Predicting anxiety within atypical development

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List of Abbreviations

ASD	Autism spectrum disorder
ASC-ASD	Anxiety Scale for Children with Autism Spectrum Disorder
ADAMS-GA	Anxiety, Depression and Mood Scale - General anxiety subscale
BASC-2	Behaviour Assessment System for Children (version 2)
CASI-4/5	The Child and Adolescent Symptom Inventory
CAT	Critical Appraisal Tool
CBT	Cognitive Behavioural Therapy
CdCS	Cri du Chat syndrome
CdLS	Cornelia de Lange syndrome
ClinPsyD	Clinical Psychology Doctorate
CUES	Coping with Uncertainty in Everyday Situations
COSIM	Consensus Based Standards for the selection of Health Based Measurement Instruments
DSM-5	Diagnostic and Statistical Manual 5
DSM5-DAS	Diagnostic and Statistical Manual 5, Dimensional Anxiety Scale
EEG	Electroencephalogram

FXS	Fragile X syndrome
IU	Intolerance of Uncertainty
IUS-P	Intolerance of Uncertainty Scale- parent version
MDT	Multi-disciplinary team
PhD	Doctorate of Philosophy
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-analyses
PWP	Psychological Wellbeing Practitioner
RCMAS	Revised Children's Manifest Anxiety Scale
SCARED	Screen for Child Anxiety and Related Emotional Disorders
SCAS	Spence Child Anxiety Scale
SRS-2	Social Responsiveness Scale -version 2
TD	Typically developing
ToM	Theory of Mind
UK	United Kingdom
USA	United States of America
VABS	Vineland Adaptive Behaviour Scale
WS	Williams syndrome

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Declaration

This thesis has not been submitted for any other degree or to any other institution. This thesis was conducted under the academic and clinical supervision of Dr Eve Knight (Clinical Psychologist, Coventry University), Dr Tom Patterson (Clinical Psychologist, Coventry University), Dr Jo Moss (Research Fellow, University of Birmingham) and Professor Chris Oliver (Clinical Psychologist and Professor of Neurodevelopmental Disorders, University of Birmingham), all of whom were involved from the initial formulation of the research idea and design. All the material presented in this thesis is my own work. The data collection process was conducted as part of a collaboration with a larger research project at the Cerebra Centre for Neurodevelopmental Disorders at the University of Birmingham. The literature review and empirical paper are both written for submission to the Journal of Autism and Developmental Disorders.

Summary

This thesis focusses on the issue of predicting anxiety in atypical populations, namely in autism spectrum disorder and in rare genetic syndromes.

The first chapter presents a systematic review of quantitative research conducted with the aim of identifying predictors of anxiety in people with autism spectrum disorder. Nineteen papers were included in the review. A wide range of predictors were identified and organised into eight salient themes including social skills, cognitive skills, emotional regulation and physiological responses. Predictors were identified as being both as direct and through mediation. A critique of the reviewed studies is given. The review raised questions about the methodology typically used to assess anxiety in autism research and areas for future research are suggested.

Chapter two presents a quantitative research study looking at the relationship between intolerance of uncertainty and anxiety in two rare genetic syndromes associated with autism spectrum disorder. Using questionnaire data, participants with Cornelia de Lange syndrome and Fragile X syndrome were compared on measures of anxiety, autism symptomatology and intolerance of uncertainty, and the relationships between these variables were examined. The findings of this study implicate intolerance of uncertainty in the presence of anxiety in both syndromes. In Cornelia de Lange syndrome, intolerance of uncertainty was found to mediate the relationship between autism symptoms and anxiety. Results are discussed in line with clinical and research implications.

The final chapter is the author's reflective account of conducting this research. The chapter reflects on the experience of conducting quantitative research as a trainee clinical psychologist and of managing the scientist-practitioner position whilst doing so. Reflections on the research process and the discovery of parallels with the author's clinical work are also discussed.

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Chapter One

Predictors of anxiety in autism spectrum disorder: a systematic review

Written in preparation for submission to the Journal Of Autism and Developmental Disorders (See Appendix A for author guidelines)

Total chapter word count: 6902

Abstract

Aim: This systematic review of quantitative research aimed to identify and summarise the key predictors of anxiety in autism spectrum disorders. **Method:** A literature search was conducted with PsychInfo, Medline, Embase and PubMed. Nineteen papers were identified which met the inclusion criteria of being quantitative and using analysis methods allowing for predictive relationships of anxiety in autism spectrum disorders to be identified. **Findings:** Several predictors were identified across the studies which were organised into key themes including cognitive skills, emotional regulation skills, physiological arousal, social skills and sensory sensitivities. **Conclusion:** The findings from this review highlight the complexity of relationships between predictors and anxiety in autism spectrum disorders. Inconsistencies in anxiety measurement and a reliance on parent-report across studies reveal methodological difficulties with investigating anxiety in people with autism spectrum disorders. Future work is needed to address these methodological limitations in order to better understand anxiety in autism spectrum disorders.

Keywords: Autism, anxiety, predictors, mediators

1.1 Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterised by impairments in social communication and interaction and the presence of repetitive restricted behaviours as well as sensory sensitivities and/or sensory seeking behaviour (American Psychiatric Association, 2013). The estimated prevalence of ASD in the United Kingdom (UK) is approximately 1% of the typically developing (TD) population (Simonoff et al., 2008).

Whilst research initially focused on describing and understanding the core qualitative social and behavioural differences seen in ASD, more recently research has focused on the social and mental health needs of people with ASD (Hollocks, Lerh, Magiati, Meiser-Stedman, & Brugha, 2019). The delay in examining the relationship between anxiety and ASD may have been in part due to diagnostic overshadowing, whereby mental health difficulties are overlooked as they seem to be a feature of ASD (Mason & Scior, 2004). It has been debated whether symptoms such as high rigidity, social fear and unusual phobias are best explained as ASD or anxiety (Kerns et al., 2015). However, there is growing evidence for a strong association with anxiety disorders (which can be distinguished from core ASD symptoms; Renno & Wood, 2013) and several studies have investigated the prevalence and nature of anxiety in ASD.

1.1.1 Anxiety in autism

People with ASD are thought to be at an increased risk of developing mental health difficulties such as anxiety and depression (Joshi et al., 2013). Most research has focussed on these difficulties in children, as ASD was primarily considered to be a diagnosis of childhood. White, Oswald, Ollendick, and Scahill (2009) reported that generalised anxiety disorder, separation anxiety, social anxiety and phobias are the most commonly reported anxiety disorders in ASD. A meta-analysis examining the prevalence of anxiety in young people with ASD (aged under 18 years) indicated a prevalence of 39.6% of young people with ASD meeting criteria for an anxiety disorder diagnosis (Van Steensel, Bögels, & Perrin, 2011). This is higher than the prevalence rate in TD children (Costello, Egger, & Angold, 2005). Specific phobias, obsessive compulsive disorder (an anxiety-related condition) and social anxiety were most commonly reported. Another meta-analysis (van Steensel & Heeman, 2017) also showed anxiety levels to be higher compared to TD populations.

In adults, Hollocks et al. (2019) conducted a meta-analysis to examine rates of anxiety in adults (mean age 30.9 years, S.D= 6.2) with ASD. Across 30 studies, the combined estimates for current and lifetime prevalence for adults with ASD were between 27-42% for any anxiety disorder. This is higher than the prevalence rate in TD adults (approximately 7.2 %; Martín-Merino, Ruigómez, Wallander, Johansson, & García-Rodríguez, 2009).

There is significant heterogeneity in the presentation of anxiety in ASD. Research has reported various anxiety 'symptoms' including; fears of loud sounds, unusual phobias, debilitating social avoidance, social distress, excessive worry around change and highly rigid behaviours (Kerns & Kendall, 2012). Kerns et al. (2015) suggested that individuals with ASD can present with both 'traditional' anxiety symptoms (consistent with the DSM 5) and also atypical anxiety which does not fit with DSM-5 defined categories but presents as 'exacerbated and clinically impairing anxiety around the hallmark features of ASD' (Kerns et al., 2015). The authors examined anxiety presentations in fifty-nine children with ASD and assessed anxiety as 'traditional' or 'atypical'. Seventeen percent of participants had traditional presentations, 15% atypical and 31% presented with both traditional and atypical anxiety.

1.1.2 Impact of anxiety

The impact of anxiety on people with ASD has been widely reported. Chang et al. (2012) suggested anxiety interferes with everyday functioning and impacts on people with ASD's ability to interact with others. Wood and Gadow (2010) suggested that anxiety may be a moderator of social skills and repetitive behaviours. Research has demonstrated an association between anxiety in ASD and both increased parental stress and lower family functioning (Kerns et al., 2015; Rao & Beidel, 2009). Kim, Szatmari, Bryson, Streiner, and Wilson (2000) demonstrated that anxiety in ASD is associated with negative family outcomes (parent-child relationships) and a limited ability to participate in social activities. Kerns et al. (2015) found that young people with ASD were more likely to display self-injurious behaviour and that parents reported higher levels of stress than parents of children with ASD but no anxiety.

1.1.3 Factors associated with anxiety

Research has identified many different variables associated with anxiety in ASD. Gadow, DeVincent, and Schneider (2008) examined the associations between demographic variables and anxiety in ASD and found associations with common demographic risk factors such as age, IQ, family psychiatric history and early intervention with anxiety.

In a parental focus group aimed at furthering understanding of anxiety presentations in ASD, Ozsivadjian, Knott, and Magiati (2012) interviewed 17 mothers of children with ASD. The parents identified factors such as changes to routine, specific phobias, sensory sensitivities and too many demands as being triggers of anxiety for their children.

Several studies have found associations between core deficits and anxiety in ASD. For example, assertiveness, social skills (Chang et al., 2012) communication difficulties, theory of mind deficits (Burnette et al., 2005), maladaptive thinking styles (Sharma, Woolfson, & Hunter, 2014) and intolerance of uncertainty (Boulter, Freeston, South, & Rodgers, 2014). Whilst some studies have conducted analyses to allow the predictive power of these variables on anxiety to be determined, many of these studies have simply explored correlations between anxiety and other variables, and so causal links cannot be made.

1.1.4 Rationale

Research has demonstrated a high prevalence of anxiety disorders in people with ASD and many studies have reported on the impact of this anxiety on everyday life, family stress, social skills and emotional wellbeing for people with ASD. Individual studies have highlighted associations between different variables and anxiety such as sensory sensitivity (Green & Ben-Sasson, 2010) ASD symptom severity (Mayes, Calhoun, Murray, & Zahid, 2011) and theory of mind skills (Burnette et al., 2005). Reviews such as van Steensel and Heeman (2017) and Hollocks et al. (2019) have reported on the prevalence of anxiety disorders in ASD but to date, no review has synthesised research regarding the different predictors of anxiety symptomatology in ASD. There is a need to understand and summarise the literature which demonstrates predictive relationships between certain variables and anxiety symptomatology.

Once predictors have been identified, they can point to potential intervention strategies to reduce anxiety symptoms in people with ASD and improve quality of life.

1.1.5 Aims

The aim of this literature review was to systematically review research investigating the predictors of anxiety symptomatology in people with ASD, in order to answer the research question "What are the key predictors of anxiety in ASD?"

1.2 Method

1.2.1 Literature Search

A systematic search of the literature was conducted for research investigating what factors predict anxiety in people with ASD. Ethical approval to conduct this review was granted by the University of Coventry Ethics Committee (Appendix B). Table 1.1 outlines the key search terms used.

Table 1.1. Key search terms used in the systematic literature review

Main concept	**Synonyms**	**Location**
Participants with ASD	autism*OR autis* OR autistic* OR ASD OR 'autism spectrum disorder' OR PDDNOS OR PDD-NOS OR 'pervasive developmental disorder not otherwise specified' OR Asperger*OR 'Asperger syndrome'	Title Abstract
Anxiety	anxi*OR anxious* OR anxiety OR 'anxiety disorder'	Title Abstract

Predictors	predict* OR predictor OR factor OR correla* OR correlate OR mediat*	Tile Abstract

Literature searches took place between February and March 2019 and focussed on the most relevant databases covering literature in psychology and medical science. The databases searched included PsychInfo, Medline, Embase and PubMed. A manual search was conducted of the reference list of extracted articles.

1.2.2 Inclusion and Exclusion Criteria

Table 1.2 Inclusion and exclusion criteria used when surveying the literature

Criteria	Include	Exclude
Language	English	Non-English
Study type	Quantitative Cross sectional or longitudinal design	Qualitative Review articles
Participants	Participants with ASD but no co-morbid neurodevelopmental disorders	Participants with ASD and comorbid intellectual disability, rare genetic syndromes and additional neurodevelopmental disorders such as ADHD
Diagnosis	A confirmed diagnosis of ASD (either by previous psychiatrist/psychologist	No confirmed diagnosis of ASD.

	assessment or using a validated measure such as the ADOS or questionnaire measure)	
Anxiety measure	Validated measure of anxiety or validated measure with an anxiety subscale included.	No validated measure of anxiety
Analysis	Analysis allowing conclusions about predictive nature of variables on anxiety- i.e. Regression analysis, Structural equation modelling and mediation analysis.	Only correlations conducted. No predictors of anxiety found/identified.

At the screening stage, titles and abstracts were reviewed (and where necessary full texts) to ensure they met the review's inclusion and exclusion criteria. The parameters for inclusion and exclusion are outlined in Table 1.2. The initial fundamental characteristics were that papers were in English, were peer-reviewed and accessible to review.

Following initial screening, full-text articles were obtained and further assessed for eligibility to be included in the review. This review was concerned with the predictors of anxiety in ASD. Therefore, articles were excluded if their analysis did not allow for conclusions to be drawn about whether a variable is predicting anxiety in their participants. Several studies conducting only correlation analyses were not included in this review as the analyses did not allow identification of predictor variables. Due to the range of anxiety disorders associated with ASD, it was decided

that studies exploring the predictors of any anxiety disorder (including generalised anxiety, specific phobias, and social anxiety disorder) should be included to widen the scope of the search. Studies exploring predictors of obsessive compulsive disorder (OCD) were not initially excluded. OCD is no longer categorised as an anxiety disorder in the DSM-V (APA, 2013) and is now considered an anxiety-related condition instead. However, no studies included in the final review examined predictors of OCD.

Whilst most literature has focussed on anxiety in children with ASD, studies were included regardless of participant age, on the basis that studies with adults may highlight different clinically relevant predictors of anxiety.

1.2.3 Classification of Studies

As outlined by Moher et al. (2015), the process of study selection for this review was recorded on a 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) flow diagram (see Figure 1.1). In total 3931 articles were initially identified following searches in PsychInfo, Medline, Embase and PubMed and manual searches of the reference lists of included studies. After removal of duplicates, 1928 articles remained. Following a review of title and abstracts against the inclusion and exclusion criteria, 1870 articles were excluded as not relevant. The majority of these papers were excluded due to methodological reasons such as studies being qualitative or case study designs or studies looking at predictors of anxiety in parents of children with ASD, rather than children with ASD themselves.

The full text for the 58 remaining articles were reviewed and a further 39 articles were excluded. Reasons for exclusion included conducting correlation analysis only, not using a sample with a confirmed ASD diagnosis or using sample populations with comorbidities such as intellectual disability or ADHD.

Following a search of the literature, a total of 19 studies met the inclusion criteria and so were retained for systematic review.

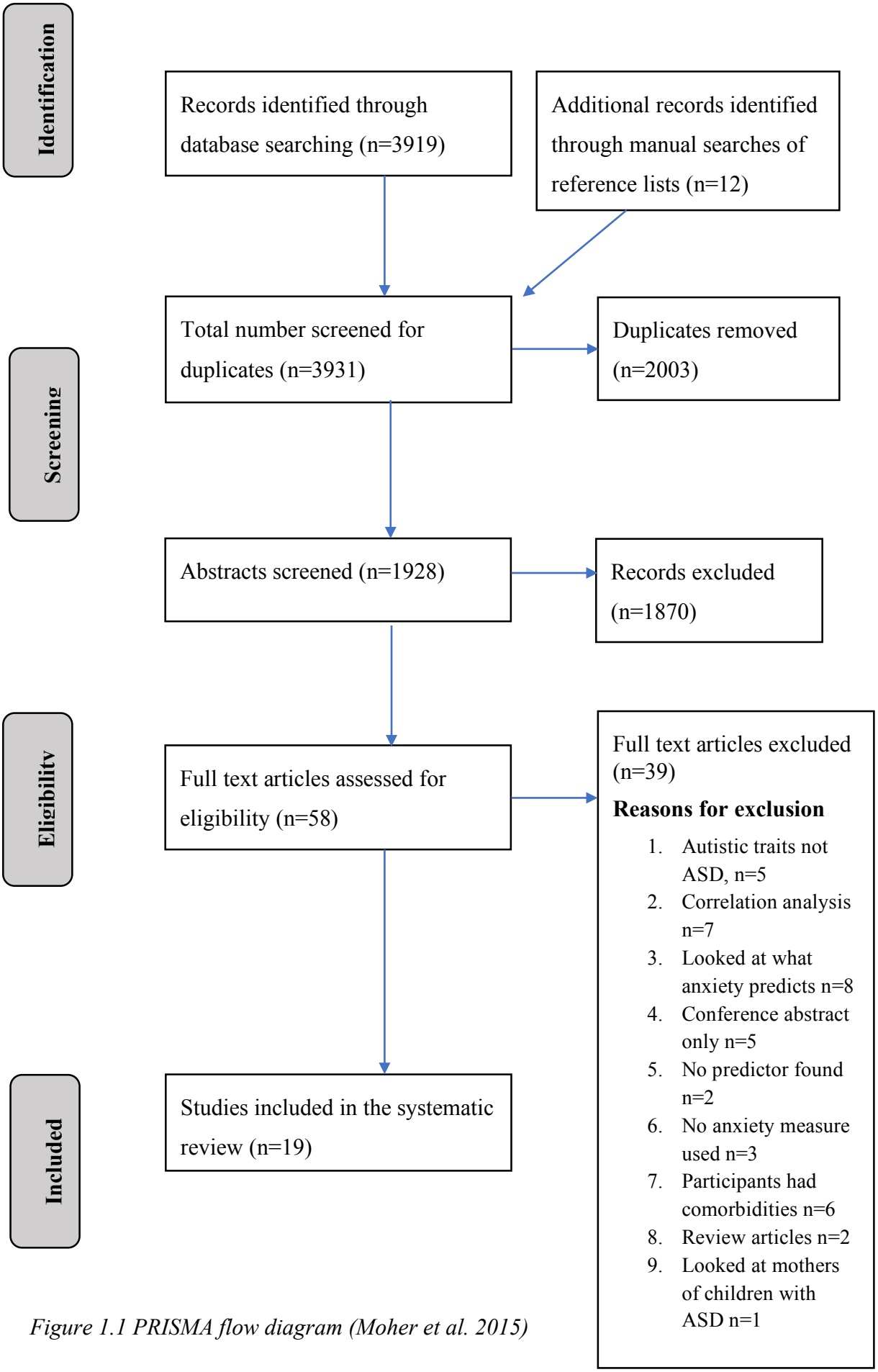

Figure 1.1 PRISMA flow diagram (Moher et al. 2015)

1.2.4 Quality Assessment

In order to assess the quality of the 19 studies identified from the systematic review process, the Critical Appraisal Tool developed by Crowe and Sheppard (2011) was used. This framework was considered suitable for the current review because it can be applied to quantitative research methodologies and has undergone reliability and validity testing (Crowe, 2013).

The CAT is divided into eight categories and 22 items in total. Each category has a multiple item description to aid appraisal and scoring of each category. The lowest score an article can achieve in a category is 0 and 5 is the highest. Half marks are not permitted. Total scores are calculated out of 40 (with a higher score indicating higher quality). Table 1.3 gives an overview of the categories and items included in the CAT. The CAT comes with a user guide and guidance questions for each category to aid scoring.

Table 1.3. Checklist for assessing the quality of research as proposed by the CAT (Crowe, 2013)

Category (Scored /5)	Items
Preliminaries	Title
	Abstract
	Text
Introduction	Background
	Objective
Design	Research design
	Intervention, treatment, exposure
	Outcome, output, predictor, measure
	Bias
Sampling	Sampling method

	Sample size
	Sample protocol
Data collection	Collection method
	Collection protocol
Ethical matters	Participant ethics
	Researcher ethics
Results	Analysis, integration, interpretation method
	Essential analysis
	Outcome, output, predictor analysis
Discussion	Interpretation
	Generalisation
	Concluding remarks
Total score	

To enhance the reliability of the quality assessment, another researcher rated 10 out of the 19 articles independently using the CAT framework. Large disagreements in scores were discussed and rating consensus was reached. Inter-rater reliability analysis using intra-class correlation coefficients (ICC) as outlined in the CAT user guide (Crowe, 2013) were use. ICC scores ranged from 0.997 to 1 and indicate excellent inter-rater reliability.

12 studies out of 19 resulted in an above average score on the quality assessment framework. All studies assessed had a higher quality score than the midline cut off (20/40). The lowest quality score was given to one paper (Bellini, 2006) receiving 24/40, the highest score was given to one paper (Bitsika, Arnold & Sharoley, 2019) scoring 38/40. Overall all studies were relevant to the review and sufficiently described their aim. All papers carried out appropriate statistical analyses and

reported the results sufficiently. Areas of lower quality were in the studies' reporting of ethical considerations and in the description of sampling and data collection methods. Many studies did not provide sufficient information in these areas to allow for replication.

1.2.5 Characteristics of Studies

A summary of the key characteristics of the 19 studies included in this review can be found in Table 1.4. All studies had similar aims, to investigate and describe relationships between anxiety and potential contributing factors.

The majority of the studies were conducted in the USA (nine), two studies (Boulter et al., 2014; Maisel et al., 2016) were a joint project with research sites in the USA and UK. Two studies (Hollocks, Pickles, Howlin & Simonoff, 2016; Palser, Fotopoulou, Pellicano & Kilner, 2018) were conducted solely in the UK, one was conducted in Canada (Kim et al., 2000) and four were conducted in Australia (Bitskia & Sharpley, 2018; Bitsika. Arnold & Sharpley, 2019; Cai. Richdale, Dissanay, Uljarevic, 2019; Uljarevic, Richdale, Evans, Cai, Leekam, 2017).

Of the 19 studies identified for review, 16 were carried out between 2010 and 2019, and the remaining three (Bellini, 2006; Gadow et al., 2008; Kim et al., 2000) were carried out post 2000. Eighteen studies used a cross-sectional design, one study (Neuhaus et al., 2016) used a longitudinal design comparing anxiety measures at time 1 and time 2.

Only five studies (Cai et al, 2018; Miasel et al., 2016; Swain, Scarpa, White & Laugeson, 2015; Uljraevic et al, 2017; Wallace et al., 2016) used adult participants (mean age over 18 years). 15 studies used sample sizes of over 50 participants. The smallest sample size was 23 participants (Neuhaus et al., 2016) and the largest was 2662 (Dubin, Lieberman-Betz, & Lease, 2015). All studies used questionnaire measures of anxiety, and all studies used anxiety measures that were validated in the general population but were not ASD specific measures of anxiety. One study used EEG to map neural responses with anxiety.

Across the 19 studies in this review, 17 different anxiety measures were used. These were:

- Adult Behaviour Checklist (Achenbach & Rescorla, 2003)

- Behaviour Assessment System for Children -2 (Reynolds & Kamphaus, 2004)
- Child Behaviour Checklist (Achenbach, 1999)
- The Child and Adolescent Psychiatric Assessment (Angold & Costello, 2000)
- The Child and Adolescent Symptom Inventory- 4 (Gadow & Sprafkin, 1997)
- The Child and Adolescent Symptom Inventory- 5 (Gadow & Sprafkin, 1997) (Sukhodolsky et al., 2008)
- DSM-5 Dimensional Anxiety Scales (Knappe et al., 2013)
- Fear of Negative Evaluation- Brief (Leary, 1983)
- Negative affectivity self statement questionnaire (Ronan, Kendall, & Rowe, 1994)
- Penn State Worry Questionnaire (Meyer, Miller, Metzger, & Borkovec, 1990)
- Pediatric Behaviour Scale (Lindgren & Koeppl, 1987)
- Revised Children's Manifest Anxiety Scale (Reynolds & Richmond, 1997)
- Revised Ontario Child Health Study (Boyle et al., 1993)
- Screen for Child Anxiety and Related Emotional Disorders (Monga et al., 2000)
- Social Anxiety Scale for Adolescents (La Greca, 1999)
- Spence Chidren's Anxiety Scale (Nauta et al., 2004; Spence, 1998)
- State Trait Anxiety Inventory Form (Spielberger & Gorsuch, 1983)

Table 1.4 Key characteristics of studies

Author/ Date	**Aim**	**ASD Sample population**	**Measure of anxiety** ***Type of anxiety focused on***	**Method of data collection**	**Main Analysis**	**Key findings**	**Predictor(s) identified**	**Quality assessment**
Bellini (2006)	To examine the contribution of social skills deficits and physiological hyperarousal to social anxiety in individuals with ASD	41 adolescents with ASD Mean age = 14.22 years 35 males 6 females Recruited from USA	Social anxiety scale for adolescents (SAS-A, (La Greca, 1999) ***Social anxiety***	Questionnaire measures (parent and self-report) gathered by researcher completed face to face with participants	Multiple regression analysis	Social skills deficits of Assertion (*B*= -1.68, SEB= 0.52, *p*=.003) and Empathy (*B*= -13.348, SEB= 4.547, *p*=.006) combined with elevated physiological arousal (*B*= 0.52, SEB= 0.16, *p*=.002) significantly contributed to variance in social anxiety Model: (*Adjusted* R^2= .34, p<.001)	-Deficits in social skills (assertion and empathy) -Elevated physiological arousal	24/40

Bitsika and Sharpley (2018)	To explore the association between matrix reasoning, social motivation and separation anxiety in children with ASD	90 boys with ASD Mean age = 8.8 years Recruited from Australia	The Child and Adolescent Symptom Inventory (CASI-4) (Gadow & Sprafkin, 1997) GAD subscale ***General anxiety*** ***Separation Anxiety*** ***Social***	Questionnaire measures (parent and self-report) gathered by parents following training from researcher. Matrix reasoning assessments conducted two weeks before questionnaire data collection.	Hierarchical regression analysis	Higher scores in matrix reasoning were associated with lower separation anxiety scores, while higher social motivation were associated with higher separation anxiety. Matrix reasoning (R^2=.09, F(1, 87) for change = 8.85, p=.004) combined with Social motivation (R^2 =.17, F(1, 86) for change = 8.08, p=.006) predicted separation anxiety scores.	-Matrix reasoning and social motivation scores (combined)	33/40 ICC = 0.997

			Anxiety					
Bitsika, Arnold, and Sharpley (2019)	To investigate correlates of general anxiety disorder in young males with ASD, including sensory profiles	150 males with ASD Mean age= 11.2 years Recruited from Australia	CASI-4 (Gadow & Sprafkin, 1997) GAD subscale ***General anxiety***	Questionnaire measures (parent and self-report) gathered by parents following training from researcher	Mediation analyses	Sensory avoidance mediated the relationship between ASD and (parent rated) anxiety scores (Total effect *B*=0.46, t= 6.02, *p*<.001) Indirect effect *B*= 0.33 (95% CI 0.017, 0.081)	-Sensory avoiding	38/40
Boulter et al. (2014)	To establish if the same relationship between intolerance of uncertainty and anxiety exists in ASD as in typically	114 children with ASD Mean age =12.7 years Recruited from USA and UK	Spence Children's Anxiety Scale, Child and Parent versions (SCAS-C and SCAS (Nauta et al., 2004;	Parent questionnaire data obtained from parent interviews. No information	Mediation analysis using ANOVAs following Baron and Kenny's (1986) causal	Intolerance of uncertainty is mediating the relationship between ASD and anxiety (in both parent and child report data). Main effect of IU (F(1,131)=50.87, *p*<.001, partial n^2= 0.28)	-Intolerance of uncertainty (plus ASD characteristics) .	34/40

	developing children		Spence, 1998) ***General anxiety***	available as to how child-report questionnaire data were gathered	steps logic			
Cai, Richdale, Dissanayake, and Uljarević (2018)	To examine the inter-relationship between emotional regulation, intolerance of uncertainty, anxiety and depression in ASD	61 adolescents and young adults with ASD. Mean age = 18.19 years Recruited from Australia	DSM-5 Dimensional Anxiety Scales (DSM-5 DAS,(Knapp e et al., 2013) ***General anxiety***	Online questionnaires	Mediation analyses	All key variables were associated with each other. Intolerance of uncertainty mediated the relationship between emotional regulation and anxiety symptoms (Total effect *B*=8.29, *p*<.002) Indirect effect *B*= 5.00 (95% CI 1.92, 9.37) Large effect size: .232	-Intolerance of uncertainty (plus emotional regulation)	36/40 ICC=1.00

Dubin et al. (2015)	To examine factors associated with anxiety in young people with ASD	2662 young people with ASD Mean age= 8.82 years Recruited from USA	Child Behaviour Checklist (Achenbach, 1999), Anxiety Problems Scale ***General anxiety***	Face to face assessment and questionnaire data collection	Logistic regression analyses	Increases in age, (*B*= 0.10, SEB= .01, *p*<.001) social withdrawal (*B*= 0.07 SEB= .00, *p*=<.001) and increased cognitive functioning (*B*=0.67 SEB= .0.11, *p*<.001) predicted higher anxiety scores.	-Increasing age -Social problems -Higher cognitive functioning	35/40
Gadow et al. (2008)	To examine mental health risk and protective factors for psychiatric symptoms in children with ASD	236 children with ASD Mean age = 8.61 204 males Recruited from USA	CASI- 4 (Gadow & Sprafkin, 1997) ***General Anxiety,*** ***Specific***	Face to face assessment and questionnaire data collection	Multiple regression analyses	***GAD*** early intervention (*r*=-.15, *p*<0.05, attending a special school (r=-.28, *B*= -0.21, *p*<.05), ever hospitalized (*r*=.17, *B*= -0.14, *p*<.05), family psychiatric history(*r*=.30, *B*=0.18 , *p*<.05) predicted the presence of anxiety. ***Specific Phobia*** IQ (*r*=.18,	-Several demographic variables typically associated with increased risk of psychiatric disorders	32/40

			phobia, ***Separation anxiety disorder***			p<.05) gender (r=-.16, B=-0.15 , p<.05) early intervention (r=-.20, B= -0.19, p<.05), pregnancy complications (r=.19, B= 0.19, p<.05), attending a special school (r=-.15, p<.05) predicted the presence of anxiety. ***SAD*** Age, (r=-0.17, B=-.14 , p<.05) pregnancy complications *(*r=.22, B= .16, p<.05, family psychiatric history(r=.23, B= .16, p<.05) predicted the presence of anxiety.		
Hollocks , Pickles, Howlin, and Simonoff (2016)	To investigate the relationship between physiological responses, cognitive	55 male participants with ASD Mean age= 13	The Child and Adolescent Psychiatric Assessment (Angold &	Face to face assessment and questionnaire data collection	Structural equation modelling	Reduced physiological responsiveness (B= -0.70, p<.01) and greater attentional bias (B= -0.37, p<.01) both predicted anxiety in ASD. However, these predictors	-Attentional bias -Reduced physiological responsiveness	33/30

	processing biases and anxiety in ASD	Recruited from UK	Costello, 2000) SCAS-C and SCAS-P (Nauta et al., 2004; Spence, 1998) **General anxiety**			represented independent pathways and were not inter-related. Full model (X^2 (7)=6.4, CFI= 1.0, RMSEA=.00, 90% CI= .), .16)		
Kerns et al. (2014)	To investigate the presentation of 'traditional' and 'atypical' anxiety in ASD	59 children with ASD Mean age=10.48 years 46 male. Recruited from	Negative affectivity self statement questionnaire (Ronan et al., 1994) Screen for Child	Face to face assessment and questionnaire data collection	Hierarchical multiple regressions	Anxious cognitive style (*B*= -0.32, t=2.49, *p*=.002) sensory hypersensitivity (*B*= 0.33, t= 2.61, *p*= .01) and language ability (*B*= 0.43, t= 2.42, *p*=.02) predicted 'traditional' (consistent with DSM-5) anxiety. ASD severity (*B*= 0.31, t=2.30	-Language ability -Sensory hypersensitivity -Anxious cognitive style -ASD severity (for atypical	35/40

		USA	Anxiety and Related Emotional Disorders (SCARED, (Monga et al., 2000) ***General anxiety***			*p*=.003) and anxious cognitive style (*B*= 0.28, t=2.08 *p*=.04) predicted 'atypical' anxiety symptoms	anxiety symptoms only)	
Kim et al. (2000)	To report on the prevalence and correlates of anxiety and mood problems in young people with ASD	59 children with ASD Mean age= 12 years 52 males Recruited from Canada	Revised Ontario Child Health Study (Boyle et al., 1993) ***General anxiety*** ***Separation anxiety***	Face to face assessment and questionnaire data collection	Regression analyses	The only variable to predict anxiety scores was the discrepancy score between verbal and non verbal ability (*B*= 9.83 *p*=.0003). Children with high verbal than non verbal ability had more anxiety and mood problems	-Higher verbal compared to non verbal ability	30/40 ICC= 1.00

Lei and Ventola (2018)	To examine the relationship between theory of mind skills and anxiety in children with ASD	29 children with ASD Mean age = 6.33 15 male Recruited from USA	CASI- 5 (Gadow & Sprafkin, 1997; Sukhodolsky et al., 2008) Anxiety subscale **General anxiety**	Face to face assessment and questionnaire data collection	Mediation analysis	Broad social impairment significantly predicted anxiety scores (*B*= 0.25 SEB= .0.05, *p*=<.001). General theory of mind skills did not predict anxiety, but early theory of mind competency mediated the relationship between broad social impairment and anxiety. Suggests that underlying common deficits in social skills and anxiety may be driven by specific set of skills rather than TOM deficits in general. Total effect R^2=0.64, *p*<.001 Indirect effect *B*= 0.16 (95% CI 0.012,0.345)	-Broad social impairment -Early theory of mind competency	32/40
Maisel et al.	To model the contributions of	76 adults with ASD	State Trait Anxiety	Questionnaire data	Structural equation	Structural equation modelling showed an excellent model fit	-Intolerance of uncertainty	32/40

(2016)	emotional acceptance, alexithymia and intolerance of uncertainty on anxiety in ASD	Mean age =33.22 59 males Recruited from USA and UK	Inventory Form (Spielberger & Gorsuch, 1983) Penn State Worry Questionnaire (Meyer et al., 1990) Fear of Negative Evaluation-Brief (Leary, 1983) ***General anxiety***	collection	modelling and mediation analysis	for intolerance of uncertainty, alexithymia and emotional acceptance predicting anxiety in people with ASD, independent of ASD symptoms severity. (X^2 (12) = 13.89, CFI= .998, RMSEA=0.02, *p*=.381) Mediation analysis showed intolerance of uncertainty alexithymia and emotional acceptance almost entirely mediating the relationship between ASD and anxiety	-Decreased emotional acceptance -Increased alexithymia	ICC= 0.997
Mayes et al.	To examine the demographic	627 children with ASD	Pediatric behavior	Parent report-	Linear regression	Of the various demographic variables entered into the	-Autism severity	28/40 ICC=0.997

(2011)	variables associated with anxiety in ASD	Mean age= 6.6 85.6% male Recruited from USA	scale (Lindgren & Koeppl, 1987) **General anxiety**	questionnaire data collection	analysis	regression analyses, increasing autism severity was the best predictor of anxiety (*B*= 0.31, t=8.7 *p*=<.0001). The best combined predictors were autism severity, verbal IQ and age (F= 68.90, *B*= 2.10 , t=5.80, *p*<.0001)	-Verbal IQ -Increasing age	
Neuhaus et al. (2016)	To explore longitudinal relationships between early face processing and anxiety symptoms in children with ASD	23 children with ASD Mean age= 3.67 years (time 1) Recruited from USA	Revised Children's Manifest Anxiety Scale-RCMAS (Reynolds & Richmond, 1997) ***General anxiety***	Face to face assessment and questionnaire data collection	Hierarchical linear modelling	Slower face processing during early childhood predicted self-reported anxiety scores in adolescence *(r*=0.84, *p*<.01). This is consistent with suggestions that basic face processing is the foundation for more complex social communication skills throughout childhood and adolescence.	-Slower face processing	36/40

Niditch, Varela, Kamps, and Hill (2012)	To examine the association between cognitive functioning (social understanding and aggression) and anxiety in children with ASD	231 children with ASD Mean age= 5 years 194 males Recruited from USA	Parent rating scales of the Behaviour Assessment System for Children-(BASC-2) (Reynolds & Kamphaus, 2004) Anxiety, aggression and social skills subscales. ***General anxiety***	Face to face assessment and questionnaire data collection	Hierarchical regressions and mediation analyses (Baron and Kenny's 1986 causal steps method)	In pre-school children a combination of high aggression (*B*=.024, SEB= .09, *p*<.01) and high social understanding (*B*=0.53, SEB= .10, *p*<.001) predicted higher anxiety.	-High aggression and high social understanding in pre school children	33/40 ICC=0.998
Palser, Fotopoul	To investigate whether	30 children with ASD	SCAS-C (Nauta et al.,	Face to face assessment	Multiple regression	A multiple regression analysis was conducted to examine	-Interoceptive sensibility	38/40

ou, Pellicano, and Kilner (2018)	interoceptive accuracy and sensibility is associated with anxiety in school-aged children with ASD	Mean age = 12.5 years 25 male Recruited from UK	2004; Spence, 1998) ***General anxiety***	and questionnaire data collection	analysis	relative contributions of interoceptive accuracy, sensibility and ASD symptoms to anxiety. Interoceptive sensibility was the only significant predictor of anxiety (*B*= 0.44, t=2.99, *p*=.004).		
Swain, Scarpa, White, and Laugeson (2015)	To test a model in which social motivation moderates the relationship between by emotion dysregulation and social anxiety	69 adults with ASD Mean age = 20.5 years 49 males Recruited from USA	SAS-A (La Greca, 1999) ***Social anxiety***	Questionnaire data collection	Linear multiple regressions	Emotion dysregulation (*B*= 0.22, *p*<.05 parent report, *B*=0.60, *p*<.001 child report) and social motivation (*B*=0. 57, *p*<.001 parent report, *B*=0.24, *p*<.05 child report) significantly predicted social anxiety. When subscales of the 'Difficulties of emotional regulation' measure were entered as predictor variables, difficulties with goal directed behavior for negative emotions	-Emotion dysregulation -Social motivation -Lack of awareness of emotions -Difficulties with goal directed behavior for negative	29/40 ICC=1.00

						(*B*= 0.25, *p*<.05), lack of awareness of emotions (*B*= 0.24, *p*<.05), and social motivation (*B*= 0.53, *p*<.001) significantly predicted care-giver reported anxiety. For self reported anxiety, predictors were non acceptance of negative thoughts (*B*= 0.29, *p*<.05), difficulties with goal directed behavior (*B*= 0.26, *p*<.05), impulse control difficulties with negative emotions(*B*=0 .36, *p*<.01), and limited access to strategies for emotional regulation (*B*= 0.51, *p*<.01), .	emotions -Non acceptance of negative thoughts -Limited access to emotional regulation strategies -Impulse control difficulties for negative emotions	

Uljarević, Richdale, Evans, Cai, and Leekam (2017)	To characterize the interrelationship between insistence on sameness, effortful control and anxiety in young people with ASD	71 adolescents and young adults with ASD Mean age = 18.7 49 males Recruited from Australia	DSM-5 DAS, (Knappe et al., 2013) ***General anxiety***	Questionnaire data collection	Mediation analyses using PROCESS	Insistence on sameness was associated with effortful control and anxiety. Anxiety was associated with effortful control. Mediation analyses showed insistence on sameness mediating the relationship between effortful control (self regulation) and anxiety. (*B*= -0.06, 95% CI -.13, -.02) A second mediation model also showed effortful control mediating the relationship between insistence on sameness and anxiety (*B*= 1.62, 95% CI .59, 3.24)	-Insistence on sameness -Effortful control (self regulation)	30/40 ICC=0.998

Wallace et al. (2016)	To explore the relationships between executive function deficits and anxiety and depression in ASD	35 adults with ASD Mean age= 21.55 31 males Recruited from USA	Adult Behaviour Checklist (Achenbach & Rescorla, 2003) ***General anxiety***	Face to face assessment and questionnaire data collection	Multiple Regression analyses	Neither age nor IQ significantly predicted anxiety or depression. Shifting skills was the only significant predictor of anxiety symptomatology (F=8.56, *p*= .022, R^2= .38). More executive function problems were associated with greater depression and anxiety symptomatology.	-Cognitive flexibility	31/40 ICC=1.00

1.3 Results

Across the 19 studies included in this review, several unique predictors of anxiety in ASD were identified. These predictors can be organised into key concepts of:

- Social skills and behaviour
- Sensory sensitivities
- Cognitive and executive related skills
- Emotional regulation and awareness
- Physiological arousal
- Language ability
- Demographic variables
- Face processing

A summary of all the studies included in this review is outlined in Table 1.4. The salient findings for each of the key concepts will now be summarised.

1.3.1 Social skills and behaviour

Six studies identified social skills-related factors to be predictive of anxiety in ASD, however the exact 'social skills' deficits varied across the studies. Bellini (2006) used the Assertion and Empathy subscales from the Social Skills Rating System (Gresham & Elliott, 1990) as these constructs are believed to be significantly impaired in people with ASD. The 'Assertion' subscale measures behaviours which initiate social interaction while the 'Empathy' subscale measures behaviours which demonstrate concern for others and respect for others' feelings. Using multiple regression analysis, the authors found that Assertiveness and Empathy scores were significant predictors of social anxiety (alongside increased physiological arousal). The authors suggested that their results support a proposed developmental pathway in which higher physiological arousal increases likelihood of social withdrawal, which impedes social skills development. Social skills deficits then increase the likelihood of negative social experiences with peers which increases social anxiety and leads to further withdrawal. Bitsika and Sharpley (2018) found that social motivation (and matrix reasoning skills) is a significant predictor of separation anxiety (from parents) in boys with ASD using the Social Motivation subscale of the Social Responsiveness Scale (SRS 2) (Constantino & Gruber, 2012). Bitsika and

Sharpley (2018) hypothesised that a lack of understanding about the link between reduced social interaction and loneliness may lead to increased seeking of parental presence as compensation. This could then result in increased separation anxiety. Swain et al. (2015) also used the SRS2 to look at the relationship between social motivation, emotional regulation and social anxiety. They found that reduced social motivation significantly predicted higher levels of social anxiety (caregiver reported). Dubin et al. (2015) found that social withdrawal predicted higher parent-reported anxiety in children with ASD. Niditch et al. (2012) found that social understanding (and aggression) (measured from the social skills subscale on the BASC-2; Reynolds & Kamphaus, 2004)) predicted anxiety in preschool aged children.

Lei and Ventola (2018) examined the role of theory of mind (ToM) skills specifically. The authors found that early ToM skills deficits mediated the relationship between social communication impairments and anxiety. These authors suggested that early ToM skills underpin components of social functioning which may also underlie anxiety in children with ASD.

The studies by Dubin et al. (2015), Bitsika and Sharpley (2018), Niditch et al. (2012) and Lei and Ventola (2018) scored particularly highly on the quality assessment rating (scores between 32 to 35) which indicates they were methodologically robust and strongly implicates social skills and behaviour in predicting anxiety in ASD.

1.3.2 Sensory sensitivities

Three studies found sensory sensitivities to be predictive of anxiety in ASD. Bitsika et al. (2019) used the Sensory Profile (Dunn, 1999) to measure participants' responses to sensory events. Sensory responses can be divided into 'low registration', 'sensory seeking', 'sensory sensitivity' and 'sensory avoidance'. Results showed that sensory avoidance mediated the relationship between autism symptomatology and anxiety (parent rated). No other sensory behaviours predicted anxiety. Kerns et al. (2014) also used the Sensory Profile and found that sensory sensitivity and sensory avoidance predicted 'traditional' anxiety symptoms in children with ASD.

Palser et al. (2018) investigated the role of interoception - the detection of the physiological state of the body, a type of sensory processing. Palser et al. (2018)

found that interoceptive sensibility (how aware an individual is of internal bodily signals) predicted anxiety in children and adolescents in ASD. The authors suggested that the more an individual is aware of their interoceptive sensations, the higher their anxiety because they engage in cognitive appraisal of these sensations with cognitions that are negatively biased and sensations are interpreted as threatening.

The studies by Bitsika et al. (2019) and Palser et al. (2018) were the highest quality rated studies in this review. This suggests the studies were highly methodologically robust and provides additional support that sensory sensitivities can predict anxiety in ASD.

1.3.3 Cognitive and executive related skills

Eight studies found cognitive factors to be predictors of anxiety, including executive function skills, anxious cognitive styles and intolerance of uncertainty. Boulter et al. (2014), Maisel et al. (2016) and Cai et al. (2018) found that 'intolerance of uncertainty' significantly predicted anxiety in people with ASD. Boulter et al. (2014) found that intolerance of uncertainty fully mediated the relationship between ASD symptomatology and anxiety in their participants which was consistent with findings from the TD population.

Intolerance of uncertainty is a construct associated with anxiety in both TD and atypical populations and is a 'broad dispositional risk factor' in the 'development and maintenance of clinically significant anxiety' in neuro-typical populations (Carleton et al., 2012, p. 939). Boulter et al. (2014) concluded that intolerance of uncertainty is a key construct in understanding the relationship between ASD symptomatology and anxiety in children with ASD.

Hollocks et al. (2016) examined both cognitive and biological factors predicting anxiety in ASD. They found that attentional biases towards threat significantly predicted anxiety in ASD. Attentional biases are common in childhood anxiety disorders (Bögels, Snieder, & Kindt, 2003) and the authors suggested that targeting cognitive differences such as attentional biases may be effective intervention for anxiety in ASD.

Wallace et al. (2016) investigated the relationship between executive function deficits and anxiety in ASD using the Behaviour Rating Inventory of Executive Functioning (Gioia, Isquith, Guy, & Kenworthy, 2000) questionnaire measure; they found that difficulties with cognitive flexibility predicted anxiety symptoms in their sample.

1.3.4 Emotional regulation and awareness

Four studies found that emotional regulation skills and/or awareness predicted anxiety in their participants. For example, Maisel et al. (2016) examined the relationships between emotional acceptance, alexithymia, intolerance of uncertainty and anxiety in adults. They found that alexithymia and emotional acceptance mediated the relationship between ASD symptomatology and anxiety. The authors concluded that people with ASD experience higher levels of anxiety because they are more likely to react negatively to their emotional experiences (decreased emotional acceptance) while also being less able to identify and understand their emotions (alexithymia). They suggested that interventions which increase emotional acceptance may be helpful in treating anxiety in ASD. Swain et al. (2015) found that in adults with ASD, emotional dysregulation measured by the Difficulties in Emotion Regulation Scale (Gratz & Roemer, 2004; and social motivation) predicted anxiety symptoms. Specific subscales on this measure; difficulties with goal directed behaviour for negative emotions, lack of emotional awareness and limited emotional regulation strategies were significant predictors of anxiety.

1.3.5 Physiological arousal

Two studies identified physiological arousal as a predictor of anxiety. However, the studies produced diverging results.

Hollocks et al. (2016) assessed physiological arousal with a 'stress test' whereby participants were exposed to stressful situations (copying a complex drawing, preparing a presentation, giving a speech and remembering the drawing) before having a 40-minute relaxation period, Biological measures of stress such as salivary cortisol and heart rate were taken and analysed throughout the task and the relaxation session. These physiological data were analysed and compared to scores on a questionnaire-based mental health assessment that also measured anxiety. The

authors found a significantly blunted heart rate and cortisol response (reduced physiological responsiveness) significantly predicted higher anxiety scores. Hollocks et al. (2016) suggested further research is needed to understand the mechanism by which physiological under-responsiveness is related to anxiety. They suggested that it may be related to exposure to chronic stress over the course of childhood which leads to this blunting of physiological responses.

Bellini (2006) also found an association between anxiety and physiological arousal, however the study did not use a direct measure of physiological arousal, rather they used the Multidimensional Anxiety Measure (March & Parker, 2004) (questionnaire measure) and used the 'Physical symptoms' scale which details different physiological symptoms of anxiety. The authors found that elevated physiological arousal was related to higher levels of social anxiety.

Comparing the quality ratings between these studies shows that the Hollocks et al. (2016) study received one of the highest ratings in this review (37) with high ratings relating to methodology and results whereas the Bellini (2006) paper received the lowest (24), with lowest ratings in the research design and results section of the paper. The findings from the Hollocks et al (2016) study could therefore be considered more robust in the context of these diverging results.

1.3.6 Language ability

Two studies suggested a predictive association between language ability and anxiety in ASD. Using hierarchical regression, Kerns et al. (2014)) found that stronger language ability was associated with higher levels of 'traditional' (consistent with the DSM-5) anxiety symptoms in children with ASD. Kim et al. (2000) found that children with a larger discrepancy between verbal and non-verbal IQ scores had higher anxiety symptoms, although this effect was small and the authors reported the mechanism for this difference is unclear.

1.3.7 Demographic variables

Three studies included analysis of common demographic risk factors for the development of anxiety in ASD (Gadow et al., 2008; Kerns et al., 2014; Mayes et al., 2011). Factors such as IQ, age, autism severity, and parental anxiety were found to predict higher anxiety scores in children with ASD. However, Gadow et al. (2008)

acknowledged that (whilst significant) the strength of the relationship was weak for many of the predictors identified in their study and suggested more research is needed to identify additional variables which could be risk factors for anxiety. Anxiety scores were not related to gender in any of the three studies. This is consistent with other studies (Hurtig et al., 2009; Sukhodolsky et al., 2008)

1.3.8 Face processing

Neuhaus et al. (2016) examined the relationships between autism symptom severity, anxiety and neural face processing responses using EEG in 26 children and longitudinal measures of anxiety and ASD symptomatology. They found that slower processing of neutral faces at aged 3 predicted higher self-reported anxiety symptoms in adolescence. Slower face processing was also related to higher levels of ASD symptomatology at adolescence. They concluded that the best outcomes for social behaviour and anxiety are associated with the ability to process faces quickly and to distinguish between neutral and negative facial expressions effectively. They also argued that slow face processing as a shared predictor of both anxiety and ASD symptomatology was not surprising as both rely on early brain development and functioning.

1.3.9 Anxiety disorders

Across the nineteen studies included in the review, 15 looked at predictors of GAD three looked at social anxiety (Bellini, 2006; Bitsika & Sharpley, 2018; Swain et al., 2015) one included specific phobias (Gadow et al., 2008) and three looked at separation anxiety (Bitsika & Sharpley, 2018; Gadow et al., 2008; Kim et al., 2000). The studies examining social anxiety and separation anxiety found predictors related to social skills such as social motivation, as well as emotional dysregulation. The only study investigating specific phobias (Gadow et al., 2008) was focused on demographic variables and so a range of relevant predictors may have been missed. The fifteen studies investigating predictors of GAD found a range of predictors including sensory sensitivities, cognitive skills, social skills, verbal ability, intolerance of uncertainty, age and emotional regulation.

1.3.10 Age related predictors

Only five studies used adult participants, (Cai et al., 2018; Maisel et al., 2016; Swain et al., 2015; Uljraevic et al., 2017; Wallace et al., 2016) therefore it is not possible to comment on whether all predictors are consistent for both adults and children with ASD. However, of the studies including adults, predictors found *were* in line with the findings in children. For example, intolerance of uncertainty, emotional regulation and social motivation were predictors identified in studies using either children or adults with ASD. This suggests similar mechanisms may be underlying anxiety across the lifespan. Further investigation and comparison is needed to determine if this is true for all predictors identified in this review.

1.3.11 Summary

Across nineteen studies, several predictors and mediators of anxiety were identified. All but one predictor (face processing ability) were identified in multiple studies. The predictors identified were synthesised into key themes which included social skills, sensory sensitivities, cognitive skills, emotional regulation skills, physiological arousal, language ability, face processing skills and demographic variables such as IQ, age and autism severity. In terms of clinical utility, the most significant predictors identified were executive function and emotional regulation skills as arguably these are variables which could be targeted for intervention.

1.3.12 Critique

All the studies included in this review gained a quality assessment score of 24 and above out of 40. The average score for quality assessment was 32, therefore these papers were of a high quality across a number of domains on the CAT (Crowe, 2013). All the studies included provided confirmation of a diagnosis of ASD, both using previous clinical diagnosis from professionals and also using either direct assessment such as the Autism Diagnostic Observation Scale (Pruette, 2013) or questionnaire measures such as the Autism Quotient (Auyeung, Baron-Cohen, Wheelwright, & Allison, 2008). This means that the findings of this review can be generalised to the ASD population. However, given the potential of the results of these papers to inform interventions for anxiety in ASD, it is important to consider the limitations of the studies when evaluating the findings. The key limitations

across the studies were the use of parent report measures of anxiety, that the majority of studies used child samples, that all but one study used a cross-sectional design and the use of a variety of different anxiety measures across the studies that have not been validated for use with an ASD population.

Nine papers used solely parent report to measure anxiety in their ASD samples (Dubin et al., 2015; Gadow et al., 2008; Hollocks et al., 2016; Kerns et al., 2014; Kim et al., 2000; Lei & Ventola, 2018; Mayes et al., 2011; Niditch et al., 2012; Wallace et al., 2016). Three studies used both parent and child report measures (Bellini, 2006; Bitsika et al., 2019; Boulter et al., 2014). In the Van Steensel et al. (2011) meta-analysis of 31 studies of anxiety in children with ASD, they found that parent-report measures were the dominant methodological strategy. While parent-report is common in ASD research, research suggests parents underestimate the frequency of internal anxiety symptoms in their children, and parent-child agreement is low for these internal experiences (Cantwell, Lewinsohn, Rohde, & Seeley, 1997). Logically, it follows that ratings may be different because parents can report on what they *see* in their child, whereas the child can report on what they feel inside. However, some studies have found high levels of agreement between parent and child reporting of anxiety (Ozsivadjian, Hibberd, & Hollocks, 2014). Of the studies reviewed here, Bitsika et al. (2019) used both parent and child report measures and found differences in how the parent and child ratings mapped on to other behaviours. In contrast, Boulter et al. (2014) found the same relationships between anxiety (whether child or parent reported) with other variables. Bitsika et al. (2019) suggested that both parent and child report ratings, while different, may be equally valid as they identify different aspects of an anxiety presentation. These authors recommended that for future research, combining ratings from both sources may equate to a more valid anxiety variable. Addressing this issue in the design of future studies will be important in furthering our understanding of the presentation of anxiety in ASD.

Fifteen studies used child and adolescent samples in their studies. This could mean that predictors linked with later developmental stages may be missed. Research indicates that anxiety in ASD increases with age (Davis III et al., 2011; Vasa et al., 2013) and so it could be that different life and environmental factors associated with adulthood are playing a role in increased anxiety in adults with ASD. By focusing

mainly on child participants, these relationships may be missed. Additionally, only one study (Neuhaus et al., 2016) used a longitudinal design to investigate predictors of anxiety. This highlights the dearth of research examining causal mechanisms of anxiety in autism using longitudinal designs, which are more methodologically robust than cross-sectional designs when attempting to draw causal links.

Finally, the measures used to assess anxiety in the studies were diverse and not validated in ASD populations. Rodgers et al. (2016) highlights the difficulties with this approach as the presentation of anxiety in ASD seems to be associated with a range of ASD phenomenology such as sensory processing difficulties, repetitive behaviour and social impairments. It can be difficult to differentiate the features of ASD and anxiety. In this review, Kerns et al. (2014) outlined the differences in 'traditional' anxiety and 'atypical' anxiety in ASD. Whilst traditional anxiety may be adequately assessed using measures from the normative population, it is possible that the 'atypical' anxiety symptoms may not. Wigham and McConachie (2014) systematically reviewed anxiety measures used to assess outcomes in CBT trials for children with ASD. They examined 63 full-text articles and assessed the quality of their anxiety measures using the COSIM checklist (Consensus Based Standards for the selection of Health Based Measurement Instruments) (Mokkink et al., 2010). Measures were assessed for internal consistency, reliability, content validity, hypothesis testing, criterion validity and construct validity. They found three measures to be suitable for children with ASD. These were the SCAS (Spence, 1998), the Revised Children's Anxiety and Depression Scale (Chorpita, Moffitt, & Gray, 2005) and the SCARED (Monga et al., 2000). Only four studies in this review used one of these measures (Boulter et al., 2014; Hollocks et al., 2016; Kerns et al., 2014; Palser et al., 2018). In addition to these three measures- 14 different measures of anxiety were used across the 19 studies reviewed. This finding highlights the variability and inconsistency in the measurement of anxiety in ASD research, and demonstrates the need for validated, consistent measures to be used in order to draw meaningful and comparable conclusions from the data.

1.4. **Discussion**

This review aimed to summarise and critique quantitative research investigating the predictors of anxiety in ASD. The results of this review brought together several disparate findings and attempted to organise them in a meaningful way.

Nineteen papers were reviewed and the results were synthesised into eight key predictor concepts; social skills and behaviour, sensory sensitivities, cognitive and executive related skills, emotional regulation and awareness, physiological arousal, language ability, face processing and demographic variables. The predictors identified from this review are summarised in Figure 1.2.

The results of this review highlight the complexity of the mechanisms underpinning anxiety in ASD. Most of the studies reviewed found several different predictor variables, while those conducting mediation analyses found interactions between variables which contributed to the presence of anxiety in ASD. What remains unclear is the precise nature of the relationships between the identified predictors, ASD symptomatology and anxiety. It is possible that the presence of deficits in social skills, ToM, executive function and sensory sensitivities result in the presentation of ASD (social communication and interaction difficulties and repetitive behaviour) which then predicts anxiety. Alternatively, it is possible that the ASD presentation make the presence of certain predictors more likely which results in anxiety. Or, perhaps it is a combination of both potential pathways which results in elevated anxiety levels in ASD. Some variables, for example, intolerance of uncertainty, have been found to mediate the relationship between ASD symptomatology and anxiety in ASD (Boulter et al., 2014). This suggests that different predictors could be influencing the pathway between ASD symptomatology and anxiety at different points.

In Kerns and Kendall (2012) review, they discussed the difficulties with separating anxiety and ASD symptoms and questioned whether anxiety in ASD should be considered a core symptom of ASD or whether it is a separate and distinguishable co-morbidity. The authors reviewed relevant literature and concluded that, whilst the research shows high variability in methodology, results suggest that it is likely that anxiety is a co-occurring disorder rather than a characteristic feature of ASD. The authors concluded that several research studies indicate that ASD may be a predisposing factor for anxiety disorders. When examining theories of causation- Kerns and Kendall (2012) outlined sensory over-responsivity and social deficits as being indicated in the research as factors causing anxiety in ASD. This review supports those assertions, with findings from several of the reviewed studies implicating sensory features (Bitsika et al., 2019; Kerns et al., 2014; Palser et al.,

2018) and social deficits (Bellini, 2006; Bitsika & Sharpley, 2018; Dubin et al., 2015; Lei & Ventola, 2018; Niditch et al., 2012; Swain et al., 2015) as having a role in anxiety in ASD.

Evaluating theories of indirect causation, Kern and Kendall (2012) cited emotional regulation difficulties and reduced cognitive abilities as examples where ASD deficits are indirectly contributing to anxiety symptoms. The findings of this review supports these predictors (Cai et al., 2018; Maisel et al., 2016; Swain et al., 2015; Uljarević et al., 2017) as playing a role in anxiety in ASD. Finally, Kerns and Kendall (2012) suggested that there are several hypothesised pathways in which ASD deficits cause anxiety symptoms and that these require further investigation. Again, this review supports those assertions

This review highlighted the dearth of literature investigating the predictors of anxiety in ASD. Of the 3931 studies originally selected, only 19 met the inclusion criteria which mainly consisted of a confirmed ASD diagnosis and statistical analyses which allowed causal links to be made between variables and anxiety in ASD. As outlined in Figure 1.2, the mechanisms behind anxiety in ASD are complex and further research is needed to understand better these relationships in order to develop effective intervention strategies. Additionally, whilst Figure 1.2 provides an overview of the predictors identified in current literature, some mediating variables of anxiety may not have been identified thus far. It is anticipated that additional variables may be implicated in anxiety in ASD in future research.

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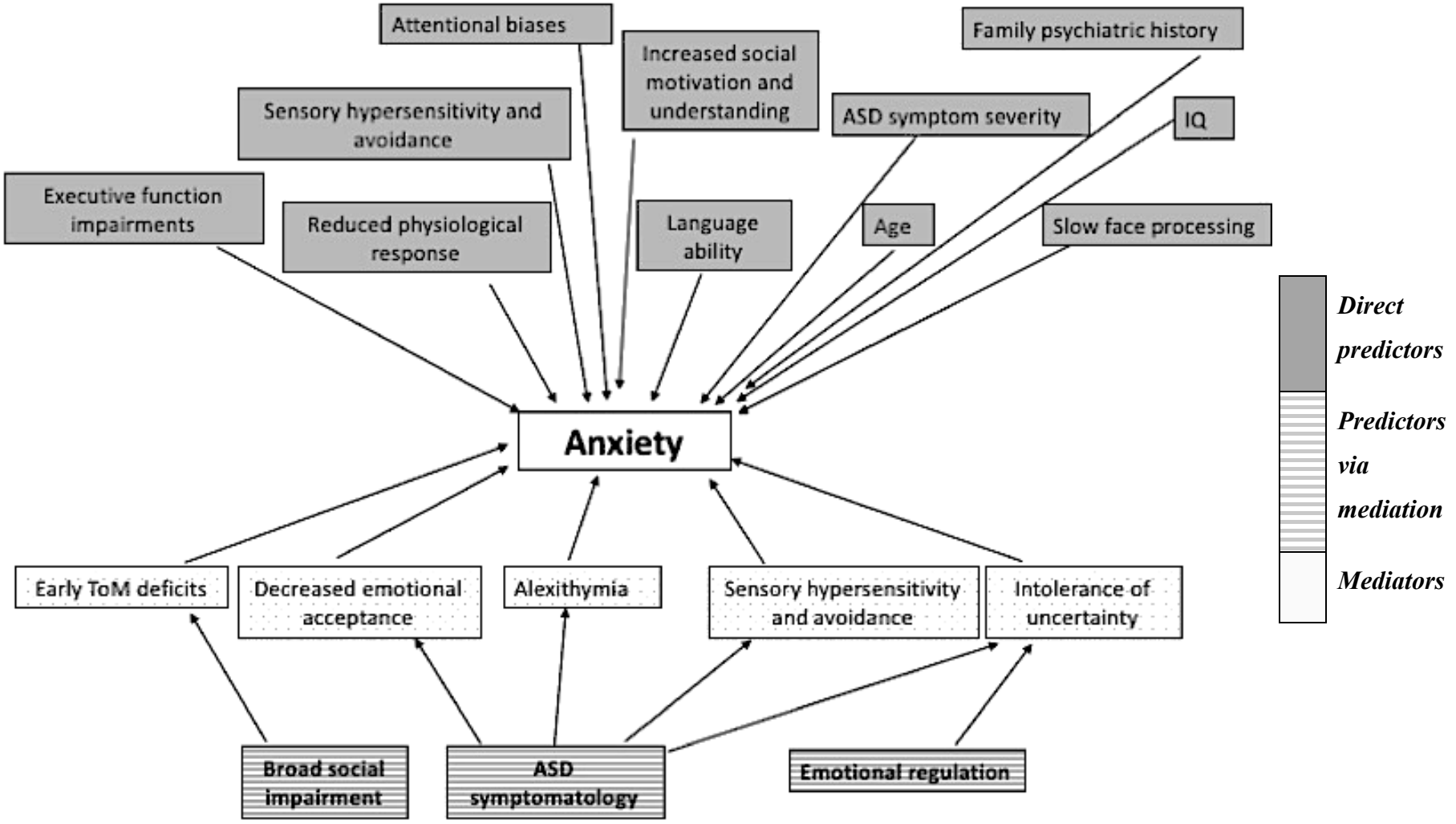

Figure 1.2 depicts the evidenced predictors and relationships between variables across the nineteen studies reviewed.

1.4.1 Limitations

This review focused on quantitative research which used statistical analysis allowing causal links to be made between variables and anxiety in ASD. The results presented must be considered in the context of certain limitations. There was high variability in the measures of anxiety utilised across the nineteen studies. None of the studies used measures of anxiety that have been validated specifically in the ASD population, although four studies (Boulter et al., 2014; Hollocks et al., 2016; Kerns et al., 2014; Palser et al., 2018) used measures that have latterly been found to be robust and suitable for ASD populations (Wigham & McConachie, 2014). Whilst the other anxiety measures used in the studies in this review may be able to identify 'typical' anxiety symptomatology, more specific ASD-related anxiety symptoms may not have been identified. This review highlights the importance of using appropriate and validated measures in ASD populations and emphasises the need for future studies to use these validated measures.

Agreement between parent and child rated measures was also variable and highlighted the difficulty in using parent-report measures of emotional difficulties in ASD. Whilst this is a common methodological difficulty in looking at anxiety in ASD, and is representative of the current literature about anxiety in ASD, it does mean that conclusions drawn about predictors of anxiety in ASD should be made with caution.

Additionally, several papers were excluded from this review because they only carried out correlation analysis, therefore meaning that causal links could not be made between predictors and anxiety. Some factors such as the functioning of the amygdala (Herrington et al., 2017; Herrington, Miller, Pandey, & Schultz, 2016) were reported in several studies and may indeed represent additional predictors of anxiety in ASD. However, due to the aims of this review it was considered important to only include papers demonstrating a direct predictive relationship between variables and anxiety. This could mean that some predictors are absent from this review. Furthermore, only one longitudinal study was identified as meeting the inclusion criteria for this review. The remaining studies were cross-sectional in design. Whilst regression analyses can point to predictive relationships between variables, the gold standard research design for inferring causality is randomised

control trials (longitudinal design) whereby data are collected at several time points (Wunsch, Russo, & Mouchart, 2010). That only one longitudinal study was identified highlights the need for further longitudinal studies to be conducted to elucidate the relationship between predictive variables (as identified in current cross-sectional studies) and anxiety in ASD.

Finally, the majority of the papers in this review examined predictors of anxiety in children with ASD as opposed to adults. Whilst arguably this is important as knowing the predictors in childhood could lead to early intervention for anxiety, and better outcomes as a consequence into adulthood, it does mean that certain predictors which may influence anxiety further along in development may not be identified by excluding adult participants.

1.4.2 Clinical implications

The high prevalence of anxiety in ASD means that interventions for anxiety in ASD have been more recently studied. Most interventions follow a cognitive behavioural therapy (CBT) structure and have demonstrated good results for people with ASD. Kester and Lucyshyn (2018) conducted a systematic review of modified CBT interventions for anxiety in ASD. Across 30 studies they concluded that CBT could be considered as an empirically supported treatment for children with ASD and anxiety.

With the identification of predictors of anxiety in ASD comes the potential for development of new, targeted interventions for anxiety. Rodgers et al. (2017) developed an intervention aiming to increase tolerance of uncertainty in children with ASD, following their research identifying intolerance of uncertainty as a predictor of anxiety. The intervention, whilst only reported as a pilot study, focused on increasing a child's tolerance of uncertain events. Rodgers et al. (2017) reported promising results in parent-reported outcomes. Rodgers, Herrema, Honey, and Freeston (2018) later trialled a similar intervention working directly with adults with autism to teach them strategies to manage uncertainty. This pilot study also showed promising results in the feasibility and applicability of the intervention. Further work is now needed to firm up these interventions and provide additional evidence of its clinical applicability. Separately, Thomson, Riosa, and Weiss (2015) delivered an intervention aimed at improving emotional regulation in children with ASD. The

intervention consisted of activities such as computer games, modelling and role play to practice emotional regulation skills, psycho-education about emotions and relaxation and mindfulness sessions. Outcome measures following intervention suggested both parent and child reported improvements in mood and an overall decrease in emotional dysfunction and an increase in emotional regulation strategies. Whilst these are single studies, they show promising results for targeting specific predictors of anxiety in ASD in order to improve anxiety and overall wellbeing.

1.4.3 Future Directions

This review has identified gaps in the literature regarding assessment of anxiety in ASD. None of the studies in this review used ASD-specific measures of anxiety. Given the risk of possible diagnostic overshadowing, it is important that future research uses population-specific assessments of anxiety such as the Anxiety Scale for Children with ASD (Rodgers et al., 2016). Furthermore, there is a need for more longitudinal studies to examine the relationship between identified predictive variables and anxiety in ASD, to be able to definitively make causal inferences about the relationships between predictors and anxiety. Understanding and summarising the predictors of anxiety in ASD will be useful for the development of specific anxiety interventions in the population. Research examining such protective factors would be useful to complement the knowledge base regarding predictors of anxiety, and intervention strategies could target both predictive and protective factors.

1.4.4 Conclusion

Research indicates a high prevalence of anxiety in ASD, a wide variety of anxiety presentations and multiple risk factors associated with the development and maintenance of anxiety in ASD. The current review set out to critically evaluate quantitative research examining the variables predicting anxiety symptoms in people with ASD. Findings from the studies reviewed here point to a complex interaction of variables influencing the presentation of anxiety. These variables could be targeted to decrease anxiety in people with ASD. Further research is needed to trial interventions targeting the identified predictors in order to improve quality of life and reduce anxiety symptoms in people with ASD.

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Chapter Two

The relationship between anxiety and intolerance of uncertainty in Cornelia de Lange and Fragile X syndrome

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Abstract

Aim: Both Cornelia de Lange syndrome and Fragile X syndrome are associated with co-morbid autism spectrum disorder and high levels of anxiety. Research in autism has found intolerance of uncertainty mediates the relationship between autism symptomatology and anxiety. The same relationships may therefore exist in these rare genetic syndromes and may inform anxiety interventions for these syndrome groups. **Method:** 68 participants with Cornelia de Lange or Fragile X syndrome took part in a cross-sectional questionnaire-based study to examine the relationship between intolerance of uncertainty, anxiety and autism symptomatology. **Findings:** Intolerance of uncertainty mediated the relationship between autism and anxiety in Cornelia de Lange syndrome participants but not in the Fragile X syndrome sample. **Conclusion**: Results are discussed in relation to the current autism literature. It is suggested that other factors may be contributing to the autism-anxiety relationship in Fragile X syndrome. Recommendations are made for future intervention-based research for the management of anxiety in Cornelia de Lange syndrome.

Keywords: Rare genetic syndromes; Cornelia de Lange; Fragile X; Autism; Anxiety; Intolerance of uncertainty

2.1 Introduction

Rare genetic syndromes associated with intellectual disability have a prevalence of approximately 1 in 213 to 1 in 448 live births (dependent on parent age; Study et al., 2017) in the general population. These syndromes are often associated with increased risk of mental health difficulties such as anxiety (Basile, Villa, Selicorni, & Molteni, 2007; Cordeiro, Ballinger, Hagerman, & Hessl, 2011; Dykens, Hodapp, & Finucane, 2000). Many rare genetic syndromes are also associated with an increased prevalence of autism spectrum disorder (ASD). Richards, Jones, Groves, Moss and Oliver (2015) systematically reviewed the prevalence of ASD in rare genetic syndromes and reported on sixteen syndromes associated with ASD across available literature. These included Fragile X, Cornelia de Lange, Williams', Rett and Down syndrome. Across all the syndromes identified, ASD phenomenology was significantly more likely compared to the general population. Given that ASD is also associated with an increased prevalence of anxiety disorders (Strang et al., 2012), research investigating the link between ASD symptomatology and anxiety in rare genetic syndromes could further our understanding of the anxiety-ASD relationship and highlight potential new interventions for anxiety in rare genetic syndromes associated with both ASD and anxiety.

2.1.1 ASD

ASD is a neurodevelopmental disorder with a prevalence of approximately 1% in the typically developing (TD) population (Simonoff et al., 2008), and approximately 40% in people with a severe to profound intellectual disability. ASD is characterised by difficulties in social-communication and by repetitive behaviours and restricted interests. Until recently, a diagnosis of ASD required impairments in a 'triad' of domains, namely social communication, reciprocal social interaction and repetitive behaviours/restrictive interests (Wing, Gould, & Gillberg, 2011). The DSM-5 (American Psychiatric Association, 2013). amended these criteria to a 'dyad' of impairments, with difficulties in reciprocal social interaction now falling under the 'social communication' category of difficulties.

2.1.1.1 Anxiety in ASD

In people with ASD, estimated prevalence rates of anxiety are in excess of 40% (Leyfer et al., 2006). Alongside high prevalence rates for anxiety in people with ASD, research indicates that at least 50% of people with ASD will experience anxiety that has a significant impact on their day to day lives. Anxiety in people with ASD can present differently from anxiety in TD people (Kerns et al., 2014; Rodgers & Ofield, 2018). This can make assessing anxiety in people with ASD problematic, as most measures of anxiety are designed for the TD population. Research indicates that when someone with ASD is anxious they may spend more time on their specific interests, their behaviour may become more repetitive and they may become more rigid and insistent on their routines (Joyce, Honey, Leekam, Barrett, & Rodgers, 2017; Rodgers & Ofield, 2018).

Other behaviours associated with anxiety in ASD include: self-injury, increased repetitive and ritualistic behaviours, and avoidance (Leyfer et al., 2006; Wigham, Rodgers, South, McConachie, & Freeston, 2015). As well as anxiety being distressing to experience, it could have additional consequences such as someone with a neurodevelopmental disorder missing out on life experiences, as well as impacting on educational and developmental goals. As anxiety can have such wide-reaching consequences for an individual experiencing it, being able to both describe and explain the presence of anxiety is important.

2.1.2 Intolerance of uncertainty

A better understanding of the nature of anxiety in neurodevelopmental disorders, and its causes can point to appropriate interventions to decrease anxiety in these disorders. In ASD, recent studies have started to answer these questions and indicated a role for 'intolerance of uncertainty' (IU) in the presence of anxiety in both typical development and in ASD (Rodgers, Glod, Connolly, & McConachie, 2012). IU is the term used to describe a 'desire for predictability' (Birrell, Meares, Wilkinson, & Freeston, 2011, p. 1205) and paralysis of cognition and action in the face of uncertainty (Birrell et al., 2011). People with IU both avoid uncertain situations, and have difficulty functioning in them (Boelen & Reijntjes, 2009). IU was initially implicated in the development and maintenance of generalised anxiety disorder and worry (Freeston, Rhéaume, Letarte, Dugas, & Ladouceur, 1994) and

has now been identified as a critical factor underpinning a wide range of anxiety disorders (Norr et al., 2013) including social anxiety disorder, panic disorder and separation anxiety and anxiety-related conditions such as obsessive compulsive disorder (OCD).

Whilst research has mainly focussed on TD adults and children, evidence is emerging for the presence of IU in individuals with ASD. For example, Boulter, Freeston, South, and Rodgers (2014) compared IU and anxiety in typically developing children and children with ASD and modelled the relationships between ASD symptomatology, IU and anxiety. They found that (both with parental and child reports) levels of anxiety and IU were significantly higher in the ASD group. Furthermore, when the effect of IU was controlled for, there was no longer a significant difference between the groups. Results were consistent with a causal model of IU mediating the relationship between ASD and anxiety. This indicates that IU may play a causal role in the development of anxiety in ASD.

Elsewhere, Wigham et al. (2015) examined the relationships between sensory processing abnormalities, anxiety, repetitive behaviour and IU in children with ASD using questionnaire measures. It was found that sensory under responsiveness (seeking sensation) was linked to repetitive behaviours and sensory over responsiveness (sensory avoiding and sensitive to stimuli) was linked to insistence on sameness. Importantly, IU was found to be a mediating factor between sensory processing abnormalities and anxiety. IU and anxiety also mediated the relationship between sensory processing abnormalities and the presence of restricted/repetitive behaviours.

In their study, Hodgson, Freeston, Honey, and Rodgers (2017) explored the concept of IU in people with ASD using parent focus groups as a preliminary step towards developing an intervention for IU in people with ASD. Parents were asked to share experiences of their child's anxiety and IU. Parents were able to reach a consensus about how IU is defined and how it presents in children with ASD. Parental examples of IU included whether an event was unexpected and if an event was expected but parts of the event were unknown. They also included events which were familiar such as being at home and novel situations such as going somewhere new on holiday.

As well as IU predicting anxiety in people with ASD, studies have demonstrated that IU is also related to other ASD specific features. Neil, Olsson, and Pellicano (2016) found using questionnaire measures that, as well as IU mediating the relationship between ASD symptomatology and anxiety, IU also mediates the relationship between ASD symptomatology and sensory sensitivities even when the effects of anxiety were controlled for. The authors suggested that IU may result in attempts to reduce uncertainty in the environment. This may increase anxiety symptoms such as rumination and increased hyper vigilance to threatening environmental stimuli. This may lead to heightened sensory sensitivity.

In their cross-sectional questionnaire study, Vasa, Kreiser, Keefer, Singh, and Mostofsky (2018) found significant relationships between both severity of social communication difficulties and severity of repetitive behaviour with IU. Furthermore, they found that emotional dysregulation was predictive of IU when controlling for anxiety. They concluded that as well as anxiety, IU has unique relationships with many features of ASD which may explain the high levels of IU seen in ASD. They also suggested that the relationship between ASD features and IU may be a result of overlapping neurobiological networks, and therefore possibly heritable.

2.1.2.1 IU in rare genetic syndromes

Given the recent findings on IU in ASD, and the implications for understanding anxiety in this population and developing effective interventions, it would be valuable to establish if similar relationships between IU and anxiety exist in other neurodevelopmental disorders.

Uljarević, Labuschagne, Bobin, Atkinson, and Hocking (2018) investigated associations between anxiety and both IU and sensory sensitivities in people with Williams Syndrome (WS) and found that IU and sensory hypersensitivity were unique predictors of anxiety in the syndrome. ASD symptomatology measured by the Social Responsiveness Scale (SRS) was not found to predict anxiety in WS. This pattern resembles that observed in current ASD literature ((Boulter et al., 2014; Wigham et al., 2015). The authors emphasised the need for interventions to address IU and beliefs about unpredictable situations for people with WS.

Uljarević et al. (2018) provided a first examination of the IU-anxiety relationship in a rare genetic syndrome associated with ASD. As different syndromes have different associated behavioural phenotypes and presentations of anxiety, it would be appropriate to investigate whether this relationship applies to other syndromes associated with anxiety and ASD symptomatology.

2.1.3 Cornelia de Lange syndrome

Cornelia de Lange syndrome (CdLS) is a rare genetic syndrome with an estimated prevalence of between 1 in 10,000 (Opitz & Reynolds, 1985) to 1 in 100,000 live births (Barisic et al., 2008). It is caused by varying mutations in the NIPBL (Krantz et al., 2004), SMCA, HDAC8, RAD21(Deardorff et al., 2012; Deardorff, Noon, & Krantz, 2016), and SMC3 (Revenkova et al., 2008) genes which disrupt gene regulation during early critical development. Mutations in the NIPBL genes have been identified in over 50% of people with CdLS (Krantz et al., 2004). Mutations in the other genes are less common. CdLS presents with a number of distinctive physical characteristics (Kline et al., 2007). These include a proportionate short stature, small hands and feet, abnormal limb development and upper extremity limb malformations (in approximately 30% of cases). Facial features include synophrys, a small nose with depressed bridge, a thin downturned lip and an elongated philtrum (Kline et al., 2007). There are also some associated health problems which include congenital heart problems, renal malformations, dental problems, hip abnormalities and a high prevalence of gastro-oesophageal reflux disease (GORD), which often requires surgical intervention. Intellectual disability (ID) in CdLS can range from mild to profound (Berney, Ireland, & Burn, 1999).

2.1.3.1 Behavioural phenotype overview

CdLS has an associated behavioural phenotype of repetitive behaviours, self-injurious behaviour, an expressive-receptive language discrepancy, ASD phenomenology and high levels of social anxiety (Berney et al., 1999; Oliver, Arron, Sloneem, & Hall, 2008). Research into social anxiety in CdLS point to social impairments consistent with a social anxiety presentation. Arron et al. (2006) showed people with CdLS demonstrating socially avoidant behaviour, while Richards, Moss, O'Farrell, Kaur, and Oliver (2009) found that people with CdLS

were significantly more likely to show behaviours indicative of social anxiety compared to another rare genetic syndrome.

2.1.3.2 ASD in CdLS

A strong association with ASD-symptomatology in CDLS has been demonstrated in several studies, although early studies found these were associated with moderate to profound intellectual disability only (Basile et al., 2007; Berney et al., 1999). However, Oliver et al. (2008) compared ASD symptomatology in CdLS to a matched ID group and found that the CdLS group were more likely to be classed as 'severely' autistic even when controlling for level of ID. The authors suggested that autism in CdLS cannot be explained by ID alone. Using the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2000), Moss, Howlin, Magiati, and Oliver (2012) found that people with CdLS showed less repetitive behaviour and stereotyped speech and more eye contact compared to people with ASD, resulting in different profiles of subscale scores on the ADOS assessment. However, the subscale scores on the ADOS still reached clinical cut-off for a diagnosis of ASD.

2.1.3.3 Anxiety in CdLS

Research has recently started to investigate the nature of anxiety in CdLS and findings indicate anxiety prevalence rates of between 10 and 64%. Arron et al. (2006) used analogue methodology (experimentally manipulating environmental variables to assess the effects of those variables on behaviour) to evaluate the impact of levels of attention on social behaviour in CdLS. They found that 77% of participants with CdLS demonstrated socially avoidant behaviour such not complying with a request or moving away from physical contact and during interactions. Richards et al. (2009) used functional analysis to compare behaviours indicative of anxiety in 12 participants with CdLS and 12 participants with Cri du Chat syndrome (CdCS) in different social situations. They found participants with CdLS to be significantly more likely to display behaviours indicating social anxiety during high social demand than the CdCS group.

Crawford, Waite, and Oliver (2017) investigated and compared anxiety profiles and symptomatology across three rare genetic syndromes, namely CdLS, Fragile X syndrome (FXS) and Rubinstein-Taybi syndrome (RTS) using questionnaire measures. The CdLS group showed higher levels of generalised anxiety disorder

(GAD) and separation anxiety compared to typically developing children and FXS and RTS syndrome comparison groups. When compared to TD children with diagnoses of GAD or separation anxiety, no significant differences were found between them and the CdLS group. The authors suggested that these results highlighted the severity and breadth of anxiety disorders in people with CdLS.

2.1.3.4 CdLS and IU

Anecdotal reports from parents of children with CdLS suggest that high levels of anxiety can occur when situations are unpredictable or novel, for example, if their child is going to a new place or to an event to which they have never previously been. Given the presence of ASD phenomenology in CdlS, it is possible that these descriptions of anxiety in CdLS could be underpinned by IU, as found in ASD (Boulter et al., 2014; Rodgers, Freeston, South, Wigham, & Boulter, 2012). This possibility provides a rationale for investigating a link between anxiety and IU in CdLS. If IU is also underpinning anxiety in CdLS as in ASD, clinical interventions and approaches could be developed for people with CdLS to manage their anxiety and could improve quality of life.

2.1. 4 Syndrome comparison group:

Whilst assessing performance of those with a particular syndrome on different measures can provide valuable information, comparisons with other syndrome groups allows for characteristics/behaviour to be identified as either related to a particular syndrome or related to the level of intellectual disability more generally. Therefore, this study used a syndrome comparison group in its methodology.

Fragile X syndrome (FXS) is a rare genetic syndrome which is the most common cause of inherited intellectual disability and has a prevalence of approximately 1 in 2,500-5,000 males (Coffee et al., 2009). FXS is caused by mutations in the Fragile X Mental Retardation 1 (FMR1) gene on the X chromosome. As FXS is an X linked disorder, far fewer females are affected and often present with phenotypic differences compared to males with FXS (Clifford et al., 2007). Due to the differences in presentation between males and females, this study only recruited males with FXS. It is associated with mild to profound intellectual disability and a range of physical and behavioural characteristics. The associated behavioural

phenotype includes social anxiety, ASD-symptomatology, hyperactivity, hyper-arousal to sensory stimuli and high levels of repetitive behaviour (Garber, Visootsak, & Warren, 2008).

The nature of anxiety in FXS has been reported in the literature and parental reports indicate the presence of high levels of anxiety in FXS. Ezell et al. (2019) compared prevalence of anxiety disorders between FXS and ASD matched participants using a diagnostic interview measure of anxiety (Weller, Fristad, Weller, & Rooney, 1999). They reported an anxiety disorder prevalence of 51.6% in the FXS group compared to 50% in the ASD group. However, in the ASD group the most prevalent disorder was GAD whereas in FXS it was specific phobia. This highlights differences in the presentation and manifestation of anxiety in FXS compared to ASD samples. Cordeiro et al. (2011) used the Anxiety Disorders Interview Schedule (Grisham, Brown, & Campbell, 2004) to assess anxiety in 97 males and female participants with FXS. They found that approximately 86% of their sample met diagnostic criteria for an anxiety disorder, with 65% meeting cut off for Specific Phobia and 35%, social phobia. Crawford et al. (2017) used questionnaire-based measures to investigate anxiety profiles in FXS and other genetic syndromes compared to TD populations. Using the Spence Child Anxiety Scale (Spence, 1998), they found that the FXS group were comparable with TD populations except for being slightly higher on the panic/agoraphobia subscale. The FXS group were also comparable for children diagnosed with an anxiety disorder on most subscales. For total anxiety scores, people with FXS scored lower that children diagnosed with an anxiety disorder.

Whilst anxiety disorders have been reported and investigated in FXS, mediating factors for the presence of anxiety in the syndrome such as IU have not previously been investigated.

2.1.5 Rationale and Aims

Understanding the nature of anxiety, and the factors underpinning it in CdLS is important for developing tailored interventions to reduce anxiety in the syndrome. As outlined previously, IU has been implicated in the presence of anxiety in ASD. Given the associations between ASD and CdLS, it is possible that the same relationship exists in CdLS and other syndromes associated with ASD.

In line with the above rationale, this study set out to answer the following research questions

1) How do IU and anxiety compare between CdLS and a syndrome comparison group (FXS)?

2) How are IU, anxiety and autism symptomatology related in CdLS and FXS?

3) Does IU mediate the relationships between autism symptomatology and anxiety in CdLS and FXS?

2.2 Method

2.2.1 Ethical approval

This study was conducted in accordance with the British Psychological Society's ethical guidelines (BPS, 2009). Ethical approval was granted from the University of Birmingham Ethics Committee and from the NHS Ethical Review for these measures, data collection methods and populations to be used as part of a larger research project. Approval was granted from Coventry University Ethics Committee to analyse the data. (See Appendix C)

2.2.2 Recruitment

Participants for this study were recruited as part of a larger ongoing cross syndrome project.

A total of 130 parents/carers of children with FXS or CdLS syndromes were contacted as part of an ongoing study investigating anxiety presentations in rare genetic syndromes. 85 parents/carers chose to take part in the ongoing study. Participants were contacted via an existing database at the Cerebra Centre for Neurodevelopmental Disorders at the University of Birmingham which was compiled through recruitment via the appropriate syndrome support groups; Cornelia de Lange Foundation UK and Ireland and the Fragile X Society.

2.2.3 Participants

Participants with CdLS or FXS were recruited based on the following inclusion criteria:

1) Having a confirmed genetic diagnosis of CdLS or Fragile X syndrome.
2) The presence of a mild to moderate intellectual disability
3) Aged four years and upwards

Participants without a confirmed diagnosis of the genetic syndrome from the medical professional (GP, clinical geneticist or paediatrician) were excluded from analysis. Participants were also excluded if less than 75% of the questionnaire had been completed. Participants were matched on chronological age and ability using the Communication subscale and the Adaptive Behaviour Composite score from the Vineland Adaptive Behaviour Scale (VABS) (Sparrow, Cicchetti, Balla, & Doll, 2005). Questionnaire measures were completed by participants' parents/carers.

Details of participant demographics are displayed in Table 2.1, and results of statistical analyses detailing significant differences between demographics are displayed.

2.2.4 Procedure

Information sheets, consent forms and questionnaire packs were sent out to families (or distributed at syndrome support group meetings or home visits) who indicated interest in participating in research at the Cerebra Centre, and whose details were therefore held on the participant database. As this was part of a larger ongoing project, some further measures were included in this pack which did not form part of the present study.

2.2.5 Measures

The following questionnaires were sent to parents/carers:

2.2.5.1Demographic information

The demographic questionnaire asks parents to confirm their child's age, gender, verbal ability, mobility status and details of diagnosis

2.2.5.2 Measure of ability:

Vineland Adaptive Behaviour Scale (VABS) second edition (Sparrow et al., 2005)

The VABS is a parent/carer interview measure that assesses adaptive behaviour in four key domains: daily living, communication, socialisation, and motor skills. It is used for typically developing children (aged from birth to 18) and is also widely used for children and adults with intellectual disabilities. Internal consistency for the total score was high when tested in children and adults with intellectual disabilities (Cronbach's Alpha = .99) and the VABS is strongly positively correlated with the Social Functioning Scale for the Mentally Retarded *(r*=.93; de Bildt, Kraijer, Sytema, & Minderaa, 2005).

Cronbach's alpha for the CdLS group on this measure was excellent (α=.94) and excellent for the FXS group (α=.93)

This measure was administered in telephone interviews between the researcher and parent/carer.

2.2.5.3 Measure of ASD symptomatology:

Social Responsiveness Scale- Second edition (SRS-2)(Constantino & Gruber, 2012)

The SRS-2 is a 65-item rating scale that measures the severity of ASD symptoms. There are five subscales: Social Awareness, Social Cognition, Social Communication, Social Motivation and Restricted Interests and Repetitive Behaviour. The SRS-2 offers three different forms, suitable for different ages (2.5-4 years, 4-18 years and 19 years +), that are completed by parents or teachers in approximately 15-20 minutes. This version is identical to its predecessor, the SRS, which has been shown to correlate strongly (*r* = .65-.77) with the Autism Diagnostic Interview – Revised (ADI-R; Le Couteur, Lord, & Rutter, 2003). The SRS-2 also has good inter-rater reliability (*r* = .75-.91) and scores are not related to IQ (Constantino & Gruber, 2007). In order to ensure a good spread of scores for statistical analyses, the total raw scores from the SRS were used in this study rather than t-scores.

Cronbach's alpha for the CdLS group on this measure was excellent (α=.93) and good for the FXS group (α=.87)

2.2.5.4 Measures of anxiety

The Anxiety Scale for Children-ASD (ASC-ASD) (Rodgers et al., 2016)

The ASC-ASD is a 24 item anxiety rating scale with four subscales: Performance Anxiety, Uncertainty, Anxious Arousal, and Separation Anxiety. This measures anxiety related items that are particularly appropriate to the specific phenomenology of anxiety in ASD. There are two versions of the ASC-ASD, a child self-report and a parent report. The parent report version was used in the current study. Internal consistency is good to excellent (Cronbach's alpha for: full scale: .94; performance: .89; separation: .87; arousal: .87; anticipatory: .91). One month test-retest reliability is excellent (r=.84) and convergent validity has been demonstrated by significant strong correlations between the ASC-ASD and the Screen for Child Anxiety Related Emotional Disorders (SCARED; Birmaher et al., 1997)

Cronbach's alpha for the CdLS group on this measure was excellent (α=.94) and acceptable for the FXS group (α=.75)

The Anxiety, Depression, and Mood Scale (ADAMS) (Esbensen, Rojahn, Aman, & Ruedrich, 2003)

The ADAMS is a 28-item informant report designed to screen for anxiety, depression and mood disorders among individuals with intellectual disability. There are five subscales: Manic/Hyperactive Behaviour, Depressed Mood, Social Avoidance, General Anxiety and Compulsive Behaviour. The ADAMS has satisfactorily high alphas for each of the subscales, with a mean Cronbach's alpha of .80 and robust test-retest correlations at the scale and subscale level (mean subscale = .78).

Cronbach's alpha for the CdLS group on this measure was good (α=.88) and acceptable for the FXS group (α=.71)

2.2.5.5 Measure of intolerance of uncertainty:

Intolerance of Uncertainty Scale – Parent Version (Rodgers, Freeston, et al., 2012)

The Intolerance of Uncertainty scale is a 12-item informant questionnaire used to assess an individual's ability to cope with uncertainty in particular situations. Parents/carers are asked to indicate on a 5-point likert scale how well 12 statements describe their child. The measure yields a total score, for which higher scores indicate greater levels of intolerance to uncertainty. The scale has been found to have excellent internal consistency reliability in both TD individuals and individuals with ASD (Boulter et al., 2014)

Cronbach's alpha for the CdLS group on this measure was excellent (α=.92) and good for the FXS group (α=.83)

2.2.6 A comment on measures of anxiety and intolerance of uncertainty

There are currently no measures of anxiety validated in both CdLS and FXS which can be used across children and adult participants. The ASC-ASD anxiety measure was validated in children (up to 16 years) with autism but without intellectual disability. Due to the ASD-links in both CdLS and FXS, it was considered a suitable measure to be used to identify ASD-related anxiety behaviours. The ADAMS (Esbensen et al., 2003) was selected as it is currently the only validated measure of anxiety and mood in people with intellectual disability. It was validated in adults. The GA (general anxiety) subscale was used in this study specifically as the total score includes subscales relating to depressive moods. Cordeiro et al. (2011) validated the use of the ADAMS in people FXS aged five-33 years using the Anxiety Disorder Interview Scale (Grisham et al., 2004). The GA scale was found to correlate highly with a number of subscales on the ADIS, suggesting it is a good measure of overall anxiety. Therefore, it was considered methodologically sound to use the subscale scores from the GA as representative of anxiety symptoms.

2.2.7 Data analysis

The distribution of IUS-P, ADAMS General anxiety subscale, ASC-ASD total scores and SRS total raw scores across participant groups were examined using visual examination of stem and leaf plots and the Shapiro-Wilk test. All scores were

found to be normally distributed with the exception of the ASC-ASD total scores in the CdLS group. Attempts to transform the data to a normal distribution were unsuccessful.

The data analysis strategy therefore includes both parametric and non parametric tests depending on the distribution of variables included in each analysis.

Power analysis

A post hoc power analysis was conducted using the software package, G*Power (Faul, Erdfelder, Lang & Buchner, 2007). The sample size of 68 and a 3 predictor variable equation with a medium effect size (f^2 = .15) were used for this analysis. The recommended effect sizes used for this assessment were as follows: small (f^2 = .02), medium (f^2 = .15), and large (f^2 = .35) (Cohen, 1977). The alpha level used for this analysis was $p < .05$. The post hoc analyses revealed the statistical power for this study was .12 for detecting a small effect, .70 for detecting a medium effect and power exceeded .97 for the detection of a large effect size. Thus, there was more than adequate power at large effect size level, but less than adequate statistical power at the small and medium effect size level. Therefore, results (especially non significant) should be interpreted with caution.

Table 2.1 Comparing demographic information across participant groups

	CdLS n= 33	**FXS n=30**	***U***	***p***
Median age in years	13.92	20.63	499	.329
Range	49.75	40.25		
Gender (% Male)	44.12	100		
Median VABS Adaptive behaviour composite	53	52.50	573	.946

Median VABS Communication subscale	54	44.50	532	.569

2.3 Results

2.3.1 Comparing anxiety and intolerance of uncertainty between groups

In order to establish whether there were any differences in key variables between the groups, the ADAMS-GA, ASC-ASD, IUS-P total scores and SRS raw scores were compared between the CdLS and FXS group with a series of t-tests. Results revealed no significant differences between CdLS and FXS on any of the measures. Table 2.2 outlines the results of t-test analyses.

Table 2.2 ASC-ASD total scores, ADAMS general anxiety subscale scores and IUS-P total scores in CdLS and FXS

		CdLS (n=33)	**FXS** (n=30)	***t* *(U)***	**df**	***p***
SRS total scores	Mean (SD)	91.36 (26.74)	102.10 (18.97)	-1.82	61	.07
ADAMS-GA subscale	Mean (SD)	7.98 (4.93)	7.85 (4.37)	0.11	61	.92
ASC-ASD total score	Median (Range)	15 (52)	15.79 (32)	(0.21)	66	.84
IUS-P total score	Mean (SD)	31.21 (13.03)	32.23 (9.74)	-0.37	61	.71

2.3.2 Regression analyses

In order to determine whether SRS, IUS-P or syndrome group could predict scores on the ASC-ASD, a hierarchical multiple regression analysis was carried out. All models had a high tolerance (ranging between 0.80-1.00) and low variance inflation factor (VIF) (ranging between 1.000-1.30) suggesting a low level of multicollinearity between predictors. The Durbin-Watson value was acceptable (2.40), suggesting the assumption of independent errors is tenable.

In the first step of hierarchical multiple regression, SRS scores were entered. This model was statistically significant. F (1,61) = 10.83 p =.002, and explained 14 % of variance in anxiety (ASC-ASD scores). After entry of IUS-P at Step 2 the total variance explained by the model as a whole was 60%, F (2,60) = 47.34, p < .001. The introduction of IUS-P explained additional 46% of variance in ASC-ASD scores, after controlling for SRS scores, R^2 = .462 *FChange* (1, 60) =71.71, p < .001). The higher IUS-P scores, the higher the ASC-ASD scores. Syndrome was entered at step 3 of the model and did not significantly contribute to the model. Table 2.3 shows the hierarchical linear models for ASC-ASD score.

The same analysis was carried out with ADAMS-GA scores as the dependent variable.

All models had a high tolerance (ranging between 0.80-1.00) and low variance inflation factor (VIF) (ranging between 1.000-1.30) suggesting a low level of multicollinearity between predictors. The Durbin-Watson value was acceptable (2.12), suggesting the assumption of independent errors is tenable.

In the first step of hierarchical multiple regression, SRS scores were entered. This model was statistically significant, F (1,61) = 15.34; p =<.001, and explained 19% of variance in anxiety (ADAMS-GA scores). After entry of IUS-P at Step 2 the total variance explained by the model as a whole was 51%, F (2,60) = 33.77; p < .001. The introduction of IUS-P explained additional 33% of variance in ADAMS-GA scores, after controlling for SRS scores, R^2*Change*= .329 *FChange* (1, 60) =41.91 p < .001. The higher IUS-P scores, the higher the ADAMS-GA scores. Syndrome was

entered at step 3 of the model and did not significantly contribute to the model.

Table 2.3 Shows the hierarchical linear models for ADAMS-GA score.

Table 2.3 The Hierarchical Linear Models for ASC-ASD and ADAMS-GA measures

	B	**SE**	***B***	***p***	**R**	**R^2**	**AdjR^2**
ASC-ASD							
Step 1					**.39**	**.15**	**.14**
Constant	-1.11	5.46		.840			
SRS	0.18	0.06	0.39	.002			
Step 2					**.78**	**.61**	**.60**
Constant	-9.50	3.85		.016			
SRS	0.03	0.04	0.06	.481			
IUS-P	0.73	0.09	0.75	<.001			
Step 3					**.79**	**.62**	**.60**
Constant	-9.43	3.85		.017			
SRS	0.04	0.04	0.08	.377			
IUS-P	0.72	0.09	0.75	<.001			
Group	-1.60	1.82	-0.07	.385			
ADAMS-GA							
Step 1					**.46**	**.21**	**.20**
Constant	-5.11	2.22		.818			
SRS	0.09	0.02	0.45	<.001			

Step 2					**.73**	**.53**	**.51**
Constant	-3.47	1.78		.056			
SRS	0.03	.019	0.18	.081			
IUS-P	0.26	.040	0.63	<.001			
Step 3					**.73**	**.54**	**.51**
Constant	-3.43	1.78		.058			
SRS	0.04	0.02	0.20	.056			
IUS-P	0.25	0.04	0.63	<.001			
Group	-0.81	0.84	-0.09	.338			

2.3.3 Mediation analyses strategy

The regression analyses showed IU strongly predicting anxiety in both CdLS and FXS, over and above ASD symptomatology (SRS scores). Therefore, the next step in the analyses was to understand the role of IU more specifically using mediational analyses. In order to examine the relationship between IU and anxiety in more detail, it was considered prudent to separate the syndrome groups and look at the syndrome specific relationships between ASD, IU and anxiety.

2.3.4 Mediation analyses

In order to establish whether IU is mediating the relationship between autism symptomatology and anxiety in CdLS and FXS mediation analysis was conducted using the computational tool for mediation and moderation, an SPSS macro called PROCESS developed by Preacher and Hayes (2004). The method using a bootstrapping procedure to obtain estimates and confidence intervals around the indirect effects. Significant relationships in the models are indicated by bootstrapped confidence intervals that do not overlap with zero. In the CdLS group, the total effect of SRS scores on anxiety was significant for both measures (ASC-ASD

(*b*=0.18, *t*= 2.30, *p*=<.05), ADAMS-GA (*b*=0.10 , *t*=3.39 , *p*=.0019). Table 2.4 shows the direct and indirect effects of SRS scores on anxiety scores with the mediator variable (IU) taken into account. After adjusting for the indirect effect of IU, the direct effect did not remain significant for either anxiety measure. Examining the 95% confidence interval confirms that ASD symptomatology has a significant indirect effect on anxiety through the mediating variable of IU, ASC-ASD b=0.23 (95% Bootstrapped CI 0.08, 0.39) and ADAMS, *b*=0.07(95% Bootstrapped CI 0.03, 0.12). These results indicate that IU is fully mediating the relationship between ASD symptomatology and anxiety in the CdLS group.

In the FXS group, the total effect of SRS scores on anxiety was significant for both measures , ASC-ASD *b*=0. 22, *t*= 2.65, *p*=.0129), ADAMS-GA (b=0. 09, *t*= 2.12, *p*=.0430). Table 2.4 shows the direct and indirect effects of SRS on anxiety with the mediator variable (IU) taken into account. After adjusting for the indirect effect of IU, the direct effect remained significant for the ASC-ASD measure but not for the ADAMS-GA measure of anxiety. Examining the 95% confidence intervals indicates that IU is NOT mediating the relationship between ASD symptomatology and anxiety scores using either measure.

Results of the mediation analyses for both CdLS and FXS were consistent using Baron and Kenny (1986)'s approach (see Appendix O).

Table 2.4: The direct and indirect effects of ASD symptoms on anxiety in CdLS and FXS.

		Direct effect: ASD symptoms on anxiety			**Indirect effect: ASD symptoms on anxiety**		
		ASC-ASD					
		B	**SE**	**95% CI**	***B***	**SE**	**95% CI**
CdLS	IU	-0.04	0.06	-0.16 to 0.08	0.22**	0.08	0.08 to 0.38
FXS	IU	0.15*	0.06	0.02 to 0.28	0.07	0.04	-0.02 to 0.16
		ADAMS-GA					
CdLS	IU	0.03	0.03	-0.02 to 0.08	0.06**	0.02	0.03 to 0.12
FXS	IU	0.06	0.03	-0.01 to 0.12	0.30	0.02	-0.01 to 0.07

*indicates $p<.05$

**indicates $p<.01$

2.4 Discussion

This study is the first to investigate the relationships between anxiety, IU and ASD symptomatology in CdLS and FXS. This study used groups that were matched for age and ability, with good sample sizes for rare populations research.

First, the total scores on measures of IU, anxiety and autism symptomatology were compared between CdLS and FXS groups using a series of t-tests and Mann Whitney U tests (for non-parametric data). Results showed no significant differences between the CdLS and FXS group on any of the measures (Intolerance of Uncertainty Scale, Anxiety Scale for Children with ASD, ADAMS General Anxiety Scale or the Social Responsiveness Scale).

In order to answer the next research question, hierarchical linear regression analyses were carried out to determine whether SRS (ASD symptomatology) or IUS-P scores (IU) or syndrome group predict anxiety in CdLS and FXS. For the ASC-ASD anxiety measure, SRS scores significantly accounted for the variance in anxiety scores at step one, but were no longer significant when IU was added in step two. IU scores predicted a significant and large part of the variance and this effect was maintained at step three. Syndrome group did not significantly predict any of the variance in anxiety scores. Results were consistent for both anxiety measures.

The results of the regression analyses indicated a significant predictive relationship between IU scores and anxiety in both CdLS and FXS, with no significant difference in the relationship between the groups. Results also suggest that the relationship between autism symptomatology and anxiety scores is no longer significant when IU is added into the model.

The final research question concerned whether IU is mediating the relationship between autism and anxiety in CdLS and FXS. As the regression analyses clearly indicated a predictive role of IU to anxiety, it was important to examine and compare this relationship in more detail according to syndrome group. Using Process Analysis (Preacher & Hayes, 2004) revealed that IU fully mediated the relationship between autism symptomatology and anxiety in CdLS. However, in FXS, the method indicated it was unlikely a mediational relationship existed.

The results from this study indicate that the relationship between autism symptomatology, IU and anxiety in CdLS is comparable to the relationship found in people with ASD. IU is a construct that explains the relationship between autism and anxiety, and therefore it is possible that targeting IU as an intervention for anxiety in CdLS may be beneficial. In FXS, however, the relationship between autism symptomatology, IU and anxiety is less clear. Whilst regression analyses indicate that IU scores can predict anxiety in FXS, mediation analyses suggested that IU is not mediating the relationship between autism symptoms and anxiety. This is somewhat surprising given that (like CdLS), FXS is a syndrome strongly associated with comorbid ASD, and high levels of anxiety are seen in the syndrome.

It was considered that the differences in gender could be influencing the results, as FXS is an X-linked disorder, participants were all male. Research in autism indicates no influence in gender on the predictors of anxiety (Hurtig et al., 2009; Sukhodolsky et al., 2008). However, this pattern could be different in these genetic groups and future research examining gender differences would be useful. Another possibility is that the *profile* of anxiety differed between CdLS and FXS. Although no significant difference was found in the total scores for the ASC-ASD between the groups, it is possible that differences in the profiles of the subscale scores may have impacted the relationship between IU and the ASC-ASD total scores between the groups. However, the same patterns of relationships between IU and anxiety between groups were identified when the ADAMS-GA subscale was used as an anxiety measure. This indicates that another factor may be influencing the difference in results between CdLS and FXS.

Since the research by Boulter et al. (2014) further studies have also indicated a role for sensory sensitivity as a mediating factor between ASD and anxiety. Whilst the present study only examined IU, it is possible that in FXS, another factor is mediating this relationship. For example, Uljarević et al. (2018) investigated the same relationships in people with Williams syndrome (WS). Whilst they found that IU predicted anxiety in WS, it was sensory sensitivity that was mediating this relationship. Hypersensitivity to sensory stimuli is a characteristic of FXS. In their study investigating anxiety profiles in FXS and other genetic syndromes, Crawford et al. (2017) suggest that sensory hypersensitivity may contribute to anxiety in environments where sensory stimuli is elevated. This may then contribute to the

presence of anxiety disorders such as agoraphobia seen in the syndrome, as sensory sensitivity leads to avoidance of highly stimulating environments. Therefore, it is possible that a factor such as sensory sensitivity may be implicated in relationship between ASD symptomatology, IU and anxiety in FXS syndrome. More research is needed to further delineate this relationship.

2.4.1 Limitations

This study had a number of limitations. First, the measures chosen were parent-report measures. Boulter et al. (2014) used both parent report and child (participant) report measures for the anxiety and IU measures in children with autism but no intellectual disability. They found strong correlations between parent and child scores, indicating good agreement. However, given the sample population of this study, it was unlikely that the participants would have been able to successfully complete the measures and reflect on their own experiences of anxiety in order to do so due to their level of intellectual disability (Cordeiro et al., 2011). In addition, participants included in the study were both children and adults who arguably could have different presentations of anxiety due to their developmental differences (Spence, 1998). However, Mian, Godoy, Briggs-Gowan, and Carter (2012) demonstrated that typically developing children as young as two years old show similar clusters of anxiety symptoms to adolescents which correspond to DSM-5 anxiety disorder diagnostic criteria indicating that anxiety presentations and differentiation remain relatively stable overtime. Furthermore, as participants in this study had associated intellectual disability, it is more likely that clinically they presented similarly in accordance with their developmental rather than chronological age.

A further limitation is that the ASC-ASD has not been validated in people with an intellectual disability, but has been validated in children (up to 16 years) with autism, while the ADAMS was validated in people with intellectual disabilities but not specifically for people with ASD symptomatology. In fact, there is no equivalent measure of anxiety for both children and adults with intellectual disability and ASD. The ADAMS (Esbensen et al., 2003) has been validated in participants aged five to 33 years with FXS syndrome and was therefore considered a good measure to use alongside the ASC-ASD, which was used to identify anxiety traits associated with

autism in CdLS and FXS. Whilst these measures are not ideal, research into rare genetic syndromes comes with such compromises with regard to measures, as it is unusual to find a measure that has been specifically validated in a certain syndrome. However, using both measures and demonstrating the same relationships with both measures of anxiety is encouraging in this regard. Ideally, the study would have utilised direct measures of anxiety such as behavioural observations, or physiological measures such as heart rate or skin conductance response (SCR). However, due to time restraints involved in recruiting such rare populations, this was not possible within the parameters of the study.

A final limitation of this study is that the measure of ability used to match participants was a parent-report measure (VABS). Whilst a direct measure of receptive language ability was available for some of the participants due to this study being part of a concurrent larger study, data were not available for all the participants. In order to match participant groups using the direct measure, the numbers of participants in each group would have been significantly reduced. It was a pragmatic decision to prioritise participant numbers over direct assessment matching. Additionally, people with CdLS and FXS syndrome have been found to have uneven profiles of skills on cognitive assessments (Johnson, 2015) which may be problematic if matching on receptive language level as participants could be significantly different on other cognitive skills depending on their syndrome. Participants were matched on the communication subscale (receptive, expressive and written communication) of the VABS as well as the adaptive behaviour composite score. Adaptive behaviour encompasses goal-directed behaviours associated with executive function which enable day-to-day functioning. It was considered reasonable to match participants on these adaptive behaviours as well as communication level using the VABS in order to match participants as well as possible without using direct assessment.

2.4.2 Clinical implications and future directions

The results from this study have clear implications for clinical practice. First, the finding that FXS did not have the same relationships between autism, IU and anxiety despite being matched with the CdLS group. This is surprising given that both

syndromes are associated with ASD presentations that the same relationships were not found. It is important, therefore, not to assume, based on autism presentations in different syndromes, that the same relationships will exist between IU and anxiety or that the same strategies and interventions targeting these relationships will be equally effective across different syndromes. It seems that the relationship between anxiety and IU is complex and needs further exploration in FXS to identify whether other mediating factors are playing a role. As outlined previously, sensory processing and sensitivity has been implicated in ASD and in WS as influencing the relationship between IU and anxiety in those disorders. It is possible that the influence of sensory processing could account for the lack of a mediating role for IU in FXS. It is possible that both sensory processing and IU can predict anxiety in FXS, or that sensory processing is mediating the relationship between IU and anxiety in FXS - as seen in WS, (Uljarević et al., 2018). This needs further exploration.

The main clinical implication from this study is that IU is playing a key role in the presence of anxiety in CdLS. This means that interventions which target IU may be successful in reducing anxiety in people with CdLS. Rodgers et al. (2017) developed and trialled a parent-based intervention for children with ASD aimed at increasing children's 'tolerance of uncertainty' called 'Coping with Uncertainty in Everyday Situations' -CUES. The intervention ran as an 8-week parent course including psychoeducation about IU, teaching parents to identify factors that may trigger IU for their child and teaching parents appropriate strategies to use to increase their child's tolerance of uncertainty. Parents were provided with support and written materials weekly to identify strategies and target a specific IU situation. These materials incorporated existing, evidence-based materials for working with people with ASD such as comic-strip conversations and visual prompts. Evaluation of the intervention via parent feedback and questionnaires including the IUS-P indicated that parents found the interventions helpful and valued the programme. Outcome measures indicated a reduction of IU (measured by the IUS-P). Whilst effect sizes were modest, the authors suggest that it would be unrealistic to expect large reductions immediately after programme completion especially as the parents trying out new strategies would potentially increase IU temporarily in people with autism as the new strategies are unfamiliar and uncertain. With that in mind, Rodgers et al, (2017) assert that a reduction in IU (albeit small) in the face of increasing

uncertainty is promising and points to the future clinical utility of the programme. Following this study, Rodgers, Herrema, Honey, and Freeston (2018) developed and trialled a direct intervention (CUES-A) for adults with ASD to improve their tolerance to uncertainty. The intervention was based on strategies used in the Rodgers et al. (2017) parent group but adapted for people with ASD. Participants had nine individual sessions of intervention including psychoeducation, learning about IU and its relationship with ASD and learning strategies to cope with IU based on CBT principles. Initial results indicate the feasibility of the approach and results showed promise and that participants valued the intervention.

The development of the CUES programme is promising and may be useful in people with CdLS with mild intellectual disability. Further work is needed to validate the efficacy of 'tolerance to uncertainty' training using the CUES programme, and it is unclear whether children with moderate intellectual disabilities could engage with an intervention like this. However, if the CUES programme is found to be helpful for children with ASD it would seem logical to suggest that people with CdLS of a similar intellectual ability would be able to engage in and find the programme useful. This an exciting area for future research to develop and trial interventions to reduce anxiety and improve quality of life for people with CdLS and other syndromes.

In conclusion, this study has demonstrated similar relationships between ASD symptomatology, IU and anxiety in CdLS as reported in the ASD population. However, the same relationships were not replicated in a matched FXS group. It is suggested that there may be other mediating factors implicated in the presence of anxiety in FXS. These results indicate the applicability of IU specific interventions in CdLS for anxiety management, but also highlights the need for tailored interventions for different syndrome groups.

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Chapter Three:

Detachment vs connection: reflecting on my identity as a researcher and clinician

Overall Word Count: 3,066

3.1 Introduction

This chapter presents a reflective account of the research process whilst conducting the research outlined in chapter two. Throughout this chapter I consider 'detachment' experienced throughout this research process, the differences between quantitative and qualitative research and draw parallels with the scientist-practitioner position as a Clinical Psychologist

I have valued the reflective process throughout my clinical training. During my clinical placements I have used reflection to consider areas for improvement and to identify what I am bringing into the therapeutic relationship. However, my previous experience of reflecting during the research process was more limited. Reflecting on the research process during my thesis research has helped me to appreciate the importance of reflective practice in research, even when conducting quantitative research. Ryan and Golden (2006) considered the usefulness of reflection in their quantitative research. They acknowledged that, whilst reflection in qualitative research is more explicit, with many researchers 'baring their souls', quantitative research seems to avoid reflexivity (Millen, 1997; Ryan & Golden, 2006). Whilst controlling the environment and minimising factors that may affect the research process (such as a researcher-participant relationships) are important for validity, Ryan and Golden (2006) argue that these complex dynamics still exist and reflecting on them is necessary. Through reflecting on this study's research process, I was able to identify and understand my research experience better, namely why I have at times felt a lack of connection, or 'detachment' from my project.

3.2 Detachment

Initially, I was drawn to this research area due to an already developed interest in rare genetic syndromes and learning disabilities. Prior to starting the doctorate, I completed a PhD at the University of Birmingham in a research team that focuses on understanding behaviour and emotions in rare genetic syndromes. My PhD focussed on Cornelia de Lange syndrome and looked at relationships between executive function, decision making and anxiety in the syndrome. I enjoyed the research area so much that I was keen to collaborate with the same research team for my ClinPsyD project.

When devising my data collection plan for this project, it was agreed that combining my data collection with another ongoing project would maximise the participant numbers whilst also reducing the burden of participating on families. If questionnaire packs were sent out separately for several projects at once, families would have to repeatedly fill in consent forms, demographics questions and it would increase the workload for them to participate. Therefore, the questionnaires I wanted to include for my research project were put together in a questionnaire pack with several other questionnaires for concurrent projects working with the same syndrome groups. This strategy meant that my interactions with participants was somewhat limited. I attended two family conferences during which I spoke to families that had previously taken part in my PhD research, and I helped recruit participants for the face to face assessments for the other ongoing project. However, part-way through the data collection process I went on maternity leave and therefore took a hiatus from the research process. Data collection was still ongoing throughout my maternity leave due to the other projects recruiting and seeing participants for face to face assessments (where they also completed questionnaire packs).

When I returned from maternity leave, I had my data to analyse, so I was in a good position to move forward. However, I reflected with a fellow trainee that I just was not feeling the enthusiasm for or connection to my project, even though I had devised it myself and felt passionate about helping the families of the syndrome groups I had previously worked with for years.

Reflecting on my experiences, I realised that there were many key differences in my experiences of research during my PhD compared to my ClinPsyD research.

3.3 The importance of connection

The life of a typical researcher can be a lonely at times. During my PhD experience, many of the other PhD students conducting research at the University of Birmingham were working alone on their projects, with no other PhD students working in the same research area to discuss ideas with or bond with others about the difficulties with their projects. In contrast, the research team I was in had at least three PhD students per year all working in the same research area and often doing data collection together due to the aforementioned practicalities. Whilst projects were individual, much of the process, frustrations and day to day work felt

collaborative and supported. There were also regular team 'socials' and work done for the 'team' in addition to our PhD projects. Reflecting on this and contrasting it with the research process I experienced during my ClinPsyD project, I can see why I may have felt detached during this research project. For my current research, meetings with research supervisors at Birmingham were done over Skype and email due to the practicalities of getting to Birmingham for regular meetings. When I did go into Birmingham to conduct my research-related work, the team had completely changed in the three years since I was there. Furthermore, due to my nine months of maternity leave, my cohort of trainees had finished when I returned to complete my final year. I also had a different timetable from my new cohort due returning to the course out of sync with their placement structure. Taken together, all of this meant that I did not have the same connection or relationship with my fellow trainees or with the research team in Birmingham. This further compounded my experiences of feeling detached from my project (as well as my year group). I have realised that a sense of belonging and connection is very important to me, as well as having relationships and a source of support from my peers and colleagues. I can liken this to working in an MDT in clinical settings. Within an MDT setting, you have colleagues to bounce ideas off, express frustration to and learn from. This is something I have really valued throughout my clinical training and something I missed whilst conducting my research.

Furthermore, whilst the main methodology throughout my PhD thesis was quantitative, with a heavy focus on operationalised, objective behavioural measures, what actually made me so passionate about the research and so motivated to do it was the *human* element. During my PhD, I had a lot of contact with the participants in my studies. I conducted face to face assessments, attended family conferences where I spoke with families and presented my findings and I visited participants at their homes to conduct some of my assessments if their anxiety was too high to come to the research centre. Whilst I used some questionnaire data in my studies, I could put faces and names to the data I analysed as I had interacted with my participants, I knew their stories and their struggles. I knew the people behind the data. This reflection made me consider my need for the qualitative element with quantitative research.

3.4 Quantitative versus Qualitative methods

Quantitative research is traditionally concerned with reducing phenomena to 'empirical indicators' which represent an 'objective reality' (Sale, Lohfeld, & Brazil, 2002). The researcher and participants- or 'the researched' are considered to be separate entities and therefore the researcher can investigate a phenomenon without either being influenced by it or influencing it (Sale et al., 2002). Data are operationalised, objective and steps are taken to reduce bias as far as possible. From my perspective, prior to clinical training I identified very much as a 'scientist'. I liked the position of 'knowing' and running statistical analysis felt exciting and satisfying, being able to see patterns in data and understanding a concept better as a result of those data. This feels ironic to reflect on now, as my clinical research project was about intolerance of uncertainty, and I liked the 'certainty' of quantitative data myself.

In contrast, qualitative research is centred around interpretivism (Sale et al., 2002). Multiple realities exist based on one's own construction of this reality. Furthermore, reality is socially constructed and therefore changeable (Golafshani, 2003). Qualitative research accepts and acknowledges the role of the researcher within the research process and sees the relationship between the researcher and participants as integral to the study's findings. Data collection is usually by in-depth interviews or focus groups and sample sizes are usually small. The data are not meant to be representative of the wider population. In my year's cohort of eleven trainees, only two of us conducted studies using quantitative methods. This seems to be a consistent pattern across year groups with a greater focus on qualitative methods. When thinking about this, I wonder whether it is because, as clinicians, qualitative methods feel more familiar. As clinicians, we are taught about how the 'relationship' with the client is the most important factor contributing to successful outcomes (Blow, Sprenkle, & Davis, 2007; Falkenström, Granström, & Holmqvist, 2013). We have many training days working on being able to build that connection with our clients, to listen in an empathetic way, reflect how they are feeling and provide a safe containing space for them to talk. In many ways, I think that a qualitative approach to research draws on a lot of these skills. It is about gaining a deep understanding of a particular issue with a participant. You often have to think about how to manage a participant's distress, as the topic of the interview can be emotive.

Prior to clinical training I felt rather dismissive of qualitative research, it did not seem like 'science' to me and felt rather 'fluffy'. The focus of the research centre was on quantitative methodology and so my understanding or appreciation of qualitative methods was not developed during my PhD. Whilst I did carry out an interview study (with parents of children with Cornelia de Lange syndrome about decision making behaviour), I made it 'quantitative' by using some fixed answer responses and then any free responses from participants were synthesised into tables and flow diagrams to describe sequences of behaviours. Looking back, I think I felt that I had to pick one approach over the other, a phenomenon described by Onwuegbuzie and Leech (2005) rather than considering the possibility of using mixed methods. As I had never carried out a qualitative study, I also lacked confidence to try one for my ClinPSyD project. Furthermore, I considered a quantitative approach to be more 'useful' for the families of the syndromes I work with. Many of the phenotypic behaviours seen in Cornelia de Lange syndrome are not well described or understood. I considered it important to be able to collect as much objective data as possible that could be generalised to the CdLS population, rather than a qualitative study which, in my view, would not further our understanding in a way that allowed the development of interventions.

It is interesting that I was so fixed on the idea of doing quantitative research that I did not consider any alternative projects or using a qualitative approach. During clinical training whilst I was being encouraged to consider alternative hypotheses, formulations and approaches in my clinical work, I remained welded to my quantitative, 'scientific' approach to research.

Onwuegbuzie and Leech (2005) considered the differences between quantitative and qualitative methodologies and discussed the importance of using a mixed methods approach. They highlighted the division between quantitative and qualitative researchers and the assertions of Howe (1988) who states that the two research approaches cannot and should not be mixed. Sieber (1973) suggested that both approaches have strengths and weaknesses, and as such we should use the strengths of both techniques to deepen our understanding of social phenomena. Sieber (1973) pointed out that the two dominant paradigms have resulted in two 'research subcultures' (Onwuegbuzie & Leech, 2005), with qualitative supporters extolling the

virtues of ‘deep, rich observational data’ and quantitative supporters, the superiority of ‘hard, generalizable data’.

Onwuegbuzie and Teddlie (2003) suggest that we should move from quantitative vs qualitative divides and reframe research as ‘exploratory’ and ‘confirmatory’ methods. This concept would bring together both quantitative and qualitative methodology under the same framework. Exploratory methods can be quantitative, using descriptive statistics and exploratory factor analysis, or qualitative using thematic analyses. Confirmatory methods can also be quantitative, using inferential statistics and qualitative using ‘confirmatory’ thematic analyses where studies are conducted to replicate previous emergent themes or to test a theory (Onwuegbuzie & Teddlie, 2003). Reflecting on this, I think this way of thinking would have helped me to consider qualitative methods and be more open to them earlier in my thesis research journey, even if I still decided that quantitative methodology was more fitting for my research questions.

Without realising it, my research philosophy had become more in line with a ‘mixed’ method approach over the course of my PhD, and I struggled to work within a purely quantitative and data-driven context for my ClinPsyD project. Whilst considering what left me feeling detached and unenthused about my research, I realised that it is about *the relationship* for me and about seeing the applicability of my research and the difference it might make to real people. I remembered that, during my undergraduate degree, I never thought I wanted to do research. I realise now that this is because my experience of research during undergraduate studies were the type of studies with minimal participant interaction and limited scope for thinking about clinical implications of the work. It was seeing how much difference research can make to the families and people with the rare genetic syndromes that made me feel passionate about the research and inspired to do more.

This realisation that I work well using quantitative methods but also need the qualitative element has parallels with my clinical work, and made me consider the scientist-practitioner position

3.5 Scientist- practitioner position

The definition of ‘scientist-practitioner’ has been debated in the literature. Some authors suggest it is about clinicians also contributing to academic research

(Kennedy & Llewelyn, 2001) however, sources suggest the majority of Clinical Psychologists do not publish their research (Pilgrim & Treacher, 1992; Richardson, 2014). This could possibly reflect the separation of academic and practitioner psychologists (Kennedy & Llewelyn, 2001). An alternative definition of a scientist-practitioner is a clinician that is engaged with current research and puts this into practice in their clinical work (Kennedy & Llewelyn, 2001; Richardson, 2014)

When talking to fellow trainees about their qualitative research projects, they spoke about finding it difficult to be in the 'researcher' position instead of being a clinician when conducting their research interviews. It was difficult for them to let go of the clinical instincts to help and support and instead focus on the research protocols. When starting this research project, I considered my identity as both a researcher and as a clinician, a scientist and a practitioner. One of my main motivations for carrying out this research is that I could see the real-world applicability of the work, I was aware of the implications for clinical practice and this is why it felt so important. I think that my research project taking a quantitative approach helped me to stay in the 'researcher' position more easily than my fellow trainees, although I missed the clinician role in doing so.

When I commenced clinical training, I had just finished training as a 'psychological wellbeing practitioner'(PWP), using CBT-based interventions with clients mainly over the phone. I started the ClinPsyD course a fervent believer in cognitive behavioural therapy, and feeling that psychodynamic approaches were a bit 'fluffy' and I could not get a firm grasp on what exactly they were. On reflection, I can draw parallels here with my approach to quantitative versus qualitative methods. In my mind, CBT had the most 'evidence' for its use with common mental health difficulties. It was also structured and straightforward and just 'made sense'. However, I had not enjoyed my work as a PWP due to the very high workload pressures, the intense focus on outcome measures and targets and the intervention delivery being primarily telephone-based. When starting clinical training, I found myself initially sceptical about working psychodynamically, yet over time something pulled me towards that way of working. I saw first hand how powerful building relationships with clients could be, and when asked to work in a purely CBT approach again during my second year, I found myself pushing against it. I think this process reflects both my experiences working in a quantitative way during my

research project, and also the struggle to find a happy medium between being a scientist and a practitioner. Whilst initially I was focussed on quantitative data, and CBT that felt more 'scientific' as it had a set protocol, I started to appreciate more qualitative ways of working, and drawing on what was happening 'in the room' as a practitioner.

In the same way I aligned myself with research that was quantitative but has the human connection 'qualitative' element, in my clinical practice I enjoyed working in a cognitive analytic therapy approach (Ryle, Poynton, & Brockman, 1990) with my clients. It has a mix of being structured and focussed whilst also placing high importance on the relationship and connection with the client, and seeing what comes up in the room. It was only when reflecting on the research process for this study that I identified the similar process I went through during my clinical training.

3.6 Conclusion

Reflecting on the whole research process, this experience has helped me to identify the kind of research I want to do in the future, and but also the kind of clinician I want to be. I value quantitative methods and using statistical analyses and the 'certainty' of these approaches, however I need the human connection with my participants and the data in order to feel excited about the research. Likewise, in my clinical work I like having some structure and using the evidence base to inform my work with clients, whilst also using my connection and more qualitative information to bring about change. It was only through reflecting on this experience that I can see how much I have changed and developed throughout this process and what common themes arose throughout my clinical training. Finding a balance between qualitative and quantitative approaches and being a scientist and a practitioner is difficult and probably one I will continue to juggle. However, as both a clinician and a researcher, I have concluded that, for me at least, connection is key.

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Appendices

Appendix A:

Journal of Autism and Developmental Disorders author guidelines

Double-Blind Peer Review

MANUSCRIPT FORMAT

All JADD manuscripts should be submitted to Editorial Manager in 12-point Times New Roman with standard 1-inch borders around the margins.

APA Style

Text must be double-spaced; APA Publication Manual standards must be followed.

As of January 20, 2011, the Journal has moved to a double-blind review process. Therefore, when submitting a new manuscript, DO NOT include any of your personal information (e.g., name, affiliation) anywhere within the manuscript. When you are ready to submit a manuscript to JADD, please be sure to upload these 3 separate files to the Editorial Manager site to ensure timely processing and review of your paper:

- A title page with the running head, manuscript title, and complete author information. Followed by (page break) the Abstract page with keywords and the corresponding author e-mail information.
- The blinded manuscript containing no author information (no name, no affiliation, and so forth).
- The Author Note

Articles, Commentaries Brief Reports, Letters to the Editor

- The preferred article length is 20-23 double-spaced manuscript pages long (not including title page, abstract, tables, figures, addendums, etc.) Manuscripts of 40 double-spaced pages (references, tables and figures counted as pages) have been published. The reviewers or the editor for your review will advise you if a longer submission must be shortened.
- Special Issue Article: The Guest Editor may dictate the article length; maximum pages allowed will be based on the issue's page allotment.
- Commentary: Approximately 20-25 double-spaced pages maximum, with fewer references and tables/figures than a full-length article.
- A Brief Report: About 8 double-spaced pages with shorter references and fewer tables/figures. May not meet the demands of scientific rigor required of a JADD article – can be preliminary findings.
- A Letter to the Editor is 6 or less double spaced pages with shorter references, tables and figures.

  Style sheet for Letter to the Editor:

- A title page with the running head, manuscript title, and complete author information including corresponding author e-mail information

- The blinded manuscript containing no author information (no name, no affiliation, and so forth):-

  - 6 or less double spaced pages with shorter references, tables and figures

  - Line 1: “Letter to the Editor”

  - Line 3: begin title (note: for “Case Reports start with “Case Report: Title”)

  - Line 6: Text begins; references and tables, figure caption sheet, and figures may follow (page break between each and see format rules)

Appendix B

Ethical approval certificate for systematic review

Certificate of Ethical Approval

Applicant:

Victoria Perry

Project Title:

Predictors of anxiety in autism spectrum disorders: a systematic review

This is to certify that the above named applicant has completed the Coventry University Ethical Approval process and their project has been confirmed and approved as Low Risk

Date of approval:

26 February 2019

Project Reference Number:

P88470

Appendix C

Ethical approval certificate for empirical chapter from Coventry University, Univetsity of Birmingham and IRAS

Certificate of Ethical Approval

Applicant:

Victoria Perry

Project Title:

The relationship between anxiety and intolerance of uncertainty in Cornelia de Lange syndrome

This is to certify that the above named applicant has completed the Coventry University Ethical Approval process and their project has been confirmed and approved as High Risk

Date of approval:

11 July 2017

Project Reference Number:

P52831

Dear Professor Oliver

Re: "Anxiety, cognition and movement in Cornelia de Lange and Fragile X syndromes"

Ethics application ERN_12-0018AP31

Thank you for the above application to use Programme of Work ERN_12-0018P. This has now been considered by the Science, Technology, Engineering and Mathematics Ethical Review Committee.

On behalf of the Committee, I can confirm a favourable ethical opinion for this application.

I would like to remind you that any substantive changes to the nature of the study as described in the Application for Ethical Review, and/or any adverse events occurring during the study should be promptly bought to the Committee's attention by the Principal Investigator and may necessitate further ethical review.

Please be aware that whilst Health and Safety (H&S) issues may be considered during the ethical review process, you are still required to follow the University's guidance on H&S and to ensure that H&S risk assessments have been carried out as appropriate. For further information about this, please contact your School H&S representative or the University's H&S Unit at healthandsafety@contacts.bham.ac.uk.

If you require a hard copy of this correspondence, please let me know.

Kind regards

Susan Cottam
Research Ethics Officer
Research Support Group
C Block Dome
Aston Webb Building
University of Birmingham
Edgbaston B15 2TT
Tel: [redacted]
Email: [redacted]

NHS
Health Research Authority
West Midlands - Coventry & Warwickshire Research Ethics Committee
The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

[redacted]

22 November 2016

Professor Chris Oliver
Cerebra Centre for Neurodevelopmental Disorders
School of Psychology
University of Birmingham
B15 2TT

Dear Professor Oliver,

Study title:	**Understanding the behavioural, cognitive and motor phenotypes of Cornelia de Lange and Fragile X syndromes**
REC reference:	[redacted]
IRAS project ID:	**208284**

Thank you for your letter of 17th November 2016, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager, Ms Rachel Nelson, NRESCommittee.WestMidlands-CoventryandWarwick@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above

research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Mental Capacity Act 2005

I confirm that the committee has approved this research project for the purposes of the Mental Capacity Act 2005. The committee is satisfied that the requirements of section 31 of the Act will be met in relation to research carried out as part of this project on, or in relation to, a person who lacks capacity to consent to taking part in the project.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett ([redacted]), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

The Committee has not yet completed any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as an SSA application(s) has been reviewed. In the meantime no study procedures should be initiated at non-NHS sites.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Copies of advertisement materials for research participants [Recruitment Flyer]	2	11 November 2016
Covering letter on headed paper [Cover letter]	1	09 August 2016
GP/consultant information sheets or letters [Genetics letter]	1	24 August 2016
Interview schedules or topic guides for participants [VABS]	1	05 August 2016
Interview schedules or topic guides for participants [K-SADS-PL]	1	05 August 2016
IRAS Application Form [IRAS_Form_05102016]		05 October 2016
IRAS Checklist XML [Checklist_17112016]		17 November 2016
Letters of invitation to participant [Participant known]	1	24 August 2016
Letters of invitation to participant [Participant unknown]	1	24 August 2016
Non-validated questionnaire [Dev. Milestones]	1	08 August 2016
Other [Assessment of capacity protocol]	1	24 August 2016
Other [Consultee sheet]	1	24 August 2016
Other [Expression of Interest]	2	24 August 2016
Other [Off-site research policy]	1	05 August 2016
Other [Cover letter to REC]	1	11 November 2016
Participant consent form [Consent able/unknown]	3	11 November 2016
Participant consent form [Consent under16/unknown]	3	11 November 2016
Participant consent form [Consent over16/unknown]	3	11 November 2016

Participant consent form [Consent able/known]	3	11 November 2016
Participant consent form [Consent under16/known]	3	11 November 2016
Participant consent form [Consent over16/known]	3	11 November 2016
Participant information sheet (PIS) [Symbol information sheet]	2	24 August 2016
Participant information sheet (PIS) [Information under 16]	3	11 November 2016
Participant information sheet (PIS) [Information over 16]	3	11 November 2016
Research protocol or project proposal [Research protocol]	1	06 September 2016
Summary CV for Chief Investigator (CI) [Chris Oliver]	1	08 August 2016
Summary CV for student [Laura Groves]	1	08 August 2016
Summary CV for student [Victoria Johnson]	1	08 August 2016
Summary CV for supervisor (student research) [Jo Moss]	1	08 August 2016
Summary CV for supervisor (student research) [Hayley Crawford]	1	09 August 2016
Validated questionnaire [SCQ]	1	05 August 2016
Validated questionnaire [SRS-2]	1	05 August 2016
Validated questionnaire [ADAMS]	1	05 August 2016
Validated questionnaire [ASC-ASD]	1	05 August 2016
Validated questionnaire [IUS-P]	1	05 August 2016
Validated questionnaire [RBQ]	1	05 August 2016
Validated questionnaire [MIPQ]	1	05 August 2016
Validated questionnaire [BRIEF-P]	1	05 August 2016
Validated questionnaire [C21st Health Checklist]		
Validated questionnaire [C21st Health Checklist]	2	11 November 2016

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.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

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

16/WM/0435	Please quote this number on all correspondence

With the Committee's best wishes for the success of this project.

Yours sincerely,

Dr Helen Brittain
Chair

Email:NRESCommittee.WestMidlands-CoventryandWarwick@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Dr Sean Jennings*

Appendix D

Intolerance of Uncertainty Scale Parent Version

ID Number: Date:

Below is a series of statements. Please use the scale to describe to what extent each item is like your child. Please enter a number (1-5) that describes them best.

1 = Not at all like them; 3 = Moderately like them; 5 = Entirely like them.

1. When things happen suddenly, s/he gets very upset ☐
2. It bothers him/her when there are things they don't know ☐
3. S/he would think that "People should always think about what will happen next. This will stop bad things from happening" ☐
4. S/he would think that "Even if you plan things really well, one little thing can ruin it" ☐
5. S/he always want to know what will happen to them in the future ☐
6. S/he can't stand it when things happen suddenly ☐
7. S/he needs to always be prepared before things happen ☐
8. Feeling unsure stops him/her from doing most things ☐

9. When s/he's not sure what to do they freeze ☐

10. When s/he doesn't know what will happen, they can't do things very well ☐

11. The smallest worry can stop them from doing things ☐

12. S/he tries to get away from all things that they are unsure of ☐

Appendix E

Anxiety Scale for Children with Autism Spectrum Disorder (ASC-ASD)

Name of child:_____ Age of Child (years/months):_____

Date:_____ Relationship to Child:_____

Please put a circle around the word that shows how often each of these things happens for your child.

1. My child suddenly gets a scared feeling when there is nothing to be afraid of	Never	Sometimes	Often	Always
2. My child worries what other people think of him/her e.g. that he/ she is different	Never	Sometimes	Often	Always
3. My child's heart suddenly starts to beat too quickly for no reason	Never	Sometimes	Often	Always
4. My child feels scared when taking a test in case they make a mistake or don't understand the questions	Never	Sometimes	Often	Always
5. My child worries that people will bump into him/ her or touch him/ her in busy or crowded environments	Never	Sometimes	Often	Always
6. My child is afraid of being in crowded places (like shopping centres, the movies, buses, busy playgrounds) in case he/ she is separated from his/ her family	Never	Sometimes	Often	Always
7. My child worries about doing badly at school work	Never	Sometimes	Often	Always
8. My child suddenly feels so anxious he/ she feels as if he/she can't breathe when there is no reason for this	Never	Sometimes	Often	Always

9. My child is afraid of new things, or new people or new places	Never	Sometimes	Often	Always
10. My child is afraid of entering a room full of people	Never	Sometimes	Often	Always
11. My child worries when in bed at night because he/ she does not like to be away from his her parents/ family	Never	Sometimes	Often	Always
12. When my child has a problem, he/she feels shaky	Never	Sometimes	Often	Always
13. My child suddenly starts to tremble or shake when there is no reason for this	Never	Sometimes	Often	Always
14. Feeling unsure stops my child from doing most things	Never	Sometimes	Often	Always
15. My child worries when he/she thinks he/she has done poorly at something in case people judge him/ her negatively	Never	Sometimes	Often	Always
16. My child always needs to be prepared before things happen	Never	Sometimes	Often	Always
17. My child feels afraid that he/she will make a fool of him/herself in front of people	Never	Sometimes	Often	Always
18. My child worries about being away from me	Never	Sometimes	Often	Always
19. My child worries that something awful will happen to someone in the family	Never	Sometimes	Often	Always
20. My child feels scared to be away from home because his/ her parents are familiar with his/ her bedtime routine	Never	Sometimes	Often	Always
21. My child worries about being in certain places because it might be too loud, or too bright or too busy	Never	Sometimes	Often	Always
22. My child suddenly becomes dizzy or faint	Never	Sometimes	Often	Always

when there is no reason for this				
23. My child worries if they don't know what will happen next e.g. if plans change	Never	Sometimes	Often	Always
24. My child worries that something bad will happen to him/her	Never	Sometimes	Often	Always

Appendix F

Anxiety Depression and Mood Scale.

Date: _____ ID: _____

Instructions: Please describe your child's behavior over the last 6 months using the ratings and list of behaviors below.

0 behavior has not occurred, or is not a problem
1 behavior occurs occasionally, or is a mild problem
2 behavior occurs quite often, or is a moderate problem
3 behavior occurs a lot, or is a severe problem

		not a problem	mild problem	moderate problem	severe problem
1.	Nervous	0	1	2	3
2.	Problems initiating communication	0	1	2	3
3.	Does not relax or settle down	0	1	2	3
4.	Has periods of over-activity	0	1	2	3
5.	Sleeps more than normal	0	1	2	3
6.	Withdraws from other people	0	1	2	3
7.	Tense	0	1	2	3
8.	Engages in ritualistic behaviors	0	1	2	3
9.	Depressed mood	0	1	2	3
10.	Sad	0	1	2	3
11.	Worried	0	1	2	3
12.	Has developed difficulty staying on task or completing work	0	1	2	3
13.	Shy	0	1	2	3
14.	Easily fatigued (not due to being overweight)	0	1	2	3
15.	Anxious	0	1	2	3
16.	Repeatedly checks items	0	1	2	3
17.	Easily distracted	0	1	2	3
18.	Lacks energy	0	1	2	3

S:\MIND\RESEARCH\Abbeduto\FX Longitudinal Adult (FXLA)\Protocol Instructions

Appendix G

Social Responsiveness Scale 2

wps. Test with Confidence

John N. Constantino, MD

Assessment ID ______________

SRS-2 AutoScore™ Form **Adult (Relative/Other Report)** ○ MALE ○ FEMALE

INSTRUCTIONS

For each question, please darken the circle that best describes this individual's behavior **over the past 6 months.**

Rated individual's name ______________ Age in years ______

Rater's name ______________ Date of rating ______________

Relationship to rated individual ☐ Mother ☐ Father ☐ Other relative ☐ Spouse ☐ Other

PLEASE PRESS HARD WHEN MARKING YOUR RESPONSES.

1 = NOT TRUE 2 = SOMETIMES TRUE 3 = OFTEN TRUE 4 = ALMOST ALWAYS TRUE

1. Seems much more uncomfortable in social situations than when alone. ① ② ③ ④
2. Expressions on his or her face don't match what he or she is saying. ① ② ③ ④
3. Seems self-confident when interacting with others. ① ② ③ ④
4. When under stress, he or she shows rigid or inflexible patterns of behavior that seem odd. ① ② ③ ④
5. Doesn't recognize when others are trying to take advantage of him or her. ① ② ③ ④
6. Would rather be alone than with others. ① ② ③ ④
7. Is aware of what others are thinking or feeling. ① ② ③ ④
8. Behaves in ways that seem strange or bizarre. ① ② ③ ④
9. Seems too dependent on others for help with meeting basic needs. ① ② ③ ④
10. Takes things too literally and doesn't get the real meaning of a conversation. ① ② ③ ④
11. Has good self-confidence. ① ② ③ ④
12. Is able to communicate his or her feelings to others. ① ② ③ ④
13. Is awkward in turn-taking interactions with others (for example, doesn't seem to understand the give-and-take of conversations). ① ② ③ ④
14. Is not well coordinated. ① ② ③ ④
15. Recognizes and appropriately responds to changes in other people's tone of voice and facial expressions. ① ② ③ ④
16. Avoids eye contact or has unusual eye contact. ① ② ③ ④
17. Recognizes when something is unfair. ① ② ③ ④
18. Has difficulty making friends, even when trying his or her best. ① ② ③ ④
19. Gets frustrated trying to get ideas across in conversations. ① ② ③ ④
20. Shows unusual sensory interests (for example, smelling his or her fingers frequently) or strange, repetitive ways of handling or manipulating small items within reach. ① ② ③ ④
21. Is able to imitate others' actions and demeanor when it is socially appropriate to do so. ① ② ③ ④
22. Interacts appropriately with other adults. ① ② ③ ④
23. Does not join group activities or social events unless forced to do so. ① ② ③ ④
24. Has more difficulty than others with changes in his or her routine. ① ② ③ ④
25. Doesn't seem to mind being out of step with or "not on the same wavelength" as others. ① ② ③ ④
26. Offers comfort to others when they are sad. ① ② ③ ④
27. Avoids starting social interactions with other adults. ① ② ③ ④
28. Thinks or talks about the same thing over and over. ① ② ③ ④
29. Is regarded by others as odd or weird. ① ② ③ ④
30. Becomes upset in a situation with lots of things going on. ① ② ③ ④
31. Can't get his or her mind off something once he or she starts thinking about it. ① ② ③ ④
32. Has good personal hygiene. ① ② ③ ④

Continue on back page

 9 8 7 6 5 4 3 2

PLEASE PRESS HARD WHEN MARKING YOUR RESPONSES.

1 = NOT TRUE 2 = SOMETIMES TRUE 3 = OFTEN TRUE 4 = ALMOST ALWAYS TRUE

33. Is socially awkward, even when trying to be polite. ..... ① ② ③ ④
34. Avoids people who want to be emotionally close to him or her. ..... ① ② ③ ④
35. Has trouble keeping up with the flow of a normal conversation. ..... ① ② ③ ④
36. Has difficulty relating to family members. ..... ① ② ③ ④
37. Has difficulty relating to other adults. ..... ① ② ③ ④
38. Responds appropriately to mood changes in others (for example, when a friend's mood changes from happy to sad). ..... ① ② ③ ④
39. Has an unusually narrow range of interests. ..... ① ② ③ ④
40. Is imaginative without losing touch with reality. ..... ① ② ③ ④
41. Wanders aimlessly from one activity to another. ..... ① ② ③ ④
42. Seems overly sensitive to sounds, textures, or smells. ..... ① ② ③ ④
43. Enjoys and is competent with small talk (casual conversation with others). ..... ① ② ③ ④
44. Doesn't understand how events relate to one another (cause and effect) the way other adults do. ..... ① ② ③ ④
45. Generally gets interested in what others nearby are paying attention to. ..... ① ② ③ ④
46. Has overly serious facial expressions. ..... ① ② ③ ④
47. Laughs at inappropriate times. ..... ① ② ③ ④
48. Has a sense of humor, understands jokes. ..... ① ② ③ ④
49. Does extremely well at a few intellectual or computational tasks, but does not do as well at most other tasks. ..... ① ② ③ ④
50. Has repetitive, odd behaviors. ..... ① ② ③ ④
51. Has difficulty answering questions directly and ends up talking around the subject. ..... ① ② ③ ④
52. Knows when he or she is talking too loud or making too much noise. ..... ① ② ③ ④
53. Talks to people with an unusual tone of voice (for example, talks like a robot or like he or she is giving a lecture). ..... ① ② ③ ④
54. Seems to react to people as if they are objects. ..... ① ② ③ ④
55. Knows when he or she is too close to someone or is invading someone's space. ..... ① ② ③ ④
56. Walks in between two people who are talking. ..... ① ② ③ ④
57. Isolative; tends not to leave his or her home. ..... ① ② ③ ④
58. Concentrates too much on parts of things rather than seeing the whole picture. ..... ① ② ③ ④
59. Is overly suspicious. ..... ① ② ③ ④
60. Is emotionally distant, doesn't show his or her feelings. ..... ① ② ③ ④
61. Is inflexible, has a hard time changing his or her mind. ..... ① ② ③ ④
62. Gives unusual or illogical reasons for doing things. ..... ① ② ③ ④
63. Touches or greets others in an unusual way. ..... ① ② ③ ④
64. Is too tense in social settings. ..... ① ② ③ ④
65. Stares or gazes off into space. ..... ① ② ③ ④

Appendix H

Sample of Vineland Adaptive Behaviour Scale –second edition.

About the Individual:

Name: _____

Sex: _____ ID: _____ Grade (if applicable): _____

Highest Grade Completed (if applicable): _____

School or Other Facility (if applicable): _____

Present Classification or Diagnosis: _____

Language Spoken at Home: _____

Age:	Year	Month	Day	Age Used for Starting Points: _____
Interview Date:	_____	_____	_____	Type (circle one): Chronological
Birth Date:	_____	_____	_____	Mental
Chronological Age:	_____	_____	_____	Social

Data from Other Tests: Intelligence _____ Achievement _____ Adaptive Behavior _____ Other _____

Reason for the Interview: _____

Vineland-II™

Record Booklet

Vineland Adaptive Behavior Scales, Second Edition

Survey Interview Form

Sara S. Sparrow, Domenic V. Cicchetti, and David A. Balla

A revision of the *Vineland Social Maturity Scale* by Edgar A. Doll

About the Respondent:

Name: _____

Sex: _____ Telephone: _____

Relationship to Individual: _____

About the Interviewer:

Name: _____

Position: _____

Sex: _____

Communication Domain

Response Options: **2** = Usually, **1** = Sometimes or Partially, **0** = Never, **DK** = Don't Know

■ Understanding ♥ Listening and Attending ○ Following Instructions

								✔ Check for Comments below
RECEPTIVE	< 1 →	■	1	Turns eyes and head toward sound.	■	2	1	0	DK	
		♥	2	Looks toward parent or caregiver when hearing parent's or caregiver's voice.	♥	2	1	0	DK	
		■	3	Responds to his or her name spoken (for example, turns toward speaker, smiles, etc.).	■	2	1	0	DK	
	1 →	■	4	Demonstrates understanding of the meaning of *no*, or word or gesture with the same meaning (for example, stops current activity briefly).	■	2	1	0	DK	
		■	5	Demonstrates understanding of the meaning of *yes*, or word or gesture with the same meaning (for example, continues activity, smiles, etc.).	■	2	1	0	DK	
		♥	6	Listens to story for at least 5 minutes (that is, remains relatively still and directs attention to the storyteller or reader).	♥	2	1	0	DK	
	2 →	■	7	Points to at least three major body parts when asked (for example, nose, mouth, hands, feet, etc.).	■	2	1	0	DK	
		■	8	Points to common objects in a book or magazine as they are named (for example, dog, car, cup, key, etc.).	■	2	1	0	DK	
		♥	9	Listens to instructions.	♥	2	1	0	DK	
		○	10	Follows instructions with one action and one object (for example, "Bring me the book"; "Close the door"; etc.).	○	2	1	0	DK	
	3+ →	■	11	Points to at least five minor body parts when asked (for example, fingers, elbows, teeth, toes, etc.).	■	2	1	0	DK	
		○	12	Follows instructions with two actions or an action and two objects (for example, "Bring me the crayons and the paper"; "Sit down and eat your lunch"; etc.).	○	2	1	0	DK	
		○	13	Follows instructions in "if-then" form (for example, "If you want to play outside, then put your things away"; etc.).	○	2	1	0	DK	
		♥	14	Listens to a story for at least 15 minutes.	♥	2	1	0	DK	
		♥	15	Listens to a story for at least 30 minutes.	♥	2	1	0	DK	
		○	16	Follows three-part instructions (for example, "Brush your teeth, get dressed, and make your bed"; etc.).	○	2	1	0	DK	
		♥	17	Follows instructions or directions heard 5 minutes before.	♥	2	1	0	DK	
		■	18	Understands sayings that are not meant to be taken word for word (for example, "Button your lip"; "Hit the road"; etc.).	■	2	1	0	DK	
		♥	19	Listens to an informational talk for at least 15 minutes.	♥	2	1	0	DK	
		♥	20	Listens to an informational talk for at least 30 minutes.	♥	2	1	0	DK	

Comments

Item Before Basal ____ × 2 = ____

Basal Item Through Ceiling Items

DK and/or Missing Total* + ____

N/O Total + ____

Sum of 2s and 1s + ____

*If the total of DK and/or Missing is greater than 2, do not score subdomain.

Receptive Raw Score = ____ SUM

Appendix I

Information sheet for parents/carers of participants under the age of 16

UNIVERSITY OF BIRMINGHAM

A

The Cerebra Centre for Neurodevelopmental Disorders

Coventry University

Understanding Behaviour, Emotion and Movement in Individuals with [insert syndrome]

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 Laura Groves (Doctoral Researcher) by telephone: [redacted], email: [redacted]; or Dr Hayley Crawford (Postdoctoral Research Fellow) by telephone: [redacted], email: [redacted]. If you have any medical/other problems which make it difficult for you to read this information, please contact Laura Groves or Hayley Crawford for a verbal explanation of the research.

You can watch a short film about this research project on our website at: [insert web address]

When you are happy that you have all of the information you need to be able to decide whether or not you and the person you care for would like to take part in the

study, please complete the enclosed consent form and return it to us in the prepaid envelope provided. If you'd prefer to, you can complete the consent forms online using [insert link] and entering the password 'cerebra'.

Background

We would like to invite you and your child/person you care for to take part in a study being conducted at the Cerebra Centre for Neurodevelopmental Disorders, University of Birmingham in collaboration with Coventry University. This research work, which is led by Professor Chris Oliver, looks at behaviour, emotion and movement in individuals with [insert syndrome].

We hope that this information will enable us to further understand what difficulties individuals with [insert syndrome] experience, as well as any associated factors. This in turn will contribute towards a better understanding of the syndrome and more targeted intervention strategies in order to improve the well-being of individuals and their families. The more people that take part in this research, the more meaningful the results will be. A good response will provide new and valuable information about [insert syndrome].

Aims of the study

1. What are the behavioural or emotional difficulties experienced by individuals with [insert syndrome]?
2. What is the association between these and cognitive and motor skills in individuals with [insert syndrome]?
3. How do behaviours, cognition and motor skills develop and change with age?
4. Are different genetic mechanisms associated with different profiles of behaviour, cognition and motor skills?

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 be conducted at the Cerebra Centre for Neurodevelopmental Disorders at the University of Birmingham, at the participant's home, or at [insert

syndrome support group] conferences if this is preferred. We will ask your child/person you care for to take part in table top activities and some movement tasks. We will also want to ask you some questions however this can be completed over the telephone before the assessment day if this is more convenient.

Who will be involved in collecting the data?

Members of the research team at the Cerebra Centre for Neurodevelopmental Disorders and at Coventry University, including Laura Groves and Hayley Crawford.

How long will participation in the study take?

The assessment day will take approximately 3-4 hours with breaks included. The following gives you an approximation of how long each individual session of the assessment day may take. Please note, these are estimates and actual timings may vary.

- Assessment of level of ability – from 40 mins to 1hr 20mins
- Cognitive assessments – 40 mins
- Assessments of behaviour – 20 mins
- Movement assessments – 20 mins

What will participants be required to do during the study?

On the assessment day, we may ask you to complete some interviews/questionnaires and to be present during your child's/person you care for's assessments. Your child/person you care for will be asked to complete some table top activities and movement tasks (e.g. walking, reaching for objects). Breaks will be included. During the movement tasks we will ask your child/person you care for to wear movement sensors on their wrists, ankles and around their middle. The sensors are about the size of a wristwatch and are attached with fabric straps. They should not cause discomfort.

We will also want to interview you about your child/person you care for which will take approximately 2hrs 30mins in total; however, this can be divided into smaller

time segments and completed over multiple sessions if this is more convenient. Additionally, these can be completed over the telephone or on the assessment day if you prefer. We will also ask you to complete some questionnaires about your child/person you care for (approx. 45 minutes). As there are multiple aspects to this study (i.e. behaviour, cognition, movement), there is an option to only participant in some parts of the study if you would prefer.

During the visit we will also ask your child/person you care for to provide two saliva samples for cortisol analysis. Cortisol is a hormone released when an individual becomes stressed; by measuring this we can assess the level of stress your child/person you care for may be feeling. These will be collected either by placing an absorbent swab inside the cheek and leaving it there for 1-2 minutes, or by placing a swab under the tongue for 60-90 seconds. These methods are non-invasive, painless and have been used widely in intellectual disability research.

If you are happy and your child/the person you care for are happy to do so we will also ask for a third saliva sample to be taken for genetic analysis. This sample can be taken before, during, or after the assessment day and returned to us using a pre-paid envelope, which we will provide you with. The genetic information extracted from this saliva sample will be used to identify genetic variation that might be important in understanding causes and consequences of [insert syndrome]. Please note that we will be unable to provide feedback regarding the results of the genetic analysis, although you will receive feedback on all other aspects of the study. If you or the person you care for decide you would prefer not to provide this sample, we would like to ask your permission to contact your G.P or consultant to request written confirmation of the genetic diagnosis. It is entirely up to you and/or the person you care for whether you give us permission to do either of these and choosing not to do so will not impact on your participation in the study.

Although not required, your child/person you care for may drink water or brush their teeth with water before the collection. In the case that your child/person you care for has eaten a meal before the procedure, they will need to wait 15–20 minutes after feeding before collecting the saliva sample. Because genetic information varies across individuals with differing ancestral backgrounds, we may also ask you to provide information about your child’s ancestral background.

Will assessments/interviews be recorded?

During the assessments, your child/person you care for's behaviour and the behaviour of people in their immediate surroundings will be recorded using a video camera. We will also take an audio recording when we interview you about your child/the person you care for. These recordings will be used in order to check the accuracy of these assessments with another researcher.

The University of Birmingham will hold the copyright for the audio/video recordings so that the confidentiality of these recordings will be protected. But, the University of Birmingham will not be able to edit or use the recordings for teaching purposes unless you give us your written permission to do this.

We may contact you again in the future to ask your permission to use some of the recordings for teaching purposes. At that time you will be able to decide whether or not you are happy for the recordings to be used for these purposes. Agreeing to participate in this study does not mean that you will have to give your permission for the use of these recordings in the future.

Are there any risks that individuals taking part in the study might face?

There is some risk that emotional upset may be caused from your child/person you care for taking part in some of the assessments. However, it is unlikely that these will be issues that they do not face in their daily life. Nonetheless, this may still be an upsetting experience for them. If distress is noticed we will stop immediately, and cease all assessments if required.

There are no known risks associated with saliva collection procedures, although your child/person you care for may not like having to provide his/her saliva sample

in the kit. You will be free to withdraw from this at any time, including if your child/person you care for becomes upset or unhappy.

Will I be able to withdraw from the research?

Should you or the person you care for decide that you no longer wish to be involved in the research; you are free to withdraw your participation at any time during the study and for a period of three months after the data collection with yourselves has been completed. If you decide to do so, information that you have provided in this time can also be withdrawn and destroyed without you giving reason. This will not restrict access to other services and will not affect the right to treatment.

If you/ the person you care for decide(s) to participate, what will happen after that participation?

You and your child/ 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. Unfortunately, we will not be able to feedback the results of the genetic analysis to you, including information regarding other genetic variations not related to the study. A summary of the overall project's findings will be circulated to anyone involved who wishes to see a copy. Any requests for clinical advice concerning your child/person you care for will be referred to Professor Chris Oliver, Clinical Psychologist.

Descriptions of research findings will be published in newsletters of the [specific syndrome support group], family support groups and educational institutions involved. The researchers will publish the findings from the study in scientific journals and will present the results at relevant research conferences. All published data will be anonymous without names or other identifying information.

Where will data be stored?

The information that you provide will be locked in a filing cabinet at the University of Birmingham or held on a password protected database/hard drive. Only members of the research team at the University of Birmingham will have access to the

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. All personal details will be kept separately from the information collected and your child/person you care for will be identifiable by a unique number throughout the study to ensure information you provide us with cannot be traced to your personal details. If published, information will be presented without reference to any identifying information.

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.

Your child's/person you care for's saliva sample for genetic testing will be stored and processed by genetic laboratories headed by Dr Jane Steele and Mr Andrew Beggs. These centres are based at the University of Birmingham and will not be provided with your child's/person you care for's personal information. Saliva samples for cortisol analysis will be stored and processed by the laboratory based at Coventry University, led by Professor Derek Renshaw. Again, this centre will not be provided with your child's/person you care for's personal information. Only researchers directly involved in this study will have access to this personal information, which will be stored on a password protected database.

In any description of research findings that we might publish, we will not include any information that will make it possible to identify a participant. Research data obtained from saliva samples collected during this study will be held indefinitely for use in potential follow up publications as well as in other associated studies conducted within the research team, including genetic testing.

Unknown participants: After 6 months of receiving your questionnaire pack, your personal details will be ***destroyed unless you tell us otherwise.*** This means that we would no longer be able to trace the results of your assessments back to you. ***The section below on 'The Regular Participant Database Information'*** gives information about a database that we use to store the personal details of some participants. Please read this section in order to decide if you would like to join that database.

If participant is known to us already and has previously agreed for us to keep their details and contact them for future research: 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.

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 [redacted] or at [redacted] or at the School of Psychology, University of Birmingham, Edgbaston, Birmingham, B15 2TT. Your details would be removed from the database immediately.

Regular Participant Database Information:

What is the regular participant database?

We have a database that we keep in the Cerebra Centre where we store the names and contact details of some previous participants. If you would like us to, we can add your details to this database. We would use this information for two things:

1) We will contact you with information about future research work to find out whether or not you would like to participate.

2) It is often important to find out how things change over time. By keeping your details we would be able to trace the results of the previous assessments that you have done with us back to you. This means that if you take part in other studies with us we would be able to look at how things have changed over time.

Who would have access to my details?

Only approved members of out research team would have access to your details. We would not share your details with anyone outside the research team.

When would I be contacted?

You would only be contacted by an approved member of the research team when we are starting another study or phase of a study that we think you might like to participate in or when we need to clarify some information that you have provided us with from participation in a research study.

What happens if I decide that I want my details to be added to the database but then I change my mind?

All you would need to do is contact Chris Oliver on [redacted] or at [redacted] 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 and the person you care for 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 [redacted] or at [redacted] in the first instance. If you remain unhappy and wish to complain formally, you can contact: Professor Kim Shapiro; Head of School; School of Psychology, University of Birmingham, Birmingham, B15 2TT, by email: [redacted] or by phone on [redacted].

Making a complaint

If you would like to make a complaint about this research please contact the Patient Advice and Liaison (PALS) office. The Birmingham PALS office can be contacted on 0121 371 3280. Alternatively, you can search for your local PALS office by going to http://www.nhs.uk/chq/pages/1082.aspx?CategoryID=68, by contacting your GP surgery/hospital, or by phoning NHS 111.

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 (name) NHS Research Ethics Committee. Contact details and ref number

Further information

If you would like any more information about the study please contact Laura Groves (Doctoral Researcher) by telephone: [redacted], email: [redacted]; or Hayley Crawford (Postdoctoral Research Fellow) by telephone: [redacted], email: [redacted].

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 Laura Groves [redacted]; or Hayley Crawford [redacted] to request a copy.

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 ***<u>is</u>* <u>able</u>** 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 <u>Consent Form A coloured YELLOW</u>** enclosed, or that you complete it with them, on their behalf. A parent/carer will need to complete **Section 2 of <u>Consent Form A coloured YELLOW</u>** 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. You can also complete this online [insert link] using the password 'cerebra'.

2. My child/ the person I care for is <u>unable to understand</u> what is involved in the study and what will be required from them if they participate (either because they are too young to understand or because they are unable to understand) and cannot communicate their decision to me:

If you are reading this information on behalf of someone you care for who is under the age of 16 years and you decide that the person ***<u>is not</u>*** able to make an 'informed' and independent decision about whether or not they would like to participate, then we would like to ask you to decide whether or not you think that it is in your child's best interests for them to participate in the study and whether you would like to provide your consent to participation on their behalf. If you would like your child/person you care for to participate in this study, please complete **<u>Consent Form B coloured PURPLE</u>** enclosed. Please return the consent form along with the questionnaire pack to us in the prepaid envelope provided. You can also complete this online [insert link] using the password 'cerebra'.

Thank you very much for taking the time to read this information – please keep this information sheet for future reference

Appendix J

Information sheet for parents/carers of participants over the age of 16

Understanding Behaviour, Emotion and Movement in Individuals with [insert syndrome]

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 Laura Groves (Doctoral Researcher) by telephone: [redacted], email: [redacted]; or Dr Hayley Crawford (Postdoctoral Research Fellow) by telephone: [redacted], email: [redacted]. If you have any medical/other problems which make it difficult for you to read this information, please contact Laura Groves or Hayley Crawford for a verbal explanation of the research.

You can watch a short film about this research project on our website at: [insert web address]

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 return it to us in the prepaid envelope provided. If you'd prefer to, you can complete the consent forms online using [insert link] and entering the password 'cerebra'.

Background

We would like to invite you and your child/person you care for to take part in a study being conducted at the Cerebra Centre for Neurodevelopmental Disorders, University of Birmingham in collaboration with Coventry University. This research work, which is led by Professor Chris Oliver, looks at behaviour, emotion and movement in individuals with [insert syndrome].

We hope that this information will enable us to further understand what difficulties individuals with [insert syndrome] experience, as well as any associated factors. This in turn will contribute towards a better understanding of the syndrome and more targeted intervention strategies in order to improve the well-being of individuals and their families. The more people that take part in this research, the more meaningful the results will be. A good response will provide new and valuable information about [insert syndrome].

Aims of the study

5. What are the behavioural or emotional difficulties experienced by individuals with [insert syndrome]?
6. What is the association between these and cognitive and motor skills in individuals with [insert syndrome]?
7. How do behaviours, cognition and motor skills develop and change with age?
8. Are different genetic mechanisms associated with different profiles of behaviour, cognition and motor skills?

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 be conducted at the Cerebra Centre for Neurodevelopmental Disorders at the University of Birmingham, at the participant's home, or at [insert syndrome support group] conferences if this is preferred. We will ask your child/person you care for to take part in table top activities and some movement tasks. We will also want to ask you some questions however this can be completed over the telephone before the assessment day if this is more convenient.

Who will be involved in collecting the data?

Members of the research team at the Cerebra Centre for Neurodevelopmental Disorders and at Coventry University, including Laura Groves and Hayley Crawford.

How long will participation in the study take?

The assessment day will take approximately 3-4 hours with breaks included. The following gives you an approximation of how long each individual session of the assessment day may take. Please note, these are estimates and actual timings may vary.

- Assessment of level of ability – from 40 mins to 1hr 20mins
- Cognitive assessments – 40 mins
- Assessments of behaviour – 20 mins
- Movement assessments – 20 mins

What will participants be required to do during the study?

On the assessment day, we may ask you to complete some interviews/questionnaires and to be present during your child's/person you care for's assessments. Your child/person you care for will be asked to complete some table top activities and movement tasks (e.g. walking, reaching for objects). Breaks will be included. During the movement tasks we will ask your child/person you care for to wear movement sensors on their wrists, ankles and around their middle. The sensors are about the size of a wristwatch and are attached with fabric straps. They should not cause discomfort.

We will also want to interview you about your child/person you care for which will take approximately 2hrs 30mins in total; however, this can be divided into smaller time segments and completed over multiple sessions if this is more convenient. Additionally, these can be completed over the telephone or on the assessment day if you prefer. We will also ask you to complete some questionnaires about your child/person you care for (approx. 45 minutes). As there are multiple aspects to this study (i.e. behaviour, cognition, movement), there is an option to only participant in some parts of the study if you would prefer.

During the visit we will also ask your child/person you care for to provide two saliva samples for cortisol analysis. Cortisol is a hormone released when an individual becomes stressed; by measuring this we can assess the level of stress your child/person you care for may be feeling. These will be collected either by placing an absorbent swab inside the cheek and leaving it there for 1-2 minutes, or by placing a swab under the tongue for 60-90 seconds. These methods are non-invasive, painless and have been used widely in intellectual disability research.

If you are happy and your child/the person you care for are happy to do so we will also ask for a third saliva sample to be taken for genetic analysis. This sample can be taken before, during, or after the assessment day and returned to us using a pre-paid envelope, which we will provide you with. The genetic information extracted from this saliva sample will be used to identify genetic variation that might be important in understanding causes and consequences of [insert syndrome]. Please note that we will be unable to provide feedback regarding the results of the genetic analysis, although you will receive feedback on all other aspects of the study. If you or the person you care for decide you would prefer not to provide this sample, we would like to ask your permission to contact your G.P or consultant to request written confirmation of the genetic diagnosis. It is entirely up to you and/or the person you care for whether you give us permission to do either of these and choosing not to do so will not impact on your participation in the study.

Although not required, your child/person you care for may drink water or brush their teeth with water before the collection. In the case that your child/person you care for has eaten a meal before the procedure, they will need to wait 15–20 minutes after feeding before collecting the saliva sample. Because genetic information varies across individuals with differing ancestral backgrounds, we may also ask you to provide information about your child's ancestral background.

Will assessments/interviews be recorded?

During the assessments, your child/person you care for's behaviour and the behaviour of people in their immediate surroundings will be recorded using a video camera. We will also take an audio recording when we interview you about your child/the person you care for. These recordings will be used in order to check the accuracy of these assessments with another researcher.

The University of Birmingham will hold the copyright for the audio/video recordings so that the confidentiality of these recordings will be protected. But, the University of Birmingham will not be able to edit or use the recordings for teaching purposes unless you give us your written permission to do this.

We may contact you again in the future to ask your permission to use some of the recordings for teaching purposes. At that time you will be able to decide whether or not you are happy for the recordings to be used for these purposes. Agreeing to participate in this study does not mean that you will have to give your permission for the use of these recordings in the future.

Are there any risks that individuals taking part in the study might face?

There is some risk that emotional upset may be caused from your child/person you care for taking part in some of the assessments. However, it is unlikely that these will be issues that they do not face in their daily life. Nonetheless, this may still be an upsetting experience for them. If distress is noticed we will stop immediately, and cease all assessments if required.

There are no known risks associated with saliva collection procedures, although your child/person you care for may not like having to provide his/her saliva sample in the kit. You will be free to withdraw from this at any time, including if your child/person you care for becomes upset or unhappy.

Will I be able to withdraw from the research?

Should you or the person you care for decide that you no longer wish to be involved in the research; you are free to withdraw your participation at any time during the

study and for a period of three months after the data collection with yourselves has been completed. If you decide to do so, information that you have provided in this time can also be withdrawn and destroyed without you giving reason. This will not restrict access to other services and will not affect the right to treatment.

If you/ the person you care for decide(s) to participate, what will happen after that participation?

You and your child/ 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. Unfortunately, we will not be able to feedback the results of the genetic analysis to you, including information regarding other genetic variations not related to the study. A summary of the overall project's findings will be circulated to anyone involved who wishes to see a copy. Any requests for clinical advice concerning your child/person you care for will be referred to Professor Chris Oliver, Clinical Psychologist.

Descriptions of research findings will be published in newsletters of the [specific syndrome support group], family support groups and educational institutions involved. The researchers will publish the findings from the study in scientific journals and will present the results at relevant research conferences. All published data will be anonymous without names or other identifying information.

Where will data be stored?

The information that you provide will be locked in a filing cabinet at the University of Birmingham or held on a password protected database/hard drive. Only members of the research team at the University of Birmingham will have access to the 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. All personal details will be kept separately from the information collected and your child/person you care for will be identifiable by a unique number throughout the study to ensure information you provide us with cannot be traced to your personal details. If published, information will be presented without reference to any identifying information.

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.

Your child's/person you care for's saliva sample for genetic testing will be stored and processed by genetic laboratories headed by Dr Jane Steele and Mr Andrew Beggs. These centres are based at the University of Birmingham and will not be provided with your child's/person you care for's personal information. Saliva samples for cortisol analysis will be stored and processed by the laboratory based at Coventry University, led by Professor Derek Renshaw. Again, this centre will not be provided with your child's/person you care for's personal information. Only researchers directly involved in this study will have access to this personal information, which will be stored on a password protected database.

In any description of research findings that we might publish, we will not include any information that will make it possible to identify a participant. Research data obtained from saliva samples collected during this study will be held indefinitely for use in potential follow up publications as well as in other associated studies conducted within the research team, including genetic testing.

Unknown participants: After 6 months of receiving your questionnaire pack, your personal details will be ***destroyed unless you tell us otherwise.*** This means that we would no longer be able to trace the results of your assessments back to you. ***The section below on 'The Regular Participant Database Information'*** gives information about a database that we use to store the personal details of some participants. Please read this section in order to decide if you would like to join that database.

If participant is known to us already and has previously agreed for us to keep their details and contact them for future research: 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.

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 [redacted] or at [redacted] or at the School of Psychology, University of Birmingham, Edgbaston, Birmingham, B15 2TT. Your details would be removed from the database immediately.

Regular Participant Database Information:

What is the regular participant database?

We have a database that we keep in the Cerebra Centre where we store the names and contact details of some previous participants. If you would like us to, we can add your details to this database. We would use this information for two things:

3) We will contact you with information about future research work to find out whether or not you would like to participate.
4) It is often important to find out how things change over time. By keeping your details we would be able to trace the results of the previous assessments that you have done with us back to you. This means that if you take part in other studies with us we would be able to look at how things have changed over time.

Who would have access to my details?

Only approved members of our research team would have access to your details. We would not share your details with anyone outside the research team.

When would I be contacted?

You would only be contacted by an approved member of the research team when we are starting another study or phase of a study that we think you might like to participate in or when we need to clarify some information that you have provided us with from participation in a research study.

What happens if I decide that I want my details to be added to the database but then I change my mind?

All you would need to do is contact Chris Oliver on [redacted] or at [redacted] 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 [redacted] or at [redacted] in the first instance. If you remain unhappy and wish to complain formally, you can contact: Professor Kim Shapiro; Head of School; School of Psychology, University of Birmingham, Birmingham, B15 2TT, by email: [redacted] or by phone on [redacted].

Making a complaint

If you would like to make a complaint about this research please contact the Patient Advice and Liaison (PALS) office. The Birmingham PALS office can be contacted on 0121 371 3280. Alternatively, you can search for your local PALS office by going to http://www.nhs.uk/chq/pages/1082.aspx?CategoryID=68, by contacting your GP surgery/hospital, or by phoning NHS 111.

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 (name) NHS Research Ethics Committee. Contact details and ref number

Further information

If you would like any more information about the study please contact Laura Groves (Doctoral Researcher) by telephone: [redacted], email: [redacted]; or Hayley Crawford (Postdoctoral Research Fellow) by telephone: [redacted], email: [redacted].

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 Laura Groves [redacted], [redacted]; or Hayley Crawford [redacted], [redacted] to request a copy.

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 ***<u>is</u>* 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 <u>Consent Form A coloured YELLOW</u>** enclosed, or that you complete it with them, on their behalf. A parent/carer will need to complete **Section 2 of <u>Consent From A coloured YELLOW</u>** 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. You can also complete this online [insert link] using the password 'cerebra'.

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 **<u>over the age of 16</u>** and you decide that the person ***<u>is not</u>*** 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 **<u>Consent Form *C(a)* coloured BLUE</u>** enclosed and return it to us in the prepaid envelope provided. You can also complete this online [insert link] using the password 'cerebra'.

Thank you very much for taking the time to read this information – please keep this information sheet for future reference

Appendix K

Consent form for participants who are able to consent

UNIVERSITY OF BIRMINGHAM

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

Understanding Behaviour, Emotion and Movement in Individuals with [insert syndrome]

Study Director: Professor Chris Oliver

SECTION 1: Please complete this section if you are a person with [insert syndrome]:

1. Has somebody else explained the project to you?
   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 happy to be video recorded as part of the study?

   YES/NO

7. Are you happy to take part?

   YES/NO

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

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

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

YES NO

8. Do you understand that we may ask you to provide a saliva sample that we will use to understand more about the cause of your syndrome/disability. 

9. If your Dr asks to see your results from this project is that OK? 

10. Are you happy for us to contact you again in the future? 

Your name:_____

_____

Date:_____

The person who explained this project to you needs to sign too. If you are under the age of 16, this should be your parent/guardian.

Print name:_____ Sign: [paper versions only]:

_____

Date:_____

SECTION 2: This is optional and allows you to provide consent for us to keep your personal details on the Regular Participant Database. See section titled 'Regular Participant Database' in the information sheet.

Please initial box [or online tick]

…

1. I have read and understood the section titled 'Regular Participant Database' and I would like my personal details to be added to the database.

2. I understand that my name and contact details will be kept by the research team at the University of Birmingham in accordance with the provisions of the Data Protection Act 1998 and I will be contacted by an approved member of the team with information about future research that I and the person I care for may like to participate in.

3. I understand that if my details are held on the database it will be possible for the research team to trace the results of the assessments that I complete in this project back to me and my child/person I care for so that they can look at changes over time if I take part in future projects.

4. I understand that even after I have agreed for my details to be added to the database, I can request that they be removed by contacting Chris Oliver on [redacted] or by post at the School of Psychology, University of Birmingham, Edgbaston, B15 2TT.

5. I understand the Professor Chris Oliver holds ultimate responsibility for the database.

Print Name: _____Signature [paper versions only]: _____

Date: _____

We will provide you with a signed copy of this consent form should you wish to refer to it at later date. A copy will also be held by the Cerebra centre as confirmation of your consent to participate in this research.

Appendix L

Consent form for parents/carers of participants who over 16 and NOT able to consent

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

Understanding Behaviour, Emotion and Movement in Individuals with [insert syndrome]

Study Director: Professor Chris Oliver

Before deciding whether to participate, please ensure you read the information on acting as a personal consultee in the (attached document/link) for the person you care for.

SECTION 1: Please read the following statements:

Please initital each statement or online tick box

1. I (your name) _____have been consulted about (name of participant) _____'s participation in the above research project. I confirm that I have read the information sheet dated [insert date] for the above study. 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 understand that as part of the above study, audio/video recordings of participants may be made and stored for further review

7. I understand that the University of Birmingham will hold the copyright of any audio/video recordings collected during the study but that this does not entitle the University of Birmingham to edit, copy or use the videos for teaching purposes without my written permission.

8. I am happy to be contacted in the future by the University of Birmingham regarding the use of audio/video recordings for teaching purposes.

9. I agree to take part in the above study.

Optional clauses: *The statements below are optional. Not consenting to these will not impact you and your child/the person you care for's involvement in this project, nor will it affect the level of feedback you will receive:*

YES NO

1. I understand that he/she may be asked to provide a saliva sample that will be used for analysis of genetic information and that the information found will not be fed back to me routinely.

2. 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 _____Signature [paper versions only]:

_____

Date: _____

SECTION 3: This is optional and allows you to provide consent for us to keep your personal details on the Regular Participant Database. See section titled 'Regular Participant Database' in the information sheet.

Please initial each statement or online tick box …

6. I have read and understood the section titled 'Regular Participant Database' and I would like my and the person I care for's personal details to be added to the database.

7. I understand that my name and contact details will be kept by the research team at the University of Birmingham in accordance with the provisions of the Data Protection Act 1998 and I will be contacted by an approved member of the team with information about future research that I and the person I care for may like to participate in.

8. I understand that if my details are held on the database it will be possible for the research team to trace the results of the assessments that I complete in this project back to me and the person I care for so that they can look at changes over time if we take part in future projects.

9. I understand that even after I have agreed for my details to be added to the database, I can request that they be removed by contacting Chris Oliver on [redacted] or at [redacted] or by post at the School of Psychology, University of Birmingham, Edgbaston, B15 2TT.

10. I understand the Professor Chris Oliver holds ultimate responsibility for the database.

Print Name: _____Signature: [paper versions only]:

_____

Date: _____

We will provide you with a signed copy of this consent form should you wish to refer to it at later date. A copy will also be held by the Cerebra centre as confirmation of your consent to participate in this research.

Appendix M

Consent form for parents/carers of participants who under 16 and NOT able to consent

UNIVERSITY OF BIRMINGHAM

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

<u>Understanding Behaviour, Emotion and Movement in Individuals with [insert syndrome]</u>

Study Director: Professor Chris Oliver

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

Please initial each statement or online tick]…

1. I confirm that I have read and understood the information sheet dated [insert date] 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 understand that as part of the above study, audio/video recordings of participants may be made and stored for further review

6. I understand that the University of Birmingham will hold the copyright of any audio/video recordings collected during the study but that this does not entitle the University of Birmingham to edit, copy or use the videos for teaching purposes without my written permission.

7. I am happy to be contacted in the future by the University of Birmingham regarding the use of audio/video recordings for teaching purposes.

8. I agree to take part in the above study.

Optional clauses: *The statements below are optional. Not consenting to these will not impact you and your child/the person you care for's involvement in this project, nor will it affect the level of feedback you will receive:*

	YES	NO
1. I understand that my child/person I care for may be asked to provide a saliva sample that will be used for analysis of genetic information and that the information found will not be fed back to me routinely.		
2. 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: _____

Signature [paper versions only]: _____Date: _____

We will provide you with a signed copy of this consent form should you wish to refer to it at later date. A copy will also be held by the Cerebra centre as confirmation of your consent to participate in this research.

Appendix N

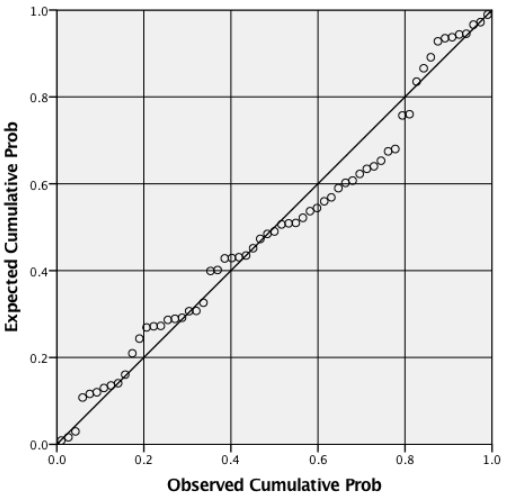
Testing for normal distribution and that the assumptions for multiple regression are met

Table 2.6 Normality tests using the Shapiro-Wilk statistic for key variables in CdLS and FXS

	Statistic	**df**	***p***
		CdLS	
SRS-2 total score	.973	31	.600
ADAMS-GA	.949	31	.148
ASC-ASD total score	.896	31	.006
IUS-P total score	.947	13	.128
		FXS	
SRS-2 total score	.952	30	.195
ADAMS-GA	.968	30	.492
ASC-ASD total score	.960	30	.307
IUS-P total score	.975	30	.686

Table 2.7 Checking assumptions for linear regression with ASC-ASD as dependent variable

Model	Cook's D	Durbin Watson	Tolerance	VIF
1 SRS-2		2.386	1.00	1.00
2 SRS-2 and IUS-P		2.386	.797	1.254
3 SRS-2, IUS-P and Group	.213	2.386	.964	1.038



Figre 2.1 Normal P-Plot of residuals with ASC-ASD as dependent variable
e indicating normal distribution

Figre 2.2 Scatter plot of residuals indicating homoscedasticity

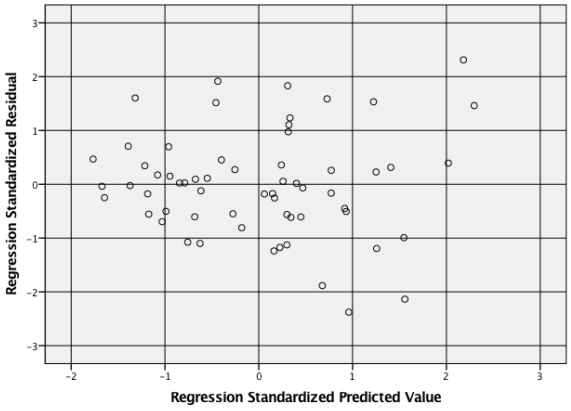
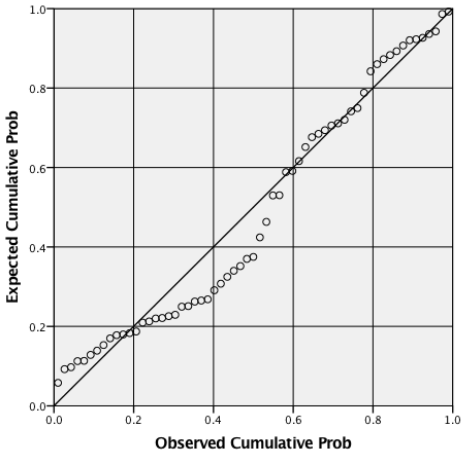


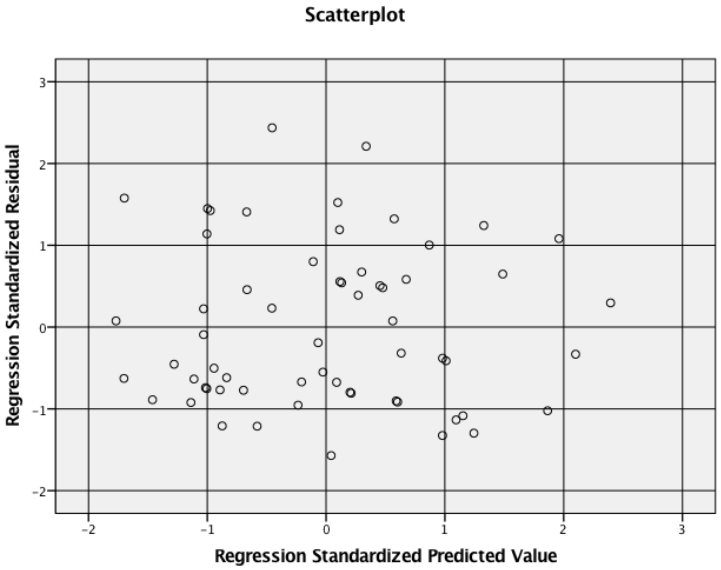
Table 2.8 Checking assumptions for linear regression with ADAMS-GA as dependent variable

Model	Cook's D	Durbin Watson	Tolerance	VIF
1 SRS-2		2.124	1.00	1.00
2 SRS-2 and IUS-P		2.124	.797	1.254
3 SRS-2, IUS-P and Group	.121	2.124	.964	1.038



Figre 2.3 Normal P-Plot of residuals with ADAMS-GA as dependent variable e indicating normal distribution

Figre 2.4 Scatter plot of residuals indicating homoscedasticity



Appendix O

Baron and Kenny's (1986) causal steps logic applied to the data presented in chapter two.

Baron and Kenny's causal steps logic (Barron & Kenny, 1986).

Figure 2.1 depicts steps 1-3 of this model for reference.

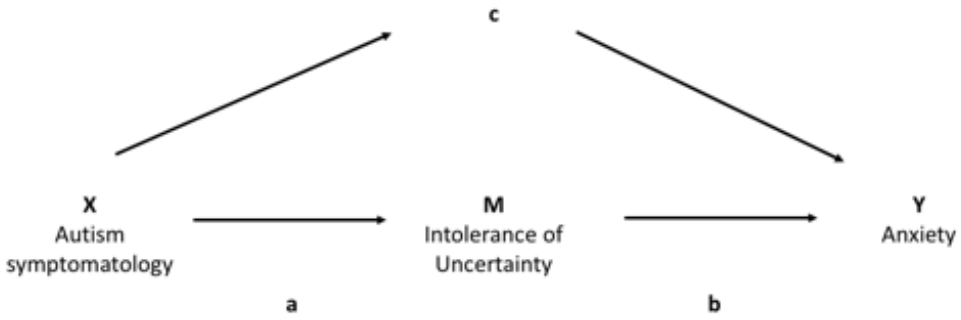


Figure 2.1, a causal mediational model of IU mediating anxiety in relations to autism symptomatology

This analysis involves four steps:

Step 1: The C Path

Does X predicts Y? (simple regression analysis)

Step 2: The a path

Does X predict M? (simple regression analysis)

Step 3 The b path

Does M predict Y? (simple regression analysis)

The first three steps demonstrate the existence of zero-order relationships variables. If one or more of these relationships are not significant, mediation is usually considered unlikely (Barron & Kenny, 1986).

Step 4- The extent of mediation (multiple regression analysis)

If X is no longer significant when M is controlled, the finding supports full mediation. If X and M both significantly predict Y, the findings support a partial mediation.

Mediation analysis was conducted in both CdLS and FXS groups, with both ASC-ASD total score and ADAMS-GA subscale score as the dependent variable. Table 2.5 outlines the results for each step.

In the CdLS group, significant relationships were found for steps 1, 2 and 3 (see Table 2.5) for both ASCASD and ADAMS-GA scores as the dependent variable. In step 4, the relationship between autism symptomatology (SRS scores) and anxiety (ASC-ASD or ADAMS-GA) scores was no longer significant at the <.05 level, while the relationship between IU (IUS-P) and anxiety was significant (see table 2.5). The results from this causal steps approach are therefore consistent with a causal mediational model in which the relationship between ASD symptomatology and anxiety is almost entirely mediated by IU in CdLS.

In the FXS group, analysis followed the same process as outlined for the CdLS group (see Table 2.5). Step 2 of the causal steps model revealed no significant relationship between X (SRS) and M (IU). This meant that it was unlikely a mediational relationship existed between IU and anxiety and therefore, the final steps of the analysis were not undertaken. The results were not consistent with a mediating role of IU between autism symptomatology and anxiety.

Table 2.5 : A summary of statistical analyses and significant regressions for each step of the causal steps model in CdLS and FXS groups

				F	df	R2	Beta	p
CdLS	Mediating model for ASC-ASD scores	Step 1		5.29	1,32	.146	.382	.028
		Step 2		13.41	1,32	.316	.562	.001
		Step 3		62.38	1,32	.683	.826	<.001
		Step 4	SRS	30.45	1,30	.685	-.059	.648
			IUS-P				.860	<.001
	Mediating model for ADAMS-GA scores	Step 1		11.67	1,32	.267	.517	.002
		Step 2		13.41	1,32	.316	.562	.001
		Step 3		40.81	1,32	.585	.765	<.001
		Step 4	SRS	23.65	1,30	.628	.253	.081
			IUS-P				.253	<.001

FXS	Mediating model for ASC-ASD scores	Step 1	6.48	1,32	.183	.427	.016
		Step 2	1.48	1,32	.050	.224	.234
	Mediating model for ADAMS-GA scores	Step 1	5.81	1,32	.162	.403	.022
		Step 2	1.48	1,32	.050	.224	234

Appendix P

Spearman's rho correlations between autism symptomatology, anxiety and IU in 15 females with CdLS

Table 2.6

	SRS total raw score	ASC-ASD total score	ADAMS GA subscale score	IUS-P total score
SRS total raw score		.534*	.532*	.559*
ASC-ASD total score			.771**	.893**
ADAMS GA subscale score				.841**
IUS-P total score				

*indicates p<.05

**indicates p<.01