PROFILE OF AUTISM SPECTRUM DISORDER PHENOMENOLOGY IN CORNELIA DE LANGE SYNDROME

by

LISA JANETTE COCHRAN

A thesis submitted to the
University of Birmingham
for the degree of
DOCTOR OF PHILOSOPHY

ABSTRACT

Background: There is a trend in recent research toward more detailed examination of autism spectrum disorder (ASD) and ASD-like characteristics in genetic syndromes. The most recent research findings support the conclusion that it is not only worthwhile but is essential to study ASD in genetic syndromes in order to aid early identification and promote access to appropriate services. Cornelia de Lange syndrome (CdLS) has been shown to have a heightened level of ASD phenomenology even when degree of intellectual disability (ID) is taken into account, although the specific manifestation of characteristics appears to be somewhat atypical. There is a lack of longitudinal research examining ASD phenomenology in CdLS.

Method: Three longitudinal studies were conducted to evaluate ASD phenomenology changes with age and over time in individuals with CdLS using appropriate contrast groups and psychometrically robust measures. The data was examined at both the broad (domain and total score level) and fine-grained (item score) levels.

Results: Older individuals with CdLS evidenced a higher prevalence of ASD characteristics and more impaired social interactions relative to younger participants with the same syndrome. Fine-grained analysis revealed that individuals with CdLS showed greater impairment in social and communication domains both with age and over time. The profile of ASD phenomenology in CdLS with age and over time differs from Fragile X and Cri du Chat in subtle but important ways.

Conclusions: It has become clear that different genetic syndromes may have different trajectories and profiles of ASD phenomenology. It is important to examine and define these specific trajectories and profiles in each syndrome. The research in this thesis has uncovered several novel findings which add to the knowledge and understanding of the behavioural phenotype of CdLS as well as the other syndrome groups employed (FXS and CdCS). There is a need for future research to examine other social factors (e.g., social anxiety) alongside the observed changes with age in CdLS.

ACKNOWLEDGEMENTS

My deepest gratitude goes to Professor Chris Oliver. His extreme passion and concern for the research he leads and the impact it has on individuals with neurodevelopmental disorders is truly inspiring. I would also like to thank Joanna Moss and Alice Welham for their support. Thank you to the Cerebra Foundation for funding my Ph.D. and giving me this amazing opportunity.

I would also like to acknowledge all of the people who helped with my studies (all team members of the Cerebra Centre at the University of Birmingham). For Chapter Two, Joanna Moss and Lisa Nelson collected data. For Chapters Three & Four, I would like to thank the following people for going on visits with me and filming the assessments: Victoria Johnson, Mary Heald, Louise Handley, Alison Jones, Kate Eden, Leah Glover and Hayley Crawford. The following people helped with visits, filming assessments and data entry: Katy Whitcombe, Becky Gallagher, Priya Mishra and Vicky Quine. A special thank you to the following people who helped with visits, filming assessments, data entry and scheduling visits: Sarah Lynch, Leanne Liddell and Lara Clark. Without all of your help, I could never have completed so many research visits.

To my loving and super supportive parents, I can’t thank you enough. You have assisted in countless ways that made all the difference. Thank you from the bottom of my heart. To big sis Angela, thank you for all the conversations on different continents talking me through another day. To Steven, thank you for inspiring me to work in this field. For my amazing daughter, who went along for the ride while I dragged her across the world and back, you have met every challenge with an awesome spirit!

PUBLICATIONS AND PRESENTATIONS

The following articles and conference abstracts were accepted for publication, in the process of preparation for publication and/or presented at conferences during the course of my postgraduate study within the School of Psychology, University of Birmingham. Where listed, the secondary authors also advised on the study design, data analysis and/or paper editing.

Paper accepted for publication directly from this doctoral research:

Cochran, L., Moss, J., Nelson, L., & Oliver, C. (2015). Contrasting age related changes in autism spectrum disorder phenomenology in Cornelia de Lange, Fragile X, and Cri du Chat syndromes: Results from a 2.5 year follow-up. *American Journal of Medical Genetics Part C* 169C:188 –197. doi:10.1002/ajmg.c.31438 (Chapter Two)

Manuscript in preparation/process of publication:

Cochran, L., Oliver, C., Welham, A., Arshad, A., & Moss, J., (2018). *Working Title*: Age-related behavioural change in Cornelia de Lange syndrome and Cri du Chat syndrome: a seven year follow-up. (Chapter Three)

Conference presentations arising from this research:

Cochran, L.J., Moss, J., Clark, L., Liddell, L. & Oliver, C. (2012, December). *Changes in autism spectrum disorder phenomenology in Cornelia de Lange and Cri du Chat Syndromes.* Oral Presentation at the Seattle Club Conference, Kendal, England.

Cochran, L.J. (2011, May). *Age related changes in autism spectrum phenomenology and repetitive behaviour in Cornelia de Lange, Fragile X and Cri du Chat syndromes.* Oral Presentation at the School of Psychology Research Event, University of Birmingham, Birmingham, England.

Cochran, L.J., Moss, J., Nelson, L., Burbidge, C., Arron' K., & Oliver, C. (2010, October). *Age related changes in autism spectrum phenomenology and repetitive behaviour in Cornelia de Lange, Fragile X and Cri du Chat syndromes.* Poster presentation at the 13th International Society for the Study of Behavioural Phenotypes (SSBP) Research conference, Pavia, Italy.

Table of Contents

List of Figures

Chapter Two

Chapter Three

Chapter Four

List of Tables

Chapter Four

CHAPTER ONE

Introduction

1.1. Introduction to behavioural phenotypes

1.1.1. Behavioural phenotypes

The practice of observing behaviours and associating them to a specific genetic cause dates back to the nineteenth century (Down, 1866/1990). On May 1, 1971 Nyhan introduced the term *behavioural phenotypes* during a presidential address to the Society for Pediatric Research to describe behaviours specifically associated with a genetic syndrome (Nyhan, 1972). The investigation of behavioural phenotypes has expanded since Nyhan's initial descriptions from case study descriptions to detailed empirical evaluation of specific behavioural characteristics and their development in syndromes using cross-sectional, longitudinal and group contrast designs. Currently, the most commonly accepted definition of a behavioural phenotype is that of Dykens (1995), which states that: "A phenotype is best described as the heightened probability or likelihood that people with a given syndrome will exhibit certain behavioural and developmental sequelae relative to those without the syndrome" (Dykens, 1995, p.523).

O'Brien (2006) expands on this, highlighting the potential for change and development:

> Behavioural phenotypes are patterns of behaviour that present in syndromes caused by chromosomal or genetic abnormalities. They have both physiological and behavioural manifestations with distinctive social, linguistic, cognitive and motor profiles. Their course is not static. Presentation typically varies according to the level of learning disability and a host of environmental, developmental and therapeutic influences, and it changes with increasing age. (O'Brien, 2006, p.338)

Harris (2002) also takes a developmental perspective, stating that each genetic syndrome provides 'a portal' (doorway) to understanding neurodevelopment. Examining the pattern of behaviours associated with genetic syndromes over the course of time and with age gives greater insight into how specific genetic causes might differentially influence behaviour and its development across different syndrome groups and inform our understanding of typical development. Identifying a behaviour that is characteristic of a specific syndrome can point research in the direction of a developmental or biological basis for that behaviour, furthering our understanding of that syndrome and typical development. More specifically, dissociations in both impairments at one point in time and the development of different behaviours, social and cognitive domains suggests different underlying processes that might be driven by structural differences in the brain and its development. Supporting this notion, Harris discussed in detail, the behavioural phenotypes of five genetic syndromes and highlighted the importance of a developmental perspective in providing a characterisation of behavioural phenotypes in neurodevelopmental disorders. The four groups that Harris described were: Lesch-Nyhan,

Prader-Willi, Angelman syndrome, fragile X and Williams syndromes. These syndromes were selected because they have well-established behavioural phenotypes and confirmed genetic causes. These four syndromes also have a variety of genetic causes (mendelian/nonmendelian inheritance and partial variants) and atypical individuals who present with only some of the features of the syndrome. According to Harris, this allowed for a broader investigation into the pathways from genes to behaviour (Harris, 2002).

Understanding behaviours associated with a specific syndrome can significantly contribute to more targeted approaches to help individuals with that syndrome. One of the most influential contributions to the study of behavioural phenotypes is in the area of treatment. O'Brien (2000) writes:

> Not only does it clarify that problems are real (not just the result of a mother's worry); it can also lead to enhanced intervention especially in education and other community settings, since the notion that a disorder has biological origins will often lend weight to bids for resourcing and support. Where long-term support might be required- which in the present state of our treatment capabilities is all too often the case- the identification of a behavioural phenotype can be crucially important. (O'Brien, 2000, p. 619)

1.1.2. Physical characteristics and medical issues in behavioural phenotypes

There are a multitude of contributing factors that might interact with behavioural phenotypes in genetic syndromes including: physical characteristics, medical conditions, broad psychiatric conditions, atypical behaviours, and cognitive and communication

impairments. The way these factors interact with the presentation of behaviour in genetic syndromes has been described in a number of studies. For example, the association between gastroesophageal reflux and self-injurious behaviour in Cornelia de Lange syndrome (CdLS) (Luzzani et al., 2003); the association between pain-related behaviours and challenging behaviour in Tuberous Sclerosis Complex (TSC; Eden et al., 2014); severe anxiety and social impairments in Williams syndrome (WS; Riby et al., 2014); expressive receptive language discrepancies and challenging behaviour in Angelman syndrome (AS; Jolleff & Ryan, 1993); visual impairments associated with optic nerve hypoplasia, Septo-optic dysplasia and psychosis in Prader-Willi syndrome (PWS; Dykens, Lee, & Roof, 2011). Each of these examples demonstrates the importance of documenting all aspects of phenotypes to understand the behavioural presentation.

1.1.3. Methodological considerations in behavioural phenotypes research

In order to accurately examine behaviours in the context of behavioural phenotypes, there are a number of methodological issues to consider. While identifying behaviours adds significantly to the detailed phenotype of a given syndrome, describing the pattern of behaviours compared to other groups with and without intellectual disability (ID) is critical (Moss & Howlin, 2009). One strategy used by previous studies in genetic syndrome groups has been to utilise an idiopathic ID group as a contrast to the syndrome group of interest (e.g., Oliver, Arron, Sloneem, & Hall, 2008; Devenny et al., 2010; Garner, Callias, & Turk, 1999). While this strategy has been helpful in order to evaluate the role of ID in the association between a given syndrome and behaviour of interest, it raises some methodological questions: Who would be included in an idiopathic ID group? Could it potentially include individuals with undiagnosed comorbid conditions or genetic

syndromes? Would the inclusion of an ID group contribute to the understanding of aetiology of differences and similarities? ID is an extremely genetically heterogeneous group with approximately 60% of cases having unknown aetiology (Topper, Ober, & Das, 2011). With so many potentially confounding factors to consider when assessing behaviour in a genetic syndrome, the use of matched contrast groups can help to identify the specific behavioural associations by controlling for levels of ID, language impairment or other coexisting conditions such as those described above. Hodapp and Dykens (2001) suggest that comparing behaviours across two syndrome groups with similar levels of ID can provide a greater understanding than comparison to a group of individuals with ID of heterogeneous cause. The 'same but different' approach suggested by Hodapp and Dykens (2001) using two syndrome groups with similar levels of ability and communication skills enables a similar contrast to that of an ID group but with the added advantage of more control over and homogeneity of group aetiology. Recent studies have often expanded this approach by contrasting several syndrome groups in order to control for multiple confounding factors. For example, several studies used this concept to compare behaviours in seven genetic syndromes (AS, Cri du Chat (CdCS), CdLS, Fragile X (FXS), PWS, Smith-Magenis (SMS) and Lowe (LS) syndromes) and identify differences in presentation and prevalence. One examined the prevalence and correlates of self-injury and aggression (Arron, Oliver, Berg, Moss, & Burbidge, 2011); another examined autism spectrum disorder (ASD) symptomatology, hyperactivity and affect (Oliver, Berg, Moss, Arron, & Burbidge, 2011).

In this thesis, the overall premise is to evaluate one particular type of behaviour (ASD behaviours) in CdLS with a focus on changes over time and with age.

1.2 Introduction to Cornelia de Lange syndrome (CdLS)

CdLS is a multiple malformation genetic syndrome that is rare and presents with a number of distinctive physical abnormalities, dysmorphic features and behaviour characteristics. Once thought to occur 1 in 40,000-100,000 live births (O'Brien & Yule, 1995), it is now estimated to occur 1 in 10,000 live births (Kline et al., 2007). CdLS is caused by deletions on chromosomes 5 (NIP-BL), 10 (SMC3), 8 (RAD21) and X (SMC1A) (Deardorff et al., 2007; Deardorff et al., 2012; Gillis et al., 2004; Krantz et al., 2004; Musio et al., 2006; Tonkin, Wang, Lisgo, Bambshad, & Strachan, 2004). Dysmorphic features common in CdLS include arched eyebrows, long eyelashes, long philtrum, rotated ears, thin upper lip and upturned nose. Small stature and medical complications including cardiac and gastro-intestinal issues are frequent within the syndrome. In their study of 49 individuals with CDLS, Kline and colleagues (2007) report, gastroesophageal reflux present in 82% of participants, congenital heart disease in 22%, cleft palate in 37%, sleep disturbance in 70% and prematurely grey hair prior to 20 years of age was noted in 18% (unrelated to familial early greying; Kline et al., 2007).

1.2.1 Cognitive and behavioural phenotype of CdLS

A range of severity of ID has been reported in CdLS with the majority of individuals falling in the moderate to severe ID categories (average IQ of 53) and as many as 76% classified as having severe and profound ID (Ajmone et al., 2014; Kline et al., 2007; Oliver, Arron, Sloneem, & Hall, 2008). More recently, a larger number of individuals with a mild presentation have been identified. Ajmone et al. (2014) report an IQ within the normal range in 17% of individuals with CdLS, although this is higher than that reported

in previous studies (Oliver et al., 2008; Kline et al., 2007) and is likely due to the smaller sample size compared to previous studies. It is possible that the use of more robust measures and non-verbal tests used in other studies could explain the differences as well. The authors also note the clear discrepancy between expressive and receptive language abilities in CdLS, which is consistent with previous literature (Basile, Villa, Selicorni & Molteni, 2007; Goodban, 1993). Behavioural characteristics associated with CdLS are social anxiety, self-injury, impulsivity, repetitive behaviours and selective mutism (Berney, Ireland, & Burn, 1999; Collis, Oliver, & Moss, 2006; Nelson, Moss, & Oliver, 2014). For example, Moss, Oliver, Arron, Burbidge, and Berg (2009) compared seven genetic syndromes on the Repetitive Behaviour Questionnaire (RBQ, Moss et al., 2008) and found that the CdLS group showed a unique profile scoring higher than two other genetic groups on tidying up and lining up behaviours. High rates of self-injurious behaviour (SIB) have been reported in CdLS, with one study (Oliver et al., 2009) reporting 56% and another (Arron et al., 2011) 70%. Rojahn et al. (2013) found more frequent SIB and stereotyped behaviours in CdLS with higher levels of intellectual impairment. Recent literature has indicated changes in behaviour with age in CdLS, which will be discussed in the following section.

1.2.2. Changes with age in CdLS

Emergent literature has highlighted age related changes in CdLS (Basile et al., 2007; Collis, Oliver, & Moss, 2006; Kline et al., 2007; Nelson et al., 2014). Most recently, Nelson, Moss, and Oliver (2014) conducted a two-year longitudinal study of individuals with CdLS, FXS and CdCS. The authors showed a dramatic decrease in mood and sociability with age in CdLS (particularly participants over the age of 15 years). More

specifically, the lowest levels of interest and pleasure were found in 19-22 year old individuals with CdLS compared to other age groups. A thorough review of age related changes in CdLS can be found in section 2.1.6.

Identifying changes with age is of particular interest because those changes may allude to an atypical pattern of brain development, which may in turn indicate the effect of genetic mechanisms underlying brain development in the syndrome. This is particularly important if the patterns of behavioural changes are similar to other syndrome groups but not all genetic syndromes. As much of the research in this area uses contrast groups in whom we do not see similar changes (one with an association to a particular behaviour and the other the opposite pattern), the observed differences are unlikely to be measurement artefact or due to interventions (which are minimal in CdLS). Therefore, any differences are likely to be reflective of the syndrome behavioural phenotype.

One area of particular interest and change in CdLS is in ASD phenomenology. A heightened prevalence of ASD in CdLS has been consistently reported and studies that have utilized appropriate contrast groups have demonstrated that the level of ASD phenomenology is not solely due to the level of ID (Moss et al., 2008; Oliver et al., 2008). More information about ASD in CdLS will be discussed in section 1.3.3.

1.3. ASD in genetic syndromes

1.3.1. Autism and autism spectrum disorder

Previously, the DSM-IV-TR (American Psychiatric Association, 2000) and ICD-10 (World Health Organization [WHO], 1992) classified ASDs as pervasive developmental

disorders (PDD) characterised by the presence of three core features: qualitative impairments in communication, social interaction and the presence of repetitive behaviour and restricted interests. The Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM-5; American Psychiatric Association, 2013) modifies this classification of ASD highlighting two core diagnostic domains: social relation/communication and restricted interests/repetitive behaviours. Although the DSM-IV-TR required a combination of twelve criteria to be met, the new DSM-5 only has seven criteria and it combines the five disorders that were previously independently grouped as PDD, into 'Autism Spectrum Disorder'. DSM-5 also creates a new diagnostic category of Social Communication Deficit to describe individuals that are experiencing social communication impairments but not significant issues with repetitive behaviours or restricted interests (Zuddas, 2013). These changes could make it difficult to compare data collected under the DSM-IV-TR criteria to data being interpreted with the new DSM-5 criteria. This is especially pertinent to the 'autism' versus 'Autism Spectrum Disorder' distinction used in diagnostic and screening measures. There is only preliminary data on the consistency of diagnosis from DSM-IV-TR to DSM-5 and therefore, the more established criteria of DSM-IV-TR will be used for the purpose of this thesis.

Fombonne (2005) derived global estimates of the prevalence of autism at (13/10,000), PDD (20.8/10,000), and Asperger Syndrome (AS; until recently, often considered to be in the same category with Pervasive Development Disorder (PDD); 2.6/10,000) using a conservative analysis of existing data. An overall best estimate of 0.6% is presented as the prevalence of ASD by the author. He also stated that up to 70% of individuals with autism has an intellectual disability (ID). Baird et al. (2006) investigated the prevalence of ASD

in children in South Thames, UK. They reported the prevalence of childhood autism in that population as 38.9/10,000, all other ASDs as 77.2/10,000 and combined overall prevalence as 116.1/10,000. Using a narrower definition which included clinical judgement, they provided a prevalence of 24.8/10,000.

1.3.2. ASD in genetic syndromes

Many known genetic disorders have been reported to be associated with ASD such as Tuberous Sclerosis Complex (TSC), Phenylketonuria, Prader-Willi syndrome (PWS), Rett syndrome (RS) and Angelman syndromes (AS; Zhao, Park, Smrt, & Jin, 2007). Several more genetic syndromes have been reported to demonstrate ASD-like characteristics including: Fragile X syndrome (FXS), Down, Coffin-Lowry, Cohen, Cornelia de Lange (CdLS) and Williams syndromes (WS; see Fombonne, 1999; Gillberg & Coleman, 2000 for review).

In 2011, Betancur carried out an extensive review of all genes and genomic imbalances implicated in ASD. This review provided data on 103 disease genes and 44 genomic loci reported in individuals with ASD or autistic behaviour. This review found that ASD is one of the clinical hallmarks in some genetic syndromes. The authors stated that:

> …the careful study of the overlap of ASD with genetic syndromes involved in ID and epilepsy is warranted. Large scale studies of well-characterised samples to evaluate the frequency of these genetic defects in autism as well as the frequency of autism in specific genetic disorders need to be performed. (Betancur, 2011, p.62)

The authors emphasised that some disorders are known for their comorbidity with ASD (such as 22q13 deletion, RS, FXS and TSC) and others with ASD manifestations (such as CdLS, CHARGE[1] and Cohen syndromes). The authors concluded that the existing data on ASD in genetic disorders (and vice versa) is not accurate (due to variability in measures and methods used in previous studies) and emphasises the need for the use of appropriate measures in future research (Betancur, 2011). It is also important to note that current literature has identified a much stronger comorbidity of ASD phenomenology in CdLS (Moss, Howlin, Magiati, & Oliver, 2012; Richards, Jones, Groves, Moss, & Oliver, 2015; Parisi, Di Filippo, & Roccella, 2015).

Zafeiriou et al. (2013) identified more than 100 syndromes/sequences associated with ASD in the literature including FXS, CdLS, TSC, Down syndrome, AS and PWS. The authors highlight the need to raise awareness of clinical features suggesting ASD in genetic syndromes or genetic syndromes in ASD patients in order for proper intervention and school placement.

The current research into ASD and genetic syndromes highlights the importance of recognising ASD characteristics (whether or not an ASD diagnosis may be appropriate) to ensure specific intervention, necessary behavioural management and educational placement (Betancur, 2011; Moss & Howlin, 2009; Falkmer, T., Anderson, Falkmer, M., & Horlin, 2013; Zafeiriou, et al., 2013).

[1] CHARGE is an abbreviation based on the core symptoms: Coloboma of the eye, Heart defects, Atresia of the choanae, Retardation of growth and/or development, Genital and/or urinary abnormalities and Ear abnormalities and deafness (National Organization for Rare Disorders).

Table 1.1: Population Prevalence, Prevalence of ASD and Key Areas of Behavioural Profile in Genetic Syndromes.

Syndrome Group	Population Prevalence	Prevalence of ASD	Key Areas of Profile Identified by previous research	Sources
22q11.2 deletion syndrome	1/4,000	10 – 40%	Social deficits (especially peer interactions in natural settings), lack of shared attention, low gestural communication, circumscribed interests, anxiety, psychiatric comorbidity and cognitive decline with age.	Oskarsdottir, Vujic, & Fasth, 2004; Antshel et al., 2007; Fine et al., 2005; Niklasson, Rasmussen, Óskarsdóttir, & Gillberg, 2009; Vorstman et al., 2006; Duijiff et al., 2013; Kates et al., 2007
Cohen syndrome	1/105,000	50 – 72%	Anti-social behaviours, communication and social deficits, preference for routine and repetitive behaviours.	Kivitie-Kallio, Larsen, Kajasto, & Norio, 1999; Howlin, Karpf, & Turk, 2005; Murphy, Flanagan, Dunne, & Lynch, 2007
Down's syndrome	10.3/10,000	5 – 39%	Varying levels of sociability, lack of imaginative play/ joint attention/shared enjoyment, repetitive stereotyped behaviours and interests.	Bell et al., 2003; Gllberg, Pearson, Grufman, & Themner, 1986; Turk & Graham, 1997; Starr, Berument, Tomlins, Papanikolaou, & Rutter, 2005
Angelman syndrome	1/40,000	50 – 81%	Happy disposition, episodes of laughter, impulsivity and hyperactivity. Individuals with Angelman and autism have social and communication impairments similar to idiopathic autism.	Thomson, Glasson, & Bittles, 2006; Sahoo et al., 2006; Bonati et al., 2007; Trillingsgaard & Ostergaard, 2004; Peters et al., 2004; Summers et al., 1995
Neurofibromatosis type 1	1/4,560	21 – 40%	Social affect deficits and communication difficulties but profile specific information is lacking.	Evans et al., 2010; Garg et al., 2015; Walsh et al., 2013; Garg et al., 2013
CHARGE syndrome	0.1-1.2/10,000	15 – 50%	Visual/hearing deficits, sensory impairments and limited social interaction.	Blake & Prasad, 2006; Smith, Nichols, Issekutz, & Blake, 2005; Hartshorne et al., 2005; Johansson et al., 2006
Fragile X syndrome	1/4,000 Males 1/8,000 Females	21 – 50%	Social anxiety, extreme shyness, selective mutism, gaze avoidance, hyperarousal, repetitive behaviours, social and communication skills less impaired than idiopathic autism with intact willingness to socially interact.	Sherman, 2002; Moss & Howlin, 2009; McCary & Roberts, 2013; Hatton et al., 2006; Cornish, Turk & Levitas, 2007; Hall, deBernardis & Reiss, 2006; Lesniak-Karpiak, Mazzocco, & Ross, 2003; Roberts, Weisenfeld, Hatton, Health, & Kaufmann, 2007; Turk, & Cornish, 1998; Kaufmann et al., 2004; Hall et al., 2010;
Cornelia de Lange syndrome	1/10,000	50 – 89%	Repetitive behaviours, social deficits, low expressive language, hyperactivity, lethargy, self-injurious behavior and impulsivity.	Kline et al., 2007; Basile, Villa, Selicorni, & Molteni, 2007; Berney, Ireland, & Burn, 1999; Bhuiyan et al., 2006; Moss et al., 2008; Oliver et al., 2008; Arron, Oliver, Berg, Moss, & Burbridge, 2011;
Tuberous sclerosis complex	1/6,000	5 – 61%	Social withdrawal, impaired social abilities, speech problems and stereotyped behaviours	O'Callaghan, 1999; Smalley et al., 1992; Gillberg et al., 1994; Webb et al., 1996; Critchley & Earl, 1932
Prader-Willi syndrome	1/25,000-1/45,000	19 - 36.5%	Increased social dysfunction and fears	Butler, 1990; Whittington et al., 2001; Descheemaeker, Govers, Vermeulen, & Fryns, 2006; Milner et al., 2005; Veltman et al., 2004

Table 1.1 shows the reported population prevalence, prevalence of ASD and key areas of the behavioural profile possibly contributing to ASD diagnosis in some of the most researched genetic syndromes (as well as the citations for the sources of the information in the table). There are a number of methodological issues in the studies used to compile this information. Most notably, a wide variety of measures (from screening questionnaires only to robust diagnostic measures) were utilised, as well as considerable differences in criteria for what was described as ASD prevalence (from autistic-like behaviours observed in case studies to clinical diagnostic criteria under DSM-IV). It is important to note that these numbers cannot be taken at face value but should be used as a guide to understand the general level of ASD symptomatology reported in the literature in genetic syndromes.

1.3.3. ASD in CdLS

Several studies have reported a heightened probability of ASD in individuals with CdLS. Prevalence estimates range from 50-89% (Basile, Villa, Selicorni, & Molteni, 2007; Berney, Ireland, & Burn, 1999; Bhuiyan et al., 2006; Moss et al., 2008; Oliver et al., 2008). Using the Childhood Autism Rating Scale (CARS; Schopler, Reichller, & Renner, 1988), Oliver et al. (2008) reported that 32.1% of 54 individuals with CdLS scored within the 'severe autism' category of the CARS compared to only 7.1% of a matched control group of individuals with ID, suggesting that the relationship between CdLS and ASD is not solely accounted for by associated degree of disability. However, the CARS only classifies individuals into categories of autistic behaviour severity (e.g., not autistic, autistic) without supplying diagnostic information. In contrast, Moss, Oliver, Berg, et al. (2008) examined ASD characteristics in CdLS in comparison to CdCS using the Autism Diagnostic Observation Schedule (ADOS; Lord, Rutter, DiLavore, & Risi, 2000) and the

Social Communication Questionnaire (SCQ; Rutter, Bailey, Lord, & Berument, 2003). The authors found the prevalence of ASD characteristics to be heightened in CdLS but the profile to be atypical to that of idiopathic autism (Moss, Oliver, Berg, et al., 2008).

There is considerable evidence in recent literature that suggests that while the prevalence of ASD is heightened in CdLS, the manifestation of these characteristics may differ, in subtle ways, to that of idiopathic ASD. Moss, Howlin, Magiati, and Oliver (2012) used the ADOS to compare a group of twenty individuals with CdLS and twenty individuals with idiopathic ASD that were matched on receptive language level and adaptive behaviour skills. The CdLS group showed more eye contact and gestures with less stereotyped speech and repetitive behaviour than the ASD group. Other studies have further demonstrated that repetitive behaviours are significantly less prominent in the profile of ASD characteristics in CdLS relative to other syndrome groups and individuals with ASD (Moss, Oliver, Nelson, et al., 2013; Oliver et al., 2011). This research shows that measurement and assessment methods are clearly influential in this area of research and therefore warrant careful consideration (Mulder et al., 2016).

1.4. Methodological considerations

1.4.1. Assessment methods in ASD

Autism is an extremely heterogeneous disorder. There have been a variety of assessments introduced over the years to diagnose and assess ASD. In a clinical setting, determining a diagnosis involves a substantial commitment of time and resources and typically involves a team of qualified professionals. The clinical diagnosis often includes a detailed history, medical examination, lengthy parental interviews, behavioural observations and

assessments (cognition, language, social and communication). There are many tools available to assess ASD including parent questionnaires or checklists/screening measures and detailed observational assessments requiring training (or even a specialised degree). Not all available measures are appropriate for use in individuals with severe ID or genetic syndromes due to low specificity (correctly identifying individuals who do not have the condition), reliability (producing consistent results) or lack of research to validate the use of the tool in this way. Checklists and screening measures are commonly used in both clinical practice and research to help identify potentially high levels of ASD symptomatology and therefore indicate the need for further assessment/investigation.

Huerta and Lord (2012) reviewed clinical best practices and research on diagnosis of ASD. The authors state a comprehensive evaluation must minimally include a parent interview and an observational measure of behaviour by an experienced clinician. Although not a comprehensive list, a summary and description of commonly used screening questionnaires, observational and informant report measures will be described. The scientific community often uses the Autism Diagnostic Interview-Revised (ADI-R; Rutter, Le Couteur, & Lord, 2003) and ADOS as the 'gold standard' assessments for diagnosis, as they are also commonly used in clinical diagnosis.

The ADI-R is a clinical diagnostic instrument for assessing autism in children and adults. It is a lengthy parent report that provides a diagnostic algorithm for autism as described in both the ICD-10 and DSM-IV. The instrument focuses on behaviour in three main areas: qualities of reciprocal social interaction, communication and language; and restricted and repetitive, stereotyped interests and behaviours. The ADI-R is appropriate for children and

adults with mental ages from about 18 months and above. However, the ADI-R requires extensive training to administer and code reliably. In addition, it takes a considerable amount of time to administer making it cumbersome for research purposes, on smaller projects, where time is limited.

The ADOS is a semi-structured, standardised observational assessment of communication and social interaction skills; play and imaginative skills; and repetitive behaviour. The ADOS is suitable for individuals with a range of developmental abilities, chronological ages and expressive language skills. The ADOS uses clear, planned social 'presses', which provide the best opportunity for the participant to display certain social and communicative behaviours or responses. The presence/absence and nature of these behaviours and responses are recorded. There are four modules (1-4) in the ADOS. Module selection is based on the chronological age and level of expressive language and all modules can be administered in 20-40 minutes. Each module has its own protocol and scoring algorithm. Sensitivity, specificity and inter-rater reliability are reported to be robust (Lord et al., 2000). Concurrent validity between the ADOS and the ADI-R ($r = .57$; $p < .001$) and between the ADOS and the SCQ ($r = .55$; $p = .001$) is good (Howlin & Karpf, 2004; Rutter, Bailey, & Lord, 2003). There is a broad range of studies that have used the ADOS to measure ASD symptomatology and/or the stability of those symptoms. Yet, there is only a limited selection of research that uses the original ADOS in a longitudinal fashion and often includes groups of younger children. The research on the stability of the measure itself is limited to individuals with idiopathic autism. Additional algorithms were created to help with the comparability across the ADOS modules and add ratings of severity (Gotham et al., 2009). However, these new algorithms were still

preliminary until the release of the ADOS-2 in 2012 and Module 4 revised algorithm and severity scores not released until 2014 (Hus & Lord, 2014). Overall, the ADOS offers one of the widest bases of comparison in the literature as well as robust psychometric properties, which make it a good measure to be utilised in research examining ASD symptomatology.

The Developmental, Dimensional and Diagnostic Interview (3di; Skuse et al., 2004) offers a computerized parent interview administered by a trained interviewer for the assessment of ASD. It offers the option for the parent to answer a packet of questions prior to the appointment to help expedite the interview. Suitable for ages 4 to 25 years, the questions gather background and demographic information, and address characteristics of ASD and other conditions. It produces profiles for autistic and non-autistic conditions (such as ADHD, Tourette syndrome, OCD, conduct disorders and pragmatic language disorders). Administers must go through a 2-day training course at Institute of Child Health, University College London or regionally if a group of professionals need training in a common area. Although this measure has an impressive sensitivity (1.0) and specificity (> 0.97), other studies replicating these findings are lacking. Therefore, this is a promising measure that should be considered for future research but is not currently utilised widely enough for the purposes of the research in this thesis.

The Childhood Autism Rating Scale (CARS; Schopler, Reicher, & Renner, 1988) is a rating scale used for the detection and diagnosis of autism. The scale consists of 14 domains which assess behaviours related with autism and one domain to cover more general impressions of autism. Total scores range from 15-60, with higher scores

indicating a higher level of impairment. Time to administer is approximately 30-60 minutes. There is variability in reported cut-off scores appropriate for autism and a lack of cut-off score for ASD. The CARS does not distinguish PDD-NOS from autistic disorder or ASD from non-spectrum (Perry et al., 2005). There is no consideration for developmental level in the scoring of the CARS and has been shown to have a strong negative correlation with level of IQ and adaptive behaviour (Perry et al., 2005). This would make the CARS unsuitable for use in research of genetic syndromes that have a high level of ID.

The Diagnostic Interview for Social and Communicatory Disorders (DISCO; Wing et al., 2002) is an expanded version of the Handicaps Behaviour and Skills schedule (HBS) previously developed by Wing and Gould. It is a semi-structured interview which includes a section for clinical judgement, and covers all ages and levels of ability. In order for an examiner to obtain a license to use the DISCO, a five-day course must be attended and reliability on scoring at least two full assessments achieved. One advantage of the DISCO includes the ability for a qualified professional to use their clinical judgement and current information to make a working diagnosis if no informant is available to give a developmental history for an adult. According to the National Autistic Society (UK), this approach is helpful in identifying comorbid conditions, planning treatment and understanding the individual's needs. However, they also highlight that the DISCO was developed primarily as a clinical measure. Although the DISCO has been adapted to identify diagnostic categories for research, it is primarily intended as a systematic way of collecting a clinical history of the whole individual and takes a significant investment of time to administer. These factors make it better suited for use in clinical practice. In

addition, the DISCO has excellent sensitivity (0.98) but low specificity (0.57). This means that although it may have a high likelihood of correctly identifying individuals with ASD that do indeed meet criteria, it is also probable that it may incorrectly identify individuals who do not (false positives).

Falkmer et al. (2013) systematically reviewed diagnostic procedures for ASD in order to identify the best diagnostic instruments available. They reviewed 68 articles and assessed 17 diagnostic tools. The authors employed strict criteria to make sure that all areas (sensitivity, specificity, reliability, validity, simplicity, briefness and appropriateness for all ages) were considered when evaluating the diagnostic instruments and screening tools (with strong potential to be diagnostic tools). After all evidence was considered:

> The Autism Diagnostic Interview-Revised (ADI-R) and Autism Diagnostic Observation Schedule (ADOS) stood out with the largest evidence base and highest sensitivity and specificity…the combined use of the ADI-R and ADOS revealed the strongest accuracy, followed closely by the ADOS individually. (Falkmer et al., 2013, p. 329)

The authors also found that the combined use of the ADI-R and ADOS produced an equivalent classification rate to that of a multi-disciplinary team performing a complete clinical work up. However, due to the extensive length of time it takes to administer the ADI-R interview and the substantial amount of training required for the examiner, another measure must be considered in some research.

One screening measure that was not considered by Falkmer was the Social Communication Questionnaire (SCQ; Rutter et al., 2003). The SCQ is a screening measure consisting of only 40 questions and filled out directly by the parent or caretaker of the individual being assessed. The SCQ's content parallels that of the ADI-R and has been established to be unaffected by gender, language level, age (over 4 years) and performance IQ (Western Psychological Services website). The SCQ is reported to be accurate at discriminating between autism spectrum disorders and other conditions, including individuals with ID (Brooks & Benson, 2013). The authors suggest a cut-off score of 15 or above to screen for ASDs, differentiating ASD from other diagnoses, not including intellectual impairments (specificity= .80; sensitivity= .96) and for ASD from intellectual impairments (specificity= .67; sensitivity= .96). A higher cut-off of 22 is used to screen for autism, differentiating those with autism to individuals with PDD (specificity= .60; sensitivity= .75). Although, the authors caution that the SCQ by itself is not appropriate for diagnostic use (Howlin & Karpf, 2004). The combination of the ADOS and the SCQ facilitates accuracy (sometimes better than the ADOS and ADI-R combination) while providing an economical way to assess autism and ASD (Oosterling et al., 2010). The use of the SCQ as a substitute for the ADI-R in combination with the ADOS is often used (Charman & Baird, 2002).

Using the SCQ and ADOS together in research allows for both parental report of behaviours (that might not occur during a short assessment) and for the trained eye of a professional (who may notice subtle behaviours overlooked by the parent). Although the ADOS requires substantial training to administer, once the researcher is trained it is a fairly quick assessment. The combination of the two assessments (SCQ & ADOS) is a

practical way for researchers to gain the best insight into ASD behaviours and takes into account (both) information from the individual's caregiver and trained observations.

1.4.2 Methodological issues inherent in studies of ASD in genetic syndromes

When evaluating ASD and related characteristics in genetic syndromes, there are further challenges to be considered. The most notable is the association of ID and ASD. ASD occurs in up to 40% of individuals with ID (La Malfa et al., 2004). The presence of ID is associated with a higher prevalence of certain behaviours (such as repetitive behaviours) that can overlap with common ASD characteristics. Furthermore, Skuse (2007) argues that associated ID in genetic syndromes might explain the increased prevalence of ASD and related characteristics in these populations. While Moss and Howlin (2009) argue that associated degree of ID often does not fully account for the raised prevalence of ASD in a given syndrome group, this debate highlights the need for the use of a contrast group with a similar level of ID to help separate ASD from non-ASD behaviours. With matched contrast groups where both groups have a genetic syndrome and a similar level of ID, it is more likely that any observed differences are due to the syndrome's behavioural phenotype.

As discussed in section 1.3.3, a further challenge in understanding the association between ASD and a given genetic syndrome is the fact that while the presence of a genetic syndrome appears to be a risk marker for ASD characteristics, individual syndrome groups often appear to have a different profile of characteristics and a different developmental trajectory compared to that of idiopathic autism. So, although an individual with a genetic syndrome may meet criteria for ASD, it is possible that they may do so for different

reasons than those with idiopathic ASD. RS for example, has an established association with ASD and yet Howlin (2002) found that repetitive hand movements in this group were very different to the motor stereotypies typical of individuals with ASD. Furthermore, Moss & Howlin (2009) state:

> Even when diagnostic criteria for autism are met, individuals with Rett syndrome demonstrate an atypical profile of phenomenology... It seems that each syndrome group may have their own, unique, syndrome-specific 'signature' of ASD characteristics and impairments that are different from those observed in idiopathic ASD. (Moss & Howlin, 2009, p.857 & p.864)

This highlights the importance of looking at the profiles at a fine-grained level of ASD in any genetic syndrome and how these behaviours change over time and with age in many syndromes.

When investigated at a fine-grained level (looking at individual items on a measure of ASD), many genetic syndromes (such as FXS, CdLS syndrome, TSC & Cohen's syndrome) may meet the suggested cut off scores on diagnostic measures for ASD but the quality and profile of these behaviours, along with the trajectory of development of these characteristics, may be quite different from idiopathic ASD (Moss, Howlin, & Oliver, 2011). Therefore, it is important to account not only for the presence of ASD phenomenology and whether it meets criteria for diagnosis but also to look carefully at the patterns of these characteristics.

1.4.3. Longitudinal follow-up studies in ASD

Magiati, Wei Tay & Howlin (2014) conducted a systematic literature review of twenty-five longitudinal studies of individuals with ASD. They looked at cognitive, language, social and behavioural outcomes presented in the literature that included childhood assessments as well as follow-up assessments into adolescence or adulthood. There were large differences and variability in the outcomes within and between studies. This is to be anticipated in such a heterogeneous group as ASD. Some of the findings were surprisingly consistent, such as intellectual functioning, which remained stable or only slightly decreased over time. This was particularly true if the overall IQ of the childhood cohort was higher. Although there was large variability in adult IQs across the studies reviewed, the findings suggest that childhood IQ has predictive value in relation to individual outcomes. Interestingly, adaptive functioning (particularly daily living and possibly communication) improved over time while still showing impairments. ASD related phenomenology generally improved with age and diagnostic status remained stable. It is pointed out by the authors that studies published prior to 2000 did not have as good outcomes as more recent studies due to a number of diagnostic and methodological factors. It is suggested also that better community support, treatment and integration is crucial to improving outcomes for individuals with ASD and may be responsible for some of the improvements seen in more recent studies.

1.5. Summary

There is a trend in recent research examining ASD and ASD-like characteristics in genetic syndromes. Some have argued that there is no point in distinguishing and defining the patterns of ASD in genetic syndromes and that only the genetic syndrome is worth

consideration. Hall, Lightbody, Hirt, Rezvani, and Reiss (2010) argue that it is necessary to maintain a distinction between the genetic syndrome (biological disease) and idiopathic autism (a behaviourally defined disorder) to facilitate effective interventions (Hall et al., 2010). However, there is a compelling argument that fine-grained analysis of the profile of ASD behaviours and further exploration of associated behaviours in specific syndromes has a substantial contribution to make to the literature on behavioural phenotypes in genetic syndromes (Moss & Howlin, 2009). The most recent research findings support the conclusion that it is not only worthwhile but essential to study ASD in genetic syndromes in order to aid early identification and access to appropriate services (Betancur, 2011; Falkmer et al., 2013). CdLS has been shown to have a heightened level of ASD phenomenology even when degree of ID is taken into account, although the specific manifestation of characteristics appears to be somewhat atypical. It is reasonable to question whether the genetic syndrome explains the ASD phenomenology seen in CdLS or if there is another cause to be found by examining these behaviours in detail. The association between CdLS and ASD phenomenology noted in recent research studies suggests that more comprehensive and detailed examinations of not only the behaviours but the profiles of these behaviours and how they change with time and age are necessary and valuable.

It has been established that what is needed is research conducted longitudinally and with appropriate contrast groups (CdLS compared to matched syndrome groups) using psychometrically robust measures (such as the SCQ and ADOS) to examine ASD phenomenology at a broad (domain and total score level) and fine-grained (item) level. This will provide the clearest picture of these behaviours in genetic syndromes and how

they develop and change with age and over time. The way in which the profile of ASD behaviours change over time and with age within and between syndrome groups can yield valuable insight to determining treatment and outcomes for CdLS.

1.6. Thesis Aims

Aims of this thesis

- The first aim of this thesis is to evaluate the profile of autism spectrum disorder phenomenology in Cornelia de Lange syndrome **at a single point in time** compared to appropriate contrast groups using informant and observational measures. This aim is addressed in all three chapters.
- The second aim of this thesis is to conduct a longitudinal follow-up and to evaluate **changes** in the prevalence of autism and autism spectrum disorder in Cornelia de Lange syndrome and examine **changes at a broad domain and total score level** using psychometrically robust measures. This aim is addressed in Chapter Two and Chapter Three: '*Age related changes in autism spectrum phenomenology and repetitive behaviour in Cornelia de Lange, Fragile X and Cri du Chat syndromes'*. and '*Autism spectrum disorder phenomenology over time in Cornelia de Lange and Cri du Chat syndromes'*.
- The third aim of this thesis is to conduct a longitudinal follow-up and to evaluate **changes in autism spectrum disorder phenomenology** over time in Cornelia de Lange syndrome at a **fine-grained level** using psychometrically robust measures. This aim is addressed in Chapter Four: *'Determining the profile of autism spectrum disorder phenomenology in Cornelia de Lange and Cri du Chat syndromes'*.

CHAPTER TWO

Age related changes in autism spectrum phenomenology and repetitive behaviour in Cornelia de Lange, Fragile X and Cri du Chat syndromes.

2.1. Introduction

The previous chapter discussed the need for further research into the behavioural phenotype of Cornelia de Lange syndrome (CdLS) and specifically autism spectrum disorder (ASD) phenomenology with age and over time. This chapter will examine the profile of ASD phenomenology in CdLS at a single point in time and longitudinally to evaluate changes in the prevalence of autism and ASD in CdLS at a broad domain and total score level using psychometrically robust measures compared to appropriate contrast groups using informant measures.

2.1.1. Background

The research literature regarding behavioural phenotypes of genetic syndromes has seen major advances in recent years. Our knowledge of these syndromes no longer relies upon

clinical descriptions of behaviours in single case study reports, but now includes detailed investigations of associated behaviour and the developmental trajectories of cognition and behaviour (see Chapter One, section 1.1.1). Behavioural phenotypes offer valuable information and insight into many syndromes. For parents and loved ones of an individual with a genetic syndrome, it can be reassuring to know that certain features of behaviour can be as characteristic of the disorder as intellectual disability or facial dysmorphology (Skuse, 2010).

One area in behavioural phenotypes that has sparked interest in the scientific community in recent years is the presence of autism spectrum disorders (ASD) and autistic-like behaviours within particular genetic syndromes.

2.1.2. Autism spectrum disorders

Section 1.3.1 described the diagnostic criteria for ASD and the modification of these criteria in the recently updated DSM-5 (APA, 2012). For the purpose of this study the criteria outlined in the earlier DSM-IV-TR (APA, 2000) will be used, in which ASD is defined by the presence of impairments in social interaction, communication and restricted interests or repetitive behaviours.

As reviewed in section 1.3.2, there is an increased risk of ASD in genetic syndromes. However, the profiles of ASD characteristics differ from idiopathic autism at a broad domain level and on an item-level on some measures (see section 1.4.2). This highlights the need to examine such behaviours at a more detailed level, while using measures that capture these key areas, such as repetitive behaviour.

As mentioned in Chapter One, distinguishing between behaviours associated with severe ID and ASD phenomenology can often be challenging. This can become especially difficult in individuals with genetic syndromes. The complex cognitive, communicative, behavioural, emotional and physical difficulties might mask ASD characteristics in individuals with a genetic syndrome. Moss, Oliver, et al. (2009) investigated the prevalence and phenomenology of repetitive behaviours in genetic syndromes. They employed the Repetitive Behaviour Questionnaire (RBQ; Moss & Oliver, 2008) to do a fine-grained analysis of repetitive behaviour in Angelman (n=104), Cornelia de Lange (n=101), Cri du Chat (n=58), Fragile X (n=191), Prader-Willi (n=189), Lowe (n=56), Smith-Magenis (n=42) and individuals with ID of a heterogeneous aetiology (n=56). Although repetitive behaviour was variable across syndromes, FXS scored highly on all subscales. They found evidence of syndrome specific profiles in the results. Of particular interest was an item-level analysis, which identified items on the RBQ where the syndrome group scored significantly higher than two or more other groups ($p < .001$). This degree of difference was considered to indicate behaviours that might contribute to the behavioural phenotype of a particular syndrome group. For example, the FXS group met this criteria on several repetitive behaviour items, the most prevalent being 'hand stereotypies', 'lining up objects', 'restricted conversation', 'preference for routine' and 'echolalia'. Whereas the CdCS group was the only group to score significantly on the item of 'attachment to people', and that was the only significantly different item for this group. 'Tidying up' and 'lining up behaviours' were significantly more prevalent for the CdLS group. The authors also note that the CdLS and Lowe groups showed "notable similarities" with the FXS group in their repetitive behaviour profiles. However, this was

not identified at a statistical level. Therefore, it is worthy of further investigation. Accurate identification of ASD symptomatology in genetic syndromes may have substantial implications for an individual's education programming and behaviour intervention strategies (Howlin, Wing & Gould, 1995; Moss & Howlin, 2009). Understanding these trajectories can provide valuable insight into behavioural phenotypes, allow a better understanding and predict and ensure appropriate intervention for behavioural phenotypes associated with neurodevelopmental disorders.

One genetic syndrome, CdLS, has recently been identified as having a heightened presence of ASD characteristics alongside an apparently atypical presentation of characteristics (Moss et al., 2008; Moss, Howlin, Magiati, & Oliver, 2012; Oliver, Arron, Sloneem, & Hall, 2008).

2.1.3. Cornelia de Lange syndrome

CdLS is a multi-systemic congenital syndrome that affects approximately one child in every 10,000 (Kline et al., 2007). It is a malformation disorder with a distinctive physical appearance, small stature, medical complications and developmental and behavioural issues. There is a broad range of severity of intellectual disability ranging from mild to profound (Kline et al., 2007). In Chapter One a detailed description of the syndrome was discussed (see section 1.2).

Chapter One (section 1.3.3) summarised the literature showing a high prevalence of ASD phenomenology in CdLS that is not solely accounted for by the level of ID. In addition to the literature cited in Chapter One, there are other studies that highlight an association

between CdLS and ASD phenomenology. For example, Srivastava et al. (2014) used the Childhood Autism Rating Scale (CARS), the Aberrant Behavior Checklist and Vineland Adaptive Behavior Scales (VABS) to assess 41 children with CdLS aged 5-18 years. The authors stated:

> Characteristic items were abnormal emotional response, stereotypies, odd object use, rigidity, lack of verbal communication, and low intellectual functioning. Verbal communication deficits and repetitive behaviors were higher compared to sensory, social cognition, and behavior abnormalities. Maladaptive behaviors associated with autism traits were stereotypies, hyperactivity, and lethargy. (Srivastava et al., 2014, p. 1400)

The authors also noted that although socialisation adaptive skills were a relative strength, both socialisation and communication domains declined significantly with age (Srivastava et al., 2014). It is apparent that it is important to consider not only the presence of ASD phenomenology in CdLS but also how it might change with age.

The literature clearly reveals that CdLS is one syndrome group of interest when looking at ASD phenomenology. While investigating this possibility it is vital to include appropriate contrast groups both for level of ID and ASD symptomatology within a genetic syndrome (Hodapp & Dykens, 2001). Cri du Chat syndrome (CdCS) has a similar level of ID and expressive language deficits to CdLS and therefore is one appropriate comparison group for this study.

2.1.4. Cri du Chat

Lejeune et al. (1963), a group of French physicians, first described CdCS. It takes its name from 'cat-like cry', which is a distinguishing characteristic associated with the syndrome. CdCS affects approximately 1 in 50,000 births (Dykens, Hodapp, & Finucane**,** 2000). Defining features of CdCS include delayed growth, microcephaly, micrognathia, rounded face (dysmorphic facial features and head abnormalities), frequent infections, low set ears, broad nasal ridge, short neck and feeding problems (Goodart et al., 1994; Dykens et al., 2000; Collins & Eaton-Evans, 2001). CdCS results from a deletion of chromatin from the short arm of chromosome 5 (5p). The deletion is present in 85% of cases; 10-15% are familial with more than 90% due to a parental translocation and 5% due to an inversion of chromosome 5 (Van Buggenhout et al., 2000).

Behaviours associated with CdCS include self-stimulatory/repetitive behaviours involving self-injurious behaviour, aggression, temper tantrums, hyperactivity, poor concentration/distractibility and impulsivity (Cornish & Pigram, 1996; Dykens & Clarke, 1997; Cornish, Munir, & Bramble, 1998; Dykens et al., 2000; Collins & Cornish, 2002; Sarimski, 2003). Although there are many medical and behavioural problems associated with CdCS, ASD characteristics are not commonly reported. Some of the research describes individuals with CdCS in a very positive light as both sociable and capable of learning (Carlin, 1990). In fact, Carlin (1983) reports social interaction skills are considered to be a relative strength of individuals with CdCS who are noted to have a 'friendly and happy' demeanour. The social description of individuals with CdCS suggests that ASD characteristics are not common in this syndrome. Campbell et al. (2004)

describe the marked improvement in quality of life for individuals with CdCS who are 'home-reared', have supportive families and access to early intervention.

Just as CdCS is well matched with CdLS on level of ID and expressive language, FXS is the second appropriate contrast group to address level of ASD symptomatology within a genetic syndrome.

2.1.5. Fragile X syndrome

Fragile X syndrome (FXS) is the most common identifiable cause of inherited ID (Cornish, Turk, & Hagerman, 2008). The prevalence rate is estimated to be 1 in 4,000 males and 1 in 8,000 females (Sherman, 2002). FXS is caused by a trinucleotide (CGG) repeat expansion in the 5' untranslated region of the Fragile X Mental Retardation 1 (FMR1) gene located in the X chromosome (Vererk et al., 1991). The size of the CGG repeat determines if the FMR1 allele is classified as either normal (5-44), gray zone (55-200) or full mutation (>200) (Maddalena et al., 2001). ID is reported to be within the mild to severe range in males, whereas females typically show a mild level of ID (Cornish, Turk, & Hagerman, 2008). Physical characteristics common in FXS are: facial dysmorphism, prominent ears, velvet-like skin, hyperextensible finger joints, a high-arched palate, flat feet and pectus excavatum (Hagerman, 2002). Also, FXS is associated with an increased risk of deficits in other domains such as sustained attention, executive function, working memory and social function (Farzin et al., 2006).

Behavioural characteristics common in FXS include: self-injury, hyperactivity, attention deficit, gaze aversion, social anxiety, language impairment and stereotyped behaviours

(Hatton et al., 2006; Turk, & Cornish, 1998; Cornish, Turk, & Hagerman, 2008). FXS has a well-established association with high levels of ASD phenomenology with the most consistent estimates in studies ranging from 21% to 50% (see Moss & Howlin, 2009; Moss, Howlin, & Oliver, 2011; McCary & Roberts, 2013 for reviews). Hatton et al., (2006) found approximately 21% of 179 children with FXS had a prevalence of ASD behaviours as measured by the CARS in a longitudinal study. The authors also found that the CARS scores increased slowly yet significantly over time (Hatton et al., 2006). Up to 90% of individuals with FXS present with characteristically autistic atypical behaviour such as avoidant eye contact, social anxiety, repetitive and stereotyped behaviours (Hernandez et al., 2009). The presentation of ASD in FXS is somewhat different (in subtle ways) to the social impairments that are characteristic of individuals with idiopathic autism, with social anxiety, selective mutism and gaze avoidance reported to be particularly characteristic of the syndrome, but also an apparently preserved motivation for social interaction (Cornish, Turk, & Levitas, 2007; Hall, deBernardis, & Reiss, 2006; Lesniak-Karpiak, Mazzocco, & Ross, 2003; Moss et al., 2013; Roberts, Weisenfeld, Hatton, Health, & Kaufmann, 2007; Bouras et al., 1998). Similarities to CdLS, with regard to prevalence estimates of ASD symptomatology and atypicalities in the nature of ASD characteristics make FXS an interesting contrast group in this study. In addition, the well-established and researched profile of ASD characteristics in FXS allows for a more refined interpretation of these characteristics in CdLS. The similarities and differences in ASD profiles between the FXS and CdLS groups can give an insight into the behavioural phenotype of the specific syndrome. An additional benefit of having this type of contrast group is that it can help distinguish if changes with age are due to high levels of ASD symptomatology and a genetic syndrome or if they could be specific to CdLS.

2.1.6. Changes with age in ASD characteristics

There is currently very limited information available about the way in which ASD characteristics associated with genetic syndromes develop and change over time. An extensive survey conducted by Nelson, Moss, and Oliver (2014) provided preliminary data regarding the profile of social anxiety, low mood, repetitive behaviour and ASD characteristics across the age span in CdLS and a number of other neurodevelopmental disorders. The data demonstrated that individuals with CdLS evidence a significant decline in mood and sociability with significant increases in repetitive behaviour and severity of autistic-like characteristics with age (Nelson et al., 2014). As mentioned in Chapter One (see section 1.2.2.), Nelson et al. (2014) demonstrated that individuals with CdLS (n=101) aged 16 years and over evidence significantly lower scores on measures of mood, interest and pleasure, and significantly higher scores on measures of repetitive behaviour and ASD in comparison to those aged under 16 years. Individuals with ASD (n=281) also evidence a decline in scores on mood, interest and pleasure across these age groups but no other changes in repetitive behaviour or ASD were evident in this group. It is of particular interest that ASD characteristics show an apparent increase in severity with age for individuals with CdLS. The findings also suggest that after the age of 16, individuals with CdLS may demonstrate a syndrome specific global change in behavioural characteristics that is not evident in other syndrome groups.

Very little is known about the developmental profile of behaviours in CdCS and the outcome for adults with the syndrome. Consequently, it is not clear whether the reported strength in social interaction skills remains stable over time or whether these areas of behaviour demonstrate changes with age. Reports from parents and carers of individuals

with CdCS suggest that there may be improvements in global behavioural difficulties over time in CdCS. Our preliminary analysis suggests that the behavioural phenotype in CdCS, particularly scores on measures of ASD symptomatology, mood and repetitive behaviour remain relatively stable over time (Nelson et al., 2014). However, further empirical work is required in order to further understand these changes.

There are very few studies that have evaluated the trajectory of ASD symptomatology in individuals with FXS. Using the CARS, Hatton et al. (2006) examined scores in children with FXS over time. They reported the CARS classification to be stable despite a slow but significant increase in total score over time. Once again these findings have to be taken with caution due to the limitations of the CARS usage mentioned earlier (see Chapter One, section 1.3.3.). In addition, this study only looked at children and therefore lacks the component of age in a longitudinal design. Sabaratnam et al. (2003) reported on a 10-year follow-up study of the autistic-like behaviour of older males with FXS. The individuals had a wide age range of 6-76 years (mean age at baseline 35.8 ± 18.8 years). They used the Brief Disability Assessment Schedule (B-DAS; Holmes et al., 1982) and the Handicaps, Behaviour and Skills Schedule (HBS; Wing, 1980). The authors reported stability over time in the autistic-like behaviours in FXS with the exception of an increase in resistance to change over time. Sabaratnam and co-authors also noted a ten-fold increase in psychiatric morbidity in FXS compared to the general population over time (Sabaratnam et al., 2003). Hernandez et al. (2009) looked at the stability of ASD over time. Based on Rogers et al. (2001), they separated the participants into two categories of FXS+ASD or FXS+None. Their findings indicated that the ASD diagnosis was relatively stable over time. There was a general improvement in ASD behaviours observed in

FXS+ASD and a concurrent worsening in FXS+None, resulting in less differentiation over time. Although FXS+None non-verbal IQ scores declined, FXS+ASD IQ scores remained stable. Some limitations of the study are the relatively young age of the sample (30-88 months at baseline) and limited length of the follow-up (3 years). Overall, the current literature is lacking the use of robust measures of ASD symptomatology and the insight into possible associations with age.

2.1.7. Summary

In summary, behavioural phenotypes can give important insight into neurodevelopmental disorders and offer valuable guidance for future interventions and treatments. Behaviours characteristic of ASD have been identified in a number of genetic syndromes. Most recently, CdLS has come to the forefront as displaying these types of behaviours. Although there is some association between degree of ID and ASD symptoms, it cannot account for the high rate of ASD symptomatology identified in individuals with CdLS. In order to look more closely at this in CdLS, it is vital to have appropriate contrast groups. CdCS is an appropriate contrast group for level of ID and expressive language and FXS for the level of ASD in a genetic syndrome. Individuals with CdCS show a very different profile of association to CdLS with a lower prevalence rate of ASD and reported strengths in social interaction. Currently, there is very little literature about how these impairments and skills in CdLS and CdCS develop and change over time. The limited research into the trajectory of ASD symptoms in FXS is mixed. However, preliminary research in CdLS has shown a significant decline in mood and sociability with significant increases in repetitive behaviour and severity of autistic-like characteristics with age, while individuals with CdCS and FXS show a more stable profile over time. Detailed longitudinal investigation

of these changes with age and why the trajectory across CdLS, CdCS and FXS is so different is needed. This would enable better prediction of outcome in these syndromes and ensure better intervention and prevention strategies for the future. Part of this investigation should include a fine-grained analysis of the Repetitive Behaviour Questionnaire (RBQ; Moss & Oliver, 2008) in these syndromes, building on the current information available.

Aims:

In this study, the course of ASD phenomenology with age and time in CdLS is evaluated. Based on previous research findings the following hypotheses are proposed:

1) Individuals with CdLS and FXS will show a heightened prevalence for ASD characteristics compared to the CdCS group.

2) Older individuals with CdLS will be more likely to meet criteria for ASD and show more severe ASD compared to younger individuals with CdLS.

3) Individuals with CdLS will show an increased severity and frequency of autism spectrum phenomenology (within the syndrome) over time.

A secondary aim of this study is to explore the differences in repetitive behaviours between and within the CdLS, FXS and CdCS syndromes. These comparisons will be made across syndromes, age bands and time.

2.2. Methods

2.2.1. Recruitment

This study was conducted as part of a larger questionnaire survey study comparing aspects of behavioural phenotypes of multiple syndromes. The Coventry NHS Research Ethics Committee granted ethical approval for the study. Questionnaire packs were sent out to parents/carers of children and adults with genetic syndromes and other neurodevelopmental disorders creating a unique database of normative data. Individuals with CdLS, CdCS and FXS syndromes who participated in the larger study between 2003 and 2004, Time one (T1; Arron et al., 2011; Moss et al., 2009; Oliver et al., 2011), were invited to participate in the current follow-up study; Time two (T2) study, took place between 2006 and 2007. Data from Time 2 were cleaned, prorated, coded and analysed in 2009 by the author of this thesis in addition to matching participant groups on relevant variables.

All parents/carers were sent a letter, an information sheet, consent forms, a demographic questionnaire, questionnaire pack and a prepaid envelope at each time point. (For a detailed description of the recruitment procedure, see Arron et al., 2011; Moss et al., 2009; Oliver et al., 2011).

2.2.2. Participants

At T1, 142 carers of individuals with CdLS who were already known to the research team and had provided consent to be contacted for further research were contacted directly and invited to take part in the questionnaire study. The remaining members of the Cornelia de Lange Syndrome Foundation (UK and Ireland; n= 234) were contacted and invited to take

part in the study via the Foundation. Individuals with CdCS (n= 180) and FXS (n= 762), were contacted via the relevant support groups (the Cri du Chat Syndrome Support group and the Fragile X Society, respectively) and invited to participate. At T1, 211 individuals with FXS returned questionnaires. However, only 193 were analysed because 18 were returned after the deadline for data analysis. In total, 116 individuals with CdLS, 65 individuals with CdCS and 193 individuals with FXS took part in the study.

At T2, participants were invited to take part if they had participated at T1 and consented to be contacted for future research. 385 individuals were invited to take part in the study at T2 (CdLS= 114, CdCS= 63 and FXS= 208). Nine questionnaire packs were undelivered due to address change (CdLS= 3, CdCS= 4 and FXS= 2) and two carers from each syndrome group did not agree to participate in future research. Additionally, one carer of an individual with FXS agreed to participate in future research but did not provide contact details. At T2, 274 carers completed and returned the questionnaire packs (CdLS= 80, CdCS= 46 and FXS= 148). The overall return rate at T2 was 71.1% (CdLS= 70.2%, CdCS= 73.0% and FXS= 70.2%).

To ensure that all groups had comparable data, participants were only included in this study if they had complete data at both time points (T1 and T2). The inclusion criteria also consisted of the following: confirmed diagnosis of the relevant syndrome from an appropriate professional (clinical geneticist, paediatrician, or a GP); no additional chromosomal abnormalities (other than those causing the syndrome); completion of at least 75% of the total questionnaire pack at both T1 and T2; and aged four years or over at T1. Participants were required to be at least four years at T1 because the Social

Communication Questionnaire (SCQ; formerly the Autism Screening Questionnaire; Berument et al, 1999) contains items regarding the participant's behaviour when aged between four and five years. In total, 251 individuals met the inclusion criteria and were included in the study (CdLS= 67, CdCS= 42 and FXS=142).

At T1, participants were aged between 4 and 47 years (mean = 17.31yrs; SD = 9.45), 184 (73.3%) were male and 226 (90%) were mobile. 193 (76.9%) were verbal (more than 30 words/signs in their vocabulary). At T2, participants were aged between 6 and 49 years (mean = 19.83; SD = 9.36), 230 (91.6%) were mobile and 200 (79.7%) were verbal. There were no significant differences between the groups or over time in age (p >.05). Although there were some group differences in the percentage of participants who were verbal and mobile across the groups, this also stayed consistent over time. This does present the possibility of certain behaviours related to characteristics of ASD (such as verbal behaviours) being more likely in a group that is more verbal (such as FXS) and needs to be considered when interpreting any findings. See Table 2.1 for information about participant characteristics at each time point (T1 and T2).

Table 2.1: Mean age, standard deviation and range, percentage of males, percentage and number of participants who were mobile and verbal in each group at each time point (T1 and T2).

Demographics		CdLS	FXS	CDCS	F/X^2	*df*	*p* value	Post Hoc
N		67	142	42				
Time 1								
Age *	M	17.33	17.23	17.65	.01	2	.99	-
	(SD)	(9.22)	(8.84)	(11.75)				
	Range	4-40	6-47	4-44				
Gender	% Male	41.8	100**	33.3	120.01	2	<.001	FXS>CdLS,CdCS
	(n)	(28)	(142)	(14)				
Speech[1]	% Verbal	52.2	89.4	73.8	35.70	2	<.001	FXS>CdCS>CdLS
	(n)	(35)	(127)	(31)				
Mobility[1]	% Mobile	82.1	97.2	76.2	20.17	2	<.001	FXS>CdCS,CdLS
	(n)	(55)	(138)	(32)				
Time 2								
Age *	M	20.08	19.63	19.89	.09	2	.92	-
	(SD)	(9.25)	(8.60)	(11.79)				
	Range	6-43	9-49	6-47				
Speech[1]	% Verbal	53.7	92.3	78.6	41.76	2	<.001	FXS>CdCS>CdLS
	(n)	(36)	(131)	(33)				
Mobility[1]	% Mobile	86.6	97.9	78.6	18.83	2	<.001	FXS>CdLS,CdCS
	(n)	(58)	(139)	(33)				

* In years
** Only male participants with Fragile X syndrome were recruited
[1] data derived from the demographic questionnaire

2.2.3. Measures

The questionnaire pack included multiple informant based questionnaire measures which are all appropriate for children and adults with intellectual disabilities. For the purpose of this study, the following questionnaires were completed: A demographic questionnaire, the RBQ (Moss & Oliver, 2008) and the SCQ (Rutter et al., 2003).

2.2.3.1. Demographic Questionnaire (Appendix 1)

The Demographic Questionnaire was used to obtain information regarding each participant's age, gender and diagnostic status. Specific questions in the Demographic Questionnaire address whether a formal diagnosis had been made and by whom in order to make sure the participant met inclusion criteria.

2.2.3.2. The Social Communication Questionnaire (SCQ; Rutter, Bailey, Lord & Berument, 2003; Appendix 2)

Chapter One (see section 1.4.1) described the SCQ and reviewed the psychometric properties of the measure. As a reminder, the SCQ is based on the Autism Diagnostic Interview-Revised (ADI-R), is comprised of 40 items completed by the main carer and takes minimal time to complete (less than 10 minutes). The items are grouped into three subscales: communication, social interaction and repetitive or stereotyped behaviours. All questions are yes-or-no with a score of one for 'Yes' (or the presence of abnormal behaviour) and a score of zero for 'No'. In addition, all scores are summed to provide a total score between 0-39 (one question on the current language level is not included in the total score). According to the authors, the higher the score, the more autistic characteristics are present. Importantly, the SCQ is reported to be accurate at discriminating between autism spectrum disorders and other conditions including individuals with intellectual disabilities. The authors suggest a cut-off score of 15 or above to screen for ASDs and a higher cut-off of 22 is used to screen for autism.

2.2.3.3. The Repetitive Behaviour Questionnaire (RBQ; Moss & Oliver 2008; Appendix 3)

The RBQ examines the presence and frequency of repetitive behaviours including stereotyped and compulsive behaviours, repetitive use of language, restricted preferences and insistence on sameness. It is used for children and adults with a range of intellectual disability. Informants use a five-point Likert scale to rate the frequency of each behaviour over the preceding month. The scale ranges from 'never' to 'more than once a day'. Moss et al., (2009) examined the psychometric properties of the RBQ and found good inter-rater reliability (range .46-.80) and test-retest reliability at item-level (range .61-.93).

2.2.4. Data analysis

The distribution of the SCQ and RBQ data was tested for normality using Kolmogorov-Smirnov tests. The data were *not* normally distributed at subscale score level ($p < .05$). Therefore, non-parametric techniques were employed throughout the analysis. For the sake of conciseness, only significant findings are reported with statistics. All non-significant statistics can be found in the appendices.

Data analysis was divided into several stages. All stages looked for differences in repetitive behaviours and ASD symptomatology (SCQ and RBQ scores). All stages (beyond testing for distribution) used an alpha level of $p < .02$, which is still conservative (as it is less than the standard $p < .05$) but not overly so. Stage one involved comparing ASD phenomenology between syndrome groups. The percentages of individuals meeting the cut-off scores for ASD and autism on the SCQ for each syndrome group were calculated. Each set of analyses were repeated for both of the cut-off categories (ASD and

autism). Chi-Square analyses were employed to examine the differences in percentages between syndrome groups (CdLS, CdCS and FXS) and age (under 15 and over 15). McNemar analyses were employed to examine the differences in percentages within syndrome groups over time (T1 to T2). This was used to look at absence (not meeting cut-off at either time), remission (meeting cut-off at T1 but not at T2), incidence (not meeting cut-off at T1 but meeting it at T2), and persistence (meeting cut-off at both T1 and T2). In addition, stage one looked at how scores on the SCQ and RBQ differed between the syndrome groups (CdLS, CdCS and FXS) as a whole at T1. Stage two evaluated the effect of age on ASD phenomenology. For this part of the analysis, participants in each syndrome group were subdivided into two groups according to their age. Participants within that syndrome at or below 15 years created a group (<=15) and those over 15 years created another (>15). These age bands were chosen because they allowed for the most equal distribution of participants across the smaller groups. At T1, 137 (54.6%) participants were at or below 15 years. Of those 137, there were 35 participants with CdLS (52.2%), 23 with CdCS (54.8%) and 79 with FXS (55.6%). Additionally, there were 114 (45.4%) participants over 15 years of age. Of those, there were 32 participants with CdLS (47.8%), 19 with CdCS (45.2%) and 63 with FXS (44.4%). To examine the interaction between group and age, two sets of analyses were employed. Kruskal-Wallis tests were used to identify any between syndrome group's differences on the SCQ and RBQ within the stated age bands. Any significant differences were followed up with pair-wise Mann-Whitney to identify the source of the difference. Within syndrome group analysis comparing <=15s and >15s was carried out using Mann Whitney U tests. The analyses were conducted only for T1 because some of the participants would have changed age groups by T2. Stage three evaluated the effect of time on ASD phenomenology. This

comparison looked for differences between T1 and T2 within syndrome groups in order to examine whether SCQ and RBQ scores had changed significantly between T1 and T2. Wilcoxon-signed rank tests were employed for this analysis.

At each stage, a more fine-grained analysis was employed to examine the differences in the RBQ scores at the item-level. Based on the findings from Moss et al. (2009), the items that were significantly different in the FXS, CdLS or CdCS groups from two or more other syndrome groups in that study were evaluated further. These items included: hand stereotypy, tidying, attachment to objects, repetitive phrase, restricted conversation, echolalia, preference for routine and lining up objects (questions 3, 5, 10, 11, 13, 14, 15 and 16). Kruskal-Wallis with pair-wise Mann-Whitney tests was employed for analysis of these items between syndrome groups at T1 and T2. Mann-Whitney analyses were employed to test for differences on the items between age groups (<=15 and >15) within syndrome groups. In order to examine whether RBQ item-level scores changed significantly between T1 and T2 within each syndrome group, Wilcoxon-signed rank tests were employed for this analysis.

2.3. Results

2.3.1. Comparison of ASD phenomenology between syndrome groups

In order to assess differences in the prevalence of ASD phenomenology between syndrome groups, Chi-square tests were used. Table 2.2 shows the results of the Chi-square analysis between syndrome groups.

Table 2.2: Percentage of individuals who scored above the cut-off for autism (AU) and ASD on the SCQ at T1 and T2.

	CdLS %	FXS %	CdCS %	x^2	*df*	*p value*	Post Hoc
T1- AU cut-off	45.8	45.8	8.1	18.38	2	<.001	CdLS, FXS > CdCS
T1- ASD cut-off	79.7	85.5	37.8	36.67	2	<.001	CdLS, FXS > CdCS
T2- AU cut-off	43.1	45.3	10.5	15.53	2	<.001	CdLS, FXS > CdCS
T2- ASD cut-off	74.1	83.6	44.7	23.33	2	<.001	CdLS, FXS > CdCS

The data in Table 2.2 and the results of the analysis show that the FXS and CdLS groups had a significantly higher percentage of individuals meeting the cut-offs for both AU and ASD than the CdCS group at both T1 and T2.

In order to assess differences in the severity of ASD phenomenology, the main effect of *syndrome group* was examined using Kruskal-Wallis tests to compare SCQ and RBQ scores between the three syndrome groups. Any significant differences identified were further examined with pair wise Mann-Whitney tests to identify the source of the difference.

The results of the SCQ analysis (see Appendix 8, Table 1) show that at T1 there was a significant difference between groups on the *repetitive behaviour* subscale (X^2 (2, N = 250) = 20.67, p <.001) the *communication* subscale (X^2 (2, N = 250) = 32.66, p <.001) and *social interaction* subscales (X^2 (2, N = 250) = 31.88, p <.001). Post hoc tests showed that the FXS group scored significantly higher than the CdLS and CdCS groups on *repetitive behaviour*. Also, the FXS and CdLS groups scored significantly higher than the CdCS group on *communication* and *social interaction.*

The results of the RBQ analysis (see Appendix 8) show that at T1, there was a significant difference between groups on *insistence of sameness* (X^2 (2, N = 250) = 29.49, p <.001), *repetitive use of language* (X^2 (2, N = 250) = 30.27, p <.001), *compulsive behaviour* (X^2 (2, N = 250) = 11.61, p = .003) and total score (X^2 (2, N = 250) = 31.97, p <.001). Post hoc tests showed the FXS group scored significantly higher than CdCS and CdLS groups on *insistence on sameness*, *repetitive use of language* and total score. The FXS group also scored significantly higher than CdCS on *compulsive behaviour*. There were no significant differences on the *stereotyped behaviour* or *restricted preference* subscales. T2 shows a similar pattern with the only change being that the CdLS group no longer scored significantly lower than the FXS group on *repetitive use of language*.

In order to further assess differences in the frequency of repetitive behaviours on a fine-grained level, the same tests were used in the same way to compare RBQ item-level scores (questions 3, 5, 10, 11, 13, 14, 15 and 16) between the three syndrome groups. The results of the RBQ item-level analysis (see Appendix 8) show that at T1 there were significant differences between the syndrome groups on *restricted conversation* (X^2 (2, N = 191) = 31.03, p <.001), *echolalia* (X^2 (2, N = 192) = 25.17, p <.001), *preference for routine* (X^2 (2, N = 249) = 36.60, p <.001), *lining up objects* (X^2 (2, N = 251) = 14.48, p =.001), *repetitive phrase*, (X^2 (2, N = 250) = 22.25, p <.001), *hand stereotypy* (X^2 (2, N = 250) = 16.94, p <.001) and *attachment to objects* (X^2 (2, N = 250) = 10.67, p =.005). Post hoc tests showed the FXS group scored significantly higher than the CdLS and CdCS groups on *restricted conversation*, *echolalia*, *preference for routine* and *lining up objects*. The FXS group also scored significantly higher than the CdLS group on *repetitive phrase* and the CdCS group on *hand stereotypy*. The CdCS group scored significantly higher than the FXS group on

attachment to objects. The results of the RBQ item-level analysis also show that at T2 there were significant differences between the syndrome groups on *restricted conversation* (X^2 (2, N = 250) = 53.12, p <.001), *echolalia* (X^2 (2, N = 249) = 37.41, p <.001), *preference for routine* (X^2 (2, N = 249) = 30.12, p <.001), *tidying* (X^2 (2, N = 251) = 11.19, p =.003), *repetitive phrase* (X^2 (2, N = 250) = 13.25, p =.001) and *attachment to objects* (X^2 (2, N = 250) = 10.69, p =.005). Post hoc tests showed the FXS group scored significantly higher than the CdLS and CdCS groups on *restricted conversation*, *echolalia* and *preference for routine*. The FXS and CdLS groups scored significantly higher than the CdCS group on *tidying*. The FXS group also scored significantly higher than the CdLS group on *repetitive phrase*. The CdCS group scored significantly higher than the FXS group on *attachment to objects*.

In summary these analyses show that the FXS and CdLS groups had a significantly higher percentage of individuals meeting the cut-offs for both autism and ASD at both T1 and T2. The FXS group scored significantly higher than the CdCS group on *reciprocal social interactions* and both groups on *restricted, repetitive and stereotyped behaviour*. It is also notable that the CdLS group scored significantly higher than the CdCS group on *reciprocal social interactions* and on *communication*. T2 shows a similar pattern with a shift in only the *restricted, repetitive and stereotyped behaviour* where the FXS group scored significantly higher than only the CdCS group.

2.3.2. The effect of age on ASD phenomenology

In order to assess differences in the prevalence of ASD phenomenology between age bands (<=15 versus >15), Chi-square tests were used to compare percentage of individuals

within each syndrome group who scored above the cut-offs on the SCQ. Table 2.3 shows the results of the Chi-square analysis between age bands.

Table 2.3: Percentage of individuals within the age bands (Under=15 and Over15) who scored above the cut-off for autism (AU) and ASD on the SCQ.

	Under/= 15 % (n)	Over 15 % (n)	x^2	*df*	*p* value <.02	Post Hoc
T1- AU cut-off						
CdLS	35.5 (31)	57.1 (28)	2.78	1	.095	
FXS	49.4 (77)	40.7 (54)	.948	1	.330	
CdCS	5.0 (20)	11.8 (17)	.564	1	.452	
T1- ASD cut-off						
CdLS	67.7	92.9	5.73	1	.017	O15 > U15
FXS	87.0	83.3	.347	1	.556	
CdCS	35.0	41.2	.149	1	.699	

The data in Table 2.3 and the results of the analysis show that at T1, a greater percentage of individuals >15 with CdLS met the cut-off for ASD than those <=15 (p = .017).

In order to asses any differences in the levels of ASD phenomenology with age, the *effect of age between groups* was examined using Kruskal-Wallis tests to compare SCQ and RBQ scores between syndrome groups within the <=15s and >15s age bands at T1. Any significant differences identified were examined with pair wise Mann-Whitney tests to identify the source of the difference. Figures 2.1 - 2.3 show the results of the Kruskal-Wallis and Mann-Whitney analyses (see Appendix 8, Table 6) between syndrome groups at T1 on the SCQ.

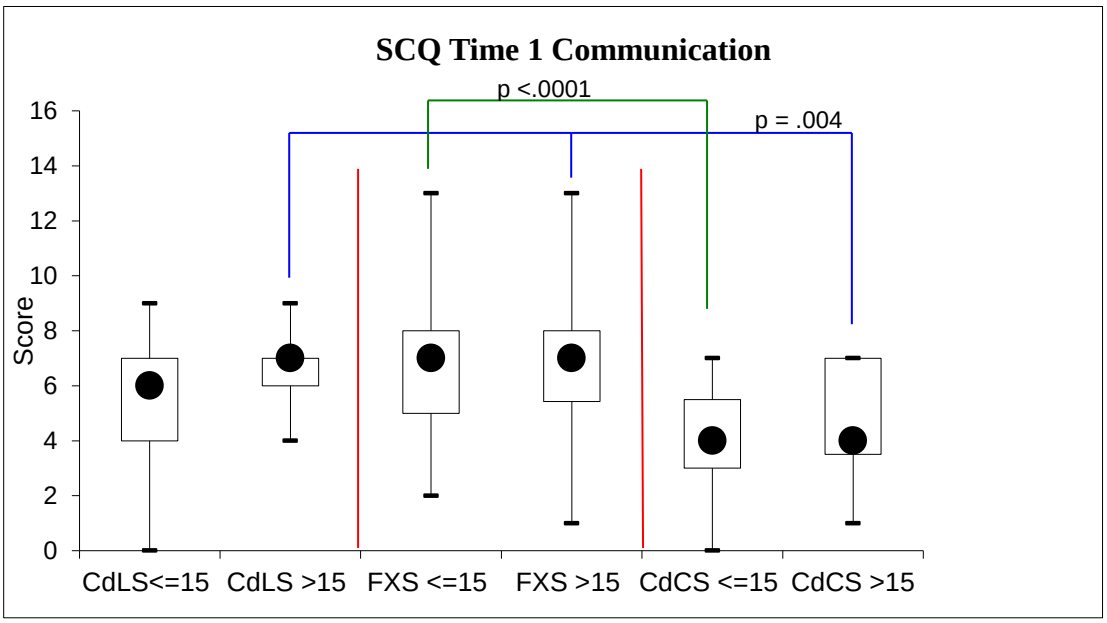


Figure 2.1: Median scores at T1 on the Communication subscale of the SCQ by syndrome group (CdLS, FXS and CdCS) and age group (<=15 and >15).

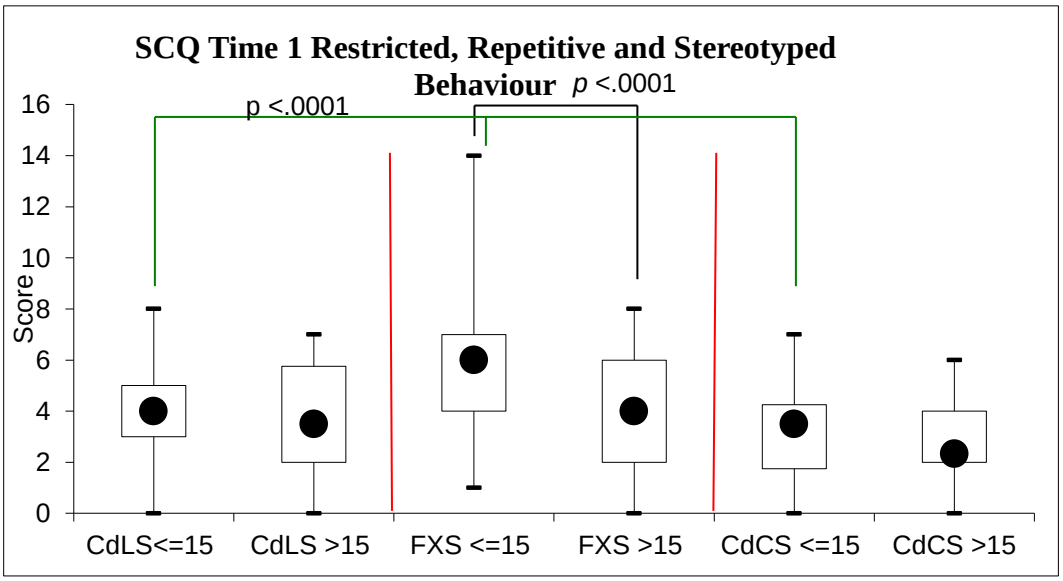


Figure 2.2: Median scores at T1 on the Restricted, Repetitive and Stereotyped Behaviour subscale of the SCQ by syndrome group (CdLS, FXS and CdCS) and age group (<=15 and >15).

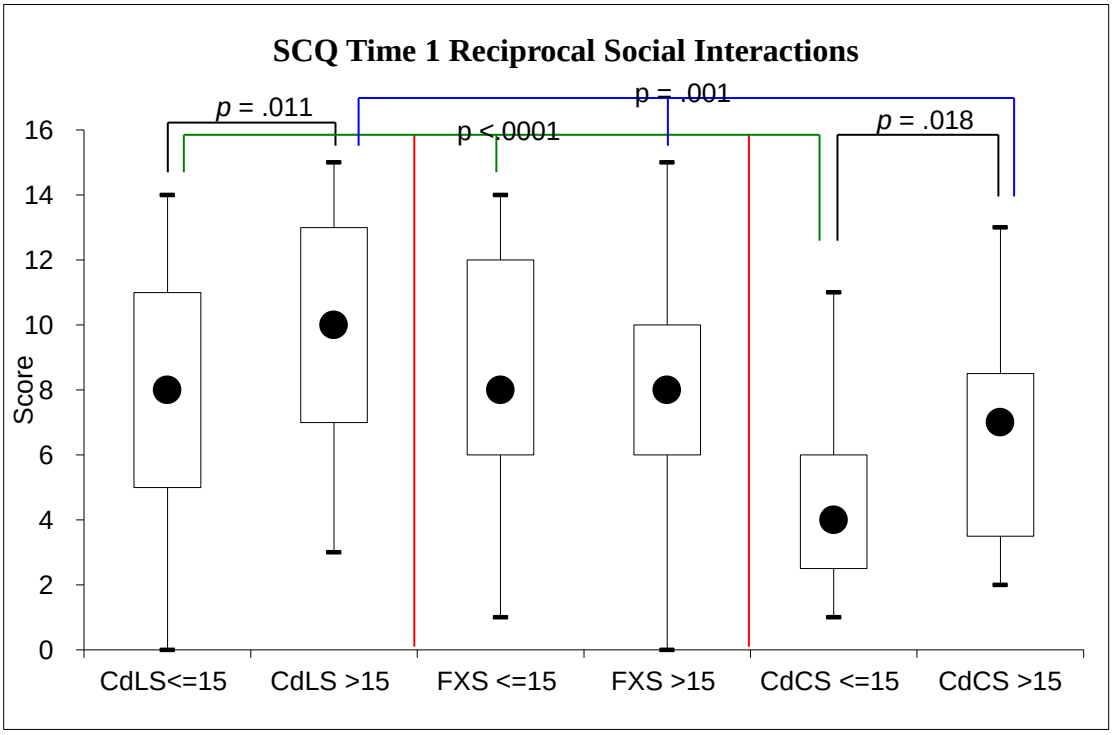


Figure 2.3: Median scores at T1 on the Reciprocal Social Interactions subscale of the SCQ by syndrome group (CdLS, FXS and CdCS) and age group (<=15 and >15).

The data in Figures 2.1 – 2.3 and the results of the SCQ analysis (Appendix 8, Table 4) shows that there was a significant between groups difference within the individual age bands. In the <=15s band there was a significant syndrome group difference on the *communication* subscale (X^2 (2, N = 136) = 23.52, p <.001), the *restricted, repetitive and stereotyped behaviour* subscale (X^2 (2, N = 136) = 22.41, p <.001) and the *social interaction* subscale (X^2 (2, N = 136) = 28.10, p <.001). Post hoc tests showed that the FXS <=15 group scored significantly higher than the CdCS <=15 group on the *communication* subscale. Individuals in the FXS <=15 group scored significantly higher than both the CdCS <=15s and CdLS <=15s on the *restricted, repetitive and stereotyped behaviour* subscale. On the *social interaction* subscale, the FXS <=15s and CdLS <=15s groups scored significantly higher than the CdCS <=15s. In the >15 groups, there was a significant syndrome group difference on the *communication* subscale (X^2 (2, N = 114) =

11.10, p = .004) and the *social interaction* subscale (X^2 (2, N = 136) = 13.51, p =.001). Post hoc tests showed that FXS >15s and CdLS >15s group scored significantly higher than CdCS >15s on the *communication* and *social interaction* subscales. There were no significant syndrome group differences on the *restricted, repetitive and stereotyped behaviour* subscale in >15s.

The results of the RBQ analysis (see Appendix 8, Table 5) showed a significant between syndrome groups difference in the <=15s on the *insistence on sameness* subscale (X^2 (2, N = 136) = 18.27, p <.001), the *repetitive use of language* subscale (X^2 (2, N = 136) = 24.36, p <.001) and the total score (X^2 (2, N = 136) = 29.56, p <.001). Post hoc tests showed that the <=15s FXS group scored significantly higher than the CdCS and CdLS <=15s groups on *insistence on sameness, repetitive use of language* and total score. In the >15s, there was a significant difference on the *insistence on sameness* subscale (X^2 (2, N = 114) = 14.94, p =.001). The >15s in the FXS group scored higher than the CdCS >15s group on the *insistence on sameness* subscale.

To examine the effect of *age within syndrome groups,* Mann-Whitney tests were used to compare SCQ and RBQ scores between older (>15) and younger (<=15) individuals within each syndrome at T1. In order to further assess differences in the frequency of repetitive behaviours with finer granularity, the same tests were used in the same way to compare RBQ item-level scores (questions 3, 5, 10, 11, 13, 14, 15 and 16). Figures 2.1-2.3 and Appendix 8 (Tables 5 & 6) show the results of the Mann-Whitney analyses within syndrome groups between age groups (<=15 and >15).

The data in figures 2.1 – 2.3 and the results of the SCQ analysis (Appendix 8, Table 6) show that at T1 there was a significant difference within syndrome group by age for CdLS and CdCS on the *social interaction* domain, U = -2.55, p = .011, U = -2.37, p = .018, and FXS on the *repetitive behaviour* domain, U = -3.79, p < .001. Post hoc tests showed the >15s in the CdLS group scored significantly higher on the *social interaction* domain, than <=15s with CdLS. The >15s in the CdCS group scored significantly higher on the *social interaction* domain compared to <=15s with CdCS. The <=15s in the FXS group scored significantly higher on the *repetitive behaviour* domain compared to >15s with FXS.

The RBQ analyses (see Appendix 8, Table 7) show that there was a significant difference within syndromes by age on the *stereotyped behaviour* subscale, U = -3.42, p = .011 and at the item-level on *hand stereotypy*, U = -4.39, p < .001. The <=15s in the FXS group scored significantly higher than >15s with FXS on *stereotyped behaviour*. The results of the RBQ item-level analysis show <=15s with FXS show significantly more frequent *hand stereotypy* than >15s with FXS.

In summary these analyses show that at T1 older (>15s) individuals with CdLS were more likely to meet the cut-off for ASD than younger (<=15s) individuals with CdLS. Similarly, older individuals with CdLS were found to show greater severity of social impairments compared to younger individuals with the syndrome. The CdCS group was found to have this same pattern. However, in the FXS group repetitive behaviours were found to become less prominent with age.

2.3.3. The effect of time on ASD phenomenology

In order to assess differences in the persistence of ASD phenomenology with time analyses were conducted in order to evaluate change in the percentage of participants within each syndrome who met the cut-offs (AU and ASD) on the SCQ at T1 compared to T2. McNemar tests were employed to evaluate the change in cut-off scores over time. The McNemar tests evaluated change in meeting the cut-offs (Yes or No) at T1 versus T2. Change would include meeting the cut-off at T1 but not T2 (Yes at T1 and No at T2) or the reverse (No at T1 and Yes at T2). Table 2.4 shows the results of the McNemar analysis of meeting cut-offs at T1 verses T2 within syndrome groups and presents a breakdown of the percentage of participants in each syndrome group meeting cut-offs at each time point. For example, 51.7% of CdLS participants were classified as 'Absent' and 3.4% as ‘Incidence’ for the autism cut-off. 'Absence' refers to participants who scored below the cut-off at Time 1 and also at Time 2. 'Incidence' refers to participants who scored below the cut-off at Time 1 but scored above the cut off at Time 2. 'Remission' refers to participants who scored above the cut-off at Time 1 but no longer met the cut-off at Time 2. 'Persistence' refers to participants who scored above the cut-off at both time points.

Table 2.4: Percentage and number of participants, broken down by syndrome group, meeting the cut-offs for AU and ASD on the SCQ and analysis examining the persistence of meeting cut-off between T1 and T2.

SCQ Cut-off	Absent (Below at T1, Below at T2)	Incidence (Below at T1, above at T2)	Remission (Above at T1, Below at T2)	Persistent (Above at T1, Above at T2)	*P* (2 tailed)
AU Cut-off					
CdLS	51.7 (30)	3.4 (2)	5.2 (3)	39.7 (23)	1.00
FXS	45.3 (58)	7.8 (10)	9.4 (12)	37.5 (48)	.83
CdCS	86.5 (32)	5.4 (2)	2.7 (1)	5.4 (2)	1.00
ASD Cut-off					
CdLS	19.0 (11)	1.7 (1)	6.9 (4)	72.4 (42)	.38
FXS	9.4 (12)	5.5 (7)	7.0 (9)	78.1 (100)	.80
CdCS	54.1 (20)	8.1 (3)	2.7 (1)	35.1 (13)	.63

The results presented in Table 2.4 reveal there were no significant differences in the change of meeting cut-offs for ASD or autism from T1 to T2 in any of the syndrome groups. This suggests that the percentage of participants meeting the cut-offs is persistent and stable over time in all three syndrome groups.

In order to assess any differences in the severity of ASD with time, analyses were conducted in order to examine whether SCQ and RBQ scores changed significantly between T1 and T2 within each syndrome group. To evaluate the effect of *time*, Wilcoxon Signed Ranks tests were used. In order to further assess differences in the frequency of repetitive behaviours on a fine-grained level the same tests were used in the same way to compare RBQ item-level scores (questions 3, 5, 10, 11, 13, 14, 15 and 16). Figures 2.4 – 2.6 and Appendix 8 (Table 9) show the results of the SCQ Wilcoxon Signed Ranks analyses within syndrome groups and between T1 and T2. Appendix 8 (Table 10) shows the results of the RBQ Wilcoxon Signed Ranks analyses within syndrome groups and between T1 and T2.

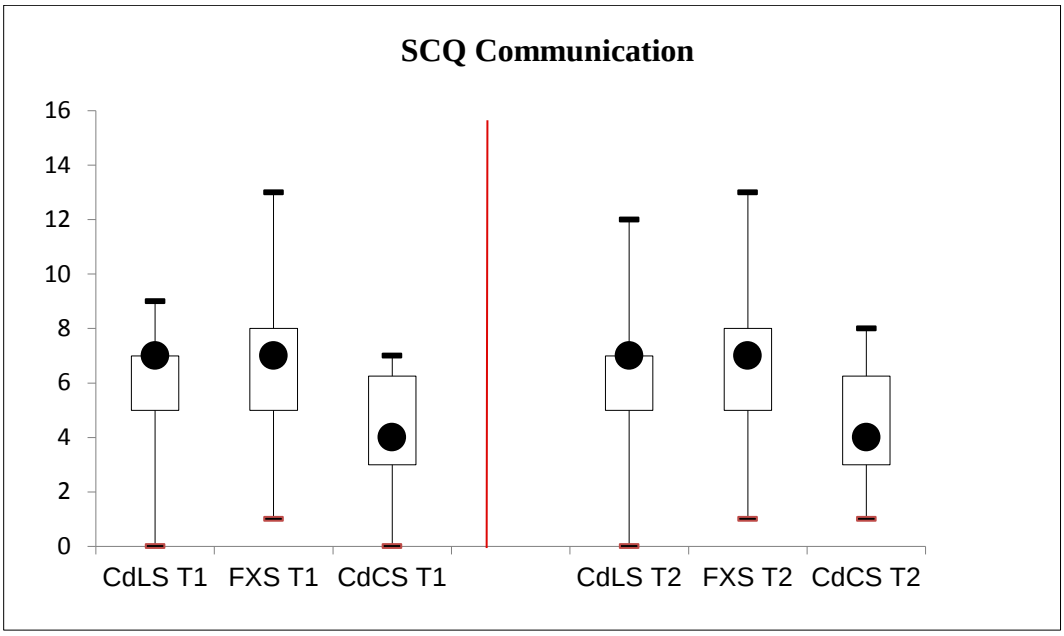


Figure 2.4: Scores at T1 on the Communication subscale of the SCQ by syndrome group.

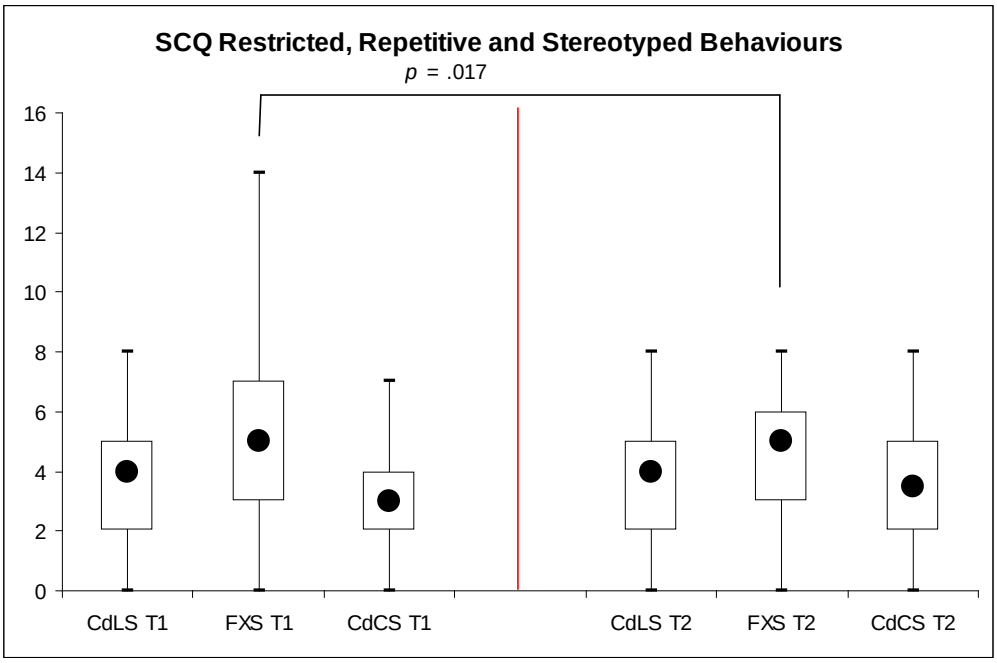


Figure 2.5: Scores at T1 and T2 on the Restricted, Repetitive and Stereotyped Behaviour subscale of the SCQ by syndrome group.

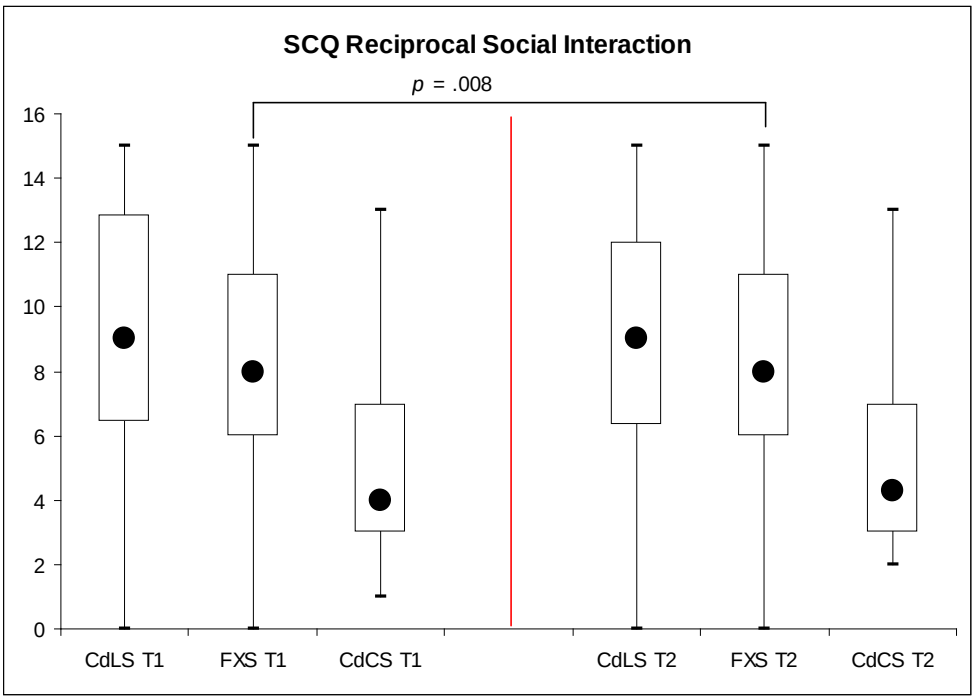


Figure 2.6: Scores at T1 and T2 on the Reciprocal Social Interactions subscale of the SCQ by syndrome group.

The data in Figures 2.4, 2.5 and 2.6 and the results of the analysis (see Appendix 8) show that there were no significant differences between SCQ and RBQ scores at T1 and T2 in

the CdCS and CdLS groups. There was a significant difference identified for the FXS group on the *repetitive behaviour* (z = -2.38, p = .017) and *social interaction* (z = -2.64, p = .008) subscales of the SCQ. The FXS group showed significantly lower scores on *repetitive behaviour* and *social interaction* subscales of the SCQ at T2. The results of the RBQ item-level analysis show no significant differences between T1 and T2 in any of the syndrome groups.

In summary, these analyses reveal that although individuals with CdCS and CdLS are not showing significant differences in SCQ scores over the follow-up period, those with FXS are showing significantly fewer restricted, repetitive and stereotyped behaviours and social interaction impairments at T2 compared to T1.

2.4. Discussion

2.4.1. Overview

In this study, the primary aim was to evaluate the course of ASD phenomenology with age and time in CdLS. Two appropriate contrast groups were selected based on reported similarities within the literature to CdLS with regard to degree of intellectual disability and communication skills (CdCS) and severity and nature of ASD symptomatology (FXS). A standardised ASD screening measure (the SCQ) and the RBQ questionnaire were used to evaluate ASD symptomatology. We hypothesised that: 1. Individuals with CdLS and FXS will show a heightened prevalence for ASD characteristics compared to the CdCS group. 2. Older individuals with CdLS will be more likely to meet criteria for ASD and show more severe ASD compared to younger individuals with the syndrome. 3. Individuals with CdLS will show an increased severity and frequency of autism spectrum phenomenology

over time. A secondary aim was to explore the differences in ASD phenomenology and repetitive behaviours between and within the CdLS, FXS and CdCS groups across age bands and time. This is the first study to look at ASD phenomenology in these three syndromes in this way.

2.4.2. Primary Aims

In accordance with our first prediction, the CdLS and FXS groups were significantly more likely than the CdCS group to meet the SCQ cut-offs for autism and ASD at both T1 and T2. At both time points, the CdLS and FXS groups showed greater severity of ASD related behaviours than the CdCS group in the *communication* and *reciprocal social interaction* domains while the FXS group showed the highest frequency of repetitive behaviours compared to both groups. These findings are consistent with previous reports of a heightened prevalence of ASD phenomenology in CdLS compared to CdCS (Moss et al., 2008) and broad similarities with regard to severity of ASD characteristics in CdLS and FXS (Oliver et al., 2011; Moss et al., 2013). The increased weighing of repetitive behaviours within the profile of ASD characteristics in FXS has also been reported previously (Moss et al., 2013).

The results also supported our second prediction that older individuals with CdLS would show an increased prevalence and severity of ASD characteristics than younger individuals with the syndrome. Analysis confirmed that individuals over the age of fifteen years with CdLS were significantly more likely to meet the SCQ cut-off score for ASD relative to those fifteen or younger. In FXS and CdCS, the proportion of individuals meeting SCQ cut-off scores for autism and ASD remained stable across these age bands.

Older individuals with CdLS were also significantly more likely to achieve a higher score on the *social interaction* domain of the SCQ compared to younger individuals. This indicates increased severity of social impairments with age in CdLS. This change in *social interaction* scores was also identified in the CdCS group suggesting that this might, in part, be accounted for by a degree of intellectual disability. However, the findings are consistent with previous studies that have reported increased social isolation in older children with CdLS (Sarimski, 1997), broader changes in behaviour, mood and anxiety (Berney, Ireland & Burn, 1999; Nelson et al., 2014; Oliver et al., 2011) and physical changes described by Kline et al. (2007) as individuals with CdLS age. Further research is required to better understand the nature and aetiology of this change. Some researchers have speculated that it may be related to biological effects that occur downstream from the genetic mutations responsible for CdLS (Gimigliano et al., 2012; Kline et al, 2007).

Despite broad stability in the proportion of individuals with FXS meeting SCQ cut-off scores, younger individuals with FXS scored significantly higher than older individuals on the *repetitive behaviour* domain of the SCQ. Furthermore, there was a significant decrease on the *repetitive behaviour* and *social interaction* domains between T1 and T2. Stability of diagnostic classification of ASD in FXS has been reported in previous studies (Hatton et al., 2006; Hernandez et al., 2009; Sabaratnam et al., 2003). However, the apparent improvement in repetitive behaviours is in direct contrast to the findings from Sabaratnam et al. (2003) who described an increased preference for routine over a ten-year period. These discrepancies might be accounted for by differences in the follow-up length between these two studies or the level of specificity regarding repetitive behaviours.

Further research is required in order to better understand the trajectory of ASD characteristics in FXS.

Our final prediction regarding change over time was not supported. There were no significant differences in the proportion of individuals with CdLS meeting ASD and autism SCQ cut-off scores at T1 and T2 and no significant differences between T1 and T2 with regard to the severity of SCQ domain scores in this group. The significant age band differences identified in this study, alongside previous reports of age related changes in CdLS suggest that the follow-up length in this study may not have been sufficient to detect changes over time in this group. Alternatively, it is possible that the age related changes identified in this study could be accounted for by a cohort effect. However, the consistency of these findings with previous reports within the CdLS literature suggests that this is unlikely to fully account for the observed changes. It would be beneficial for future research to include a wide enough age range (further into adulthood) to look at the effect of age in more detail and also increase the length of the follow-up.

2.4.3. Secondary Aim

In support of the secondary aim to examine repetitive behaviours within and between CdLS, FXS and CdCS, the RBQ items were analysed. The CdLS and CdCS groups exhibited significantly less frequent behaviours than the FXS group at T1 on the subscales *insistence on sameness, repetitive use of language* and total score. There is a possibility that these group differences could be accounted for by the significantly increased proportion of verbal participants with FXS. However at follow-up (T2), unlike the CdCS group, the CdLS group no longer scored significantly lower than the FXS group on the *repetitive use of language* subscale which suggests that this result was due to something

other than the amount of verbal participants in the FXS group, otherwise it would have stayed consistent at T2. The FXS group also scored significantly higher than CdCS on the *compulsive behaviour* subscale. When examining the age bands, the CdLS and CdCS participants over the age of fifteen years scored significantly lower than the FXS group again on *insistence on sameness, repetitive use of language* and total score. In the groups with younger individuals (fifteen years and under), the FXS group scored significantly higher than the CdCS group on the *insistence on sameness* subscale. The results of the analysis evaluating the effect of time showed that there were no significant differences on the RBQ between T1 and T2 in any of the syndrome groups. As suggested earlier, this could be due to the insufficient length of the follow-up period. It is possible if the follow-up period was longer, such as the 10-year period in the Sabaratnam (2003) study, the findings may have been different.

Based on the findings from Moss, Oliver, et al., (2009), a more fine-grained analysis of the differences in the RBQ scores at the item-level was also employed. The results from the analysis show that at T1 the CdLS and CdCS groups scored significantly lower than the FXS group on *restricted conversation, echolalia, preference for routine* and *lining up objects* on the RBQ. The CdLS group also scored significantly lower than the FXS group on *repetitive phrases* at both time points. As the FXS group had more verbal participants these findings need to be taken with caution as *restricted conversation* and *echolalia* both involve expressive language. The CdCS group scored significantly lower than the FXS group on *hand stereotypy*. At both time points the CdCS group showed a significantly higher level of attachment to objects than the FXS group. This pattern is consistent with the findings from Moss, Oliver, et al., (2009). At T2 the only differences in the results on

these items were on the *restricted, repetitive and stereotyped behaviour* scale where the FXS group scored significantly higher than only the CdCS group. Also at T2 the FXS and CdLS groups scored significantly higher than the CdCS group on *tidying*. The results of the RBQ item-level analysis addressing the effect of age on repetitive behaviours within syndromes show that over fifteen year olds with FXS engage in significantly more frequent hand stereotypy than those aged fifteen and under. There were no other significant differences within the syndrome groups and between age bands. Similarly, there were no significant differences at the item-level analysis within syndrome group from T1 to T2.

2.4.4. Limitations and future directions

The sample size and the short length of the follow-up potentially limited this study. While the size of the study samples were very good given the rarity of the syndromes (particularly CdLS and CdCS) they were somewhat uneven, with a large number of FXS participants (142) and a much smaller number of CdLS (67) and CdCS (42) participants. Comparing groups with very different sample sizes may have an impact on statistical power and thus the potential to identify significant group differences. However, the statistical software used for these analyses (SPSS) takes uneven sample size into account when running the statistics. It uses the smallest sample size to determine the power (Grace-Martin, 2008). Looking at the effect of time was also limited in this study as three years might not have been sufficient time to see an effect. The follow-up time was sufficient to see some changes but further research with a longer time period would reveal whether additional changes are seen. A longer follow-up would also allow analyses of change over time at different ages. It would be beneficial for future research to include a

wide enough age range (including further into adulthood) to look at the effects of age in more detail and also increase the length of follow-up. Ideally, future research would also ensure a genetic confirmation of diagnosis. This was not possible in this study as the method of questionnaire survey and limited availability of participants with rare genetic syndromes were added challenges. However, not having a genetic confirmation of diagnosis does add the risk that milder cases of CdLS could be misdiagnosed or not included in the study. In addition, the different genetic causes of CdLS may present with different profiles of ASD symptomatology. This study was able to use a more robust measure than some of the previous studies (SCQ), however, the SCQ is a screening measure and not a diagnostic tool. Moving forward, it is important to include an observational measure of autism, such as the Autism Diagnostic Observation Schedule (ADOS, Lord, et al., 2000). As an observation based, interactive assessment it can offer much more insight into the overall picture than the previously used questionnaire and interview methods. This would also allow for consideration of the syndrome group with and without ASD as done by Hernandez et al., (2009).

2.4.5. Summary

In summary, consistent with previous findings, individuals with CdLS demonstrated a heightened prevalence for ASD relative to individuals with CdCS. The severity of these characteristics was similar to that observed in individuals with FXS, although the profile of impairments were slightly different, with repetitive behaviour being a more prominent feature in FXS. Despite the broad similarities in CdLS and FXS, the presentation of ASD characteristics in these two groups showed different trajectories. In FXS, the proportion of individuals meeting SCQ cut-off scores was stable, although repetitive behaviour scores

showed a significant decline with age and over time indicating improvements in this domain. In CdLS, social interaction skills were reported to be more impaired in older individuals compared to younger and this contributed to a greater proportion of older individuals meeting SCQ cut-off scores for ASD than the younger individuals within the syndrome. Although there was no significant effect of time in this group, this may be accounted for by the relatively short follow-up period. Further studies, evaluating ASD characteristics over a longer period of time are required to fully understand the changes. If prevalence of ASD is, indeed, increasing with age in CdLS, this could have important implications for planning support services and advice given to families about what to expect in the future. O'Brien (2006), Howlin, Wing, and Gould (1995); and Moss and Howlin (2009) all stress the importance of this type of information to help families gain vital early intervention services, especially in education settings.

CHAPTER THREE

Autism Spectrum Disorder Phenomenology over time in Cornelia de Lange and Cri du Chat Syndromes

3.1. Introduction

The study in the previous chapter utilised informant questionnaires to investigate and reveal changes in autism spectrum disorder (ASD) phenomenology in Cornelia de Lange Syndrome (CdLS) over time and with age. These changes highlight the importance of further investigation with more robust measures including observational measures of ASD and level of intellectual disability (ID) over a longer time period. This chapter will further investigate the profile of ASD phenomenology, as well as changes in the prevalence of autism and ASD in Cornelia de Lange syndrome at a single point in time and longitudinally, at a broad domain and total score level, compared to an appropriate contrast group and using psychometrically robust informant and observational measures.

3.1.1. Background

There has been much discussion in literature over the last few years about ASD phenomenology in genetic syndromes. Moss and Howlin (2009) looked at the implications of diagnosis of ASD in several genetic syndromes (FXS, Rett (RS), TSC, DS, AS, CHARGE and Phenylketonia). They found "subtle but qualitative differences in the presence of ASD-like phenomenology in particular syndromes" (Moss & Howlin, 2009). Each syndrome may present with a unique profile and prevalence of ASD characteristics. Moss et al. (2013) evaluated ASD characteristics and social behaviour in AS, CdLS and Cri du Chat (CdCS) syndromes. They found higher levels of ASD characteristics in AS and CdLS than in CdCS. More specifically, social motivation, social communication and enjoyment were much lower in CdLS. The behavioural phenotype of CdLS (see Chapter One, section 1.2. for a full description of this syndrome) is interesting in that elevated levels of ASD symptomatology and a high prevalence of ASD are accompanied by a profile of ASD-related characteristics which differs from that of idiopathic autism (Moss, Howlin, Magiati, & Oliver, 2012). However, the possible development over time in ASD symptomatology in CdLS has not been extensively investigated.

3.1.2. Change over time and with age in genetic syndromes

It is increasingly recognised that the behavioural phenotypes of genetic neurodevelopmental syndromes are not static over time. For instance, Adams, Horsler, and Oliver (2011) found a decline in smiling and laughing in their oldest AS group under conditions involving social interaction and Devenny et al. (2010) found decreases in long-term episodic memory that were age associated and chronologically early in adults with

Williams syndrome. A 2008 study by Hall, Burns, Lightbody, and Reiss found that slower learning in FXS contributes to low and declining standardized IQ scores over four years.

The temporal trajectory of ASD symptomatology in children with a diagnosis of ASD has been assessed by Gotham, Pickles, and Lord (2012) who found that ASD severity scores in the majority of children stayed stable over 8-12 years. However, in the cross-sectional study reported in Chapter Two there were clear differences in the Social Communication Questionnaire (SCQ; Rutter et al., 2003) subscale scores between older and younger participants with CdLS. The percentage of individuals meeting the SCQ cut-offs for autism and ASD was also significantly higher in CdLS participants over 15 years of age than those 15 years and younger. Both the CdCS and FXS groups over 15 scored significantly higher than the CdCS group on the SCQ *communication* and *social interaction* subscales. This suggests the possibility that the ASD phenomenology in these syndrome groups is increasing as the participants get older. The study in Chapter Two also highlighted changes in FXS on the *restricted and repetitive behaviour* subscale, which increased over time. That study also showed the CdCS group's ASD phenomenology to be stable with age and over time. All these studies allude to change in some syndromes and the possibility of change in CdLS. Based on the changes found in Chapter Two, it is possible that autistic-like behaviours change over time in CdLS, particularly in the *communication* and *social interaction* domains. However, whilst cross-sectional studies provide a useful indication of possible effects of age, they leave open the possibility of sampling differences between younger and older participants. In the case of genetic neurodevelopmental syndromes such as CdLS, there are particular reasons to anticipate that this might be the case, such as an increased rate of diagnosis in younger cohorts and

differing levels of engagement with syndrome support groups through which recruitment occurs.

3.1.3. Evaluating ASD phenomenology

Chapter One highlighted a number of approaches to evaluating ASD phenomenology. The Autism Diagnostic Interview-Revised (ADI-R; Rutter, Le Couteur, & Lord, 2003) and the Autism Diagnostic Observation Schedule (ADOS; Lord, Rutter, DiLavore & Risi, 2000) are the most widely used tools (along with clinical judgement) to diagnose ASD. The ADI-R is an extremely detailed parent report interview that gives a full developmental history of the individual being evaluated. Although it gathers a great deal of information, it can be difficult for parents to remember the pertinent information accurately so many years later. The ADI-R takes 2-3 hours to administer and can be emotionally draining for the parents. In contrast, the ADOS, a very direct observation of behaviour and social skills, can be administered in 30 minutes to an hour. The ADOS gives the most specific information about the individual's behaviours but is only a sample of what is displayed during a very short observation. Both the ADOS and ADI-R require a substantial investment of time to learn to administer accurately. The SCQ is a short screening measure for ASD. It is not as sensitive as the longer ADI-R but is quick, easy and inexpensive to administer. As discussed in Chapter One (see section 1.4.1.), Oosterling (2010) reports that the combination of the ADOS and SCQ accurately identifies ASD. Due to the limited time and resources of this study, it was decided that using the ADOS and SCQ would give the most accurate information possible within these limitations.

3.1.4. Contrast groups

To identify syndrome-specific changes over time, as opposed to more general temporal changes, appropriate contrast groups of similar levels of ID are crucial. Chapter One (see section 1.1.3) discussed the need for a contrast group that is comparable on the level of ID. This is of primary importance because low IQ is typically associated with behaviours that look like ASD phenomenology. CdCS is comparable to CdLS in level of adaptive behaviour, mental age/IQ, receptive language and has been used in other studies as a contrast group (Moss et al., 2008; Richards, Moss, O'Farrell, Kaur, & Oliver, 2009; Griffith et al., 2011; Moss, Howlin, et al., 2013). As one of the two comparison groups used in the Chapter Two study, CdCS was utilized as the most appropriate contrast group for CdLS in this chapter allowing for consistency across studies.

3.1.5. Study

It is increasingly apparent that ASD is common in CdLS with a specific profile of symptomatology which differs from that in idiopathic ASD (e.g., Moss, Oliver, et al., 2013). In addition, the cross-sectional and longitudinal data reported in Chapter Two indicate possible changes over a short period of time (2.5 years) in the behavioural phenotype of the disorder with a possible increase in ASD-like behaviours. This study expands on the use of a longitudinal design to assess ASD phenomenology over time in CdLS. It follows up a cohort of individuals with CdLS and a contrast group of participants with CdCS, first described by Moss et al. in 2008.

In this study, ASD phenomenology and changes over time in CdLS are evaluated with more robust measures (ADOS) and a longer follow-up period. The following hypotheses are proposed:

1. The proportion of participants with CdLS reaching cut-off on the ADOS and SCQ will increase over time compared to individuals with CdCS.
2. The scores on domains of the ADOS and SCQ will increase for the CdLS group in contrast to the CdCS group.
3. Adaptive behaviour skills will remain stable over time in individuals with CdLS.

3.2. Method

3.2.1. Design

This study is a 6.5–7.5 year longitudinal follow-up of behavioural, cognitive and linguistic abilities in CdLS and CdCS. Each participant was assessed initially as part of a previous study conducted at the University of Birmingham between 2004 and 2005 (Time 1; T1). In this study, outcomes 6.5–7.5 years later (Time 2; T2) in the areas of autism spectrum symptomatology, cognitive level, language ability and adaptive behaviour skills were investigated.

3.2.2. Recruitment

Parents and carers of individuals with CdLS and CdCS and their children/the person they care for were invited to participate in this follow-up study (2011/12). 32 individuals with CdLS and 21 individuals with CdCS and their carers who participated in a research study

between 2004 and 2005 at the University of Birmingham (Moss et al., 2008) investigating the nature of ASD phenomenology in these syndromes were invited to take part in the current study. In the original study (T1), participants were recruited through a database at the University of Birmingham of individuals with CdLS and CdCS who had previously participated in research at the university and had agreed to be contacted for future research projects. In addition, some of the participants with CdCS were contacted indirectly through the Cri du Chat Syndrome Support group. At T1, 86 carers of individuals with CdLS and 54 carers of individuals with CdCS were invited to participate in the study. 34 participants with CdLS and 23 participants with CdCS took part in the study at T1.

Participants were included at T1 if they met the following criteria:

- Aged from 5 to 19 years.
- Had a confirmed diagnosis of the given syndrome from a professional (pediatrician, clinical geneticist, or GP).
- Had no other known genetic abnormality (other than that associated with CdLS and CdCS).
- Lived within reasonable travelling distance of Birmingham (approximately 100 miles).

Participants were included in the current study (T2) if they meet the following criteria:

- They met all stated T1 criteria.
- Completed all relevant assessments at T1.
- Agreed to be contacted with information about future research projects.

- Agreed to participate in this follow-up.

Each syndrome group had 2 participants whom it was not possible to invite to participate in the current study because they did not meet the inclusion criteria (2 due to death, 1 did not agree to future contact and 1 with a questionable diagnosis).

This study was comprised of data collection involving questionnaire measures, an interview conducted by phone, followed by a research visit where assessments and additional interview data were collected. Due to the nature of the study population, all contact was initially directed towards the parent/carer of participants.

3.2.3. Participants

3.2.3.1. Participants from Chapter Two

Of the participants involved in the Chapter Two study (see section 2.2.2.), 17 individuals with CdLS and 12 with CdCS also participated in the study described in this chapter. As age was a component that significantly impacted the results in Chapter Two, it is noteworthy that only one participant with CdLS and none with CdCS moved from the under 15 years old age band to the 15 years and older age band (used for analysis in Chapter Two) between the studies.

3.2.3.2. Cornelia de Lange syndrome group

Of the 32 participants with CdLS that met criteria and were invited to participate in the current study, 2 participants refused because the families were experiencing a difficult time due to extreme behavioural problems. Thirty participants with CdLS returned the

consent form for the current study. Mean follow-up time for the CdLS group was 81.67 months; SD=5.23. Table 3.1 describes the characteristics of the participants (CdLS and CdCS) who participated at both time points (T1 and T2).

At T1, the participants with CdLS were aged between 5 and 18 years (mean= 12.24; SD= 3.90). Age equivalence scores on the *Adaptive Behavior Composite* on three domains (determined by the Vineland Adaptive Behavior Scale, VABS; Sparrow et al., 1984) ranged from 9.67 months to 98.67 months (mean= 43.83 months; SD= 28.38). Receptive language age equivalence (determined by the British Picture Vocabulary Scales, BPVS; Dunn et al., 1997) ranged from 28.00 months to 104.00 months (mean= 50.17; SD= 26.00). 14 with CdLS (46.7%) were male, 20 (66.7%) were verbal (participants were considered to be verbal if they had more than 30 words or signs in their vocabulary) and 28 (93.3%) were mobile (participants were considered to be mobile if they could walk unaided).

At T2, the participants with CdLS were aged between 12 and 26 years (mean= 19.20; SD= 3.91). Age equivalence on the VABS (*Adaptive Behavior Composite* on three domains) scores ranged from 8.00 months to 144.00 months (mean= 43.03 months; SD= 35.26). Receptive language age equivalence ranged from 28.00 months to 156.00 months (mean= 55.03; SD= 34.87). 14 participants with CdLS (46.7%) were male, 20 (66.7%) were verbal and 30 (100%) were mobile.

3.2.3.3. Cri du Chat syndrome group

Of the 22 participants with CdCS who met criteria and were invited to participate in the current study, 3 participants did not respond to invitations to participate and 1 participant declined to take part in the study. 18 participants with CdCS returned the consent form for the current study. Mean follow-up time for the CdCS group was 81.67 months; SD=2.54. Table 3.1 describes the characteristics of the participants (CdLS and CdCS) who participated at both time points (T1 and T2).

At T1, the participants with CdCS were aged between 5 and 14 years (mean= 9.64; SD= 2.72). Age equivalence on the VABS (*Adaptive Behavior Composite* on three domains) scores ranged from 14.67 months to 77.00 months (mean= 33.64 months; SD= 17.40). Receptive language age equivalence ranged from 28.00 months to 96.00 months (mean= 51.39; SD= 23.41). 5 participants with CdCS (27.8%) were male, 13 (72.2%) were verbal and 17 (94.4%) were mobile.

At T2, the participants with CdCS were aged between 12 and 21 years (mean= 16.58; SD= 2.81). Age equivalence on the VABS (*Adaptive Behavior Composite* on three domains) scores ranged from 14.00 months to 79.00 months (mean= 34.72 months; SD= 18.46). Receptive language age equivalence ranged from 28.00 months to 136.00 months (mean= 63.39; SD= 33.31). 5 participants with CdCS (27.8%) were male, 16 (88.9%) were verbal and 17 (94.4%) were mobile.

Table 3.1: Mean age, standard deviation and range, percentage of males, levels of mobility, levels of speech, adaptive age equivalence and receptive language equivalence in each group at each time point (T1 and T2).

Demographics		CdLS	CdLS	CdCS	CdCS
Time		T1	T2	T1	T2
N		30	30	18	18
Age *	M (SD) Range	12.24 (3.90) 5-18.96	19.20 (3.91) 12.33-26.54	9.64 (2.72) 5.62-14.56	16.58 (2.81) 12.39-21.69
Gender	% Male (N)	46.70 (14)	46.70 (14)	27.80 (5)	27.80 (5)
Speech[1]	% Verbal (N)	66.70 (20)	66.70 (20)	72.20 (13)	88.90 (16)
Mobility[1]	% Mobile (N)	93.30 (28)	100.00 (30)	94.40 (17)	94.40 (17)
Level of ability[2]	% Profound (N) % Severe (N) % Moderate (N) % Mild (N) % 70+ (N)	20.00 (6) 53.30 (16) 20.00 (6) 6.70 (2) 0 (0)	66.70 (20) 13.30 (4) 6.70 (2) 10.00 (3) 3.30 (1)	11.10 (2) 66.70 (12) 11.10 (2) 5.60 (1) 5.60 (1)	44.40 (8) 50.00 (9) 5.60 (1) 0 (0) 0 (0)
Age equivalence[3]	M (SD) Range	43.83 (28.38) 9.67-98.67	43.03 (35.26) 8.00-144.00	33.64 (17.40) 14.67-77.00	34.72 (18.46) 14.00-79.00
Receptive language[4,5] Raw Scores	M (SD) Range	32.80 (31.81) 0-88.00	35.03 (38.15) 0-117.00	38.44 (24.75) 0-82.00	47.89 (33.35) 3.00-107.00
Receptive language age equivalence[4,5]	M (SD) Range	50.17 (26.00) 28.00-104.00	55.03 (34.87) 28.00-156.00	51.39 (23.41) 28.00-96.00	63.39 (33.31) 28.00-136.00

* In years

[1] Data derived from the demographic questionnaire

[2] Adaptive Behavior Composite classification; derived from the Vineland Adaptive Behavior Scales (Sparrow *et al.*, 1984)

[3] Adaptive Behavior Composite age equivalence on three domains; derived from the Vineland Adaptive Behavior Scales (Sparrow *et al.*, 1984)

[4] Data derived from the British Picture Vocabulary Scales (Dunn *et al.*, 1997)

[5] At T1, 12 participants (11 CdLS 1 CdCS) could not perform the task and 1 participant (CdLS) refused. At T2, 11 participants (all CdLS) could not perform the task and 3 participants (all CdLS) refused. Those participants were given a minimum score.

3.2.4. Measures

3.2.4.1. Background information

As in Chapter Two (see section 2.2.3.1.), the demographic questionnaire was utilized to collect background information about the participant.

3.2.4.2. Adaptive behaviour

3.2.4.2.1. Vineland Adaptive Behavior Scales – Survey form (VABS; Sparrow et al., 1984; see Appendix 5)

The VABS was conducted over the phone with parents or carers in order to assess each child's personal and social adaptive behaviour levels and level of ID. The measure is a semi-structured interview which is suitable for use with individuals with or without ID. The VABS focuses on what the individual 'usually' does rather than what they are able to do. The four domains covered by the VABS are: *communication, daily living, socialization* and *motor skills*. Each of the four domains includes subdomains. The *communication skills* domain includes: *expressive language, receptive language* and *written* subdomains. The *daily living skills* domain includes: *personal, domestic* and *community* subdomains. The *socialization skills* domain includes: *interpersonal relationships, play* and *leisure and coping* subdomains. To be consistent with T1, the optional *maladaptive behavior* domain was not used and the *Adaptive Behavior Composite* was calculated from the three main domains. Standard and age equivalence scores can be calculated for each domain and for the *Adaptive Behavior Composite*. Each subdomain offers an age equivalence score. In addition, the *Adaptive Behavior Composite* determines a severity classification: borderline, mild, moderate, severe and profound. The authors

report good validity and high reliability ranging from .83 to .90 for the domains and .94 on the *Adaptive Behavior Composite*.

3.2.4.3. Autism spectrum disorder symptomatology

3.2.4.3.1. Social Communication Questionnaire (SCQ; Rutter et al., 2003; Appendix 2)

As in Chapter Two (see section 2.2.3.2.), the SCQ was utilized to collect information about potential impairments in reciprocal social interaction, communication, repetitive and stereotyped behaviours. There are two versions of the SCQ available: the lifetime version which includes the full developmental history of the individual; and the current version which focuses on the past three months. The current version was used at both time points. As a reminder, each question requires a *yes* (score of one) or *no* (score of zero) response. The presence of abnormal behaviour on each question is indicated by a score of one. The first item is not included in the score and therefore the total scores range from zero to thirty-nine. The authors suggest a cut-off score of fifteen for ASDs, which was found to differentiate individuals with autism from those with ID (specificity of .80 and sensitivity of .67). The suggested cut-off for autism is significantly higher at twenty-two (specificity of .60 and sensitivity of .75; Berument et al., 1999).

3.2.4.3.2. Autism Diagnostic Observation Schedule (ADOS; Lord, Rutter, DiLavore, & Risi, 2000)

The ADOS is a semi-structured standardised observational assessment of communication and social interaction skills, play and imaginative skills and repetitive behaviour (see Chapter One, section 1.4.1. for full description). The ADOS is suitable for individuals

with a range of developmental abilities, chronological ages and expressive language skills. The use of clear, planned social 'presses', provides a good opportunity for the participant to display certain social and communicative behaviours or responses. The presence/absence and nature of these behaviours and responses are recorded. There are four modules (1-4) in the ADOS and module selection is based on the chronological age and level of expressive language of the participant. All modules can be administered quickly (approximately 20-40 minutes) and each module has its own protocol and scoring algorithm.

3.2.4.4. Language ability

3.2.4.4.1. British Picture Vocabulary Scales- 2nd Edition (BPVS; Dunn, et al., 1997; Appendix 6)

The BPVS was used at both time points to assess each participant's receptive language level. The BPVS consists of a flipbook with black and white pictures, four to a page. There are fourteen sets of twelve items. Each set of twelve should be completed once started and they are increasingly difficult. The participant is asked to select the picture they think best represents the word given orally by the examiner. Split-half reliability and internal consistency are reported by the authors to be good.

3.2.5. Procedure

3.2.5.1. Data collection

All participants were first contacted by post. Included with the letter was a brief information sheet about the study, an expression of interest form and a postage paid return envelope (see Appendix 4). A researcher made follow-up calls if there was no response to

initial mailing and a detailed information sheet was made available to all participants. Upon receipt of the expression of interest form, consent forms were posted and arrangements were made by telephone with the main caregiver to conduct the VABS interview and a daylong visit with the participant at home or school. The Nottingham research committee granted NHS ethical approval for this study (Appendix 10).

3.2.5.2. Autism Diagnostic Observation Schedule (ADOS; Lord, et al., 2000)

At both time points, every attempt was made to make sure the ADOS assessments were conducted in a quiet, distraction free room. Each assessment was video recorded using a Sony TRV-48E camera. Scoring was done immediately after live administration and again with the use of the video recording by the examiner. Module selection for the ADOS is based on verbal ability. Due to a high rate of selective mutism in CdLS, module selection for this study was based on parent/carer reported expressive language level if the participant was selectively mute. All module appropriate presses and prompts were given despite the level of responsiveness of the participant. If the participant used a wheel chair, every attempt was made to have them out of the chair for this assessment. If a module 1 was appropriate for an older individual, the researcher forewarned parents/carers that some of the activities would not be age appropriate. The ADOS 1 was used at both time points.

3.2.6. Inter-rater reliability

Establishing good inter-rater reliability is an important step to ensure that the scores from the assessments at both time points are reliably comparable. Without this, the potential for findings to be based on scoring differences between examiners exists. Inter-rater reliability of the T2 scores on the ADOS was established between the main researcher for T1 and the

main researcher for T2 on 15 (31.25%) randomly selected participants across the CdLS and CdCS groups. 8 CdLS participants and 7 CdCS participants were selected across modules. Scoring of video recordings of the assessments were used. There were 7 males (36.84%) and 8 females (27.59%) aged between 12.33 years and 26.54 years (mean= 17.63; SD= 4.51) included. To account for the unequal number of participants administered each of the four modules, 5 participants with module 1, 2 participants with module 2, 4 participants with module 3 and 4 participants with module 4 were evaluated. These included assessments given throughout the entire data collection phase of the study to account for any possible examiner drift in administration. Both raters were trained and coded the assessment independently from each other.

Raters at both time points were not blind to the participant syndrome group as both syndrome groups present with distinctive dysmorphic features. However, the researcher who did the rating at T2 was blind to the T1 ADOS scores until after data collection and scoring of the T2 ADOS. In a longitudinal study, the rater not being blind to the syndrome group while collecting and scoring data could potentially have an experimenter bias effect toward the syndrome group with a predicted outcome. However, because the rater at T2 did not have prior knowledge of the T1 ADOS scores, if that type of bias was present, it would be evident in the inter-rater reliability. Table 3.2 presents the domain level, total score and cut-off scores for the inter-rater reliability analysis.

Kappa coefficients are considered to be in high agreement if greater then .75, fair agreement to good agreement if .40 to .75 and low agreement if under .40 (Fleiss, 1981). Inter-rater reliability was established with Kappa coefficients as having good agreement

for the *Communication* domain (.73) and fair to good agreement for the total score (.59) and *Social Interaction* domain (.62). Pearson correlations also reveal good agreement between the raters on domain and total scores (*Communication* .73, *Social Interaction* .67 and *Total* .60).

Table 3.2: Inter-rater reliability, Pearson correlation and Kappa coefficients for diagnostic cut-offs on the ADOS at T2.

ADOS Domain	Pearson Correlation N=15	Kappa Coefficients for autism diagnostic cut-off N=15
Communication	.73**	.73
Social Interaction	.67**	.62
Total	.60*	.59

* <.05
** <.01

3.2.7. Procedure used for the British Picture Vocabulary Scales- 2nd Edition (BPVS; Dunn, et al., 1997)

Although some participants had very limited receptive language skills, the BPVS was attempted for all participants at both time points. If the participant did not respond to the oral prompt given by the examiner during the teaching phase of the assessment the following protocol was used to ensure all possible opportunities were given to participate in the assessment. The following protocol was used at both time points:

1. Oral prompt alone
2. Oral prompt with modelling of response (examiner points to the correct response)
3. Oral prompt accompanied by a physical prompt (hand over hand)

If after 4 attempts the participant appeared to be unresponsive to the task, the examiner discontinued the assessment.

3.2.8. Data Analysis Strategy

3.2.8.1. Overall strategy

All data were tested for normality prior to analysis using Kolmogorov-Smirnov tests. Any data found not to be normally distributed were examined by converting the skewness and kurtosis to a z score. Those items with a z score above 1.96 were analysed using nonparametric tests.

A within syndrome group approach was used to look at any changes within the syndrome groups at each time point (T1 & T2) separately. A between group approach was used to identify differences between the CdLS and CdCS groups at each time point (T1 & T2). A within syndrome group over time approach was used to identify changes with time within the individual syndrome group. An over time, and between syndrome group approach was used to look at any differences between the CdLS and CdCS groups over time. A standard alpha level of $p < .05$ was employed throughout the analysis in this chapter.

3.2.8.2. Participant group's demographic characteristics comparison

In order to assess the comparability of the participants who were involved in the follow-up study, the participant groups with CdLS and CdCS were compared on a number of demographic variables and profile scores on the VABS and BPVS at T1 including: gender, speech, mobility, level of ability, mental age and receptive language skills. Chi-square tests were used where data were categorical, McNemar tests with dichotomous nominal

data (gender, speech, mobility and VABS ABC classification), t tests were used where data were normally distributed and Mann-Whitney U tests were used where data were not normally distributed for continuous variables (chronological age, VABS ABC mean age equivalence and BPVS receptive language age equivalence).

3.2.8.3. British Picture Vocabulary Scale score comparison

Mann-Whitney tests were used to evaluate differences at each time point (T1 & T2) between the CdLS and CdCS groups on the receptive language raw scores and age equivalence scores received on the BPVS. A mixed ANOVA was used to look for main effects of time and group as well as interaction effects while controlling for T1 chronological age. Due to the low level of ability and selective mutism in the participant groups, a floor score of 28 was used at both time points for analysis purposes if the participant was unable to do the task.

3.2.8.4. Vineland Adaptive Behavior Scale score comparison

To examine change over time within syndrome groups, Chi-square analyses were used on the VABS classification scores and t tests were used on the *Adaptive Behavior Composite* (ABC) age equivalence scores. Mixed ANOVAs were used to look for main effects of time and group as well as interaction effects while controlling for T1 chronological age on the ABC age equivalence and the subdomain scores.

3.2.8.5. Autism Diagnostic Observation Schedule (ADOS; Lord, Rutter, DiLavore, & Risi, 2000) score comparison

To compare the percentage of participants scoring above the suggested cut-off scores for autism and ASD in the CdLS and CdCS groups between T1 and T2, McNemar tests were used. Cut-off scores were evaluated for the *communication* and *social interaction* domains and the total ADOS score.

For comparison of domain scores on the ADOS, mean domain item scores were calculated by dividing the total domain score by the number of items in that domain. The resulting mean item scores made it possible to compare scores across different modules that had a different number of items contributing to the domain scores. Mixed ANOVAs were used to analyse mean domain item scores on the ADOS *communication, social interaction, restricted, repetitive and stereotyped behavior* and *play/imagination* domains. Analyses looked for main effects of time and group as well as interaction effects while controlling for T1 chronological age.

3.2.8.6. Social Communication Questionnaire score comparison

To compare the percentage of participants in the CdLS and CdCS groups who scored above the suggested cut-off scores for autism and ASD at T1 and T2, McNemar tests were used. Mixed ANOVAs were used to compare subscale scores on the *communication, social interaction* and *repetitive behaviour* subscales of the SCQ. Analyses looked for main effects of time and group as well as interaction effects while controlling for T1 chronological age.

3.3. Results

3.3.1. Demographic characteristics comparison

The objective of this analysis was to evaluate the demographic characteristics and to ensure comparability between the CdLS and CdCS groups at T1. In order to evaluate any potential confounding variables chronological age, gender, verbal ability, mobility, receptive language (as measured by the BPVS; Dunn et al., 1997) and adaptive behaviour (as measured by the VABS; Sparrow et al., 1984) were compared at T1 between the syndrome groups. Table 3.3 describes the demographic data regarding age, gender, verbal ability, mobility, level of ability and receptive language for all participants at T1. Analysis revealed a significant group difference in T1 chronological age with the CdLS group being older (mean = 12.24 years; SD = 3.90) than the CdCS group (mean = 9.64 years; SD = 2.71). There were no significant between group differences for gender, verbal ability, mobility, level of ability, ABC age equivalence or receptive language age equivalence at T1. The two syndrome groups were comparable on all demographic variables except chronological age. The difference in chronological age was necessary for the participants to be matched on mental age to account for the level of ID. Differences in T1 chronological age have been taken into consideration and controlled for when necessary in all analysis.

Table 3.3: Demographic characteristics at T1 of participants in the CdLS and CdCS groups.

		CdLS	CdCS	*t/X*	df	*p* value
N		30	18			
Age *	M	12.24	9.64	2.49	46	
	(SD)	(3.90)	(2.72)			.02
	Range	5-18.96	5.62-14.56			
Gender	% Male	46.70	27.80	1.68	1	.20
	(N)	(14)	(5)			
Speech[1]	% Verbal	66.70	72.20	.16	1	.69
	(N)	(20)	(13)			
Mobility[1]	% Mobile	93.30	94.40	.02	1	.88
	(N)	(28)	(17)			
Level of ability[2]	% Profound	20.00	11.10			
	(N)	(6)	(2)			
	% Severe	53.30	66.70			
	(N)	(16)	(12)			
	% Moderate	20.00	11.10			
	(N)	(6)	(2)			
	% Mild	6.70	5.60			
	(N)	(2)	(1)			
	% 70+	0.00	5.60			
	(N)	(0)	(1)			
Age equivalence[3]	M	43.83	33.64	1.37	46	.18
	(SD)	(28.38)	(17.40)			
	Range	9.67-98.67	14.67-77.00			
Receptive language age equivalence[4]	M	50.17	51.39	-.16	46	.87
	(SD)	(26.00)	(23.41)			
	Range	28.00-104.00	28.00-96.00			

* In years
[1] data derived from the demographic questionnaire
[2] Adaptive Behavior Composite classification; derived from the Vineland Adaptive Behavior Scales (Sparrow *et al.*, 1984)
[3] Adaptive Behavior Composite age equivalence on three domains; derived from the Vineland Adaptive Behavior Scales (Sparrow *et al.*, 1984)
[4] data derived from the British Picture Vocabulary Scales (Dunn *et al.*, 1997)

3.3.2. Adaptive behaviour comparison

In order to assess any overall differences in adaptive behaviour over time a mixed ANOVA was used to analyse the ABC age equivalence scores on the VABS including T1 chronological age as a covariate. Figure 3.1 shows the mean ABC scores for the VABS for the CdLS and CdCS groups for T1 and T2. There was no significant interaction between time and syndrome group on the VABS ABC score, $F(1,45) = 0.03$, $p = .875$. In addition, there were no main effects of time or syndrome group, $F(1,45) = 1.71$, $p = .197$, $F(1,45) = 0.08$, $p = .775$. These findings indicate that overall adaptive behaviour skills remained stable over time in both syndrome groups.

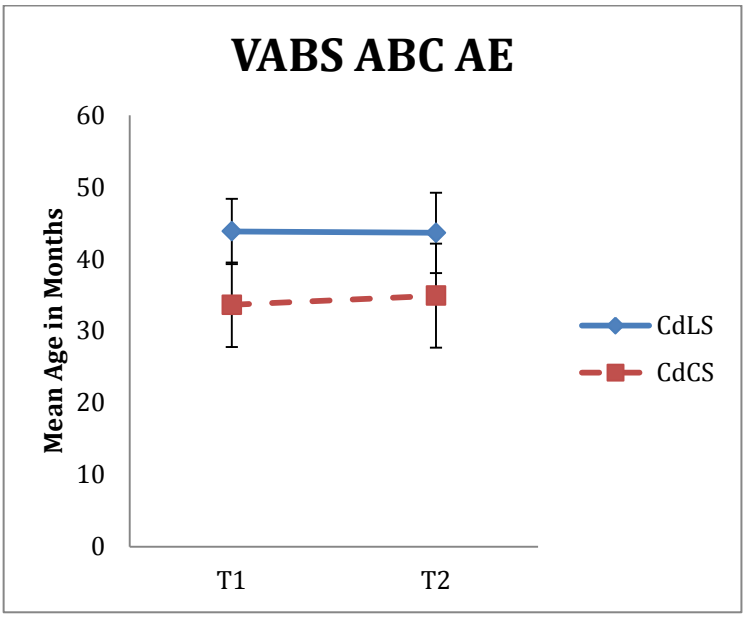


Figure 3.1: Mean age equivalence scores in months over time and between the CdLS and CdCS groups on the ABC derived from the VABS.

In order to assess any specific differences in adaptive behaviour over time mixed ANOVAs were used to analyse the subdomain age equivalence scores on the VABS including T1 chronological age as a covariate. Three domains were examined

(*communication, daily living skills* and *socialization*). Each domain had three subdomains: *Communication* had *receptive, expressive* and *written language*; *daily living skills* had *personal*, *domestic* and *community*; *socialization* had *interpersonal relationships*, *play* and *leisure time and coping skills*. Figure 3.2 shows the mean age equivalence scores at the subdomain level on the VABS for the CdLS and CdCS groups for T1 and T2. The *receptive language* subdomain of the VABS showed a significant interaction between time and syndrome group, $F(1,45) = 8.78$, $p = .005$. Pairwise comparisons revealed that the CdLS group's scores on the *receptive language* subdomain decrease while the CdCS group's scores improve over time, $F(1,45) = 5.10$, $p = .029$. There was no significant interaction between time and syndrome group, or main effect of time or syndrome group on the *expressive language* subdomain of the VABS, $F(1,45) = 0.54$, $p = .390$, $F(1,45) = 0.09$, $p = .759$ and $F(1,45) = 0.20$, $p = .660$. There was no significant interaction between time and syndrome group or main effects of time or syndrome group on the *written language* subdomain of the VABS, $F(1,45) = 1.29$, $p = .261$, $F(1,45) = 0.40$, $p = .528$ and $F(1,45) = 0.20$, $p = .889$. There was no significant interaction between time and syndrome group or main effects of time or syndrome group on the *personal* subdomain of the VABS, $F(1,45) = 0.07$, $p = .794$, $F(1,45) = 0.15$, $p = .700$ and $F(1,45) = 1.01$, $p = .320$. There was no significant interaction between time and syndrome group or main effects of time or syndrome group on the *domestic* subdomain of the VABS, $F(1,45) = 0.66$, $p = .422$, $F(1,45) = 0.31$, $p = .580$ and $F(1,45) = 1.07$, $p = .307$. There was no significant interaction between time and syndrome group or main effects of time or syndrome group on the *community* subdomain of the VABS, $F(1,45) = 0.68$, $p = .413$, $F(1,45) = 0.36$, $p = .550$ and $F(1,45) = 0.66$, $p = .420$. There was no significant interaction between time and syndrome group or main effects of time or syndrome group on the *interpersonal*

subdomain of the VABS, $F(1,45) = 1.34$, $p = .254$, $F(1,45) = 0.01$, $p = .951$ and $F(1,45) = 1.38$, $p = .246$. There was no significant interaction between time and syndrome group or main effects of time or syndrome group on the *play and leisure* subdomain of the VABS, $F(1,45) = 0.25$, $p = .623$, $F(1,45) = 0.83$, $p = .367$ and $F(1,45) = 0.01$, $p = .906$. There was no significant interaction between time and syndrome group or main effects of time or syndrome group on the *coping skills* subdomain of the VABS, $F(1,45) = 0.21$, $p = .885$, $F(1,45) = 1.68$, $p = .201$ and $F(1,45) = 0.09$, $p = .767$. These results show that although most adaptive behaviour skills remain stable over time in both syndrome groups, receptive language skills decrease in CdLS whilst increasing in the CdCS group.

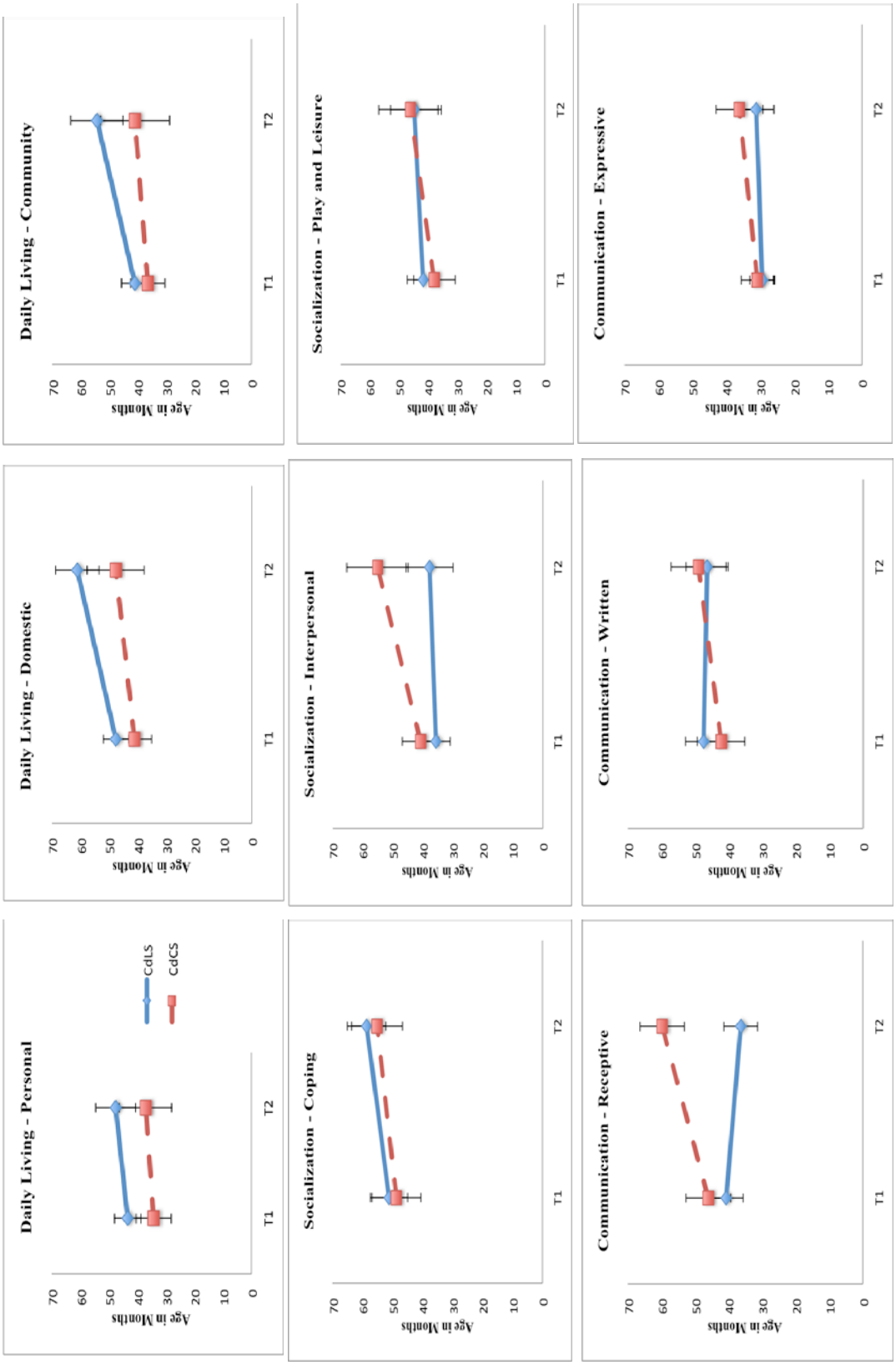

Daily Living - Personal
Daily Living - Domestic
Daily Living - Community
Socialization - Coping
Socialization - Interpersonal
Socialization - Play and Leisure
Communication - Receptive
Communication - Written
Communication - Expressive
CdLS
CdCS
Age in Months
0
10
20
30
40
50
60
70
T1
T2

Figure 3.2: Mean age equivalence scores in months over time and between the CdLS and CdCS groups on the subdomains of the VABS.

3.3.3. Receptive language comparison

In order to assess any differences in receptive language level over time for the CdLS and CdCS groups a mixed ANOVA was used while controlling for T1 chronological age. Figure 3.3 shows the mean age equivalence scores on the BPVS for the CdLS and CdCS groups at T1 and T2. There was no significant interaction between time and syndrome group on the BPVS, $F(1,45) = 0.60$, $p = .444$. There was a main effect of time, $F(1,45) = 4.35$, $p = .043$ but no main effect of syndrome group, $F(1,45) = 2.00$, $p = .164$ on the BPVS. Both syndrome groups' scores increased in very similar ways over time, suggesting an improvement in receptive language abilities.

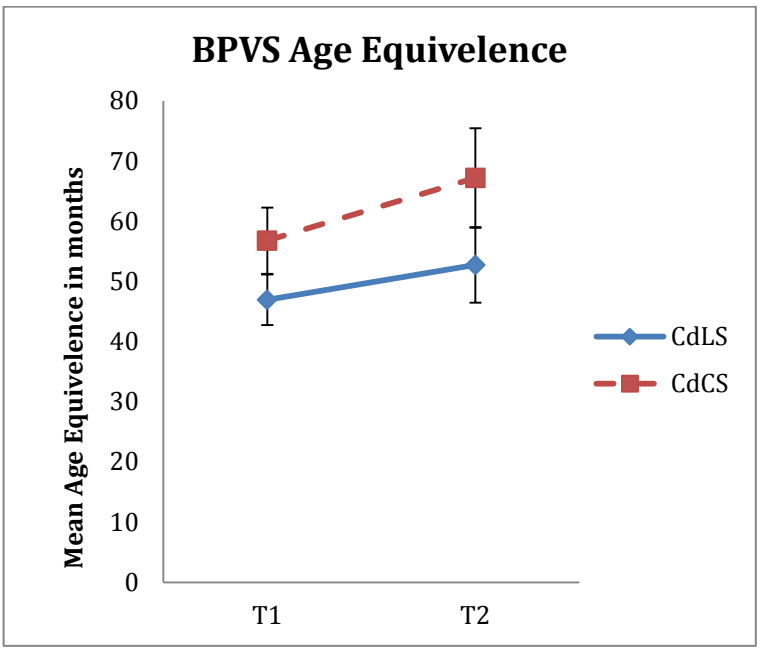


Figure 3.3: Mean age equivalence scores in months over time and between the CdLS and CdCS groups on receptive language as derived from the BPVS.

3.3.4. Comparison of percentage of participants meeting cut-offs on the Autism Diagnostic Observation Schedule and the Social Communication Questionnaire

The objective of this analysis was to investigate differences in autism symptomatology over time within the CdLS and CdCS groups on scores of the ADOS and the SCQ separately. Based on previous findings, (such as the results in Chapter Two and Moss et al., 2013) it was hypothesized that there would be an increase in the proportion of participants with CdLS reaching cut-off on the ADOS and SCQ over time, a one-tailed approach was used in this analysis. A one-tailed approach is appropriate if there is good reason to believe the findings will be in a given direction (such as an increase in the symptomatology in CdLS) or there is a small sample size. It does increase the chances of a type 1 error, where the null hypothesis is true but rejected. Therefore, any findings should be interpreted with this in mind. Table 3.4 presents the percentage of participants scoring above the suggested cut-off for autism and ASD on the *communication, social interaction* domains and total score of the ADOS. In the CdCS group, there were no significant differences in the percentages of participants meeting criteria for either autism or ASD on either of the domains or on the total score. However, in the CdLS group the McNemar tests showed a significant difference between T1 and T2 in the proportion of participants meeting cut-off on the *social interaction* domain, total score for ASD and on the total score for autism. In the CdLS group, the change from T1 to T2 in the proportion of participants meeting criteria for autism on the *social interaction* domain showed an increase, although not statistically significant (p = .05). No significant differences were found on the *communication* domain for either syndrome group. There is marked increase in the percentage of participants in the CdLS group meeting both cut-offs in the *social*

interaction domain over time. The CdCS group actually shows a slight decrease over time in the broader ASD cut-off category.

Table 3.4: Percentage of participants scoring above the suggested cut-off for autism and ASD on the communication and social interaction domains and total score of the ADOS for the CdLS and CdCS groups at each time point (T1 and T2) (One-Tailed)

	% scoring above autism Cut-off (N)						*% scoring above autism spectrum disorder cut-off (N)*					
	T1 CdLS (N=30)	T2 CdLS (N=30)	*p* value	T1 CdCS (N=18)	T2 CdCS (N=18)	*p* value	T1 CdLS (N=30)	T2 CdLS (N=30)	*p* value	T1 CdCS (N=18)	T2 CdCS (N=18)	*p* value
Communication	60.0 (18)	76.7 (23)	.11	16.7 (3)	33.3 (6)	.19	80.0 (24)	90.0 (27)	.19	55.6 (10)	77.8 (14)	.11
Social Interaction	66.7 (20)	86.7 (26)	.05	38.9 (7)	50.0 (9)	.36	73.3 (22)	93.3 (28)	.04	88.9 (16)	83.3 (15)	.50
Total	56.7 (17)	76.7 (23)	.04	27.8 (5)	27.8 (5)	.50	70.0 (21)	90.0 (27)	.04	50.0 (9)	55.6 (10)	.50

Table 3.5 presents the percentage of participants within the CdLS and CdCS groups who scored above the suggested cut-off for autism and ASD on the SCQ. There were no significant differences in the percentage of participants meeting the suggested cut-offs within either syndrome group from T1 to T2. It is interesting to note that none of the participants in the CdCS group met the cut-off criteria for autism at either time point. This is in contrast to the ADOS data which showed five CdCS participants at each time point meeting the criteria for autism. This is most likely due to the greater sensitivity of the ADOS than the SCQ.

Table 3.5: Percentage of participants scoring above the suggested cut-off for autism and ASD on the SCQ for the CdLS and CdCS groups at each time point (T1 and T2). (One tailed)

	T1 CdLS (N=30)	T2 CdLS (N=30)	*p* value	T1 CdCS (N=18)	T2 CdCS (N=18)	*p* value
% scoring above autism cut-off	20.0 (6)	20.0 (6)	.50	0 (0)	0 (0)	*
% scoring above the autistic spectrum disorder cut-off	36.7 (11)	53.3 (16)	.06	5.6 (1)	16.7 (3)	.25

*** Value cannot be calculated due to no participants within this category.**

3.3.5. Autism Diagnostic Observation Schedule score comparison

To assess change over time in the individual domains of the ADOS, the scores on the ADOS for the CdLS and CdCS groups were analysed using a mixed ANOVA at the mean domain level while including T1 chronological age as a covariate. Figure 3.4 shows the results of the

mixed ANOVA analysis of the ADOS domains between the CdLS and CdCS groups and over time. There was no significant interaction between time and syndrome group on the *communication* domain of the ADOS, $F(1,45) = 0.36$, $p = .552$. There were main effects of time and syndrome group on the *communication* domain, $F(1,45) = 7.79$, $p = .008$, $F(1,45) = 15.67$, $p < .001$. Overall, participants' scores increased over time. It should perhaps be noted that the increase over time was significant for the CdLS group, $F(1,45) = 6.00$, $p = .018$, but not the CdCS group, $F(1,45) = 1.19$, $p = .281$, although the lack of interaction means this result should be treated with caution. On the *social interaction* domain, there was a significant interaction between time and syndrome group, $F(1,45) = 5.69$, $p = .021$. Pairwise comparisons revealed the CdLS group was significantly more impaired than the CdCS group at T2, $F(1,45) = 16.82$, $p < .001$, but not at T1, $F(1,45) = 1.23$, $p = .273$. Scores within the CdLS group were significantly higher at time 2 compared to time 1, $F(1,45) = 8.27$, $p = .006$, this effect was not observed for the CdCS group, $F(1,45) = 0.80$, $p = .377$. There was no significant interaction between time and syndrome group on the *restricted, repetitive and stereotyped behaviour* domain, $F(1,45) = 1.28$, $p = .264$. There were no main effects of time or syndrome group on the *restricted, repetitive and stereotyped behaviour* domain, $F(1,45) = 0.26$, $p = .872$, $F(1,45) = 0.61$, $p = .438$. No significant interaction between time and syndrome group on the *play/imagination* domain was found, $F(1,20) = 0.55$, $p = .468$. Although there was no main effect of time, $F(1,20) = 3.19$, $p = .089$, there was a main effect of syndrome group, $F(1,20) = 8.71$, $p = .008$ on the *play/imagination* domain. Pairwise comparisons revealed the CdCS group had significantly lower scores at T2 than at T1, $F(1,20) = 5.08$, $p = .036$. This effect was not observed in the CdLS group $F(1,20) = 1.64$, $p = .215$.

On the majority of the domains the groups produced very similar patterns of results. The exception was the divergent pattern reflected by the groups on the *social interaction* domain. Just as with the cut-off scores, the CdLS group is showing a decline in social ability (increase in scores) while the CdCS group may improve (decrease in scores) slightly (although not significantly) over time.

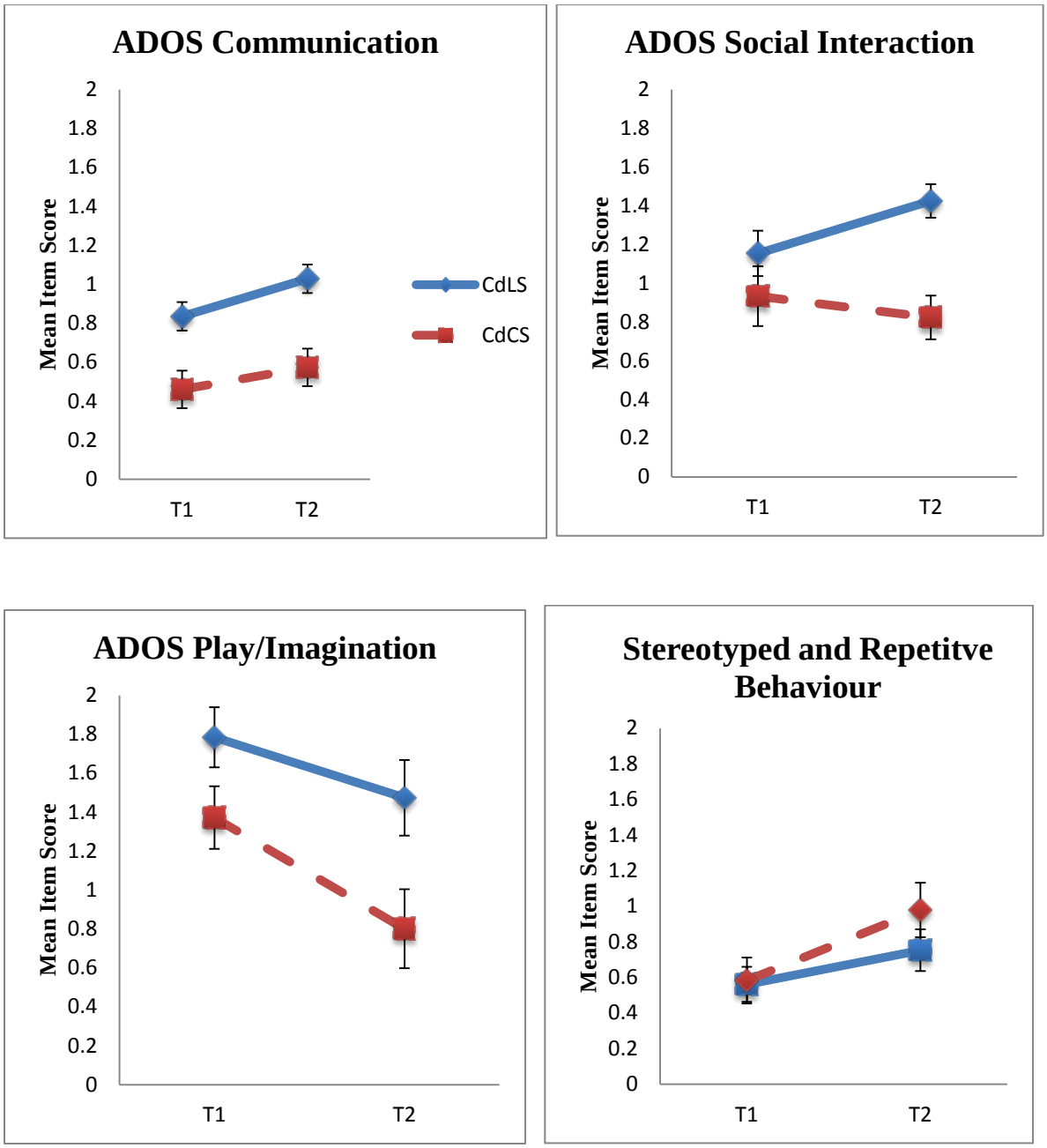


Figure 3.4: Mean item scores over time and between the CdLS and CdCS groups on the four domains of the ADOS (Communication, social interaction, play/imagination & stereotyped and repetitive behaviour).

3.3.6. Social Communication Questionnaire score comparison

To assess change over time in the individual domains of the SCQ the scores for the CdLS and CdCS groups were analysed using a mixed ANOVA at the subscale level including T1 chronological age as a covariate. Figure 3.5 shows the results of the mixed ANOVA analysis of the SCQ domains between the CdLS and CdCS groups and over time. There was a significant interaction between time and syndrome group, $F(1,40) = 6.39$, $p = .016$ on the *communication* subscale. At T2, the scores of the CdLS group differed significantly from the CdCS group, $F(1,40) = 13.83$, $p = .001$. Within syndrome groups, the CdLS group showed significantly higher scores over time, $F(1,40) = 22.02$, $p < .001$, while the CdCS group remained fairly stable, $F(1,40) = .03$, $p = .869$. The *social interaction* subscale also revealed a significant interaction between time and syndrome group, $F(1,41) = 5.65$, $p = .022$. Pairwise comparisons showed that the CdLS group was significantly more impaired than the CdCS group at T2, $F(1,41) = 11.79$, $p = .001$, but not at T1, $F(1,41) = 1.94$, $p = .172$. Within syndrome groups, there were no significant differences over time for either the CdLS, $F(1,41) = 3.72$, $p = .061$, or the CdCS group, $F(1,41) = 2.68$, $p = .109$. There was no significant interaction between time and syndrome group on the *repetitive behaviour* subscale of the SCQ, $F(1,41) = 0.17$, $p = .683$, or main effects of time or syndrome group, $F(1,41) = 0.15$, $p = .701$, $F(1,41) = 0.01$, $p = .910$.

The CdLS group experienced a significant decline in their communication level over time whereas the CdCS group showed little change. The CdLS group started out more socially impaired (although not significantly) than the CdCS group at T1 and over time their abilities continued to decline whereas the CdCS group's abilities improved. The repetitive behaviour in both groups was very similar and stable over time.

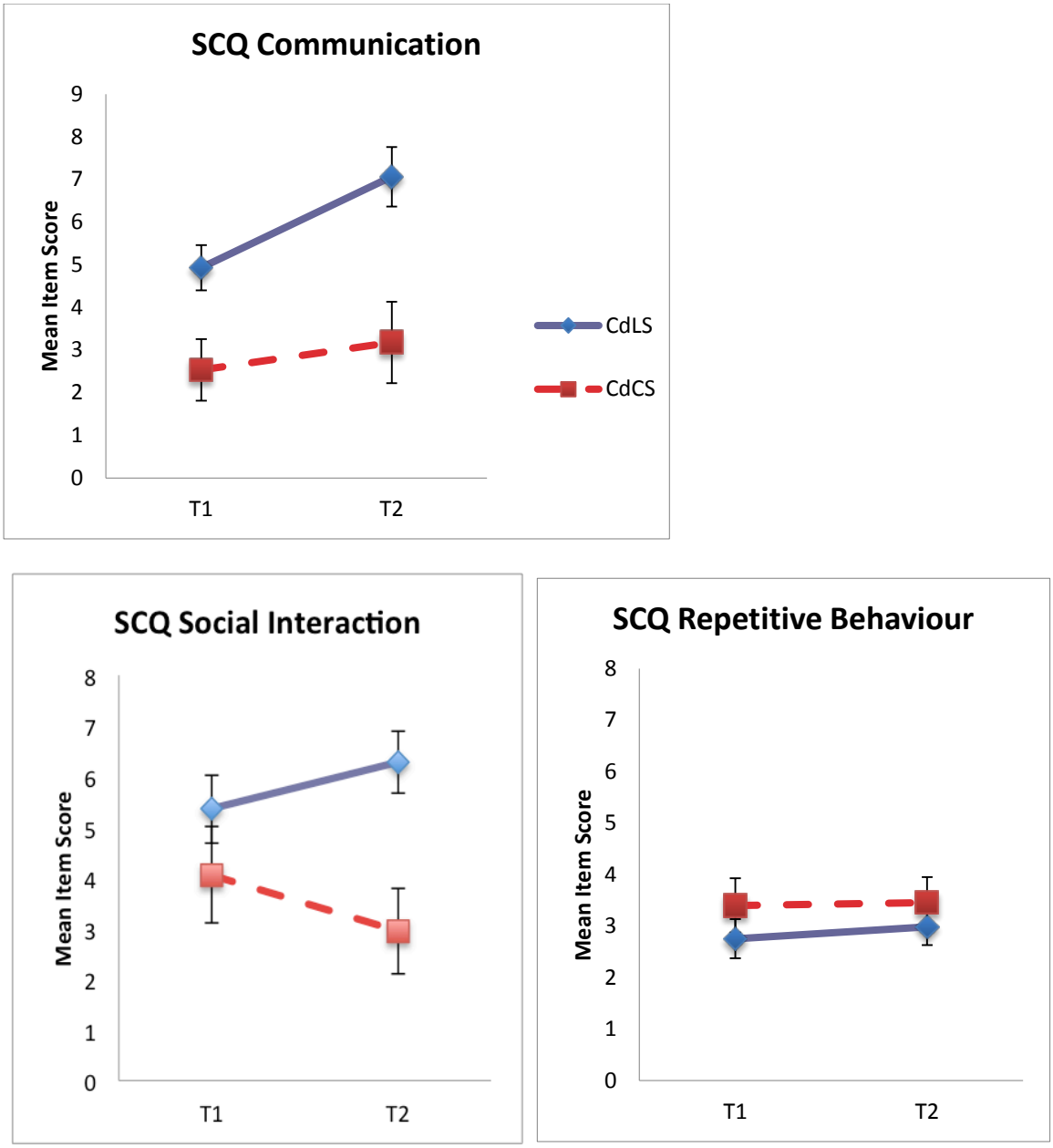


Figure 3.5: Mean item scores over time and between the CdLS and CdCS groups on the three domains of the SCQ (communication, social interactions and repetitive behaviour).

3.3.7. Summary of results

While receptive language skills increased in both syndrome groups over time on the BPVS, the VABS revealed a slightly more complex pattern with the CdLS group's skills decreasing and CdCS group's increasing over time. All other areas of adaptive behaviour skills remained stable over time in both syndrome groups. The percentage of CdLS participants meeting the cut-off for autism and ASD on the ADOS increased over time, suggesting a worsening of autism symptomatology. The increase in the CdLS group meeting the cut-off for ASD in the *social interaction* domain over time reveals an interesting pattern that highlights the social domain as an area of specific change. The ADOS domain level analysis confirms this pattern with the CdLS group showing a decline in social ability and the CdCS group improving slightly in this area over time. The SCQ *communication* domain level analysis revealed that the CdLS group experienced a significant decline in their communication level over time whereas the CdCS group showed little change. On the SCQ *social interaction* domain, the CdLS group started out more impaired (although not significantly) than the CdCS group at T1. Over time, the CdLS group's social interaction abilities continued to decline and the CdCS group's abilities improved, causing the significant difference in their scores at T2 on both the ADOS and SCQ. There was very little change observed over time in either group for the SCQ *repetitive behaviour* domain.

3.4. Discussion

The hypotheses of this study were: 1) The proportion of participants with CdLS reaching cut-off on the ADOS and SCQ will increase over time compared to CdCS; 2) The scores

on domains of the ADOS and SCQ will increase for the CdLS group in contrast to the CdCS group; 3) Adaptive behaviour skills will remain stable over time in individuals with CdLS. The increase in ASD phenomenology over time seen in CdLS (while not seen in CdCS) in this study adds to the current understanding of the behavioural phenotype of CdLS. This study employed a contrast group that was well matched on presence of a genetic syndrome and similar level of ID. This was the first research study to look at ASD phenomenology over time in CdLS and CdCS. The high proportion of participants in both syndrome groups who participated at both time points and the high level of inter-rater reliability on the ADOS strengthens the findings of this research. The main finding of this study was the specific changes over time in social behaviours and communication in CdLS.

Receptive language skills, as measured by the BPVS, increased over time in both syndrome groups while the adaptive behaviour skills, measured by the VABS, remained stable. These results show that there is not a general decline in abilities in either syndrome group over time. In contrast to the literature on ASD symptomatology over time in autism staying stable (Gotham et. al., 2012), this study found that the percentage of CdLS participants meeting the cut-off for autism and ASD on the ADOS increased over time, suggesting a worsening of autism symptomatology. The SCQ *communication* and *social interaction* domain level analysis revealed that the CdLS group experienced a significant decline in abilities over time while the CdCS group didn't experience these declines. The lack of change observed over time in either group for the SCQ *repetitive behaviour* domain was unexpected but gives important insight into the specificity of the areas of decline for future research.

The proportion of participants who were invited versus those who chose to participate in T1 as well as the recruitment method (family support groups) presents a potential for sampling bias, such as self-selection. A bias of this type would bring into question the generalizability of any findings to the group as a whole. However, the participant numbers are similar to other studies in rare genetic syndromes which supports the likelihood that the samples are representative of what other researchers in the literature have seen in this type of population (Howlin, Karpf, & Turk, 2005; Richards, Oliver, Nelson, & Moss, 2012; Arron, Oliver, Berg, Moss, & Burbidge, 2011). Research in rare genetic syndromes presents a restricted potential for recruitment of sufficient participants due to the limited number of known individuals with the syndrome in question. This makes it unlikely to achieve a completely random sample of participants in this area of research. The issue of recruitment method and its potential impact on the data could be addressed in future studies by including the addition of recruitment through medical practices. Although the study was restricted in size due to the longitudinal method, the extremely high participant retention allowed for a healthy sample size for a study of rare genetic syndromes. The unequal sample sizes at T2 (CdLS n= 30 and CdCS n= 18) raises the issue of possible confounds. It raises the question of whether there were enough participants in the smaller group (CdCS) to see an effect. However, disproportionate sample sizes are a common problem in research (especially in rare genetic syndromes) and the proportions of participants in each syndrome group are approximately the same as at T1. Any differences cause by an unequal sample size would be consistent over time. Severe levels of ID have been shown to impact autistic-like behaviours (Zafeiriou et al., 2013) but the use of mental age matched groups in this study and the lack of any decline over time in overall ability

level of the groups limits the possibility that this accounts for increased ASD symptomatology over time in the CdLS group. Another potential limitation was time and resources available to implement the most thorough measures. The ADI-R and ADOS are both 'gold standards' used in diagnosing and/or researching ASD, however, due to the substantial time and practicality restrictions the ADOS was chosen and utilised as a reliable measure of ASD phenomenology. Data from several other measures were collected but could not be included primarily due to the small sample size as a result of participants in both syndrome groups being unable to sufficiently perform the tasks (see Appendix 7 for a description of those measures). The additional measures attempted but not included in the analysis were: Expressive One-Word Picture Vocabulary Test (EOWPVT; Brownell, 2000), Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999), Wechsler Preschool and Primary Scale of Intelligence-Third Edition (WPPSI-III; Wechsler, 2002) and Repetitive Behaviour Questionnaire (RBQ; Moss and Oliver, 2008). For the expressive language and cognition measures there was not sufficient sample size due to varying levels of ability in both syndrome groups.

Previous research has highlighted CdLS as a syndrome with high levels of ASD phenomenology (Moss, 2008; Moss et. al., 2012; see also Chapter One). However, this study has shown that the strongest autistic-like behaviours are mostly in the social domain and not the other two domains. While this may be different from idiopathic autism, where deficits are seen in all three domains (communication, social interaction, repetitive and restricted behaviour), it is possible that therapies and treatments traditionally used in autism but specific to the social domain may be useful for individuals with CdLS. Future

research should aim a specific in depth look at individual social behaviours and fine-grained analysis of the ADOS.

CHAPTER FOUR

A longitudinal analysis of the profile of Autism Spectrum Disorder Phenomenology in Cornelia de Lange and Cri du Chat Syndromes (Item-level analysis)

4.1. Introduction

In Chapter Three, the presentation of autism spectrum disorder (ASD)-related characteristics in Cornelia de Lange syndrome (CdLS) and Cri du Chat syndrome (CdCS) was considered alongside how these might develop over time. Analyses of the current data indicated an increase in ASD characteristics specifically in CdLS, most markedly in the domains of social interaction and possibly communication. This chapter will further evaluate possible changes in ASD phenomenology over time in CdLS at a fine-grained level using psychometrically robust measures.

Recent research (e.g., Moss, Howlin, et al., 2013; Moss, Oliver, et al., 2013) has delineated differences in the specific profiles of ASD-related behaviours found in different neurodevelopmental syndrome groups including CdLS. In essence, it is possible to score highly on measures of ASD symptomatology and to meet criteria for clinical diagnosis for many different sets of reasons. Whilst the broad areas of impairment defining ASD - social deficits, communication problems and repetitive behaviours (DSM-IV-TR, APA, 2000; ICD-10, WHO, 1992) are by definition consistent to some degree between individuals who meet diagnostic criteria, there are many possible variants of these characteristics. Not only can people meet diagnostic criteria by showing different levels of symptomatology across the main triad of impairments (e.g., an individual whose impairments lie more with communication than with social interaction versus an individual displaying the opposite pattern), but also by displaying different behaviours *within* each of these domains (e.g., there are many different behaviours indicative of ASD-related interaction difficulties, and different individuals with ASD will display different combinations of these) (see Chapter One, section 1.3. for more details). This is reflected in widely used and robust measures of ASD symptomatology such as the SCQ and the ADOS, which assess a broad range of different behaviours contributing to the diagnoses.

As discussed in Chapter One, section 1.3.3, Moss, Oliver, et al. (2013) describe the atypical presentation of ASD in CdLS in contrast to idiopathic autism, and outline implications for intervention. The authors highlight the importance of understanding the unique profiles of ASD phenomenology in genetic syndromes, CdLS in particular. However given that the levels of ASD symptomatology may not be stable over time in

CdLS, evaluation of how the specific profile of ASD characteristics change over time (in relation to another syndrome with a similar level of ID) is crucial. This could have important implications for the focus and direction of treatment/intervention for CdLS.

In Chapter Two the prevalence of ASD phenomenology at different ages and over time in CdLS is examined, with CdCS and Fragile X (FXS) syndromes as appropriate contrast groups using parent report questionnaires. That chapter uncovered that although CdLS and FXS had similar overall percentages of individuals meeting cut-off for ASD and autism, differences emerged when examined by age groups. In the previous chapter (Chapter Three), how individuals with CdLS and CdCS presented ASD phenomenology on the broader levels (subscale and total scores) on the ADOS and SCQ were examined. In addition, it was examined how this phenomenology changed over seven years in CdLS and CdCS. Although the CdCS group's phenomenology remained fairly stable over time on all measures, the CdLS group did experience declines in social functioning. With changes over time shown in the previous studies on a broader scale, the next step is to evaluate these characteristics at a fine-grained level to see if specific items (and the related symptomatology) are contributing to the profile of ASD phenomenology in CdLS. Although this has been done at a single time point, this is the first study to look at this detailed level in a longitudinal design.

This chapter examines the profile of ASD phenomenology in CdLS and CdCS over seven years, at a fine-grained level, using methodology adapted and extended to a longitudinal design from Moss et al. (2012) and Moss et al. (2013).

The aim of this study is to determine which ASD-related characteristics change over time for participants with CdLS.

4.2. Method

4.2.1. Background of analysis

This chapter is a more detailed analysis of ASD phenomenology data collected for the study reported in the previous chapter (see Chapter Three). The study is a longitudinal follow-up in CdLS (n=32) and CdCS (n=18) syndromes focusing on the analysis of the Autism Diagnostic Observation Schedule (ADOS; Lord, Rutter, DiLavore, & Risi, 2000) and the Social Communication Questionnaire (SCQ; Rutter et al., 2003; Appendix 2) at a fine-grained level. Chapter Three explains the method used for design, recruitment and participant demographics. Data collection for this study involved a parent questionnaire measure and a research visit where assessments of social behaviours were conducted.

Table 3.3 in Chapter Three describes in full the demographic characteristics of the participants (CdLS and CdCS) who participated at both time points (Time 1, T1; and Time 2, T2).

As described in Chapter Three, at T1 the syndrome groups were comparable on all demographic variables (including gender, verbal ability, mobility, level of ability and receptive language) except chronological age which was necessary for the participants to be matched on mental age to account for the level of intellectual disability (ID). T1 chronological age has been included as a covariate where appropriate and possible in this chapter.

4.2.2. General data Analysis Strategy

4.2.2.1. Normality of data

Prior to analysis all data at the subscale and total level were tested for normality using Kolmogorov-Smirnov tests. Any data not normally distributed were examined using both parametric and nonparametric (or non-parametric equivalent) analyses. The purpose of running both parametric and non-parametric analyses is to ensure that the results are appropriately interpreted. As per convention, non-parametric analyses were run to ensure that results were the same as the parametric equivalent used to present the data in a more efficient and succinct way. Although parametric analyses are not traditionally used on skewed data, they are more likely to correctly identify a true significant effect due to more statistical power. The term "non-parametric equivalent" is used to describe the bootstrapping analysis as it is not technically a non-parametric statistic but accomplishes the same function by accounting for the distribution of the sample.

4.2.2.2. Data analysis for ADOS and SCQ

Scores on individual items on the ADOS and SCQ were assessed at two time points for CdLS and CdCS groups. Moss (2012) and Moss (2013) provided a basis for the data analysis strategy for examining these measures at item-level. Additional elements of the method of analysis were added due to the longitudinal design of the current study. Due to the number of analyses, a conservative alpha level of $p < .01$ was employed throughout. The $p < .01$ alpha level reduces the chances of Type 1 errors (identification of a significant difference when none exists) and increases the chances of Type 2 errors (not identifying significant differences when they exist). The number of analyses run in this study increase

the chances of finding significant differences and therefore it was decided to employ the more conservative alpha level. Conventionally, a Bonferoni correction might be employed. However, it is increasingly recognised that such an approach is perhaps too conservative against the background of rare disorders, available resources and the clinical importance of identifying potentially treatable conditions. Consequently, $p < .01$ was selected as an alpha level that acknowledges both sides of the debate.

4.2.2.3. ADOS measure

The ADOS (Lord, Rutter, DiLavore, & Risi, 2000) was used to measure ASD phenomenology and is a semi-structured observational assessment (see Chapter One section 1.4.1. for a full description of the ADOS). Each module provides four domain scores: *1*) *communication 2) social interaction 3*) *imagination and creativity 4) repetitive behaviour* and a total social-communication score. Each module offers a slightly different cut-off score for ASD and autism. Not all items on the ADOS are included in the algorithm for meeting cut-off scores. Therefore, all data will be presented separating the items into 'algorithm' and 'non-algorithm' items to help the reader distinguish between behaviours that lead to a diagnosis and those that do not. Item scores range from 0 (no observed impairment) to 3 (marked observed impairment). Item-level scores were converted per the ADOS manual (scores of 3 became 2 and scores of 8 became 0).

4.2.2.4. Parametric analyses of the ADOS items

The analysis of the ADOS was done at the item-level and followed the basic method used in the 2012 Moss paper, although, adapted to a longitudinal design and extended to measure change over time. Mixed ANOVAs, with time point (2 levels, within-

participants) and syndrome group (2 levels, between-participants) as independent variables, were used to analyse each ADOS item score. T1 chronological age was included as a covariate.

4.2.2.5. Bootstrapping

To allow for possible violations of the assumptions of the linear models, further analyses were carried out using bootstrapping methodology (Efron, 1979; Field, 2013). Bootstrapped linear regressions (1,000 samples) were used due to their lack of distributional assumptions to analyse the effect of syndrome group change in ADOS item scores from T1 to T2. To assess change over time a new "change" variable was created for each ADOS item by subtracting each participant's T1 score for the item from their T2 score. Chronological age at T1 and syndrome group were both included in the analyses as independent variables. Beta values for syndrome group and age were considered to differ from 0 (indicating a significant impact on scores) if the 99% confidence intervals did not include 0. Due to the number of analyses a more conservative confidence interval of 99% was used instead of the standard 95%.

4.2.2.6. The Social Communication Questionnaire (SCQ) items (Appendix 2)

SCQ item scores are yes/no (yes=1/no=0). Some of the SCQ items are reverse scored (no=1/yes=0). Therefore the implication of severity from a score of 'yes' or 'no' changes from item to item, a 'yes' score may mean more severity on one question and less on another. To clarify the results displayed in figures they are displayed in terms of percentage of participants scoring "impaired" (i.e., gaining a score on that item which contributes to a higher overall SCQ score indicating higher levels of ASD traits). The SCQ

scoring algorithm uses questions 2 through 40 (except for questions 17, 18 & 38) to compile three domains: *1) communication, 2) repetitive behaviour* and *3) restricted interests and reciprocal social interaction*. To remain consistent with Moss (2013), item 20 'Social Chat' was excluded and all analyses were done with and without verbal participants to exclude a bias based on the number of non-verbal participants in one group. McNemar analyses were utilized to assess changes within syndrome groups from T1 to T2 on the SCQ items. Chi-square analyses were utilized to assess possible differences in frequencies of yes/no responses between the syndrome groups at each time point.

4.3. Results

4.3.1. ADOS

Mixed ANOVAs were used to assess change over time for the CdLS and CdCS groups on the individual ADOS items, including T1 chronological age as a covariate. Both algorithm and non-algorithm items were included in the analyses. Figures 4.1 and 4.2 show the adjusted mean scores of the two groups on the ADOS algorithm and non-algorithm items, respectively, at each time point.

4.3.2. ADOS Algorithm items

ANOVAs indicated no significant interactions between group and time point on any of the ADOS algorithm items (see Appendix 9 for a complete list of p values). There was a main effect of time for *eye contact* $F(1,45) = 7.93$, $p = .007$ and *quality of social overtures* $F(1,45) = 16.78$, $p < .001$. Both items showed increased scores over time in both syndrome groups. There was a main effect of group on *Gestures* $F(1,45) = 8.23$, $p = .006$

and *Imagination and creativity* $F(1,45) = 11.74$, $p = .001$. The CdCS group scored lower than the CdLS group on both items.

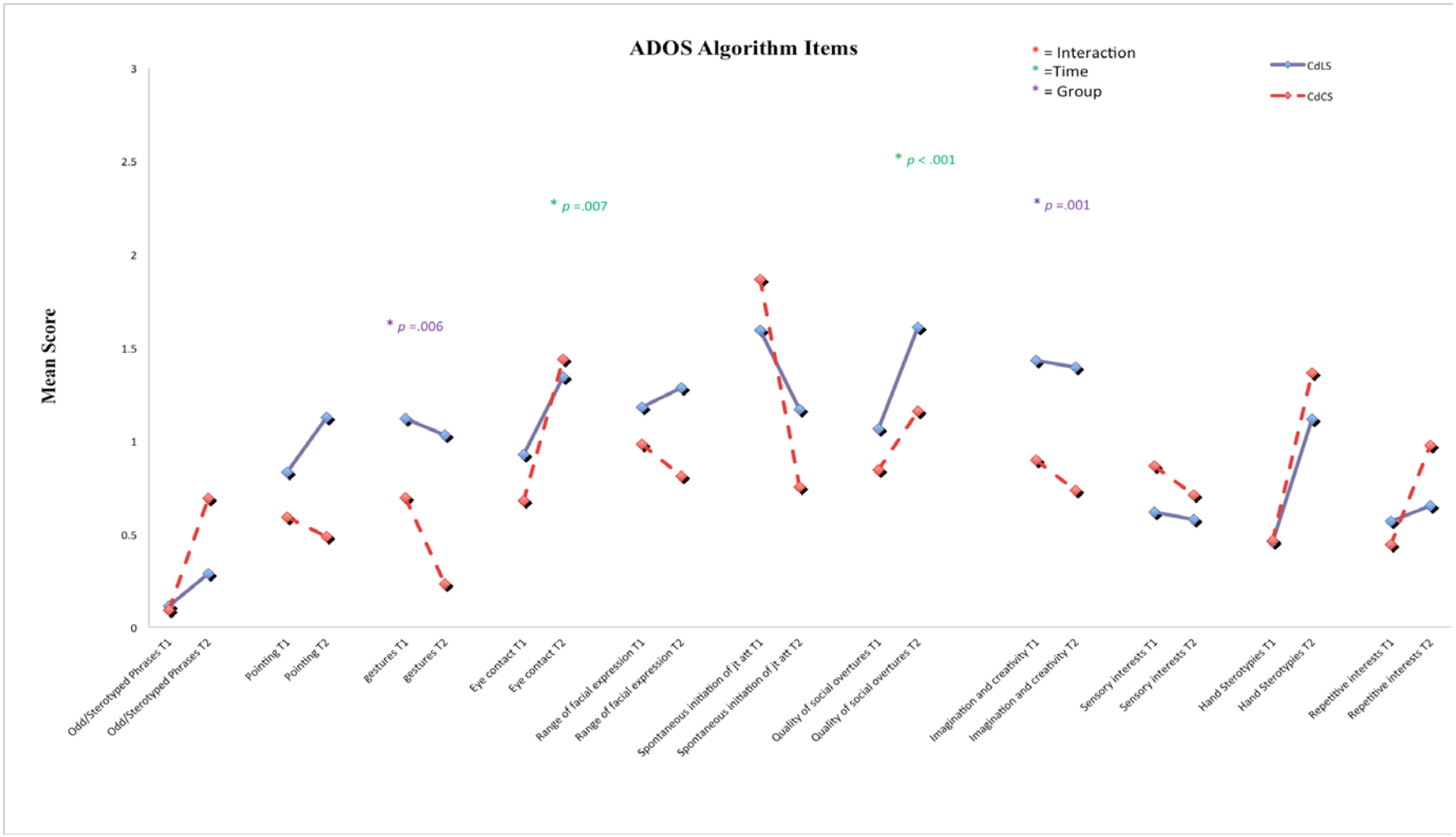


Figure 4.1: ADOS algorithm item mean scores with age covariate (A higher score is indicative of greater impairment).

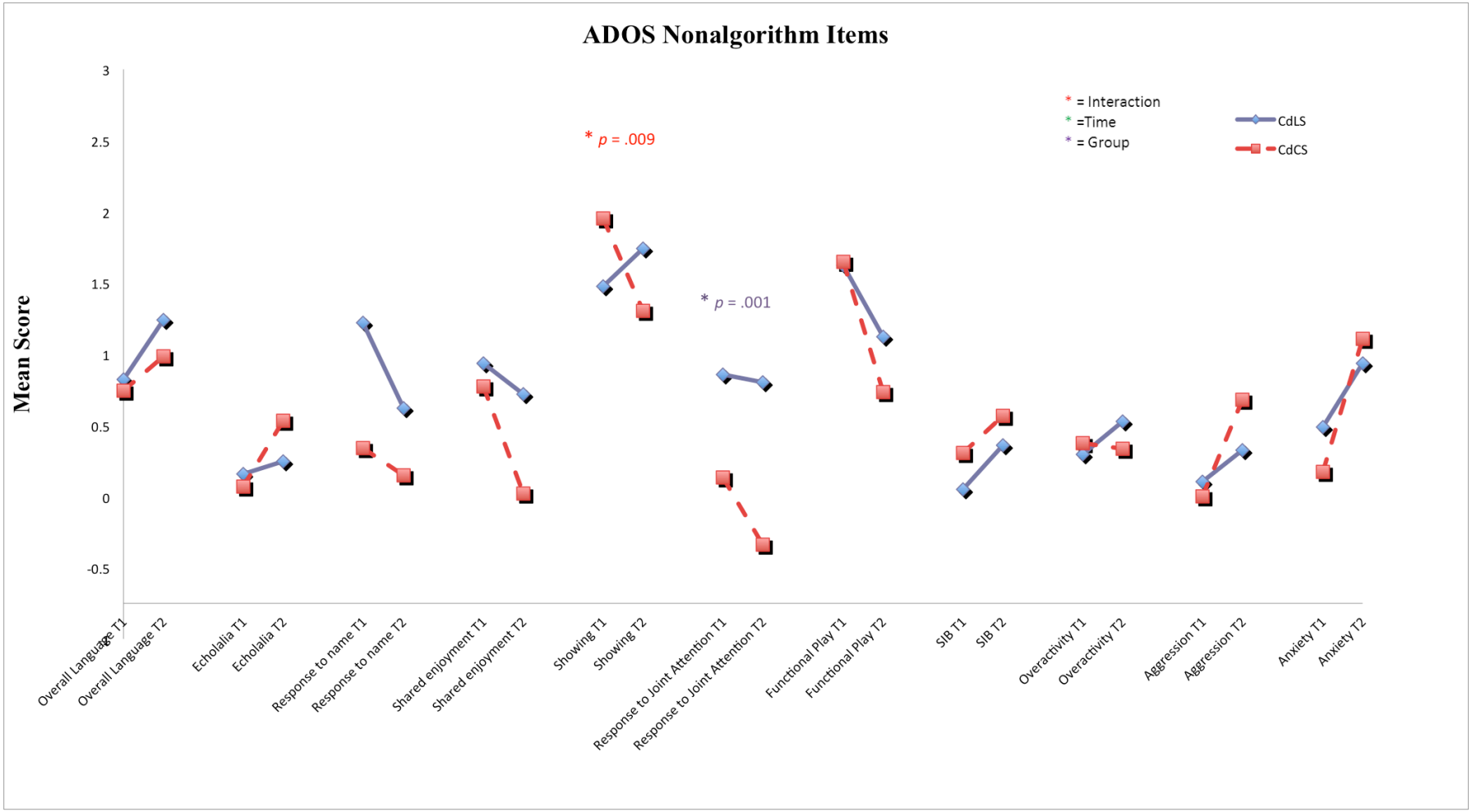


Figure 4.2: ADOS non-algorithm item mean scores with age as covariate (A higher score is indicative of greater impairment).

4.3.3. ADOS Non-algorithm items

On the ADOS non-algorithm items there was a significant interaction between time and syndrome group on *showing* $F(1,27) = 7.85$, $p = .009$. Pairwise comparisons showed that the CdLS group's scores increased over time while the CdCS group's scores decreased. There was a main effect of group on *response to joint attention* $F(1,27) = 13.06$, $p = .001$, with the CdLS group scoring significantly higher than the CdCS group. There were no other significant main effects or interactions on any item at the $p < .01$ level (see Appendix 9 for a complete list of *p* values).

4.3.4. Bootstrapping

Linear regression with bootstrapping revealed a significant effect of syndrome group on *change in showing* behaviour only. Table 4.1. presents the results for change on each item (T2 score minus T1 score) arranged by domains.

Table 4.1: Results of the linear regression with bootstrapping for the ADOS algorithm and non-algorithm items arranged by domain. Change in behaviour (T2 minus T1 score) variables.

		Change in behaviour		
			99% CI	
Variable	***P* value**	***B***	**Lower**	**Upper**
Algorithm Items				
Communication				
Odd/Stereotyped Phrases	.05	0.422	-0.056	1.077
Pointing	.24	-0.397	-1.172	0.485
Gestures	.11	-0.375	-0.929	0.206
Social Interaction				
Eye contact	.32	0.344	-0.609	1.371
Range of facial expression	.25	-0.272	-0.885	0.423
Spontaneous initiation of joint atten.	.09	-0.690	-1.797	0.237
Quality of social overtures	.30	-0.230	-0.809	0.327
Play				
Imagination and creativity	.72	-0.126	-1.014	0.723
Repetitive Behaviour				
Sensory interests	.33	-0.115	-1.009	0.738
Hand Stereotypies	.40	0.242	-0.493	0.997
Repetitive interests	.10	0.450	-0.207	1.118
Non-algorithm Items				
Communication				
Overall Language	.54	-0.178	-1.020	0.535
Echolalia	.03	0.376	-0.012	0.838
Social Interaction				
Response to name	.24	0.407	-0.392	1.377
Shared enjoyment	.14	-0.531	-1.495	0.307
Showing	.007*	-0.912	-1.811	-0.182
Response to Joint Attention	.62	-0.111	-0.666	0.366
Play				
Functional Play	.29	-0.412	-1.380	0.608
Repetitive Behaviour				
SIB	.84	-0.050	-0.711	0.57
Other				
Overactivity	.26	-0.271	-0.819	0.333
Aggression	.14	0.453	1.670	0.102
Anxiety	.03	0.485	-0.129	1.001

4.3.5. SCQ

McNemar analyses were used on the SCQ items to look for change over time within each syndrome group. Neither syndrome group showed significant changes on any SCQ item between T1 and T2 at the $p < .01$ alpha level. Chi-square analyses were used to look for differences between syndrome groups at each time point in the frequency of "yes" and "no" answers for each SCQ item. At T1 there was a significant difference between syndrome groups for the following items: *Pointing to express interest* and *Interested in children (s)he doesn't know*. With both items the CdLS group showed a higher percentage of participants scoring as impaired compared to the CdCS group. Results were similar when the analyses were run on questions 2-7 for verbal participants only. At T2 there was a significant difference between syndrome groups for the following questions: *Pointing to express interest, Gestures, Offering to share, Imaginative play, Interested in children (s)he doesn't know* and *Respond to other children's approaches*. Consistent with T1, the CdLS group showed a higher percentage of participants scoring as impaired compared to the CdCS group. Results were similar when the analyses were run on questions 2-7 for only verbal participants. It is interesting that *Gestures, Offering to share, Imaginative play* and *Respond to other children's approaches* did not show a significant difference at T1 but did at T2. Table 4.2 presents the results of the Chi-square analyses for each SCQ item organised by domain (*communication, repetitive behaviour* and *reciprocal social interaction*) for each time point (T1 and T2). Figures 4.3, 4.4 and 4.5 show the percentage of participants in each syndrome group whose scores indicated impairment on each of the SCQ items by domain (*communication, repetitive behaviour* and *reciprocal social interaction*) respectively.

Table 4.2: Results of the Chi-square statistical analyses of the SCQ items by domain for T1 and T2 and the percentage of impairment at each time point for each syndrome group.

		T1				T2			
Domain	**Item**	X^2	***p* value**	**Percentage of Impairment CdLS n=30**	**CdCS n=18**	X^2	***p* value**	**Percentage of Impairment CdLS n=29**	**CdCS n=15**
Communication	Conversation	0.27	.60	6	11	0.68	.41	17	30
	Stereotyped utterances	0.68	.41	50	66	0.45	.50	53	67
	Inappropriate quest.	3.76	.05	28	66	6.25	.01	18	67
	Pronoun reversal	0.31	.58	44	33	0.20	.65	47	38
	Neologisms	0.01	.94	24	22	0.16	.69	29	38
	Imitation	5.69	.02	63	28	3.43	.06	69	40
	Pointing to express interest	10.00	.002*	50	6	8.67	.003*	52	7
	Gestures	5.44	.02	43	11	9.81	.002*	55	7
	Nodding *yes*	5.44	.02	43	11	4.71	.03	46	13
	Head shaking *no*	3.60	.06	43	17	4.20	.04	44	13
	Imitative social play	0.35	.56	30	22	4.52	.03	54	20
	Imaginative play	1.68	.20	47	28	7.09	.008*	75	33
Repetitive Behaviour	Verbal rituals	0.07	.79	50	56	2.10	.15	44	75
	Compulsions and rituals	0.02	.88	47	44	2.15	.14	67	43
	Unusual preoccupations	0.74	.39	28	17	0.16	.69	30	36
	Rept. use of objects	0.46	.50	40	50	0.30	.59	48	57
	Circumscribed interest	0.01	.93	27	28	3.93	.05	15	43
	Unusual sensory interests	0.03	.87	30	28	0.01	.94	30	29
	Hand and finger mannerisms	0.51	.47	45	56	0.30	.59	52	43
	Complex body mannerisms	0.46	.50	40	50	0.29	.59	37	29
Reciprocal Social Interaction	Inappropriate facial expression	2.46	.12	31	11	2.13	.15	14	0
	Use of other's body to communicate	0.82	.36	37	50	5.98	.01	34	73
	Friends	0.94	.33	47	61	0.35	.55	69	60
	Eye gaze	0.10	.75	13	17	2.66	.10	28	7
	Social smiling	0.37	.55	11	6	2.84	.09	18	0
	Showing and directing attention	3.29	.07	27	6	4.48	.03	25	0
	Offering to share	0.06	.82	37	33	7.62	.006*	48	7
	Seeking to share enjoyment	1.65	.20	27	11	6.69	.01	34	0
	Offering comfort	1.01	.31	48	33	2.63	.11	45	20
	Quality of social overtures	1.13	.29	17	6	3.74	.05	21	0
	Range of facial expression	0.05	.82	21	24	0.72	.40	32	20
	Interest in children	10.33	.001*	60	12	12.37	<.001*	62	7
	Response to other children's approaches	3.63	.06	50	22	7.30	.007*	52	8
	Imaginative play with peers	0.02	.88	63	61	5.34	.02	90	60
	Group play	0.29	.59	37	44	2.87	.09	54	27

* Degree of Freedom df=1 for all..

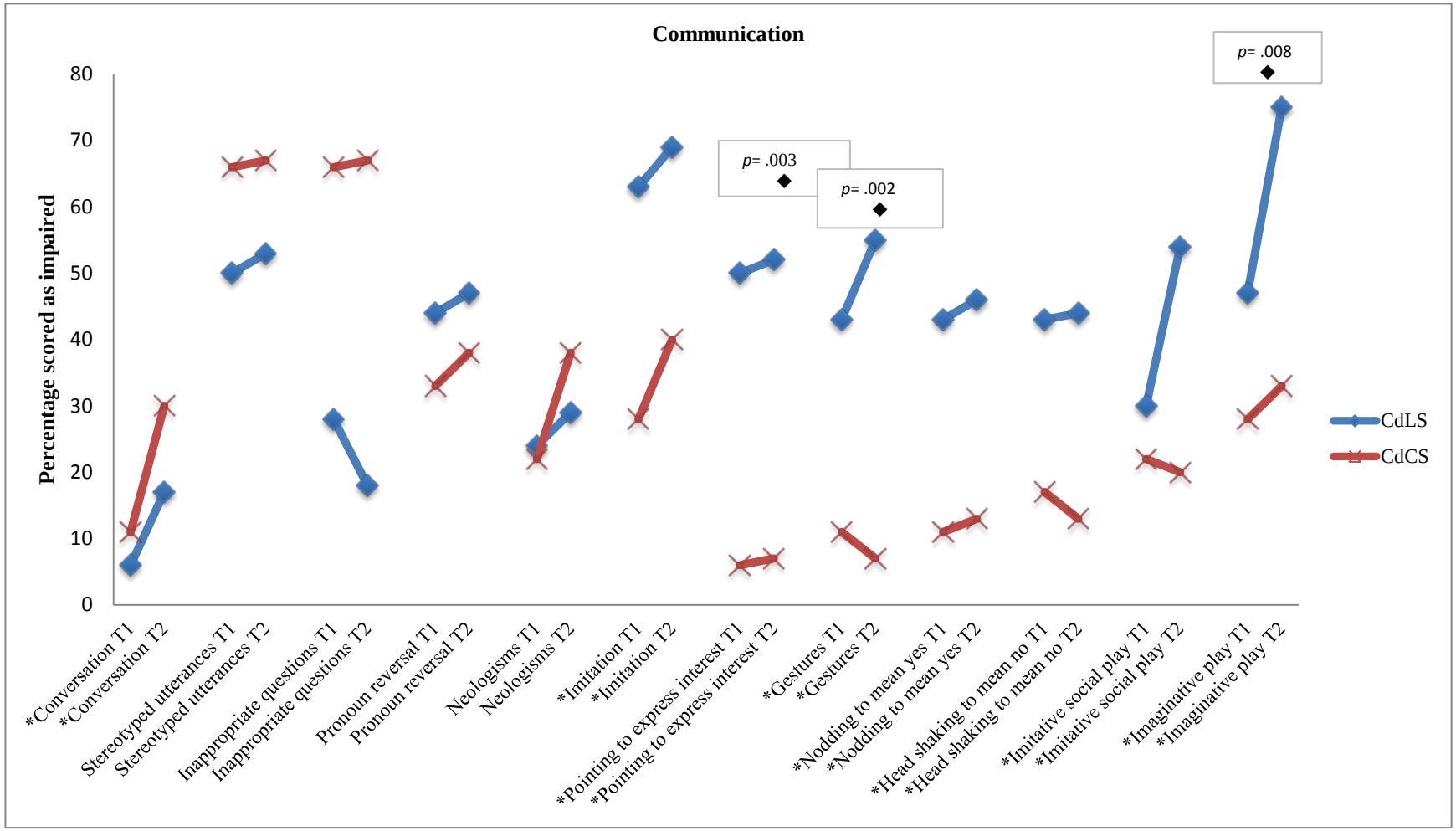


Figure 4.3: Percentage of participants with a score showing impairment on the SCQ communication domain items for T1 and T2. Chi-Square analysis between syndrome groups.

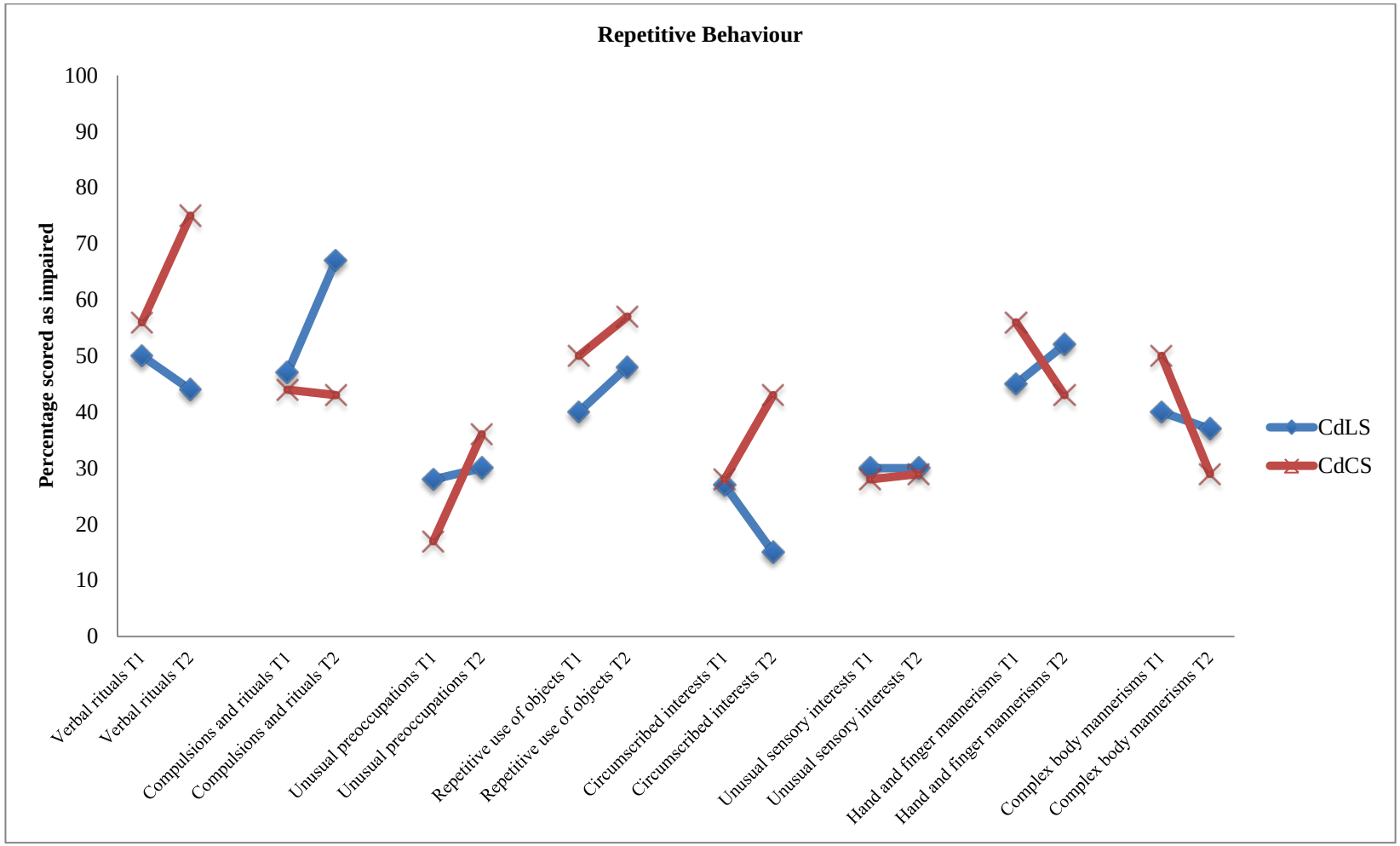


Figure 4.4: Percentage of participants with a score showing impairment on the SCQ repetitive behaviour domain items for T1 and T2.

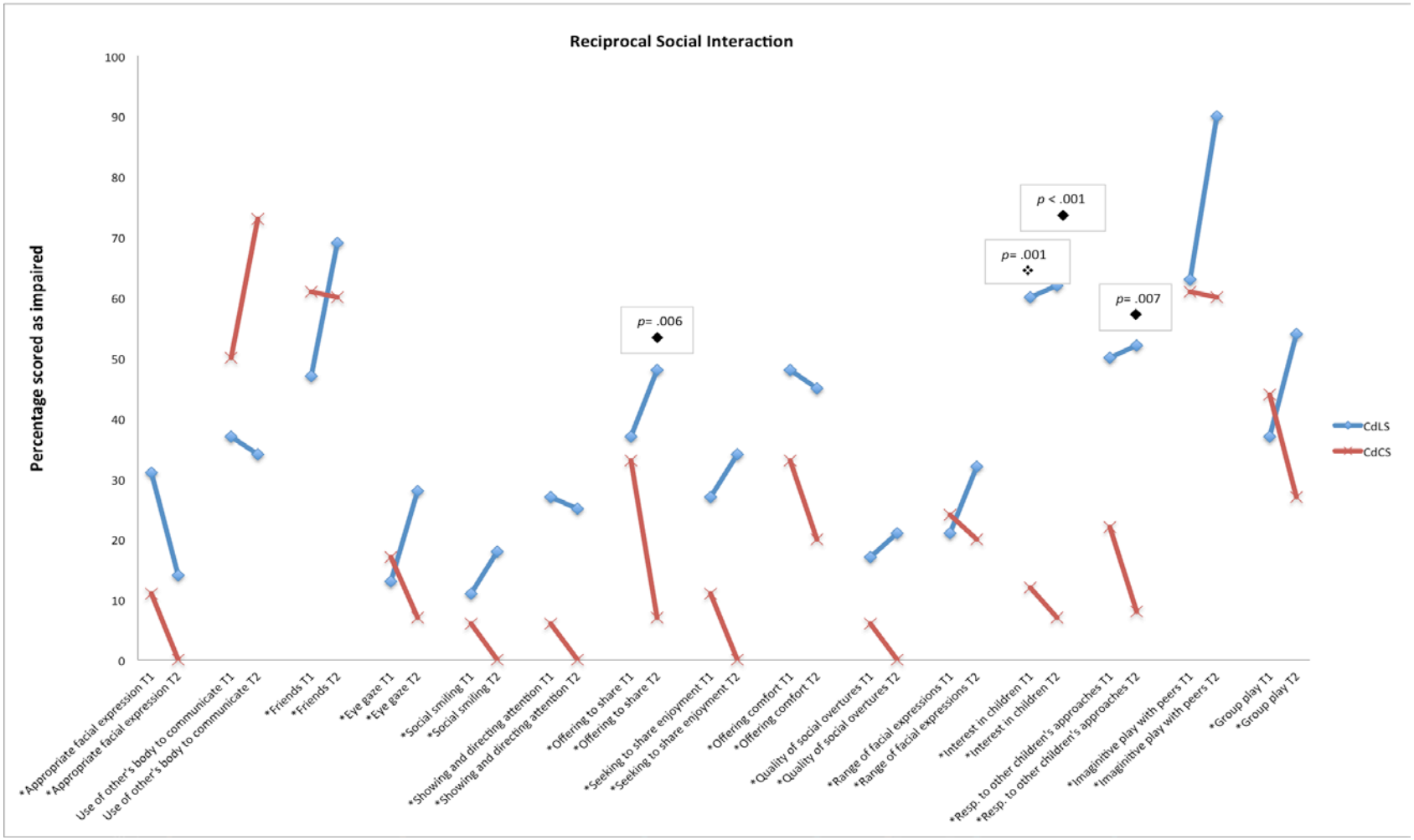


Figure 4.5: Percentage of participants with a score showing impairment on the SCQ reciprocal social interaction domain items for T1 and T2.

4.3.6. Summary of results

The mixed ANOVAs revealed that on the ADOS algorithm items *Eye contact* and *Quality of social overtures* there was a main effect of time with an increase in severity over time across both syndrome groups. There was a main effect of group on *Gestures* and *Imagination and creativity* items, with the CdCS group scoring lower (less impaired) than the CdLS group. On the ADOS non-algorithm items, there was a significant interaction between time and syndrome group on *Showing* with the CdLS group's scores reflecting an increase in severity over time and a divergent pattern in the CdCS group. The bootstrapped linear regression also showed a significant association between syndrome group and change in behaviour over time on *Showing*. The McNemar analyses did not show any significant changes over time on the SCQ items within either syndrome group. However, the Chi-square analysis identified a different pattern of significant differences between the syndrome groups at the two time points. At T1, the items *Pointing to express interest* and *Interested in children he doesn't know* showed a significant difference between the groups with greater impairments in the CdLS group. At T2, there remained group differences in both of the items and additional group differences in *Gestures, Offering to share, Imaginative play* and *Respond to other children's approaches*. On all these items the CdLS group had a significantly higher percentage of participants scoring impaired than the CdCS group (CdLS > CdCS). There were a number of items that fell between $p = .01$ and $p = .05$ (at T1 *Imitation, Gestures* and *Nodding to mean Yes* with CdLS > CdCS; at T2 *Nodding to mean Yes, Head shaking to mean No, Imitative social play, Seeking to share enjoyment* and *Imaginative play with peers* with CdLS > CdCS; also *Inappropriate questions* and *Use of other's body to communicate* with CdCS > CdLS). It is noteworthy that all of the items with a significant difference between the syndrome groups (or those

between *p* .01 and *p* .05) are on the *communication* and *reciprocal social interaction* domains. Although those findings may warrant further investigation, they need to be taken with extreme caution due to the number of statistical analyses run in this study. None of the results for items on the *repetitive behaviour* domain approached a significant difference.

4.4. Discussion

This is the first study to look at the profile of ASD phenomenology in either CdLS or CdCS over time at a fine-grained level. Moss et al. (2012 & 2013) established profiles of ASD characteristics for individuals with CdLS with item-level analyses of the SCQ and ADOS respectively at one time point. This study endeavours to expand on those profiles with a longitudinal methodology and a contrast group that closely matches the CdLS group's level of ID. The aim of this study is to determine which ASD-related characteristics change over time for participants with CdLS. Item-level scores were compared between the syndrome groups (CdLS and CdCS) at each time point (T1 and T2) as well as over the seven years.

Some findings did not show a change over time in ASD-related characteristics in CdLS as there was not a main effect of time on the ADOS algorithm items *Eye contact* and *Quality of social overtures.* On these two items both syndrome groups showed a worsening of impairment over time. In contrast to this, Moss (2012) showed that their CdLS group used eye contact and gestures significantly more than their ASD group. In addition, Reid, Moss, Nelson, Groves, and Oliver (2017) reported that when compared to individuals with Down syndrome, individuals with CdLS had prolonged eye contact. These current findings

would suggest that over time this increased level of eye contact in CdLS (and CdCS) might diminish. The basis and correlates of this change require further study, including possible relationships with social abilities and motivations.

Other findings, however, in this study did reveal changes in ASD characteristics. For example, a main effect of group was discovered on the ADOS algorithm items of *Gestures* and *Imagination and Creativity* with the CdLS group showing greater impairment than the CdCS group (across both time points). A significant interaction between time and syndrome group was uncovered for the ADOS item of *Showing*. The CdLS group displayed less showing behaviour (increased impairment) over time whereas the CdCS group displayed more showing over time (less impairment). Consistent with this, the bootstrapping analyses also indicated a significant effect of syndrome group on *Change in showing* behaviour. It is unclear what is causing the marked relative deterioration of showing behaviour in the CdLS group. It may relate to deteriorating social abilities, but it could also be due to a decline in mood or lack of desire to be social (either lack of motivation or anxiety) or a combination of factors. This is consistent with changes in mood observed by Nelson et al. (2014).

Although the non-algorithm items on the ADOS do not contribute to the final determination of whether they meet criteria for ASD or autism on that measure, they are included due to the importance of those behaviours in the overall picture of ASD characteristics. Taking both time points into account, the CdLS group had greater impairment on the ADOS item of *Response to joint attention* than the CdCS group. The CdLS group may be less interested in attending to something with someone else because

they do not have the same level of interest in social behaviours as the CdCS group. *Response to joint attention* is a highly social behaviour that requires the individual to draw someone else's attention to an item or task, often prompted by the need for their assistance or to share pleasure. Despite the differences between the CdCS and CdLS groups on *Response to joint attention*, results indicated no significant change in this behaviour within the CdLS group which is relatively stable over time. This suggests that whatever the possible cause for the lack of social interaction it is consistent over time.

The results on the SCQ were mixed; the McNemar analyses did not reveal any significant changes over time in either syndrome group. However, Chi-square analyses of the SCQ items indicated some between group differences at each time point. The CdLS group had a significantly higher percentage of participants scoring impaired than the CdCS group (at both time points) on *Pointing to express interest* and *Interested in children he doesn't know*. At T2, there were additional group differences (with the CdLS group having a significantly higher percentage scoring impaired) on *Gestures*, *Offering to share*, *Imaginative play*, and *Respond to other children's approaches*. It is worth consideration that a number of SCQ items fell between $p = .01$ and .05. The items that fell into this category at T1 were: *Imitation*, *Gestures* and *Nodding to mean Yes* with CdLS > CdCS; at T2: *Nodding to mean Yes*, *Head shaking to mean No*, *Imitative social play*, *Seeking to share enjoyment* and *Imaginative play with peers*, again, with CdLS > CdCS. In addition, two items at T2 showed the opposite pattern (CdCS > CdLS): *Inappropriate questions* and *Use of other's body to communicate*. Interestingly, these latter two items represent behaviours with social intent, though potentially inappropriately executed, which may be consistent with higher social motivation in the CdCS group than CdLS group. It is

noteworthy that all of the items with a significant difference between the syndrome groups (or those between *p* .01 and *p* .05) are on the *communication* and *reciprocal social interaction* domains. None of the results for items on the *repetitive behaviour* domain approached a significant difference. This is especially interesting because repetitive behaviours are such an important part of idiopathic autism and other associate genetic syndromes (such as FXS, where repetitive behaviours are a strong contributor to the ASD diagnosis).

Taken together, the SCQ and ADOS data indicate specific ASD-related behaviours, which differ between the CdLS and CdCS groups, all within the domains of *social interaction* and *communication*. Some of these differences may be relatively stable over time (e.g., impaired pointing and reduced interest in other children, as assessed by the SCQ), but for some behaviours there are indications of increasing impairments, specifically in the CdLS group. This is perhaps most marked for "showing" (as assessed by the ADOS). This is a category of behaviour arguably representing both motivation to communicate specific information and the ability to initiate a state of shared attention with another person. This is consistent with Sarimski (2002) where it was reported that the numbers of intentional communicative acts, specifically in the communication domain, were significantly fewer in CdLS than the matched control groups (Down and CdCS). However, Sarimski's study had a modest sample size (n=13), only included participants with CdLS who were 2-8 years with severe cognitive impairments and no expressive language. This makes it impossible to generalize to the syndrome group as a whole. The findings in this chapter's study also indicate there may be increasing impairments in the CdLS group relative to the CdCS group in gestures, imaginative play and responses to the social approaches of others

(as assessed by the SCQ). These are all areas requiring social motivation and skills, the relative contributions of which remain to be elucidated. It should also be noted that worsening mood might be hypothesised to contribute to the apparently increasing ASD phenomenology in the CdLS group over time. For instance, Nelson, Moss, and Oliver (2014) showed significantly lower levels of mood, interest and pleasure in older individuals with CdLS compared to older individuals with FXS or CdCS. It is possible that this impacts the motivation and/or skillset of those with CdLS of more advanced age.

There were some possible differences between the SCQ and ADOS in the patterns of ASD phenomenology they describe in the two groups over time. For instance, only the SCQ found a difference on *Pointing to express interest, Offering to share* and *Response to other children's approaches.* Whereas only the ADOS found group differences on *Eye gaze, Quality of social overtures* and *Showing*. Although both measures look at similar behaviours, differing levels of sensitivity (true positive) and specificity (true negative) on the measures could be affecting the findings. It may also be that the SCQ relies on parent/carer reports and the ADOS uses the ratings of an unrelated assessor, which detect qualitatively different atypicalities. Parent reports are often very different than the view of a trained professional and are prone to issues with bias, however, they also include valuable data and an overall bigger picture of the individual's abilities/behaviours.

It is important to consider a few factors that could limit interpretation of the findings in this current study. The difference in T1 chronological age, whilst necessary for matching developmental age, may make the findings slightly more difficult to interpret. It would also be beneficial for future research to look at using an idiopathic autism group alongside

the CdLS group with a longitudinal design. Although it is known from Moss (2012) how these two groups compare at one time point, it would be helpful to see how the ASD group changes over time and to compare changes in CdLS directly to changes in an idiopathic ASD comparison group. This might help separate some of the differences that are solely due to the presence of a genetic syndrome. In addition, it would be useful for future research to allow for a longer follow-up length with more time points to show a true trajectory of change. The multiple follow-up visits could correspond to developmental milestone ages or the predicted age in CdLS when these might occur. Based on the findings of this study, it would also be beneficial to look at the items that fall between p = .01 and p = .05 to see if there is more to be discovered about these items in relation to the CdLS group when compared to a group (like CdCS) with an equivalent mean mental age. However, the low attrition rate, the length of the follow-up period, the use of a reliable observational measure of ASD (the ADOS) and employing a contrast group with similar levels of ID (CdCS) to CdLS are all strengths of this study.

CHAPTER FIVE

Discussion

5.1. Background

Chapter One (sections 1.1. and 1.3.) provided a brief review of the current literature on behavioural phenotypes and autism spectrum disorder (ASD) phenomenology pertinent to this thesis. Descriptions of observable behaviours in genetic syndromes have made a significant contribution to our knowledge of behavioural phenotypes. Research has also evolved to include detailed studies of behaviour profiles that have helped to predict trajectories of development and to direct personalised treatment plans (Down, 1866/1990; Nyhan, 1972; Harris, 2002; O'Brien, 2006).

Section 1.3 described the overlap and/or presence of ASD phenomenology and autistic-like behaviours in a range of genetically defined syndromes including, amongst others, Cornelia de Lange syndrome (CdLS) and Fragile X syndrome (FXS). This literature suggests that there may be critical information about the nature and aetiology of ASD and related characteristics to be discovered by examining these characteristics in genetic

syndromes in which they are particularly prominent (see Chapter One section 1.3.2. for detailed information on these syndromes). Betancur (2011) elaborates on this point stating:

> Detailed investigation of ASD phenomenology within individual genetically determined syndromes, taking into account the intellectual functioning and looking also for the presence of other neuropsychiatric disorders such as obsessive compulsive disorder, attention deficit-hyperactivity disorder, schizophrenia and bipolar disorder, would contribute to strengthen the emerging notion of shared genetic bases among some or all of these conditions (Betancur, 2011, p. 62).

The literature review (section 1.3.3.) indicated that one syndrome of particular interest is CdLS as it has a high prevalence of ASD phenomenology but shows an atypical profile relative to that observed in idiopathic autism, particularly when these characteristics are examined at a fine-grained level (Moss, Oliver, et al., 2013; Moss & Howlin, 2009; Oliver, Berg, Moss, Arron, & Burbidge, 2011). The literature review identified a lack of longitudinal research in CdLS that examined how the profile or ASD phenomenology changes with age or over time. Knowing how these behaviours change with age and over time gives individuals with CdLS and their families priceless information about what might be expected in the future.

In this thesis, several methodological issues were addressed that have been problematic in previous studies (see sections 1.1.3 and 1.4.). These issues included: the use of appropriate contrast groups, psychometrically robust measures, strong inter-rater reliability, longitudinal design and fine-grained analyses. First and foremost, appropriate contrast

groups were utilised to allow for comparison between genetic syndromes with similar levels of intellectual disability (ID) (Cri du Chat; CdCS) and/or similar presence of ASD symptomatology (FXS). This was imperative in order to distinguish between phenomenology associated with ID and that of ASD (section 1.1.3.). This is further discussed in section 5.4. The use of the Autism Diagnostic Observation Schedule (ADOS; Lord, Rutter, DiLavore, & Risi, 2000) assessment, along with other standardised measures such as the Social Communication Questionnaire (SCQ; Rutter et al., 2003), provided a solid foundation for measuring ASD phenomenology (section 1.4.1). The study presented in Chapter Three is the first to use this observational measure to evaluate changes in ASD symptomatology across such a long follow-up (7 years) in CdLS and CdCS. The level of inter-rater reliability between the ADOS examiners at each time point was good and adds assurance that the findings are valid and representative of these two groups. The detailed analysis of the profiles of ASD phenomenology in CdLS and CdCS at both time points offers vital information about how individuals with these syndromes may progress over time (Moss et al., 2011; section 1.2.2). Detailed information about what to expect in the future is of the highest importance to the families of individuals with CdLS. This thesis strived to provide as much information as possible in this respect.

5.2. Aims of this thesis

- The first aim of this thesis was to evaluate the profile of autism spectrum disorder phenomenology in Cornelia de Lange syndrome **at a single point in time** compared to appropriate contrast groups using informant and observational measures. This aim was addressed in all three chapters.

- The second aim of this thesis was to conduct a longitudinal follow-up and to evaluate **changes** in the prevalence of autism and autism spectrum disorder in Cornelia de Lange syndrome and examine **changes at a broad domain and total score level** using psychometrically robust measures. This aim was addressed in Chapter Two and Chapter Three: '*Age related changes in autism spectrum phenomenology and repetitive behaviour in Cornelia de Lange, Fragile X and Cri du Chat syndromes'* and '*Autism spectrum disorder phenomenology over time in Cornelia de Lange and Cri du Chat syndromes'*.
- The third aim of this thesis was to conduct a longitudinal follow-up and to evaluate **changes in autism spectrum disorder phenomenology** over time in Cornelia de Lange syndrome at a **fine-grained level** using psychometrically robust measures. This aim was addressed in Chapter Four: '*Determining the profile of autism spectrum disorder phenomenology in Cornelia de Lange and Cri du Chat syndromes'*.

5.3. Key findings

5.3.1 Key findings overview

There were several key findings:

1) ***Chapter Two***: Despite CdLS and FXS groups having a similar proportion of individuals meeting SCQ cut-offs for ASD and autism, a significant effect of age was only identified in the CdLS group with older individuals (>15 years) being significantly more likely to meet the SCQ cut-off for ASD than younger individuals with CdLS (<=15 years). The older CdLS group also showed more impaired social interaction skills than the CdCS group at T1, highlighting this as an

area of specific age related change in CdLS. The analyses in Chapter Two also revealed that younger individuals with FXS showed more restricted, repetitive and stereotyped behaviours than older FXS participants suggesting that these become less prominent with age. This was not identified in the CdLS and CdCS groups.

2) ***Chapter Three:*** While adaptive behaviour skills remained stable, receptive language skills increased over time in both the CdLS and CdCS groups. Although this study did not show a general decline in abilities in either syndrome group over time, the percentage of CdLS participants meeting the cut-offs for autism and ASD on the ADOS increased over time suggesting a worsening of autism symptomatology. The SCQ *communication* and *social interaction* domain level analysis revealed that the CdLS group experienced a significant increase in impairment in these domains over time whereas there was no significant change on the *repetitive behaviour* domain.

3) ***Chapter Four:*** A select few items on the ADOS showed a significant interaction or effect of time and/or group including effect of time on *Showing, Eye Contact* and *Quality of Social Overtures;* effect of group on *Gestures, Imagination and creativity* and *Response to joint attention*. More detail is given about these findings in section 5.3.4. Interestingly, all of the items that differed significantly between the syndrome groups were on the *communication* and *reciprocal social interaction* domains, but not the *repetitive behaviour* domain. At a fine-grained level, CdLS showed impairments in social and communication items but repetitive behaviours remain stable.

These key findings are discussed in greater detail below.

5.3.2. Key findings from Chapter Two:

Chapter Two presented the data regarding age-related changes in ASD phenomenology in CdLS, FXS and CdCS. When the percentage of individuals who scored above the cut-off for autism and ASD on the SCQ were evaluated for CdLS, CdCS and FXS groups, it revealed some interesting similarities and differences. As a whole, CdLS and FXS had very similar percentages meeting the cut-off for ASD and comparable percentages meeting the cut-off for autism (section 2.3.1; Table 2.2). This reinforced previous findings that CdLS has a heightened level of ASD phenomenology (Basile, Villa, Selicorni, & Molteni, 2007; Berney, Ireland, & Burn, 1999; Bhuiyan et al., 2006; Moss et al., 2008; Oliver et al., 2008) and that this occurs at a similar rate to those with FXS (Moss & Howlin, 2009; Moss, Howlin, & Oliver, 2011; McCary & Roberts, 2013). However, only the CdLS group showed a significant effect of age on the prevalence of ASD characteristics with the over fifteen year olds having a significantly higher percentage of individuals meeting the ASD cut-off compared to those aged fifteen and under (section 2.3.2; Table 2.3). Older individuals with CdLS also showed greater impairments in social interaction relative to younger individuals. This is consistent with previous findings of increased social isolation in older children with CdLS (Sarimski, 1997) and broader changes in behaviour, mood and anxiety (Nelson et al., 2014; Oliver et al., 2011).

The finding that younger individuals with FXS showed more restricted, repetitive and stereotyped behaviours than older FXS participants is also important because the previous

literature regarding the trajectory of ASD phenomenology in FXS has been mixed (Hatton et al., 2006; Hernandez et al., 2009; Rogers et al., 2001; Sabaratnam et al., 2003;). The findings of this study indicate that repetitive behaviours may be getting better over time in FXS. This could possibly be due to an improvement in executive functioning (EF) and working memory (WM) skills as individuals with FXS get older which has only recently been identified (Cornish, Cole, Longhi, Karmiloff-Smith, & Scerif, 2013). This is in contrast to the previous literature which showed deficits in EF and WM (Garner, Callias, & Turk, 1999). If individuals with FXS are showing a delayed (versus arrested) development of EF skills as Cornish et al. (2013) suggests, the associated problem solving skills may help in reducing repetitive behaviours caused by lack of EF at younger ages.

5.3.3. Key findings from Chapter Three:

Chapter Three presented the results of the second study in this thesis, which examined changes in ASD phenomenology over time in CdLS and CdCS using an observation assessment, the ADOS. Despite the improvement of receptive language and the stability of adaptive behaviour skills, the increased percentage of CdLS participants meeting criteria for ASD and autism on the ADOS over time suggests a syndrome related change in the prevalence of ASD phenomenology in CdLS (section 3.3.4; Table 3.4). There were divergent patterns of *social interaction* on the ADOS domain level of percentage of participants meeting the cut-off for ASD from T1 to T2 with the CdLS group presenting with a significant increase (p =.04) and the CdCS showing a slight decrease over time. These findings in the presence of no obvious decline in ability and receptive language highlight these social impairments as a specific area of change in CdLS. The findings from the SCQ largely mirrored the ADOS results at the domain level with the CdLS and CdCS

groups scoring significantly different in the area of *social interaction* at T2, the CdLS group scoring more impaired than the CdCS group (section 3.3.6; Figure 3.5). The lack of significant change over time in the area of repetitive behaviour on the SCQ in either syndrome makes the change in social impairments identified in CdLS more interesting. These findings support the previous literature regarding social anxiety and reduced mood and sociability (Nelson, Moss, & Oliver, 2014) as well as increased social isolation (Sarimski, 2007) in CdLS with age.

5.3.4. Key findings from Chapter Four:

Chapter Four presented the results of a more fine-grained analysis of ADOS scores in CdLS and CdCS. The findings from this analysis support the suggestion that the deficits in ASD phenomenology seen in CdLS are primarily in the areas of social and communication skills. The ADOS items that had a significant interaction, effect of time or effect of group were as follows: (interaction between time and syndrome group) on *Showing* with the CdLS group presenting with more impairment over time and the CdCS group presenting with less impairment over time; (effect of time) *Eye Contact, Quality of Social Overtures* with both syndrome groups presenting with increased scores over time; (effect of group) on *Gestures, Imagination and creativity* and *Response to joint attention* with the CdLS group scoring higher than the CdCS group. The ADOS item *showing*, which is both a communicative and social act, was consistently found to change over time (on both the mixed ANOVA and linear regression with bootstrapping; section 4.3.6). Anecdotally, in observing these behaviours as a researcher, the quality of social behaviours appears to be different than seen in idiopathic autism. For example, some participants with CdLS appeared quite happy to have the researcher present, looking and/or smiling intently but

not responsive to social presses (such as participating in a pretend birthday party or questions) where individuals with idiopathic autism might not typically attend to the researcher at all. However, these are just anecdotal observations that are not quantifiable at this time. If the qualities of these behaviours are different, then it is possible the mechanisms that have caused the behaviours are also different.

One possible explanation for these differences could be due to deficits in executive functioning (EF) in CdLS potentially due to delayed brain development. Broadly defined, EF includes three main elements: working memory (WM), cognitive flexibility (also referred to as shifting) and inhibition (including self-control and behavioural inhibition; Diamond, 2013; Lehto, Juujärvi, Kooistra, & Pulkkinen, 2003; Miyake, Friedman, Emerson, Witzki, Howerter, & Wagner, 2000). Deficits in EF are thought to be associated (at least in part) to behavioural problems in several disorders such as autism (O'Hearn, Asato, Ordaz, & Luna, 2008; Lopez, Lincoln, Ozonoff, & Lai, 2005), Attention Deficit Hyperactivity Disorder (ADHD; Diamond, 2005; Lui & Tannock, 2007), as well as several genetic syndromes such as Prader-Willi syndrome (Woodcock, Oliver, & Humphreys, 2009), Down syndrome (DS; Adams & Oliver, 2010) and fragile X syndrome (FXS; Wilding, Cornish, & Munir, 2002). The frontal lobes (the last area of the brain to develop, occurring during late adolescence) are thought to impact and contribute greatly to EF abilities (Anderson, Jacobs, & Anderson, 2008). Malenka, Nestler, and Hyman (2009) reported damage to the prefrontal cortex produces significant harmful effects on social behaviour and the ventromedial prefrontal cortex regulates social cognition. Reid, Moss, Nelson, Groves, and Oliver (2017) conducted a study examining EF in adolescents and adults with CdLS and a contrast group of individuals with DS. The authors discuss the

previous literature on front lobes and their relationship to EF and that autopsy studies have revealed frontal lobe hypoplasia in CdLS (Vuilleumier et al., 2002). In their study, the authors looked at EF with the intent to identify a syndrome specific to CdLS and an age related profile of cognitive impairment. The study employed both a range of researcher administered tasks of EF, WM, receptive language and adaptive behaviour, as well as a broad informant measure of EF skills completed by parents/carers. It was revealed that individuals with CdLS showed significantly more impairment on tasks requiring generativity (verbal fluency), flexibility/task-switching and inhibition than those with DS, but not working memory. CdLS (but not DS) showed a negative correlation with digit span (backwards) and verbal fluency with chronological age. Although this study demonstrates a distinct pattern of EF in CdLS that warrants further investigation, it is postulated by the authors that it could be contributing to the repetitive behaviours in the syndrome. However, the most significant findings in this thesis were in the areas of social and communication, not repetitive behaviours. As EF covers such a broad area of behaviours and abilities, it is possible that the repetitive behaviours are being influenced by one area of EF (such as cognitive flexibility/shifting) and the social behaviours another (such as inhibition). The study by Malenka and colleagues (2009) mentioned above, does lend some insight to the connection between social behaviours, specific parts of the frontal lobes and EF. The findings of EF impairments in CdLS do suggest it would be beneficial to study this alongside social behavioural changes to see how they map onto each other.

5.4. Strengths and Limitations

There are several limitations to the research studies presented here that should be considered. In Chapter Two a significant effect of time on SCQ scores was not identified.

This was possibly due to the short length of the follow-up time (three years). Furthermore, the reliance on questionnaire measures in this study might have limited generalisability of the findings. The study described in Chapters Three and Four was able to overcome some of these limitations. This study employed a much longer follow-up (seven years) and used a more robust, observational assessment (the ADOS) in two rare genetic syndrome groups. Attrition at follow-up could have been selective, in that individuals experiencing more problems may have been more likely to participate in the research studies. However, this study experienced a very low attrition rate which should ensure that this was not the case.

The use of standardised measures such as the ADOS, SCQ and Vineland Adaptive Behavior Scales (VABS; Sparrow et al., 1984) adds substantial strength to this research (Betancur, 2011), especially considering it has been a point of weakness in previous research on ASD phenomenology in genetic syndromes. Both studies used participants gathered via family support groups. This does add the potential for selection bias since individuals who are more severely affected by a genetic syndrome may be more likely to be in touch with the family support groups and participate in research, therefore, it is possible that more mild cases would not be represented in the research group to the same degree that is common within the syndrome group as a whole. However, this would not affect the studies in this thesis because of the longitudinal design and the distribution of the participant's level of ID, language impairment and adaptive behaviour were found to be similar to levels previously reported in studies involving these syndrome groups. This would indicate that there was not a threat to the external validity due to the source of recruitment of participants. The other consideration when recruiting from family support groups is that it does not guarantee the diagnosis was given by an appropriately trained

professional, such as a clinical geneticist. Nonetheless, care was taken at all stages of the research to ensure all participants had a diagnosis from a professional (Paediatrician, GP or clinical geneticist) and any potential problem would have been equally distributed across the groups as they were recruited in the same fashions.

Another possible limitation is that the nature of the comparison group might influence the pattern of findings and therefore different comparison groups might yield different results. There are a number of strategies for selecting a comparison group: 1) comparison with an ID/ASD group; 2) comparison with an idiopathic ASD group; or 3) comparison with a defined syndrome group. The problem with using an idiopathic ASD comparison group (#2) is that it is a behaviourally defined disorder with widely variable causes that may not contribute to the understanding of aetiological pathways in CdLS. Given the severity of ID in CdLS, the ASD group would need to be comprised of individuals with severe/moderate ID in order to be representative of the level of ID in CdLS and to ensure any performance differences on the ADOS are not due to ID over and above ASD. The addition of an ASD group with comparable levels of ID (#1) is therefore preferable to enhance the comparability of groups. However, within a group of severe/moderate ID, there is likely to be individuals with unknown genetic causes, many have syndromes but no genetic markers, as well as a variety of genetic causes (Topper, Ober, & Das, 2011). In addition, many individuals with severe/moderate ID present with communication, physical, social and sensory impairments or differences that are unknown but could influence performance on the ADOS. These impairments or differences could introduce several potentially confounding variables that are difficult to control for. ASD has a disproportionate amount of males versus females (Baio, 2012). Not only does ASD have a greater number of males,

but we do not know a lot about the gender differences and it has been reported that females have a greater camouflaging of symptoms (Lai et. al., 2017). These issues can be addressed in a few ways: a) matching based on these differences, but that is problematic because if you match on one and something else differs it is unknown which variable is more influential; b) matching based on social or communicative impairments, but that could result in no differences being identified because that is the criteria groups were matched on; or c) having a very large group to even out the difference but this would mean recruiting a very large sample to negate the influence of outliers and putting limited resources into the 'control' group as opposed to the group of interest. Combined with the gender issues above, that is likely to be a less productive research strategy at this stage. Now that we know the areas of interest, it would be a good idea to conduct a study with an ID/ASD group. However, this would take considerable resources to address the sampling issues. The rational for not using an idiopathic ID comparison group is covered in Chapter One (see section 1.1.3.). Given the points above, the strategy of using a defined syndrome group (#3) is preferable as they have a single genetic aetiology and hence likely homogeneous behavioural and social phenotype for the purpose of contrast. This minimises within group variability, allowing for a smaller sample size, as well as matching on gender and critically ID. As mentioned above (see section 5.1), this was the strategy employed for the studies in this thesis. Both studies used CdCS as a comparison group for CdLS. Differences in trajectory might be due to atypical changes in either syndrome group because CdCS does have its own phenotype. However, CdCS does have a comparatively well documented behavioural phenotype and changes in trajectory would be evident and comparable with published research. Also, CdCS is easier than other groups to match on gender. The behavioural phenotype of CdCS does not include a high

prevalence of ASD and therefore is more like a non-ASD ID group and does include similar expressive communication to CdLS in form, but perhaps not in cause. The CdCS group is appropriate to match with CdLS on expressive language impairment and most importantly, ID. Given the use of this strategy, we cannot necessarily say anything specific or unique about the CdLS profile and trajectory based on the results of the studies in this thesis. It can be said, as studies in rare genetic syndromes often uses this strategy of using contrast groups where differing behaviours are part of the syndrome's phenotype, it is unlikely for observed differences to be measurement artefact or due to interventions (which are minimal in CdLS and CdCS). Therefore, differences observed in these studies are likely to be part of the syndrome phenotype. The main goal of this research was to add to the body of knowledge by describing the profile and trajectory in CdLS while controlling as far as possible for the critical variables (expressive language and ID) as they can impact the ADOS performance. The results of these studies show the profile and trajectory of CdLS does differ from a reasonable comparable contrast group in an unusual way from the existing literature.

The final limitation of this thesis is the potential for unaccounted factors (possible confounds) that would not have been captured within the measures used (e.g., social anxiety) to influence the findings. To overcome this issue, it would be beneficial for future research to include measures of social anxiety, social motivation and/or life events that may cause social withdrawal (such as death of a loved one or trauma). This is further discussed in the section on directions of future research (section 5.6). Previous research has established high levels of social anxiety in CdLS (Richards, Moss, O'Farrell, Kaur, & Oliver, 2009; Grados, Alvi, & Srivastava, 2017; Basile, Villa, Selicorni, & Molteni, 2007;

Crawford, Waite, & Oliver, 2017). Social anxiety in individuals with CdLS may explain some of the deficits in social and communication behaviours observed within the studies of this thesis. If an individual is socially anxious, they are less likely to initiate social acts or communication with another individual. Parental reports of higher ability and frequency of use of language with select people (such as their mother) by the CdLS participants in the study included in Chapters Three and Four of this thesis, contributes to the author's suspicion that social anxiety may play a role in the lack of communication observed. Wenzel (2009) reinforces this hypothesis, stating that socially anxious individuals are more likely to display social skill deficits in unfamiliar situations or with new people. Conversely, they are less likely to show those deficits with people they are the most comfortable with, such as close family members (Wenzel, 2009). The DSM-5 (2013) definition of social anxiety disorder includes, in part, a persistent fear of unfamiliar social performance situations or people leading to avoiding situations or enduring them with intense anxiety/distress. These parts of the definition highlight the behaviours observed in individuals with CdLS that might be contributing to meeting diagnostic criteria for ASD but could be stemming from anxiety. The clear overlap of ASD symptomatology and behaviours related to social anxiety make it difficult to separate (Kuusikko et. al., 2008). Both individuals with ASD and those with social anxiety exhibit social avoidance, hyper vigilance, escape from social demands, selective mutism and repetitive behaviours.

5.5. Implications of the research

5.5.1. Clinical implications

There are several clinical implications of the findings from the research conducted in this thesis. Identification of behaviours related to behavioural phenotypes of genetic

syndromes (through research) is used by clinicians to direct the treatment and advice given to those with a genetic syndrome and their families. The research in this thesis can be used to raise awareness with clinicians/practitioners of the prevalence of ASD symptomatology in CdLS, how the profile differs from other syndromes (FXS and CdCS) and how they change over time as the individual ages. Given this information, it would be advantageous for clinicians to give the Diagnostic Interview for Social and Communication Disorders (DISCO; Wing et al., 2002) along with the ADOS as part of their evaluation for patients with CdLS. The DISCO interview allows for an extensive history, parental perspective and the diagnosis of comorbid conditions, while the ADOS allow clinicians to observe and evaluate ASD behaviours directly.

In addition, based on this research, it would be important for evaluations to be repeated later in adolescence (which is not current practice) as the symptomatology may present later than expected with other groups (such as autism). Early identification of problem behaviours is well documented to be a key factor in achieving a more positive outcome in individuals with ASD (Dawson & Osterling, 1997; McCary & Roberts, 2013; Woods & Weatherby, 2003). Knowing which behaviours are likely to be particularly challenging would also influence educational placement based on more detailed information of the support that may be needed as the individual ages.

Targeted interventions can be more accurately implemented if it is known which behaviours are more likely to be problematic for individuals with CdLS. This will allow for focused interventions on areas of concern and, more importantly, avoid missing areas where intervention could be most useful in improving the quality of life of individuals and

their families. Based on the findings of the research in this thesis, it might be beneficial for interventions focused on social and communicative behaviours may help to avoid declines with age in these areas for individuals with CdLS. Reciprocal imitation training (RIT) is a parent based naturalistic intervention used to help empower parents and improve spontaneous imitation skills in young children with ASD (Ingersoll & Gergans, 2007). RIT emphasises the social role in imitation and could potentially be used to improve the early social-communication skill in individuals with CdLS. Improving early developing social-communication skills, such as imitation, could lead to further gains as the individual ages. However, Ingersoll (2010) found an association between baseline spontaneous play acts and improvements in imitation during intervention (RIT) with a group of children with autism. The author found that children with higher amounts of spontaneous play at baseline gained the greatest improvement. Therefore, being that individuals with CdLS are likely to have low levels of spontaneous play, it could limit the benefits of this particular intervention. Although, it is possible that individuals with CdLS will not have that restriction as they are more communicative and attentive with their parents (who would be administering the intervention) than unfamiliar people. This increased attention may produce different results from an RIT intervention in CdLS than previously studied in ASD. Clinicians could use the knowledge from the literature based on ASD phenomenology and associated interventions to benefit individuals with CdLS by focusing on the behaviours that apply specifically to this syndrome and not other more general ASD behaviours.

5.5.2. Broader implications

The broader implications of the research findings of this thesis involve the impact on the individuals and their families. The importance of any information about what to expect in the future cannot be underestimated. The identification of ASD symptomatology is beneficial for families in that it can help gain access to services, resources and materials that are already established for autism. Any information disseminated to families about outcomes must be treated with caution, as it could be disheartening if the changes over time are perceived as negative. They must be relayed to the families and support groups in the most accurate but sensitive way possible. A balanced approach of presenting new information alongside the potential ways to use this information to enhance the possible treatments or quality of life should be employed whenever possible.

5.5.3. Research implications

The research implications of the results from this thesis are multi-layered. It has become clear that different genetic syndromes have different trajectories and profiles of ASD phenomenology. It is important to examine and define what these trajectories and profiles look like in each syndrome. This information could help direct future research specifically related to areas identified by these types of analyses. For example, based on the research in this thesis, it would direct future research to look more closely at social changes in adolescence and adulthood in CdLS. This may add to the body of scientific knowledge about key functions or cause of some of these behaviours in syndromes. The differences in these trajectories and profiles between syndromes, especially comparing those to syndromes where longitudinal data are available, can add valuable insight into specific areas of deficits and relative strengths. In addition, detailed profiles might help identify

potential differences in the behavioural phenotype of more refined genetic subtypes, such as mosaicism in FXS (Stöger, Genereux, Hagerman R., Hagerman P., Tassone, & Laird, 2011) or SMC1A mutations in CdLS (Huisman, Redeker, Maas, Mannens, & Hennekam, 2013).

5.6. Direction of future research

The research in this thesis has uncovered several novel findings that add to the knowledge and understanding of the behavioural phenotype of CdLS as well as the other syndrome groups employed (FXS and CdCS). Of primary interest is the reduced impact of repetitive behaviours over time in CdLS. Repetitive behaviours were previously identified by Moss, Oliver, et al. (2013) as part of the atypical profile of ASD characteristics in CdLS. However, the current research revealed a focused change in the areas of communication and social interaction in CdLS over time. The contrast in the current findings with those of previous research warrants further investigation and reinforces the need for longitudinal studies in CdLS.

Future research could further investigate changes with age and over time in CdLS, with a focus on potential developmental processes involved at the age of noted changes. For example, based on these studies, looking at brain development and changes in adolescence with MRI alongside behavioural and cognitive measures would be recommended. Roshan Lal and colleagues (2016) conducted a retrospective study comparing MRI scans of 15 individuals with CdLS and the Aberrant Behavior Checklist (ABC; Aman, Singh, Stewart, & Field, 1986), which is a symptom checklist used to identify problem behaviours in children and adults with ID. The authors hypothesized that there would be a correlation

between the location and severity of brain abnormalities and the clinical phenotype of CdLS. Although no statistically significant correlations were found, the study did provide some interesting findings that warrant further investigation and align with the findings of the research in this thesis. The ABC is comprised of five subscales and the following is the percentages of participants that were reported to have problems with each subscale: 53% 'irritability/agitation', 53% 'lethargy/social withdrawal', 20% 'stereotypic behavior', 47% 'hyperactive' and 67% 'inappropriate speech'. Despite no statistically significant findings, the authors report that cerebral atrophy and/or more severe MRI changes appear to be correlated with high scores on the 'irritability/agitation' and 'lethargy/social withdrawal' subscales of the ABC. Obviously no conclusions can be made from insignificant findings, but it does suggest that this possible association should be further investigated. The authors also postulate that the participants with clinically significant levels of 'lethargy/social withdrawal' as having more abnormal MRI findings suggest that those findings could correlate with social isolation, depression and/or autistic behaviours in the syndrome. However, the findings from the study must be taken with caution as there were some significant limitations: a small sample size, the majority of participants were female (87%), it was retrospective with the behavioural data being collected 0 days to 10 years after the MRI, there were no observational measures of behaviour (only parent report) and no serial MRIs (so no way to look at change over time). The authors did report that this was only the first phase of many studies in which they hope to improve on the design. This does show the current thought in the field around the importance of looking at the possible connections between neuroanatomical findings and behaviour.

As discussed above (section 5.3.4.), there could also be a component of executive function or working memory that fails to progress. The combination of MRI, EF tasks, behavioural observation measures of ASD symptomatology and social anxiety within a longitudinal design would allow for a more comprehensive picture of the presentation and possible aetiology of ASD phenomenology in CdLS.

Another possible avenue for future research would be to look at environmental and/or life events during the ages of change in CdLS. For instance, there may be an association between times of transition (e.g., moving from home to a care facility or going from one educational phase to another) or life events (e.g., the death of a close friend or family member) and the decline in social behaviour identified in CdLS. In a large study of typically developing adolescents, a significant relationship between negative life events (along with passive coping strategies) and anxiety was reported, with more negative life events and passive coping strategies resulting in higher levels of anxiety (Lewis, Byrd, & Ollendick, 2012). The use of parental reports of negative life events alongside psychophysiological measures of Central Nervous System (CNS) reactions typical of social anxiety (e.g., heart rate and sweat responses) during social presses could reveal whether the social communication deficits in CdLS are due to anxiety. As psychophysiological measures don't rely on accurate reporting, this method may be particularly appropriate for individuals with CdLS due to their reduced communication and level of ID. There is a need for intervention trials (both psychological and pharmacological) of anxiety (social anxiety and General Anxiety Disorder), possibly across syndrome groups to see if the interventions would reduce ASD characteristics in CdLS.

It would also be very useful to conduct a longitudinal design with an ID/ASD comparison group for CdLS utilizing the ADOS, DISCO and ADI-R, as well as possibly an observational method of specific social behaviours. The use of the ADOS and ADI-R alongside the DISCO would allow for investigation of change over time and possible differences in profile due to measurement as opposed to group differences. The DISCO would also allow a greater depth of historical information to be gathered and the ability to identify comorbid conditions that may offer an alternate explanation for certain behaviours.

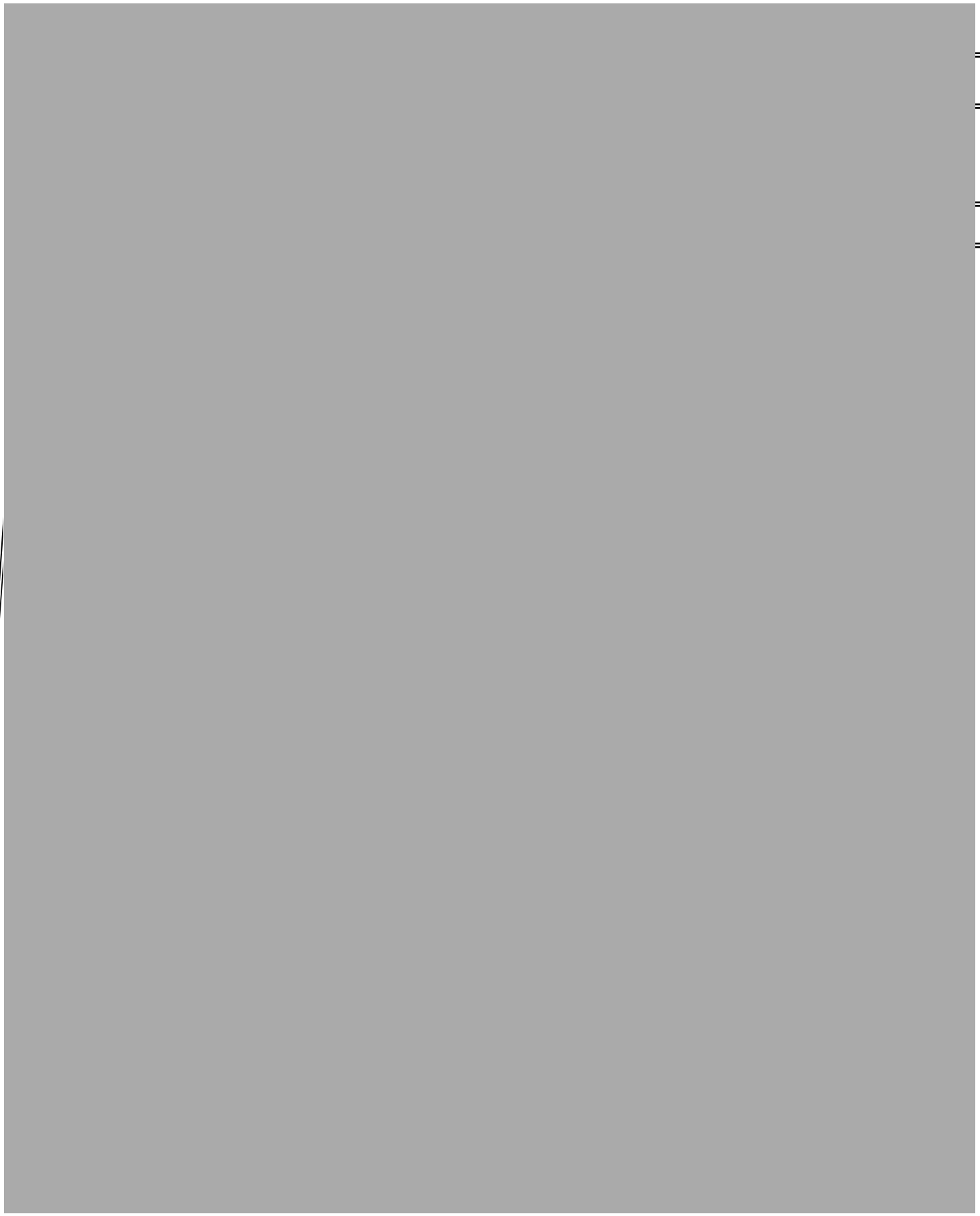
It would be of interest to see if the new ADOS-2 (Rutter, DiLavore, Risi, Gotham, & Bishop, 2012) algorithms reveal a different pattern to the original ADOS used in the study presented in Chapters Three and Four. The ADOS-2 still includes the classifications of Autism Spectrum (previously Autism Spectrum Disorder) and Autism. However, it also includes a new comparison score (1-10/ minimal to High), which compares the level of presenting symptoms to those of an autism group of similar age and language level. This comparison score may add valuable insight to how an individual with a genetic syndrome symptoms are similar or different from the autism group without the need to include an idiopathic autism group in the study design. In addition, Hus, Gotham, and Lord (2014) created calibrated domain scores for *Social Affect* and *Repetitive Behaviour* severity. The authors suggest that these new scores could be utilized to better examine trajectories of ASD symptoms. It would be beneficial as well to see how the new DSM-5 impacts or changes the percentage of participants with CdLS who meet criteria for ASD (Zuddas, 2013).

The research findings in this thesis can act as a foundation for directing future studies of ASD phenomenology in CdLS. It also serves as a reminder that what is significant at one time point (like repetitive behaviours in CdLS) might not be significant over time and therefore, resources may need to be adjusted and adapted to account for behaviours that are relevant at different ages.

APPENDICES

APPENDIX 1

Demographic Questionnaire



APPENDIX 2

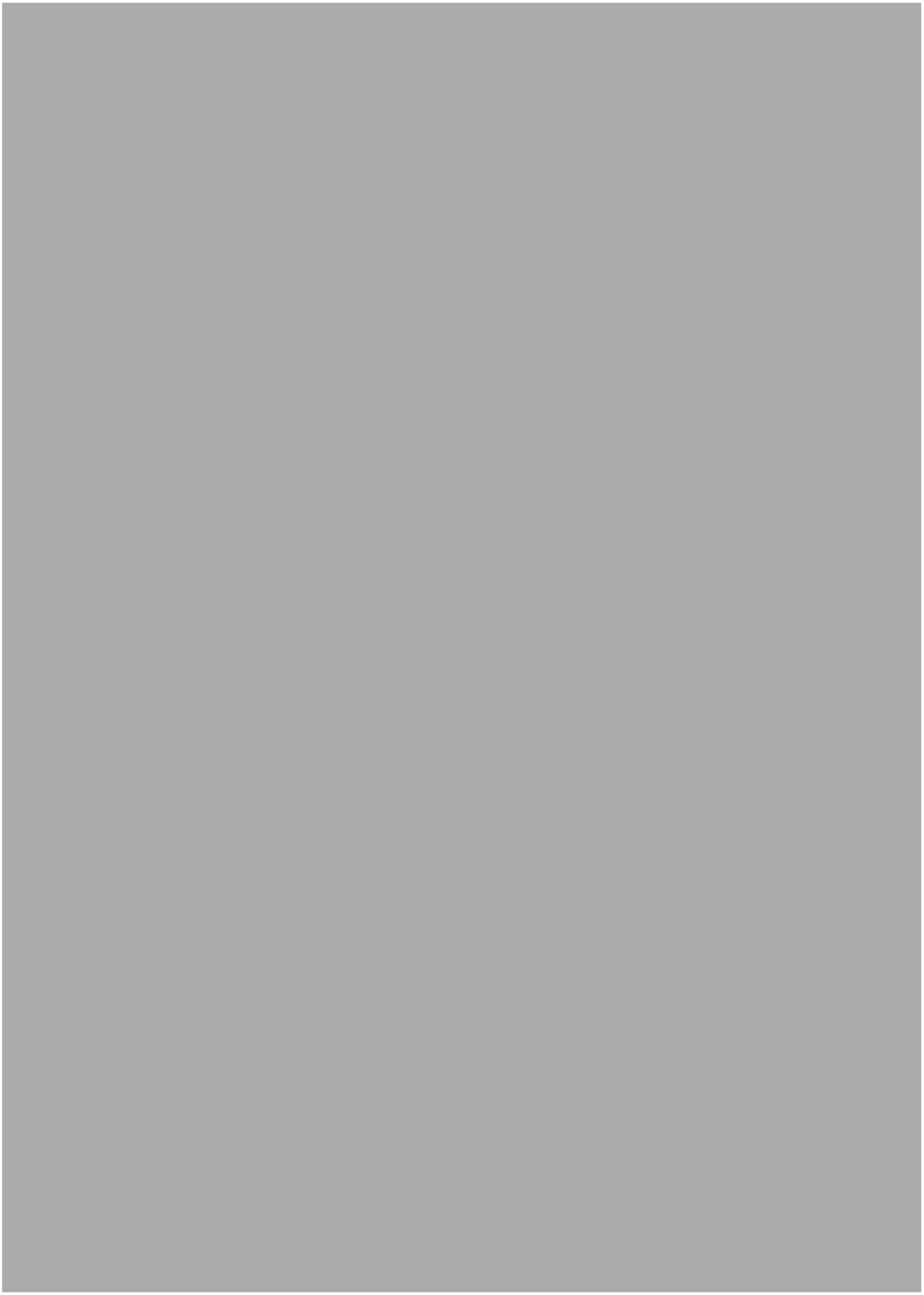
Social Communication Questionnaire

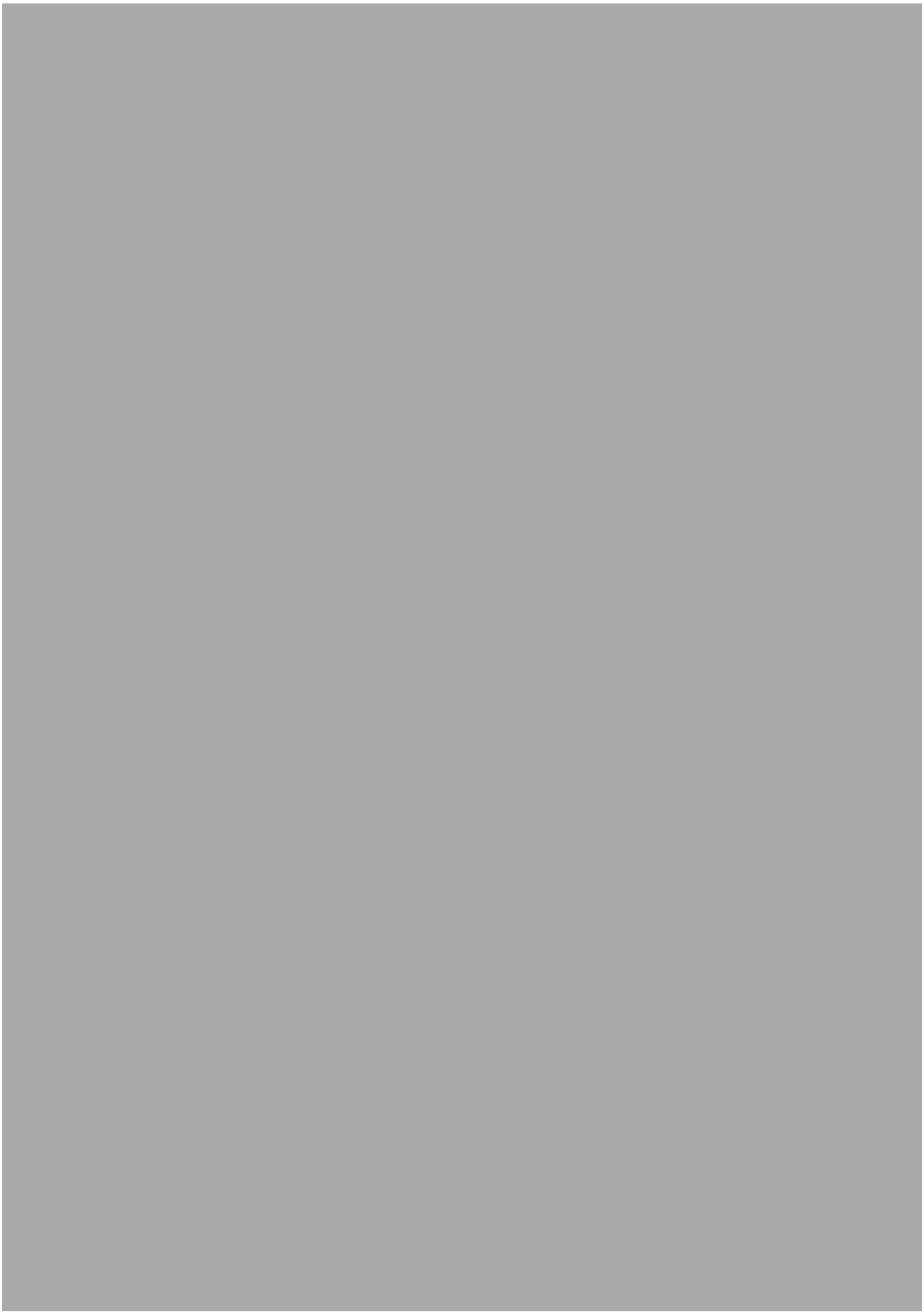
APPENDIX 3

Repetitive Behaviour Questionnaire

APPENDIX 4

Chapter Three and Four recruitment materials





The Cerebra Centre for Neurodevelopmental Disorders

UNIVERSITY OF BIRMINGHAM

Long term outcomes of individuals with X Syndrome.

Brief Information Sheet

- ***What kind of study is this?***

This is a follow up study so that we may look at how individuals with X syndrome develop and progress over time. The results of this study will be important for understanding how people change as they grow older. This is the longest follow up of its kind that we are aware of.

- ***What will it involve?***

The research will involve several steps. The first step will involve completing a questionnaire pack. This can be completed by you in your own time. Next, a phone interview and research visit will be arranged at a time and location that is convenient for you. These can take place at your home, a school or the Cerebra Centre.

- ***Who will I be dealing with?***

Members of the research team at the Cerebra Centre for Neurodevelopmental disorders including Professor Chris Oliver, Dr. Joanna Moss and Lisa Cochran. This study is a collaboration between the Cerebra Centre and the Institute of Psychiatry, London. Therefore, it will also include Professor Pat Howlin.

- ***Will I get anything in return?***

You will receive a personalised feedback regarding you or your child/ the person you care for. This study will help us to find out more about the lives of people with X syndrome and the difficulties that these people face. The results might help us to improve things for people with X syndrome in the future.

- ***Who can I contact with questions?***

If you have any further questions please contact the project coordinator [redacted]

- ***How do I let you know that I am interested?***

If you and the person you care for would like to take part in the study or would like additional information, please complete the enclosed expression of interest form and return it to us in the prepaid envelope provided or contact [redacted]. Completing the expression of interest form does not commit you or the person you care for to participate in the study.

- ***Can I change my mind?***

At any point, even after consent has been granted, participants can request to be withdrawn from the study at any time, without giving a reason.

Long term outcomes of individuals with X Syndrome: Detailed 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 the project coordinator [redacted]. If you have any medical/ other problems which make it difficult for you to read this information, please contact Lisa Cochran for a verbal explanation of the research.

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

Background to the study:

This is a follow up study so that we may look at how individuals with X syndrome develop and progress over time. The results of this study will be important for understanding how people change as they grow older. Currently, very little is known about how people with X syndrome progress and change over time. Your participation at this follow up will provide new and valuable information that cannot be gained any other way. This is also the longest follow up of its kind that we are aware of.

Aims of the study:

1. To further our understanding of cognitive, language and behavioural characteristics in individuals with X syndrome.
2. To understand what happens to these cognitive, language and behavioural characteristics as children and adults with X syndrome develop.

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

Where will the research take place?

The research will involve several steps. The first step will involve completing a questionnaire pack. This can be completed by you in your own time. Next, a phone interview and research visit will be arranged at a time and location that is convenient for you. These can take place at your home, a school or the Cerebra Centre.

Who will be involved in collecting the data?

[redacted].

How long will participation in the study take?

The questionnaire pack will take approximately 45 minutes to complete. The phone interview may vary but is likely to take about an hour. The research visit will take 3-6 hours and lots of breaks can be built in. Sometimes, after you have participated in the

study, we may contact you again to clarify some of the information that you have provided or to ask if you would be willing to provide us with some further information. This helps us to ensure that the outcome of our study is as useful as possible. If this happens then we would contact you again within 6 months of receiving your questionnaire pack to ask whether or not you would be willing to provide us with the extra information.

What will participants be required to do during the study?
Parents/carers will be asked to complete a questionnaire pack in their own time and return it to us in a pre-paid envelope or have it ready for when we visit. They will also be asked to respond to an interview that will be conducted by a researcher either over the phone or in person. This interview will ask parents/cares to talk about different aspects of behaviour and abilities of the person they care for. Phone interviews may be audio recorded and/or responses will be noted down on paper by the researcher.

The research visit will be arranged with the parent/ carer in advance. The child/person you care for will be involved in the research visit. During this visit a member of the research team will interact with your child/ person you care for while completing tasks such as pointing to pictures and semi-structured play based activities.

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

What are the potential benefits for participants from taking part?
You will receive a personalised feedback regarding you or your child/ the person you care for. In the past some families who have participated in our research have told us that they have found these reports useful.

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

How video recordings will be made?
Video recordings will take place during the assessments and interviews and will be agreed by teachers and parents/ carers. Your child's/ person you care for's privacy and dignity will be respected and video recordings will not take place if the they are in a state of undress or when there is evidence that the observations are causing distress. Parents/ carers and teachers can ask to see a copy of the videotape. When videotapes are not in use they will be stored in a locked cabinet in the School of Psychology, University of Birmingham and will only be viewed by research workers from the University of Birmingham. Information identifying your child will not be stored on or with the tape. The video recordings may only be viewed by legal guardians, individuals providing a service to the person, Professor Chris Oliver and research staff at the University of Birmingham. Any data that are derived from the tape will remain anonymous. Video recordings will not be shown for the purpose of teaching.

If you/ the person you care for decide(s) to participate, what will happen after that participation?
You and your child or person you care for will receive an individual feedback report describing the results of all of the assessments that were carried out during the study.

Any request for advice concerning the person you care for will be referred to Professor Chris Oliver, Clinical Psychologist.

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

What will happen to the data afterwards?

The information that you provide will be locked in a filing cabinet at the University of Birmingham or held on a password protected database. Participants will be identified by a unique number so that the information you provide us with cannot be traced to your personal details. This research data will not be made available to anyone other than the research team at the University of Birmingham. Video recordings will be stored until completion of the project and publication of the last reports associated with the project or until no longer than 3 years following your participation in the project.

Consent

After having read all of the information and having received appropriate responses to any questions that you may have about the study if you decide that you do wish to participate the next thing we need to do is deal with the consent process The section below on 'Giving consent' will explain this process. This consent process needs to be completed in with anyone who would like to participate before they begin their participation.

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.

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 stored in an anonymous format except when viewed in conjunction with the database containing personal identifying information. In the unlikely event of any evidence of abuse being identified, this information will be disclosed by the research workers.

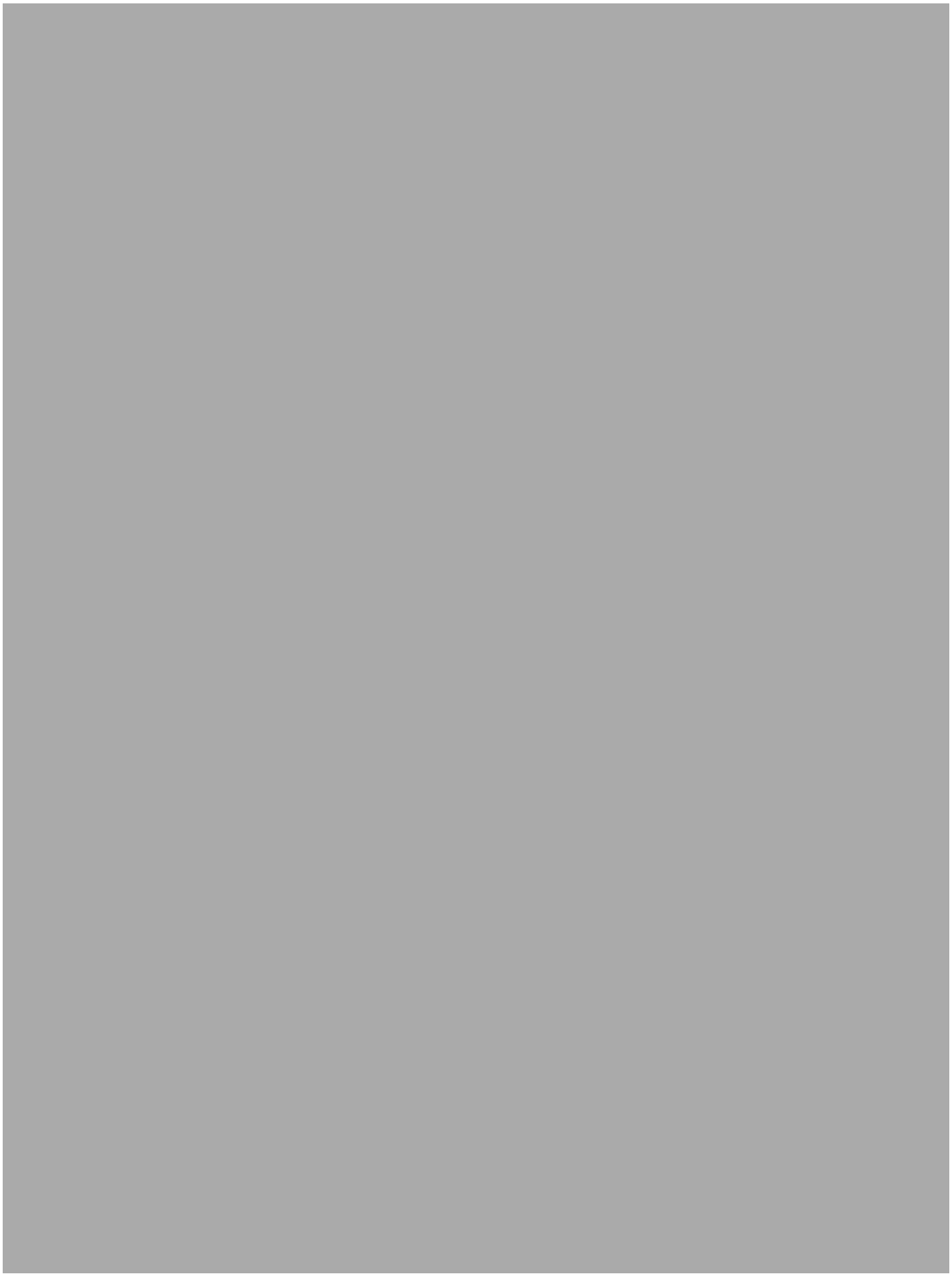
Review

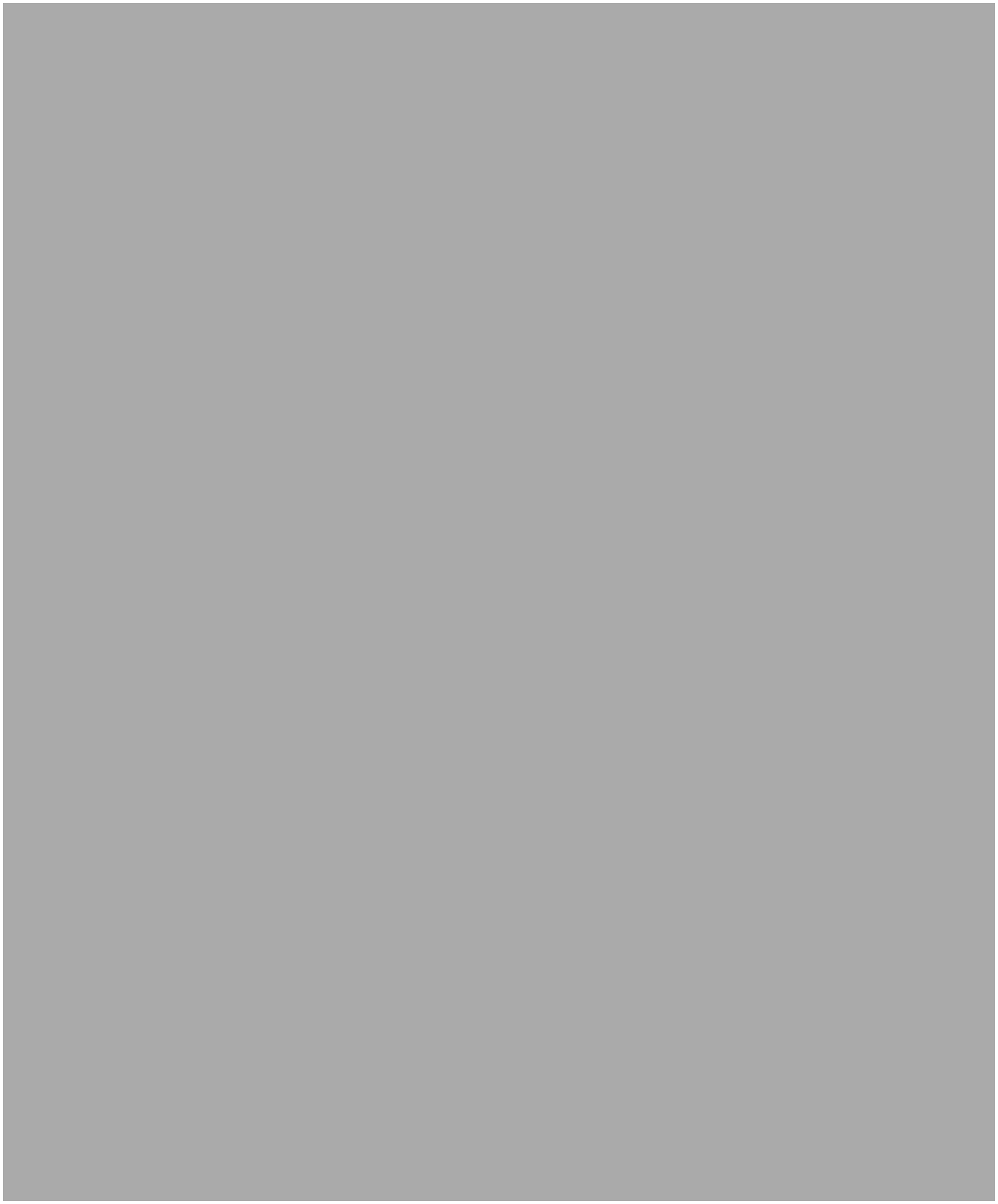
The study has been approved by Nottingham NHS Research Ethics Committee 1. REC reference number .

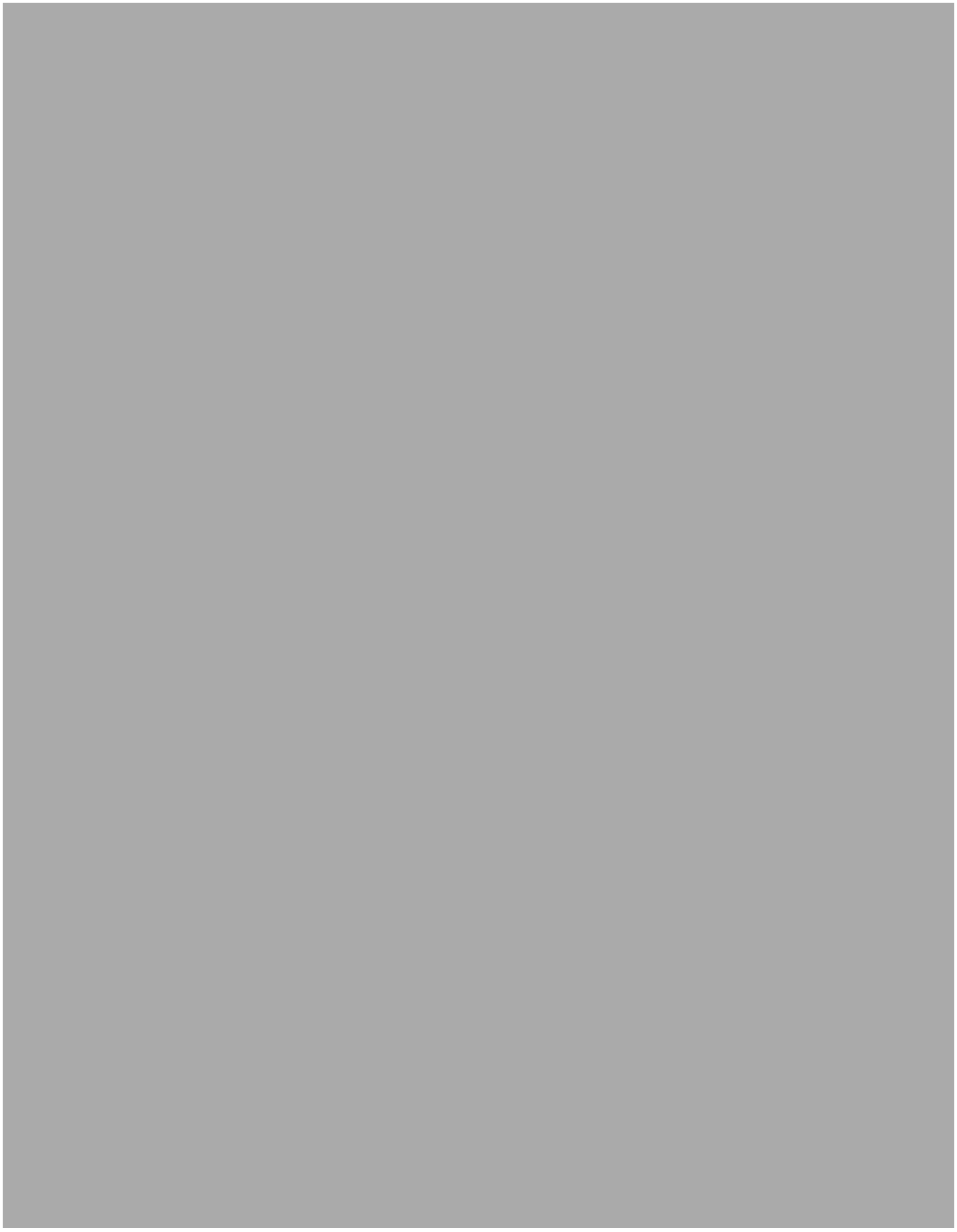
Any concerns of queries?

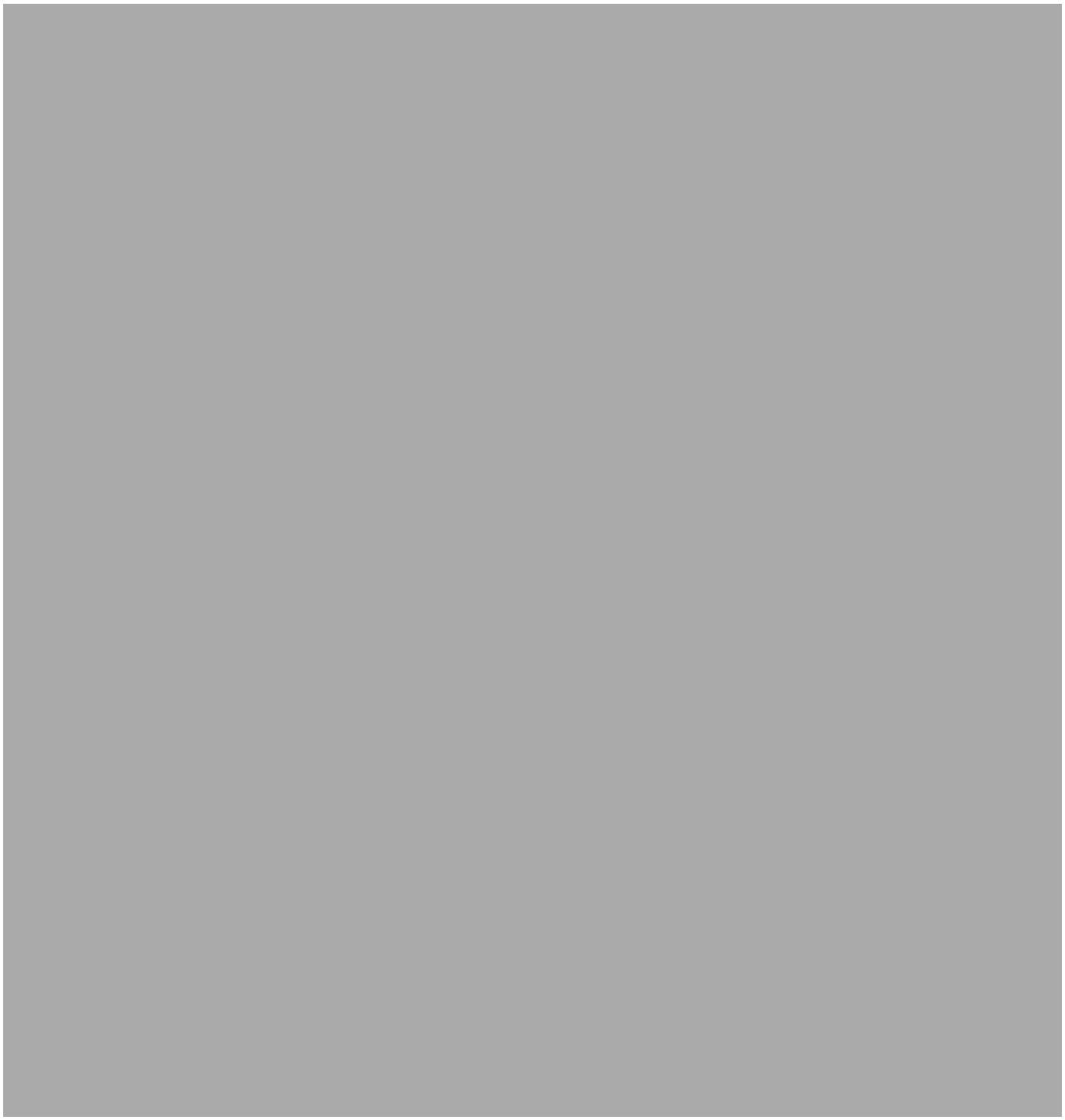
If you are unclear about any aspect of the study or have any questions, please do not hesitate to contact [redacted] or at the following address:

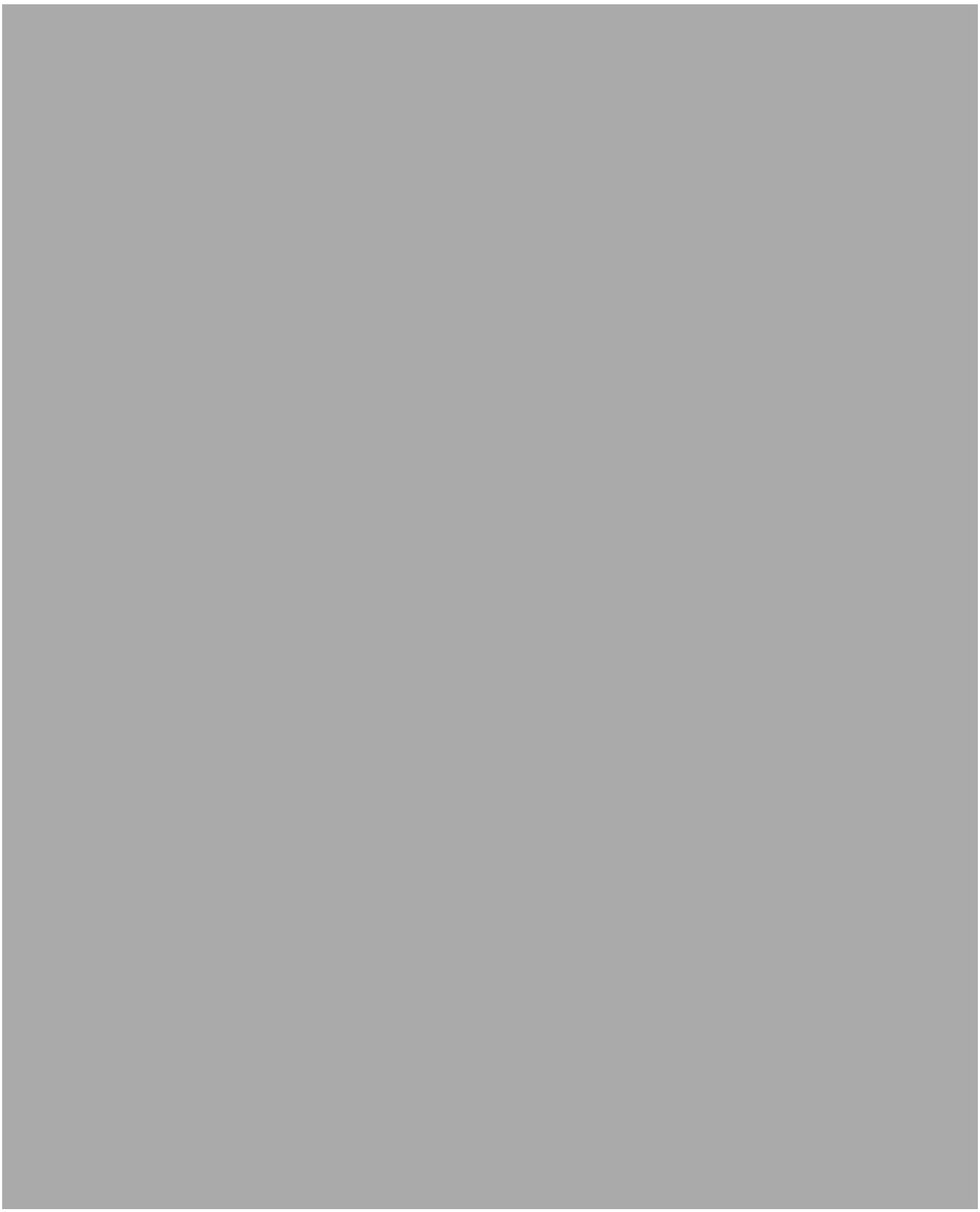
[redacted]

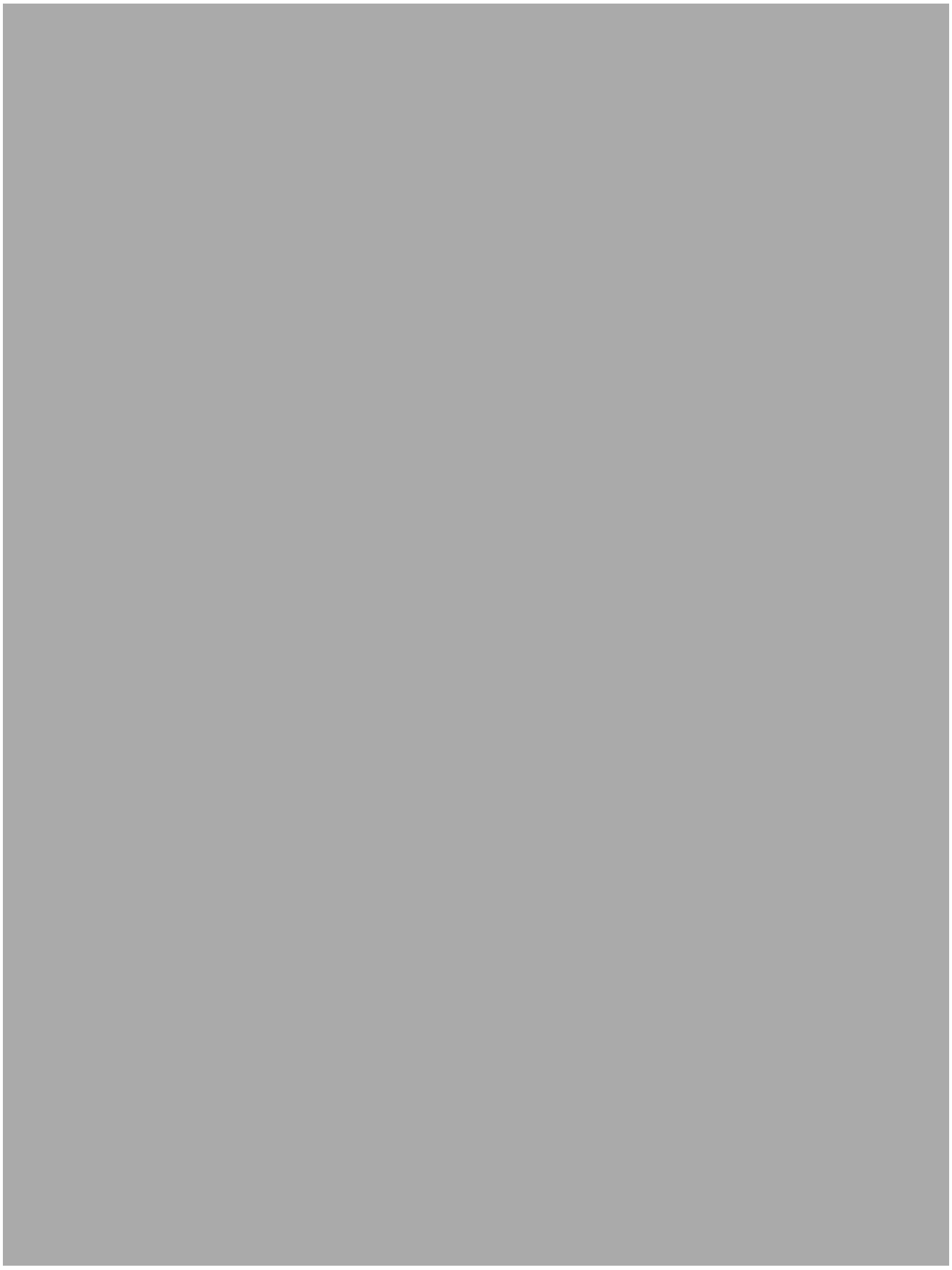


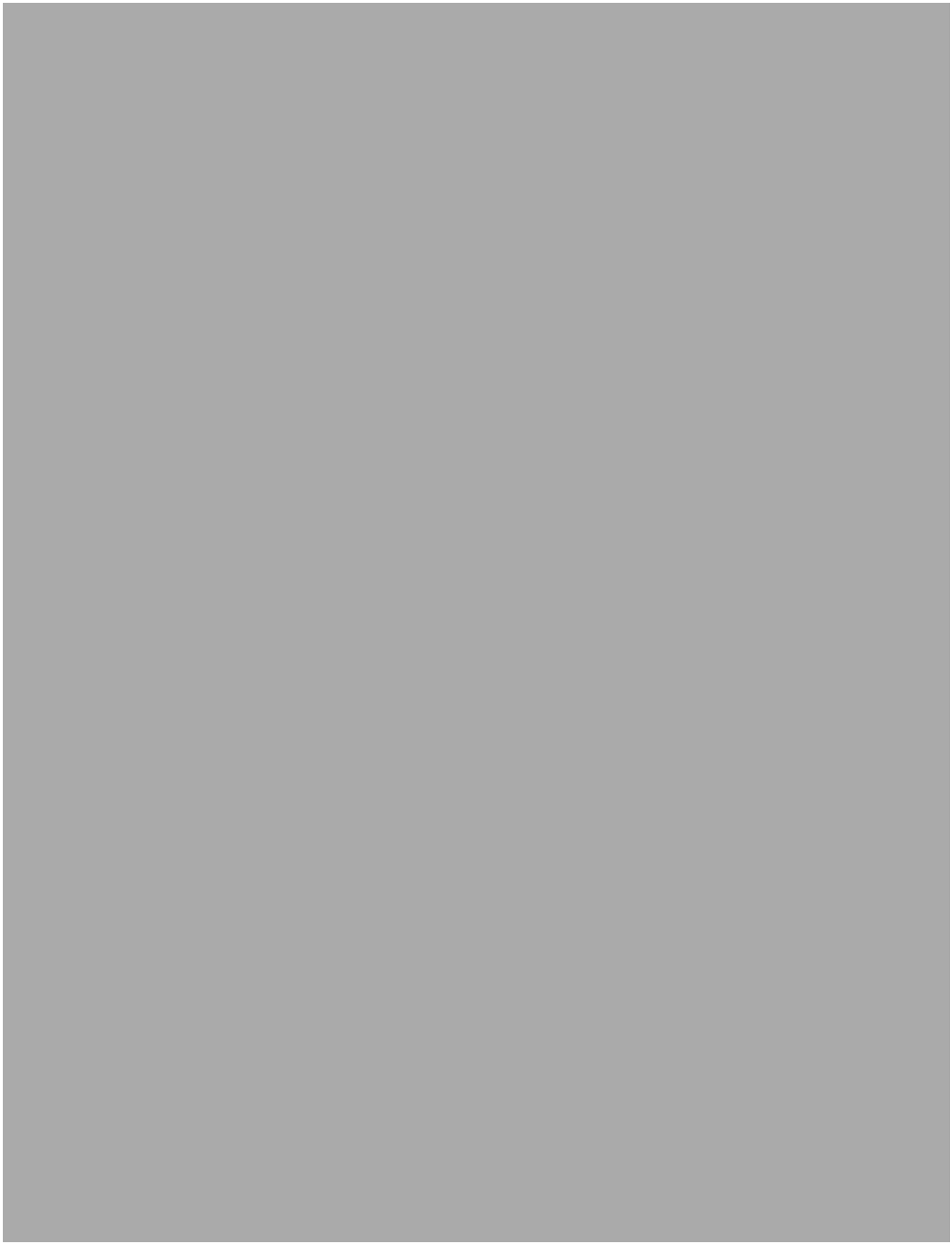




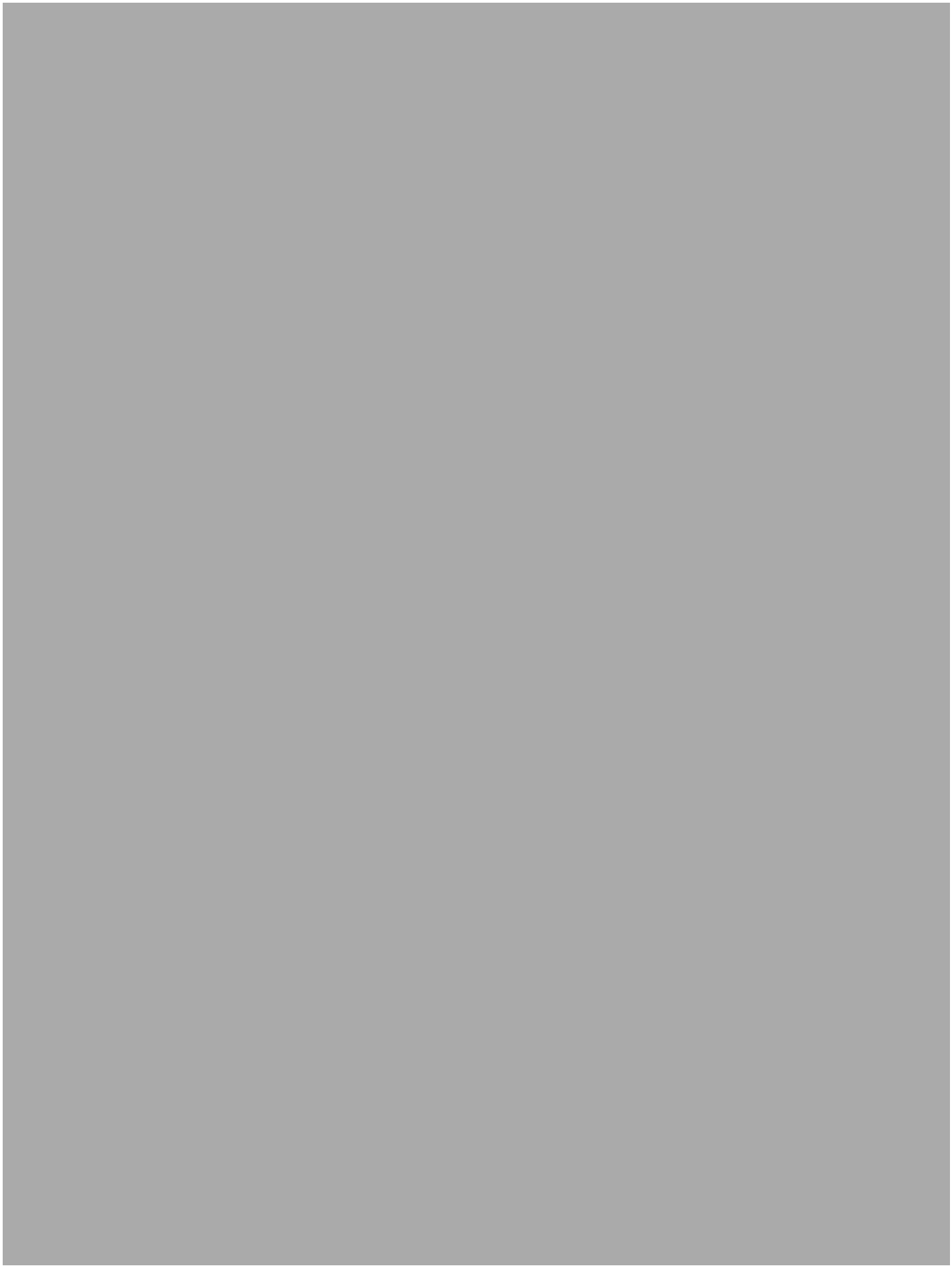








PTO…continued overleaf



Personal and Nominated Consultee Information Sheet

You may remember a member of the research team asking you a series of questions on the telephone regarding the person you care for and their ability to understand and retain information about the study. Please read this information sheet if you care for a person who is over the age of 16, who you have judged *is not* able to make an 'informed' decision about whether or not they would like to take part in the study or *is not* able to communicate that decision to you.

In order to understand disability, and to improve treatment and care, research is essential. That research may focus on the people with the disability and may invite those people to participate. Some people will have capacity to make their own decision whether to take part in the research. Others, possibly those most affected by the disability, may not have that capacity. They may not be able to understand enough of the research to be able to give 'informed consent'. They may not be able to communicate a decision. The research provisions of the Mental Capacity Act are designed to allow such people to take part in research even though they cannot give valid consent of their own.

First, the research has to be approved by a Research Ethics Committee. Then, instead of asking the research participant for consent, the researcher must ask a consultee for an opinion whether the research participant would have wished to take part in the research. If you are an unpaid carer (e.g. parent, legal guardian etc) we would like to invite you to act as a ***personal consultee*** for the person that you care for. If you are a paid carer (e.g. paid carer, key worker, support worker etc) and there are no unpaid carers (e.g. parent, legal guardian etc) to act as a personal consultee for the person you care for then we would like to invite you to act as a ***nominated consultee*** (go straight to page 2).

Who can be a personal consultee?

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

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

Who cannot be a personal consultee?

- Paid carers and professionals
- People connected with the research (e.g. members of the research team)

Why have I been asked?

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

Who can be a nominated consultee?

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

Who cannot be a nominated consultee?

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

Why have I been asked?

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

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

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

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

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

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

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

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

The research project has been approved by the Nottingham NHS Research Ethics Committee 1. If you wish to see proof of approval from this body, or you wish to discuss any concerns about acting as a personal consultee for the person that you care for, please contact [redacted]

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

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

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

Where can I get more information and guidance?

More information is available from:

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

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

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

I have decided that I want to be a personal consultee- what do I do?
Please go back to the Information Sheet and continue reading.

APPENDIX 5

Vineland Adaptive Behavior Scales

APPENDIX 6

British Picture Vocabulary Scales

APPENDIX 7

Measures collected but not used in analysis

Assessments attempted/given but not included in analysis:

The measures listed below we attempted/given as part of the study described in Chapters Three and Four but not included in the analysis. The Expressive Language and Cognitive tests were not collected at Time 1 and it was the intention of the researcher to collect them at Time 2, potentially adding useful information. However, due to limited abilities in both syndromes, these measures were only successfully completed by a limited number of participants. The Repetitive behaviour measure was collected and utilized in the Chapter Two study, but due to lack of findings in that chapter, it was not analysed as part of the Chapter Three study.

Expressive Language:

Expressive One-Word Picture Vocabulary Test (EOWPVT; Brownell, 2000)

The Expressive One-Word Picture Vocabulary test (EOWPVT) was only administered at Time 2 to assess each participant's current expressive language. The EOWPVT is a standardized measure of expressive language level. During administration, the examiner encourages the individual to attend to a series of colour illustrations of objects, actions, or concepts. The examinee is asked to name each illustration, usually with one word. This edition and permits the examiner to prompt, calling his or her attention to pertinent aspects of the pictures. Administration is usually very brief, 15 to 20 minutes, due to the use of basal and ceilings. Age equivalents, standard scores and percentile ranks can all be obtained from raw scores. Given only at Time 2, the Expressive One-Word Picture Vocabulary Test was attempted if the participant was verbal. Some participants had extremely limited expressive language skills. For those participants, several attempts were

made to ensure the participant's attention was gained and the instruction given clearly by the examiner. After 3 failed attempts to gain a response, the examiner discontinued the assessment. (CdLS n=15; CdCS n=11)

Cognitive ability:

Wechsler Abbreviated Scale of Intelligence™ (WASI™; Wechsler, 1999) The *Wechsler Abbreviated Scale of Intelligence*™ (WASI) is a standardized intelligence measure designed for a wide range of ages. The WASI was used only at Time 2 for those participants with a higher level of ability. The WASI is a reliable measure of intelligence appropriate for use in clinical, educational, and research settings. The WASI produces the three traditional Verbal, Performance, Full Scale IQ scores, The WASI consists of four subtests: Vocabulary, Similarities, Block Design, and Matrix Reasoning. Administration takes about 30 minutes and produces VIQ, PIQ, and FSIQ scores. (CdLS n=7; CdCS n=5)

Wechsler Preschool and Primary Scale of Intelligence™ – Third Edition (WPPSI™-III; Wechsler, 2002)

The Wechsler Preschool and Primary Scale of Intelligence™-Third Edition (WPPSI) is a standardised measure of intelligence appropriate for use with children as young as 2.5 years. The WPPSI was used only at Time 2 for those participants with less ability than was required for the WASI. Administration is made easier due to simple instructions and scoring methods. The WPPSI has two forms depending on age/ability level. Between the two forms, there are five subtests: Receptive Vocabulary, Block Design, Information, Object Assembly and Picture Naming. Administration takes about 30 minutes and

produces VIQ, PIQ and FSIQ scores. The Block Design and Picture Naming tasks were attempted with all participants who would attend to determine ability to perform the required tasks. If the participant was unable to respond successfully to either task, the assessment was abandoned.

Given only at Time 2, either the Wechsler Abbreviated Scale of Intelligence or the Wechsler Preschool and Primary Scale of Intelligence were administered depending on the participant's level of ability. The language measures were used as a guide to basic abilities and therefore if the participant was unable to do both the BPVS and the EOWPVT, neither cognitive measure was attempted. However, if the participant was able to do one of the language measures, the Block Imitation and Information sections of the WPPSI were administered. If the participant was able to do those subtests, the examiner proceeded with the rest of the measure's subtests. If the participant was not able to complete both subtest, the examiner discontinued the assessment. If the participant showed a significant level of receptive and expressive language, the examiner administered the WASI. (CdLS n=8; CdCS n=5)

Repetitive behavior:

Repetitive Behaviour Questionnaire (Moss *et. al.*, 2009)

The Repetitive Behaviour Questionnaire (RBQ) is a teacher/parent report questionnaire specifically designed for use regarding individuals with intellectual disabilities that inspects the incidence and frequency of repetitive behaviours. Stereotyped and compulsive behaviours, repetitive use of language, restricted preferences and insistence on sameness are all examined in the RBQ. Behaviours are rated by the informant on response to

interruption of behaviour, level of interference on everyday life and level of insistence of carrying on with the behaviour. Based on a sample of 103 individuals will intellectual disability of heterogeneous cause, test-retest reliability is reported to range from 0.61 to 0.93 at item level, with 52.6% of items above 0.80. Correlations between raters ranged from 0.46 to 0.80 at item level with 73% of items above 0.60 (Moss *et. al.*, 2009).

APPENDIX 8

RBQ and SCQ analyses

The following tables report median values (rather than mean values) due to the use of non-parametric analyses, which test group medians.

Table 1: Median values of syndrome group scores on the subscale items of the Social Communication Questionnaire at T1 and T2 (separately).

	CdCS (n=41)*	**FXS** (n=142)*	**CdLS** (n=67)*	***X²***	***df***	***P value*** (<.02)	**Post Hoc** (<.01)
T1							
Communication Not Proportional	4.00	7.00	7.00	32.66	2	<.0001	FXS, CdLS > CdCS
**Communication Proportional	5.57	7.43	9.29	13.85	2	.001	CdLS > CdCS, FXS
Restricted, Repetitive and stereotyped behaviours	3.00	5.00	4.00	20.67	2	<.0001	FXS > CdCS, CdLS
Reciprocal social interaction	4.00	8.00	9.00	31.88	2	<.0001	FXS, CdLS > CdCS
	(n=38)*	(n=128)*	(n=59)*				
T2							
Communication Not Proportional	4.00	7.00	7.00	28.51	2	<.0001	FXS, CdLS > CdCS
**Communication Proportional	5.00	7.00	9.00	17.82	2	<.0001	FXS > CdCS CdLS > CdCS, FXS
Restricted, Repetitive and stereotyped behaviours	3.5	5.00	4.00	10.92	2	.004	FXS > CdCS
Reciprocal social interaction	4.29	8.00	9.00	30.67	2	<.0001	FXS, CdLS > CdCS

* Ns varied due to missing data

** Communication Proportional was calculated but not reported in the results because it is not included in the manual for the measure

Table 2: Median values on the Repetitive Behaviour Questionnaire between syndrome groups at T1 and T2 (separately).

	CdCS (n=42)*	**FXS** (n=141)*	**CdLS** (n=67)*	X^2	***df***	***p*** (<.008)	**Post Hoc** (<.01)
T1							
Stereotyped behaviour	5.50	7.75	6.00	1.34	2	.512	N/A
Compulsive behaviour	2.00	6.00	4.00	11.61	2	.003	FXS > CdCS
Insistence on Sameness	0	4.00	2.00	29.49	2	<.0001	FXS > CdCS, CdLS
Restricted preference	4.00	6.00	5.00	4.86	2	.088	N/A
Repetitive use of Language	4.00	8.00	5.00	30.27	2	<.0001	FXS > CdCS, CdLS
Total	16.00	30.00	18.00	31.97	2	<.0001	FXS > CdCS, CdLS
T2	(n=42)*	(n=140)*	(n=67)*				
Stereotyped behaviour	5.50	6.00	6.00	.34	2	.845	N/A
Compulsive behaviour	2.00	6.00	3.00	11.80	2	.003	FXS > CdCS
Insistence on Sameness	0	4.00	2.00	25.96	2	<.0001	FXS > CdCS, CdLS
Restricted preference	4.00	5.00	5.50	2.30	2	.317	N/A
Repetitive use of Language	4.00	7.50	6.00	17.25	2	<.0001	FXS > CdCS
Total	16.50	29.50	17.00	22.88	2	<.0001	FXS > CdCS, CdLS

* n values varied due to missing data.

Table 3: Median values on the Repetitive Behaviour Questionnaire Item Level scores between syndrome groups at T1 and T2 (separately).

	CdCS	FXS	CdLS	*p* <.008	Post Hoc <.01
T1					
Q3- Hand Stereotypy	1.00	4.00	3.00	.000	FXS > CdCS
Q5- Tidying	.00	.00	.00	.014	*N/A*
Q10- Attachment to objects	3.00	.00	3.00	.005	CdCS > FXS
Q11- Repetitive phrase	.00	3.00	.00	.000	FXS > CdLS
Q13- Restricted conversation	.00	3.00	.00	.000	FXS > CdCS, CdLS
Q14- Echolalia	.00	3.00	.00	.000	FXS > CdCS, CdLS
Q15- Preference for routine	.00	3.00	1.00	.000	FXS > CdCS, CdLS
Q16- Lining up objects	.00	.00	.00	.001	FXS, CdLS > CdCS
T2					
Q3- Hand Stereotypy	2.50	3.00	3.00	.174	*N/A*
Q5- Tidying	.00	.00	.00	.003	FXS > CdCS CdLS > CdCS
Q10- Attachment to objects	3.00	.00	2.50	.005	CdCS > FXS
Q11- Repetitive phrase	.00	2.00	.00	.001	FXS > CdLS
Q13- Restricted conversation	.00	2.00	.00	.000	FXS > CdCS, CdLS
Q14- Echolalia	.00	2.00	.00	.000	FXS > CdCS, CdLS
Q15- Preference for routine	.00	3.00	2.00	.000	FXS > CdCS, CdLS
Q16- Lining up objects	.00	.00	.00	.023	*N/A*

Table 4: Median scores on the Social Communication Questionnaire by age groups (under15 / over15) **and syndrome groups.**

	CdCS	FXS	CdLS	X^2	*df*	*P value* <.02	Post Hoc <.01
T1- Under/= 15	(n=22)*	(n=79)*	(n=35)*				
Communication Not Proportional	4.00	7.00	6.00	23.52	2	<.0001	FXS > CdCS
**Communication Proportional	3.43	7.43	9.29	13.35	2	.001	FXS, CdLS > CdCS
Restricted, Repetitive and stereotyped behaviours	3.50	6.00	4.00	22.41	2	<.0001	FXS > CdCS, CdLS
Reciprocal social interaction	4.00	8.00	8.00	28.10	2	<.0001	FXS, CdLS > CdCS
T1- Over 15	(n=19)*	(n=63)*	(n=32)*				
Communication Not Proportional	4.00	7.00	7.00	11.10	2	.004	FXS, CdLS > CdCS
**Communication Proportional	7.43	7.14	9.79	7.13	2	.028	N/A
Restricted, Repetitive and stereotyped behaviours	2.33	4.00	3.50	3.10	2	.212 (.106)	N/A
Reciprocal social interaction	7.00	8.00	10.00	13.51	2	.001	FXS, CdLS > CdCS

* n values varied due to missing data.

** Communication Proportional was calculated but not reported in the results because it is not included in the manual for the measure

Table 5: Median values on the Repetitive Behaviour Questionnaire by syndrome groups and age groups (Under= 15 and Over 15) at T1.

	CdCS	**FXS**	**CdLS**	X^2	***df***	***P value*** <.008	**Post Hoc** <.01
T1- Under/= 15	(n=23)*	(n=78)*	(n=35)*				
Stereotyped behaviour	4.00	8.00	6.00	9.23	2	.010	*N/A*
Compulsive behaviour	1.00	5.00	3.00	7.44	2	.024	*N/A*
Insistence on Sameness	1.00	4.00	.00	18.27	2	<.0001	FXS > CdCS, CdLS
Restricted preference	3.00	6.00	6.00	7.28	2	.026	*N/A*
Repetitive use of Language	4.00	8.00	5.00	24.36	2	<.0001	FXS > CdCS, CdLS
Total	15.00	30.00	14.00	29.56	2	<.0001	FXS > CdCS, CdLS
T1- Over 15	(n=19)*	(n=63)*	(n=32)*				
Stereotyped behaviour	6.00	5.00	7.00	3.41	2	.181	*N/A*
Compulsive behaviour	3.00	7.00	7.00	5.49	2	.064	*N/A*
Insistence on Sameness	.00	4.00	3.00	14.94	2	.001	FXS > CdCS
Restricted preference	5.50	6.00	4.50	.58	2	.747	*N/A*
Repetitive use of Language	3.50	8.00	5.00	7.27	2	.026	*N/A*
Total	18.00	29.50	22.00	6.35	2	.042	*N/A*

* n values varied due to missing data.

Table 6: Median values of scores on the Social Communication Questionnaire within syndrome groups and between age groups (<=15 and >15) at T1.

	Under/= 15	Over 15	*U*	*Z*	*p* <.02	
T1- CdCS	(n=22)*	(n=19)*				
Communication Not Proportional	4.00	4.00	140.50	-1.13	.268	
**Communication Proportional	3.43	7.43	79.00	-2.94	.003	O15 > U15
Restricted, Repetitive and stereotyped behaviours	3.50	2.33	183.50	-.68	.500	
Reciprocal social interaction	4.00	7.00	98.50	-2.37	.018	O15 > U15
T1- FXS	(n=79)*	(n=63)*				
Communication Not Proportional	7.00	7.00	1956.00	-.40	.687	
**Communication Proportional	7.43	7.14	2056.00	-.109	.914	
Restricted, Repetitive and stereotyped behaviours	6.00	4.00	1574.50	-3.79	<.0001	U15 > O15
Reciprocal social interaction	8.00	8.00	1887.50	-.73	.466	
T1- CdLS	(n=35)*	(n=32)*				
Communication Not Proportional	6.00	7.00	317.50	-1.85	.064	
**Communication Proportional	9.29	9.79	366.00	-1.06	.290	
Restricted, Repetitive and stereotyped behaviours	4.00	3.50	532.50	-.349	.727	
Reciprocal social interaction	8.00	10.00	267.00	-2.55	.011	O15 > U15

* n values varied due to missing data.

** Communication Proportional was calculated but not reported in the results because it is not included in the manual for the measure

Table 7: Median values on the Repetitive Behaviour Questionnaire by syndrome groups and age groups (Under= 15 verses Over 15) at T1.

	Under/= 15	**Over 15**	***U***	***Z***	***p* value <.008**	
T1- CdCS	(n=23)*	(n=19)*				
Stereotyped behaviour	4.00	6.00	168.00	-1.28	.199	
Compulsive behaviour	1.00	3.00	201.00	-.461	.645	
Insistence on Sameness	1.00	.00	186.50	-.89	.375	
Restricted preference	3.00	5.50	73.00	-1.68	.093	
Repetitive use of Language	4.00	3.50	100.00	-.58	.559	
Total	15.00	18.00	163.00	-1.41	.160	
T1- FXS	(n=78)*	(n=63)*				
Stereotyped behaviour	8.00	5.00	1609.50	-3.42	.001	U15 > O15
Compulsive behaviour	5.00	7.00	2265.00	-.80	.422	
Insistence on Sameness	4.00	4.00	2246.00	-.73	.466	
Restricted preference	6.00	6.00	1955.50	-.10	.918	
Repetitive use of Language	8.00	8.00	1787.00	-.93	.350	
Total	30.00	29.50	2198.00	-.49	.627	
T1- CdLS	(n=35)*	(n=32)*				
Stereotyped behaviour	6.00	7.00	486.00	-.93	.350	
Compulsive behaviour	3.00	7.00	436.50	-1.57	.116	
Insistence on Sameness	.00	3.00	387.00	-2.13	.033	
Restricted preference	6.00	4.50	141.50	-.38	.702	
Repetitive use of Language	5.00	5.00	130.50	-.75	.453	
Total	14.00	22.00	408.50	-1.72	.085	

* n values varied due to missing data.

Table 8: Median values on the Repetitive Behaviour Questionnaire Item Level scores by syndrome groups and age groups (Under= 15 verses Over 15) at T1.

	Under/= 15	Over 15	*p* <.008	
T1- CdCS				
Q3- Hand Stereotypy	1.00	1.00	.787	
Q5- Tidying	.00	.00	.805	
Q10- Attachment to objects	3.00	4.00	.116	
Q11- Repetitive phrase	.00	.00	.404	
Q13- Restricted conversation	.00	.00	.772	
Q14- Echolalia	.00	.00	.624	
Q15- Preference for routine	.00	.00	.360	
Q16- Lining up objects	.00	.00	.803	
T1- FXS				
Q3- Hand Stereotypy	4.00	3.00	.000	U15 > O15
Q5- Tidying	.00	.00	.749	
Q10- Attachment to objects	1.00	.00	.576	
Q11- Repetitive phrase	3.00	2.00	.198	
Q13- Restricted conversation	2.00	3.00	.401	
Q14- Echolalia	2.00	3.00	.811	
Q15- Preference for routine	3.00	3.00	.595	
Q16- Lining up objects	.00	.00		
T1- CdLS				
Q3- Hand Stereotypy	3.00	3.00	.188	
Q5- Tidying	.00	.00	.404	
Q10- Attachment to objects	2.00	3.00	.394	
Q11- Repetitive phrase	.00	.00	.229	
Q13- Restricted conversation	.00	.00	.369	
Q14- Echolalia	1.00	.00	.883	
Q15- Preference for routine	.00	3.00	.069	
Q16- Lining up objects	.00	.00	.658	

Table 9: Median values on the Social Communication Questionnaire at T1 compared to T2 within each syndrome group.

	T1	T2	*P value* <.02	Post Hoc
CdCS				
Communication Not Proportional	4.00	4.00	.110	
**Communication Proportional	5.57	5.00	.482	
Restricted, Repetitive and stereotyped behaviours	3.00	3.50	.662	
Reciprocal social interaction	4.00	4.29	.899	
FXS				
Communication Not Proportional	7.00	7.00	.774	
**Communication Proportional	7.43	7.00	.609	
Restricted, Repetitive and stereotyped behaviours	5.00	5.00	.017	T1 > T2
Reciprocal social interaction	8.00	8.00	.008	T1 > T2
CdLS				
Communication Not Proportional	7.00	7.00	.531	
**Communication Proportional	9.29	9.00	.019	T1 > T2
Restricted, Repetitive and stereotyped behaviours	4.00	4.00	.934	
Reciprocal social interaction	9.00	9.00	.759	

* n values varied due to missing data.
** Communication Proportional was calculated but not reported in the results because it is not included in the manual

Table 10: Median values on the Repetitive Behaviour Questionnaire by syndrome group at T1 verses T2.

	T1	T2	*p* <.008
CdCS (n=42)*			
Stereotyped behaviour	5.50	5.50	.973
Compulsive behaviour	2.00	2.00	.329
Insistence on Sameness	.00	.00	.490
Restricted preference	4.00	4.00	.628
Repetitive use of language	4.00	4.00	.627
Total	16.00	16.50	.611
FXS (n=141)*			
Stereotyped behaviour	7.75	6.00	.076
Compulsive behaviour	6.00	6.00	.362
Insistence on Sameness	4.00	4.00	.454
Restricted preference	6.00	5.00	.926
Repetitive use of language	8.00	7.50	.180
Total	30.00	29.50	.411
CdLS (n=67)*			
Stereotyped behaviour	6.00	6.00	.910
Compulsive behaviour	4.00	3.00	.631
Insistence on Sameness	2.00	2.00	.393
Restricted preference	5.00	5.50	.797
Repetitive use of language	5.00	6.00	.660
Total	18.00	17.00	.892

* n values varied due to missing data.

APPENDIX 9

ADOS Algorithm and Non-algorithm items analysis

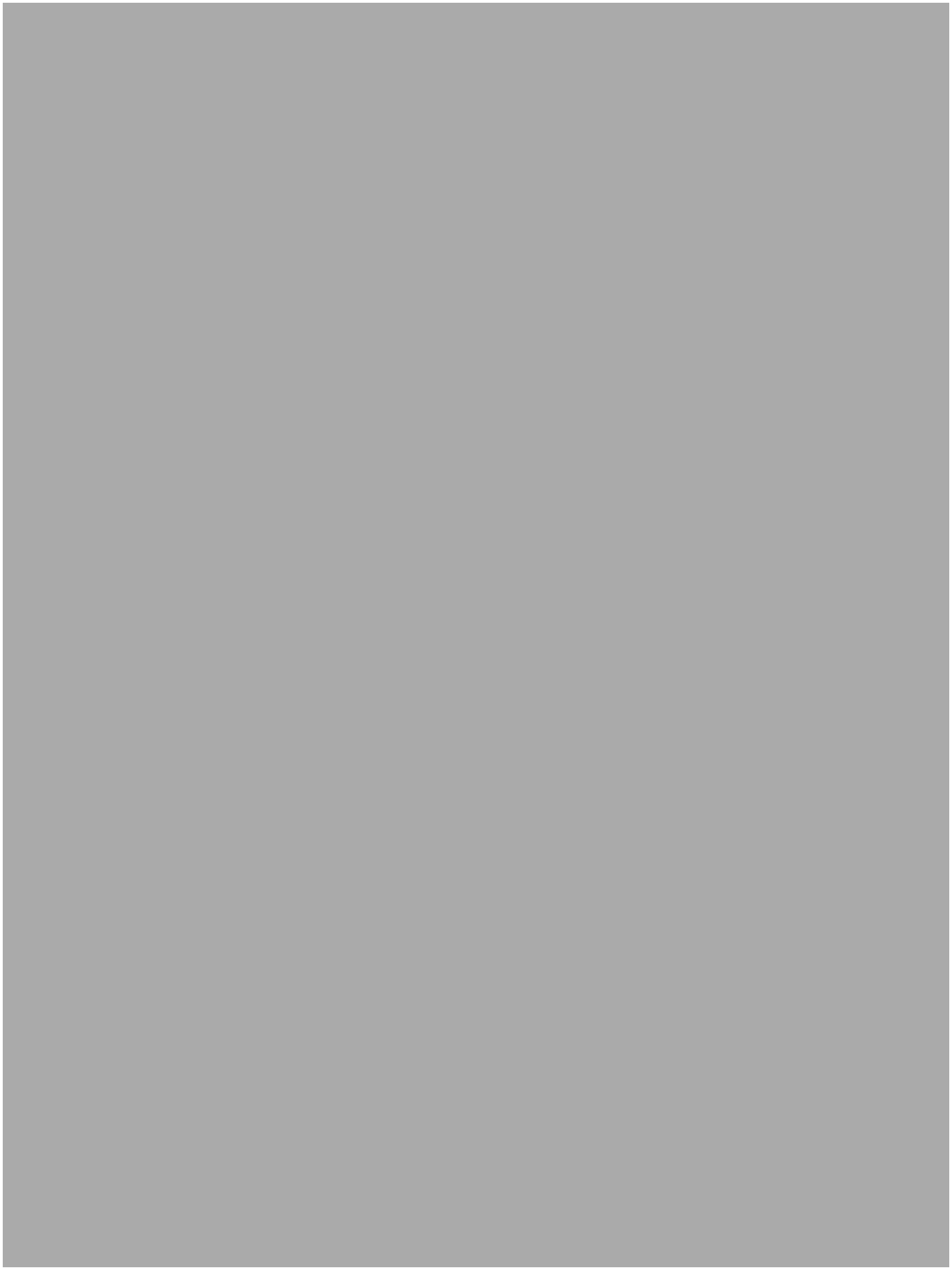
ADOS ANOVAs for Algorithm and Non-algorithm items

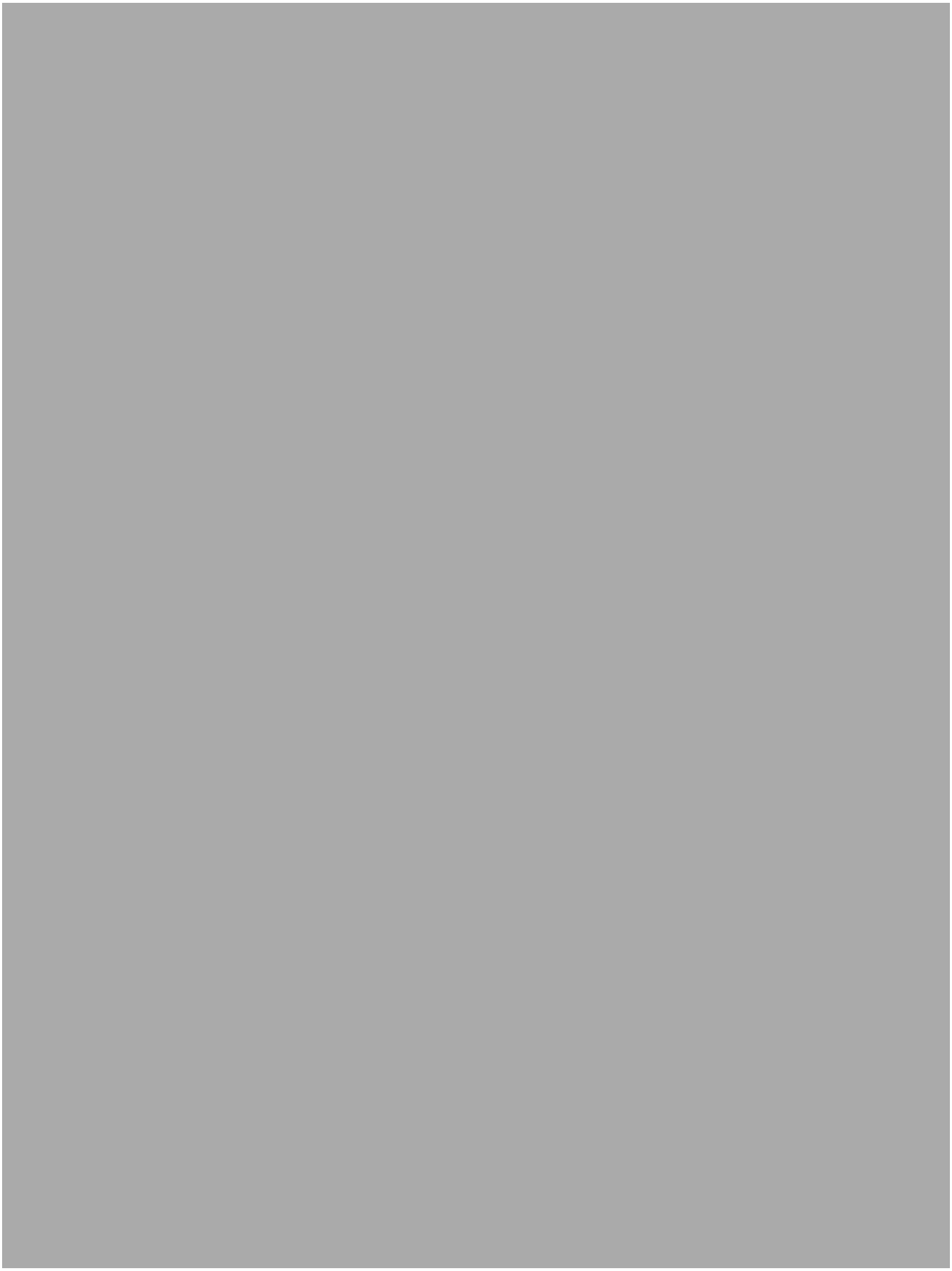
ANOVAs	Interaction	Main Time	Main Group
Alogrithm Items			
Communication			
Odd/Sterotyped Phrases	*p* .050	*p* .144	*p* .112
Pointing	*p* .233	*p* .378	*p* .040
Gestures	*p* .106	*p* .679	*p* .006
Social Interaction			
Eye contact	*p* .331	*p* .007	*p* .763
Range of facial expression	*p* .274	*p* .324	*p* .104
Spontaneous initiation of joint	*p* .107	*p* .788	*p* .757
Quality of social overtures	*p* .287	*p* .000	*p* .121
Play			
Imagination and creativity	*p* .686	*p* .592	*p* .001
Repetitive Behaviour			
Sensory interests	*p* .702	*p* .694	*p* .293
Hand Stereotypies	*p* .400	*p* .118	*p* .573
Repetitive interests	*p* .064	*p* .802	*p* .607

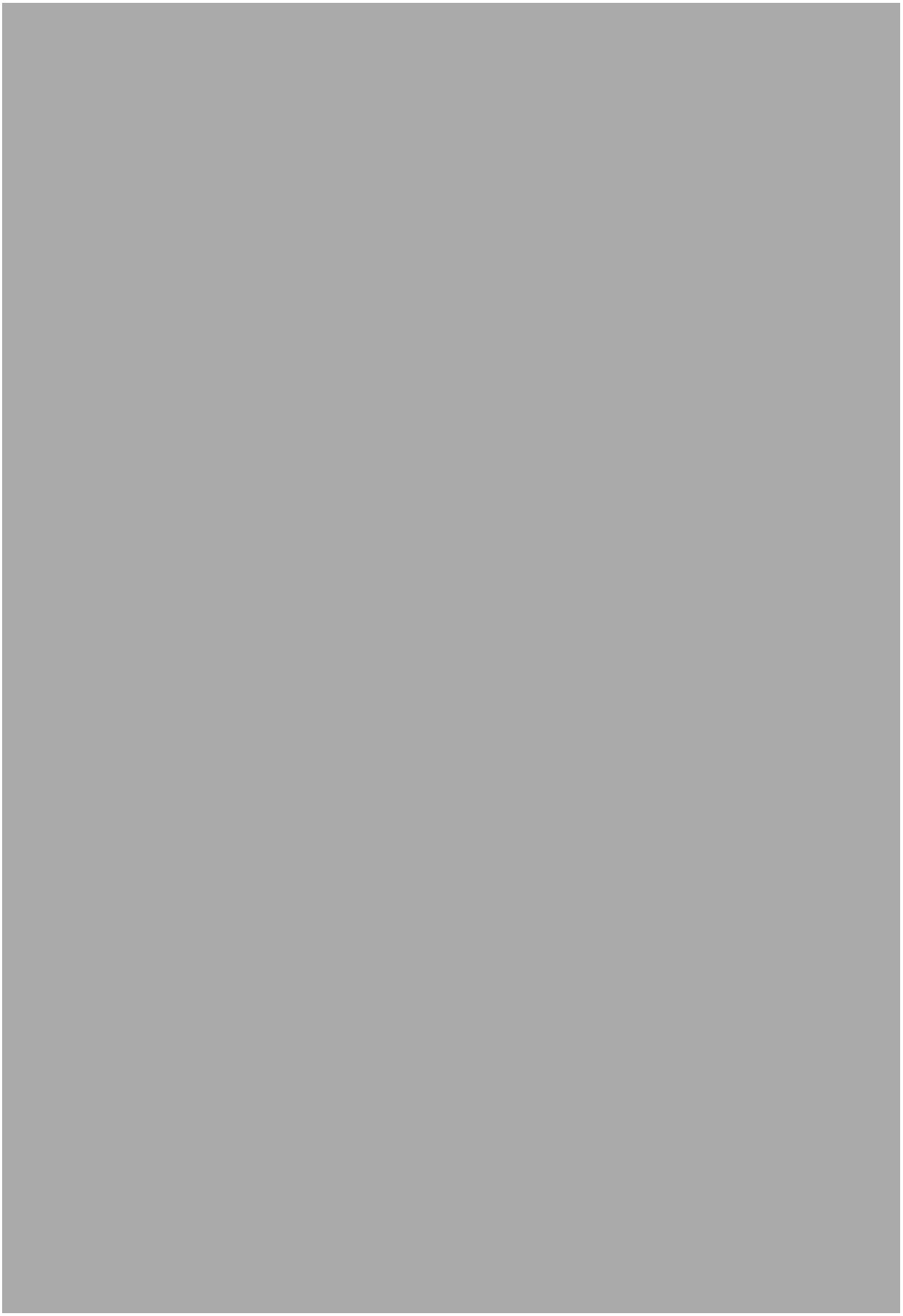
Non-algorithm Items	**Interaction**	**Main Time**	**Main Group**
Communication			
Overall Language	*p* .526	*p* .183	*p* .497
Echolalia	*p* .061	*p* .645	*p* .372
Social Interaction			
Response to name	*p* .214	*p* .958	*p* .015
Shared enjoyment	*p* .129	*p* .875	*p* .026
Showing	*p* .009	*p* .076	*p* .923
Response to Joint Attention	*p* .644	*p* .772	*p* .001
Play			
Functional Play	*p* .269	*p* .235	*p* .434
Repetitive Behaviour			
SIB	*p* .836	*p* .273	*p* .131
Other			
Overactivity	*p* .214	*p* .019	*p* .718
Aggression	*p* .102	*p* .114	*p* .324
Anxiety	*p* .052	*p* .051	*p* .642

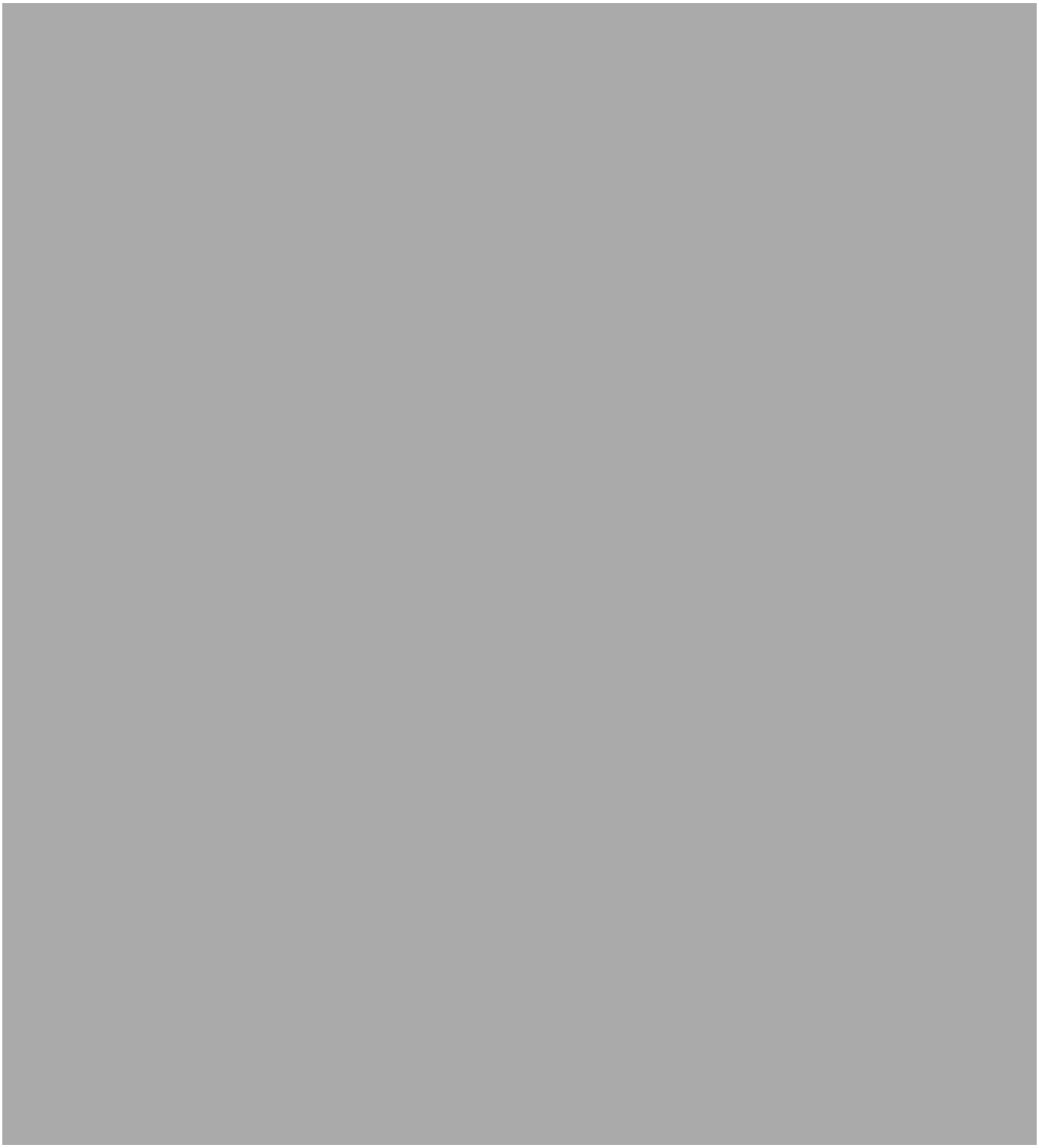
APPENDIX 10

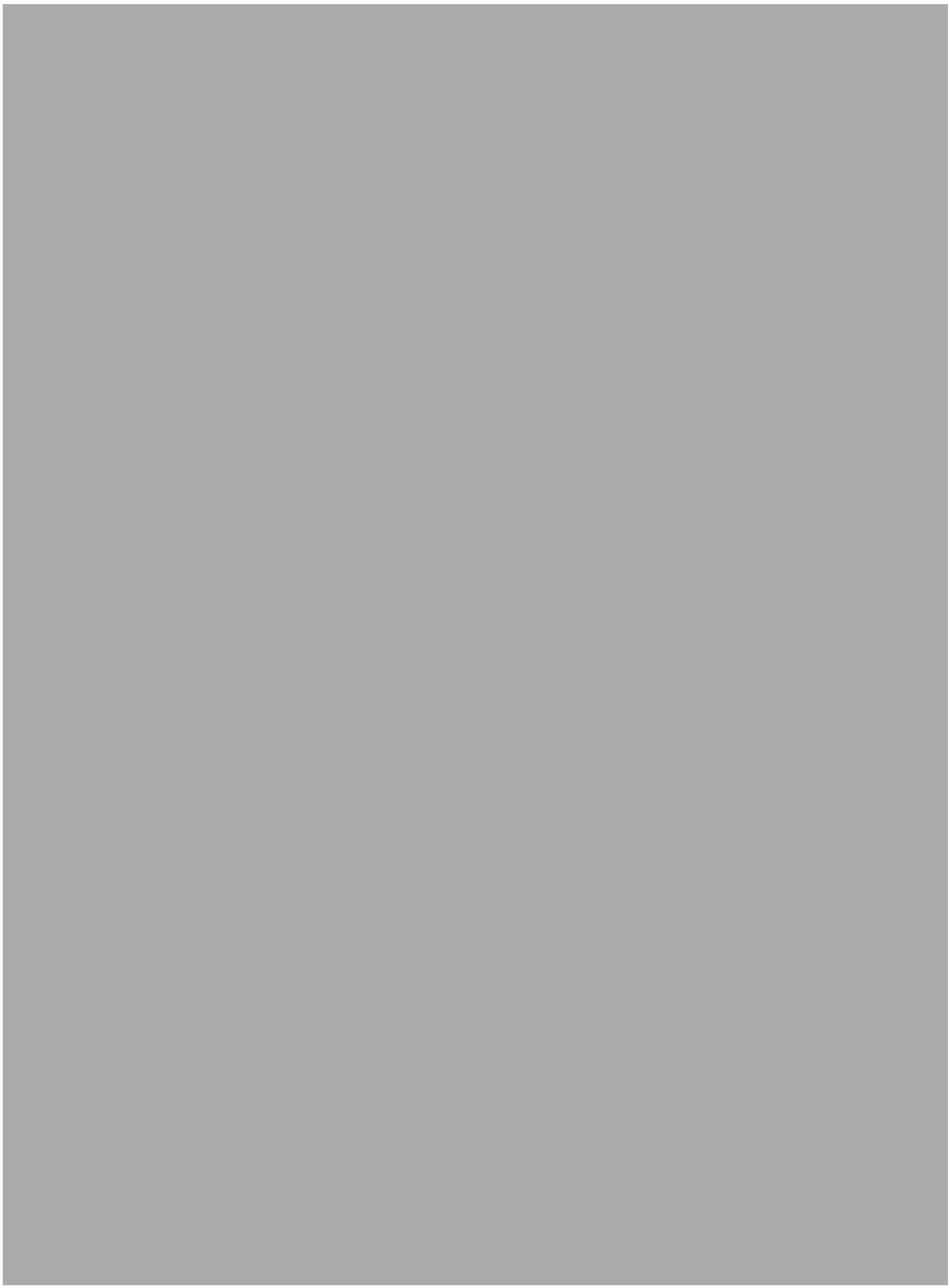
NHS ethical approval letters

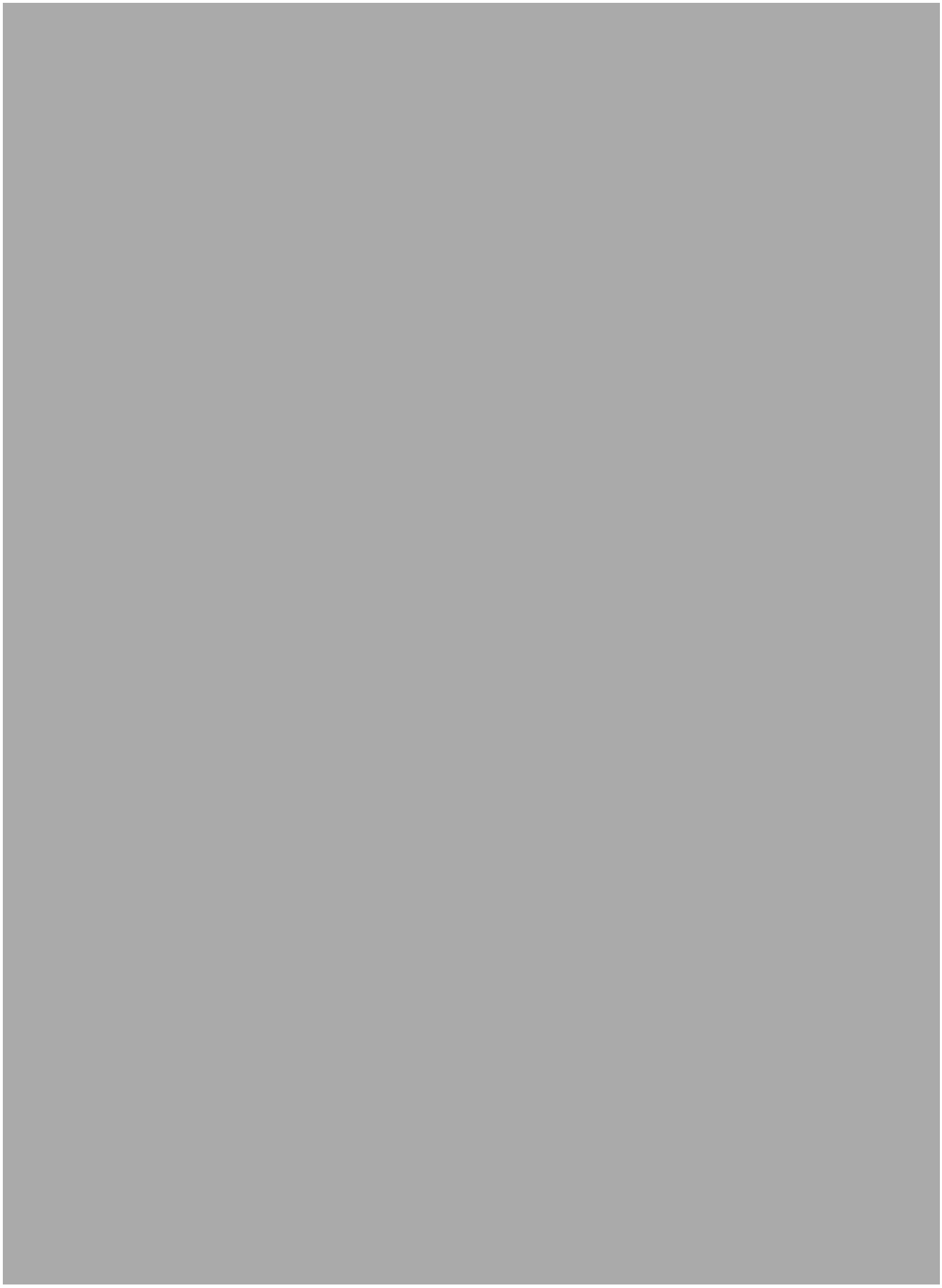


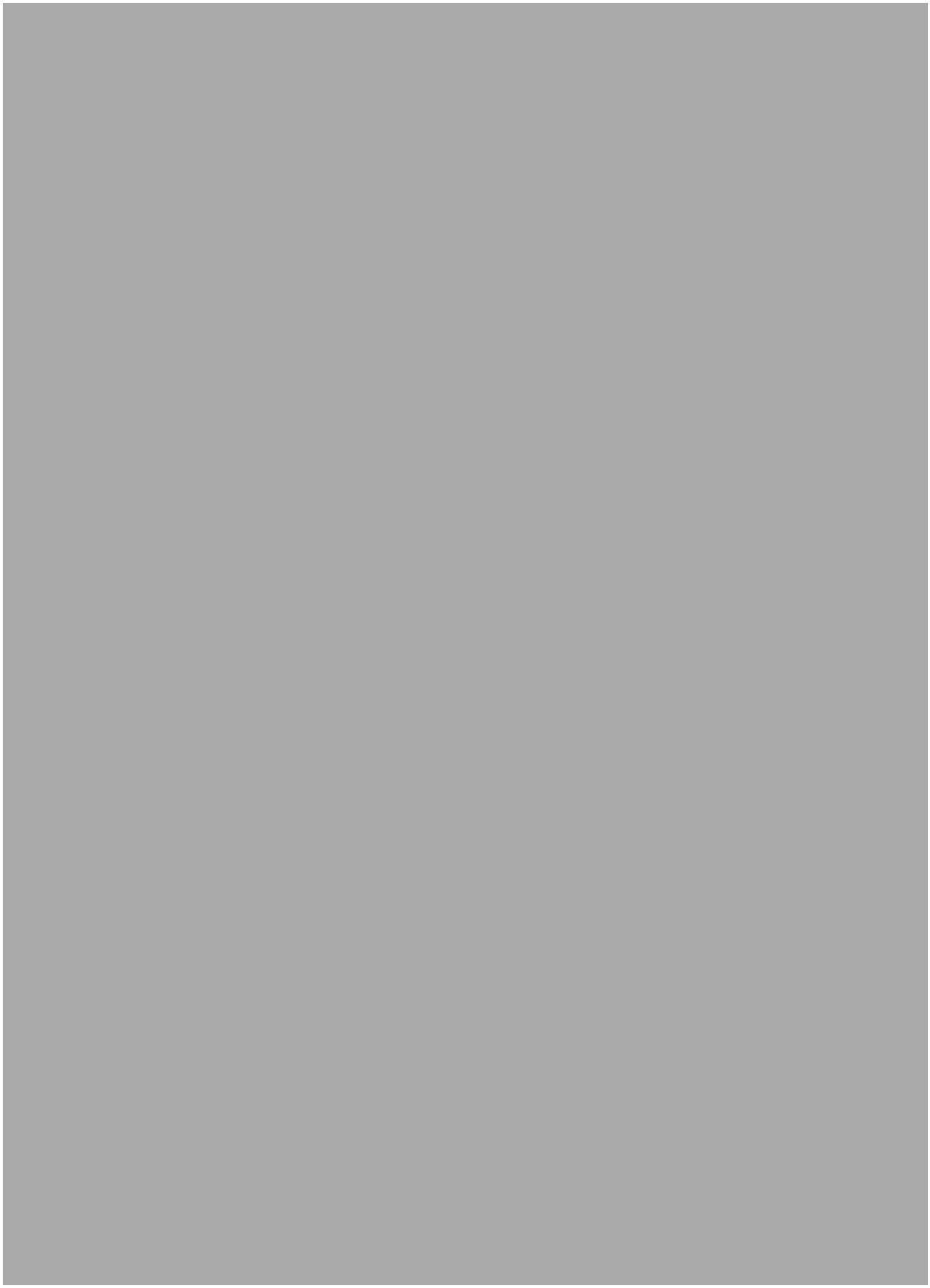












References

Adams D., Horsler K., & Oliver, C. (2011). Age related change in social behavior in children with Angelman Syndrome. *American Journal Medical Genetics,* Part A 155, 1290-1297. doi:10.1002/ajmg.a.33964

Adams, D., & Oliver, C. (2010). The relationship between acquired impairments of executive function and behaviour change in adults with Down syndrome. *Journal of Intellectual Disability Research*, *54*(5), 393-405. doi:10.1111/j.1365-2788.2010.01271.x

Ajmone, P., Rigamonti, C., Dall'Ara, F., Monti, F., Vizziello, P., Milani, D.,...Costantino, A. (2014). Communication, cognitive development and behaviour in children with Cornelia de Lange Syndrome (CdLS): Preliminary results. *American Journal Medical Genetics*, Part B 165B, 223-229. doi:10.1002/ajmg.b.32224

Aman, M., Singh, N., Stewart, A., & Field, C. (1986). *The aberrant behaviour checklist: manual*. East Aurora, NY: Slosson Educational Publications.

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., text revision). Washington, DC: American Psychiatric Association.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing.

Anderson, V., Jacobs, R., & Anderson, P. (2008). *Executive functions and the frontal lobes: A lifespan perspective*. London, England: Taylor & Francis.

Antshel, K. M., Aneja, A., Strunge, L., Peebles, J., Fremont, W. P., Stallone, K., ... & Kates, W. R. (2007). Autistic spectrum disorders in velo-cardio facial syndrome (22q11. 2 deletion). *Journal of autism and developmental disorders*, *37*(9), 1776-1786. doi:10.1007/s10803-006-0308-6

Arron, K., Oliver, C., Berg, K., Moss, J., & Burbidge, C. (2011). Prevalence and phenomenology of self-injurious and aggressive behaviour in genetic syndromes. *Journal of Intellectual Disability Research*, *55*(2), 109-120. doi:10.1111/j1365-2788.2010.01337.x

Baio, J. (2012). Prevalence of autism spectrum disorders- autism and developmental disabilities monitoring network, 14 sites, United States, 2008. *Morbidity and Mortality Weekly Report*, *61*(SS-3), 1-19.

Baird, G., Simonoff, E., Pickles, A., Chandler, S., Loucas, T., Meldrum, D., & Charman, T. (2006). Prevalence of disorders of the autism spectrum in a population cohort of children in South Thames: the Special Needs and Autism Project (SNAP). *The Lancet*, *368*(9531), 210–215. doi:10.1016/s0140-6736(06)69041-7

Basile, E., Villa, L., Selicorni, A., & Molteni, M . (2007). The behavioural phenotype of Cornelia de Lange Syndrome: a study of 56 individuals. *Journal of Intellectual Disability Research*, *51*(9), 671–681. doi:10.111/j.1365-2788.2007.0097.x

Bell, R., Rankin, J., & Donaldson, L. J. (2003). Down's syndrome: occurrence and outcome in the north of England, 1985–99. *Paediatric and perinatal epidemiology*, *17*(1), 33-39. doi:10.1046/j.1365-3016.2003.00463.x

Berney, T., Ireland, M., & Burn, J. (1999). Behavioural phenotype of Cornelia de Lange syndrome. *Archives of Disease in Childhood*, *81*(4), 333-336.

Berument, S. K., Rutter, M., Lord, C., Pickles, A., & Bailey, A. (1999). Autism screening questionnaire: Diagnostic validity. *The British Journal of Psychiatry*, *175*(5), 444–451. doi:10.1192/bjp.175.5.444

Betancur, C. (2011). Etiological heterogeneity in autism spectrum disorders: More than 100 genetic and genomic disorders and still counting. *Brain Research, 1380,* 42-77. doi:10.1016/j.brainres.2010.11.078

Bhuiyan, Z. A., Klein, M., Hammond, P., van Haeringen, A., Mannens, M. M. A. M., Van Berckelaer-Onnes, I., & Hennekam, R. C .M. (2006). Genotype-phenotype correlations of 39 patients with Cornelia de Lange syndrome: the Dutch experience. *Journal of Medical Genetics*, *43*(7), 568–575. doi:10.1136/jmg.2005.038240

Blake, K. D., & Prasad, C. (2006). CHARGE syndrome. *Orphanet journal of rare diseases*, *1*(1), 34. doi:10.1186/1750-1172-1-34

Bonati, M. T., Russo, S., Finelli, P., Valsecchi, M. R., Cogliati, F., Cavalleri, F., ... & Larizza, L. (2007). Evaluation of autism traits in Angelman syndrome: a resource to unfold autism genes. *Neurogenetics*, *8*(3), 169-178. doi:10.1007/s10048-007-0086-0

Bouras, N., Turk, J., & Cornish, K. (1998). Face recognition and emotion perception in boys with fragile-X syndrome. *Journal of Intellectual Disability Research*, *42*(6), 490-499. doi:10.1046/j.1365-2788.1998.4260490.x

Brooks, W., & Benson, B. (2013). The validity of the social communication questionnaire in adults with intellectual disability. *Research in Autism Spectrum Disorders*, *7*(2), 247-255. doi:10.1016/j.rasd.2012.10.002

Brownell, R. (Ed.). (2000). *Expressive one-word picture vocabulary test: Manual*. Novato, CA: Academic Therapy Publications.

Butler, M. G. (1990). Prader-Willi syndrome: current understanding of cause and diagnosis. *American Journal of Medical Genetics Part A, 35*(3), 319-332. doi:10.1002/ajmg.1320350306

Campbell, C. L. (2003). Septo-optic dysplasia: a literature review. *Optometry (St. Louis, Mo.), 74*(7), 417-426.

Campbell, D. J., Carlin, M. E., Justen III, J. E., & Baird, S. M. (2004) Cri-du-chat Syndrome: A Topical Overview. *Journal of the 5P Minus Society, 1*, 1-7.

Carlin, M. E. (1983). *5P-/Cri-du-chat syndrome*. Unpublished paper, Division of Genetics, University of Miami - Mailman Center for Child Development, Miami, FL.

Carlin, M. E. (1990). The improved prognosis in Cri-du-chat (5P-) syndrome. In W. I. Fraser (Ed.), *Proceedings of the 8th Congress of the International Association of Scientific Study of Mental Deficiency* (pp. 64–73). Edinburgh, UK: Blackwell.

Charman, T., & Baird, G. (2002). Practitioner review: Diagnosis of autism spectrum disorder in 2-and 3-year-old children. *Journal of Child Psychology and Psychiatry, 43*(3), 289-305. doi:10.1111/1469-7610.00022

Clarke, D. J., & Dykens, E. M. (1997). Correlates of maladaptive behaviour in individuals with 5p- (cri du chat) syndrome. *Developmental Medicine & Child Neurology, 39*(11), 752–756. doi:10.1111j.1469-8749.1997.tb07377.x

Cohen, D., Pichard, N., Tordjman, S., Baumann, C., Burglen, L., Excoffier, E.,...Heron, D. (2005). Specific genetic disorders and autism: Clinical contribution towards their identification. *Journal of Autism and Developmental Disorders, 35*(1), 103-116. doi:10.1007/s10803-004-1038-2

Collins, M. S. R., & Eaton-Evans, J. (2001). Growth study of cri du chat syndrome. *Archives of Disease in Childhood, 85*(4)**,** 337-338. doi:10.1136/adc.85.4.337

Collis, L., Oliver, C., & Moss, J. (2006). Low mood and social anxiety in Cornelia de Lange syndrome. *Journal of Intellectual Disability Research*, *50*(11), 792-792.

Cornish, K., Turk, J., & Hagerman, R. (2008). The fragile X continuum: new advances and perspectives. *Journal of Intellectual Disability Research, 52*(6), 469-482. doi:10.1111/j.1365-2788.2008.01056.x

Cornish, K., Turk, J., & Levitas, A. (2007). Fragile X syndrome and autism: common developmental pathways? *Current Pediatric Reviews, 3*(1), 61-68. doi:10.2174/157339607779941660

Cornish, K., & Pigram, J. (1996). Developmental and behavioural characteristics of cri du chat syndrome. *Archives of Disease in Childhood*, *75*(5), 448-450. doi:10.1136/adc.75.5.448

Cornish, K., Cole, V., Longhi, E., Karmiloff-Smith, A., & Scerif, G. (2013). Mapping developmental trajectories of attention and working memory in fragile X syndrome: Developmental freeze or developmental change?. *Development and Psychopathology*, *25*(2), 365-376. doi:10.1017/s0954579412001113

Cornish, K., Munir, F., & Bramble, D. (1998). Adaptive and maladaptive behaviour in children with cri-du-chat syndrome. *Journal of Applied Research in Intellectual Disabilities*, *11*(3), 239-246. doi:10.1111/j.1468-3148.1998.tb00064.x

Crawford, H., Waite, J., & Oliver, C. (2017). Diverse profiles of anxiety related disorders in fragile X, Cornelia de Lange and Rubinstein-Taybi syndromes. *Journal of Autism and Developmental Disorders*, *47*(12), 3728-3740. doi:10.1007/s10803-016-3015-y

Critchley, M., & Earl, C. (1932). Tuberose sclerosis and allied conditions. *Brain, 55*(3), 311-346. doi:10.1093/brain/55.3.311

Dawson, G., & Osterling, J. (1997). Early intervention in autism. *The Effectiveness of Early Intervention*, 307-326.

Deardorff, M. A., Kaur, M., Yaeger, D., Rampuria, A., Korolev, S., Pie, J.,…Krantz, I. (2007). Mutations in cohesin complex members SMC3 and SMC1A cause a mild variant of Cornelia de Lange syndrome with predominant mental retardation. *The American Journal of Human Genetics*, *80*(3), 485–494. doi:10.1086/511888

Deardorff, M. A., Wilde, J. J., Albrecht, M., Dickinson, E., Tennstedt, S., Braunholz, D.,... Kaiser, F. J. (2012). RAD21 mutations cause a human cohesinopathy. *The American Journal of Human Genetics*, *90*(6), 1014-1027. doi:10.1016/j.ajhg.2012.04.019

Descheemaeker, M. J., Govers, V., Vermeulen, P., & Fryns, J. P. (2006). Pervasive developmental disorders in Prader–Willi syndrome: the Leuven experience in 59 subjects and controls. *American Journal of Medical Genetics Part A*, *140*(11), 1136-1142. doi:10.1002/ajmg.a.31235

Devenny, D. A., Krinsky-McHale, S. J., Kittler, P. M., Flory, M., Jenkins, E., & Brown W. T. (2010). Age-associated memory changes in adults with Williams syndrome. *Developmental Neuropsychology*, *26*(3), 691-706. doi:10.1207/s15326942dn2603_3

Diamond, A. (2005). Attention-deficit disorder (attention-deficit/hyperactivity disorder without hyperactivity): A neurobiologically and behaviorally distinct disorder from attention-deficit/hyperactivity disorder (with hyperactivity). *Development and Psychopathology*, *17*(3), 807-825. doi:10.1017/s0954579405050388

Diamond, A. (2013). Executive functions. *Annual Review of Psychology*, *64*(1), 135-168. doi:10.1146/annurev-psych-113011-143750

Down, J. L. H. (1990). Observations on an ethnic classification of idiots. In Down, J. L. H. (MacMillan Press), *Mental affection of childhood and youth* (pp. 127-131). (Original work published 1866).

Duijff, S. N., Klaassen, P. W., de Veye, H. F. S., Beemer, F. A., Sinnema, G., & Vorstman, J. A. (2013). Cognitive and behavioral trajectories in 22q11DS from childhood into adolescence: a prospective 6-year follow-up study. *Research in developmental disabilities*, *34*(9), 2937-2945. doi:10.1016/j.ridd.2013.06.001

Dunn, L. M., Whetton, C., & Burley, J. (1997). *British Picture Vocabulary Scale (2nd ed.)*. Windsor, England: NFER-Nelson.

Dykens, E. M. (1995). Measuring behavioural phenotypes: Provocations from the "new genetics." *American Journal on Mental Retardation*, *99*(5), 522-532.

Dykens, E. M., Hodapp, R. M., & Finucane, B. M. (2000). *Genetics and mental retardation syndromes: A new look at behavior and interventions*. Baltimore, MD: Paul H Brookes Publishing.

Dykens, E. M., Lee, E., & Roof, E. (2011). Prader–Willi syndrome and autism spectrum disorders: an evolving story. *Journal of Neurodevelopmental Disorders*, *3*(3), 225-237. doi:10.1007/s11689-011-9092-5

Eden, K. E., de Vries, P. J., Moss, J., Richards, C., & Oliver, C. (2014). Self-injury and aggression in tuberous sclerosis complex: cross syndrome comparison and associated risk markers. *Journal of Neurodevelopmental Disorders*, *6*(10). doi:10.1186/1866-1955-6-10

Efron, B. (1979). Bootstrap methods: another look at the jackknife. *The annals of statistics* (pp. 1-26).

Evans, D. G., Howard, E., Giblin, C., Clancy, T., Spencer, H., Huson, S. M., & Lalloo, F. (2010). Birth incidence and prevalence of tumor-prone syndromes: estimates from a UK family genetic register service. *American journal of medical genetics Part A, 152*(2), 327-332. doi:10.1002/ajmg.a.33139

Falkmer, T., Anderson, K., Falkmer, M. & Horlin, C. (2013). Diagnostic procedures in autism spectrum disorders: a systematic literature review. *European Child & Adolescent Psychiatry, 22*(6), 329-340. doi:10.1007/s00787-013-0375-0

Farzin, F., Perry, H., Hessl, D., Loesch, D., Cohen, J., Bacalman, S.,...Hagerman, R. (2006). Autism spectrum disorders and attention-deficit /hyperactivity disorder in

boys with the fragile X premutation. *Journal of Developmental & Behavioral Pediatrics, 27*(2), S137-S144.

Field, A. P. (2013). *Discovering statistics using IBM SPSS statistics and sex and drugs and rock 'n' roll*. London, England: SAGE Publications Ltd.

Fine, S. E., Weissman, A., Gerdes, M., Pinto-Martin, J., Zackai, E. H., McDonald-McGinn, D. M., & Emanuel, B. S. (2005). Autism spectrum disorders and symptoms in children with molecularly confirmed 22q11. 2 deletion syndrome. *Journal of autism and developmental disorders, 35*(4), 461-470. doi:10.1007/s10803-005-5036-9

Fleiss, J. (1981). Balanced incomplete block designs for inter-rater reliability studies. *Applied Psychological Measurement, 5*(1), 105-112. doi:10.1177/014662168100500115

Fombonne, E. (1999). The epidemiology of autism: A review. *Psychological Medicine, 29*(4), 769-786.

Fombonne, E. (2005). The changing epidemiology of autism. *Journal of Applied Research in Intellectual Disabilities, 18*(4), 281-294. doi:10.1111/j.1468-3148.2005.00266.x

Garg, S., Green, J., Leadbitter, K., Emsley, R., Lehtonen, A., Evans, D. G., & Huson, S. M. (2013). Neurofibromatosis type 1 and autism spectrum disorder. *Pediatrics*, *132*(6), e1642-e1648. doi:10.1542/peds.2013-1868

Garg, S., Plasschaert, E., Descheemaeker, M. J., Huson, S., Borghgraef, M., Vogels, A., ... & Green, J. (2015). Autism spectrum disorder profile in neurofibromatosis type I. *Journal of autism and developmental disorders*, *45*(6), 1649-1657. doi:10.1007/s10803-014-2321-5

Garner, C., Callias, M., & Turk, J. (1999). Executive function and theory of mind performance of boys with fragile-X syndrome. *Journal of Intellectual Disability Research*, *43*(6), 466-474. doi:10.1046/j.1365-2788.1999.00207.x

Gillberg, C., & Coleman, M. (2000). *The biology of the autistic syndromes*. London, England: Mac Keith Press.

Gillberg, J. C., Gillberg, C., & Ahlsén, G. (1994). Autistic behaviour and attention deficits in tuberous sclerosis: a population-based study. *Developmental Medicine & Child Neurology*, *36*(1), 50-56. doi:10.1111/j.1469-8749.1994.tb11765.x

Gillberg, C., Persson, E., Grufman, M., & Themnér, U. (1986). Psychiatric disorders in mildly and severely mentally retarded urban children and adolescents: epidemiological aspects. *The British journal of psychiatry*, *149*(1), 68-74. doi:10.1192/bjp.149.1.68

Gillis, L. A., McCallum, J., Kaur, M., DeScipio, C., Yaeger, D., Mariani, A.,…Krantz, I. D. (2004). NIPBL mutational analysis in 120 individuals with Cornelia de Lange syndrome and evaluation of genotype-phenotype correlations. *The American Journal of Human Genetics*, 75(4), 610-623. doi:10.1086/424698

Gimigliano, A., Mannini, L., Bianchi, L., Puglia, M., Deardorff, M., Menga, S.,…Bini, L. (2012). Proteomic profile identifies dysregulated pathways in Cornelia de Lange syndrome cells with distinct mutations in SMC1A and SMC3 genes. *Journal of Proteome Research*, *11*(12), 6111-6123. doi:10.1021/pr300760p

Goodart, S. A., Simmons, A. D., Grady, D., Rojas, K., Moyzis, R. K., Lovett, M., & Overhauser, J. (1994). A yeast artificial chromosome contig of the critical region for cri-du-chat syndrome. *Genomics*, *24*(1), 63–68. doi:10.1006/geno.1994.1582

Goodban, M. T. (1993). Survey of speech and language skills with prognostic indicators in 116 patients with Cornelia de Lange syndrome. *American Journal of Medical Genetics Part A, 47*(7), 1059-1063. Doi:10.1002/ajmg.1320470725

Gotham K., Pickles, A., & Lord, C. (2008). Standardizing ADOS scores for a measure of severity in autism spectrum disorders. *Journal of Autism and Developmental Disorders*, *39*(5), 693-705. doi:10.1007/s10803-008-0674-3

Gotham, K., Pickles, A., & Lord, C. (2012). Trajectories of autism severity in children using standardized ADOS scores. *Pediatrics*, *130*(5), e1278-e1284. doi:10.1542/peds.2011-3668

Grace-Martin, K. (2008). The analysis factor Ebook. Retrieved from http://www.analysisfactor.com

Grados, M. A., Alvi, M. H., & Srivastava, S. (2017). Behavioral and psychiatric manifestations in Cornelia de Lange syndrome. *Current Opinion in Psychiatry*, *30*(2), 92-96. doi:10.1097/yco.0000000000000311

Griffith, G. M., Hastings, R. P., Oliver, C., Howlin, P., Moss, J., Petty, J. & Tunnicliffe, P. (2011). Psychological well-being in parents of children with Angelman, Cornelia de Lange and Cri du Chat syndromes. *Journal of Intellectual Disability Research*, *55*(4), 397-410. doi:10.1111/j.1365-2788.2011.01386.x

Hagerman, R. J. (2002). The physical and behavioral phenotype. In R. J. Hagerman, A. Cronister (Eds.), Fragile X syndrome diagnosis, treatment, and research (pp. 3-109). Baltimore, MD: The Johns Hopkins University Press.

Hall, S., Burns, D. D., Lightbody, A. A., & Reiss, A.L. (2008). Longitudinal changes in intellectual development in children with fragile X syndrome. *Journal of Abnormal Child Psychology*, *36*(6), 927-939. doi:10.1007/s10802-008-9223-y

Hall, S., DeBernardis, M., & Reiss, A. (2006). Social escape behaviors in children with fragile X syndrome. Journal of Autism and Developmental Disorders, 36(7), 935-947. doi:10.1007/s10803-006-0132-z

Hall, S., Lightbody, A. A., Hirt, M., Rezvani, A., & Reiss, A. L. (2010). Autism in fragile X syndrome: A category mistake?. *Journal of the American Academy of Child & Adolescent Psychiatry*, *49*(9), 921-933. doi:10.1016/j.jaac.2010.07.001

Harris, J. C. (2002). Behavioral phenotypes of neurodevelopmental disorders: Portals into the developing brain. *Neuropsychopharmacology*: *The Fifth Generation of Progress*, *46*, 625-638.

Hartshorne, T. S., Grialou, T. L., & Parker, K. R. (2005). Autistic-like behavior in CHARGE syndrome. *American Journal of Medical Genetics Part A*, *133*(3), 257-261. doi:10.1186/1750-1172-1-34

Hatton, D. D., Sideris, J., Skinner, M., Mankowski, J., Bailey, D. B. Jr, Roberts, J., & Mirrett, P. (2006). Autistic behavior in children with fragile X syndrome: Prevalence, stability, and the impact of FMRP. *American Journal of Medical Genetics*, *140A*(17), 1804-1813. doi:10.1002/ajmg.a.31286

Hernandez, R. N., Feinberg, R. L., Vaurio, R., Passanante, N. M., Thompson, R. E., & Kaufmann, W. E. (2009). Autism spectrum disorder in fragile X syndrome: A

longitudinal evaluation. *American Journal of Medical Genetics, 149A*(6), 1125-1137. doi:10.1002/ajmg.a.32848

Hodapp, R. M., & Dykens, E. M. (2001). Strengthening behavioral research on genetic mental retardation syndromes. *American Journal on Mental Retardation, 106*(1), 4-15.

Holmes, N., Shah, A., & Wing, L. (1982). The disability assessment schedule: A brief screening device for use with the mentally retarded. *Psychological Medicine, 12*(4), 879-890. doi:10.1017/s0033291700049175

Howlin, P., & Karpf, J. (2004). Using the social communication questionnaire to identify 'autistic spectrum' disorders associated with other genetic conditions - findings from a study of individuals with Cohen syndrome. *Autism, 8*(2), 175–182. doi:10.1177/1362361304042721

Howlin, P., Karpf, J., & Turk, J. (2005). Behavioural characteristics and autistic features in individuals with Cohen syndrome. *European Child & Adolescent Psychiatry, 14*(2), 57-64. doi:10.1007/s00787-005-0416-4

Howlin, P., Wing, L., & Gould, J. (1995). The recognition of autism in children with Down syndrome: Implications for intervention and some speculations about pathology. *Developmental Medicine & Child Neurology, 37*(5), 406-414. doi:10.1111/j.1469-8749.1995.tb12024.x

Howlin, P. (2002). Autism related disorders. In G. O'Brien (Ed.), *Behavioural phenotypes in clinical practice* (2 ed., pp. 31-43). Cambridge, England: Cambridge University Press.

Huerta, M., & Lord, C. (2012). Diagnostic evaluation of autism spectrum disorders. *Pediatric Clinics of North America*, *59*(1), 103-111. doi:10.1016/j.pcl.2011.10.018

Huisman, S. A., Redeker, E. J. W., Maas, S. M., Mannens, M. M., & Hennekam, R. C. M. (2013). High rate of mosaicism in individuals with Cornelia de Lange syndrome. *Journal of Medical Genetics*, *50*(5), 339-344.

Hus, V., Gotham, K., & Lord, C. (2014). Standardizing ADOS domain scores: Separating severity of social affect and repetitive behaviors. *Journal of Autism and Developmental Disorders*, *44*(10), 2400-2412. doi:10.1007/s10803-012-1719-1

Hus, V., & Lord, C. (2014). The autism diagnostic observation schedule, module 4: Revised algorithm and standardized severity scores. *Journal of Autism and Developmental Disorders*, *44*(8), 1996-2012. doi:10.1007/s10803-014-2080-3

Hustyi, K. M., Hall, S., Jo, B., Lightbody, A., Reiss, A. L. (2014). Longitudinal trajectories of aberrant behaviour in fragile X syndrome. *Research in Developmental Disabilities*, *35*(11), 2691-2701. doi:10.1016/j.ridd.2014.07.003

Ingersoll, B. (2010). Brief report: Pilot randomized controlled trial of reciprocal imitation training for teaching elicited and spontaneous imitation to children with autism. *Journal of Autism and Developmental Disorders*, *40*(9), 1154-1160. doi:10.1007/s10803-010-0966-2

Ingersoll, B., & Gergans, S. (2007). The effect of a parent-implemented imitation intervention on spontaneous imitation skills in young children with autism. *Research in Developmental Disabilities*, *28*(2), 163-175. doi:10.1016/j.ridd.2006.02.004

Johansson, M., Råstam, M., Billstedt, E., Danielsson, S., Strömland, K., Miller, M., & Gillberg, C. (2006). Autism spectrum disorders and underlying brain pathology in CHARGE association. *Developmental medicine and child neurology*, *48*(1), 40-50. doi:10.1017/S0012162206000090

Jolleff, N., & Ryan, M. M. (1993). Communication development in Angelman's syndrome. *Archives of Disease in Childhood*, *69*(1), 148-150. doi:10.1136/adc.69.1.148

Kates, W. R., Antshel, K. M., Fremont, W. P., Shprintzen, R. J., Strunge, L. A., Burnette, C. P., & Higgins, A. M. (2007). Comparing phenotypes in patients with idiopathic autism to patients with velocardiofacial syndrome (22q11 DS) with and without autism. *American Journal of Medical Genetics Part A*, *143*(22), 2642-2650. doi:10.1002/ajmg.a.32012

Kaufmann, W. E., Cortell, R., Kau, A. S., Bukelis, I., Tierney, E., Gray, R. M., ... & Stanard, P. (2004). Autism spectrum disorder in fragile X syndrome: communication, social interaction, and specific behaviors. *American Journal of Medical Genetics Part A, 129*(3), 225-234. doi:10.1002/ajmg.a.30229

Kivitie-Kallio, S., Larsen, A., Kajasto, K., & Norio, R. (1999). Neurological and psychological findings in patients with Cohen syndrome: a study of 18 patients aged 11 months to 57 years. *Neuropediatrics, 30*(04), 181-189. doi:10.1055/s-2007-973488

Kline, A. D., Grados, M., Sponseller, P., Levy, H. P., Blagowidow, N., Schoedel, C.,...Tuchman, D. (2007). Natural history of aging in Cornelia de Lange syndrome. *American Journal of Medical Genetics, 145C*(3), 248-260. doi:10.1002/ajmg.c.30137

Krantz, I. D., McCallum, J., DeScipio, C., Kaur, M., Gillis, L. A., Yaeger, D.,…Jackson, L. G. (2004). Cornelia de Lange syndrome is caused by mutations in NIBPL, the human homolog of Drosophila melanogaster Nipped–B. *Nature Genetics, 36*, 631–635. doi:10.1038/ng1364

Kuusikko, S., Pollock-Wurman, R., Jussila, K., Carter, A. S., Mattila, M., Ebeling, H.,...Moilanen, I. (2008). Social anxiety in high-functioning children and

adolescents with autism and Asperger syndrome. *Journal of Autism and Developmental Disorders, 38*(9), 1697-1709. doi:10.1007/s10803-008-0555-9

Lai, M., Lombardo, M. V., Ruigrok, A., Chakrabarti, B., Auyeung, B., Szatmari, P., Happé, F. & Baron-Cohen, S. (2017). Quantifying and exploring camouflaging in men and women with autism. *Autism, 21*(6), 690-702. doi:10.1177/1362361316671012

La Malfa, G., Lassi, S., Bertelli, M., Salvini, R., & Placidi, G. F. (2004). Autism and intellectual disability: a study of prevalence on a sample of the Italian population. *Journal of Intellectual Disability Research, 48*(3), 262-267. doi:10.1111/j.1365-2788.2003.00567.x

Lehto, J. E., Juujärvi, P., Kooistra, L., & Pulkkinen, L. (2003). Dimensions of executive functioning: Evidence from children. *British Journal of Developmental Psychology, 21*(1), 59-80. doi:10.1348/026151003321164627

Lejeune, J., Lafourcade, J., Berger, R., Vialatte, J., Boeswillwald, M., Seringe, P., Turpin, R. (1963). Trois cas de deletion partille du bras courtd'un chromosome 5. *Comptes rendus de l'Academie des Sciences Paris, 257*, 3098-3102.

Lesniak-Karpiak, K., Mazzocco, M. M. M., & Ross, J. L. (2003). Behavioral assessment of social anxiety in females with Turner or fragile X syndrome. *Journal of Autism and Developmental Disorders, 33*(1), 55-67. doi:10.1023/A:1022230504787

Lewis, K. M., Byrd, D. A., & Ollendick, T. H. (2012). Anxiety symptoms in African-American and Caucasian youth: Relations to negative life events, social support, and coping. *Journal of Anxiety Disorders*, *26*(1), 32-39. doi:10.1016/j.janxdis.2011.08.007

Lopez, B. R., Lincoln, A. J., Ozonoff, S., & Lai, Z. Examining the relationship between executive functions and restricted, repetitive symptoms of autistic disorder. *Journal of Autism and Developmental Disorders*, *35*(4), 445-60. doi:10.1007/s10803-005-5035-x

Lord, C., Rutter, M., DiLavore, P. C. & Risi, S. (2000). *The autism diagnostic observation schedule (ADOS).* Los Angeles, CA: Western Psychological Services.

Lui, M., & Tannock, R. (2007). Working memory and inattentive behaviour in a community sample of children. *Behavioral Brain Functions*, 3(12). doi:10.1186/1744-9081-3-12

Luzzani, S., Macchini, F., Valadè, A., Milani, D., & Selicorni, A. (2003). Gastroesophageal reflux and Cornelia de Lange syndrome: Typical and atypical symptoms. *American Journal of Medical Genetics*, *119A*(3), 283-287. doi:10.1002/ajmg.a.20191

Maddalena, A., Richards, C. S., McGinniss, M. J., Brothman, A., Desnick, R. J., Grier, R.,...Wolff, D. J. (2001). Technical standards and guidelines for fragile X: the first of a series of disease-specific supplements to the Standards and Guidelines for Clinical Genetics Laboratories of the American College of Medical Genetics. Quality Assurance Subcommittee of Laboratory Practice Committee. *Genetics in Medicine, 3,* 200-205. doi:10.1097/00125817-200105000-00010

Magiati, I., Wei Tay, X., & Howlin, P. (2014). Cognitive, language, social and behavioural outcomes in adults with autism spectrum disorders: A systematic review of longitudinal follow-up studies in adulthood. *Clinical Psychology Review*, 34(1), 73-86. doi:10.1016/j.cpr.2013.11.002

Malenka, R., Nestler, E., & Hyman, S. (2009). Higher Cognitive Function and Behavioral Control. In A. Sydor, R. Y. Brown (Eds.). *Molecular neuropharmacology: A foundation for clinical neuroscience* (2nd ed., pp. 315). New York: McGraw-Hill Medical.

McCary, L. M., & Roberts, J. E. (2013). Early identification of autism in fragile X syndrome: a review. *Journal of Intellectual Disability Research*, *57*(9), 803-814. doi:10.1111/j.1365-2788.2012.01609.x

Milner, K. M., Craig, E. E., Thompson, R. J., Veltman, M. W., Simon Thomas, N., Roberts, S., ... & Bolton, P. F. (2005). Prader-Willi syndrome: intellectual abilities

and behavioural features by genetic subtype. *Journal of Child Psychology and Psychiatry, 46*(10), 1089-1096. doi:10.1111/j.1469-7610.2005.01520.x

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: A latent variable analysis. *Cognitive Psychology, 41*(1), 49-100. doi:10.1006/cogp.1999.0734

Moss, J., & Howlin, P. (2009). Autism spectrum disorders in genetic syndromes: implications for diagnosis, intervention and understanding the wider autism spectrum disorder population. *Journal of Intellectual Disability Research, 53*(10), 852-873. doi:10.1111/j.1365-2788.2009.01197.x

Moss, J., Howlin, P., Hastings, R. P., Beaumont, S., Griffith, G. M., Petty, J.,...Oliver, C. (2013). Social behavior and characteristics of autism spectrum disorder in Angelman, Cornelia de Lange, and cri du chat syndromes. *American Journal on Intellectual and Developmental Disabilities, 118*(4), 262-283. doi:10.1352/1944-7558-118.4.262

Moss, J., Howlin, P., Magiati, I., & Oliver, C. (2012). Characteristics of autism spectrum disorder in Cornelia de Lange syndrome. *Journal of Child Psychology and Psychiatry, 53*(8), 883-891. doi:10.1111/j.1469-7610.2012.02540.x

Moss, J., Howlin, P., & Oliver, C. (2011). The assessment and presentation of autism

spectrum disorder and associated characteristics in individuals with severe intellectual disability and genetic syndromes. In J. Burack, R. Hodapp, G. Larocci, & E. Zigler (Eds.), *The oxford handbook of intellectual disability and development.* Oxford, England: Oxford University Press.

Moss, J., Oliver, C., Berg, K., Kaur, G., Jephcott, L., & Cornish, K. (2008). Prevalence of autistic spectrum phenomenology in Cornelia de Lange and cri du chat syndromes. *American Journal on Mental Retardation*, *113*(4), 278-291.

Moss, J., & Oliver, C. (2008). *The repetitive behaviour questionnaire - Manual for administration and score interpretation*. University of Birmingham.

Moss, J., Oliver, C., Arron, K., Burbidge, C., & Berg, K. (2009). The prevalence and phenomenology of repetitive behaviour in genetic syndromes. *Journal of Autism and Developmental Disorders*, *39*(4), 572-588. doi:10.1007/s10803-008-0655-6

Moss, J., Oliver, C., Nelson, L., Richards, C. & Hall, S. (2013). Delineating the profile of autism spectrum disorder characteristics in Cornelia de Lange and fragile X syndromes. *American Journal on Intellectual and Developmental Disabilities, 118*(1), 55-73. doi:10.1352/1944-7558-118.1.55

Mulder, P. A., Huisman, S. A., Hennekam, R. C., Oliver, C., Balkom, I. D., & Piening, S. (2016). Behaviour in Cornelia de Lange syndrome: a systematic review.

Developmental Medicine & Child Neurology, *59*(4), 361-366. Doi:10.1111/dmcn.13361

Murphy, A. M., Flanagan, O., Dunne, K., & Lynch, S. A. (2007). High prevalence of Cohen syndrome among Irish travellers. *Clinical dysmorphology*, *16*(4), 257-259. doi:10.1097/MCD.0b013e3282742530

Musio, A., Selicorni, A., Focarelli, M. L., Gervasini, C., Milani, D., Russo, S.,...Larizza, L. (2006). X-linked Cornelia de Lange syndrome owing to SMC1L1 mutations. *Nature Genetics*, *38*, 528–530. doi:10.1038/ng1779

Nelson, L., Moss, J., & Oliver, C. (2014). A longitudinal follow-up study of affect in children and adults with Cornelia de Lange syndrome. *American Journal of Intellectual and Developmental Disabilities*, *119*(3), 235-252. doi:10.1352/1944-7558-119.3.235

Niklasson, L., Rasmussen, P., Óskarsdóttir, S., & Gillberg, C. (2009). Autism, ADHD, mental retardation and behavior problems in 100 individuals with 22q11 deletion syndrome. *Research in developmental disabilities*, *30*(4), 763-773. doi:10.1016/j.ridd.2008.10.007

Nyhan, W. L. (1972). Behavioral phenotypes in organic genetic disease: Presidential address to the Society for Pediatric Research. *Pediatric Research*, *6*, 1-9. doi:10.1203/00006450-197201000-00001

O'Brien, G., & Yule, W. (Eds.). (1995). *Behavioural phenotypes - Clinics in developmental medicine* (Vol. 138). Cambridge, England: Cambridge University Press.

O'Brien, G. (Ed.). (2000). Behavioural phenotypes. *Journal of the royal society of Medicine*, *93*, 618-620.

O'Brien, G. (2006). Behavioural phenotypes: causes and clinical implications. *Advances in Psychiatric Treatment, 12*, 338-348.

O'Callaghan, F. J. (1999). Tuberous sclerosis: Epidemiological research is needed to complement new findings in genetics. *BMJ: British Medical Journal*, *318*(7190), 1019. doi:10.1136/bmj.318.7190.1019

O'Hearn, K., Asato, M., Ordaz, S., & Luna, B. (2008). Neurodevelopment and executive function in autism. *Development and Psychopathology*, *20*(4), 1103-1132. doi:10.1017/s0954579408000527

Oliver, C., Arron, K., Sloneem, J., & Hall, S. (2008). Behavioural phenotype of Cornelia de Lange syndrome: Case–control study. *British Journal of Psychiatry, 193*(6), 466-470. doi:10.1192/bjp.bp.107.044370

Oliver, C., Berg, K., Moss, J., Arron, K., & Burbidge, C. (2011). Delineation of behavioral phenotypes in genetic syndromes: Characteristics of autism spectrum disorder, affect and hyperactivity. *Journal of Autism and Developmental Disorders*, *41*(8), 1019-1032. doi:10.1007/s10803-010-1125-5

Oosterling, I., Rommelse, N., de Jonge, M., Jan van der Gaag, R., Swinkels, S., Roos, S.,...Buitelaar, J. (2010). How useful is the social communication questionnaire in toddlers at risk of autism spectrum disorder? *Journal of Child Psychology and Psychiatry*, *51*(11), 1260-1268. doi:10.1111/j.1469-7610.2010.02246.x

Oskarsdottir, S., Vujic, M., & Fasth, A. (2004). Incidence and prevalence of the 22q11 deletion syndrome: a population-based study in Western Sweden. *Archives of disease in childhood*, *89*(2), 148-151.

Parisi, L., Di Filippo, T., & Roccella, M. (2015). Behavioral phenotype and autism spectrum disorders in Cornelia de Lange Syndrome. *Mental Illness*, *7*(2), 5988. doi:10.4081/mi.2015.5988

Perry, A., Condillac, R. A., Freeman, N. L., Dunn-Geier, J., & Belair, J. (2005). Multi-site study of the childhood autism rating scale (CARS) in five clinical groups of young children. *Journal of Autism and Developmental Disorders*, *35*(5), 625-634. doi:10.1007/s10803-005-0006-9

Peters, S. U., Beaudet, A. L., Madduri, N., & Bacino, C. A. (2004). Autism in Angelman syndrome: implications for autism research. *Clinical genetics*, *66*(6), 530-536. doi: 10.1111/j.1399-0004.2004.00362.x

Reid, D., Moss, J., Nelson, L., Groves, L., & Oliver, C. (2017). Executive functioning in Cornelia de Lange syndrome: domain asynchrony and age-related performance. *Journal of Neurodevelopmental Disorders, 9*(29). doi:10.1186/s11689-017-9208-7

Riby, D. M., Hanley, M., Kirk, H., Clark, F., Little, K., Fleck, R.,...Rodgers, J. (2014). The interplay between anxiety and social functioning in Williams syndrome. *Journal of Autism and Developmental Disorders*, *44*(5), 1220-1229. doi:10.1007/s10803-013-1984-7

Richards, C., Moss, J., O'Farrell, L., Kaur, G., & Oliver, C. (2009). Social anxiety in Cornelia de Lange syndrome. *Journal of Autism Developmental Disorders*, *39*(8), 1155-1162. doi:10.1007/s10803-009-0730-7

Richards, C., Jones, C., Groves, L., Moss, J., & Oliver, C. (2015). Prevalence of autism spectrum disorder phenomenology in genetic disorders: a systematic review and meta-analysis. *The Lancet Psychiatry*, 2(10), 909-916. doi:10.1016/S2215-0366(15)00376-4

Richards, C., Oliver, C., Nelson, L., & Moss, J. (2012). Self-injurious behaviour in individuals with autism spectrum disorder and intellectual disability. *Journal of*

Intellectual Disability Research, 56(5), 476-489. doi:10.1111/j.1365-2788.2012.01537.x

Roberts, J. E., Weisenfeld, L. A. H., Hatton, D. D., Heath, M., & Kaufmann W. E. (2007). Social approach and autistic behavior in children with fragile X syndrome. *Journal of Autism and Developmental Disorders*, *37*(9), 1748-1760. doi:10.1007/s10803-006-0305-9

Rogers, S. J., Wehner, E. A., & Hagerman, R. (2001). The behavioral phenotype in fragile X: symptoms of autism in very young children with fragile X syndrome, idiopathic autism, and other developmental disorders. *Journal of Developmental & Behavioral Pediatrics*, *22*(6), 409-417.

Rojahn, J., Barnard-Brak, L., Richman, D., Dotson, W., Medeiros, K., Wei, T., & Abby, L. (2013). Behavior problems in individuals with Cornelia de Lange syndrome: population-specific validation of the behavior problem inventory-01. *Journal of Developmental and Physical Disabilities*, *25*(5), 505-515. doi:10.1007/s10882-012-9329-6

Roshan Lal, T. R., Kliewer, M. A., Lopes, T., Rebsamen, S. L., O'Connor, J., Grados, M. A.,...Kline, A. D. (2016). Cornelia de Lange syndrome: correlation of brain MRI findings with behavioral assessment. *American Journal of Medical Genetic*, 172C(2), 190-197. doi:10.1002/ajmg.c.31503

Rutter, M., Bailey, A., Lord. C., & Berument, S.K. (2003). *The social communication questionnaire.* Los Angeles, CA: Western Psychological Services.

Rutter, M., DiLavore, P. C., Risi, S., Gotham, K., & Bishop, S. (2012). *Autism diagnostic observation schedule: ADOS-2*. Los Angeles, CA: Western Psychological Services.

Rutter, M., Le Couteur, A., & Lord, C. (2003). *The autism diagnostic interview- revised* (ADI-R). Torrance, CA: Western Psychological Services.

Sabaratnam, M., Murthy, N. V., Wijeratne, A., Buckingham, A., & Payne, S. (2003). Autistic-like behaviour profile and psychiatric morbidity in fragile X syndrome: A prospective ten-year follow-up study. *European Child & Adolescent Psychiatry, 12*(4), 172-177. doi:10.1007/s00787-003-0333-3

Sahoo, T., Peters, S. U., Madduri, N. S., Glaze, D. G., German, J. R., Bird, L. M., ... & Bacino, C. A. (2006). Microarray based comparative genomic hybridization testing in deletion bearing patients with Angelman syndrome: genotype-phenotype correlations. *Journal of Medical Genetics, 43*(6), 512-516. doi:10.1136/jmg.2005.036913

Sarimski, K. (1997). Communication, social-emotional development and parenting stress in cornelia-de-lange syndrome. *Journal of Intellectual Disability Research*, *41*(1), 70-75. doi:10.1111/j.1365-2788.1997.tb00678.x

Sarimski, K. (2003). Early play behaviour in children with 5p- (Cri-du-Chat) syndrome. *Journal of Intellectual Disability Research, 47*(2), 113-120. doi:10.1046/j.1365-2788.2003.00448.x

Sarimski, K. (2007). Infant attentional behaviours as prognostic indicators in Cornelia-de-Lange syndrome. *Journal of Intellectual Disability Research, 51*(9), 697-701. doi:10.1111/j.1365-2788.2007.00975.x

Schopler, E., Reichier, R., & Renner, B. R. (1988). *The childhood autism rating scale (CARS)*. Los Angeles, CA: Western Psychological.

Sherman, S. (2002). In: R. J. Hagerman, P. J. Hagerman (Eds.). *Fragile X syndrome: diagnosis, treatment, and research* (3rd ed., pp. 136-139). Baltimore, MD: Johns Hopkins University Press.

Skuse, D. H. (2010). Behavioural phenotypes: what do they teach us? *Archives of Disease in Childhood, 82*(3), 222-225. doi:10.1136/adc.82.3.222

Skuse D. H. (2007). Rethinking the nature of genetic vulnerability to autistic spectrum disorders. *Trends in Genetics, 23*(8), 387-395. doi:10.1016/j.tig.2007.06.003

Skuse, D., Warrington, R., Bishop, D., Chowdhury, U., Lau, J., Mandy, W., & Place, M. (2004). The developmental, dimensional and diagnostic interview (3di): A novel

computerized assessment for autism spectrum disorders. *Journal of the American Academy of Child & Adolescent Psychiatry, 43*(5), 548-558. doi:10.1097/00004583-200405000-00008

Smalley, S. L. (1998). Autism and tuberous sclerosis. *Journal of autism and developmental disorders, 28*(5), 407-414.

Smith, I. M., Nichols, S. L., Issekutz, K., & Blake, K. (2005). Behavioral profiles and symptoms of autism in CHARGE syndrome: preliminary Canadian epidemiological data. *American Journal of Medical Genetics Part A, 133*(3), 248-256. doi:10.1002/ajmg.a.30544

Sparrow, S., Balla, D., & Cicchetti, D. (1984). *Vineland adaptive behavior scales* (VABS). Circle Pines, MN: American Guidance Service.

Srivastava, S., Landy-Schmitt, C., Clark, B., Kline, A. D., Specht, M., & Grados, M. A. (2014). Autism traits in children and adolescents with Cornelia de Lange syndrome. *American Journal of Medical Genetics, 164A*(6), 1400-1410. doi:10.1002/ajmg.a.36573

Starr, E. M., Berument, S. K., Tomlins, M., Papanikolaou, K., & Rutter, M. (2005). Brief report: autism in individuals with Down syndrome. *Journal of autism and developmental disorders, 35*(5), 665-673. doi:10.1007/s10803-005-0010-0

Stöger, R., Genereux, D. P., Hagerman, R. J., Hagerman, P. J., Tassone, F., & Laird, C. D. (2011). Testing the FMR1 promoter for mosaicism in DNA methylation among CpG sites, strands, and cells in FMR1-expressing males with fragile X syndrome. *PLoS ONE*, *6*(8), e23648. doi:10.1371/journal.pone.0023648

Summers, J. A., Allison, D. B., Lynch, P. S., & Sandier, L. (1995). Behaviour problems in Angelman syndrome. *Journal of Intellectual Disability Research*, *39*(2), 97-106. doi: 10.1111/j.1365-2788.1995.tb00477.x

Thomson, A. K., Glasson, E. J., & Bittles, A. H. (2006). A long-term population-based clinical and morbidity profile of Angelman syndrome in Western Australia: 1953–2003. *Disability and rehabilitation*, *28*(5), 299-305. doi:10.1080/09638280500190631

Tonkin, E. T., Wang, T., Lisgo, S., Bamshad, M. J., & Strachan, T. (2004). NIPBL, encoding a homolog of fungal Scc2-type sister chromatid cohesion proteins and fly Nipped-B, is mutated in Cornelia de Lange syndrome. *Nature Genetics*, *36*, 636-641. doi:10.1038/ng1363

Topper, S., Ober, C., & Das, S. (2011). Exome sequencing and the genetics of intellectual disability. *Clinical Genetics*, *80*(2), 117-126. doi:10.1111/j.1399-0004.2011.01720.x

Trillingsgaard, A., & Østergaard, J. R. (2004). Autism in Angelman syndrome: an exploration of comorbidity. *Autism, 8*(2), 163-174. doi: 10.1177/1362361304042720

Turk, J., & Graham, P. (1997). Fragile X syndrome, autism and autistic features. *Autism, 1*(2), 175-197. doi:10.1177/1362361397012005

Turner, G., Webb, T., Wake, S., & Robinson, H. (1996). Prevalence of fragile X syndrome. *American Journal of Medical Genetics, 64*(1), 196-197. doi:10.1002/(SICI)1096-8628(19960712)64:1<196::AID-AJMG35>3.0.CO;2-G

Van Buggenhout, G. J. C. M., Pijkels, E., Holvoet, M., Schaap, C., Hamel, B. C. J., & Fryns, J. P. (2000). Cri du chat syndrome: Changing phenotype in older patients. *American Journal of Medical Genetics, 90*(3)**,** 203-215. doi:10.1002/(SICI)1096-8628(20000131)90:3<203::AID-AJMG5>3.0.CO;2-A

Veltman, M. W., Thompson, R. J., Roberts, S. E., Thomas, N. S., Whittington, J., & Bolton, P. F. (2004). Prader-Willi syndrome. *European child & adolescent psychiatry, 13*(1), 42-50. doi:10.1007/s00787-004

Verkerk, A. J. M. H., Pieretti, M., Sutcliffe, J. S., Fu, Y., Kuhl, D. P. A., Pizzuti, A.,...Warren, S. T. (1991). Identification of a gene (FMR-1) containing a CGG repeat coincident with a breakpoint cluster region exhibiting length variation in fragile X syndrome. *Cell, 65*(5), 905-914. doi:10.1016/0092-8674(91)90397-H

Vorstman, J. A., Morcus, M. E., Duijff, S. N., Klaassen, P. W., Beemer, F. A., Swaab, H., ... & van Engeland. (2006). The 22q11. 2 deletion in children: high rate of autistic disorders and early onset of psychotic symptoms. *Journal of the American Academy of Child & Adolescent Psychiatry*, *45*(9), 1104-1113. doi:10.1097/01.chi.0000228131.56956.c1

Vuilleumier, N., Kövari, E., Michon, A., Hof, P. R., Mentenopoulos, G., Giannakopoulos, P., & Bouras, C. (2002). Neuropathological analysis of an adult case of the Cornelia de Lange syndrome. *Acta Neuropathologica*, *104*(3), 327-332. doi:10.1007/s00401-002-0562-4

Walsh, K. S., Velez, J. I., Kardel, P. G., Imas, D. M., Muenke, M., Packer, R. J., ... & Acosta, M. T. (2013). Symptomatology of autism spectrum disorder in a population with neurofibromatosis type 1. *Developmental Medicine & Child Neurology*, *55*(2), 131-138. doi:10.1111/dmcn.12038

Webb, D. W., Carke, A., Fyer, A., & Osborne, J. P. (1996). The cutaneous features of tuberous sclerosis: a population study. *British Journal of Dermatology*, *135*(1), 1-5. doi: 10.1046/j.1365-2133.1996.d01-923.x

Wechsler, D. (1999). *Manual for the Wechsler abbreviated intelligence scale (WASI).* San Antonio, TX: The Psychological Corporation.

Wechsler, D. (2002). *WPPSI-III administration and scoring manual.* San Antonio, TX: The Psychological Corporation.

Wenzel, A. (2009). Social Anxiety. In H. Reis, & S. Spreacher, *Encyclopedia of human relationships* (pp. 1514-1516). Thousand Oaks, CA: SAGE Publications.

Whittington, J. E., Holland, A. J., Webb, T., Butler, J., Clarke, D., & Boer, H. (2001). Population prevalence and estimated birth incidence and mortality rate for people with Prader-Willi syndrome in one UK Health Region. *Journal of medical genetics*, *38*(11), 792-798. doi:10.1136/jmg.38.11.792

Wilding, J., Cornish, K., & Munir, F. (2002). Further delineation of the executive deficit in males with fragile-X syndrome. *Neuropsychologia*, *40*(8), 1343-1349. doi:10.1016/S0028-3932(01)00212-3

Wing, L. (1980). The MRC handicaps, behaviour & skills (HBS) schedule. *Acta Psychiatrica Scandinavica*, *62*(S285), 241-248. doi:10.1111/j.1600-0447.1980.tb07696.x

Wing, L., Leekam, S. R., Libby, S. J., Gould, J., & Larcombe, M. (2002). The diagnostic interview for social and communication disorders: background, inter-rater reliability and clinical use. *The Journal of Child Psychology and Psychiatry*, *43*(3), 307-325. doi:10.1111/1469-7610.00023

Woodcock, K., Oliver, C., & Humphreys, G. W. (2009). A specific pathway can be identified between genetic characteristics and behaviour profiles in Prader-Willi syndrome via cognitive, environmental and physiological mechanisms. *Journal of Intellectual Disability Research, 53*(6), 493-500. doi:10.1111/j.1365-2788.2009.01167.x

Woods, J. J., & Wetherby, A. M. (2003). Early identification of and intervention for infants and toddlers who are at risk for autism spectrum disorder. *Language, Speech, and Hearing Services in Schools, 34*(3), 180-193. doi:10.1044/0161-1461(2003/015)

World Health Organisation. (1992) *The ICD-10 classification of mental and behavioral disorders: clinical descriptions and diagnostic guidelines*. Geneva, Switzerland: World Health Organisation.

Zafeiriou, D. I., Ververi, A., Dafoulis, V., Kalyva, E., Vargiami, E. (2013). Autism spectrum disorders: The quest for genetic syndromes. *American Journal of Medical Genetics, 162B*(4), 327-366. doi:10.1002/ajmg.b.32152

Zhao, X., Park, C., Smrt, R. D., & Jin, P. (2007). Epigenetics and neural developmental disorders. *Epigenetics, 2*(2), 126-134. doi:10.4161/epi.2.2.4236

Zuddas, A. (2013). Autism assessment tools in the transition from DSM-IV to DSM-5. *European Child & Adolescent Psychiatry*, *22*(6), 325-327. doi: 10.1007/s00787-013-0424-8