelopmental Disorders, University of Birmingham, is working with Dr Louise Handley from the University of Manchester on an exciting new study. They will be looking at movement in people with different genetic syndromes and how this might change as people get older. The study will be run by Dr Louise Handley (Clinical Psychologist in Training and former PhD student with the Cerebra Centre). If you think you might want to help us with this study then please read more about it below!



Movement in neurodevelopmental disorders

The goal of our new research project is to learn more about a number of different aspects of movement in children and adults with Cornelia de Lange syndrome (CdLS) and fragile X syndrome (fraX). We are very interested to see how people initiate movements, and how fast and fluid these movements are. We want to assess movement in people with CdLS and fraX, to see if there are similarities or differences in movement abilities in different neurodevelopmental disorders. We may also be able to compare the results of this research with a previous study of people with Autism Spectrum Disorder (ASD). This will help us to see if certain movement problems are more likely in some groups than others. We will also be looking at whether movement problems are more likely to happen in people who already show other behaviours (such as repetitive behaviours). This research could help professionals to better understand what to look out for in CdLS and fraX so that any problems can be spotted as early as possible. It will also help us to work out what other research is still needed.

What does our research involve?

We are looking for parents and carers of children and adults with CdLS or fraX, who have taken part in our questionnaire studies in the past. We will be contacting people who filled in questionnaires looking at repetitive behaviour and social communication several years ago. We will be asking these people to complete an online follow up questionnaire. This should take no more than 10 minutes. As part of the study, we will ask people to fill in:

- **Some background information.**
- **A 13 item questionnaire asking about different aspects of movement.**

We may also call you to check how you are getting on with the questionnaire.

What will happen if you take part?

If you are interested in helping with the study you will be emailed a link to follow. This will take you to an online questionnaire. There will also be some important information that you need to read before you decide whether you want to take part. After you have taken part in our study, we will send you a feedback report about the questionnaire that you complete as part of our study.

Interested?

If you want to find out more about the study, or think you would like to take part, please contact Dr Louise Handley at l.r.handley@bham.ac.uk or contact the Cerebra Centre on 0121 414 7206.

Appendix G – Repetitive Behaviour Questionnaire

THE RBQ

INSTRUCTIONS

1. The questionnaire asks about 19 different behaviours.
2. Each behaviour is accompanied by a brief definition and examples. The examples given for each behaviour are not necessarily a complete list but may help you to understand the definitions more fully.
3. Please read the definitions and examples carefully and circle the appropriate number on the scale to indicate how frequently the person you care for has engaged in each of the behaviours **within the last month**.
4. If a particular behaviour does not apply to the person you care for because they are not mobile or verbal please circle the number 0 on the scale

	Never	Once a month	Once a week	Once a day	More than once a day
1. Object stereotypy: repetitive, seemingly purposeless movement of objects in an unusual way *E.g. twirling or twiddling objects, twisting or shaking objects, banging or slapping objects.*	**0**	**1**	**2**	**3**	**4**
2. Body stereotypy: repetitive, seemingly purposeless movement of whole body or part of body (other than hands) in an unusual way. *E.g. body rocking, or swaying ,or spinning, bouncing, head shaking, body posturing..* Does not include self-injurious behaviour.	**0**	**1**	**2**	**3**	**4**
3. Hand stereotypy: repetitive, seemingly purposeless movement of hands in an unusual way. *E.g. finger twiddling, hand flapping, wigging or flicking fingers, hand posturing.* Does not include self-injurious behaviour.	**0**	**1**	**2**	**3**	**4**
4. Cleaning: Excessive cleaning, washing or polishing of objects or parts of the body *E.g. polishes windows and surfaces excessively, washes hands and face excessively,*	**0**	**1**	**2**	**3**	**4**
5. Tidying up: Tidying away any objects that have been left out. This may occur in situations when it is inappropriate to put the objects away. Objects may be put away into inappropriate places. *E.g. putting cutlery left out for dinner in the bin, removes all objects from surfaces.*	**0**	**1**	**2**	**3**	**4**
6. Hoarding: Collecting, storing or hiding objects to excess, including rubbish, bits of paper, and pieces of string or any other unusual items.	**0**	**1**	**2**	**3**	**4**
7. Organising objects: Organising objects into categories according to various characteristics such as colour, size, or function. *E.g. ordering magazines according to size, ordering toy cars according to colour, ordering books according to topic.*	**0**	**1**	**2**	**3**	**4**
8. Attachment to particular people: Continually asking to see, speak or contact a particular 'favourite' person. *E.g. continually asks to see or speak to particular friend, carer, babysitter or schoolteacher.*	**0**	**1**	**2**	**3**	**4**
9. Repetitive questions: Asking specific questions over and over. *E.g. always asking people what their favourite colour is, asking who is taking them to school the next day over and over*	**0**	**1**	**2**	**3**	**4**
10. Attachment to objects: Strong preference for a particular object to be present at all times. *E.g. Carrying a particular piece of string everywhere, taking a particular red toy car everywhere, attachment to soft toy or particular blanket.*	**0**	**1**	**2**	**3**	**4**

	Never	Once a month	Once a week	Once a day	More than once a day
11. Repetitive phrases/signing: Repeating particular sounds, phrases or signs that are unrelated to the situation over and over. *E.g. repeatedly signing the word 'telephone'.*	**0**	**1**	**2**	**3**	**4**
12. Rituals: carrying out a sequence of unusual or bizarre actions before, during or after a task. The sequence will always be carried out when performing this task and will always occur in the same way. *E.g. turning round three times before sitting down, turning lights on and off twice before leaving a room, tapping door frame twice when passing through it.*	**0**	**1**	**2**	**3**	**4**
13. Restricted conversation: Repeatedly talks about specific, unusual topics in great detail. *E.g. conversation restricted to: trains, buses, dinosaurs, particular film, country, or sport.*	**0**	**1**	**2**	**3**	**4**
14. Echolalia: Repetition of speech that has either just been heard or has been heard more than a minute earlier. *E.g.: Mum:' Jack don't do that' Jack: 'Jack don't do that'.*	**0**	**1**	**2**	**3**	**4**
15. Preference for routine: Insist on having the same household, school or work schedule everyday. *E.g. likes to have the same activities on the same day at the same time each week, prefers to eat lunch at exactly the same time every day, wearing the same jumper everyday.*	**0**	**1**	**2**	**3**	**4**
16. Lining up or arranging objects*: Arrangement of objects into lines or patterns E.g. placing toy cars in a symmetrical pattern, precisely lining up story books,*	**0**	**1**	**2**	**3**	**4**
17. Just right behaviour: Strong insistence that objects, furniture and toys always remain in the same place. *E.g. all chairs, pictures and toys have a very specific place that cannot be changed.*	**0**	**1**	**2**	**3**	**4**
18. Completing behaviour: Insists on having objects or activities 'complete' or 'whole' *E.g. Must have doors open or closed not in between, story must be read from beginning to end, not left halfway through.*	**0**	**1**	**2**	**3**	**4**
19. Spotless behaviour: Removing small, almost unnoticeable pieces of lint, fluff, crumbs or dirt from surfaces, clothes and objects. *E.g. Picking fluff off a jumper, removing crumbs from the kitchen table.*	**0**	**1**	**2**	**3**	**4**

Appendix H – The Wessex Scale

WESSEX QUESTIONNAIRE

These items refer to the person you care for. For each question (A, B, C, D etc ...), please enter the appropriate code in each box.

(Frequently = more than once a week)

A) Wetting (nights) **1** = frequently **2** = occasionally **3** = never ☐

B) Soiling (nights) **1** = frequently **2** = occasionally **3** = never ☐

C) Wetting (days) **1** = frequently **2** = occasionally **3** = never ☐

D) Soiling (days) **1** = frequently **2** = occasionally **3** = never ☐

E) Walk with help **1** = not at all **2** = not up stairs **3** = up stairs and elsewhere ☐

(note: if this person walks *by himself* upstairs and elsewhere, please also code '3' for 'walk with help')

F) Walk by himself **1** = not at all **2** = not up stairs **3** = up stairs and elsewhere ☐

G) Feed himself **1** = not at all **2** = with help **3** = without help ☐

H) Wash himself **1** = not at all **2** = with help **3** = without help ☐

I) Dress himself **1** = not at all **2** = with help **3** = without help ☐

J) Vision **1** = blind or almost **2** = poor **3** = normal ☐

K) Hearing **1** = deaf or almost **2** = poor **3** = normal ☐

L) Speech **1** = never a word **2** = odd words only **3** = sentences and normal **4** = can talk but doesn't ☐

If this person talks in sentences, is his/her speech:

1 = Difficult to understand even by acquaintances, impossible for strangers?

2 = Easily understood for acquaintances, difficult for strangers?

3 = Clear enough to be understood by anyone? ☐

M) Reads **1** = nothing **2** = a little **3** = newspapers and/or books ☐

N) Writes **1** = nothing **2** = a little **3** = own correspondence ☐

O) Counts **1** = nothing **2** = a little **3** = understands money values ☐

Appendix I – Social Communication Questionnaire (Lifetime version)

SOCIAL COMMUNICATION QUESTIONNAIRE © Rutter et al 2003

Please circle 'yes' if <u>any</u> one of the following behaviours is present. Although you may be uncertain about whether some behaviours are present or not, please do answer 'yes' or 'no' to every question on the basis of what you think.

1. Is she/he now able to talk using short phrases or sentences? If no, skip to question 8.	**Yes**	**No**
2. Can you have a to and fro "conversation" with her/him that involves taking turns or building on what you have said?	**Yes**	**No**
3. Has she/he ever used odd phrases or said the same thing over and over in almost exactly the same way (either phrases that she/he has heard other people use or ones that she/he has made up?	**Yes**	**No**
4. Has she/he ever used socially inappropriate questions or statements? For example, has she/he ever regularly asked personal questions or made personal comments at awkward times?	**Yes**	**No**
5. Has she/he ever got her/his pronouns mixed up (e.g., saying you or she/he for I)?	**Yes**	**No**
6. Has she/he ever used words that she/he seemed to have invented or made up her/himself; put things in odd, indirect ways; or used metaphorical ways of saying things (e.g., saying hot rain for steam)?	**Yes**	**No**
7. Has she/he ever said the same thing over and over in exactly the same way or insisted that you say the same thing over and over again?	**Yes**	**No**
8. Has she/he ever had things that she/he seemed to have to do in a very particular way or order or rituals that she/he insisted that you go through?	**Yes**	**No**
9. Has her/his facial expression usually seemed appropriate to the particular situation, as far as you could tell?	**Yes**	**No**
10. Has she/he ever used your hand like a tool or as if it were part of her/his own body (e.g., pointing with your finger, putting your hand on a doorknob to get you to open the door)?	**Yes**	**No**
11. Has she/he ever had any interests that preoccupy her/him and might seem odd to other people (e.g., traffic lights, drainpipes, or timetables)?	**Yes**	**No**
12. Has she/he ever seemed to be more interested in parts of a toy or an object (e.g., spinning the wheels of a car), rather than using the object as it was intended?	**Yes**	**No**
13. Has she/he ever had any special interests that were unusual in their intensity but otherwise appropriate for her/his age and peer group (e.g., trains, dinosaurs)?	**Yes**	**No**
14. Has she/he ever seemed to be unusually interested in the sight, feel, sound, taste, or smell of things or people?	**Yes**	**No**
15. Has she/he ever had any mannerisms or odd ways of moving her/his hands or fingers, such as flapping or moving her/his fingers in front of her/his eyes?	**Yes**	**No**
16. Has she/he ever had any complicated movements of her/his whole body, such as spinning or repeatedly bouncing up and down?	**Yes**	**No**
17. Has she/he ever injured her/himself deliberately, such as by biting her/his arm or banging her/his head?	**Yes**	**No**
18. Has she/he ever had any objects (other than a soft toy or comfort blanket) that she/he had to carry around?	**Yes**	**No**
19. Does she/he have any particular friends or a best friend?	**Yes**	**No**
20. When she/he was 4 to 5, did she/he ever talk with you just to be friendly (rather than to get something)?	**Yes**	**No**
21. When she/he was 4 to 5, did she/he ever spontaneously copy you (or other people) or what you were doing (such as vacuuming, gardening, or mending things)?	**Yes**	**No**
22. When she/he was 4 to 5, did she/he ever spontaneously point at things around her/him just to show you things (not because she/he wanted them)?	**Yes**	**No**
23. When she/he was 4 to 5, did she/he ever use gestures, other than pointing or pulling your hand, to let you know what she/he wanted	**Yes**	**No**

24. When she/he was 4 to 5, did she/he nod her/his head to mean yes?	**Yes**	**No**
25. When she/he was 4 to 5, did she/he shake her/his head to mean no?	**Yes**	**No**
26. When she/he was 4 to 5, did she/he usually look at you directly in the face when doing things with you or talking with you?	**Yes**	**No**
27. When she/he was 4 to 5, did she/he smile back if someone smiled at her/him?	**Yes**	**No**
28. When she/he was 4 to 5, did she/he ever show you things that interested her/him to engage your attention?	**Yes**	**No**
29. When she/he was 4 to 5, did she/he ever offer to share things other than food with you?	**Yes**	**No**
30. When she/he was 4 to 5, did she/he ever seem to want you to join in her/his enjoyment of something?	**Yes**	**No**
31. When she/he was 4 to 5, did she/he ever try to comfort you if you were sad or hurt?	**Yes**	**No**
32. When she/he was 4 to 5, when she/he wanted something or wanted help, did she/he look at you and use gestures with sounds or words to get your attention?	**Yes**	**No**
33. When she/he was 4 to 5, did she/he show a normal range of facial expressions?	**Yes**	**No**
34. When she/he was 4 to 5, did she/he ever spontaneously join in and try to copy the actions in social games, such as The Mulberry Bush or London Bridge Is Falling Down?	**Yes**	**No**
35. When she/he was 4 to 5, did she/he play any pretend or make-believe games?	**Yes**	**No**
36. When she/he was 4 to 5, did she/he seem interested in other children of approximately the same age whom she/he did not know?	**Yes**	**No**
37. When she/he was 4 to 5, did she/he respond positively when another child approached her/him?	**Yes**	**No**
38. When she/he was 4 to 5, if you came into a room and started talking to her/him without calling her/his name, did she/he usually look up and pay attention to you?	**Yes**	**No**
39. When she/he was 4 to 5, did she/he ever play imaginative games with another child in such a way that you could tell that they each understood what the other was pretending?	**Yes**	**No**
40. When she/he was 4 to 5, did she/he play cooperatively in games that required joining in with a group of other children, such as hide-and-seek or ball games?	**Yes**	**No**

Appendix J – Attenuated Behaviour Questionnaire (Core and Movement domains)

ACQ©

This questionnaire asks about a number of different behaviours that your child/ the person you care for might show or may have shown in the past.

Each question describes a behaviour and then asks you to say whether your child/ the person you care for currently shows that behaviour and how this compares to what the behaviour was like in the past. For some of the questions you will also be asked to rate how often the behaviour happens and how severely it affects them.

For some of the items examples are given to help you think about what that behaviour might look like.

Please read each of the definitions and examples and then circle your response.

PART A: CORE SYMPTOMS

Question no.	Description	Please circle one answer				
1	**Are there times when he/she is very still for long periods of time, almost like a statue?**	*Yes more than before*	*Yes the same as before*	*Yes but less than before*	*No – not at the moment but it used to happen*	*No-never*
	If you answered 'No' go to Question 2					
1a)	How often does the individual experience these periods of stillness at the moment?	*All/almost all the time they are awake*	*Most of the time they are awake*	*Some of the time they are awake*	*Rarely when they are awake*	
1b)	How severely does the individual experience these periods of stillness at the moment?	*Very severely* (they seem unable to focus on or do anything else at this time)	*Quite severely* (it is difficult for them to focus on or do anything else at this time)	*Moderately* (there seems to be an effect on their ability to focus on or do things)	*Slightly* (this seems to have little or no effect on their life)	
2	**Does he/she seem to get 'stuck' when trying to do something?** (e.g. stopping mid-air half way through reaching for something & looking like they are trying to move but can't OR beginning to pick up a cup to drink but lifting it only half way and then putting it down again)	*Yes more than before*	*Yes the same as before*	*Yes but less than before*	*No – not at the moment but it used to happen*	*No-never*
	If you answered 'No' go to Question 3					
2a)	How often does the individual experience these periods of 'stuckness' at the moment?	*All/almost all the time they are awake*	*Most of the time they are awake*	*Some of the time they are awake*	*Rarely when they are awake*	
2b)	How severely does the individual experience these periods of 'stuckness' at the moment?	*Very severely* (they seem unable to focus on or do anything else at this time)	*Quite severely* (it is difficult for them to focus on or do anything else at this time)	*Moderately* (there seems to be an effect on their ability to focus on or do things)	*Slightly* (this seems to have little or no effect on their life)	
3	**Does he/she seem to find it difficult to stop doing actions once they have started them?** (e.g. repeatedly putting a coat on & taking it off again & again for a long period of time)	*Yes more than before*	*Yes the same as before*	*Yes but less than before*	*No – not at the moment but it used to happen*	*No-never*
	If you answered 'No' go to Question 4					

Question no.	Description	Please circle one answer				
3a)	How often does the individual experience these periods of problems stopping actions at the moment?	*All/almost all the time they are awake*	*Most of the time they are awake*	*Some of the time they are awake*	*Rarely when they are awake*	
3b)	How severely does the individual experience these periods of problems stopping actions at the moment?	*Very severely* (they seem unable to focus on or do anything else at this time)	*Quite severely* (it is difficult for them to focus on or do anything else at this time)	*Moderately* (there seems to be an effect on their ability to focus on or do things)	*Slightly* (this seems to have little or no effect on their life)	
4	**Does he/she seem to find it difficult to start moving?** (e.g. lying still and looking like he/she wants to get up or reach for something but can't)	*Yes more than before*	*Yes the same as before*	*Yes but less than before*	*No – not at the moment but it used to happen*	*No-never*
	If you answered 'No' go to Question 5					
4a)	How often does the individual experience these periods of difficulty initiating movement at the moment?	*All/almost all the time they are awake*	*Most of the time they are awake*	*Some of the time they are awake*	*Rarely when they are awake*	
4b)	How severely does the individual experience these periods of difficulty initiating movement at the moment?	*Very severely* (they seem unable to focus on or do anything else at this time)	*Quite severely* (it is difficult for them to focus on or do anything else at this time)	*Moderately* (there seems to be an effect on their ability to focus on or do things)	*Slightly* (this seems to have little or no effect on their life)	
5	**Does he/she move very slowly and takes a long time to finish actions?** (e.g. moving very slowly when doing things like picking up a cup to drink or eating dinner)	*Yes more than before*	*Yes the same as before*	*Yes but less than before*	*No – not at the moment but it used to happen*	*No-never*
	If you answered 'No' go to Question 6					
5a)	How often does the individual experience these periods of slowness in movement at the moment?	*All/almost all the time they are awake*	*Most of the time they are awake*	*Some of the time they are awake*	*Rarely when they are awake*	
5b)	How severely does the individual experience these periods of slowness in movement at the moment?	*Very severely* (they seem unable to focus on or do anything else at this time)	*Quite severely* (it is difficult for them to focus on or do anything else at this time)	*Moderately* (there seems to be an effect on their ability to focus on or do things)	*Slightly* (this seems to have little or no effect on their life)	
6	**Are there times when he/she needs physical OR verbal prompts to complete actions?** (e.g. needing someone to tell them or touch their arm to enable them to lift a cup to their mouth to drink)	*Yes more than before*	*Yes the same as before*	*Yes but less than before*	*No – not at the moment but it used to happen*	*No-never*
	If you answered 'No' go to Question 7					
6a)	How often does the individual experience these periods of requiring prompts to complete actions at the moment?	*All/almost all the time they are awake*	*Most of the time they are awake*	*Some of the time they are awake*	*Rarely when they are awake*	
6b)	How severely does the individual experience these periods of requiring prompts to complete actions at the moment?	*Very severely* (they seem unable to focus on or do anything else at this time)	*Quite severely* (it is difficult for them to focus on or do anything else at this time)	*Moderately* (there seems to be an effect on their ability to focus on or do things)	*Slightly* (this seems to have little or no effect on their life)	

PART B: OTHER RELATED BEHAVIOURS AND SYMPTOMS

Question no.		Yes more than before	Yes the same as before	Yes but less than before	No – not at the moment but it used to happen	No -never
7	**Does he/she like to move their body in repetitive ways?** (This includes any frequent body movement such as body rocking, twisting wrists, flicking fingers etc?)	5	4	3	2	1
8	**Does he/she strike and hold stiff poses?**	5	4	3	2	1
9	**Does he/she experiences 'tics' (speech or movement)?** (e.g. suddenly & repetitively move their body or saying a word/phrase in a way they seem unable to control?)	5	4	3	2	1
10	**Does he/she move their hands or feet in an odd way?** (e.g. twisting, waving or shaking)	5	4	3	2	1
11	**Does he/she twist or flick their hands in front of their eyes?**	5	4	3	2	1
12	**Does he/she move in a very jerky way?**	5	4	3	2	1
13	**Does he/she walk unusually?**	5	4	3	2	1
14	**Does he/she display examples of mood changeability internally?** (e.g. has he/she lost enjoyment in their favourite activities? OR Withdraws from others?)	5	4	3	2	1
15	**Does he/she display examples of mood changeability externally?** (e.g. does he/she scream, cry or laugh suddenly for no reason? OR Behave aggressively towards themselves or others at times? OR Displays impulsive or excitable phases?)	5	4	3	2	1
16	**Does he/she find it difficult to walk through doorways?**	5	4	3	2	1
17	**Does he/she find it difficult to walk across lines on the floor or changes in flooring?** (e.g. from a carpet to a wooden floor)	5	4	3	2	1
18	**Is he/she doing less than they used to?** (e.g. is it harder than it used to be to encourage them to do activities?)	5	4	3	2	1
19	**Are there periods where he/she communicates with others less or not at all?** (This includes all communication methods - it could be reduced speech or other communication such as signing, PECS etc)	5	4	3	2	1
20	**Are there periods where he/she is incontinent OR refuses to use the toilet when they used to?** (e.g. the person is not using skills that they have used in the past and are soiling themselves when they would use the toilet before)	5	4	3	2	1
21	**Does he/she have sleep problems?** (e.g. finds it difficult to get to sleep at night, wants to sleep in the day but not at night, gets little sleep etc.)	5	4	3	2	1
22	**Are there periods where he/she refuses to eat OR eats less than they used to?**	5	4	3	2	1
23	**Does he/she move or roll their eyes unusually?** (e.g. rolls their eyes around again & again or looks from left to right again & again)	5	4	3	2	1
24	**Does he/she pull unusual facial expressions or 'grimaces'?**	5	4	3	2	1
25	**Does he/she ignore instructions?** (This must be for instructions that you know the individual understands)	5	4	3	2	1
26	**Does he/she refuse to wash or change his/her clothes?**	5	4	3	2	1
27	**Does he/she make groaning or other unusual noises regularly?**	5	4	3	2	1
28	**Does he/she stare into space or fix their gaze onto certain things?**	5	4	3	2	1

Appendix K – Substantial amendment favourable opinion letter

NHS
Health Research Authority

West Midlands - Coventry & Warwickshire Research Ethics Committee

The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

Tel: 0115 8839269

01 December 2015

Professor Chris Oliver
Professor of Neurodevelopmental Disorders
University of Birmingham
School of Psychology
University of Birmingham
Edgbaston
B15 2TT

Dear Professor Oliver

Study title:	**Understanding Behaviour and Family Adjustment in Individuals with Neurodevelopmental Disorders.**
REC reference:	**10/H1210/1**
Protocol number:	**RG_09-081**
Amendment number:	**Substantial Amendment 3 23.09.2015**
IRAS project ID:	**20638**

The above amendment was reviewed on 27 November 2015 by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Notice of Substantial Amendment (non-CTIMP)	Substantial Amendment 3 23.09.2015	
Other [Autism Catatonia Questionnaire]	1	23 September 2015
Other [OG-575 Salvia Self-Collection Manufacturer's Instructions]	1	23 September 2015
Other [A31_inforfu_over16]	4	23 September 2015
Other [A31_inforfu_under16]	4	23 September 2015

Other [A31_infoknown_over16]	4	23 September 2015
Other [A31_infoknown_under16]	4	23 September 2015
Other [A31_infounknown_over16]	4	23 September 2015
Other [A31_infounknown_under16]	4	23 September 2015
Other [A31_consentknownA]	5	23 September 2015
Other [A31_consentknownB]	5	23 September 2015
Other [A31_consentknownC]	5	23 September 2015
Other [A31_consentunknownA]	5	23 September 2015
Other [A31_consentunknownB]	5	23 September 2015
Other [A31_consentunknownC]	5	23 September 2015
Other [A31_Coverletterfu_salivacollection]	1	23 September 2015
Research protocol or project proposal	4	23 September 2015

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

10/H1210/1:	**Please quote this number on all correspondence**

Yours sincerely

P.P

Dr Helen Brittain (Chair)
Chair

E-mail: NRESCommittee.WestMidlands-CoventryandWarwick@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

Copy to:

West Midlands - Coventry & Warwickshire Research Ethics Committee

Attendance at Sub-Committee of the REC meeting on 27 November 2015

Committee Members:

Name	*Profession*	*Present*	*Notes*
Dr Helen Brittain (Chair)	Clinical Psychologist Retired	Yes	
Dr Karen Schofield	Retired Consultant Haematologist	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Ms Teagan Allen	REC Assistant

Appendix L – Information sheets provided to parents

Appendix L1 – Online version

UNIVERSITY OF BIRMINGHAM

The Cerebra Centre for Neurodevelopmental Disorders

Understanding Behaviour in Individuals with Neurodevelopmental Disorders: Information Sheet

Please read this information carefully before deciding whether you wish to take part in the study. If you have any further questions please contact Professor Chris Oliver on (0121) 414 7206 or at cndd-enquiries@contacts.bham.ac.uk. If you have any medical/ other problems which make it difficult for you to read this information, please contact Professor Chris Oliver for a verbal explanation of the research.

When you are happy that you have all of the information you need to be able to decide whether or not you and your child/the person you care for would like to take part in the study, please complete the online consent form and questionnaire pack.

Background to the study:

You may remember that you have taken part in our research before by completing questionnaires about the person you care for. We hope you found the feedback that we sent to you helpful. We are now extending this project by carrying out a 4 year follow-up to find out about changes since we first contacted you. The results of this study will be important for understanding how people change as they grow older. Currently, very little is known about how people with X syndrome progress and change over time. The more people that take part in this research, then the more meaningful the results are. A good response at this 4 year follow up will provide new and valuable information concerning age related behaviour changes seen in (disorder name).

Aims of the study:

1. To further our understanding of challenging behaviour, repetitive behaviour, hyperactivity, mood and social functioning in individuals with X syndrome
2. To understand what happens with regard to these behaviours as children and adults develop.
3. To understand what, if any, changes may occur with regard to these behaviours when the individuals reach a certain age.
4. To understand the impact of having a child with a disability has on the family.

What will happen if you and your child/the person you care for decide(s) to participate?

Where will the research take place?

The research will involve completing the online questionnaire. This can be completed by you in your own time.

Who will be involved in collecting the data?

Members of the research team at the Cerebra Centre for Neurodevelopmental disorders including disorders including Professor Chris Oliver and Dr. Joanna Moss.

How long will participation in the study take?

The questionnaire pack will take approximately 45 minutes to complete.

In the future you may be asked if you would like to complete the questionnaire again so that we can start to understand what happens to people with X syndrome across their lifetime. We will only contact you with this invitation if you have previously agreed to be contacted by the research team at the University of Birmingham with information about research studies conducted by the team.

Sometimes after you have completed the questionnaire, we may need to contact you again in order to clarify any information that you have provided or to ask you for further information regarding the diagnosis of the person you care for. This helps us to ensure that our data is as useful and as accurate as possible. If this happens then we would contact you again within 6 months of receiving your questionnaire pack to ask whether or not you would be willing to provide us with the extra information.

What will participants be required to do during the study?
We will ask parents and caregivers to complete the online consent form and questionnaire.

Are there any risks that individuals taking part in the study might face?
There will not be any risks associated with participation in this study.

What are the potential benefits for participants from taking part?
You will receive a personalised feedback regarding your child/ the person you care for. This study will help us to find out more about the lives of people with (disorder name) and the difficulties that these people face. The results might help us to improve things for people with (disorder name) in the future.

Where will data be stored?
The data collected will be kept in password protected storage at the University of Birmingham and on servers in the high security data centres of our survey-hosting partner (LimeSurvey). Information will be treated as strictly confidential and handled in accordance with the provisions of the Data Protection Act 1998.

If you/ the person you care for decide(s) to participate, what will happen after that participation?
You and your child or person you care for will receive an individual feedback report describing the results of all of the assessments that were carried out during the study. If requested, this feedback report will be circulated to other interested individuals. Descriptions of research findings will be published in newsletters of the relevant family support groups and educational institutions involved. Any request for advice concerning the person you care for will be referred to Professor Chris Oliver, Clinical Psychologist.

The researchers will publish the findings from the study in scientific journals and will present the results at relevant conferences.

What will happen to the data afterwards?
The information that you provide will be held on password protected databases and on servers in a high security data centre. Participants will be identified by a unique number so that the information you provide us with cannot be traced to your personal details. You will be able to decide whether or not you want to make your research data available to any professionals or clinicians working with you and the person you care for should they wish to see it. This is optional and will not affect your participation in the current study. If you agree to this, then your research data will only be made available to relevant clinicians or professionals should they contact us directly and request to see it. If you do not agree to this then research data will not be made available to anyone other than the research team at the University of Birmingham.

What will happen to my personal details afterwards?
Since you have previously been involved in our research projects at the University of Birmingham and have agreed to be contacted by the research team with information about future research work, we have a copy of your personal details on the 'Regular Participant Database'. This database is password protected and only approved members of our research team have access to your details. We do not share your details with anyone outside the research team unless you tell us to.

What happens if I decide that I no longer want my details on the Regular Participant Database?
All you would need to do is contact Chris Oliver on 0121 414 7206 or at cndd-enquiries@contacts.bham.ac.uk or at the School of Psychology, University of Birmingham, Edgbaston, Birmingham, B15 2TT. Your details would be removed from the database immediately.

Consent
After having read all of the information and having received appropriate responses to any questions that you may have about the study you will be asked to give your and your child's/ person you care for's consent to participate in the study if you decide that you do wish to participate. The section below on 'Giving consent' will explain this process. We need to receive consent from/ on behalf of potential participants in order for them to participate.

Withdrawal
Even after consent has been granted, participants can request to be withdrawn from the study at any time, without giving a reason. Even after participation has taken place, consent can be withdrawn and any data collected will be destroyed. This will not restrict the access of you/ the person you care for to other services and will not affect their right to treatment.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. Please contact Chris Oliver on 0121 414 7206 or at cndd-enquiries@contacts.bham.ac.uk in the first instance. If you remain unhappy and wish to complain formally, you can contact: Professor Chris Miall; Head of School; School of Psychology, University of Birmingham, Birmingham, B15 2TT, by email: hos.psychology@contacts.bham.ac.uk or by phone on 0121 414 4931

Confidentiality

The company with whom we have chosen to host our questionnaires (LimeSurvey) adheres to stringent security practices. However, the transmission of data over the Internet can never be guaranteed to be entirely secure. By taking part in this study the risk to your personal information is no greater than at any other time that you provide this information online (e.g. shopping, banking). Nevertheless, please participate in this research only if you are comfortable with this.

If details from the study are published, information on participants will be presented without reference to their name or any other identifying information. All personal details held at the University of Birmingham will be kept separately from the information collected so that it will only be possible to connect results to individuals via a special code. This will ensure that results are kept anonymous. In the unlikely event of any evidence of abuse being identified, this information will be disclosed to you by the research workers

Review
The study has been approved by Coventry NHS Research Ethics Committee. Ref: 10/H1210/01. Tel: 01527 587688

Further information
If you would like any more information about the study please contact Professor Chris Oliver on 0121 414 7206 or at cndd-enquiries@contacts.bham.ac.uk. Or write to Chris Oliver, School of Psychology, University of Birmingham, Edgbaston, Birmingham, B15 2TT.

Giving consent
Now it is up to you whether you decide that you and your child/the person you care for would like to participate. The decision about whether or not to take part in the study must be 'informed'. This means that anyone making the decision must understand exactly what is involved in the study, what will be required from participants and why.

UNIVERSITY OF BIRMINGHAM

The Cerebra Centre for Neurodevelopmental Disorders

Understanding Behaviour in Individuals with Neurodevelopmental Disorders: Information Sheet

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When you are happy that you have all of the information you need to be able to decide whether or not you and your child/the person you care for would like to take part in the study, please complete the enclosed consent form and questionnaire pack return them to us in the prepaid envelope provided

Background to the study:

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4. To understand the impact of having a child with a disability has on the family.

What will happen if you and your child/the person you care for decide(s) to participate?

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The research will involve completing the enclosed questionnaire pack. This can be completed by you in your own time.

Who will be involved in collecting the data?

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The questionnaire pack will take approximately 45 minutes to complete.

In the future you may be asked if you would like to complete the questionnaire again so that we can start to understand what happens to people with X syndrome across their lifetime. We will only contact you with this invitation if you have previously agreed to be contacted by the research team at the University of Birmingham with information about research studies conducted by the team.

Sometimes after you have completed the questionnaire, we may need to contact you again in order to clarify any information that you have provided or to ask you for further information regarding the diagnosis of the person you care for. This helps us to ensure that our data is as useful and as accurate as possible. If this happens then we would contact you again within 6 months of receiving your questionnaire pack to ask whether or not you would be willing to provide us with the extra information.

What will participants be required to do during the study?
We will ask parents and caregivers to complete the enclosed questionnaire pack and return it to us alongside the consent form in the pre-paid envelope provided.

Are there any risks that individuals taking part in the study might face?
There will not be any risks associated with participation in this study.

What are the potential benefits for participants from taking part?
You will receive a personalised feedback regarding your child/ the person you care for. This study will help us to find out more about the lives of people with (disorder name) and the difficulties that these people face. The results might help us to improve things for people with (disorder name) in the future. You will have the option to decide whether or not you would be happy to be contacted by the University of Birmingham on behalf of Great Ormond Street Hospital for a full clinical/medical evaluation by the clinical genetics team should this be considered appropriate. This is optional and will not affect your participation in the current study. Unfortunately it will not be possible for everyone who participates in the study to be invited for this clinical evaluation.

Where will data be stored?
The data collected will be kept in locked or password protected storage at the University of Birmingham. Only members of the research team at the University of Birmingham will have access to information that we collect about you. Information will be treated as strictly confidential and handled in accordance with the provisions of the Data Protection Act 1998.

If you/ the person you care for decide(s) to participate, what will happen after that participation?
You and your child or person you care for will receive an individual feedback report describing the results of all of the assessments that were carried out during the study. If requested by, this feedback report will be circulated to other interested individuals. Descriptions of research findings will be published in newsletters of the relevant family support groups and educational institutions involved. Any request for advice concerning the person you care for will be referred to Professor Chris Oliver, Clinical Psychologist.

The researchers will publish the findings from the study in scientific journals and will present the results at relevant conferences.

What will happen to the data afterwards?
The information that you provide will be locked in a filing cabinet at the University of Birmingham or held on a password protected database. Participants will be identified by a unique number so that the information you provide us with cannot be traced to your personal details. . You will be able to decide whether or not you want to make your research data available to any professionals or clinicians working with you and the person you care for should they wish to see it. This is optional and will not affect your participation in the current study. If you agree to this, then your research data will only be made available to relevant clinicians or professionals should they contact us directly and request to see it. If you do not agree to this then research data will not be made available to anyone other than the research team at the University of Birmingham.

What will happen to my personal details afterwards?
Since you have previously been involved in our research projects at the University of Birmingham and have agreed to be contacted by the research team with information about future research work, we have a copy of your personal details on the 'Regular Participant Database'. This database is password protected and

only approved members of out research team have access to your details. We do not share your details with anyone outside the research team unless you tell us to.

What happens if I decide that I no longer want my details on the Regular Participant Database?
All you would need to do is contact Chris Oliver on 0121 414 7206 or at c.oliver@bham.ac.uk or at the School of Psychology, University of Birmingham, Edgbaston, Birmingham, B15 2TT. Your details would be removed from the database immediately.

Consent
After having read all of the information and having received appropriate responses to any questions that you may have about the study you will be asked to give your and your child's/ person you care for's consent to participate in the study if you decide that you do wish to participate. The section below on 'Giving consent' will explain this process. We need to receive consent from/ on behalf of potential participants in order for them to participate.

Withdrawal
Even after consent has been granted, participants can request to be withdrawn from the study at any time, without giving a reason. Even after participation has taken place, consent can be withdrawn and any data collected will be destroyed. This will not restrict the access of you/ the person you care for to other services and will not affect their right to treatment.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. Please contact Chris Oliver on 0121 414 7206 or at c.oliver@bham.ac.uk in the first instance. If you remain unhappy and wish to complain formally, you can contact: Professor Chris Miall; Head of School; School of Psychology, University of Birmingham, Birmingham, B15 2TT, by email: hos.psychology@contacts.bham.ac.uk or by phone on 0121 414 4931.

Confidentiality

The confidentiality of participants will be ensured. If published, information on the participant will be presented without reference to their name or any other identifying information. All personal details will be kept separately from the information collected so that it will only be possible to connect results to individuals via a special code. This will ensure that results are kept anonymous. In the unlikely event of any evidence of abuse being identified, this information will be disclosed by the research workers.

Review
The study has been approved by Coventry NHS Research Ethics Committee. Ref: 10/H1210/01. Tel: 01527 587688

Further information
If you would like any more information about the study please contact Professor Chris Oliver on 0121 414 7206 or at c.oliver@bham.ac.uk. Or write to Chris Oliver, School of Psychology, University of Birmingham, Edgbaston, Birmingham, B15 2TT.

Giving consent
Now it is up to you whether you decide that you and your child/the person you care for would like to participate. The decision about whether or not to take part in the study must be 'informed'. This means that anyone making the decision must understand exactly what is involved in the study, what will be required from participants and why.

IMPORTANT:

You need to decide whether your child/the person you care for is able to understand enough about the study to make an 'informed' decision independently about whether or not they would like to participate and to communicate this decision to you. If you are unsure whether or not your child/person you care for is able to understand enough to make a decision independently then we can provide you with some guidelines to help you to assess this A symbol information sheet can also be made available to you if this would be of help.

Please contact Professor Chris Oliver 0121 414 7206 or c.oliver@bham.ac.uk to request a copy of this.

Please choose from one of the following options:

1. My child/ the person I care for is <u>able to understand</u> what is involved in the study and what will be required from them if they participate and has communicated their decision to me:

If you think that the person is ***is*** **able** to understand enough about the study in order to make an 'informed' decision and they decide that they would like to participate then please ensure that they complete **Section 1 of Consent Form A coloured YELLOW** enclosed, or that you complete it with them, on their behalf. A parent/carer will need to complete **Section 2 of Consent From A coloured YELLOW** in order to indicate that they also agree to participate in the study. A symbol information sheet can be made available in order to support your child/person you care for in making this decision if it would be of help. Please contact the research team if you would like a copy of the symbol consent form or if you need us to adapt this information further in order to suit your child's needs. Please return the consent form along with the questionnaire pack to us in the prepaid envelope provided.

2. My child/ the person I care for is <u>over the age of 16</u> and <u>cannot understand</u> what is involved in the study or cannot communicate their decision to me:

If you are reading this information on behalf of someone you care for who is **over the age of 16** and you decide that the person ***is not*** able to make an 'informed' decision about whether or not they would like to participate, then we would like to invite you to act as a 'personal consultee' (or 'nominated consultee' where an unpaid carer e.g. parent, legal guardian etc is not able to act as a 'personal consultee') for that person. Please read the enclosed 'Personal and Nominated Consultee Information Sheet' coloured **PINK**. Once you have finished reading the 'Personal and Nominated Consultee Information Sheet' please decide whether or not you feel able to act as a personal or nominated consultee for the person you care for.

If you feel able to act as a personal or nominated consultee for the person you care for please think about whether the person would decide to participate if they were able to make an 'informed' decision themselves about whether or not to participate. If you decide that the person would decide to participate, please complete **Consent Form *C* coloured BLUE** enclosed and return it to us alongside the questionnaire pack in the prepaid envelope provided.

Appendix M – Consent forms

Appendix M1 – For those able to provide consent

UNIVERSITY OF BIRMINGHAM

The Cerebra Centre for Neurodevelopmental Disorders

Consent Form A : For individuals who are able to provide consent to participate in the study

Understanding behaviour and family adjustment in individuals with neurodevelopmental disorders

Study Director: Professor Chris Oliver

SECTION 1: Please complete this section if you are a person with X syndrome

1. Has somebody else explained the project to you or have you read the information? YES☐ NO☐
2. Do you understand what the project is about? YES☐ NO☐
3. Have you asked all of the questions you want? YES☐ NO☐
4. Have you had your questions answered in a way you understand? YES☐ NO☐
5. Do you understand it is OK to stop taking part at any time? YES☐ NO☐
6. Are you are happy to take part? YES☐ NO☐

If you checked no to any answers or you don't want to take part, don't type your name!

If you do want to take part, you can type your name below

You can also choose if you want to say 'yes' to these:

7. If your Dr asks to see your results from this project it is OK for us to share this with them? YES☐ NO☐

8. Are you are happy for us to contact you again in the future YES☐ NO☐

Your name: _____

Date: _____

The person who explained this project to you needs to sign too. If you are not aged 16 or above, this should be your parent/guardian.

Print name: _____

Check box to confirm information ☐

Date: _____

<u>SECTION 2:</u> Please complete this section if you are a parent/carer/guardian of a person with X syndrome who has provided their consent to participate in the study.

Please check box…

1. I confirm that I have read and understood 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 and that of my child/person I care for is voluntary and that I am free to withdraw at any time without giving any reason, without my or that of my child's/person I care for's medical care or legal rights being affected. ☐

3. I understand that relevant sections of my child's/person I care for's GP medical notes or records confirming genetic diagnosis and health status may be looked at by members of the Cerebra Centre for Neurodevelopmental Disorders research team at the University of Birmingham, where it is relevant to this research project. I give permission for these individuals to have access to these records. ☐

4. I agree to my child's/person I care for's GP being informed of my participation and that of my child/person I care for's in the study, where access to my child's/person I care for's medical records is required. ☐

5. I agree to take part in the above study. ☐

Optional clause: The statement below is <u>optional</u>:

1. I agree to the University of Birmingham research team sharing my research data with any professionals or clinicians working with me and the person I care for should they request to see them. ☐

Print Name: _____ Telephone number: _____

Address: _____

_____Email: _____

Relationship to participant: _____

Check box to confirm information: ☐

Date: _____

Appendix M2 – For those under 16 who are not able to provide consent

UNIVERSITY OF BIRMINGHAM

The Cerebra Centre for Neurodevelopmental Disorders

Consent Form B: For children under the age of 16 who are not able to provide consent.

Understanding behaviour and family adjustment in individuals with neurodevelopmental disorders

Study Director: Professor Chris Oliver

Please complete this section if you are a parent/ guardian of a child (under 16 years) with X syndrome who is not able to provide consent.

Please check box…

1. I confirm that I have read and understood 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 and that of my child/person I care for is voluntary and that I am free to withdraw at any time without giving any reason, without my or that of my child's/person I care for's medical care or legal rights being affected. ☐

3. I understand that relevant sections of my child's/person I care for's GP medical notes or records confirming genetic diagnosis and health status may be looked at by members of the Cerebra Centre for Neurodevelopmental Disorders research team at the University of Birmingham, where it is relevant to this research project. I give permission for these individuals to have access to these records. ☐

4. I agree to my child's/person I care for's GP being informed of my participation and that of my child/person I care for's in the study, where access to my child's/person I care for's medical records is required. ☐

5. I agree to take part in the above study. ☐

Optional clause: The statement below is optional:

1. I agree to the University of Birmingham research team sharing my research data with any professionals or clinicians working with me and the person I care for should they request to see them. ☐

Print Name: _____ Name of person you care for:_____

Address: _____ Email: _____

Telephone number: _____ Relationship to participant: _____

Check box to confirm information: ☐

Date: _____

Appendix M3 – For those over 16 who are not able to provide consent

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UNIVERSITY OF BIRMINGHAM

The Cerebra Centre for Neurodevelopmental Disorders

Consent Form C: For individuals over the age of 16 who are not able to provide consent.

Understanding behaviour and family adjustment in individuals with neurodevelopmental disorders

Study Director: Professor Chris Oliver

Please read the following statements:

Please check box…

1. I (your name)_____have been consulted about (name of participant)_____'s participation in the above research project. I have had the opportunity to ask questions about the study and understand what is involved. ☐
2. In my opinion he/she would have no objection to taking part in the above study. ☐
3. I understand that I can request he/she is withdrawn from the study at any time without giving any reason and without his/her care or legal rights being affected. ☐
4. I understand that relevant sections of his/her GP medical notes or records confirming genetic diagnosis and health status may be looked at by members of the Cerebra Centre for Neurodevelopmental Disorders research team at the University of Birmingham, where it is relevant to this research project. I give permission for these individuals to have access to these records. ☐
5. I agree to his/her GP being informed of their participation in the study, where access to medical records is required. ☐
6. I agree to take part in the above study. ☐

Optional clause: The statement below is optional:

1. I agree to the University of Birmingham research team sharing his/her research data with any professionals or clinicians working with them should they request to see them. ☐

Print Name: _____ Telephone number: _____

Address: _____Email: _____

Relationship to participant: _____

Check box to confirm information: ☐

Date: _____

Appendix N – Nominated and personal consultee information sheet

UNIVERSITY OF BIRMINGHAM

The Cerebra Centre for Neurodevelopmental Disorders

Personal and Nominated Consultee Information Sheet

Please read this information sheet if you care for a person who you have judged *is not* able to make an 'informed' decision about whether or not they would like to take part in the study or *is not* able to communicate that decision to you.

If you are an unpaid carer (e.g. parent, legal guardian etc) we would like to invite you to act as a ***personal consultee*** for the person that you care for. If you are a paid carer (e.g. paid carer, key worker, support worker etc) and there are no unpaid carers (e.g. parent, legal guardian etc) to act as a personal consultee for the person you care for then we would like to invite you to act as a ***nominated consultee*** **(go to page 3)**.

Information for Personal Consultees

What is a Personal Consultee?

In order to understand illness and disability, and to improve treatment and care, research is essential. That research may focus on the people with the illness or disability or on children under the age of 16, and may invite those people to participate. Some people will have capacity to make their own decision whether to take part in the research.

Others, possibly the youngest children or those most affected by the illness or disability, may not have that capacity. They may not be able to understand enough of the research to be able to give 'informed consent'. They may not be able to communicate a decision. The research provisions of the Mental Capacity Act are designed to allow such people to take part in research even though they cannot give valid consent of their own.

First, the research has to be approved by a Research Ethics Committee. Then, instead of asking the research participant for consent, the researcher must ask a consultee for an opinion whether the research participant would have wished to take part in the research.

Who can be a personal consultee?

Any person interested in the welfare of the proposed participant, for example:

- A family member, unpaid carer or friend
- A person acting under a Lasting Power of Attorney
- A court appointed deputy

Who cannot be a personal consultee?

- Paid carers and professionals (if you are a paid carer or professional please refer to **page 3**)
- People connected with the research (e.g. members of the research team)

Why have I been asked?

You have been asked to act as a personal consultee by a researcher because the researcher thinks you might be willing and able to do this because of your close relation with the proposed research participant.

If I agree to be a personal consultee, what will I have to do?

You will need to think about what the proposed participant's wishes and feelings about the research would be if they had capacity to make an informed decision and decide whether in your view the person should be involved in the research or not. This means you need to

- Look at the study information sheet.
- Think about whether or not the person would want to be involved in the research project if he or she had the capacity to make that decision.

You should not put forward your personal views on participation in the specific project or research in general, you must consider only what the person's views and interests are or would likely be. You should think about:

- What the broad aims of the research and the practicalities of taking part will mean for the proposed participant.
- How the specific activities in the research might impact the participant. For example, if the study involves activities in the afternoon when the person is most tired they might find it a strain or the research might involve an activity that the person particularly enjoys and thus would give them more pleasure.
- Any view previously expressed by the person on the overall nature of the research.

If you advise that the proposed participant would not have wanted to be involved in the research, they cannot be included in the research.

If you advise that the proposed participant would want to be involved, they may be included in the research. If the research commences but the person shows any sign at any stage that they are not happy to be involved in the research you can change your advice at any time without giving a reason, whereby the researcher must withdraw the person from the research. If the person seems unhappy at any point or shows any signs of objection, then they will be withdrawn from the research.

The research project has been approved by the Coventry NHS Research Ethics Committee. If you wish to see proof of approval from this body, or you wish to discuss any concerns about acting as a personal consultee for the person that you care for, please contact Chris Oliver on 0121 414 7206 or by email at c.oliver@bham.ac.uk.

I don't want to be a personal consultee/ I am a paid carer and so cannot be a personal consultee- what do I do?

Please try to suggest an alternative person who might like to act as a personal consultee for the potential participant, please pass the project information pack on to that person.

Where can I get more information and guidance?

More information is available from:

Department for Constitutional Affairs (2007) *Mental Capacity Act 2005 Code of Practice*
http://www.dca.gov.uk/legal-policy/mental-capacity/mca-cp.pdf

Department of Health (2007) *Guidance on nominating a consultee for research involving adults who lack capacity to consent* (consultation)
http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_076207

Mental Capacity Implementation Programme (2007) *Making Decisions: a guide for family, friends and unpaid carers. Second edition*
http://www.dca.gov.uk/legal-policy/mental-capacity/mibooklets/booklet02.pdf
A printed copy of this booklet is available by telephoning 023 80878038.

I have decided that I want to be a personal consultee- what do I do?

Please go back to the 'understanding behaviour in neurodevelopmental disorders' Information Sheet and continue reading.

Information for Nominated Consultees

What is a Nominated Consultee?

In order to understand illness and disability, and to improve treatment and care, research is essential. That research may focus on the people with the illness or disability or on children under the age of 16, and may invite those people to participate. Some people will have capacity to make their own decision whether to take part in the research.

Others, possibly the youngest children or those most affected by the illness or disability, may not have that capacity. They may not be able to understand enough of the research to be able to give 'informed consent'. They may not be able to communicate a decision. The research provisions of the Mental Capacity Act are designed to allow such people to take part in research even though they cannot give valid consent of their own.

First, the research has to be approved by a Research Ethics Committee. Then, instead of asking the research participant for consent, the researcher must ask a consultee for an opinion whether the research participant would have wished to take part in the research.

Who can be a nominated consultee?

- Any person interested in the welfare of the proposed participant who works with the participant in a professional capacity.

Who cannot be a nominated consultee?

- People connected with the research (e.g. members of the research team)

Why have I been asked?

You have been asked to act as a nominated consultee by a researcher because the researcher thinks you might be willing and able to do this because of your professional relationship with the proposed research participant.

If I agree to be a nominated consultee, what will I have to do?

You will need to think about what the proposed participant's wishes and feelings about the research would be if they had capacity to make an informed decision and decide whether in your view the person should be involved in the research or not. This means you need to

- Look at the study information sheet.
- Think about whether or not the person would want to be involved in the research project if he or she had the capacity to make that decision.
- You may need to seek the advice of friends/ family/ other paid carers of the person you care for in order for you to best advise us on what the person's wishes and feelings would be.

You should not put forward your personal views on participation in the specific project or research in general, you must consider only what the person's views and interests are or would likely be. You should think about:

- What the broad aims of the research and the practicalities of taking part will mean for the proposed participant.

- How the specific activities in the research might impact the participant. For example, if the study involves activities in the afternoon when the person is most tired they might find it a strain or the research might involve an activity that the person particularly enjoys and thus would give them more pleasure.
- Any view previously expressed by the person on the overall nature of the research.

If you advise that the proposed participant would not have wanted to be involved in the research, they cannot be included in the research.

If you advise that the proposed participant would want to be involved, they may be included in the research. If the research commences but the person shows any sign at any stage that they are not happy to be involved in the research you can change your advice at any time without giving a reason, whereby the researcher must withdraw the person from the research. If the person seems unhappy at any point or shows any signs of objection, then they will be withdrawn from the research.

The research project has been approved by the Coventry NHS Research Ethics Committee. If you wish to see proof of approval from this body, or you wish to discuss any concerns about acting as a personal consultee for the person that you care for, please contact Chris Oliver on 0121 414 7206 or by email at c.oliver@bham.ac.uk.

I don't want to be a nominated consultee - what do I do?

Please try to suggest an alternative person who might like to act as a nominated consultee for the potential participant, please pass the project information pack on to that person.

If no-one can be found who is willing and able to act as a consultee for the person you care for then the person will not be able to participate in the research study.

Where can I get more information and guidance?

More information is available from:

Department for Constitutional Affairs (2007) *Mental Capacity Act 2005 Code of Practice*
http://www.dca.gov.uk/legal-policy/mental-capacity/mca-cp.pdf

Department of Health (2007) *Guidance on nominating a consultee for research involving adults who lack capacity to consent* (consultation)
http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_076207

Mental Capacity Implementation Programme (2007) *Making Decisions: a guide for family, friends and unpaid carers. Second edition*
http://www.dca.gov.uk/legal-policy/mental-capacity/mibooklets/booklet02.pdf
A printed copy of this booklet is available by telephoning 023 80878038.

I have decided that I want to be a nominated consultee- what do I do?

Please go back to the 'understanding behaviour in neurodevelopmental disorders' Information Sheet and continue reading.