MOOD AND SOCIABILITY IN CORNELIA DE LANGE SYNDROME

By

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ABSTRACT

Background: Recent literature on the behavioural phenotype of Cornelia de Lange syndrome suggests that the trajectory of a number of behaviours may be atypical in the syndrome, including mood and sociability however there is a lack of quantitative research to support these findings.

Methods: Three empirical studies were conducted. The first study employed a questionnaire design to follow up mood, interest and pleasure over a two-year period in individuals with Cornelia de Lange syndrome. The second study involved the development of an informant-based questionnaire to examine the age-related pattern of sociability in Cornelia de Lange syndrome. The third study employed an experimental design to examine indicators of social anxiety in adolescents and adults with Cornelia de Lange syndrome.

Results: Low mood and reduced initiation of social interactions with unfamiliar people is characteristic of older adolescents and adults with Cornelia de Lange syndrome. Reduced verbalisation is also evident in this group when demands involving the initiation of speech are placed upon these individuals and this is related to impairments in both planning and working memory. A high rate of selective mutism is also characteristic of Cornelia de Lange syndrome.

Conclusion: The age-related pattern of both mood and sociability appears atypical in Cornelia de Lange syndrome. Cognitive impairments may underpin these behavioural differences in adolescents and adults with the syndrome. A hypothetical model of the pathway from genes to behaviour via cognition is proposed for older adolescents and adults with the syndrome.

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CONTRIBUTION TO THE THESIS

Each person that contributed to the studies in this thesis has worked for what is now the Cerebra Centre for Neurodevelopmental Disorders as Phd students, trainee clinical psychologists or research associates.

The first stage of the MIPQ follow-up study was conducted by my supervisor, Chris Oliver. Chris undertook this study with Jo Moss, Kate Arron, Cheryl Burbidge and Katy Berg. I then took the lead on conducting the follow-up study and obtained ethics for this study with help from my supervisor (Chris Oliver) and Jo Moss. Caroline Richards, Laura O'Farrell and Kate Woodcock helped to input the data for the follow-up study. The SQID data was also collected during the follow-up study. I developed the SQID with help from my supervisor (Chris Oliver) and Jo Moss.

I set up the final experimental study on sociability, developed the social tasks for the study and obtained ethics for this study with help from my supervisor (Chris Oliver) and Jo Moss. Sarah Gorniak arranged the research visits for the CdLS participants during this project. Sarah also came on research visits with me to administer the unfamiliar conditions of the social tasks and the VABS. Kristina Stockdale, Laurie Powis and Jane Appleby came on several research visits for the CdLS participants to administer the unfamiliar conditions of the social tasks and the VABS. Donna Reid conducted all the research visits for the Down syndrome participants and helped me to input the data into SPSS. Leah Bull and I conducted the inter-rater reliability for the social tasks. Leah then coded the rest of the social tasks during this project and inputted this data into SPSS.

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CHAPTER ONE

Literature Review

1.1. PREFACE TO LITERATURE REVIEW: BEHAVIOURAL PHENOTYPES

1.1.1. Introduction to behavioural phenotypes

Nyhan first coined the term "behavioural phenotype" in 1972 after he observed "compulsive" self-mutilation in individuals with Lesch-Nyhan and Cornelia de Lange syndromes. He believed that the behaviour observed was due to the genetic basis of each disorder, indicating an association between genes and behaviour. This observation gave rise to the idea that the phenotypic outcome of a genetic disorder included observable behavioural characteristics in addition to physical characteristics.

1.1.2. Behavioural phenotype defined

The definition of a "behavioural phenotype" has been debated in the field of intellectual disability research. Some have argued for a definition based on the notion of total specificity, whereby a "behavioural phenotype" is considered to

"…consist of a distinctive behaviour that occurs in almost every case of a genetic or chromosomal disorder, and rarely….in other conditions", Flint & Yule (1994), p666.

This definition implies that there is a single and potentially unique pathway from genes to behaviour. However, only a limited number of behaviours in a limited number of syndromes have been identified as showing total specificity. For example, severe biting of the lips and finger tips has been identified as being unique to Lesch-Nyhan syndrome (Anderson & Ernst, 1994; Dykens, Hodapp & Finucane, 2000). As research into behavioural phenotypes has developed, however, behaviours originally considered to show total specificity are now being identified in other genetic syndromes. For example, hyperphagia was originally considered to be unique to Prader-Willi syndrome but recent evidence suggests that it is also evident in individuals with Monosomy 1p36 (Cassidy, 1997; D'Angelo et al., 2006; Dykens et al., 2000; Dykens & Cassidy, 1996).

Most research to date on behavioural phenotypes has shown that it is rare for *all* individuals diagnosed with a specific syndrome to express any one of the syndrome's behavioural characteristics due to within-group variability (Dykens et al., 2000). For example, there is a heightened probability of specific repetitive behaviours in individuals with Fragile X syndrome in comparison to the general intellectual disability population but these behaviours are *not* characteristic of *all* individuals with the syndrome (Moss et al., 2009). A more widely accepted definition of a "behavioural phenotype" is therefore based on the notion of partial specificity (Hodapp, 1997). In line with this notion, Dykens (1995) described a "behavioural phenotype" 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), p523.

This definition accounts for the heightened prevalence of a behaviour in a genetic syndrome in comparison to the intellectual disability population, yet allows for between and within-syndrome variability. Hence, Dykens' (1995) definition accounts for the fact that the majority of behaviours considered characteristic of most genetic syndromes are *not* typically shown by *all* individuals with that syndrome. This within-syndrome variability may be accounted for by variability in a genetic disorder, the presence of other genes and other factors, including the influence of the environment on behaviour. The less restrictive nature of Dykens' (1995) definition also allows for similar behaviours to be shown across genetic syndromes, giving rise to the possibility that there are shared aetiological pathways underpinning behaviour. For example, a recent study by Moss et al. (2009) demonstrated that both individuals with Prader-Willi and Fragile X syndromes were reported to show an increased prevalence of compulsive behaviour and insistence on sameness. Dykens' (1995) definition of a behavioural phenotype will be used when referring to this term in the thesis.

1.1.3. Important areas of research in the study of behavioural phenotypes

The study of behavioural phenotypes originally focused predominantly on the increased probability of a behaviour being shown in a specific genetic syndrome, e.g., the increased probability of self-injurious behaviour in Cornelia de Lange syndrome (e.g., Beck, 1987; Hyman et al., 2002). As research on behavioural phenotypes has developed, different

strategies have been highlighted. These include, identifying pathways from genes to behaviour, identifying gene-environment interactions and understanding age-related changes in genetic syndromes. These areas of research are important when considering both models of the causes of behaviour and clinical issues that may arise in genetic syndromes.

1.1.3.1. Identifying pathways from genes to behaviour

Identifying pathways from genes to behaviour via cognition will help to explain why there is an increased probability of a specific behaviour being shown by individuals with a given genetic syndrome. This will mean that interventions can be developed at the cognitive as well as the behavioural level. Investigations into pathways from genes to behaviour have been conducted in a number of neurodevelopmental disorders. For example, research in Williams syndrome has shown that frontal lobe impairment, particularly, poor response inhibition may underpin indiscriminate approach behaviour characteristically reported in these individuals (Porter, Coltheart and Langdon, 2007). Also, Woodcock et al. (2009a, 2009b, 2009c) demonstrated that individuals with Prader-Willi syndrome show a difficulty with attention switching which can give rise to phenotypic behaviours (temper outbursts and repetitive questioning) when an unexpected change in the environment places a demand on this capacity. These examples show that it is important to understand the pathway from genes to behaviour via cognition because the pathway may be important in informing effective intervention strategies.

1.1.3.2. Gene-environment interactions

Individuals with a given genetic syndrome may have a predisposition for a certain phenotypic outcome but the environment may serve to maintain a given behaviour in a functional way. The importance of the effect of the environment on behaviours considered characteristic of a syndrome has been demonstrated in several genetic syndromes. For example, laughing and smiling is considered to be characteristic of individuals with Angelman syndrome (e.g., Horsler & Oliver, 2006a). The environment has been shown to affect levels of laughing and smiling in Angelman syndrome, with increased laughing and smiling being demonstrated during social interaction (Oliver, Demetriades, and Hall, 2002). Laughing and smiling in individuals with Angelman syndrome has also been shown to influence the environment, with people being more likely to smile after individuals with Angelman syndrome smile (Oliver et al., 2007). These studies show the two-way relationship between the person's behaviour and the environment so that a person's behaviour can effect change on the environment but also the environment can effect change on the person's behaviour.

Environments may also have a more detrimental effect upon behaviour in genetic syndromes. For example, hyperacusis is commonly experienced by individuals with Williams syndrome (Van Borsel, Curfs & Fryns, 1997). O'Reilly, Lacey and Lancioni (2000) demonstrated that background noise was associated with an increase in escape-maintained aggressive behaviour in a five-year old girl with Williams syndrome. This example shows that a genetic predisposition can alter the reinforcing properties of environmental events. It is therefore important to understand how the environment

impacts upon behaviour in genetic syndromes because it may be possible to develop effective intervention strategies based on operant learning theory.

1.1.3.3. Age-related changes in a syndrome

More recent literature on behavioural phenotypes has highlighted the importance of understanding behaviours from a developmental perspective. Some researchers have argued that the study of developmental trajectories in individuals with neurodevelopmental disorders can offer a 'window of opportunity' for understanding typical and atypical development processes (Cornish, Scerif & Karmiloff-Smith, 2007; Thomas et al., 2009).

The most well documented age-related change in a syndrome is the onset of dementia in Down syndrome. Age specific prevalence rates for the clinical presentation of dementia in adults with Down syndrome range from 0-2% of 30-39 year olds, to 33.3-54.5% of 60-69 year olds (Holland et al., 1998). The development of Alzheimer's disease has a significant impact upon cognitive and behavioural characteristics, such as changes in personality and a decline in working memory, executive function and language (e.g. Ball et al., 2006; Oliver et al., 1998). Age-related changes in behaviour have also been reported in other syndromes. For example, the high levels of smiling and laughing behaviour demonstrated in response to social contact in Angelman syndrome may decline with age (Horsler & Oliver, 2006b). Also, the trajectory of social anxiety in individuals with Cornelia de Lange syndrome may change with age, with social anxiety becoming more evident in adolescence and young adulthood (Collis, Oliver & Moss, 2006).

Understanding age-related changes in genetic syndromes will allow for the identification of future risk for experiencing difficulties. Proactive screening and planning may be then implemented. Increasing awareness in carers and professionals of early indicators of difficulties during certain age periods may also help in the early identification and thus intervention. It may be that behaviours considered to be strengths for individuals with a given syndrome, also increase with age. Being aware of and using these strengths may be of value for individuals with a genetic syndrome.

1.1.4. Conclusion

Research on behavioural phenotypes has advanced in recent years to examine not only whether there is a heightened probability of a behaviour associated with a genetic syndrome but also how the trajectory of that behaviour changes with age. Furthermore, there is increased research into understanding the relationship between genotype and phenotype and thus understand whether there are specific pathways from genes to behaviour via cognition. Understanding the pathways from genes to behaviour may be fruitful when considering age-related changes in a given syndrome because it may be that there is a biological cause for such changes in a syndrome. In addition, examining the effect of the environment on behaviour is also important because it may be that such behaviours are operantly reinforced. Considering the effect of the environment at critical time points may be important if behaviour changes with age in a given genetic syndrome.

The issues highlighted above are important to consider in Cornelia de Lange syndrome, which is less well-researched compared to other syndromes, such as Down, Fragile X and

Williams syndromes. Recent evidence suggests that there is a heightened probability of age-related behavioural and emotional changes in Cornelia de Lange syndrome (Basile et al., 2007; Collis et al., 2006; Kline et al., 2007a; Kline et al., 2007b; Oliver, Berg, Moss, Arron & Burbidge, in review). When delineating the behavioural phenotype of Cornelia de Lange syndrome, it will be important to understand the developmental trajectory of these behaviours. Behaviours found to change with age may be caused by biological changes associated with the syndrome but may also be influenced by the environment. Therefore, it will be important to understand whether there are changes at a biological level in Cornelia de Lange syndrome that underpin changes in behaviour with age. Also, it will be important to establish the effect of the environment on such behaviours because adaptations to the environment may provide the basis for effective intervention strategies for these behaviours.

1.2. LITERATURE REVIEW

1.2.1. Cornelia de Lange syndrome

1.2.1.1. Introduction to Cornelia de Lange syndrome

Cornelia de Lange syndrome was first described by Brachmann in 1916 and then by Cornelia de Lange, a Dutch paediatrician, in 1933. Cornelia de Lange syndrome has a prevalence rate of approximately one in 50,000 live births (Beck, 1976; Beck & Fenger, 1985). The genetic cause of the syndrome has been established for approximately 55% of this population. A deletion in the NIPBL gene on chromosome 5 (locus 5p13) is reported to account for between 20-50% of individuals with the syndrome (Gillis et al., 2004; Krantz et al., 2004; Miyake et al., 2005; Tonkin et al., 2004), whilst mutations on the SMC3 gene on chromosome 10 and the X-linked SMC1 gene are reported to account for approximately 5% of this population (Deardorff et al., 2007; Musio et al., 2006). The genetic cause is yet to be determined for the remaining population of individuals with the syndrome so currently diagnosing Cornelia de Lange syndrome relies predominantly on assessing clinical characteristics.

1.2.1.2. The physical phenotype of Cornelia de Lange syndrome

The physical phenotype of Cornelia de Lange syndrome has been well documented; low birth weight, small stature, limb abnormalities and distinctive facial features, such as, synophrys, a long philtrum, thin lips and a crescent shaped mouth, are reported to be

common features (Jackson, Kline, Barr & Koch, 1993). Cornelia de Lange syndrome is also associated with many health problems including: hearing and eye problems, cardiac, genito-urinary and gastro-intestinal disorders (Jackson et al., 1993; Luzzani, Macchini, Valade, Milani & Selicorni, 2003). Degree of intellectual disability ranges from mild to profound, although there are reports of individuals with IQ in the normal range (Ireland, Donnai & Burn, 1993; Jackson et al., 1993; Saal et al., 1993). Most individuals with Cornelia de Lange syndrome show a severe (30.43%) to profound (45.6%) intellectual disability. Poor expressive communication (specifically limited or absent speech) in relation to receptive language skills has also been documented in the syndrome (Berney, Ireland & Burn, 1999; Goodban, 1993; Oliver et al., 2003; Sarimski, 1997).

1.2.1.3. The behavioural phenotype of Cornelia de Lange syndrome

1.2.1.3.1. An introduction to the behavioural phenotype of Cornelia de Lange syndrome

A number of behaviours are reported to form part of the behavioural phenotype of Cornelia de Lange syndrome. These include: self-injurious behaviour, compulsive behaviour, stereotyped behaviour, hyperactivity and Autism spectrum disorder (Arron et al., 2005; Berney, Ireland & Burn, 1999; Goodban, 1993; Hyman, Oliver & Hall, 2002; Moss et al., 2005; Moss et al., 2008; Oliver et al., 2003). Age-related changes have also been reported more recently in the syndrome, with suggestions of changes in behaviour and emotion with age (Basile et al., 2007; Collis et al., 2006; Kline et al., 2007a; Kline et al., 2007b; Oliver, Berg, Moss, Arron & Burbidge, in review). The review below will specifically examine self-injurious behaviour, Autism spectrum disorder and age-related changes in Cornelia de

Lange syndrome. Self-injurious behaviour and Autism spectrum disorder have been chosen because they are two of the more widely investigated areas in Cornelia de Lange syndrome. Age-related change has been chosen because more recent research suggests that there is a heightened probability of behavioural and emotional changes with age, in the syndrome.

1.2.1.3.2. Self-injurious behaviour in Cornelia de Lange syndrome

One of the most well-documented behaviours in Cornelia de Lange syndrome is self-injurious behaviour. Research from a number of studies indicates that there is a high prevalence of self-injury in Cornelia de Lange syndrome with reported rates varying from 16.6% to 63.6% (Beck, 1987; Hyman et al., 2002). Interestingly, a recent study by Oliver, Sloneem, Hall and Arron (2009) found that there was no difference in the prevalence of clinically significant self-injury in Cornelia de Lange syndrome when compared to a matched comparison group. Self-injury in Cornelia de Lange syndrome has been reported to be severe and individuals with Cornelia de Lange syndrome and self-injury have even been reported to show self-restraint (Dossetor et al., 1991; Shear, Nyhan, Kirman & Stern, 1971). Hyman et al. (2002) found that 53% of participants with Cornelia de Lange syndrome showed at least one form of self-restraint and a significant association was found between self-injury and self-restraint. It has been reported that the self-injury in Cornelia de Lange syndrome has a compulsive nature (Bryson et al., 1971; Shear et al., 1971). Hyman et al. (2002) demonstrated a relationship between compulsive behaviour, self-injury and self-restraint in Cornelia de Lange syndrome. The authors concluded that self-injury in Cornelia de Lange syndrome is not necessarily an involuntary, compulsive

behaviour; rather the self-injury has a compulsive quality but there may be a number of causes leading to this behaviour.

A number of research studies have demonstrated the effect of the environment on self-injury in Cornelia de Lange syndrome (Moss et al., 2005; Oliver et al., 2006; Singh & Pullman, 1979). For example, Moss et al. (2005) conducted a descriptive analysis of observational data on eight children with Cornelia de Lange syndrome and found that nearly all (seven of eight) participants showed at least one form of self-injury that was associated with a particular setting event. Oliver et al. (2006) also demonstrated that levels of social attention influenced self-injury in three of nine participants with Cornelia de Lange syndrome who displayed self-injury. This further demonstrates the effect of the environment on self-injury in Cornelia de Lange syndrome. As other environmental factors were not examined in this study, it was not possible to understand the impact of other environmental variables on self-injury in Cornelia de Lange syndrome. The evidence to date suggests that the environment is important in the development and maintenance of self-injury in some people with Cornelia de Lange syndrome indicating that self-injury is not necessarily an inevitable consequence. This perhaps indicates that environmental interventions may be effective in the reduction of self-injury in Cornelia de Lange syndrome (Oliver et al., 2006).

1.2.1.3.3. Autism spectrum disorder in Cornelia de Lange syndrome

A number of studies have investigated the relationship between Autism spectrum disorder and Cornelia de Lange syndrome (e.g., Berney, Ireland & Burn, 1999). The estimated

prevalence of Autism spectrum disorder in Cornelia de Lange syndrome varies between 47% and 61.8% (Basile, Villa, Selicorni & Molteni, 2007; Berney et al., 1999; Moss et al., 2008; Oliver et al., 2008). These rates are significantly higher than those seen in individuals without Cornelia de Lange syndrome, who have a similar degree of intellectual disability (e.g., Moss et al., 2008; Oliver et al., 2008; Oliver et al., 2009). The relationship between Autism spectrum impairments and degree of disability remains unclear in Cornelia de Lange syndrome. Basile et al. (2007) found that degree of disability may be important in the association between Autism spectrum disorder and Cornelia de Lange syndrome because Autism spectrum impairments were only found for participants with a moderate to profound degree of disability. Oliver et al. (2008) however, found that 32.1% of participants with Cornelia de Lange syndrome compared to 7.1% of individuals in a matched contrast group of heterogeneous cause were reported to show severe Autism in accordance with their scores on the Childhood Autism Rating Scale, indicating that there are other important factors in the relationship between Autism spectrum disorder and Cornelia de Lange syndrome.

Only one study to date has conducted a fine-grained analysis of the phenomenology of Autism spectrum disorder in Cornelia de Lange syndrome, using a psychometrically sound assessment (Moss, Oliver, Berg, Kaur & Jephcott, 2008). Moss et al. (2008) found that individuals with Cornelia de Lange syndrome presented with an atypical profile of Autism spectrum disorder. Individuals showed significant deficits in the domain of communication with a significantly higher proportion of individuals with Cornelia de Lange syndrome scoring above the cut-off for communication impairments than individuals in a matched contrast group. Individuals with Cornelia de Lange syndrome

showed no significant impairments in the domain of social interaction suggesting that any social impairments associated with Cornelia de Lange syndrome are different to those reported in Autism spectrum disorder.

1.2.1.3.4. Age-related changes in Cornelia de Lange syndrome

Age-related changes in Cornelia de Lange syndrome are less well-researched in comparison to other aspects of the syndrome. However, recent literature has started to demonstrate that age-related changes may be important and characteristic of individuals with Cornelia de Lange syndrome (Basile et al., 2007; Collis et al., 2006; Kline et al., 2007a; Kline et al., 2007b; Oliver, Berg, Moss, Arron & Burbidge, in review). These studies are reviewed in detail in section 2.2 and section 3.3 and so will not be examined in detail below.

The studies reviewed in section 2.2 and section 3.3 provided preliminary evidence for age-related changes in Cornelia de Lange syndrome and so provided the basis for a pilot study to examine the possible behavioural and emotional age-related changes in Cornelia de Lange syndrome (Collis et al., 2006). The pilot study involved conducting open-ended interviews with parents and/or carers of nine adolescents and adults with Cornelia de Lange syndrome who were reported to experience changes in mood and/or anxiety levels, with age. The interviews were used to obtain detailed information regarding events that occurred around the time of change. Content analysis was used to identify common themes across the interviews. Low mood and social anxiety were the most commonly reported changes with age. The most commonly reported behaviours which may relate to

low mood were tearfulness (6/9), increased tiredness (5/9), feeling "unwell" (5/9), loss of interest in activities previously enjoyed (4/9) and reduced appetite (4/9). Commonly reported behaviours which may relate to social anxiety were a reluctance to speak to unfamiliar people (9/9), preferring to watch peers rather than join in with their activities (8/9), having one or two good friends rather than lots of friends (7/9), experiencing selective mutism (6/9), appearing very shy (6/9) and being reluctant to speak in a group setting (6/9). All participants were reported to have a strong preference for routine and experienced difficulty coping with change. These behavioural and emotional changes were frequently reported to occur at a time of change in day or residential setting, indicating that changes in a person's environment may be related to the onset of low mood and/or social anxiety. The evidence from this pilot study, in combination with the evidence in the literature (section 2.2 and section 3.3) on age-related changes in Cornelia de Lange syndrome, provided the basis for the research conducted in this thesis.

1.3. ISSUES THAT NEED TO BE ADDRESSED IN THE REMAINING LITERATURE REVIEW

Section 1.2.1.3.4 has highlighted the need for research to empirically examine age-related changes in individuals with Cornelia de Lange syndrome. The evidence suggests that individuals in late adolescence and/or early adulthood may experience low mood and/or heightened levels of social anxiety. However, the confounding variables associated with this research means that it is difficult to have confidence in such findings and so there is a need for more robust studies to be conducted to ensure that the results are reliable and valid.

Before conducting this empirical research in Cornelia de Lange syndrome, it is important to consider the clinical diagnostic criteria for such psychopathologies in the typically developing population and secondly consider how these constructs can be examined in individuals with Cornelia de Lange syndrome. The review below will examine the diagnostic criteria for and prevalence of depression and social anxiety in the typically developing population. These psychopathologies will then be reviewed in neurodevelopmental disorders known to be associated with such psychopathologies. Measures assessing mood and social anxiety will then be examined. As the measures of mood have been better developed for the intellectual disability population, these measures will only be reviewed in this population. Due to the lack of measures available for examining social anxiety in individuals with intellectual disabilities, these measures will be reviewed in typically developing children as this information may help to inform the assessment of social anxiety in individuals with a range of intellectual disabilities. Examining measures will provide information about the most effective way to examine such disorders in Cornelia de Lange syndrome. The diagnostic criteria for and assessment of selective mutism will also be examined because there is strong evidence in the literature to suggest that selective mutism may be an extreme form of social anxiety (Black & Uhde, 1992; Vecchio & Kearney, 2005). Therefore, when examining social anxiety in Cornelia de Lange syndrome, it will also be important to consider the assessment of selective mutism.

1.4. DEPRESSION

1.4.1. Depression defined

The most widely used criteria for diagnosing depressive conditions are the American Psychiatric Association's (2000) revised fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR), and the World Health Organization's (1992) International Statistical Classification of Diseases and Related Health Problems (ICD-10). The former criteria are often used in the USA and many other non-European nations, whilst the latter criteria are typically used in European countries.

According to the DSM-IV-TR criteria (American Psychiatric Association, 2000), a single episode of major depressive disorder is diagnosed when five (or more) specified symptoms have been present during the same two-week period and represent a change from previous functioning. The symptoms include: (1) depressed mood most of the day, nearly every day; (2) markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day; (3) significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day; (4) insomnia or hypersomnia nearly every day; (5) psychomotor agitation or retardation nearly every day; (6) fatigue or loss of energy nearly every day; (7) feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick); (8) diminished ability to think or concentrate, or indecisiveness, nearly every day; (9) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide

attempt or a specific plan for committing suicide (American Psychiatric Association, 2000). At least one of the symptoms must be depressed mood or loss of interest or pleasure. The symptoms must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning (American Psychiatric Association, 2000). Recurrent major depressive disorder is the presence of two or more major depressive episodes. Similar criteria are used in the ICD-10 criteria (1992), however, depressive episodes are categorised according to severity (mild, moderate, severe).

1.4.2. Prevalence of depression

The twelve-month prevalence of major depressive disorder in the general population is 10.3% (Kessler et al., 1994). The life-time prevalence of major depressive disorder in the general population is 16.6% (Kessler et al., 2005). Individuals with intellectual disabilities show an increased prevalence of depression compared to the typically developing population (e.g., Emerson, 2003).

1.4.3. Depression in neurodevelopmental disorders

1.4.3.1. Depression in Autism spectrum disorder

Autism spectrum disorder has been associated with several types of psychopathology, one of the most common being depression (Howlin, 1997). The prevalence rate of depression in Autism spectrum disorder varies between 4% and 38% (Lainhart, 1999). The varying prevalence rate between studies is possibly due to methodological factors, such as, age and

ability of participants (Stewart et al., 2006). Tantam's (1991) study found that the rate of depression in a group of adults with Asperger syndrome was 15%. More recently, Kim, Szatmari, Bryson, Streiner and Wilson (2000) assessed the prevalence of mood problems among 59 children aged 9 to 14 years with high functioning autism and Asperger syndrome. The authors found that the percentage of children scoring two standard deviations above the population mean (i.e. clinically significant scores) on a measure of depression was 16.9%.

Individuals with Autism spectrum disorder appear to be at an increased risk of experiencing depression even when the presence of an intellectual disability is taken into consideration. Bradley, Summers, Wood & Bryson (2004) used the Diagnostic Assessment for the Severely Handicapped-II (DASH-II; 1995) to compare psychiatric and behaviour disorders in twelve individuals with severe intellectual disabilities and Autism spectrum disorder to twelve participants with severe intellectual disabilities but with no diagnosis of Autism spectrum disorder. Participants with Autism spectrum disorder scored significantly higher on seven of the thirteen sub-scales of the DASH-II, including the depression subscale. Furthermore, 50% of participants with Autism spectrum disorder met the clinical cut-off for depression. However, only 8% of participants without Autism spectrum disorder reached the clinical cut-off for depression. Although a small sample size was used, this study reflects the potentially high prevalence of depression in individuals with Autism spectrum disorder even when the presence and severity of an intellectual disability is taken into account.

1.5. ANXIETY

1.5.1. Anxiety disorders defined

The most widely used criteria for diagnosing anxiety disorders are the American Psychiatric Association's (2000) revised fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR), and the World Health Organization's (1992) International Statistical Classification of Diseases and Related Health Problems (ICD-10). According to the DSM IV-TR criteria (American Psychiatric Association, 2000) anxiety disorders include: generalised anxiety disorder (GAD), panic disorder with and without agoraphobia, agoraphobia without history of panic disorder, specific phobia, social phobia (also known as social anxiety disorder), obsessive-compulsive disorder (OCD), posttraumatic stress disorder (PTSD) and acute stress disorder (ASD) (American Psychiatric Association, 2000). The ICD-10 criteria (1992) are categorised differently under the broad-heading of Neurotic, stress-related and somatoform disorders. The categories under this broad-heading are phobic anxiety disorders, other anxiety disorders, obsessive-compulsive disorder, reaction to severe stress and adjustment disorders, dissociative [conversion] disorders, somatoform disorders and other neurotic disorders. These categories are then subdivided further into specific disorders. For example, agoraphobia with and without panic disorder, social phobias, specific (isolated) phobias, other phobic anxiety disorders and phobic anxiety disorder unspecified are categorised under the heading of Phobic anxiety disorders.

1.5.2. Prevalence of anxiety disorders

The twelve-month prevalence of anxiety disorders in the general population are as follows: Panic disorder (2.3%), Agoraphobia without panic (2.8%), Simple phobia (8.8%), Social phobia (7.9%) and Generalised anxiety disorder (3.1%) (Kessler et al., 1994).

The life-time prevalence of anxiety disorders in the general population are as follows: Panic disorder (4.7%), Agoraphobia without panic (1.4%), Specific phobia (12.5%), Social phobia (12.1%), Generalised anxiety disorder (5.7%), Posttraumatic stress disorder (6.8%), Obsessive-compulsive disorder (1.6%) and Separation anxiety disorder (5.2%) (Kessler et al., 2005).

The prevalence of anxiety disorders is raised in individuals with intellectual disabilities in comparison to the typically developing population (Borthwick-Duffy, 1994; Deb et al. 2001; Eaton & Menolascino, 1982).

1.6. SOCIAL ANXIETY

1.6.1. Social anxiety defined

Social anxiety disorder (SAD) was formally conceptualised and defined as an independent psychopathology in the publication of the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III; American Psychiatric Association, 1980). It has been referred to as the "neglected anxiety disorder" because the late recognition of the disorder has meant that both knowledge and research on social anxiety has lagged behind that of other anxiety disorders (Liebowitz, Gorman, Fyer & Klein, 1985).

According to the DSM-IV-TR criteria, a diagnosis of social anxiety may only be warranted if a person shows a marked and persistent fear of embarrassment or humiliation in one or more social interaction or performance situations in which the person is exposed to unfamiliar people or possible scrutiny by others (American Psychiatric Association, 2000). Social interaction situations may include, going 'on a date', speaking to someone in authority or talking to a stranger. Social performance situations may include, speaking to an audience, eating in front of other people or playing a musical instrument in front of an audience. There are two subtypes of social anxiety: generalised social anxiety and non-generalised social anxiety. Individuals with the generalised subtype fear most social interaction or performance situations, whereas individuals with the non-generalised subtype fear only one or some social situations (American Psychiatric Association, 2000).

A person with social anxiety will typically show an anxiety response in the feared social situation, which in some instances can be a panic attack and the feared situation will be either avoided or endured with extreme anxiety. The person's avoidance or anticipatory anxiety of the social situation or anxiety experienced in the feared situation will significantly interfere with day-to-day life (American Psychiatric Association, 2000). For a child to be given a diagnosis of social anxiety they must demonstrate anxiety in peer settings and not just with adults; and they must show capacity for social relationships with familiar people and demonstrate a relationship outside their immediate family with someone their own age.

The presentation of social anxiety may differ between children and adults (American Psychiatric Association, 2000). Adults will show typical anxiety symptoms, such as, blushing, a shaky voice, or cold clammy hands. Children may show other signs, such as crying, freezing, staying close to a familiar person or showing inhibited interactions, which may present as selective mutism. Children may typically stay on the periphery of social activities, may refuse to participate in activities at school and/or may refuse to go to school. Social anxiety is the only anxiety or mood disorder that has been shown to be consistently associated with early withdrawal from school (Stein, 2000).

Typically, the onset of social anxiety is in adolescence, although some studies report onset for some individuals in early childhood (Rapee, 1995; Wittchen et al., 1999). The typical onset in adolescence may be a result of the increasing importance of social interactions at this stage (Rapee & Spence, 2004). The course of social anxiety is often life-long but may attenuate in severity or remit in adulthood (American Psychiatric Association, 2000). Those with the generalised subtype are more likely to experience a more long-term chronic pathway. The severity of social anxiety may fluctuate in response to life events or other stressors and some individuals report onset of social anxiety after a stressful period (Hofman, 2004; Reiger et al., 1998).

1.6.2. Prevalence of social anxiety

Social anxiety is the second most common anxiety disorder and the fourth most common psychopathology following major depressive disorder, substance use disorders and specific phobia (Kessler et al., 2005). Research on community-based samples has found social

anxiety to be more common in females than males, although both genders are equally represented in clinical samples. A reported life time prevalence of social phobia in Western societies ranges from 7% to 13% (Furmark, 2002).

1.6.3. Social anxiety in neurodevelopmental disorders

1.6.3.1. Social anxiety in Fragile X syndrome

Fragile X syndrome is the most commonly inherited form of intellectual disability. It affects approximately 1 in 4,000 males and 1 in 8,000 females (Crawford et al., 1999). Fragile X syndrome is caused by a mutation on the FMR1 gene on the long arm of the X chromosome, which causes an abnormal expansion of CGG nucleotide repeats (Kaufmann & Reiss, 1999; Verkerk et al., 1991). Individuals with an expansion of over 200 CGG nucleotide repeats are considered to have the full mutation of the disorder. It is believed that a reduction in FMR protein levels, caused by the mutation of the gene, leads to the clinical manifestations of the syndrome (Pieretti et al., 1991). A number of behaviours are considered characteristic of individuals with Fragile X syndrome. Social difficulties, including social anxiety, social withdrawal and gaze avoidance are some of the behaviours reported to be characteristic of these individuals (Bregman et al., 1988; Hagerman & Sobesky, 1989; Lachiewicz, 1992). Social difficulties are reported to affect both males and females with the syndrome.

Studies which have utilised comparison groups have shown that social anxiety-related behaviours are characteristic of individuals with Fragile X syndrome. For example,

Einfeld et al. (1994) found that children with Fragile X syndrome experienced significantly more shyness and showed more avoidance of eye contact than a contrast group of individuals with a non-specific cause of intellectual disability. A study examining social functioning in females with Fragile X syndrome found that girls with Fragile X syndrome were rated as having significantly more social problems, being more withdrawn and showing less social competence than their sisters (Mazzocco et al., 1998). Three of the eight girls in the Fragile X syndrome sample scored in the borderline to clinical range on withdrawn behaviours and social problems on the Child Behavior Checklist (CBCL; Achenbach & Edelbrock, 1983). In another study, significantly more social difficulties were reported for females with Fragile X syndrome group in relation to a contrast group (Lesniak-Karpiak, Mazzocco & Ross, 2003).

Experimental studies have also been used to examine social anxiety in Fragile X syndrome (Cohen et al., 1988; Hall et al., 2006; Hessl et al., 2006; Lesniak-Karpiak, et al., 2003). The use of experimental conditions has provided a clearer, more detailed, picture of the behavioural response of individuals with Fragile X syndrome to specific social situations. Thus, this methodology has allowed researchers to determine whether there are specific social situations which evoke anxiety-behaviours. These experimental studies are reviewed in detail in Chapter Four (4.3.).

Extreme forms of social anxiety, most notably avoidant personality disorder and selective mutism, have been documented in Fragile X syndrome. A study of seventeen females with Fragile X syndrome and seventeen comparable females without Fragile X syndrome showed that 65% of the Fragile X syndrome group met the criteria for *Avoidant disorder of*

childhood and adolescence or *Avoidant personality disorder* according to DSM-III-R criteria in contrast to only 12% of the comparison group (Freund, Reiss & Abrams, 1993). A case study has also been published detailing selective mutism in a girl with Fragile X syndrome (Hagerman et al., 1999). The female was described as shy, experiencing social anxiety and having poor eye contact. Although this is a case report, it is interesting to see how social anxiety, poor eye contact and selective mutism have presented simultaneously. These two studies show the variation in the presentation of social anxiety in Fragile X syndrome, with some individuals experiencing extreme forms of the disorder.

There is limited description of the trajectory of social difficulties in Fragile X syndrome. Hatton et al. (2002) followed up 59 young boys with Fragile X syndrome over a period of three years and found that behavioural and emotional difficulties, including social problems, remained stable over time. Another study which involved following up adolescents with Fragile X syndrome and individuals with a mixed aetiology of intellectual disabilities after seven years, also found that behavioural and emotional problems remained relatively stable over time for both groups (Einfeld, 1999). The two behaviours, *shyness* and *avoiding eye contact*, which distinguished the two groups at the first time point continued to do so at follow up, with the Fragile X syndrome group demonstrating significantly more shyness and avoidance of eye contact than the comparison group at both time points (Einfeld, 1999). The measures utilised in both studies (the DBC and the CBCL) were general measures of psychopathology. These measures may not be sensitive enough to assess changes in social anxiety. Specific measures examining social anxiety should be developed for future studies because they can encompass the sensitivity needed to detect changes in the presence and nature of social anxiety over time.

1.6.3.2. Social anxiety in Autism spectrum disorder

More recent literature on Autism spectrum disorder has suggested that individuals may experience social impairments that are not typically associated with idiopathic autism, most notably, social anxiety. It seems that little research to date has assessed the association between social anxiety and autism, particularly in those who have a more severe degree of intellectual disability. However, the research conducted has found an association between social anxiety and impaired social functioning (a core feature of autism) as indicated by difficulties with both initiation of interactions and maintenance of eye contact in individuals with autism (e.g., Baron-Cohen, 1989).

Bellini (2004) investigated the relationship between anxiety and social skill deficits in 41 high-functioning adolescents with autism spectrum disorders. It was found that social anxiety specifically was associated with Autism spectrum disorder. Nearly 49% of participants obtained scores indicative of social anxiety on the Social Anxiety Scale for Adolescents (SAS-A; La Greca, 1999). An association between social anxiety and social skill deficits (measured by the Social Skills Rating System (SSRS; Gresham & Elliot, 1990) was also found, although the relationship was dependent on the nature of the social skill being assessed. In particular, significant negative correlations were found between the assertion subscale of the SSRS and two of the three subscales of the SAS-A. This indicates that as assertion levels decreased, social anxiety increased. La Greca and Lopez (1998) have suggested that social skills deficits may cause social anxiety in individuals with Autism spectrum disorder by heightening the probability that the individual will experience negative peer interactions. In order to further research in this area, it is

necessary to discover whether these results are also applicable to individuals with Autism spectrum disorder who have a more severe degree of intellectual disability and also whether levels of social anxiety are related to age.

1.7. SELECTIVE MUTISM

1.7.1. Selective mutism defined

Selective mutism is characterised as a "consistent failure to speak in specific social situations (in which there is an expectation for speaking, e.g., at school) despite speaking in other situations" (American Psychiatric Association, 2000). This failure to speak must have an impact upon achievement at school or work or must effect social communication. The failure to speak must last for at least one month and not be better accounted for by another condition or due to lack of knowledge or comfort with the language being spoken. The onset of selective mutism typically occurs before five years of age and the course of the disorder is variable (Garcia et al., 2004; Giddan, Ross, Sechler & Becker, 1997). For some, it may only last a few months, whilst for others it can persist for a number of years.

1.7.2. Prevalence of selective mutism

Selective mutism is comparatively rare in relation to other childhood disorders, with estimated prevalence rates varying between .03% and 2% (Brown & Lloyd, 1975; Kopp & Gillberg, 1997; Kumpulainen et al., 1998). Reasons for variation in prevalence estimates are likely to be due to methodological differences, such as, the diagnostic criteria used or the age of children included in the study. Prevalence rates are higher in children than

adults but it has been suggested that this may be due in part to the ability of adults to control their environment and thus avoid certain social situations (Garcia et al., 2004).

1.7.3. The aetiology of selective mutism

To date, no single cause of selective mutism has been identified and there is ongoing debate about which factors are important in causing selective mutism (Cohan, Chavira & Stein, 2006). Early research tended to focus on psychodynamic theories and family-systems theory, which proposed that selective mutism may be related to trauma, unresolved intra-psychic conflicts and controlling behaviour but more recent research has emphasised the importance of anxiety (Dow et al., 1995; Black & Uhde, 1992). High rates of anxiety disorders, particularly, social anxiety, have been found in individuals with selective mutism and it has been proposed that selective mutism is a symptom of social anxiety rather than a distinct disorder (Black & Uhde, 1992; Vecchio & Kearney, 2005). Kristensen (2000), for example, found that 74.1% of children with selective mutism had an anxiety disorder and this was most commonly found to be social anxiety (67.9%). Similar findings have been reported in other research studies, although prevalence rates vary (Arie et al., 2006; Manassis et al., 2003).

Communication and developmental disorders have been implicated in the cause of selective mutism (Kristensen, 2000; Manassis et al., 2003). In one study, 38% of children with selective mutism were found to have speech or language disorders, most commonly expressive language disorders (28%) and articulation disorders (20%). Some researchers have related these communication and developmental difficulties to the cause of anxiety in

selective mutism (Kristensen, 2000). A recent study examined the relationship between language abilities, cognition and anxiety in children with selective mutism and found that children with selective mutism scored significantly lower than two contrast groups on phonological awareness, receptive vocabulary and grammar (Manassis et al., 2007). Interestingly, children with selective mutism also had significant deficits in visual memory in comparison to the two contrast groups and in nonverbal working memory in comparison to one of the contrast groups, although this was not consistent across all the non-verbal measures. Perhaps, this indicates that specific executive functioning deficits are implicated in the cause of selective mutism.

Rates of selective mutism have also been found to be higher in bilingual immigrant children, implicating the acquisition of a second language in the cause of selective mutism (Elizur & Perednik, 2003). Other research has demonstrated that selective mutism may be related to temperament characteristics, namely, behavioural inhibition and shyness (Bergman et al., 2002; Kristensen & Torgersen, 2002). For example, children with selective mutism have been reported to be more shy and have a greater preference for being on their own than children without the disorder (Kristensen & Torgersen, 2002). A genetic predisposition has also been implicated in the cause of selective mutism. Viana, Beidel and Rabian (2009) conducted a review of the literature and suggested that avoidance, anxiety, a preference for being alone and general psychopathology may be characteristic of families of individuals with selective mutism.

The evidence to date indicates that there may be an interplay between different factors in the cause of selective mutism (Cohan et al., 2006). Given the ongoing debate about the

causes of selective mutism, research on selective mutism in atypical populations, such as neurodevelopmental disorders, may help to inform theories on the aetiology of selective mutism in typically developing individuals.

1.8. ASSESSMENT MEASURES

1.8.1. The assessment of depression in individuals with intellectual disabilities

The assessment of depression in individuals with intellectual disabilities, particularly those with a more severe degree of intellectual disability, has been challenging for a number of reasons, including difficulties in accessing and/or reporting internal states and the presence of 'atypical' symptoms of depression (Meins, 1995; Meins, 1996). Despite this, a number of researchers have attempted to adapt existing measures of depression designed for the typically developing population or design new measures of psychopathology or depression for individuals with intellectual disabilities. Adaptations of existing measures of depression used in the typically developing population, such as, a modified version of the Zung self-rating depression scale (Zung, 1965), have been reported to be suitable for individuals with mild and moderate intellectual disabilities (Stenfert Kroese, 1997). The self-report nature of these measures may mean that they are not suitable for individuals with a more severe and profound intellectual disability.

General measures of psychopathology with depression subscales have been designed for the intellectual disability population. These measures include the Reiss Screen (Reiss, 1988), the Psychiatric Assessment Schedule for Adults with a Developmental Disability

(PAS-ADD; Moss et al., 1993; Moss et al., 1998), the Psychopathology Inventory for Mentally Retarded Adults (PIMRA; Senatore, Matson & Kazdin, 1985) and the Diagnostic Assessment for the Severely Handicapped-II (DASH-II; Matson, 1995). General measures of psychopathology are limited by the fact that they screen for a number of disorders and so may not be as sensitive to identifying the phenomenology of depression in individuals with intellectual disabilities.

Meins (1996) developed the first informant-based measure of depression in individuals with a range of intellectual disabilities (the Mental Retardation Depression Scale; MRDS). However, the psychometric properties of this measure have yet to be established. Furthermore, items from this measure and the general measures of psychopathology noted above may not be applicable to individuals with severe intellectual disabilities. Example of such questions, include, 'inner tension' in the MRDS, 'loss of self-confidence' in the PAS-ADD and 'complaints about mental disabilities' in the DASH-II.

The Glasgow Depression Scale-Learning Disability (GDS-CS, Cuthill, 2001) has been developed to measure depression in adults with mild and moderate intellectual disabilities and the psychometric properties are reasonable. However, as this measure was developed for individuals with a mild or moderate intellectual disability it cannot be used for individuals with a severe and profound intellectual disability, thus limiting its applicability.

The Mood, Interest and Pleasure Questionnaire (MIPQ; Ross & Oliver, 2003a) was the first informant-based questionnaire of mood that based all items on informant-based behavioural observations relating to internal states. Hence, all items are applicable to

individuals with a range of intellectual disabilities. The MIPQ has been shown to demonstrate good psychometric properties (Ross & Oliver, 2003a). In summary, this questionnaire appears to be the most robust measure of mood to date in individuals with a range of intellectual disabilities and would be suitable for examining mood in individuals with Cornelia de Lange syndrome.

1.8.2. The assessment of anxiety in individuals with intellectual disabilities

The only measure of anxiety that has been developed for the intellectual disability population is the Glasgow Anxiety Scale for people with an Intellectual Disability (GAS-ID; Mindham & Espie, 2003). It is a 27-item self-report measure consisting of three subscales: worries, specific fears and physiological symptoms. A higher total score is indicative of increased anxiety. This measure appears relatively robust; it has good test-retest reliability ($r = .95$), good internal consistency ($\alpha = .96$) and is relatively well correlated with the Beck Anxiety Inventory (BAI; Beck et al., 1988). The main limitation of this measure is that it was designed for individuals with a mild intellectual disability only and so cannot be used with individuals who a have a more severe degree of intellectual disability.

There are currently no available measures specifically of anxiety in people with severe or profound intellectual disabilities. General measures of psychopathology with subscales relating to anxiety are the only measure of anxiety for this population. Examples of these measures include, the Diagnostic Criteria for Psychiatric Disorders for Use with Adults with Learning Disabilities / Mental Retardation (DC-LD, Royal College of Psychiatrists,

2001), the Psychiatric Assessment Schedule for Adults with a Developmental Disability (PAS-ADD; Moss et al., 1998), the Developmental Behavior Checklist (DBC; Einfeld & Tongue, 1992) and the Diagnostic Assessment for the Severely Handicapped-II (DASH-II; Matson, 1995). The DASH-II, for example, is one of the most widely used scales to assess psychopathology in individuals with severe and profound intellectual disabilities. It has been deemed reliable and most of the subscales have been validated, although the validity of the anxiety subscale still seems limited (Matson, Smiroldo, Hamilton & Baglio, 1997).

A major limitation to using general measures of psychopathology in individuals with intellectual disabilities is that these measures may be not as sensitive to assessing the various types of anxiety disorders that exist. In contrast, reliable and valid scales solely focusing on different aspects of anxiety have been developed for the typically developing population. For example, the Children's Yale-Brown Obsessive Compulsive Scale (Goodman et al., 1986) assesses obsessive-compulsive disorder in typically developing children and the Social Phobia and Anxiety Inventory (SPAI; Turner et al., 1995) assesses social anxiety in typically developing adults. Given the raised prevalence of anxiety disorders in the intellectual disability population (see section 1.5.2.) there is a need to develop psychometrically sound assessments of anxiety for this population.

1.8.3. The assessment of social anxiety in typically developing children

Examining the assessment of social anxiety in typically developing children is important for informing the assessment of social anxiety in individuals with a range of intellectual disabilities because child measures may include items that are more applicable to

individuals with a more severe degree of intellectual disability. A comprehensive assessment of social anxiety in typically developing children should involve the assessment of behaviour, cognition and physiology. A variety of assessment tools are available, including: clinical interviews, child self-report measures, informant-based questionnaires and behavioural observation.

1.8.3.1. Clinical interviews

Semi-structured diagnostic interviews allow for the assessment of a wide range of symptoms and consideration of a number of diagnoses. The most reliable diagnoses are made using this methodology (Velting et al., 2004). The Anxiety Disorders Interview Schedule for DSM-IV-Child and Parent Versions (ADIS-IV-C/P; Silverman & Albano, 1996) is often the preferred interview of choice if a diagnosis of anxiety is suspected because it focuses specifically on diagnosing childhood anxiety disorders, whereas other interviews examine childhood psychopathology more broadly (Silverman & Albano, 1996).

1.8.3.2. Clinician rating scales

Clinician rating scales may be used as a further source of information regarding the nature of the child's social anxiety. Most clinician rating scales developed for children focus on anxiety generally. The Liebowitz Social Anxiety Scale for Children and Adolescents (LSAS-CA; Masia, Hofmann, Klein & Liebowitz, 1999) is the exception, which has been developed to examine social anxiety specifically. This measure compromises two

subscales: social interaction and social performance. Ratings are provided for level of anxiety and avoidance for each subscale. Psychometric properties are reported to be good (Storch, Masia, Pincus, Klein & Liebowitz, 2001).

1.8.3.3. Self-report measures

Self-report measures are also seen as an integral part of the assessment procedure. Few self-report measures have been developed to specifically focus on social anxiety in children. The Social Anxiety Scale for Children-Revised (SASC-R; La Greca & Stone, 1993) was developed to examine social anxiety in children specifically and consists of three factors: Fear of Negative Evaluation, Generalised Social Avoidance and Distress, and Social Avoidance of New Situations involving unfamiliar peers. Adequate reliability and internal consistency have been reported for the measure, whilst more research is need on convergent and discriminant validity. The Social Phobia and Anxiety Inventory for Children (SPAI-C; Beidel, Turner & Morris, 1995) has also been developed for children aged eight years and upwards. The measure consists of three factors: Assertiveness/general conversation, Traditional social encounters and Public performance. The measure has been found to differentiate socially anxious and non-anxious children and the test-retest reliability is good. Further research is being conducted on the measure's ability to discriminate between populations of children with anxiety.

1.8.3.4. Informant-based measures

Informant-based measures of social anxiety are appropriate when children are too young to complete self-report measures. However, no informant-based measures of social anxiety specifically have been developed for children. Some self-report measures have been adapted in research to allow for a comparison across informants. For example, Beidel et al. (2000) reported a modest correlation between child and parent versions of the Social Phobia and Anxiety Inventory for Children. Informant measures of broad childhood psychopathology are typically used instead in clinical settings. The Child Behavior Checklist (CBCL; Achenbach, 1991) is one of the most commonly used informant measures and this contains nine subscales, including, Anxious/Depressed, Social Problems and Withdrawn subscales. Given that none of these subscales focus specifically on social anxiety, it may be difficult to accurately screen for this disorder using the CBCL. Clearly, there is a need for further research into informant-based measures of social anxiety in children.

1.8.3.5. Behavioural measures

A variety of behavioural measures are available in the assessment of social anxiety in children. Self-monitoring, such as the use of daily diaries, has been found to be an important and reliable part of the behavioural assessment of social anxiety in children (Antony, 1997). Also, the direct observation of behaviour has been used when assessing social anxiety in children.

Behavioural observation can take place in structured or unstructured situations. Unstructured situations typically involve observing the child during the interview process or during a visit to the child at home or at school. Structured situations may consist of role-plays devised for the assessment of social anxiety (e.g., Beidel et al., 2007). It is important to note that no 'gold-standard', direct, structured observational methodology exists for assessing social anxiety in children.

A variety of role plays have been designed and used with children to assess for social anxiety. For example, Rao et al. (2007) devised and used a behavioural assessment of social anxiety in study for children and adolescents. The assessment consisted of role-play and a read-aloud task. In the role-play task, participants were asked to interact with the same-aged peer who was trained to give friendly but neutral responses. The role-play included: starting a conversation with an unfamiliar peer, offering to help another peer, giving a compliment, receiving a compliment and responding assertively to a peer's inappropriate behaviour. During the read-aloud task, participants were asked to read from a set text for ten minutes in front of an adult experimenter and a same-aged peer. The behavioural assessments were then coded for speech latency (time to respond to a verbal prompt), anxiety and effectiveness (quality of the social interaction / public performance). This study provides an example of the type of direct behavioural assessments used in the literature.

1.8.4. Problems with assessment in typically developing populations

A fundamental problem in diagnosing social anxiety in the typically developing population is defining the threshold for the clinical cut-off of social anxiety. Given that 40% of the population describe themselves as shy, it is difficult to determine at what point 'extreme shyness' becomes a psychopathology. Stein et al. (1994) found that the prevalence of social anxiety ranged from 1.9% to 18.7% in the same population depending on the diagnostic cut-off that was used and the degree to which the symptoms were investigated. Remaining mindful of the criteria used to diagnose social anxiety is important in both typical and atypical populations.

1.8.5. The assessment of social anxiety in individuals with intellectual disabilities

There are no standardised measures that examine social anxiety specifically in individuals with intellectual disabilities. Therefore, it is important for clinical purposes that a reliable and valid measure of social anxiety is developed for this population. The assessment of social anxiety in the intellectual disability population has largely been informed by the literature on Fragile X syndrome. In this literature, the assessment of social anxiety has been based upon the use of questionnaire measures or experimental manipulations of social interactions (e.g., Cohen et al, 1988). The use of experimental methods represents a real advancement in the literature, as this methodology is applicable to individuals with a range of intellectual disabilities. Table 1.1 shows the experimental methods used to assess social anxiety in the Fragile X syndrome literature. These studies are examined in more detail in

Chapter Four (see 4.3.). The studies show the variability in both experimental designs and behavioural indicators employed to assess social anxiety in Fragile X syndrome.

In summary, the absence of questionnaire measures of social anxiety in the intellectual disability population, highlight the clinical need for such measures to be developed. The experimental designs vary between studies as there is no "gold-standard" for conducting a behavioural assessment of social anxiety in the intellectual disability population. Standardised experimental procedures are needed so that comparisons can be conducted across studies and thus across different genetic syndromes.

Table 1.1: Experimental Studies of Social Anxiety in Fragile X Syndrome.

Author	Target Group	Comparison Group	Comparability of groups	Description of Experiment	Behavioural indicators assessed	Method for rating behaviour	Findings
Cohen et al. (1988): study 1	12 males with Fragile X syndrome (FXS) (mean age: 7.1 yrs)	7 males with Down syndrome (DS) (mean age: 8.5 yrs) and 8 typically developing males (mean age: 4.7 yrs)	CA* of typically developing children was matched to mean communication age equivalent score on VABS for FXS and DS groups.	1. Parent in room with child but *did not* initiate interactions with them (*n.b. this condition was not used in the analysis*). 2. Parent interacted with their son using a variety of activities appropriate for the child's level of communication. 3. A stranger interacted with the participant using a variety of activities appropriate for the child's level of communication. Each condition lasted for 10 mins.	*Participant behaviours*: (1) Relative frequency of social gaze to social avoidance, (2) Social gaze and (3) Social avoidance *Adult behaviours*: (1) Communication requests, (2) Object gaze/manipulation requests, (3) Attention requests and (4) Manual guidance.	Occurrence of behaviours recorded in alternating 6-sec intervals beginning in the 2nd min of interaction.	FXS participant showed a significantly lower percentage of *relative* social gaze to social avoidance and significantly more social avoidance than DS participants or typically developing children across both familiar and unfamiliar interaction conditions.
Cohen et al. (1988): study 2	12 males with FXS (mean age: 7.1 yrs) *n.b. same group used in study 1*	7 males with FXS and Autism (mean age: 7.9 yrs), 10 males with atypical PDD (mean age: 6.5 yrs) and 7 males with autism (mean age: 7 yrs)	All groups were matched as closely as possible on CA. Groups were not matched on level of communication	1. Parent in room with child but *did not* initiate interactions with them (*n.b. this condition was not used in the analysis*). 2. Parent interacted with their son using a variety of activities appropriate for the child's level of communication. 3. A stranger interacted with the participant using a variety of activities appropriate for the child's level of communication. Each condition lasted for 10 mins.	*Participant behaviours*: (1) Relative frequency of social gaze to social avoidance, (2) Social gaze and (3) Social avoidance *Adult behaviours*: (1) Communication requests, (2) Object gaze/manipulation requests, (3) Attention requests and (4) Manual guidance.	Occurrence of behaviours recorded in alternating 6-sec intervals beginning in the 2nd min of interaction.	The relative frequency of social gaze to avoidance was significantly higher for the FXS groups in the interaction with the parent than the Autism groups but they did not differ in the stranger interaction. The FXS participants showed significantly more preference for social gaze to avoidance in comparison to FXS participants with Autism. The FXS groups showed significantly more social avoidance in the stranger interaction than the Autism groups.
Lesniak-Karpiak et al. (2003)	21 females with FXS	34 females who had neither FXS or TS and 29 females with Turner syndrome (TS)	Participants with FXS were significantly older and had lower VIQ* scores than the comparison group of females without FXS or TS	The role-play involved the participant assuming the role of a neighbour and having to initiate and maintain a conversation with a stranger who had just moved into the area where the person lived. The stranger responded in a minimal fashion, using a neutral tone and placed the burden of maintaining the conversation on the participant. The conversation lasted for a minimum of 105 secs.	*Participant behaviours*: (1) Total duration of silence, (2) Time to first utterance, (3) Number of pauses during the conversation,(4) Eye contact avoidance, (5) Rigid body posture, (6) Fidgeting, (7) Wringing of hands and (8) Facial movements.	Partial interval time-sampling for 15-sec durations	Females with Turner syndrome showed significantly less facial movements than females in the other two groups. Females with Fragile X syndrome took significantly longer to initiate the conversation and showed significantly more hand wringing than females in the other two groups.

Author	Target Group	Comparison Group	Comparability of groups	Description of Experiment	Behavioural indicators assessed	Method for rating behaviour	Findings
Hessl et al. (2006)	90 children with the full mutation of FXS	90 unaffected siblings of FXS children participants	Sibling-pair match so matched on family characteristics. Groups matched on age and gender when possible.	1. The experimenter interviewed the participant about several specific topics. Throughout the condition the experimenter reminded the child to maintain eye contact as much as possible with the experimenter. 2. The participant read a passage silently (single words or letters for children who couldn't read). 3. The participant read a similar passage loud enough for everyone to hear in the room. 4. The participant sang two 2 songs.	*Participant behaviours*: (1) Gaze, (2) Vocal quality, (3) Discomfort and (4) Task avoidance.	Coders rated each behavioural indicator on a five-point scale for each task. A lower rating was indicative of greater impairment.	Boys with FXS demonstrated significantly poorer gaze and vocal quality, increased discomfort and more task avoidance than their unaffected male siblings. The same result was also found for girls with FXS in comparison to their siblings.
Hall et al. (2006)	74 males and 40 females with FXS	No comparison group	N/A	1 .The experimenter interviewed the participant about several specific topics. Throughout the condition the experimenter reminded the child to maintain eye contact as much as possible with the experimenter. 2. The participant read a passage silently (single words or letters for children who couldn't read). 3. The participant read a similar passage loud enough for the experimenter to hear. *4. Singing*: The participants were asked to sing a song of their choice if they wanted, then two of three pre-specified songs.	*Participant behaviours*: (1) Eye contact, (2) talking/singing, (3) fidgeting, (4) face-hiding, (5) eye-rubbing, (6) hand-biting, (7) leaving chair and (8) Refusals. *Experimenter behaviours*: (1) Social demands, (2) Eye contact prompts and (3) Song prompts.	Real-time coding. Eye contact prompts and refusals were coded as events. All other behaviours were coded as durations.	The three most prevalent problem behaviours for males and females with FXS were face hiding, fidgeting and refusals. Males showed eye contact with the experimenter for 18% of the interview condition, whilst higher levels were found for females (40%). For male participants, refusals, face-hiding and leaving chair were more likely to occur in the Signing condition, whilst hand biting was more likely to occur in the Interview condition. For females, refusals, hiding and eye rubbing were more likely to occur in the Singing condition. For both males and females, most problem behaviours were significantly less likely to occur in both Reading conditions.

*CA=chronological age; VIQ=verbal IQ

1.8.6. The assessment of selective mutism

Dow et al. (1995) highlight the importance of conducting a multi-modal assessment of selective mutism. Interviews with parents and teachers will provide information about to whom the person speaks and in which settings, as well as other important information, such as a full developmental history. The Anxiety Disorders Interview Schedule for Children and Parents (ADIS-C/P; Silverman, & Albano, 1996) is a semi-structured interview that can be used to assess selective mutism, in addition to other disorders. It is also important to interview the individual, despite the nature of the condition, and observe the individual directly to assess fully the nature of their presenting difficulties (Dow et al., 1995; Yeganeh et al., 2003). It has been suggested that a formal functional analysis under a variety of conditions may be useful in determining the maintenance of an individual's selective mutism (e.g., Schill, Kratochwill, & Gardner, 1996). Finally, a speech and language assessment is important to examine whether these difficulties contribute to the person's selective mutism (Cleator & Hand, 2001; Manassis et al., 2007). The assessment may include either a non-verbal measure of receptive language and/or an assessment of the person's speech via a tape recording (Viana et al., 2009).

1.9. SUMMARY OF LITERATURE REVIEW

The literature review has demonstrated that the criteria developed to assess mood and social anxiety are based on definitions constructed for the typically developing population and the criteria may *not* always be suitable for people with intellectual disabilities, especially those with a severe or profound disability. Interestingly, the prevalence of these

psychopathologies is reported to be raised for individuals with intellectual disabilities in comparison to typically developing individuals and thus provides further evidence for a need to develop appropriate criteria and assessments of these psychopathologies for this population. The literature review has shown that the prevalence of low mood and social anxiety appears raised in several neurodevelopmental disorders, including Cornelia de Lange syndrome, supporting the need for further empirical research on low mood and social anxiety in Cornelia de Lange syndrome.

When considering the assessment of mood and social anxiety in the intellectual disability population the tools deemed appropriate for this population remain far more limited than for the typically developing population. Assessment measures of mood have been better developed than measures of social anxiety for the intellectual disability population. The Mood, Interest and Pleasure Questionnaire (MIPQ; Ross & Oliver, 2003a), is a robust measure of mood for individuals with a range of intellectual disabilities, and thus will be useful in assessing mood in Cornelia de Lange syndrome. The assessment of social anxiety, however, remains far more under-researched in this population and no measure specifically of social anxiety exists for this population. There is clearly a need to develop a measure of social anxiety for this population. The development of a questionnaire measure and a standardised, experimental, observational measure to assess social anxiety in individuals with a range of intellectual disabilities would be ideal. The questionnaire measure could be used to screen for social anxiety in a large number of individuals, whilst the experimental measure could be used to detail the phenomenology of social anxiety. If such measures were developed, they could then be utilised for the assessment of social anxiety in Cornelia de Lange syndrome.

1.10. AIMS OF THE THESIS AND OVERVIEW OF THE CHAPTERS

The broad aim of the thesis is to examine age-related changes in Cornelia de Lange syndrome, with particular focus on mood and social anxiety. Quantitative, empirical methodologies will be employed in this thesis to address the lack of quantitative research in this area (see section 1.2.1.3.4.). This thesis has four main aims.

The first aim of the thesis is to examine age-related changes in mood, interest and pleasure in Cornelia de Lange syndrome. This aim will be addressed in Chapter Two which describes a two-year follow-up study of mood, interest and pleasure in individuals with Cornelia de Lange syndrome and individuals in two comparable contrast groups (Cri du Chat syndrome and Fragile X syndrome). Cross-sectional and longitudinal comparisons will be employed to investigate whether the trajectory of mood, interest and pleasure in Cornelia de Lange syndrome appears atypical.

The second aim of the thesis is to develop an informant-based questionnaire of sociability for individuals with a range of intellectual disabilities and use this measure to examine the developmental trajectory of sociability in Cornelia de Lange syndrome. This aim will be addressed in Chapter Three which describes the development of the Sociability Questionnaire for Individuals with Intellectual Disabilities (SQID; an informant-based measure of sociability for individuals with a range of intellectual disabilities), which will be used to compare levels of sociability between individuals with Cornelia de Lange syndrome and individuals in five comparable contrast groups. Cross-sectional comparisons will also be employed to compare levels of sociability within and between the six groups to

examine whether the trajectory of sociability appears atypical in Cornelia de Lange syndrome. Prevalence rates of selective mutism in Cornelia de Lange syndrome will also be investigated in this study because the literature demonstrates a strong relationship between social anxiety and selective mutism (see section 1.7.3.).

The third aim of the thesis is to develop an experimental, observational-based assessment of social anxiety and use it to assess social anxiety in adolescents and adults with Cornelia de Lange syndrome. This aim will be addressed in Chapter Four which describes the development of a novel experimental design to examine behavioural indicators of social anxiety in individuals with Cornelia de Lange syndrome and individuals in a comparable contrast group (Down syndrome). The experimental design will allow for a fine-grained analysis of social impairments in adolescents and adults with Cornelia de Lange syndrome and determine whether there are social impairments that are characteristic of adolescents and adults with Cornelia de Lange syndrome.

The fourth aim of the thesis is to conduct a preliminary investigation into the relationship between social impairments in Cornelia de Lange syndrome and executive functioning. This aim will also be addressed in Chapter Four. Any social impairments identified in the Cornelia de Lange syndrome group in Chapter Four, will be correlated with an informant-based measure of executive functioning to examine if there is a relationship between these variables.

CHAPTER TWO

A Follow-up Study of Mood, Interest and Pleasure in Cornelia de Lange syndrome

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2.1. ABSTRACT

2.1.1. Background: There is limited research regarding cognitive, emotional and behavioural change with age in Cornelia de Lange syndrome. A recent comparison study of a number of syndrome groups indicated that low mood, interest and pleasure may be characteristic of older individuals with Cornelia de Lange syndrome (Oliver, Berg, Moss, Arron & Burbidge, in review). The aim of the current study was to follow-up individuals with Cornelia de Lange syndrome from Oliver et al.'s (in review) study to examine potential changes in mood, interest and pleasure in Cornelia de Lange syndrome over a two-year period.

2.1.2. Method: 67 individuals with Cornelia de Lange syndrome, 42 individuals with Cri du Chat syndrome and 142 individuals with Fragile X syndrome from Oliver et al.'s (in review) study were followed-up after approximately two years. Caregivers of participants completed a number of questionnaires including the Mood, Interest and Pleasure

Questionnaire-Short version (MIPQ-S; Ross, Arron & Oliver, 2008; Ross & Oliver, 2003a).

2.1.3. Results: Cross-sectional analysis indicated that low mood, interest and pleasure was characteristic of older adolescents and adults (above 15 years) with Cornelia de Lange syndrome. Individuals with Cornelia de Lange syndrome, aged between 19 years and 22 years, experienced the lowest levels of mood, interest and pleasure. The follow-up analysis showed that low mood, interest and pleasure remained stable over a two-year period for both older (above 15 years) and younger (15 yrs and below) individuals with Cornelia de Lange syndrome. Factors important in predicting mood, interest and pleasure in Cornelia de Lange syndrome were age and insistence on sameness.

2.1.4. Conclusion: Atypical, age-related differences in mood, interest and pleasure are evident in Cornelia de Lange syndrome. A longer follow-up may be needed to determine whether the differences identified using the cross-sectional comparisons are evident when using a follow-up methodology. The differences reported in mood, interest and pleasure in Cornelia de Lange syndrome may be part of a broader difference in behaviour, cognition and emotion with age.

2.2. INTRODUCTION

The literature of behavioural phenotypes has expanded significantly in the past two decades and has progressed from description of single syndrome groups toward more fine-grained research on the developmental trajectories of behaviour and cognitive processes. Some researchers have argued that the study of developmental trajectories in individuals with neurodevelopmental disorders can offer a 'window of opportunity' for understanding typical and atypical development processes (Cornish, Scerif & Karmiloff-Smith, 2007; Thomas et al., 2009).

The most well researched profile of development and change within a behavioural phenotype is that for behaviour and cognition in Down syndrome, with studies ranging from descriptions of infant-mother interactions to the onset and course of Alzheimer's disease (e.g., Holland et al., 1998). More recently other investigations have been undertaken in several genetic syndromes to examine the developmental trajectory for behaviour and cognition over time. For example, individuals with Williams syndromes are reported to show an overall decrease in emotional and behavioural problems with age (with rates of anxiety and compulsions decreasing but rates of depression and overactivity increasing), whilst cognitive abilities remain relatively stable over time (Elison, Stinton, & Howlin, 2010; Howlin, Elison, Udwin & Stinton, 2010; Stinton, Elison, Udwin & Howlin, 2010). In Fragile X syndrome, the rate of Autism spectrum disorder and social avoidance behaviours are reported to increase with age in males with full mutation Fragile X syndrome (Hatton et al., 2006; Roberts et al., 2007). Another more recent study of Fragile X syndrome reported improvements in those with Fragile X syndrome and Autism

spectrum disorder and decline in those with Fragile X syndrome only, indicating that there may be different trajectories within the syndrome group (Hernandez et al., 2009). Deterioration in IQ and adaptive functioning from adolescence has also been reported in individuals with Fragile X syndrome (e.g. Fisch et al. 2002). These detailed studies of the developmental trajectory of behaviour and cognition in individuals with genetic syndromes will not only enhance understanding of typical and atypical development, but will also be important for identifying syndrome specific, age related changes. In turn, this will enable identification of risk for psychological disorder and may contribute to prevention and intervention strategies.

Cornelia de Lange syndrome is one syndrome in which age-related changes in behaviour, and mood have been described (Basile et al., 2007; Collis et al., 2006; Kline et al., 2007a; Kline et al., 2007b). Previously, a focus on other areas of behaviour, particularly self-injurious behaviour, overshadowed other important characteristics and impairments in Cornelia de Lange syndrome. Emerging evidence indicates that less prominent problems, particularly low mood, may be common in this syndrome. Kline et al. (2007a) reported that in a sample of 49 adolescents and adults with Cornelia de Lange syndrome, depression was diagnosed in 11%. Sarimski (1997) reported that 12% of a sample of 27 individuals with Cornelia de Lange syndrome were found to show low mood, whilst 46.2% of the sample showed frequent changes in mood. In a large-scale cross syndrome questionnaire study examining mood, interest and pleasure across seven different syndrome groups and a group of individuals with intellectual disability of heterogeneous cause, Oliver, Berg, Moss, Arron and Burbidge (in review) reported that individuals with Cornelia de Lange syndrome scored significantly lower on scales of mood, interest and pleasure than at least

three other syndrome groups (Angelman, Lowe and Fragile X syndromes). This level of specificity suggests that low mood, interest and pleasure may be a syndrome-related characteristic.

Another study has also shown that a lower ratio of positive to negative affect is evident in individuals with Cornelia de Lange syndrome in comparison to individuals with Cri du Chat syndrome and individuals with intellectual disability of heterogeneous cause comparable on age, gender, mobility and degree of intellectual disability, further supporting the suggestion that low mood and affect is characteristic of the syndrome (Collis, Moss, Jutley, Cornish and Oliver, 2007). In this study, however, significant differences were not found between the groups on the *duration* of positive and negative affect. It is likely that the young age of the study sample (mean age 6.0 years) may account for this outcome because evidence suggests that low mood may be related to age in individuals with the syndrome (Collis et al., 2006; Kline et al., 2007a).

Although very little is known about the developmental trajectory of behaviour and mood in Cornelia de Lange syndrome, emerging evidence suggests that adolescents and adults with Cornelia de Lange syndrome demonstrate an increase in behavioural difficulties and, specifically, decreases in mood, interest and pleasure. Preliminary evidence of a change in behaviour and emotion with age was demonstrated in a pilot study conducted with families of nine individuals with Cornelia de Lange syndrome (aged 14-20 years), who were reported to show changes in mood and / or anxiety with age (Collis et al., 2006). Open-ended interviews were conducted with at least one of the participant's primary caregivers about changes in behaviour and mood with age. Behaviours indicative of low mood and

social anxiety were most evident in the group. The most commonly reported behaviours which may relate to low mood were tearfulness (6/9), increased tiredness (5/9), feeling "unwell" (5/9), loss of interest in activities previously enjoyed (4/9) and reduced appetite (4/9). Whilst caution must be exercised when interpreting the data due to methodological flaws (including a biased sampling method, a small sample size, the absence of a psychometrically sound assessment and no comparison group), the interviews have provided preliminary evidence of changes in mood with age in Cornelia de Lange syndrome and so provide a basis for further quantitative research.

Description of age-related changes in Cornelia de Lange syndrome have been reported within the literature. Kline et al. (2007a; 2007b) reported both behavioural and emotional changes in approximately 80% of individuals with Cornelia de Lange syndrome. Reported changes, included an increase in levels of depression, self-injurious behaviour, obsessive-compulsive behaviours, anxiety, aggression and hyperactivity. Kline et al. (2007a) reported that the onset and development of these behavioural difficulties was often a primary concern for parents and carers. A review of 74 questionnaires completed by caregivers on puberty in Cornelia de Lange syndrome identified that these behavioural issues worsened with the onset of puberty (Blagowidow, Kline & Audette, 2005). In a recent cross-syndrome comparison, Oliver, Berg, Moss, Arron and Burbidge (in review) also found that significantly more adults with Cornelia de Lange syndrome (25%) showed impulsivity than children with the syndrome (10%). Consistent with these findings, Basile et al. (2007) found a significant relationship between chronological age and a range of behavioural problems in a group of 56 individuals with Cornelia de Lange syndrome aged 11 to 31 years, with significantly more behavioural problems in older individuals.

A specific association between low mood and age has also been identified. Berney, Ireland and Burn (1999), for example, reported the presence of a cyclical mood disturbance, as evidenced by a change in mood or behaviour lasting for weeks or months, in 27% of participants, with 77% of those individuals being over 12 years old. Finally, the results from a large-scale cross-syndrome questionnaire study examining mood, interest and pleasure across several syndrome groups, including individuals with Cornelia de Lange syndrome (Oliver et al., in review), demonstrated that 13.2% of adults (over the age of 18) with Cornelia de Lange syndrome experienced abnormal levels of negative affect compared to 3.2% of children with the syndrome. The difference between adults and children with Cornelia de Lange syndrome in levels of abnormal affect approached statistical significance ($p = .056$). This profile of behaviour was not reported in any of the other six genetic syndrome groups assessed in this study or in individuals with intellectual disability of heterogeneous cause, indicating there may be an atypical trajectory for mood in Cornelia de Lange syndrome. The research so far has demonstrated that a number of behavioural difficulties emerge in adolescence in Cornelia de Lange syndrome and it may be that the emergence of low mood is part of a broader change in behaviour and emotion with age. A follow-up study is required in order to overcome the potential cohort effects of cross-sectional comparisons.

One of the issues apparent from previous research conducted on mood in Cornelia de Lange syndrome, is whether the low mood reported in Cornelia de Lange syndrome meets the clinical diagnostic criteria for depression. A number of studies have referred to the low mood described in Cornelia de Lange syndrome, as depression (e.g., Kline et al., 2007a).

However, three of the nine possible symptoms for diagnosing depression (DSM-IV^{tr} criteria; American Psychiatric Association; 2000) involve accessing cognitions (feelings of worthlessness, diminished ability to think, recurrent thoughts of death) meaning that it is difficult to diagnose depression in individuals with a more severe degree of intellectual disability and/or those who have poor expressive communication, such as individuals with Cornelia de Lange syndrome (Ross & Oliver, 2003b). Given the difficulty in applying the current diagnostic criteria for depression to individuals with Cornelia de Lange syndrome, the term *low mood* will be used in the current study.

A small number of studies have considered the factors which may contribute to the low mood reported in Cornelia de Lange syndrome. The literature already described on mood in Cornelia de Lange syndrome has identified that increasing age may be related to low mood in the syndrome (Berney et al., 1999; Sarimski, 1997). Several studies have also demonstrated that individuals with Cornelia de Lange syndrome have a preference for predictability and routine, and that changes in these variables may lead to episodes of low mood and a loss of interest in activities previously enjoyed (Collis et al., 2006; Jackson, 1992; Sarimski, 1997; Van Allen et al., 1993). Sarimski (1997), for example, found that 61.5% of participants with Cornelia de Lange syndrome became "upset" by changes in routine and this was significantly more prominent in older children with the syndrome. Furthermore, a pilot study of nine adolescents and adults with Cornelia de Lange syndrome reported to show a change in mood and / or anxiety with age, revealed that all participants were reported to have a strong preference for routine and experienced difficulty coping with change (Collis et al., 2006). Interestingly, in the pilot study, the onset of low mood was frequently reported to occur at a time of change in day or residential setting, again

indicating that changes in a person's environment may be related to the onset of low mood. These studies suggest that there is a relationship between preference for routine, age and low mood in Cornelia de Lange syndrome. 'Preference for routine' forms part of the class of repetitive behaviour of 'insistence on sameness' (Moss et al., 2009) and so 'insistence on sameness' will be examined in the current study as a predictor of mood outcome in Cornelia de Lange syndrome, in addition to age.

A study of health problems in individuals with genetic syndromes has identified that individuals with a health problem are approximately three times more likely to experience low affect than those with no health problems, demonstrating the relationship between low mood and health problems (Berg, Arron, Burbidge, Moss & Oliver, 2007). The severity of health problems will therefore be assessed as a predictor of low mood in Cornelia de Lange syndrome because individuals with Cornelia de Lange syndrome experience a significant number of health problems, most notably gastro-oesophageal reflux (Hall, Arron, Sloneem & Oliver, 2008; Jackson et al., 1993; Luzzani et al., 2003).

In the wider literature, a relationship has also been demonstrated between low mood and Autism spectrum disorder (ASD), with increased levels of depression being found in individuals with Autism spectrum disorder (Kim et al., 2000) (see section 1.4.3.1.). Furthermore, there is evidence to suggest that rates of depression in Autism spectrum disorder increase with age and may account for the behavioural deterioration seen in individuals with Autism spectrum disorder around adolescence (Ghaziuddin et al., 1998; Ghaziuddin et al., 2002). Given that there is an increased prevalence of ASD symptomatology in Cornelia de Lange syndrome, the presence and severity of autism

spectrum related characteristics will also be assessed as a predictor of low mood in Cornelia de Lange syndrome.

Together, previous findings provide strong evidence that low mood, interest and pleasure is characteristic of individuals with Cornelia de Lange syndrome. More specifically, these difficulties may become more pronounced with age and may be related to insistence on sameness, autism spectrum phenomenology and health problems. Investigation of the factors that significantly predict low mood, interest and pleasure in individuals with Cornelia de Lange syndrome will be critical to understanding the underlying aetiology of these changes and enable identification of high risk individuals with the syndrome.

Much of the research conducted to date on behavioural phenotypes involves single group descriptions of the nature and trajectory of these age-related changes. Few studies have used appropriate contrast groups in order to identify the specificity of these characteristics, in particular the degree to which the trajectory of development is atypical in comparison to other individuals with similar levels of intellectual ability and no study to date has examined the factors which may predict mood in Cornelia de Lange syndrome. Furthermore, none of the above studies have employed a follow-up approach, thus limiting the ability to assess the extent to which these changes represent a cohort effect. Dykens and Hodapp (2001) have stressed the importance of utilising appropriate contrast groups in behavioural phenotypes research. Of utmost importance is the inclusion of a contrast group that is comparable on degree of disability, age and gender, in order to ensure that any findings are not just an artefact of these characteristics. For the purpose of the current study, two contrast groups will be employed. A group of individuals with Cri du Chat

syndrome will be used as a contrast group because they are reported within the literature to be comparable to individuals with Cornelia de Lange syndrome on degree of disability, age and gender (Cornish & Bramble, 2002; Cornish, Bramble, Munir, & Pigram, 1999; Cornish & Munir, 1998; Neibhur, 1978).

Cri du Chat syndrome is caused by a partial deletion on the short arm of chromosome 5 and has an estimated prevalence of 1 in 50,000 live births (Neihbur, 1978). Individuals with Cri du Chat syndrome typically have a severe or profound intellectual disability and often show a discrepancy between expressive and receptive language, with expressive language being significantly more impaired than receptive language (Cornish et al., 1999; Cornish & Munir, 1998). This profile is similar to that seen in Cornelia de Lange syndrome. However, the groups differ on their association with Autism spectrum disorder. Individuals with Cri du Chat syndrome show significantly less Autism spectrum-related impairments than individuals with Cornelia de Lange syndrome (Moss et al., 2008). Given the reports of an association between Autism spectrum disorder impairments and low mood (Ghaziuddin et al., 1998; Ghaziuddin et al., 2002), a second contrast group, Fragile X syndrome, in which an association with Autism spectrum disorder is well established (Moss & Howlin, 2009), will also be included in the current study.

Fragile X syndrome is the most commonly inherited form of intellectual disability, affecting approximately 1 in 4000 males and 1 in 6000 females (Turner et al., 1996). Fragile X syndrome is caused by a mutation on the FMR1 gene on the long arm of the X chromosome, which causes an abnormal expansion of CGG nucleotide repeats (Kaufmann & Reiss, 1999; Verkerk et al., 1991). Males with Fragile X syndrome typically show more

severe cognitive impairments than females and have a mild to moderate intellectual disability (Hatton et al., 2002). An increased prevalence of Autism spectrum disorder is a prominent feature of the syndrome and this is more evident in males with the syndrome (Clifford et al., 2006). Due to variability between males and females with Fragile X syndrome, and the fact that males with Fragile X syndrome show a more severe degree of disability and a stronger association with Autism spectrum disorder, only males with Fragile X syndrome were included in current study.

The current study is a two-year follow-up of individuals with Cornelia de Lange, Fragile X and Cri du Chat syndromes who participated in Oliver et al.'s (in review; Arron et al., in review; Moss et al., 2009) cross syndrome comparison study between 2003 and 2004. The study employs both follow-up and cross-sectional methodologies. This study will focus on the presentation of mood in individuals with Cornelia de Lange syndrome and two contrast groups; individuals with Fragile X syndrome comparable for Autism spectrum characteristics and age; and individuals with Cri du Chat syndrome, comparable for degree of intellectual disability, gender and age. The current study will be the first follow-up case-control study to examine changes in mood, interest and pleasure with age and examine factors that are predictive of these changes in individuals with Cornelia de Lange syndrome. Age, insistence on sameness, Autism spectrum symptomatology and health problems, will be examined as predictors of mood, interest and pleasure in the syndrome. Based on the literature to date, it is predicted that:

1. Individuals with Cornelia de Lange syndrome will show significantly lower levels of mood, interest and pleasure than individuals with Cri du Chat and Fragile X syndromes at baseline (Time 1) and at follow-up (Time 2).
2. Lower mood will be evidenced by older than younger individuals with Cornelia de Lange syndrome at baseline (Time 1) and at follow-up (Time 2).
3. Analysis of mood, interest and pleasure scores for participants with Cornelia de Lange syndrome will show that individuals in early adulthood will experience the lowest levels of mood, interest and pleasure.
4. Individuals with Cornelia de Lange syndrome will show a decline in mood, interest and pleasure over a two-year follow-up period.

Due to the limited information on predictors of mood in Cornelia de Lange syndrome, there will be an additional research aim to identify the factors that significantly predict mood, interest and pleasure in Cornelia de Lange syndrome.

2.3. METHOD

2.3.1. Participants

Individuals with Cornelia de Lange, Fragile X and Cri du Chat syndromes who participated in the cross syndrome questionnaire survey between 2003 and 2004 (*Time 1*; Arron et al., in review; Moss et al., 2009; Oliver et al., in review) were invited to participate in the current follow-up study (*Time 2*), which took place between 2006 and 2007. This study was conducted as part of a larger follow-up project involving other groups (Angelman, Lowe, Smith-Magenis syndromes and a group of individuals with an intellectual disability of heterogeneous aetiology), which were not included in the current analysis. Ethical approval for the current study was obtained from the School of Psychology Ethical Review Board at the University of Birmingham.

At Time 1, 142 parents and / or carers of individuals with Cornelia de Lange syndrome, who had been involved in previous 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) and individuals with Cri du Chat syndrome (n = 180) and Fragile X syndrome (n = 762) who had not taken part in previous research were invited to take part via the relevant syndrome support groups (the Cornelia de Lange Syndrome Foundation, Cri du Chat Syndrome Support Group and the Fragile X Society). At Time 1, 116 individuals with Cornelia de Lange syndrome, 65 individuals with Cri du Chat syndrome and 193 individuals with Fragile X syndrome took part in the study.

In the current study (Time 2), individuals were invited to take part if they had participated in the study at Time 1 and had given consent to be contacted with information about future research. In total, 385 individuals (114 with Cornelia de Lange syndrome, 63 with Cri du Chat syndrome and 208 with Fragile X syndrome) were invited to participate at Time 2. Of the questionnaires sent out to caregivers, nine (three Cornelia de Lange syndrome, four Cri du Chat syndrome and two Fragile X syndrome) were undelivered because caregivers had moved address since Time 1 and no forwarding address had been provided. 274 caregivers completed and returned the questionnaires at Time 2. The return rate for the current study was at least 70% for each group. Table 2.1 shows details of the number of participants invited to take part in the current study, the return rate of questionnaires and the number of participants who met the inclusion criteria for the current study.

Table 2.1: The number of individuals with Cornelia de Lange syndrome (CdLS), Fragile X syndrome (FXS) and Cri du Chat syndrome (CDCS) invited to take part at Time 2, the number of questionnaires returned at Time 1 and Time 2, the return rate at Time 2 and the number of participants who met the inclusion criteria at Time 2.

	CdLS	CDCS	FXS	Total
No. of questionnaires returned at Time 1 [a]	116	65	211	392
No. of participants invited to take part at Time 2[b]	114	63	208	385
No. of questionnaires returned at Time 2	80	46	148	274
% return rate at Time 2	70.2	73.0	70.2	(mean:71.1)
No. of participants who met the inclusion criteria for current study at Time 2	**67**	**42**	**142**	**251**

[a] At Time 1, 211 participants with FXS returned their questionnaires but only 193 were analysed because 18 were returned after the deadline for data analysis. These 18 participants were still invited to take part at Time 2 because their data were available from Time 1.
[b] Two caregivers of CDCS participants, two caregivers of CdLS participants and two caregivers of FXS participants did not agree to take part in future research. Additionally, one caregiver of a FXS participant agreed to take part in future research but did not provide their contact details.

Participants were included in the current study if they met the following criteria: confirmed diagnosis of the relevant syndrome from an appropriate professional (a paediatrician, a clinical geneticist); no additional chromosomal abnormalities (other than those causing the syndrome); completion of at least 75% of the total questionnaire pack at *both* Time 1 and Time 2; completion of the Mood, Interest and Pleasure Questionnaire – Short Version (MIPQ; S, Ross, Arron & Oliver, 2008; Ross & Oliver, 2003a) at Time 1 and Time 2; and aged four years or over at Time 1. Participants were required to be at least four years at Time 1 because the Autism Screening Questionnaire (ASQ; Berument, Rutter, Lord, Pickles & Bailey, 1999) was administered and this questionnaire contains items regarding the participant's behaviour when aged between four and five years.

251 individuals (67 with Cornelia de Lange syndrome, 42 with Cri du Chat syndrome and 142 with Fragile X syndrome) met the inclusion criteria for the current study. Table 2.2 shows information about participant characteristics. In the current study (Time 2), all participants were aged between 6 years and 49 years and 73.3% of the sample was male. The three groups were comparable in terms of age, although, as expected, significant differences were identified on other demographic variables. There were significantly more males in the Fragile X syndrome group than the Cornelia de Lange syndrome and Cri du Chat syndrome groups because only males were recruited for the Fragile X syndrome group. The Fragile X syndrome group were also reported to be significantly more able, in terms of self help skills, mobility and speech, than the Cornelia de Lange syndrome and Cri du Chat syndrome groups. The Cornelia de Lange syndrome and Fragile X syndrome groups showed significantly more features of Autism spectrum disorder than the Cri du Chat syndrome group. The Cornelia de Lange syndrome group were reported to experience more vision and hearing impairments than both the Cri du Chat syndrome and Fragile X syndrome groups (apart from vision at Time 1). In summary, the Cri du Chat syndrome group was comparable to the Cornelia de Lange syndrome group for level of ability, gender and age, whilst the Fragile X syndrome group was comparable to the Cornelia de Lange syndrome group on age and features of Autism spectrum disorder. There were no significant differences on demographics between participants taking part at Time 1 and Time 2.

Table 2.2: Demographic information about participants in each syndrome group at Time 1 and Time 2.

		CdLS	CDCS	FXS	F / χ^2	df	*p value*	Post hoc analyses
*n**		67	42	142				
Gender	% Male	41.8	33.3	100[a]	120.01	2	$p < .0001$	FXS>CdLS, CDCS
DEMOGRAPHICS AT TIME 1								
Age at Time 1 (years)	*M* (*SD*) Range	17.33 (9.22) 4-40	17.65 (11.75) 4-44	17.23 (8.84) 6-47	.033	2	ns	
Self help skills at Time1[b]	% Partly able/able[c]	50.7	64.3	90.8	43.36	2	$p < .0001$	FXS>CdLS, CDCS
Mobility at Time1[b]	% Fully mobile[d]	67.2	70.7	95.1	31.46	2	$p < .0001$	FXS>CdLS, CDCS
Vision at Time 1[b]	% Normal[e]	67.2	90.5	90	19.13	2	$p < .0001$	FXS,CDCS > CdLS
Hearing at Time 1[b]	% Normal[f]	62.1	81.0	97.1	43.70	2	$p < .0001$	FXS>CdLS, CDCS
Speech at Time 1[g]	% Partly verbal/ verbal	59.1	80.50	97.8	52.07	2	$p < .0001$	FXS>CdLS, CDCS
ASQ	Mean score (SD)	20.13 (6.35)	13.90 (5.53)	21.30 (6.42)	20.21	2	$p < .0001$	FXS,CdLS> CDCS
DEMOGRAPHICS AT TIME 2								
Age at Time 2 (years)	*M* (*SD*) Range	20.08 (9.25) 6-43	19.89 (11.79) 6-47	19.63 (8.60) 9-49	.06	2	ns	
Self help skills at Time2[b]	% Partly able/able[c]	50.7	61	95	58.36	2	$p < .0001$	FXS>CdLS, CDCS
Mobility at Time 2[b]	% Fully mobile[d]	71.2	65.9	97.1	36.68	2	$p < .0001$	FXS>CdLS, CDCS
Vision at Time 2[b]	% Normal[e]	65.7	90.2	93.5	29.09	2	$p < .0001$	FXS,CDCS > CdLS
Hearing at Time 2[b]	% Normal[f]	64.2	87.8	96.4	39.93	2	$p < .0001$	FXS,CDCS > CdLS
Speech at Time 2[g]	% Partly verbal/ verbal	59.1	82.9	95.6	43.38	2	$p < .0001$	FXS>CdLS, CDCS
ASQ	Mean score (SD)	20.54 (6.51)	14.4 (5.01)	20.79 (6.17)	16.89	2	$p < .0001$	FXS,CdLS> CDCS

*N may vary across the groups for the analysis of demographic variables due to missing data.
[a] Females with FXS were excluded from the study because the syndrome characteristics vary between males and females in the syndrome (Dykens *et al*., 2000).
[b] Information obtained from the Wessex Scale (Kushlick *et al.*, 1973).
[c] Partly able/able if obtain a score of six or above on the self help sub-scale (QG+QH+QI).
[d] Fully mobile if obtain a score of three on QF. The mobility sub-scale (QE+QF) from the Wessex Scale (Kushlick *et al.*, 1973) was not used because we noted that there were a high proportion of people answering QE incorrectly.
[e] Normal if score three on QJ.
[f] Normal if score three on QK.
[g] Partly verbal/verbal if score between 2 and 4 on QL

2.3.2. Measures

The measures utilised for this follow-up study were the Demographic questionnaire (see *Appendix A1)*, the Wessex Scale (Kushlick, Blunden & Cox, 1973), the Mood, Interest and Pleasure Questionnaire – Short Version (MIPQ-S, Ross, Arron & Oliver, 2008; Ross & Oliver, 2003a; see *Appendix A2*), the Health Questionnaire (Hall, Arron, Sloneem, & Oliver, 2008; see *Appendix A3*), the Repetitive Behaviour Questionnaire (Moss et al., 2009; see *Appendix A4*) and the Autism Screening Questionnaire (ASQ; Berument, Rutter, Lord, Pickles & Bailey, 1999).

2.3.2.1. Demographic Questionnaire

The Demographic Questionnaire (see *Appendix A1)* was developed for this study and used to obtain background information about participants. For the current study, information regarding age, gender and diagnostic status (whether a diagnosis had been made and by whom the diagnosis was made by) was used.

2.3.2.2. The Wessex Scale (Kushlick, Blunden & Cox, 1973)

The Wessex Scale is an informant based questionnaire designed to examine social and physical abilities of children and adults with intellectual disability. Subscales include continence, mobility, self help skills, speech and literacy. Additional questions regarding vision and hearing are also included in the questionnaire. Informants complete ratings based on a three point scale for each question (apart from a question regarding speech comprehensibility). The Wessex scale has good inter-rater reliability at subscale level for

both children and adult with intellectual disabilities (Kushlick et al., 1973; Palmer & Jenkins, 1982). For the purpose of the current study, information regarding self-help skills (Question G + Question H + Question I), mobility (Question F), hearing (Question K), vision (Question J) and speech (Question L), were used.

2.3.2.3. The Mood, Interest and Pleasure Questionnaire – Short Version (MIPQ; S, Ross, Arron & Oliver, 2008; Ross & Oliver, 2003a)

The Mood, Interest and Pleasure Questionnaire (Ross et al., 2008; Ross & Oliver, 2003a; see *Appendix A2)* is an informant based questionnaire used to assess two constructs related to depression: mood and, interest and pleasure. It is designed for use with people with intellectual disability including those with severe or profound intellectual disabilities. Informants rate twenty five items describing operationally defined observable behaviours to give a total score, a Mood subscale score and an Interest and Pleasure subscale score. A shorter version of this measure is available (MIPQ-S), in which twelve items from the original measure were selected (six from each subscale) on the basis of their item total correlation and ensuring that all the original constructs of mood, interest and pleasure were included. This version shows good internal consistency (Cronbach's alpha coefficients: total = .88, Mood = .79, Interest and Pleasure = .87), test-retest (.97) and inter-rater reliability (.85). Each item is rated using a five point Likert scale to give a total score of between 0 and 48 where 48 is the maximum score indicating positive affect and elevated interest and pleasure. The two subscale scores range between 0 and 24.

2.3.2.4. The Health Questionnaire (Hall et al., 2008)

The Health Questionnaire (see *Appendix A3)* is an informant based questionnaire, which measures the presence and severity of fifteen health problems. Informants are required to rate the presence and severity (0 = never occurred to 3 = severe problem) of problems occurring ever in the person's life and over the last month. Scores are summed to produce an Overall Health Score indicating severity of health problems for the previous month and during the person's life. A higher score is indicative of a greater severity of health problems. The total number of health problems during the person's life and the previous month can also be calculated. Inter-rater reliability was collected on a sample of 24 individuals. Mean item level reliability Kappa co-efficient for health problems ever occurring was .72. Mean item level reliability for the occurrence of health problems over the last month was .76. Intra-class correlation co-efficient scores for the overall health problem score and total number of health problems occurring over the last month were .65 and .73 respectively. Intra-class correlation co-efficient scores for the overall health problem score and total number of health problems occurring ever during the person's life were .71 and .68 respectively. For the purposes of the current study, the Overall Health Score was used to determine if health problems significantly predicts mood outcome in Cornelia de Lange syndrome.

2.3.2.5. The Repetitive Behaviour Questionnaire (RBQ; Moss et al., 2009)

The Repetitive Behaviour Questionnaire (RBQ; see *Appendix A4)* is an informant measure of repetitive behaviour for use in children and adults with a range of intellectual disability.

The RBQ consists of nineteen items that comprise five subscales: stereotyped behaviour, compulsive behaviour, restricted preferences, insistence on sameness, and repetitive use of language. Informants rate the frequency of each behaviour over the preceding month on a five-point Likert scale ranging from 'never' to 'more than once a day'. Reliability coeffiecients for both inter-rater reliability and test-retest reliability range from .46 to .80 and .61 to .93, respectively, at item level. Concurrent validity and content validity between the RBQ and the repetitive behaviour subscale of the Autism Screening Questionnaire (Berument et al., 1999) is good (.6). Internal consistency is good at full-scale level ($\alpha >$ .8). At subscale level, internal consistency is also reasonable ($\alpha > .5$ for all subscales). For the purpose of the current study, only the insistence on sameness subscale score was used in order to determine whether insistence on sameness significantly predicts mood outcome in Cornelia de Lange syndrome.

2.3.2.6. The Autism Screening Questionnaire (ASQ; Berument, Rutter, Lord, Pickles & Bailey, 1999)

The Autism Screening Questionnaire (Berument et al., 1999*)* was developed as a tool for screening for autistic spectrum disorders in children and adults and is based on the Autism Diagnostic Interview (Lord, Rutter & Lecouteur, 1994). The measure consists of 40 items which are grouped into three subscales: communication; social interaction and repetitive and stereotyped patterns of behaviours. Items are scored for the presence of abnormal behaviours to yield a total score of between 0 and 39 (one item evaluates the current language level of the individual and is not included in the total score) with higher scores indicating the presence of a higher number of abnormal behaviours. The authors identify a

cut off score of 15 as indicative of Autistic Spectrum Disorder and a higher cut off of 22 to differentiate between individuals with autism and those with other Pervasive Developmental Disorders. The ASQ shows good concurrent validity with the Autism Diagnostic Interview and with the Autism Diagnostic Observation Schedule (Howlin & Karpf, 2004). Internal consistency is also good (α = .90 for the total scale; 26) but inter-rater reliability data are not yet available. For the purpose of the current study, the ASQ total score was used to determine if number of autism spectrum disorder characteristics significantly predicts mood outcome in Cornelia de Lange syndrome.

2.3.3. Procedure

Each caregiver received a letter of invitation for the study, an information sheet and a questionnaire pack. Caregivers who wished to take part in the study at Time 2 were asked to complete the questionnaire pack and return it in the pre-paid envelope provided. The questionnaire pack was counterbalanced in five ways to reduce any order effects on completion of the questionnaire pack. Equal proportions of the counterbalanced questionnaires were sent to each group taking part in the study. Approximately four to six weeks after sending questionnaire packs to caregivers, duplicate packs were sent out (covering letter changed) to those caregivers who had not returned their pack during that time period, in order to maximise participation in the study.

2.4. GENERAL DATA ANALYSIS STRATEGY

2.4.1. General Data Analysis Strategy

The distribution of MIPQ-S data was examined via visual inspection of Q-Q plots and utilising the Kolmogrov-Smirnov test. The data were *not* normally distributed at subscale level or at total score level ($p < .05$). Several methods of transformation were employed but it was not possible to create homogenous variances across the dataset. Consequently, non-parametric tests were employed throughout the analysis. Kruskal-Wallis tests, with pair-wise Mann-Whitney post hocs, were employed for between-group analyses. Wilcoxon rank-sum tests were employed for within-group analyses.

Effect sizes were calculated for any significant difference identified at post hoc level. Pearson's correlation coefficient, *r*, was calculated as an estimation of effect size (see Field, 2005). The following formula was used to calculate, *r* (Rosenthal, 1991, p19.).

$$r = \frac{z}{\sqrt{n}}$$

r = Pearson's correlation coefficient

z = z-score

n = number of participants in sample

The relative size of an effect was measured using the following criteria: $r = .1$ is a *small* effect size; $r = .3$ is a *medium* effect size and $r = .5$ is a *large* effect size (Cohen, 1992).

The analysis was divided into three stages. Part one examined how MIPQ-S scores differ between the three syndrome groups as a whole and how age affected MIPQ-S scores between and within the syndrome groups. This involved both cross-sectional and longitudinal analyses. Part two, analysed in more detail the differences in MIPQ-S scores with age in the Cornelia de Lange syndrome group. Part one and Part two of the analyses addressed the four hypotheses proposed in the current study. Part three addressed the additional research aim which was to examine the factors that might significantly predict mood, interest and pleasure in Cornelia de Lange syndrome.

2.4.2. Data Analysis Strategy for Part One: Analysis of MIPQ-S scores

All analyses on the MIPQ-S were conducted at subscale level (Mood; and Interest and Pleasure). Any reference made in the Results section to the comparison of MIPQ-S scores, reflects comparisons of subscale MIPQ-S scores. A conservative alpha level ($p < .01$) was employed throughout these analyses because multiple comparisons were conducted.

In order to examine how MIPQ-S scores differed between people of different ages within the syndrome groups, individuals in each syndrome group (Cornelia de Lange syndrome, Cri du Chat syndrome and Fragile X syndrome) were subdivided into two groups according to their age. Participants who were *15 yrs and below* at Time 1, formed one group and participants who were *above 15 years* at Time 1 formed another group. These

age bands were chosen because it allowed for the most equal distribution of participants across these smaller groups. Six groups were formed in total: Cornelia de Lange syndrome *above 15 years* (n=32); Cornelia de Lange syndrome *15 yrs and below* (n=35); Cri du Chat syndrome *above 15 years* (n=19); Cri du Chat syndrome *15 yrs and below* (n=23); Fragile X syndrome *above 15 years* (n=63); Fragile X syndrome *15 yrs and below* (n=79).

The main effect of *group* was examined using Kruskal-Wallis tests to compare MIPQ-S scores between the three syndrome groups (Cornelia de Lange syndrome, Cri du Chat syndrome and Fragile X syndrome). This comparison was conducted at both Time 1 and Time 2. Any significant differences identified were examined with pairwise Mann-Whitney tests.

Two sets of analyses were conducted to examine the interaction between *group* and *age*. The first analysis examined MIPQ-S scores within each syndrome group. Mann-Whitney tests were used to compare MIPQ-S scores between older and younger individuals within each syndrome group. The second analysis examined differences in MIPQ-S scores between syndrome groups, for younger individuals and for older individuals.

Wilcoxon rank-sum tests were employed to examine whether MIPQ-S scores changed significantly between Time 1 and Time 2 within each syndrome group. Where no significant differences were identified between older and younger individuals within a syndrome group, this analysis was conducted for the group as a whole. Where differences were identified between younger and older individuals within a syndrome group, this analysis was conducted separately for older and younger individuals.

2.4.3. Data Analysis Strategy for Part Two: Identifying a more specific age band during which individuals with Cornelia de Lange syndrome are most at risk of showing low levels of mood, interest and pleasure.

This analysis focused solely on the Cornelia de Lange syndrome group. Individuals with Cornelia de Lange syndrome were split into six age bands in accordance with their age at Time 2: 11 years and under (n = 12); 12 to 15 years (n = 13); 16 to 18 years (n = 10); 19 to 22years (n = 9); 23 to 28 years (n = 12); 29 years and above (n = 11). These age bands allowed for the most equal distribution of participants between groups.

Pair-wise comparisons using Mann-Whitney tests were conducted to compare MIPQ-S subscale scores between the age groups at Time 2. This analysis was conducted at one time point since the Cornelia de Lange syndrome group showed no significant difference in MIPQ-S scores over time. A more liberal alpha level ($p < .05$) was employed as this was an exploratory analysis.

2.4.4. Data Analysis Strategy for Part Three: Assessing which factors significantly predict mood, interest and pleasure in individuals with Cornelia de Lange syndrome?

This analysis again focused solely on the Cornelia de Lange syndrome group and examined which variables predicted mood, interest and pleasure in Cornelia de Lange syndrome. Predictor variables were chosen if there was evidence in the literature for an association between a variable and mood in Cornelia de Lange syndrome specifically, or if

there was evidence that a variable was associated with mood in the wider literature. Using this criterion, age (years), severity of Autism spectrum disorder characteristics (as indicated by the total score on the ASQ; Berument et al., 1999), insistence on the sameness (as measured by the Insistence on the Sameness subscale score on the RBQ; Moss et al., 2009) and severity of health problems (as measured by the Health severity score on the Health Questionnaire; Hall et al., 2008) were chosen as predictor variables for this analysis (see section 2.2. for evidence of an association between the chosen predictor variables and mood).

Low mood and *high mood* were outcome (dependent) variables. *Low mood* and *high mood* were defined in the following way: individuals with Cornelia de Lange syndrome who had the lowest third of MIPQ-S total scores were considered to have *low mood* and individuals with Cornelia de Lange syndrome who had the top third of MIPQ-S total scores were considered to have *high mood*.

The analysis was conducted in two parts. Firstly comparisons were conducted using Mann-Whitney tests to compare whether there were significant differences between the *low mood* and *high mood* groups on the four predictor variables. Secondly, a binary logistic regression analysis, using the *Enter* method, was conducted to examine if any of the four variables significantly predicted mood, interest and pleasure in the Cornelia de Lange syndrome group. Field (2005) states that between 10 and 15 cases of data are needed per predictor variable in a regression analysis. In this analysis, 4 predictor variables were chosen for the analysis as there were 44 cases of data used.

Again data from Time 2 were used for this analysis because only detailed information regarding health was available at this time point and the analysis need only be conducted at one time point because no significant difference was found across time in mood, interest and pleasure, for the Cornelia de Lange syndrome group.

2.5. RESULTS

2.5.1. Part One: Analysis of MIPQ-S scores

2.5.1.1. Differences between syndrome groups on scores of mood, interest and pleasure

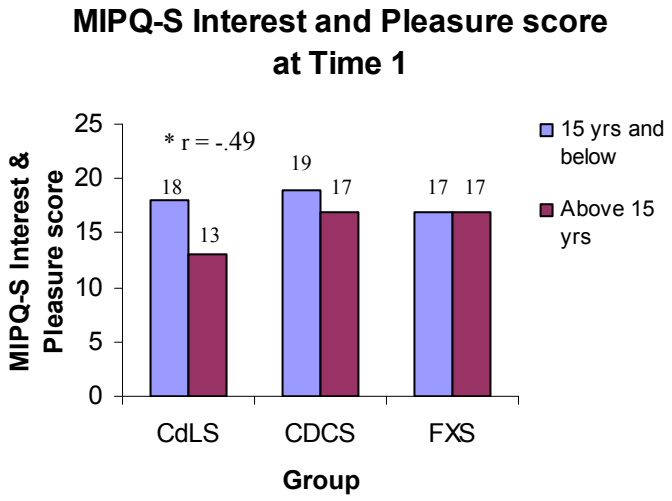
Table 2.3 shows median scores, inter-quartile range, results of statistical analyses of subscale scores on the Mood, Interest and Pleasure Questionnaire-Short version for each syndrome group at Time 1 and Time 2. Kruskal-Wallis tests revealed an effect of group at both Time 1 and Time 2 for MIPQ-S scores. The Cornelia de Lange syndrome group scored significantly lower than the Cri du Chat and the Fragile X syndrome groups on both the Mood subscale score at Time 1 and Time 2 and the Interest and Pleasure subscale score at Time 1. Both the Cornelia de Lange and the Fragile X syndrome groups scored significantly lower than the Cri du Chat syndrome group on the Interest and Pleasure subscale at Time 2. Medium effect sizes were evident in these comparisons. The difference between the Cornelia de Lange and Fragile X syndrome groups on this subscale approached significance (p = .02). These analyses show that the Cornelia de Lange syndrome group are reported to experience significantly lower mood than both the comparison groups at Time 1 and Time 2, significantly lower interest and pleasure than both comparison groups at Time 1 and significantly lower interest and pleasure than the Cri du Chat group only at Time 2.

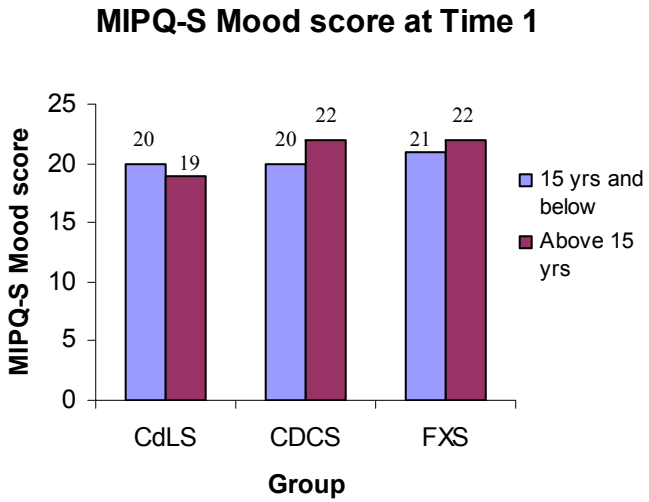
Table 2.3: Median scores, inter-quartile range, results of statistical analyses of subscale scores on the Mood, Interest and Pleasure Questionnaire-Short version for each syndrome group at Time 1 and Time 2.

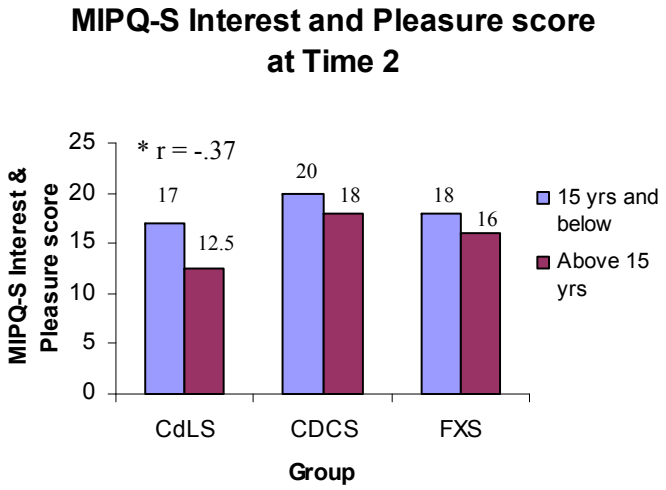
	Median (Inter-quartile range)			χ^2	*df*	*p* value	Post hoc	Effect size (*r*)
	CdLS (n=67)	**CDCS (n=42)**	**FXS (n=142)**					
TIME 1								
Mood subscale	20.00 (17.00-21.00)	21.00 (19.00-22.52)	21.00 (20.00-23.00)	24.2	2	$p < .0001$	FXS,CDCS > CdLS	FXS & CdLS: -.34 CDCS & CdLS: -.25
Interest and Pleasure subscale	15.00 (12.00-18.00)	18.50 (15.75-20.25)	17.00 (14.00-20.00)	12.68	2	$p < .005$	FXS,CDCS > CdLS	FXS & CdLS: -18 CDCS & CdLS: -.32
TIME 2								
Mood subscale	20.00 (16.00-22.00)	22.00 (19.75-23.66)	22.00 (20.00-23.00)	26.3	2	$p < .0001$	FXS,CDCS > CdLS	FXS & CdLS: -.34 CDCS & CdLS: -.36
Interest and Pleasure subscale	14.00 (12.00-19.00)	19.00 (16.75-21.25)	17.00 (14.00-19.25)	19.37	2	$p < .0001$	CDCS > CdLS, FXS	CDCS & CdLS: -.40 CDCS & FXS: -.23

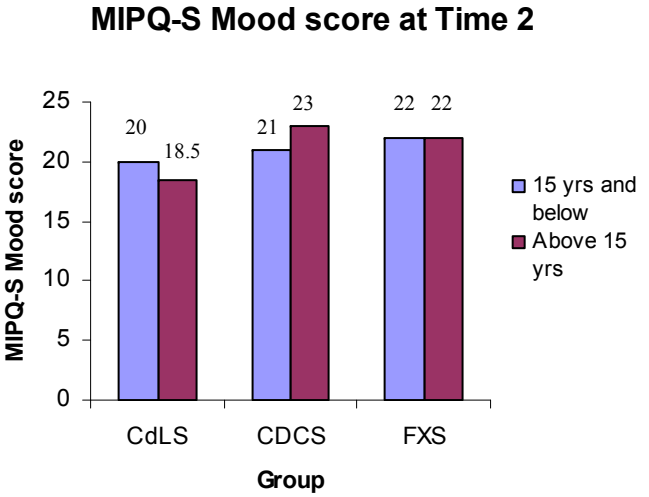
2.5.1.2. Interaction between syndrome group and age

Figure 2.1 shows the differences between older and younger individuals in each syndrome group on MIPQ-S subscale scores at Time 1 and Time 2. Significant differences were found only in the Cornelia de Lange syndrome group. Mann-Whitney tests revealed that older individuals with Cornelia de Lange syndrome (*over 15 years*) scored significantly lower than younger individuals with Cornelia de Lange syndrome *(15 yrs and below*) on the Interest and Pleasure subscale at both Time 1 ($U = 241.5$, $p < .0001$, $r = -.49$) and Time 2 ($U = 319.5$, $p < .005$, $r = -.37$). There were no significant differences found between younger and older individuals with Cornelia de Lange syndrome on the Mood subscale at Time 1 or Time 2. Also, there were no significant differences found between older and younger individuals with Fragile X syndrome or Cri du Chat syndrome on the MIPQ-S scores at either time point. These analyses show that older adolescents and adults with Cornelia de Lange syndrome appear to experience significantly lower interest and pleasure than younger individuals with Cornelia de Lange syndrome. This difference appears to be stable over time. The medium-to-large effect sizes found show the magnitude of the differences between younger and older individuals with Cornelia de Lange syndrome on interest and pleasure scores.









* Indicates significant difference ($p < .01$) and effect size

Figure 2.1: Median MIPQ-S subscale scores for younger individuals (*15 years and below*) and older individuals (*over 15 years*) in each syndrome group, with significant differences indicated between individuals in each syndrome group.

Kruskal-Wallis tests were conducted to examine whether there was a significant difference in MIPQ-S scores between older individuals (*over 15 years*) with Cornelia de Lange, Cri du Chat and Fragile X syndromes and secondly, between younger individuals (*15 years and below*) with Cornelia de Lange, Cri du Chat and Fragile X syndromes at Time 1 and Time 2. See Table 2.4 for statistical analyses between younger individuals and Table 2.5 for statistical analyses between older individuals. Between-group analyses for younger individuals revealed that there was only a significant difference on the Mood subscale at Time 1, with the younger Cornelia de Lange syndrome group (*15 years and below*) obtaining a significantly lower Mood score than the Fragile X syndrome group (*15 years and below*). Analyses conducted across the older age groups showed that the older Cornelia de Lange syndrome group scored significantly lower than the Cri du Chat and Fragile X syndrome groups on both MIPQ-S subscales, at Time 1 and Time 2, with medium-to-large or large effect sizes being found. These analyses show that older individuals with Cornelia de Lange syndrome experience significantly lower mood, and interest and pleasure in comparison to older individuals with Cri du Chat syndrome and Fragile X syndrome and this difference appears to be stable over a two year period. The size of the effects found, also demonstrate the magnitude of the difference between these older age groups.

Table 2.4: Median scores, inter-quartile range, statistical analyses and post hoc analyses on subscale level scores on the Mood, Interest and Pleasure Questionnaire-Short version for younger individuals (15 yrs and below) in each syndrome group.

	Median (Inter-quartile range)			χ^2	*df*	*p value*	*Post hoc*	Effect size (*r*)
	CdLS (n=35)	**CDCS (n=23)**	**FXS (n=79)**					
TIME 1								
Mood subscale	20.00 (18.00-21.00)	20.00 (18.00-22.00)	21.00 (20.00-23.00)	9.62	2	$p < .01$	FXS > CdLS	FXS & CdLS: -.25
Interest and Pleasure subscale	18.00 (15.00-20.00)	19.00 (18.00-21.00)	17.00 (14.00-20.00)	5.23	2	$p = .07$		
TIME 2								
Mood subscale	20.00 (17.00-22.00)	21.00 (19.00-23.00)	22.00 (20.00-23.00)	8.26	2	$p = .02$		
Interest and Pleasure subscale	17.00 (13.00-21.00)	20.00 (17.00-22.00)	18.00 (14.00-20.00)	5.43	2	$p = .07$		

Table 2.5: Median scores, inter-quartile range, statistical analyses and post hoc analyses on subscale level scores on the Mood, Interest and Pleasure Questionnaire-Short version for older individuals (above 15 yrs) in each syndrome group.

	Median (Inter-quartile range)			χ^2	*df*	*p value*	*Post hoc*	Effect size (*r*)
	CdLS (n=32)	**CDCS (n=19)**	**FXS (n=63)**					
TIME 1								
Mood subscale	19.00 (16.36-21.00)	22.00 (20.00-24.00)	22.00 (21.00-23.00)	20.67	2	$p < .0001$	FXS,CDCS > CdLS	FXS & CdLS: -.44 CDCS & CdLS: -.48
Interest and Pleasure subscale	13.00 (11.00-15.00)	17.00 (14.00-20.00)	17.00 (15.00-19.00)	19.50	2	$p < .0001$	FXS,CDCS > CdLS	FXS & CdLS: -.44 CDCS & CdLS: -.42
TIME 2								
Mood subscale	18.50 (15.00-21.00)	23.00 (20.00-24.00)	22.00 (20.00-23.00)	21.65	2	$p < .0001$	FXS,CDCS > CdLS	FXS & CdLS: -.42 CDCS & CdLS: -.51
Interest and Pleasure subscale	12.50 (11.00-17.00)	18.00 (16.00-21.00)	16.00 (14.00-19.00)	17.99	2	$p < .0001$	FXS,CDCS > CdLS	FXS & CdLS: -.31 CDCS & CdLS: -.54

2.5.1.3. Within group change in mood interest and pleasure over time

Wilcoxon rank-sum tests were conducted in order to examine whether MIPQ-S scores changed significantly between Time 1 and Time 2, in each syndrome group. See Figure 2.2 for differences in MIPQ-S scores over time, for each group. As there were no significant differences in MIPQ-S scores between younger and older individuals with Cri du Chat syndrome and Fragile X syndrome, these analyses were conducted for the groups as a whole. The analyses revealed that the Cri du Chat syndrome group showed a significant increase in the mood score (z = -2.62, p < .01, r = -.29) between Time 1 and Time 2. The Fragile X syndrome group, however, showed no significant change over time in MIPQ-S scores.

The same analysis was conducted for the Cornelia de Lange syndrome group on the Mood subscale and no significant difference was found over time. The analyses were then conducted separately for older and younger individuals with Cornelia de Lange syndrome on the Interest and Pleasure subscale score because significant differences were identified in the previous analysis between older and younger individuals with Cornelia de Lange syndrome on this subscale. No significant differences were found over time for either the younger (*15 years and below*) or older (*over 15 years*) group of individuals with Cornelia de Lange syndrome on the Interest and Pleasure subscale score.

These analyses show that only the Cri du Chat syndrome group experienced a significant change in scores over time, with a significant increase in mood evident over a two-year period.

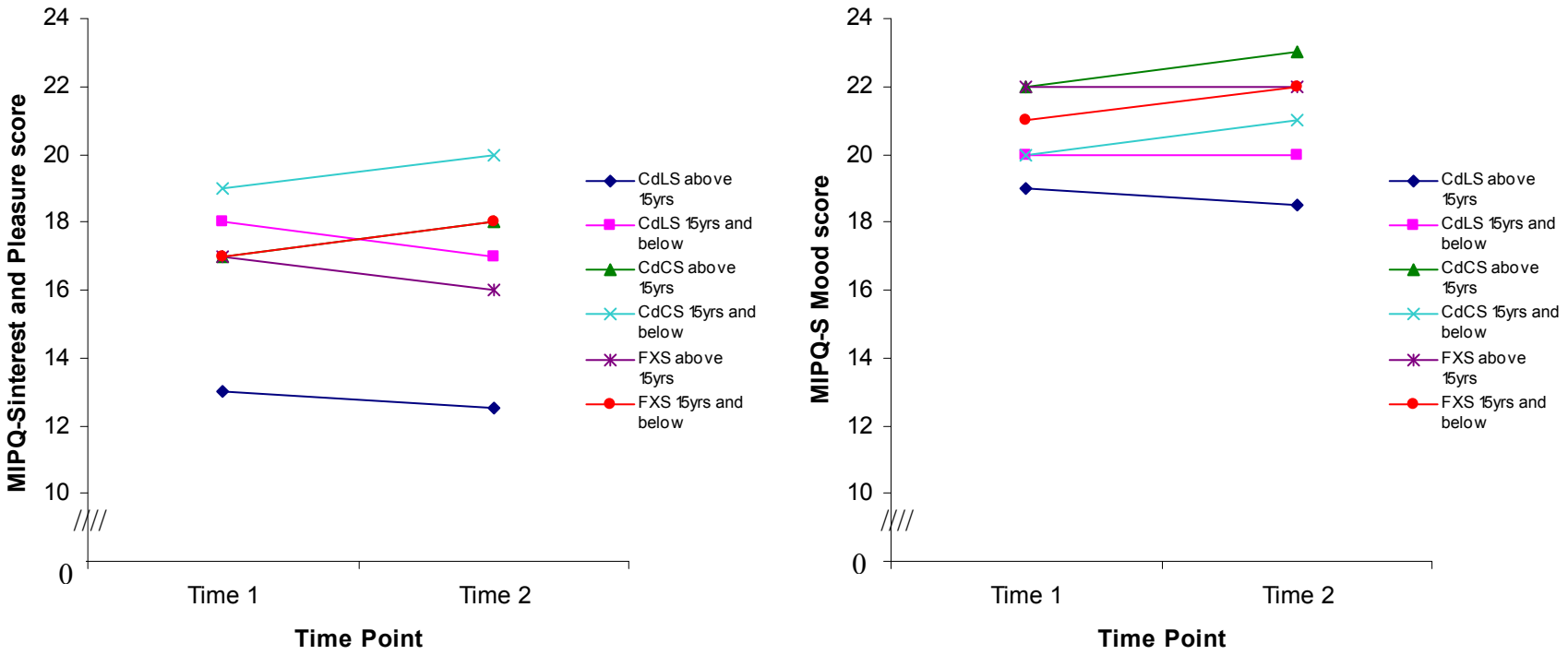


Figure 2.2: Median MIPQ-S subscale scores across time for older and younger individuals in each syndrome group.

2.5.1.4. Summary of Part one

In summary, the Cornelia de Lange syndrome group were reported to experience significantly lower mood, interest and pleasure than both the Cri du Chat syndrome and Fragile X syndrome groups at Time 1 and Time 2 (the difference between the Cornelia de Lange syndrome group and the Fragile X group for Interest and Pleasure at Time 2 approached significance). Older individuals with Cornelia de Lange syndrome obtained a significantly lower Interest and Pleasure subscale score than younger individuals with the syndrome. Older individuals with Cornelia de Lange syndrome also scored significantly lower on both subscale scores than the older Cri du Chat syndrome and Fragile X syndrome groups at Time 1 and Time 2. The only group to show a change in MIPQ-S scores over time was the Cri du Chat syndrome group, who showed a significant increase in mood over time.

2.5.2. Part two: Identifying a more specific age band during which individuals with Cornelia de Lange syndrome are most at risk of showing low levels of mood, interest and pleasure.

Figure 2.3 shows the median MIPQ-S subscale scores across the six age groups for the Cornelia de Lange syndrome group. This exploratory analysis revealed that individuals with Cornelia de Lange syndrome aged *19-22 years* obtained a significantly lower MIPQ-S Interest and Pleasure score than individuals aged *11 years and under* ($U = 12$, $p < .005$, $r = -.66$), *12 to 15 years* ($U = 22$, $p = .01$, $r = -.52$) and those aged *23 to 28 years* ($U = 22$, $p < .05$, $r = -.50$). Individuals aged *29 years and above* also obtained a significantly lower MIPQ-S Interest and Pleasure score than individuals aged *11 years and under* ($U = 19.5$, $p < .005$, $r = -.60$). Individuals with Cornelia de Lange syndrome aged *19-22 years* also obtained a significantly lower MIPQ-S Mood score than individuals aged *12 to 15 years* ($U = 29$, $p < .05$, $r = -.42$). Additionally, it is worth noting that another comparison approached significance; Individuals aged *19-22 years* obtained a lower mood score than individuals aged *11 years and under* ($U = 26.5$, $p = .05$, $r = -.43$). All differences reported for this analysis, including those that approached significance, demonstrated medium-to-large or large effect sizes reflecting the magnitude of these findings.

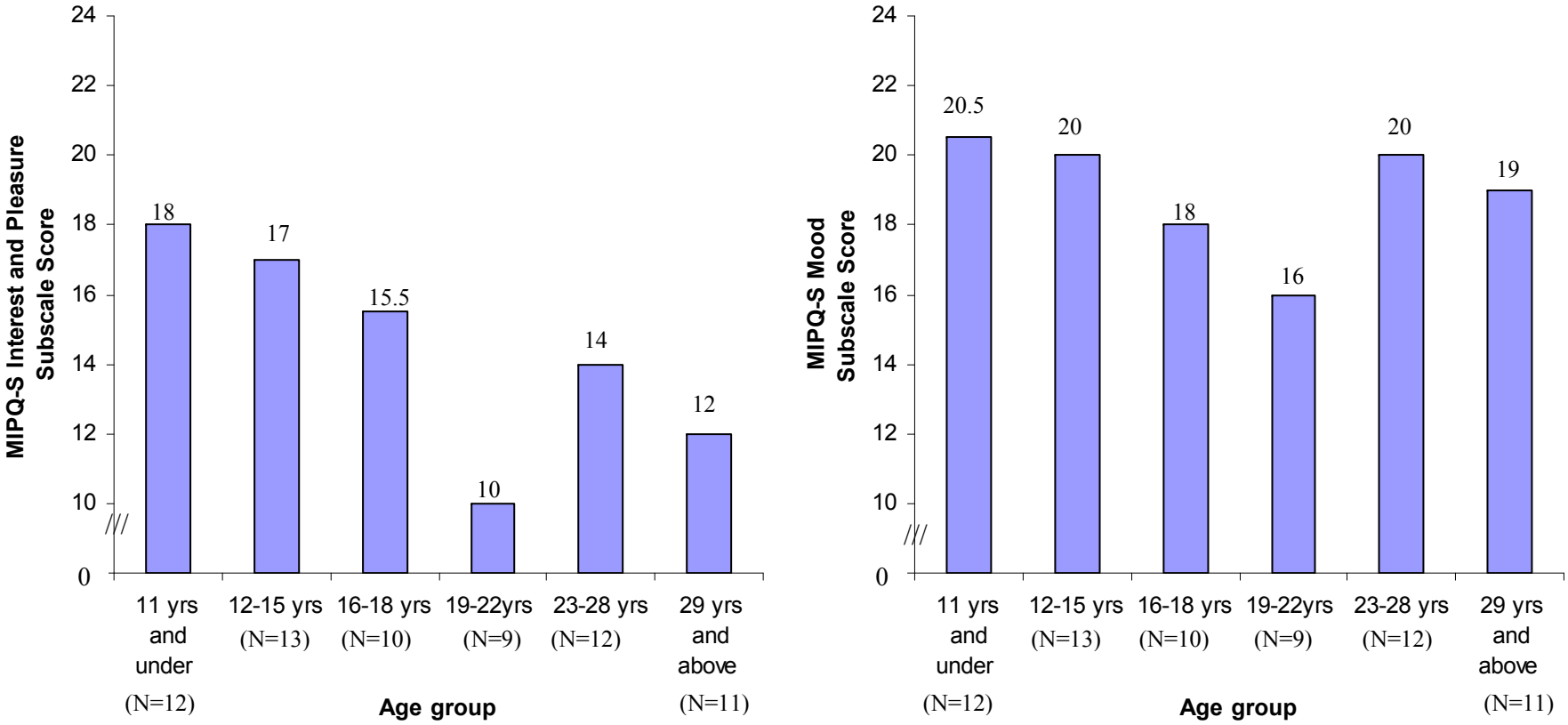


Figure 2.3: Median MIPQ-S subscale scores for the six age bands in the Cornelia de Lange syndrome group.

This analysis showed that individuals aged *19-22 years* showed significantly lower interest and pleasure than individuals in two younger age groups and one older age group; and showed significantly lower mood than one younger age group. Individuals in the *29 years and above* age group also showed significantly lower interest and pleasure than one of the younger age groups. It should be noted that caution must be exercised when interpreting these results due to the low numbers of participants in each age band.

2.5.3. Part three: What factors significantly predict mood, interest and pleasure in individuals with Cornelia de Lange syndrome?

Figure 2.4 shows differences between the low mood and high mood group with Cornelia de Lange syndrome on the predictor variables. A series of Mann-Whitney tests revealed that there were significant differences between the groups on the insistence on the sameness subscale score ($U = 117$, $p < .005$, $r = -.46$), total ASQ score ($U = 121.5$, $p < .05$, $r = -.34$) and age ($U = 124$, $p < .01$, $r = -.42$). The group of individuals with *low mood* showed significantly more insistence on the sameness, a greater number of Autism spectrum disorder-like impairments and were significantly older than individuals in the *high mood* group. A medium-to-large effect size was found for comparisons on both insistence on the sameness and age, demonstrating the strength of these significant findings. A comparison of the number of participants with low mood and high mood meeting the criteria for Autism was also conduced. 14 of 22 participants with low mood and 8 of 22 participants with high mood were reported to score above the cut-off for autism (total BSC score of 22 or above). A Chi-square test showed that there was no significant association between mood outcome and whether participants met the cut-off for autism.

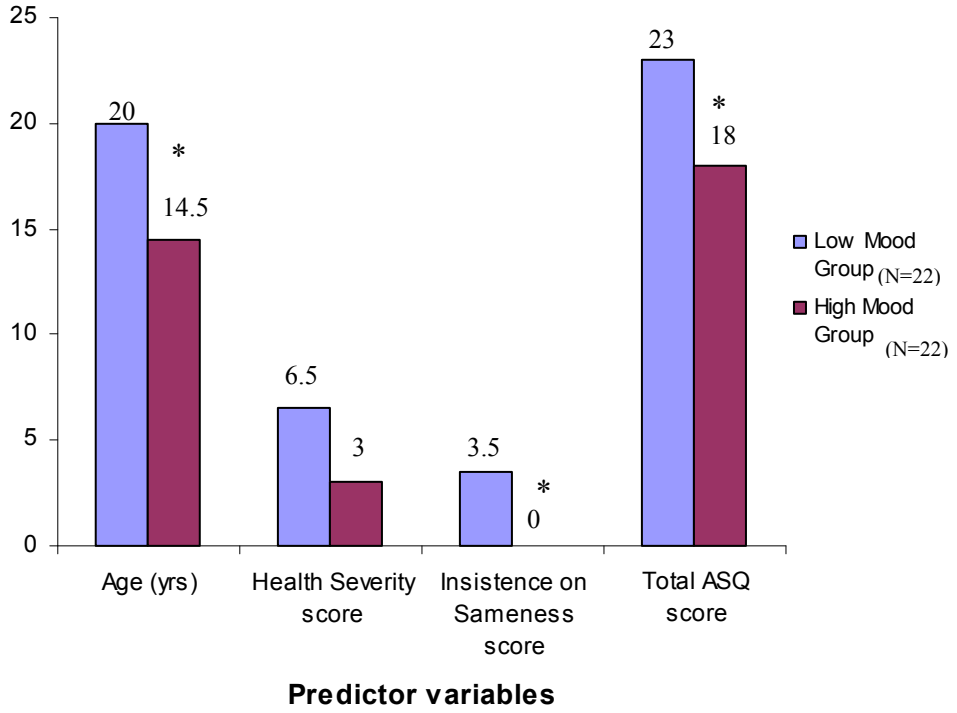


Figure 2.4: Median Age (yrs), Total Health Severity score, Insistence on the Sameness subscale score and Total ASQ score for the Low Mood and High Mood groups with Cornelia de Lange syndrome.

A binary logistic regression was then conducted to examine whether any of the four variables significantly predicted mood, interest and pleasure in the Cornelia de Lange syndrome group. The full model produced by the regression analysis was significantly reliable ($\chi = 15.96$, df = 4, $p < .005$). This model accounted for between 32.9% and 43.9% of the variance in mood, interest and pleasure scores. 80% of those with high mood were successfully predicted and 65% of those with low mood were successfully predicted. Overall, 72.5% of predictions were accurate, an increase of 22.5% in accuracy from a model without these factors. Insistence on the Sameness was identified as the only significant predictor of mood, interest and pleasure in participants with Cornelia de Lange

syndrome ($p < .05$); each unit increase in the Insistence on the Sameness score was associated with a decrease in the odds of high mood by a factor of .726.

2.6. DISCUSSION

This is the first case-control study to examine the trajectory of mood, interest and pleasure in individuals with Cornelia de Lange syndrome and two contrast groups using both cross-sectional and follow-up methodologies. The broad aim was to examine how mood, interest and pleasure differed between the three syndromes groups at both points in time and compare how their scores changed over a two-year period. Systematic comparisons were employed to determine whether low mood, interest and pleasure was specific to the Cornelia de Lange syndrome group and whether this was, broadly, age related. Using a more fine-grained analysis, the time period during which individuals with Cornelia de Lange syndrome specifically showed the lowest levels of mood, and interest and pleasure, was examined. This provided a more detailed picture of the developmental trajectory of mood, interest and pleasure in the syndrome. Finally, an examination of variables which may significantly predict mood, interest and pleasure in individuals with Cornelia de Lange syndrome, was undertaken. This study has a number of strengths including the use of appropriate psychometric assessments, the inclusion of appropriate, comparable contrast groups and a high rate of follow-up of participants.

Group comparisons of MIPQ-S scores, revealed that the Cornelia de Lange syndrome group scored significantly lower than both comparison groups on both subscale scores at Time 1 and Time 2, apart from on the Interest and Pleasure subscale at Time 2, where both the Fragile X syndrome and Cornelia de Lange syndrome group scored significantly lower than the Cri du Chat syndrome group. Further analysis showed that these differences were underpinned by low mood, interest and pleasure experienced by the older Cornelia de

Lange syndrome group. The Cornelia de Lange syndrome older age group (*over 15 years*) were reported to experience significantly lower mood; and interest and pleasure scores, than older individuals with both Fragile X syndrome and Cri du Chat syndrome. This difference was found at both time points so the difference was consistent over a two-year period. These findings suggest that low mood, interest and pleasure is characteristic of older individuals with the syndrome and provides support for other research published on mood in Cornelia de Lange syndrome. Kline et al. (2007) reported that 11% of a sample of 49 adolescents and adults with Cornelia de Lange syndrome were diagnosed with depression, indicating that low mood is a specific problem for older individuals with the syndrome. Furthermore, Berney et al. (1999) found an association between low mood and age in Cornelia de Lange syndrome. They reported the presence of a cyclical mood disturbance, as evidenced by a change in mood or behaviour lasting for weeks or months, in 27 % of participants with Cornelia de Lange syndrome, with 77% of those individuals being over 12 years old. The current findings, in line with previous research, suggest that low mood, interest and pleasure is characteristic of older individuals with the syndrome and supports the first two hypotheses proposed in the current study. These findings do show that it is important to understand low mood in Cornelia de Lange syndrome from a developmental perspective because the trajectory appears to change with age.

Further evidence of age-related differences comes from cross-sectional comparisons of mood, interest and pleasure scores between younger and older individuals in each syndrome group. The analyses revealed that only the Cornelia de Lange syndrome group showed significant differences between the two age groups. Older individuals with Cornelia de Lange syndrome were reported to experience significantly lower interest and

pleasure than the younger age group, whilst no significant difference was identified in mood. These results could be interpreted in different ways. First, individuals with Cornelia de Lange syndrome may show age-related differences in both mood, and interest and pleasure but each of these constructs has different developmental trajectories. It may be that individuals with Cornelia de Lange syndrome show a decline in mood before they show a decline in interest and pleasure, which is why no significant differences were found between the age bands on the mood subscale. Alternatively, there may be a decline in mood which is not as pronounced as the decline in interest and pleasure, which is again why there may be no significant difference between the older and younger age groups. Another explanation may be that both younger and older individuals with Cornelia de Lange syndrome experience consistently low mood, which is why no differences were found on the mood subscale. This may also explain why the younger Cornelia de Lange syndrome group were reported to have significantly lower mood than the younger Fragile X syndrome group.

A more fine-grained analysis of the data indicated that individuals with Cornelia de Lange syndrome experienced both lower mood; and interest and pleasure with age but the low levels of interest and pleasure was more pronounced. The *19-22 years* age group were reported to experience significantly lower interest and pleasure than two younger age groups, and significantly lower mood than one of the younger age groups. As a small n was employed, caution must be exercised when interpreting these results. Further research employing a larger sample size is needed. No previous research has sought to identify a specific time period when these age-related differences may occur in Cornelia de Lange syndrome but most evidence indicates that these differences become apparent in

adolescence or adulthood. Basile et al. (2007), for example, identified that in a group of individuals with Cornelia de Lange syndrome aged between 11 to 31 years, significantly more behavioural problems were associated with older individuals. However, the study did not specify the time period when individuals may be most vulnerable to these changes. Evidence from the pilot study suggested that the changes in mood occurred around late adolescence or early adulthood, which provides further support for the current findings (Collis et al., 2006). The results from the current study have provided evidence for low levels of mood, interest and pleasure around early adulthood in Cornelia de Lange syndrome and provide support for the third hypothesis.

The results from the current study reported so far have only referred to the cross-sectional comparisons so caution must be exercised when interpreting these results due to potential cohort effects. One cohort effect that may be relevant to the Cornelia de Lange syndrome group is the significant number of health problems associated with the syndrome, in particular gastro-oesophageal reflux (Luzzani et al., 2003). Research shows that there is a significant association between health problems and low affect (Berg et al., 2007). Individuals with a health problem have been found to be approximately three times more likely to experience low affect than those with no health problems (Berg et al., 2007). The number of health problems associated with Cornelia de Lange syndrome has only come to light in recent years so it may be that older individuals with Cornelia de Lange syndrome have undiagnosed health problems leading to low mood. This explanation may then account for the differences reported in mood between older and younger individuals with the syndrome. Although, this may have caused a potential cohort effect, it is unlikely to be the case given that Part Three of the analysis demonstrated that health problems did not

significantly predict mood, interest and pleasure in Cornelia de Lange syndrome (see below for further discussion). If health problems did account for the differences in mood between older and younger individuals with the syndrome, health problems would have significantly predicted the outcome for mood, interest and pleasure in the syndrome. Therefore, it unlikely, that any findings from the cross-sectional analysis are accounted for by cohort effects related to health problems.

The follow-up analysis of mood, interest and pleasure scores over the two-year period revealed that only the Cri du Chat syndrome group showed a change over time, with a significant increase in mood being reported at follow-up. This is an interesting as Oliver et al. (in review) also found that adults with Cri du Chat syndrome experienced significantly higher levels of abnormal positive affect (28.6%) compared to children with the syndrome (0%). It may be that this reported increase in mood with age is a protective factor for individuals with Cri du Chat syndrome and so this finding should be explored further in future research.

Individuals with Cornelia de Lange syndrome demonstrated no significant change in mood, interest and pleasure over time and therefore did not provide support for the fourth hypothesis. Older individuals with Cornelia de Lange syndrome (*over 15 years)* continued to experience low mood, interest and pleasure after a two-year follow-up period. This finding provides additional information which has not been previously reported in the literature by providing information about the stability of low mood in older individuals over this time period. Younger individuals with Cornelia de Lange syndrome showed no significant change in mood, interest and pleasure scores over the two-year period. This

was surprising given that the cross-sectional data indicated that there may be a decline in mood with age. It may be that the two-year follow-up period was not long enough to detect a significant change in mood, interest and pleasure for younger individuals with Cornelia de Lange syndrome. Furthermore, the younger age group consisted of all individuals under 15 years old. It may be that older individuals in this group showed changes in mood, interest and pleasure but this was masked by the fact that the youngest individuals showed no change over the two-year period. A longer follow-up is needed to fully explore the trajectory of mood, interest and pleasure over time and examine whether the trajectory is the same as that predicted by the cross-sectional analysis.

An investigation of the factors that significantly differentiated individuals with Cornelia de Lange syndrome with high mood and low mood revealed that the *low mood* group were reported to show significantly more insistence on sameness and a greater number of autism spectrum related impairments and were significantly older than individuals in the *high mood* group. It is unclear whether the differences seen in insistence on sameness also account for the differences found in number of Autism spectrum disorder impairments because insistence on the sameness is one of the impairments reported in Autism spectrum disorder. Given that the binary logistic regression showed that only insistence on the sameness was a significant predictor of mood, interest and pleasure in Cornelia de Lange syndrome, it would perhaps indicate that differences seen in insistence on sameness also account for the differences found in number of Autism spectrum disorder impairments.

The current findings suggest that insistence on sameness and age, are important factors contributing to mood outcome in Cornelia de Lange syndrome. These findings do provide

support for previous research, although the number of studies published on this area, are quite limited. There is evidence to suggest that individuals with Cornelia de Lange syndrome have a preference for routine/predictability and that changes in routine or unpredictable environments, may lead to episodes of low mood and a loss of interest in activities previously enjoyed (Collis et al., 2006; Jackson, 1992; Sarimski, 1997; Van Allen et al., 1993). For example, in a pilot study of nine adolescents and adults with Cornelia de Lange syndrome who were reported to show a change in mood and / or anxiety with age, all participants were also reported to have a strong preference for routine and found it 'difficult' coping with change (Collis et al., 2006). Interestingly, the onset of low mood was frequently reported to occur at a time of change in day or residential setting. Further support has been provided by a quantitative study, which demonstrated that 61.5% of participants with Cornelia de Lange syndrome became "upset" by changes in routine and this pattern of behaviour was significantly more prominent in older children with the syndrome (Sarimiski, 1997). The findings from the previous studies appear to demonstrate the equal importance of both age and insistence on the sameness when considering the causal mechanisms of low mood in the syndrome, whilst the findings in the current study appear to emphasise the importance of insistence on the sameness but also show that age is still an important factor that differentiates those with high mood and low mood. An explanation of why this may have occurred is provided below. The current findings in combination with previous research, perhaps suggest that both age and insistence on sameness are important factors which contribute to low mood in Cornelia de Lange syndrome.

An important consideration that needs to be taken into account when considering the factors contributing to mood outcome in Cornelia de Lange syndrome is whether insistence on sameness significantly predicts interest and pleasure because these variables are actually measuring the same construct. This may indeed be the case and needs exploring in future research. Even if this is the case, however, the fact that insistence on sameness is a more clearly, defined, observable behaviour is an important advancement in identifying the specific-age related changes observed in Cornelia de Lange syndrome. Therefore, rather than a general decline in interest and pleasure with age in Cornelia de Lange syndrome, it may be that there is a specific increase in insistence on sameness, which perhaps is underpinned by cognitive changes with age in the syndrome.

Several factors may limit the interpretation of the findings from the current study. First and foremost, the relatively short time period over which participants were followed-up limited the ability to draw conclusions about the developmental trajectory of mood, interest and pleasure over time. Furthermore, the sampling bias and the attrition rate at follow-up may mean that the results are not generalisable to the wider population of individuals with these syndromes. Despite this, the relatively large sample size recruited for the current study may to some extent help to resolve this issue. Finally, the current study only involved comparisons of median scores between groups. As clinical cut-offs were not used in the analysis, it was not possible to examine the proportion of individuals with Cornelia de Lange syndrome who actually experienced clinically significant low mood, which may have been useful in determining prevalence rates of low mood in the syndrome. A final, important consideration is the possibility that insistence on sameness was found to

significantly predict interest and pleasure in Cornelia de Lange syndrome because both variables measure the same construct.

Despite these limitations, the study has produced important research findings. It is the first follow-up study of mood, interest and pleasure in individuals with Cornelia de Lange syndrome, which provides important information about the stability of low mood, interest and pleasure in older individuals with Cornelia de Lange syndrome over a two-year period. The cross-sectional data from the study have also provided valuable information about the developmental trajectory of mood, interest and pleasure in individuals with Cornelia de Lange syndrome. The study is the first to identify that the vulnerable time period for individuals with Cornelia de Lange syndrome is between 19-22 years of age when individuals experience the lowest levels of mood, interest and pleasure. A consideration of the factors contributing to mood, interest and pleasure outcome in Cornelia de Lange syndrome have identified that both insistence on sameness and age are important factors which may affect mood outcome. Ultimately, the current findings do allude to a change in mood, interest and pleasure with age and give rise to the possibility that there are neurological changes occurring in the syndrome which underpin these emotional changes, especially given that the difference in mood, interest and pleasure appears to be part of a broader difference in behaviour and emotion with age (e.g., Oliver et al., in review). Further research examining the biological underpinnings of these differences is crucial to understand why this may be occurring. The current study has also demonstrated the importance of considering behaviours in genetic syndromes from a developmental perspective and understanding how the trajectory of behaviour may differ across syndromes and thus allow for the identification of atypical development.

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CHAPTER THREE

Sociability in Cornelia de Lange syndrome: A comparative study

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3.1. PREFACE TO CHAPTER THREE

The results from Chapter Two demonstrated a number of interesting findings that contribute to the literature on mood in Cornelia de Lange syndrome. The study provided further empirical evidence that low mood, interest and pleasure is characteristic of older adolescents and adults with Cornelia de Lange syndrome. The study was also the first to demonstrate that individuals aged between 19 years to 22 years experience the lowest levels of mood, interest and pleasure; and that levels of interest and pleasure appear lower than mood for these individuals.

By employing appropriate contrast groups, the study in Chapter Two was able to demonstrate that the age-related pattern of mood, interest and pleasure appears, at this stage, specific to Cornelia de Lange syndrome. Furthermore, as neither contrast group showed significant differences in mood, interest and pleasure between the age bands, it further suggests that the age-related pattern of mood, interest and pleasure in Cornelia de

Lange syndrome is atypical. This has not been clearly demonstrated in previous research. Apart from the original questionnaire study conducted by Oliver et al. (in review), there are no published case-control studies to show that the age-related pattern of mood in Cornelia de Lange syndrome is atypical. This research shows the importance of utilising appropriate contrast groups for empirical research.

The research to date on behaviour in Cornelia de Lange syndrome also suggests that there are other age-related changes. Kline et al. (2007a; 2007b) reported both behavioural and emotional changes in approximately 80% of individuals with Cornelia de Lange syndrome. Reported changes, included an increase in levels of depression, self-injurious behaviour, obsessive-compulsive behaviours, anxiety, aggression and hyperactivity. However, the absence of a contrast group means that it is difficult to determine whether these changes are syndrome-specific, how they might be related to other impairments, such as degree of disability, and whether these changes are atypical. Oliver et al. (in review) employed several comparable contrast groups in a recent cross-syndrome comparison and found a significant difference in the proportion of individuals with Cornelia de Lange syndrome showing impulsivity between childhood (10%) and adulthood (25%). It does seem therefore that the difference in mood, interest and pleasure between children and adolescents and adults with Cornelia de Lange syndrome is part of a broader difference in emotion and behaviour that is characteristic of the syndrome (Basile et al., 2007; Blagowidow et al., 2005; Oliver et al., in review).

A pilot study conducted with adolescents and adults with Cornelia de Lange syndrome found that two changes particularly evident in Cornelia de Lange syndrome were a decline

in mood and an apparent increase in indicators of social anxiety (Collis, Oliver & Moss, 2006). Research on sociability remains very limited in Cornelia de Lange syndrome. In part, this may be due to the lack of suitable measures for examining sociability in individuals with a range of intellectual disabilities. An examination of the age-related pattern of sociability in Cornelia de Lange syndrome in relation to other comparable contrast groups is needed to understand whether there are social impairments related to social anxiety in Cornelia de Lange syndrome and also understand whether these impairments are age-related. The collection of quantitative information on a large number of individuals with Cornelia de Lange syndrome is needed. Therefore, a questionnaire study involving a number of groups seems to be the first appropriate step in understanding the age-related pattern of social impairments in Cornelia de Lange syndrome.

3.2. ABSTRACT

3.2.1. Background: Recent evidence suggests that there is a heightened probability of extreme shyness and social anxiety in Cornelia de Lange syndrome, however, there is little empirical evidence (e.g., Collis et al., 2006). A lack of suitable measures for assessing sociability in individuals with intellectual disabilities, has perhaps contributed to the lack of empirical case-control studies examining sociability. The current study describes the development of a measure of sociability for individuals with intellectual disabilities. This will then be used to examine sociability in Cornelia de Lange syndrome.

3.2.2. Method: The Sociability Questionnaire for People with Intellectual Disabilities (SQID) was developed to measure sociability in people with a range of intellectual disabilities. The SQID was administered to caregivers of individuals with Cornelia de Lange syndrome (n = 98), Angelman syndrome (n = 66), Fragile X syndrome (n = 142), Down syndrome (n = 117), Rubinstein Taybi syndrome (n = 88) and Autism spectrum disorder (n = 107). Each group was subdivided into three age bands (under 12yrs; 21-18yrs and over 18yrs). SQID total and subscale scores were compared across the groups as a whole and then a more fine-grained analysis was conducted between individuals in each age band. Prevalence rates of extreme sociability, extreme shyness and selective mutism were also examined across the groups.

3.2.3. Results: The Cornelia de Lange syndrome group showed similar levels of sociability to individuals with Autism spectrum disorder in unfamiliar social situations, with significantly more shyness being reported in all unfamiliar social situations than the

Angelman, Down and Rubinstein Taybi syndrome groups. Extreme shyness appeared characteristic of individuals with Cornelia de Lange syndrome with prevalence rates of extreme shyness in four unfamiliar situations ranging from 14.4% to 24.5%. Individuals with Cornelia de Lange syndrome aged between *12-18 years* were reported to show significantly less initiating behaviour with unfamiliar people than the *under 12 years* age group. The Cornelia de Lange syndrome group were also reported to show the highest rate of selective mutism (approximately 40%).

3.2.4. Conclusion: Adolescents and adults with Cornelia de Lange syndrome appear to experience a characteristic shyness with unfamiliar people that may be part of a broader difficulty in emotion and behaviour. The results allude to a change in the age-related pattern of sociability with unfamiliar individuals, with age in Cornelia de Lange syndrome. Further investigations are needed to understand the unusually high prevalence of selective mutism in Cornelia de Lange syndrome.

3.3. INTRODUCTION

The literature on behavioural phenotypes has expanded significantly over the past 20 years with notable interest in areas, such as, the presence of Autism spectrum disorder in a number of genetic syndromes (Moss & Howlin, 2009). This interest in Autism spectrum disorder has linked research describing the phenomenology of behavioural and cognitive phenotypes of genetic syndromes with basic cognitive research on Autism spectrum disorder and the wider typically developing literature. This has been particularly evident in the research undertaken on theory of mind and executive function impairments in genetic syndromes, which has directly contributed to theories about typical and atypical development of these domains and their underlying role in social functioning (e.g., Grant, Apperly & Oliver, 2007). However, alongside this growing interest in social cognition, relatively little attention has been paid at a behavioural level to the phenomenology of sociability in genetic syndromes.

The term sociability is an umbrella term encompassing various aspects of social functioning and is often undefined in the literature (Cook, 2009). Similarly, the constructs which fall under or are related to the term of sociability (e.g. social cognition, social behaviour, social skills, social competence, social functioning) are frequently used interchangeably within the literature and without reference to a definition, which makes comparisons across research difficult (e.g., Matson & Wilkins, 2007). In the current study, only observable, behavioural indicators of sociability, based on the previous literature, will be examined in a specific number of social situations (initiate interaction, ongoing interaction, being approached by another person and behaviour in a group situation) (see

section 3.4.2.4.1.). This is so that sociability can be objectively examined in relevant social situations for individuals with a range of intellectual disabilities.

Although sociability is a relatively under-researched area, there are detailed descriptions published of several genetic syndromes which have striking social profiles. At one end of the spectrum are genetic syndromes, such as, Williams and Angelman syndromes, each of which are associated with heightened levels of sociability (e.g., Doyle, Bellugi, Korenberg & Graham, 2004; Jones et al., 2000; Oliver et al., 2007). Individuals with Angelman syndrome, for example, are considered to show extremely high levels of laughing and smiling during social interactions and also show social approach behaviours (Horsler & Oliver, 2006b; Strachan et al., 2009). This excessive sociability appears to be independent of degree of disability given that most individuals with Angelman syndrome have a severe or profound intellectual disability. At the other end of the spectrum are Fragile X and Turner syndromes which evidence extreme and potentially clinically significant levels of shyness and social anxiety (Hall et al., 2006; Hessl et al., 2006; Lesniak-Karpiak, Mazzocco & Ross, 2003). Some individuals with Fragile X syndrome have also been reported to show selective mutism, which is considered to be an extreme manifestation of social anxiety (Hagerman, Hills, Scharfenaker & Lewis, 1999).

Cornelia de Lange syndrome is a comparatively less well-researched syndrome and there is relatively little information on sociability in individuals with this syndrome. Some evidence suggests that there is a heightened probability of social impairments associated with the syndrome (Sarimski, 1997). The literature to date has presented a somewhat mixed picture about the phenomenology of social impairments. Some research findings suggest that the social impairments are similar to that seen in individuals with Autism

spectrum disorder. Individuals with Autism spectrum disorder show characteristic social deficits, such as a lack of social reciprocity, that form part of the triad of impairments (Kanner, 1943; Wing & Gould, 1979). Johnson et al. (1976), for example, recorded the behavioural responses of nine children with Cornelia de Lange syndrome to various interactions with familiar and unfamiliar adults and found that seven of the nine participants displayed more negative responses than positive responses to *both* familiar and unfamiliar adults. The authors concluded that individuals with Cornelia de Lange syndrome are "non-social" and refrain from physical contact with other people. A further study by Sarimski (1997) also found that individuals with Cornelia de Lange syndrome showed social impairments typical of those with Autism spectrum disorder; 50% of participants showed abnormal eye contact and 54% were reported to be isolated as if in their own world. Together, these studies would suggest that social impairments in Cornelia de Lange syndrome are similar to those seen in Autism spectrum disorder. However, the methodological issues associated with both of these studies, such as, a lack of a comparison group and the absence of psychometrically sound assessments, means that it is difficult to identify whether these impairments are typical of individuals with Cornelia de Lange syndrome or are just an artefact of the degree of disability associated with the syndrome (see chapter 1 for discussion of the methodological issues).

A number of recent studies have considered the prevalence of Autism spectrum disorder in Cornelia de Lange syndrome in more detail, using appropriate comparison groups. Prevalence estimates range between 47% and 61.8% (Basile, Villa, Selicorni & Molteni, 2007; Berney, Ireland & Burn, 1999; Moss et al., 2008; Oliver et al., 2008). These rates are significantly higher than those seen in individuals without Cornelia de Lange

syndrome, who have a similar degree of intellectual disability (e.g., Moss et al., 2008; Oliver et al., 2008; Oliver et al., 2009). To date, only one study has conducted a fine-grained analysis of the phenomenology of Autism spectrum disorder in Cornelia de Lange syndrome, using a psychometrically sound assessment (Moss et al., 2008). Moss et al. (2008) found that individuals with Cornelia de Lange syndrome presented with an atypical profile of Autism spectrum disorder. Individuals showed significant deficits in the domain of communication with a significantly higher proportion of individuals with Cornelia de Lange syndrome scoring above the cut-off for communication impairments than individuals in a matched contrast group. Individuals with Cornelia de Lange syndrome showed no significant impairments in the domain of social interaction suggesting that the social impairments in Cornelia de Lange syndrome are unrelated to those seen in Autism spectrum disorder. Anecdotal evidence from the study described several participants with Cornelia de Lange syndrome as having social impairments that were not typical of the impairments seen in Autism spectrum disorder. Participants with Cornelia de Lange syndrome were described as showing extreme shyness, selective mutism and social anxiety. These findings indicate that when a robust methodology is employed, social impairments typical of those with Autism spectrum disorder are *not* present. Instead, individuals with Cornelia de Lange syndrome may show impairments that are typical of social anxiety. While individuals with Autism spectrum disorder do show an increased prevalence of social anxiety compared to the typically developing population, it is not considered to be a core feature of the social impairments that are diagnostic of the disorder (Bellini, 2004; Gillott et al., 2001).

There is some evidence, particularly in the more recent literature on Cornelia de Lange syndrome, that social anxiety may be a significant social impairment experienced by individuals with the syndrome. Goodban (1993) reported that nearly all of 116 participants with Cornelia de Lange syndrome, including those with a more well-developed vocabulary, were "unusually quiet and talked very little". A report published on 49 individuals with Cornelia de Lange syndrome found that 40% of individuals with the syndrome were "quiet, shy and retiring" (Kline et al., 2007a). Arron et al. (2006) examined the environmental impact of adult attention on social communicative behaviours in Cornelia de Lange syndrome by assessing how social initiation and social avoidance differed between conditions of adult attention and conditions of no attention. The study found that fourteen of sixteen participants with Cornelia de Lange syndrome showed social avoidance behaviours. To date only one experimental case control study has been published on social anxiety in Cornelia de Lange syndrome (Richards, Oliver, Moss, O'Farrell & Kaur, 2009). Three behavioural indicators of social anxiety in response to two sets of social interactions with an unfamiliar adult were examined in twelve children with Cornelia de Lange syndrome and twelve matched children with Cri du Chat syndrome. Children with Cornelia de Lange syndrome were found to show significantly more hand movements, indicative of anxiety, and less eye contact at times of social interaction in comparison to the Cri du Chat syndrome group.

A pilot study involving a series of open-ended interviews with caregivers of nine adolescents and young adults with Cornelia de Lange syndrome who were experiencing periods of low mood and/or increased levels of anxiety provided preliminary evidence of increasing social anxiety with age (Collis, Oliver & Moss, 2006). Participants were

reported to show the following indicators which may relate to social anxiety: a reluctance to speak to unfamiliar people (9/9), preferring to watch peers rather than join in with their activities (8/9), having one or two good friends rather than lots of friends (7/9), experiencing selective mutism (6/9), appearing very shy (6/9) and being reluctant to speak in a group setting (6/9). These findings provide preliminary evidence for social anxiety being prevalent in adolescents and adults with Cornelia de Lange syndrome.

These findings have also been supported by quantitative research, although the quantitative research has tended to focus on anxiety generally rather than on social anxiety. In a sample of 49 adolescents and adults with Cornelia de Lange syndrome, anxiety was diagnosed in 33% (Kline et al., 2007a). Basile, Villa, Selicorni & Molteni (2007) found a significant correlation between chronological age and behavioural problems, including communication disturbances and anxiety. Furthermore, Sarimski (1997) compared behaviour in older (above 6 years) and younger children (below 6 years) with Cornelia de Lange syndrome and found that older children experienced significantly more social isolation and anxiety. Although it is unknown what proportion of these participants experienced social anxiety, the study clearly demonstrates the higher prevalence of anxiety in older children and adolescents with the syndrome. From the limited evidence available, it seems that the social impairments reported in Cornelia de Lange syndrome appear to show a similar age-related pattern to the impairments in mood, interest and pleasure identified in Chapter Two. Therefore, it is important to understand social impairments in Cornelia de Lange syndrome from a developmental perspective and understand how sociability changes with age so that it is possible to identify the extent to which the age-related pattern of sociability in Cornelia de Lange syndrome might be atypical.

When describing the age-related pattern of behaviour in syndromes (as mentioned in Chapter Two), it is important to use appropriate contrast groups, in order to examine the specificity of an age-related pattern of sociability in a genetic syndrome and also determine whether the age-related pattern is typical or atypical of what would be expected given the associated intellectual disability. In the current study, five contrast groups will be utilised: individuals with Angelman syndrome, Fragile X syndrome, Down syndrome, Rubinstein Taybi syndrome and Autism spectrum disorder. Four of the contrast groups have been chosen because they show a broad range of social profiles. Angelman and Down syndromes have been chosen because they represent groups, which lie on one end of the spectrum towards that of increased or typical sociability, whereas Fragile X syndrome and Autism spectrum disorder have been chosen because they should lie towards the other end of the spectrum of extreme shyness (Bellini, 2004; Hall et al., 2006). Rubinstein Taybi syndrome has been chosen because it is a relatively undescribed group, although some reports indicate that increased sociability is associated with the syndrome (Gotts & Liemohn, 1977; Hennekam et al., 1992). Using these five contrast groups will help to determine the face validity of the questionnaire, by examining whether the groups that have been reported to show increased sociability lie at one end of the spectrum and the groups reported to show social anxiety lie at the other end of the spectrum. Furthermore, by examining differences across the age bands in all the groups, it will be possible to examine the age-related pattern of sociability across each group and determine how the trajectories differ across the six groups.

The current lack of appropriate measures of sociability in individuals with intellectual disabilities has limited the research that can be undertaken in this population; consequently research has tended to focus on more able individuals. There has been one measure of sociability developed to date for people with intellectual disabilities. The Salk Institute Sociability Questionnaire (SISQ; Jones et al., 2000) was developed to assess aspects of sociability commonly reported in Williams syndrome, a genetic syndrome associated with a mild to moderate intellectual disability. The SISQ examines approach behaviour with familiar people, approach behaviour with unfamiliar people and social emotional behaviour. The tool specifically focuses on aspects of sociability that are characteristic of individuals with Williams syndrome and, currently, no psychometric properties have been reported. Consequently, this tool may not be appropriate for examining sociability across all individuals with intellectual disabilities.

Although there are general measures of psychopathology in individuals with intellectual disability, no measure exists to specifically examine social anxiety in individuals with intellectual disabilities (see section 1.8.5.). The Glasgow Anxiety Scale (Mindham & Espie, 2003) has been developed to measure anxiety in individuals with a mild intellectual disability but it examines anxiety globally rather than examining specific forms of anxiety, such as social anxiety. Also, the self-report nature of the questionnaire limits its applicability to individuals with severe intellectual disability. The assessments available for individuals with intellectual disabilities contrasts significantly with the number of reliable and valid scales solely focusing on sociability or social anxiety in the typically developing population (both children and adults). Examples include the Social Anxiety Scale for Children-Revised (SASC-R; La Greca & Stone, 1993), the Social Phobia and

Anxiety Inventory for Children (SPAI-C; Beidel et al., 1995) and the Social Phobia and Anxiety Inventory (SPAI; Turner, Biedel & Dancu, 1995) (see section 1.8.3. for the assessment of social anxiety in typically developing children).

It is evident that a measure of sociability is clearly needed for the intellectual disability population. In order to examine the varying profiles of sociability in individuals with genetic syndromes, the measure would have to be able to report hypersociability at one extreme in order to assess profiles similar to those seen in Williams and Angelman syndromes. The measure would also need to assess social anxiety at the other end of the spectrum, such as that seen in Fragile X syndrome. A measure that encompasses both extremes of the sociability continuum would allow comparisons to be conducted on sociability across several genetic syndromes in order to determine the specificity of hypersociability or social anxiety in a particular syndrome. When developing such a questionnaire, it is also important to ensure that it is suitable for individuals with a range of intellectual disabilities. Therefore, it would be important to develop an informant-based questionnaire given the limitations or absence of verbal communication skills in individuals who are severely or profoundly affected and/or have poor expressive communication. When developing an informant-based questionnaire, it is also important to ensure that the measure is based on observable behaviours that have clear operational definitions so that it remains an objective and reliable measure.

The development of the measure should also assess selective mutism, which is a "consistent failure to speak in specific social situations (in which there is an expectation for speaking, e.g., at school) despite speaking in other situations" because the majority of

literature on selective mutism proposes that it is an extreme form of social anxiety (American Psychiatric Association, 2000; Black & Uhde, 1995; Kristensen, 2000; Manassis et al., 2007; see section 1.7.3.). For example, Black & Uhde (1992) found that nearly all (97%) participants with selective mutism in their study experienced social anxiety, avoidant disorder, or both. Recently, there have been questions raised about the strength of the association between selective mutism and social anxiety because not all children with social anxiety have selective mutism and individuals who have recovered from social anxiety still show selective mutism (Bruce, 1996). Some evidence has been published recently indicating that selective mutism may be a simple phobia of the speaker's own speech (Omdal & Galloway, 2008). The authors suggest that as a result of selective mutism, individuals may become socially isolated and then develop social anxiety. Therefore, social anxiety is proposed to be secondary to selective mutism. This study did not employ a quantitative methodology so it is difficult to determine whether this is the case as no further studies have been conducted to investigate this theory.

Another recent study has also found that children with selective mutism had significant deficits in visual memory in comparison to two contrast groups and in nonverbal working memory in comparison to one of the contrast groups, although this was not consistent across all the non-verbal measures (Manassis et al., 2007). This evidence may indicate that specific executive functioning deficits are implicated in the cause of selective mutism. Given the evidence to date, there does still seem to be a strong association between selective mutism and social anxiety. Investigating selective mutism in atypical populations may also shed some light on the relationship between selective mutism and social anxiety in the typically developing population. In the current study, a reliable

measure of sociability in individuals with a range of intellectual disabilities will be developed. It will identify individuals who show both extreme shyness and extreme sociability at either end of the spectrum. The measure will also be used to screen for individuals who may show selective mutism.

No study to date has conducted a comparison of sociability across several syndrome groups and examined the specificity of social profiles across the groups. The current study will be the first to develop a reliable measure of sociability for individuals with a range of intellectual disabilities and examine the specificity of differing profiles of sociability across a number of syndrome groups and examine whether social anxiety is a specific characteristic of individuals with Cornelia de Lange syndrome. Cut-offs of extreme sociability and extreme shyness will be generated to provide a clearer idea of the proportions of individuals in each group that are at either end of the spectrum. The rate of selective mutism will also be examined in each group, in addition to its relationship with social anxiety. Furthermore, a detailed analysis of sociability across individuals in different age groups will provide important information about the different trajectories of sociability across the groups and help to determine whether individuals with Cornelia de Lange syndrome show an 'atypical' decline in sociability with age that is not evident in the contrast groups.

The study has three aims:

1. To develop a reliable measure of sociability in both children and adults with a range of intellectual disabilities. The measure will identify extreme sociability at one of the spectrum and extreme shyness at the other end of the spectrum.
2. To document levels of sociability and selective mutism in Cornelia de Lange syndrome by using five contrast groups (Angelman syndrome, Fragile X syndrome, Down syndrome, Autism spectrum disorder and Rubinstein Taybi syndrome) as a comparison.
3. To examine the age-related pattern of sociability in Cornelia de Lange syndrome by using the same five contrast groups as a comparison.

3.4. METHOD

3.4.1. Participants

All groups were recruited as part of a larger follow-up questionnaire study, which took place between 2006 and 2007. The Cornelia de Lange syndrome, Fragile X syndrome and Angelman syndrome groups had taken part in the questionnaire study at Time 1 between 2003 and 2004 and were being followed up in the larger study (Arron et al., in review; Moss et al., 2009; Oliver et al., in review). Other groups (Cri du Chat, Lowe, Smith-Magenis syndromes and a group of individuals with a mixed aetiology of intellectual disabilities) also took part in the larger follow-up but were not included in the current study. In the questionnaire study at Time 1, the Cornelia de Lange syndrome group were recruited in two ways. 142 carers of individuals with Cornelia de Lange syndrome, who had been involved in previous research with the research team, 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) who had not taken part in previous research were contacted via the Foundation and invited to take part in the study. Individuals with Angelman syndrome (n = 320) and Fragile X syndrome (n = 762) were invited to take part via the relevant syndrome support groups. Individuals with Angelman syndrome were contacted through the Angelman Syndrome Support Education Research Trust and individuals with Fragile X syndrome were contacted through the Fragile X Society. 116 individuals with Cornelia de Lange syndrome, 121 individuals with Angelman syndrome and 211 individuals with Fragile X syndrome returned questionnaires for the study at Time 1.

These participants were then invited to take part in the current study if they had given consent in the previous study to be contacted about future research. Seven caregivers (Cornelia de Lange syndrome (N=2), Fragile X syndrome (N=2) and Angelman syndrome (N=3) did not agree to take part in future research. Additionally, two caregivers (Fragile X syndrome (N=1) Angelman syndrome, (N=1) agreed to take part in future research but did not provide contact details to be invited for future research. An additional 66 individuals with Cornelia de Lange syndrome who had taken part in other research projects with the research team but had not taken part in the questionnaire study at Time 1, were also invited to take part in the current study. In total, 180 individuals with Cornelia de Lange syndrome, 208 individuals with Fragile X syndrome and 117 individuals with Angelman syndrome, were invited to participate in the current study.

Individuals with Down syndrome, Rubinstein Taybi syndrome and Autism spectrum disorder were recruited through the relevant family support groups. 500 families were approached through the Down Syndrome Association, 202 families were approached through the Rubinstein-Taybi Syndrome UK Support group and 1467 families were approached through eight branches of the National Autistic Society around London and the West Midlands. See Table 3.1. for further details regarding recruitment.

Table 3.1: The number of individuals from each group who were invited to take part in the current study, the percentage return rate of questionnaires and the number of participants who met the inclusion criteria for the current study.

	CdLS	AS	FXS	DS	RTS	ASD	Total
No. of participants invited to take part in current study [a, b]	180	117	208	500	202	1467	2674
No. of questionnaires returned [c]	106	74	149	141	104	288	862
% return rate at Time 2	58.89	63.25	71.63	28.20	51.49	19.63	(mean: 48.84)
No. of participants who met the inclusion criteria for current study	98	66	142	132*	88	175**	701
No of participants included in data analysis	98	66	142	117	88	107	618

* 15 participants from the Down syndrome group were randomly excluded because the *19 years and over* group was much larger than in the comparison groups.
**68 participants from the Autism spectrum disorder group were randomly excluded because the *under 12 yrs* group was much larger than in the comparison groups.

Participants were included in the current study if they met the following criteria: confirmed diagnosis from an appropriate professional (a paediatrician, a clinical geneticist); no additional chromosomal abnormalities (other that those due to the syndrome); completion of information regarding age or date of birth; aged four years or over. Individuals had to be at least four years old because either the Autism Screening Questionnaire (Berument et al., 1999) or the Social Communication Questionnaire (Rutter et al., 2003) were included in the questionnaire pack and both questionnaires contain items regarding the participant's behaviour when aged between four and five years. 862 caregivers completed and returned the questionnaire packs and the mean percentage return rate across the six groups was 48.84%.

618 participants met the inclusion criteria for the study and were included in the data analysis. The group comprised 98 participants with Cornelia de Lange syndrome, 66 participants with Angelman syndrome, 142 participants with Fragile X syndrome, 117 participants with Down syndrome, 88 participants with Rubinstein Taybi syndrome and 107 participants with Autism spectrum disorder.

Table 3.2 shows participant characteristics across the six groups. The groups were compared statistically on a number of demographic variables ($p < .005$ was used to identify a significant difference). All participants were aged between 4 and 62 years and 65.7 % of the sample was male. There were significantly more males in the Fragile X syndrome group because only males were recruited for the original questionnaire study due to variability in the phenotypic characteristics between males and females with the syndrome. There were also significantly more males in the Autism spectrum disorder group than in the other comparison groups. The Fragile X syndrome, Autism spectrum disorder, Down syndrome and Rubinstein Taybi syndrome groups were significantly more able than the Angelman and Cornelia de Lange syndrome groups. This was evident in domains such as, self help skills, mobility and speech. The Fragile X syndrome group and Down syndrome group appeared to be the most able of all the groups. Significantly more vision and hearing impairments were reported in the Cornelia de Lange syndrome and Down syndrome groups than the Angelman syndrome, Fragile X syndrome, Rubinstein Taybi syndrome and Autism spectrum disorder groups.

Table 3.2: Participant characteristics across the six groups.

		CdLS	AS	FXS	DS	RTS	ASD	F / χ^2	df	*P*	Post hoc analyses
N*		98	66	142	117	88	107				
Age (years)	Mean	18.8	15.1	19.8	22.6	19.2	13.8	11.9	5	<.0001	CdLS, DS, FXS, RTS > ASD; DS>AS
	(SD)	8.7	8.7	8.6	13.0	10.6	6.3				
	Range	4-43	4-48	9-49	4-62	4-49	4-45				
Gender [a]	% Male	45.9	50	100	42.4	55.6	82.2	145.2	5	<.0001	FXS > ASD> CdLS, AS, DS, RTS
Self Help [b]	% Partly able / able [c]	48	45.5	95.1	92.3	76.7	88.8	138.0	5	<.0001	FXS, DS, RTS, ASD > CdLS, AS; FXS, DS > RTS
Mobility [b]	% Fully Mobile [d]	66	52.3	97.8	91.5	78.4	95.3	106.0	5	<.0001	FXS, DS, ASD > CdLS, AS; FXS, ASD > RTS > AS
Vision [b]	% Normal [e]	66	87.9	92.9	63.2	52.9	92.5	67.8	5	<.0001	AS, FXS, RTS, ASD > CdLS, DS
Hearing [b]	% Normal [f]	58.2	100	96.5	66.1	84.4	94.4	108.0	5	<.0001	AS, FXS, RTS, ASD > CdLS, DS; AS, FXS > RTS
Speech [g]	%Verbal	46.9	3	92.4	93.2	73.7	88.8	260.3	5	<.0001	FXS, DS, RTS, ASD> CdLS > AS; FXS, DS > RTS
ASQ / SCQ [h]	Mean score [i]	20.3	16.9	20.6	10.2	16.8	28.4				
	(SD)	6.5	4.9	6.0	7.0	5.7	3.9				

* N may vary due to missing data

[a] Females with FXS were excluded from the study because the syndrome characteristics vary between males and females in the syndrome (Dykens *et al*., 2000).

[b] Information obtained from the Wessex Scale (Kushlick *et al.*, 1973).

[c] Partly able/able if obtain a score of six or above on the self help sub-scale (QG-I).

[d] Fully mobile if obtain a score of three on QF. The mobility sub-scale (QE+QF) from the Wessex Scale (Kushlick *et al.*, 1973) was not used because we noted that there were a high proportion of people answering QE incorrectly.

[e] Normal if score three on QJ.

[f] Normal if score three on QK.

[g] Information obtained from item three of the Demographic questionnaire. If this item had not been completed for participants, question one from the ASQ or SCQ was used.

[h] All groups apart from the Autism spectrum disorder group were screened for autism using the Autism Screening Questionnaire (ASQ). The Autism spectrum disorder group were assessed using the Social Communication Questionnaire (SCQ).

[i] The groups were not compared statistically on the measure of autism spectrum disorder because two different measures were used across the six groups.

3.4.2. Measures

The measures utilised for this study included: the Demographic questionnaire, the Sociability Questionnaire for People with Intellectual Disabilities (SQID, unpublished; see *Appendix A6*); the Wessex Scale (Kushlick, Blunden & Cox, 1973) and the Autism Screening Questionnaire (Berument et al., 1999) or the Social Communication Questionnaire (SCQ, Rutter, Bailey, Berument, Lord & Pickles, 2003; see *Appendix A5*)[1].

3.4.2.1. Demographic Questionnaire

The Demographic Questionnaire (see *Appendix A1*) was developed for this study and used to obtain background information about each participant. For the current study, only information regarding age, gender and diagnostic status (whether by whom a diagnosis had been made) was used.

3.4.2.2. The Wessex Scale (Kushlick, Blunden & Cox, 1973)

The Wessex Scale is an informant based questionnaire designed to examine social and physical abilities of children and adults with intellectual disability. Subscales include continence, mobility, self help skills, speech and literacy. Additional questions regarding vision and hearing are also included in the questionnaire. Informants complete ratings based on a three point scale for each question (apart from a question regarding speech

[1] All groups apart from the Autism spectrum disorder group received the Autism Screening Questionnaire (Berument et al., 1999), which is the unpublished version of the Social Communication Questionnaire (Rutter et al., 2003). The Autism spectrum disorder group was sent the Social Communication Questionnaire (Rutter et al., 2003).

comprehensibility). The Wessex scale has good inter-rater reliability at subscale level for both children and adult with intellectual disabilities (Kushlick et al., 1973; Palmer & Jenkins, 1982).

3.4.2.3. The Social Communication Questionnaire[2] (SCQ; Rutter et al., 2003)

The Social Communication Questionnaire (see *Appendix A5*) is a 40-item questionnaire that screens for characteristics associated with autism and Autism spectrum disorder. All items are scored on a yes/no basis and a score of one is given for the presence of abnormal behaviour and a score of zero is given for its absence. A total score is obtained by summing across items. Three subscales, which represent the triad of impairments, can also be calculated. The subscales are: Social Interaction, Communication and Repetitive Behaviour. A cut-off of 15 is used to screen for the presence of Autism spectrum disorder and a cut-off of 22 is used to screen for autism. The questionnaire demonstrates good psychometric properties, with good sensitivity and specificity, good internal consistency and good concurrent validity with the Autism Diagnostic Observation Schedule and the Autism Diagnostic Interview (Berument et al., 1999; Howlin & Karpf, 2004).

3.4.2.4. The Sociability Questionnaire for People with Intellectual Disabilities (SQID; unpublished)

The Sociability Questionnaire for People with Intellectual Disabilities (SQID; see *Appendix A6*) was developed for the current study. The questionnaire examines sociability

[2] See section 2.3.2.6. for information on the Autism Screening Questionnaire (Berument et al., 1999), which is the unpublished version of the Social Communication Questionnaire (Rutter et al., 2003).

in individuals (children and adults) with a range of intellectual and verbal abilities. It is an informant-based questionnaire consisting of 25 items. These items comprise thirteen subscales. The questionnaire is completed by the person's main caregiver based on how a person typically behaved in social situations with familiar and unfamiliar people over the last two months. The questionnaire also screens for the presence of selective mutism.

3.4.2.4.1. Development of the SQID

Initially, social situations were identified in which an individual's sociability / shyness could be examined. The DSM-IV-TR criteria for social anxiety (American Psychiatric Association, 2000), was used to delineate the types of social situations that should be examined. According to the DSM-IV-TR criteria, individuals with social anxiety may show anxiety in either performance or interaction situations (American Psychiatric Association, 2000). Performance situations, are those in which the person is exposed to possible scrutiny by others, such as, speaking in front of groups, eating or writing with other people watching and performing activities (e.g., music or sport), in front of other people. Interaction situations typically involve social interactions with unfamiliar people, such as, meeting strangers or going 'on a date' (Antony, 1997).

The categorisation employed in the DSM-IV-TR criteria for social anxiety was used to develop the questionnaire (American Psychiatric Association, 2000). Existing questionnaires were examined to identify performance and interaction situations relevant to individuals with a range of intellectual disabilities. The existing questionnaires either examined a range of psychopathology in individuals with intellectual disabilities;

psychopathology, anxiety or social anxiety in typically developing children; or examined sociability in typically developing children. The questionnaires obtained included: the Strengths and Difficulties Questionnaire (Goodman, 1997), the Spence Children's Anxiety Scale (Spence, 1998), the State-Trait Anxiety Inventory for Children (STAI-C; Spielberger, 1973); the Eysenck Personality Inventory (EPI; Eysenck & Eysenck, 1968); the Social Anxiety Scale for Children-Revised (SASC-R; La Greca & Stone, 1993), the Matson Evaluation of Social Skills for Individuals with Severe Retardation (MESSIER; Matson, 1995b), the Diagnostic Assessment for the Severely Handicapped Revised (DASH-II, Matson, 1995a), the Anxiety, Depression and Mood Scale (ADAMS; Esbensen, Rojahn, Aman & Ruedrich, 2003), the Child Behavior Checklist (CBCL; Achenbach, 1991) and the Developmental Behaviour Checklist (DBC, Einfeld & Tonge,1992).

General social situations, such as, an ongoing social interaction, rather than specific social situations (e.g., attending a party), were identified for this questionnaire to increase the applicability of the questionnaire to individuals with a range of ages and abilities. Specific examples of performance and interaction situations were considered to increase the risk of caregivers not completing the questionnaire because the situations may not be applicable. After examining the questionnaires, three social interaction situations and one social performance situation were deemed as being appropriate for this population. The social interaction situations deemed relevant were as follows: when an individual is approached by another person, when an individual is in an ongoing interaction with another person and when an individual initiates an interaction with another person. The only performance situation deemed to be suitable was a group situation because caregivers could refer to any group situation that they may have observed the person in.

When examining these social situations, it was important to stipulate the familiarity of the other person(s) in the situation, particularly when typically developing children with social anxiety must show a capacity for social relationships with familiar people (American Psychiatric Association, 2000). Therefore, corresponding familiar and unfamiliar items for each social situation identified, were incorporated into the questionnaire. As a result, the following eight subscales were devised: Familiar Receive Interaction, Familiar Ongoing Interaction, Familiar Initiate Interaction, Familiar Performance, Unfamiliar Receive Interaction, Unfamiliar Ongoing Interaction, Unfamiliar Initiate Interaction, Unfamiliar Performance. Each subscale is comprised of two items; one examining sociability with someone their own age, and one examining sociability with an adult. The subscales were constructed in this way because children who show social anxiety must demonstrate anxiety in peer settings, not just with adults (American Psychiatric Association, 2000).

The questionnaire was developed to examine sociability and shyness in these social situations. Operationalised definitions of sociability and shyness, based on observable behaviour, were developed for these constructs. Definitions were based on behavioural indicators of sociability and shyness / social anxiety that had been identified in the literature (Conger & Farrell, 1981; Fydrich et al., 1998; Glass & Arnkoff, 1989; Glennon & Weisz, 1978; Hall et al., 2006; Hessl et al., 2006; Lesniak-Karpiak et al., 2003; Millbrook et al., 1986; Monti et al., 1984; Trower et al., 1978). It was not possible to examine sociability and shyness for an initiation of a social interaction, consequently a separate scale was developed for the Familiar Initiate Interaction and the Unfamiliar Initiate Interaction subscales, also based on observable behaviour.

It was also important that the questionnaire examined the interaction between sociability with the person's main caregiver and an unfamiliar person to examine how these variables may impact upon each other. This was pertinent as typically developing children with social anxiety can be reported to stay close to a familiar person or show inhibited interactions with an unfamiliar person (American Psychiatric Association, 2000). Three subscales were therefore developed as a result of this. These subscales examined the person's interaction with their main caregiver (Main caregiver interaction), the effect of their main caregiver on an interaction with an unfamiliar person (presence of main caregiver on interaction with unfamiliar person) and also the separation from their main caregiver to interact with an unfamiliar person (separation anxiety).

Finally, it was also important that the questionnaire screened for the presence of selective mutism given that there is a wealth of evidence to suggest that selective mutism is an extreme form of social anxiety (Black & Uhde, 1992). Based on this, two items were developed. A further item examining the reduction of speech in individuals was also included because it was considered important to monitor changes in verbalisation because this may be a precursor to selective mutism. See Table 3.3 for the SQID subscales.

Table 3.3: The SQID subscales.

	SQID Item	Subscale
7.	Someone familiar that is her / his own age walks up to her /him?	Familiar Receive Interaction
14.	A familiar adult walks up to her / him?	
4.	(S)he is spending time with a familiar adult?	Familiar Ongoing Interaction
11.	(S)he is spending time with someone familiar that is her / his own age?	
18.	When there are only familiar people around, how often does (s)he try to make contact with them in any way (by talking, signing, vocalising, using gestures, moving towards them in any way etc.)?	Familiar Initiate Interaction
20.	When familiar people and people are around who (s)he does *not* know, how often does (s)he try to make contact with the familiar people in any way (by talking, signing, vocalising, using gestures, moving towards them in any way etc.)?	
5.	(S)he is the focus of attention in a group of adults (s)he knows?	Familiar Performance
12.	(S)he is the focus of attention in a group of people her / his own age that (s)he knows?	
3.	Someone (s)he does *not* know that is her / his own age walks up to her /him?	Unfamiliar Receive Interaction
9.	An adult (s)he does *not* know walks up to her / him?	
2.	(S)he is spending time with an adult (s)he does *not* know?	Unfamiliar Ongoing Interaction
6.	(S)he is spending time with someone (s)he does *not* know that her / his own age?	
19.	When familiar people and people are around who (s)he does *not* know, how often does (s)he try to make contact with the people (s)he does *not* know in any way (by talking, signing, vocalising, using gestures, moving towards them in any way etc.)?	Unfamiliar Initiate Interaction
21.	When there are only people around who (s)he does *not* know, how often does (s)he try to make contact with them in any way (by talking, signing, vocalising, using gestures, moving towards them in any way etc.)?	
10.	(S)he is the focus of attention in a group of people her / his own age that (s)he does *not* know?	Unfamiliar Performance
17.	(S)he is the focus of attention in a group of adults (s)he does *not* know?	
1.	Her / his main caregiver walks up to her / him?	Main caregiver interaction
16.	(S)he is spending time with her / his main caregiver?	
13.	(S)he is with her / his main caregiver and then someone her / his own age that (s)he does *not* know starts to talk to her / him?	Presence of main caregiver on interaction with unfamiliar person
15.	(S)he is with her / his main caregiver and then an adult (s)he does *not* know starts to talk to her / him?	
8.	(S)he has just been separated from her / his main caregiver to be with an adult (s)he does *not* know?	Separation anxiety
23.	Does the person speak *less* than (s)he used to?	Change in speech over time
24.	Does the person *only* speak or sign in some settings and not others?	Selective mutism
25.	Does the person *only* speak or sign to some people and not others?	

3.4.2.4.2. Scoring the SQID

The SQID consists of 25 items. 21 items are answered on a seven-point Likert scale and four items are answered on a yes / no basis. The questionnaire consists of thirteen subscales: Familiar Receive Interaction, Familiar Ongoing Interaction, Familiar Initiate Interaction, Familiar Performance, Unfamiliar Receive Interaction, Unfamiliar Ongoing Interaction, Unfamiliar Initiate Interaction, Unfamiliar Performance, Main caregiver interaction, Presence of main caregiver on interaction with unfamiliar person, Separation anxiety, Change in speech over time and Selective mutism.

Eight of the thirteen subscales have been designed to examine an individual's sociability in four different types of social situation with a familiar or an unfamiliar person. These subscales are as follows: Familiar Receive Interaction (Q7 + Q14), Familiar Ongoing Interaction (Q4 + Q11), Familiar Initiate Interaction (Q18 + Q20), Familiar Performance (Q5 + Q12), Unfamiliar Receive Interaction (Q3 + Q9), Unfamiliar Ongoing Interaction (Q2 + Q6), Unfamiliar Initiate Interaction (Q19 + Q21) and Unfamiliar Performance (Q10 + Q17). The minimum score on each subscale is 2 and the maximum possible score is 14. A total Familiar score is calculated by aggregating the familiar subscales (Q4 + Q5 + Q7 + Q11 + Q12 + Q14 + Q18 + Q20), and a total Unfamiliar score is calculated by aggregating the unfamiliar subscales (Q2 + Q3 + Q6 + Q9 + Q10 + Q17+ Q19 + Q21).

Three of the thirteen subscales focus on examining the interaction between the main caregiver and an unfamiliar person on an individual's sociability. These three subscales are as follows: Main caregiver interaction (Q1 + Q16), Presence of main caregiver on

interaction with unfamiliar person (Q13 +Q15) and Separation anxiety (Q8). These subscales examine the person's interaction with their main caregiver, the effect of their main caregiver on an interaction with an unfamiliar person and also the separation from their main caregiver to interact with an unfamiliar person. The minimum score on the Main caregiver interaction and Presence of main caregiver on interaction with unfamiliar person subscales is 2 and the maximum possible score is 14. The minimum score on the Separation anxiety subscale is 1 and the maximum score is 7.

Two of the thirteen subscales are only applicable for verbal individuals. Q22 is used to screen whether an individual is verbal. If the person is considered to be verbal then the caregiver is asked to complete Q23 to Q25, which compromises two subscales examining the effect of speech: Change in speech over time (answer 'yes' to Q23) and Selective mutism (answer 'yes' to Q24 and Q25). To be screened as showing selective mutism, the caregiver must answer 'yes' to both Q24 and Q25. This will also help to remain conservative about the rates of selective mutism in a population.

If a caregiver has not completed all relevant items on the SQID, the questionnaire can be pro-rated at the subscale level. If a subscale consists of two items and one item is missing then it is assumed that this missing item is of the same value as the completed item. The selective mutism subscale *cannot* be pro-rated.

For the purpose of the current study only a select number of subscales will be examined. These are as follows: Familiar Receive Interaction, Familiar Ongoing Interaction, Familiar Initiate Interaction, Familiar Performance, Unfamiliar Receive Interaction, Unfamiliar

Ongoing Interaction, Unfamiliar Initiate Interaction, Unfamiliar Performance and Selective mutism. The Familiar and Unfamiliar total scores will also be examined across the groups.

3.4.2.4.3. Inter-rater reliability of the SQID

Inter-rater reliability was the only form of reliability to be examined for the SQID in the current study due to time constraints and limited resources (test-retest reliability will be examined in future research). Inter-rater reliability is usually poorer than test-retest reliability so this was deemed to be a conservative assessment of reliability. Inter-rater reliability data were collected for 55 individuals with intellectual disabilities. The group comprised 32 individuals with Cornelia de Lange syndrome, seven individuals with Angelman syndrome, seven individuals with Cri du Chat syndrome, and nine individuals with Prader-Willi syndrome. Individuals were recruited directly from a research database of individuals who had taken part in previous research with the research team and had agreed to be contacted for future research. Individuals with Cornelia de Lange syndrome were also recruited directly at a UK & Ireland Family conference organised by the Cornelia de Lange syndrome Foundation. Participants were aged between 4 and 30 years (mean = 12.7; SD = 5.9). 32 participants (58.2%) were male.

Inter-rater reliability was examined by asking two parents and/ or carers who had regular contact with the individual, to complete the SQID on the same day. Parents and/ or carers were asked to complete the questionnaire independently. Spearman correlations were employed to examine inter-rater reliability because the data was not normally distributed. Item level analysis showed that Spearman coefficients ranged from .43 to .80 for Q1 to

Q21. 81% of items were above .60, which was deemed to be satisfactory (*Appendix B* shows inter-rater reliability of SQID scores at item-level). Inter-rater reliability for Q22, Q24 and Q25 was examined using Kappa. Kappa for Q22, Q24 and Q25 respectively were .96, .44 and .51. Inter-rater reliability was not obtained for Q23 because this item was added after data on inter-rater reliability had been collected.

3.4.3. Procedure

Each caregiver received a letter of invitation for the study, an information sheet and a questionnaire pack. Consent forms were only sent to the Down syndrome, Rubinstein Taybi syndrome and Autism spectrum disorder groups because consent to participate in the study was obtained previously for the Cornelia de Lange syndrome, Angelman syndrome and Fragile X syndrome group. Caregivers who wished to take part in the study were asked to complete the questionnaire pack and consent form (if applicable) and return them in the pre-paid envelope provided. The questionnaire pack was counterbalanced in five ways. Equal proportions of the counterbalanced questionnaires were sent to each group taking part in the study. Approximately four to six weeks after sending questionnaire packs to caregivers, duplicate packs were sent out (covering letter changed) to those caregivers who had not returned their pack during that time period in order to maximise participation in the study.

3.5. DATA ANALYSIS

3.5.1. Normality of data and data analysis

The distribution of SQID data was examined via visual inspection of Q-Q plots and utilising the Kolmogrov-Smirnov test. The data were *not* normally distributed at subscale level or at total score level ($p < .05$). Several methods of transformation (Log, Square root and Reciprocal transformation) were employed but it was not possible to create homogenous variances across the dataset. Consequently, non-parametric tests were employed throughout the analysis.

The analysis was conducted in four parts. The first part examined whether SQID scores were related to severity of Autism spectrum disorder impairments and degree of disability. Degree of disability was examined given that the measure was intended for individuals with a range of intellectual disabilities so it was important to ensure that SQID scores were not affected by degree of disability. The association with Autism spectrum disorder impairments was also examined because specific social impairments form part of the 'triad of impairments' in Autism spectrum disorder and it was important to ensure that the social impairments assessed by the SQID were not just a manifestation of social impairments related to Autism spectrum disorder, particularly given the large number of individuals with intellectual disabilities who are diagnosed with or show characteristics of Autism spectrum disorder (e.g., Moss & Howlin, 2009). The next set of analyses examined sociability across the six groups (Cornelia de Lange syndrome, Angelman syndrome, Fragile X syndrome, Down syndrome, Rubinstein Taybi syndrome and Autism spectrum

disorder). Subscale and total SQID scores were compared between the six groups as a whole and then between smaller age groups in order to provide information about the age-related pattern of sociability across the groups. Finally, the percentage of individuals who show 'extreme sociability' and 'extreme shyness' and the rates of selective mutism were compared across the six groups.

3.5.2. Data Analysis for Part One: Relationship between degree of disability and autism spectrum characteristics and SQID Subscale Scores

Partial correlations were conducted across the entire participant population between SQID subscale scores and total ASQ / SCQ scores (measure of Autism spectrum disorder characteristics), whilst controlling for age; and between the SQID subscale scores and the Wessex Self Help score (measure of degree of disability), whilst controlling for age. An alpha level of $p < .05$ was employed for these analyses in order to remain conservative about the effect that these factors may have on the SQID scores.

3.5.3. Data Analysis for Part Two: Comparison of SQID Scores

In order to examine the age-related pattern of sociability across the groups, participants from each group were divided into three age bands. The age bands were as follows: *under 12 yrs*; *12-18yrs*; and *over 18yrs*. These age bands were chosen because it allowed for the most equal distribution of participants in the smaller groups (Angelman syndrome, Rubinstein Taybi syndrome and Cornelia de Lange syndrome). Table 3.4 shows the number of participants in each age band for each group.

Table 3.4: Number of participants in each age band.

	Group					
	CdLS	**AS**	**FXS**	**DS**	**RTS**	**ASD**
under 12 yrs	21	28	14	31	28	34*
12-18yrs	33	21	63	21	18	54
over 18yrs	44	17	65	65**	42	19
Total	98	66	142	117	88	107

* 68 of the 101 participants with ASD in the *under 12 yrs* group were randomly excluded because this group was much larger than the number of participants in the comparison groups.
**15 of the 80 participants from the DS *19 years and over* group were randomly excluded because this group was much larger than the number of participants in the comparison groups.

A series of Kruskal-Wallis tests, with pair-wise Mann-Whitney post hocs, were employed to compare the SQID total and subscale sores between and within the groups. A more conservative alpha level ($p < .005$) was used to identify a difference as significant because a number of comparisons were being conducted.

Effect sizes were calculated for any significant difference identified at post hoc level. Pearson's correlation coefficient, *r*, was calculated as an estimation of effect size. See section 2.4.1. for formula used to calculate effect sizes. The relative size of an effect was measured using the following criteria: $r = .1$ is a *small* effect size; $r = .3$ is a *medium* effect size and $r = .5$ is a *large* effect size (Cohen, 1992).

3.5.4. Data Analysis Part Three: Cut-offs for Extreme Sociability and Extreme Shyness

In order to estimate the number of individuals from each group experiencing extreme sociability or extreme shyness, the percentage of individuals obtaining the maximum or minimum score on each subscale was calculated for each group. Individuals who obtained the maximum score possible on a subscale (score = 14) were classified as 'extremely sociable' and individuals who obtained the lowest score possible on a subscale (score = 2) were classified as 'extremely shy'. This is a very conservative analysis given that individuals have to obtain the maximum or minimum possible score on a subscale to be included in the cut-off. Percentile ranks were not used to determine extreme sociability and extreme shyness because the SQID data was skewed in all of the groups.

3.5.5. Data Analysis for Part Four: Selective Mutism

This analysis only included verbal individuals from each group. Therefore individuals with Angelman syndrome were excluded from this analysis because the number of verbal participants in this group was low. A series of pair-wise chi-square tests were used to compare the rate of selective mutism across the groups. The relationship between selective mutism and social anxiety was also examined. Only the Cornelia de Lange syndrome, Fragile X syndrome and Autism spectrum disorder groups were included in this analysis because only these groups contained enough verbal individuals reported to show selective mutism. These three groups were combined into one group and then individuals were divided into two groups: those reported to show selective mutism and those reported *not* to

show selective mutism. The two groups were compared on the unfamiliar subscale scores of the SQID, with the prediction that those who show selective mutism should obtain significantly lower SQID scores.

3.6. RESULTS

3.6.1. Part One: Relationship between degree of disability and autism spectrum characteristics and SQID Subscale Scores

Table 3.5 shows the partial correlations (controlling for age) for Total ASQ / SCQ scores and SQID Subscale Scores; and for Wessex Self Help Scores and SQID Subscale Scores across the whole participant population. More than half of the correlations between the Wessex Self Help Score and the SQID subscale scores were not significant. Of those correlations that were significant, Spearman's correlation coefficient was always less than .2, indicating that all significant correlations were weak. Furthermore, all significant correlations showed the opposite trend to that expected; individuals who were less able were found to be more sociable. Only one correlation between the SQID subscale scores and total ASQ / SCQ scores was significant and even this significant correlation was weak (r = .26). In summary, the SQID scores *do not* appear to be related to degree of disability or Autism spectrum disorder.

Table 3.5: Partial Correlations (controlling for age) for Total ASQ / SCQ scores and SQID Subscale Scores; and for Wessex Self Help Scores and SQID Subscale Scores across the whole participant population.

	Correlations with Wessex Self Help Scores	Correlations with ASQ / SCQ Scores
Familiar social situations		
On-going Interaction	.07	.21
Receive Interaction	-.02	.22
Group Interaction	-.04	-.01
Initiate Interaction	-.06	.26*
Unfamiliar social situations		
On-going Interaction	-.11*	-.13
Receive Interaction	-.14**	-.05
Group Interaction	-.17**	-.18
Initiate Interaction	-.10*	.06

* Significant at $p < .05$ level
** Significant at $p < .005$ level

3.6.2. Part Two: Comparison of SQID Scores

3.6.2.1. Familiar and Unfamiliar Total Score Analysis

3.6.2.1.1. Analysis conducted between groups

Table 3.6 shows the comparison of total SQID scores across the groups[3]. A series of Kruskal-Wallis tests, with pair-wise Mann-Whitney post hocs, were employed to compare the SQID total sores between the groups. The Angelman syndrome, Down syndrome and Rubinstein Taybi syndrome groups obtained both significantly higher Familiar and Unfamiliar total scores than the Cornelia de Lange syndrome, Fragile X syndrome and Autism spectrum disorder groups. This suggests that individuals with Angelman syndrome, Down syndrome and Rubinstein Taybi syndrome were significantly more sociable in both familiar and unfamiliar social situations than individuals with Cornelia de Lange syndrome, Fragile X syndrome and Autism spectrum disorder. The Fragile X syndrome group obtained the lowest Unfamiliar total score, with all other groups obtaining a significantly higher score on this variable. This provides further evidence of social anxiety being experienced by the Fragile X syndrome group in unfamiliar social situations. The Autism spectrum disorder group obtained the lowest Familiar total score, indicating that the Autism spectrum disorder group are the least sociable in familiar situations.

[3] All six groups obtained significantly higher Familiar total scores than Unfamiliar total scores ($p < .0001$ for all groups), indicating that individuals from each group were significantly more sociable in familiar social interactions than unfamiliar social interactions.

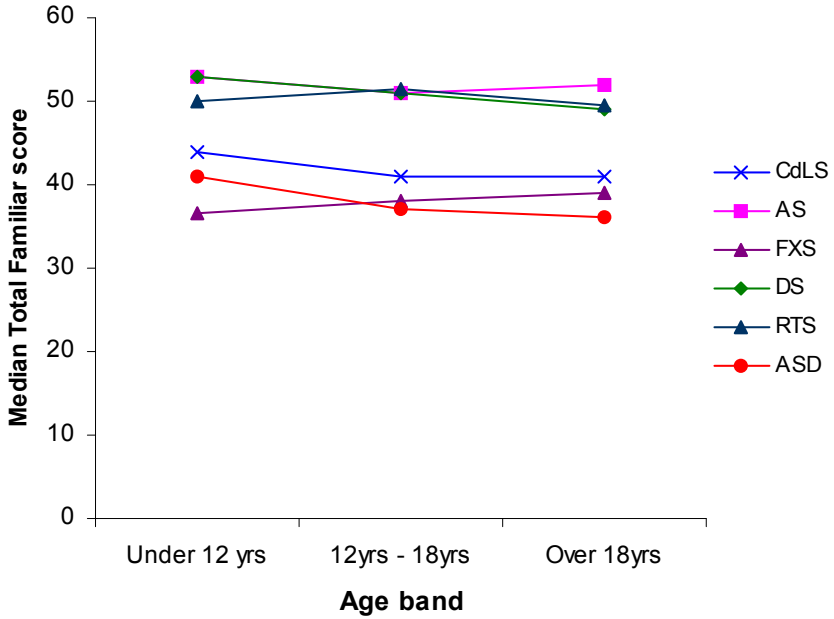
Table 3.6: A comparison of the SQID total and subscale scores between the groups.

	Group Median (Inter-quartile range)						df	X^2	*p* value	Post hoc*	Large effect size
	A **CdLS** (n=98)	B **AS** (n=66)	C **FXS** (n=142)	D **DS** (n=116)	E **RTS** (n=88)	F **ASD** (n=107)					
Total Unfamiliar Subscale	26.00 (13.50-35.00)	41.00 (31.00-48.00)	15.00 (11.00-25.00)	36.00 (24.00-46.00)	31.50 (21.25-46.00)	21.00 (14.00-29.00)	5	153.65	<.0001	B,D,E>A,F>C	
Unfamiliar Ongoing Interaction	7.00 (3.00-9.00)	11.00 (9.00-12.00)	4.00 (2.00-8.00)	10.00 (7.00-12.00)	9.00 (6.00-12.00)	5.50 (3.00-8.00)	5	139.12	<.0001	B,D,E>A,C,F	B,D>C; B>F
Unfamiliar Receive Interaction	6.50 (3.00-8.00)	10.00 (8.00-12.00)	3.00 (2.00-6.00)	9.00 (6.00-11.00)	8.00 (5.00-12.00)	6.00 (3.00-8.00)	5	142.57	<.0001	B,D,E>A,F>C	B,D>C; B>F
Unfamiliar Group situation	7.00 (2.75-9.00)	10.00 (7.00-13.00)	3.00 (2.00-6.00)	10.00 (5.00-12.00)	10.00 (4.00-12.00)	6.00 (2.00-8.00)	5	135.02	<.0001	B,D,E>A,F>C	B,D>C; B>F
Unfamiliar Initiate Interaction	5.00 (4.00-7.50)	10.00 (6.75-12.00)	4.00 (2.00-6.00)	7.00 (4.00-11.00)	6.00 (4.00-10.75)	4.00 (3.00-6.00)	5	120.34	<.0001	B>D,E>A,F; B,A,D,E>C	B>A,C,F
Total Familiar Subscale	41.50 (35.00-48.00)	53.00 (48.00-55.00)	39.00 (31.00-44.00)	51.00 (45.00-54.00)	50.50 (42.00-54.00)	37.50 (31.00-45.00)	5	179.65	<.0001	B,D,E>A,C,F; A>F	
Familiar Ongoing Interaction	11.00 (10.00-13.00)	13.50 (12.00-14.00)	12.00 (9.00-13.00)	14.00 (12.00-14.00)	13.00 (12.00-14.00)	11.00 (9.00-12.00)	5	128.03	<.0001	B,D,E>A,C,F	B,D>F; D>A
Familiar Receive Interaction	10.00 (8.75-12.00)	13.00 (12.00-14.00)	10.00 (7.00-12.00)	13.00 (12.00-14.00)	12.00 (10.00-14.00)	9.00 (8.00-12.00)	5	151.44	<.0001	B,D,E>A,C,F	B,D>A,C,F
Familiar Group situation	11.00 (9.00-13.00)	14.00 (12.00-14.00)	9.00 (6.00-12.00)	14.00 (12.00-14.00)	13.00 (11.00-14.00)	10.00 (7.00-12.00)	5	159.77	<.0001	B,D,E>A>C,F	B,D>F; D>C
Familiar Initiate Interaction	10.00 (7.00-12.00)	13.00 (10.00-14.00)	9.00 (6.00-11.00)	12.00 (8.00-13.00)	11.50 (8.00-13.00)	7.00 (6.00-10.00)	5	95.80	<.0001	B>D,E,A>F; B,D,E>C	B>F

*A=Cornelia de Lange syndrome, B=Angelman syndrome, C=Fragile X syndrome, D=Down syndrome, E=Rubinstein Taybi syndrome, F=Autism spectrum disorder

3.6.2.1.2. Analysis conducted between groups with age bands

Figure 3.1 shows a graph of the median total Familiar and Unfamiliar SQID scores for the three age bands in each group. The Familiar and Unfamiliar total scores were compared between the three age bands (*under 12 yrs*; *12-18yrs*; and *over 18yrs*) within each syndrome group using the Kruskal-Wallis test, with pair-wise Mann-Whitney post hocs. The analysis revealed that there were no significant differences between the age bands in any of the syndrome groups on either the Familiar or Unfamiliar total scores. A significant difference was almost obtained between the age bands in the Down syndrome group on the Familiar total score ($\chi^2(2) = 9.68$, $p = .008$), with a lower Familiar total score being observed in the oldest age group, suggesting that older individuals with Down syndrome are less sociable with familiar people than younger individuals. For the Cornelia de Lange syndrome group, a comparison of the Unfamiliar total scores between individuals in each age band (*under 12 yrs*; *12-18yrs*; and *over 18yrs*), revealed a difference that approached significance ($\chi^2(2) = 8.51$, $p = .01$). Individuals with Cornelia de Lange syndrome in the *12-18 years age band* obtained the lowest median Unfamiliar total score, whilst individuals with Cornelia de Lange syndrome in the youngest age band obtained the highest median score.



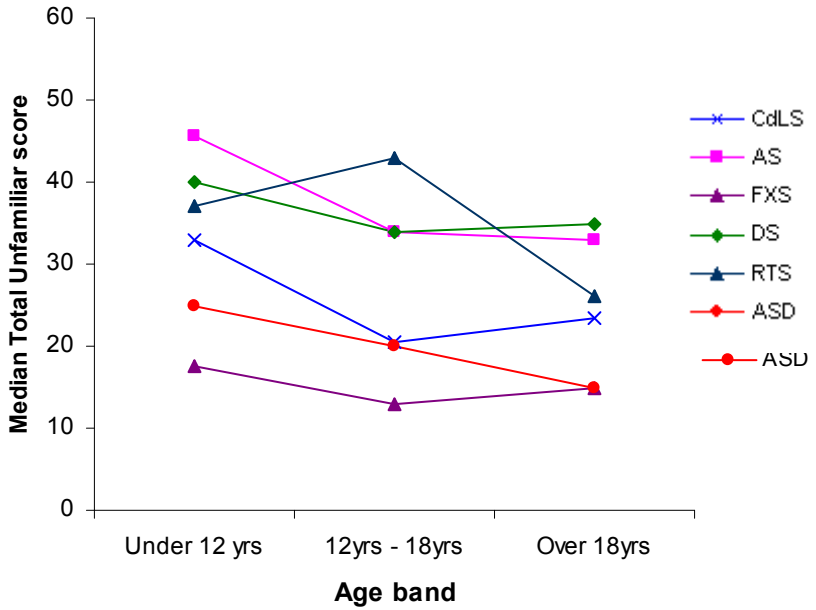


Figure 3.1: A comparison of SQID total scores between the three age bands (Under 12yrs; 12-18yrs; Over 18yrs) within each group.

3.6.2.2. Familiar and Unfamiliar Subscale score Analysis

3.6.2.2.1. Analysis conducted between groups

Table 3.6 shows the comparisons across the groups for each subscale[4]. In general, the Angelman syndrome, Down syndrome and Rubinstein Taybi syndrome groups obtained significantly higher subscale scores than the Cornelia de Lange syndrome, Fragile X syndrome and Autism spectrum disorder groups, indicating that these groups were significantly more sociable in the various types of social situations examined. Slightly different profiles of sociability were observed between the groups across the different types of social situations, as reflected in the differences reported on each subscale. For example, the Angelman syndrome group initiated significantly more social interactions with both familiar and unfamiliar people than all other groups yet showed a similar level of sociability to the Down syndrome and Rubinstein Taybi syndrome groups in the other types of social situations examined.

The Cornelia de Lange syndrome group was reported to show a similar level of sociability in unfamiliar social situations, to the Autism spectrum disorder group (no significant difference was found between these two groups on the unfamiliar subscales). Both groups were reported to be significantly less sociable than the Angelman syndrome, Down syndrome and Rubinstein Taybi syndrome groups in all types of unfamiliar social situations (ongoing interaction, receive interaction, initiate interaction and group situation),

[4] All six groups scored significantly higher on each of the Familiar Subscales than on the corresponding Unfamiliar subscales ($p < .0001$). This means that all groups were significantly more sociable in all types of familiar social interactions compared to the corresponding unfamiliar social interactions.

demonstrating shyness associated with these two groups in unfamiliar social situations. This may indicate that heightened levels of shyness (and perhaps social anxiety), are prevalent in both Cornelia de Lange syndrome and Autism spectrum disorder. The Cornelia de Lange syndrome group scored significantly higher on nearly all of the unfamiliar SQID subscales (apart from an ongoing unfamiliar interaction) than the Fragile X syndrome group (obtained lowest median scores on all unfamiliar SQID subscales), which suggests that the shyness reported in Cornelia de Lange syndrome may not be as extreme as that reported in Fragile X syndrome.

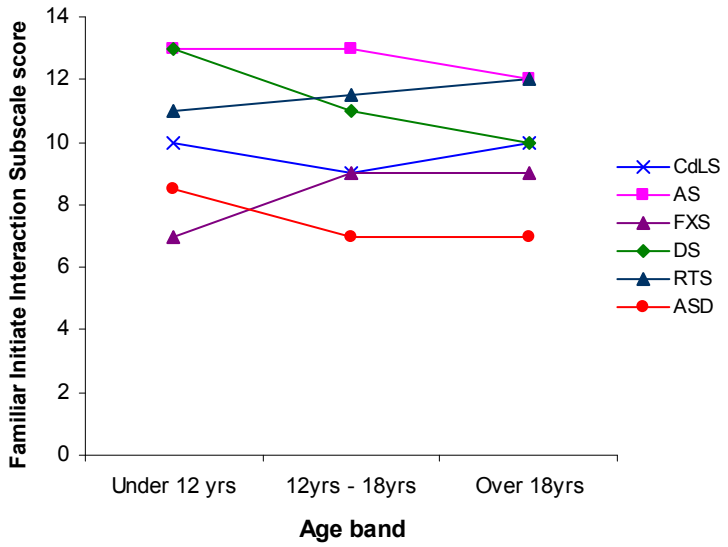
The level of sociability shown by the Cornelia de Lange syndrome group varied between the familiar social situations. The Cornelia de Lange syndrome group were reported to show a similar level of sociability to the Fragile X syndrome and Autism spectrum disorder groups when approached by a familiar person (Receive interaction) and in an on-going interaction with a familiar person. The Cornelia de Lange syndrome group, however, was reported to be significantly more sociable than the Fragile X syndrome and Autism spectrum disorder groups in a familiar group social situation. The Cornelia de Lange syndrome group was also reported to initiate significantly more social interactions with familiar people than the Autism spectrum disorder group. In all familiar social situations examined, the Cornelia de Lange syndrome group was reported to be significantly less sociable than the Angelman syndrome, Down syndrome and Rubinstein Taybi syndrome groups. In summary, a varied profile of sociability was reported across the four familiar social situations, for the Cornelia de Lange syndrome group.

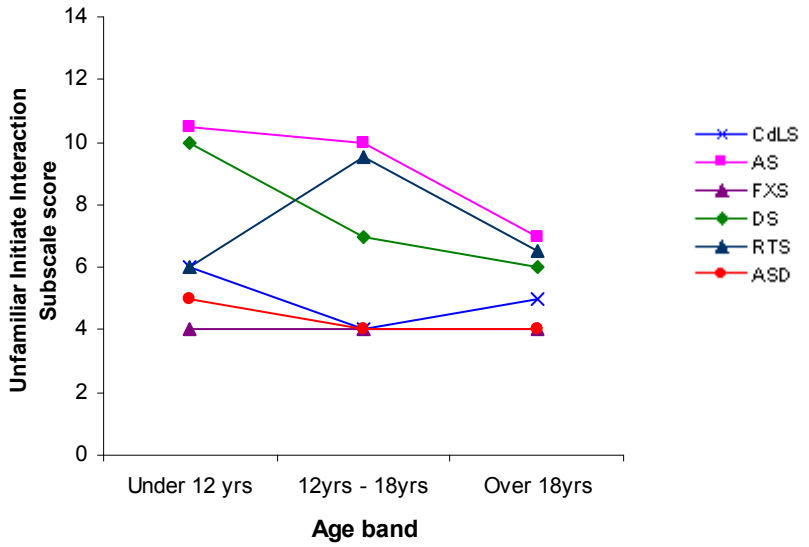
The Autism spectrum disorder group obtained the lowest median score on three of the familiar subscales (the CdLS group also obtained the lowest median score on the Familiar Ongoing Interaction subscale). The analysis indicated that the Autism spectrum disorder group had particular difficulty in initiating interactions with familiar people and were reported to initiate significantly less social interactions with familiar people than individuals in all the other groups.

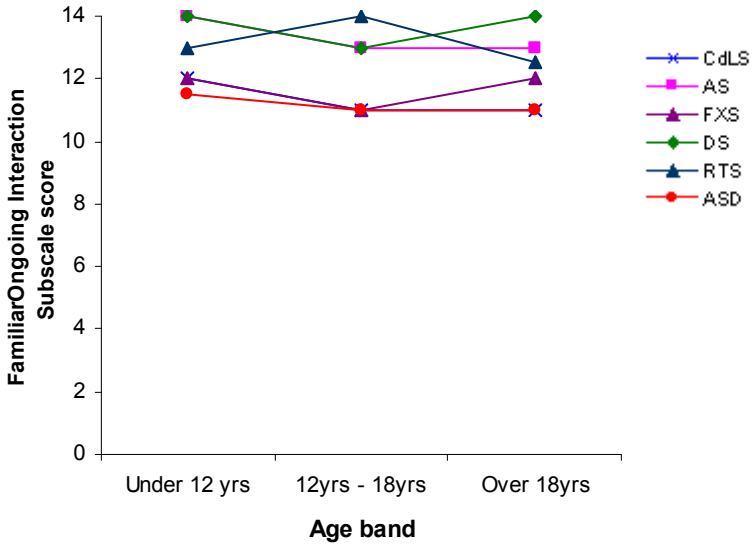
The Rubinstein Taybi group was reported to show similar levels of sociability to the Down syndrome group in all familiar and unfamiliar social situations (no significant difference was identified between these two groups of any of the subscales examined). This suggests sociability in Rubinstein Taybi syndrome is comparable to that seen in Down syndrome.

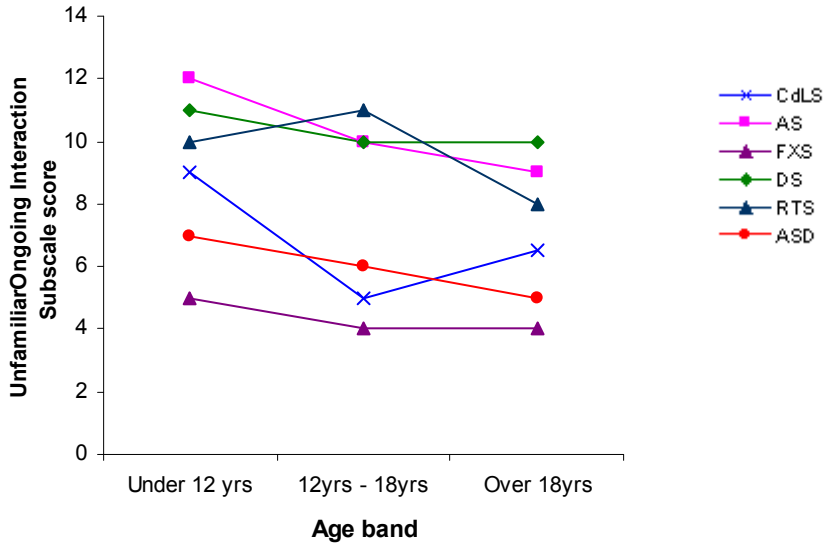
3.6.2.2.2. Analysis conducted between groups with age bands

Figure 3.2 shows the median SQID subscale scores for participants in each age band within each group. Analyses were conducted between the age bands within each group. A two-way interaction was found between *age band* and *group*. A significant difference was identified between individuals in the three age bands in the Cornelia de Lange syndrome group on the *Unfamiliar Initiate Interaction* subscale ($H(2) = 11.05$, $p < .005$). The youngest group of individuals with Cornelia de Lange syndrome (*under 12yrs*) obtained a significantly higher subscale score than those aged between *12-18yrs* ($U = 148.5$, $p = .001$, $r = -.48$). A medium to large effect size suggests the strength of the effect is high. When comparisons were conducted across the groups, the analyses showed that individuals with Cornelia de Lange syndrome in the *under 12 years* age band scored significantly lower on the *Unfamiliar Initiate Interaction* subscale than the Angelman syndrome group, whilst individuals with Cornelia de Lange in the *12-18 years* age band on the other hand, scored significantly lower than Rubinstein Taybi syndrome group as well as the Angelman syndrome group on the same subscale. This suggests that a difficulty in initiating interactions with unfamiliar people may be a specific difficulty for adolescents and young adults with Cornelia de Lange syndrome.


Familiar Initiate Interaction Subscale score
14
12
10
8
6
4
2
0
Under 12 yrs
12yrs - 18yrs
Over 18yrs
Age band
CdLS
AS
FXS
DS
RTS
ASD


Unfamiliar Initiate Interaction Subscale score
14
12
10
8
6
4
2
0
Under 12 yrs
12yrs - 18yrs
Over 18yrs
Age band
CdLS
AS
FXS
DS
RTS
ASD


FamiliarOngoing Interaction Subscale score
14
12
10
8
6
4
2
0
Under 12 yrs
12yrs - 18yrs
Over 18yrs
Age band
CdLS
AS
FXS
DS
RTS
ASD


UnfamiliarOngoing Interaction Subscale score
14
12
10
8
6
4
2
0
Under 12 yrs
12yrs - 18yrs
Over 18yrs
Age band
CdLS
AS
FXS
DS
RTS
ASD

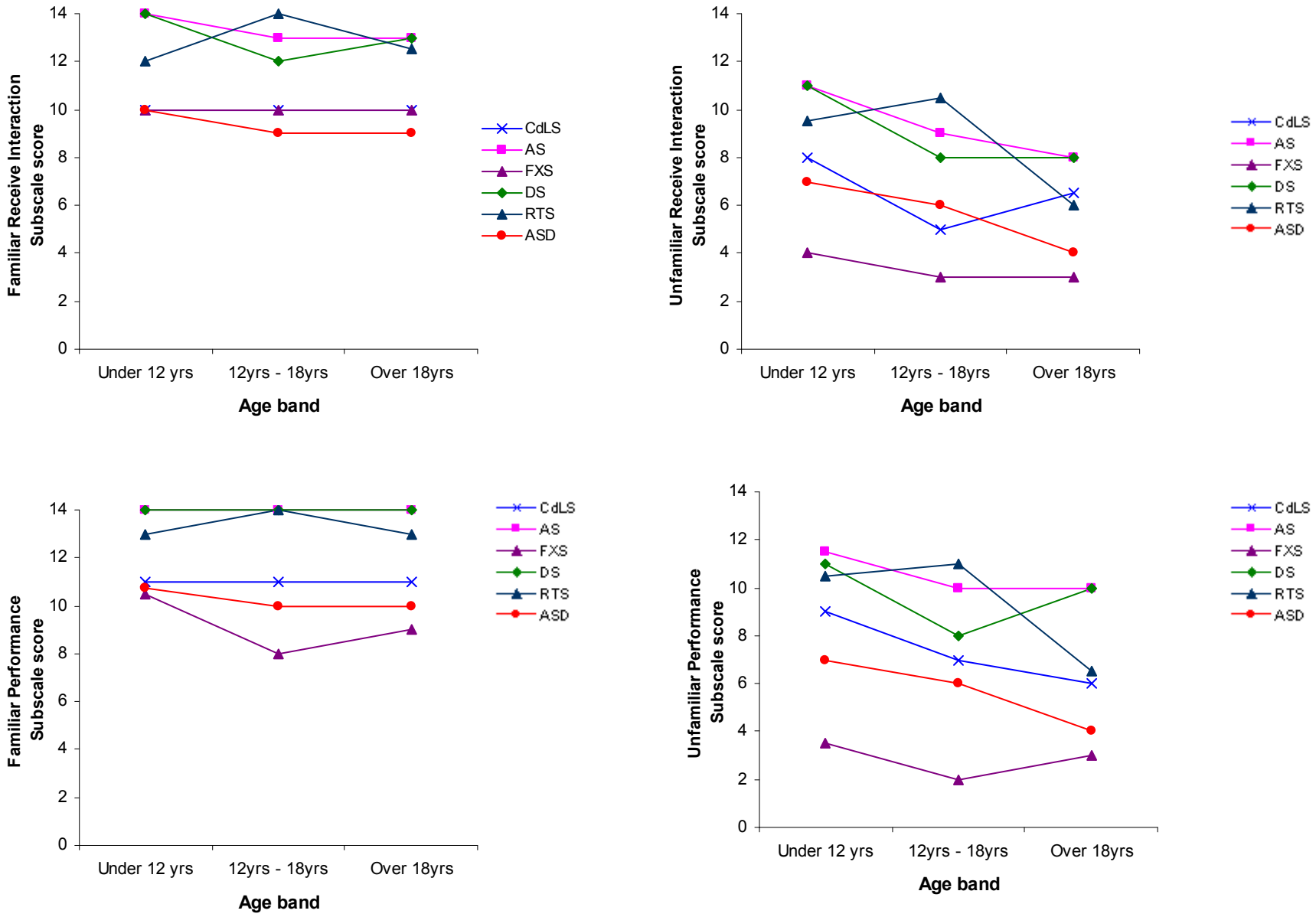


Figure 3.2: Median SQID subscale scores for participants in each age band within each group.

A significant difference was also identified on the *Familiar Initiate Interaction* subscale between individuals in the oldest and youngest age band in the Down syndrome group. The youngest individuals (*Under 12yrs*) with Down syndrome scored significantly higher than the oldest individuals (*Over 18yrs*) with Down syndrome ($U = 518.5$, $p < .0001$, $r = -.39$). When comparisons were conducted across the groups on the *Familiar Initiate Interaction* subscale, the analyses showed that the youngest individuals with Down syndrome (*Under 12yrs*) scored significantly higher than the youngest individuals with Cornelia de Lange syndrome, Fragile X syndrome and Autism spectrum disorder. However, no significant differences were found between the *Over 18yrs* age band in the Down syndrome group and other contrast groups on this subscale. This suggests that sociability in initiating interactions with familiar people is specific to younger individuals with Down syndrome.

It is worthwhile noting that the differences between the age bands in the Cornelia de Lange syndrome and Angelman syndrome groups, on the *Unfamiliar Ongoing Interaction* subscale, approached significance ($p < .05$). Also, differences between the age bands in the Cornelia de Lange syndrome and Down syndrome groups on the *Unfamiliar Receive Interaction* subscale approached significance ($p < .05$).

3.6.3. Part Three: Cut-offs for Extreme Sociability and Extreme Shyness

Table 3.7 shows the percentage of individuals from each group scoring at the cut-off for 'extreme sociability' and 'extreme shyness' on each subscale. The Cornelia de Lange syndrome group showed relatively high rates of 'extreme shyness' across the unfamiliar social situations, with prevalence rates ranging from 14.4%-24.5% across the four unfamiliar social situations. These high rates suggest that 'extreme shyness' in unfamiliar social situations is quite common in Cornelia de Lange syndrome. The rates of 'extreme shyness' in familiar social situations were as expected for the Cornelia de Lange syndrome group, with rates ranging from 1%-3.1%. This demonstrates that the 'extreme shyness' reported in Cornelia de Lange syndrome appears to be associated with *unfamiliar* social situations.

Table 3.7: The percentage of individuals in each group scoring at the cut-off for extreme sociability and extreme shyness on each subscale.

	Group					
	CdLS (n=98)	**AS (n=66)***	**FXS (n=142)**	**DS (n=117)***	**RTS (n=88)**	**ASD (n=107)***
Extreme Sociability (Score of 14)						
Unfamiliar Ongoing Interaction:	0	4.5	.7	6.8	8.0	1.9
Unfamiliar Receive Interaction	0	6.1	.7	8.5	9.1	.0
Unfamiliar Group situation	2.0	9.1	1.4	14.5	9.1	.9
Unfamiliar Initiate Interaction	3.1	13.6	1.4	11.3	5.7	1.9
Familiar Ongoing Interaction	11.2	50.0	21.1	53.0	40.9	9.3
Familiar Receive Interaction	6.1	43.9	10.6	45.3	34.8	8.4
Familiar Group situation	14.3	53.0	14.8	58.1	42.0	7.5
Familiar Initiate Interaction	13.3	37.9	4.9	22.2	19.3	5.7
Extreme Shyness (Score of 2)						
Unfamiliar Ongoing Interaction	22.4	1.5	27.5	2.6	8.0	14.2
Unfamiliar Receive Interaction	21.4	1.5	35.9	7.7	10.2	20.8
Unfamiliar Group situation	24.5	4.5	47.2	11.1	10.2	25.5
Unfamiliar Initiate Interaction	14.4	0	28.9	10.4	9.1	21.7
Familiar Ongoing Interaction	1.0	0	0	0	0	0
Familiar Receive Interaction	1.0	0	3.5	0	0	.9
Familiar Group situation	3.1	0	4.9	.9	1.1	2.8
Familiar Initiate Interaction	2.0	0	.7	.9	1.1	5.7

* n may vary between analyses due to missing data.

As expected, the Cornelia de Lange syndrome group also showed a low prevalence rate of 'extreme sociability' in unfamiliar social situations, with the prevalence rate ranging from 0%-3.1%, across the four unfamiliar social situations. The prevalence rate of 'extreme sociability' in familiar social situations was somewhat higher for the Cornelia de Lange syndrome group, with the prevalence of 'extreme sociability' ranging from 6.1%-14.3% across the four familiar social situations. This again demonstrates the difference in sociability between familiar and unfamiliar social situations, for the Cornelia de Lange syndrome group.

The Fragile X syndrome group were reported to show the highest prevalence of 'extreme shyness' in all unfamiliar social situations. It is likely that this 'extreme shyness' in unfamiliar situations is indicative of social anxiety and therefore suggests that the highest prevalence rates of social anxiety are associated with the Fragile X syndrome group.

When analysing 'extreme shyness' with familiar people, it was expected that the prevalence rate would be 0% or almost 0%. Two interesting finding were reported. First, 4.9% of the Fragile X syndrome group were reported to show extreme shyness in familiar group situations. It may be that group situations regardless of familiarity are difficult for some individuals with Fragile X syndrome. Second the Autism spectrum disorder group showed the highest prevalence (5.7%) of 'extreme shyness' when initiating interactions with familiar people, which is perhaps indicative of the type of social impairment evident in this group in familiar social situations .i.e., their predominant difficulty in familiar social situations is initiation of a social interaction.

The Down syndrome group showed the highest prevalence of 'extreme sociability' in three familiar social situations when compared to individuals in the other groups. The situations were an ongoing interaction with a familiar person, receiving an interaction from a familiar person and a group situation with familiar people. The Angelman syndrome group were reported to show the highest prevalence of initiating behaviour with familiar people when compared to the other groups. The Angelman syndrome group also showed the highest prevalence of initiating behaviour with unfamiliar people. The Rubinstein Taybi syndrome group were reported to show the highest prevalence of 'extreme sociability' with unfamiliar people when receiving an interaction and also during an ongoing interaction.

The Down syndrome group were reported to show the highest prevalence of 'extreme sociability' in a group situation with unfamiliar people.

3.6.4. Part Four: Selective Mutism

The approximate rates of selective mutism for individuals in each group who were reported to be verbal are shown in Table 3.8. The results of a chi-square test revealed that there were significant differences between the groups on rates of selective mutism (χ^2 (4) = 22.67, $p < .0001$). A significantly higher proportion of individuals with Cornelia de Lange syndrome were reported to show selective mutism than individuals in several of the contrast groups. A series of pair-wise chi-square tests revealed that significantly more individuals in the Cornelia de Lange syndrome group showed selective mutism than individuals in the Fragile X, Down and Rubinstein Taybi syndrome groups. Odds ratios showed that the Cornelia de Lange syndrome group were 3.08, 8.22 and 4.35 times more likely to show selective mutism than the Fragile X, Down and Rubinstein Taybi syndrome groups, respectively.

Table 3.8: Number of verbal individuals and approximate rates of selective mutism for each group.

	CdLS	AS	FXS	DS	RTS	ASD
n of verbal individuals	42	5	125	107	61	93
n of verbal individuals with information about selective mutism	40	N/A[d]	118	106	59	88
Approximate rate of selective mutism [c]	40%	N/A[d]	17.8%	7.5%	13.6%	18.2%

[a] N in group is based on number of individuals who have information about verbal ability.
[b] Verbal is being reported to speak or sign more than 30 words.
[c] Percentage of participants who answered *yes* to both Q24 and Q25.
[d] Group excluded from further analysis because n is too small.

Finally, the relationship between selective mutism and social anxiety was examined. A series of Mann-Whitney tests revealed that individuals reported to show selective mutism were reported to show significantly higher levels of shyness in all social situations with unfamiliar people than those reported not to show selective mutism. The group reported to show selective mutism scored significantly lower on the Unfamiliar Receive interaction subscale (U = 3550.0, p = .0001), the Unfamiliar Ongoing Interaction subscale (U = 3419.0, $p < .0001$), the Unfamiliar Initiate interaction subscale (U = 3211.0, $p < .0001$) and the Unfamiliar performance subscale (U = 3204.5, $p < .0001$) than those reported not to show selective mutism.

3.7. DISCUSSION

This is the first study to examine sociability across several neurodevelopmental disorders using a reliable measure of sociability for individuals with a range of intellectual disabilities. This study is unique because it is the first to employ contrast groups in order to identify whether social anxiety is characteristic of individuals with Cornelia de Lange syndrome. The study is also the first to empirically examine the age-related patterns of sociability in Cornelia de Lange syndrome and identify whether adolescents and adults with the syndrome demonstrate particular vulnerability to experiencing social anxiety. The results of the study will enhance knowledge of the age-related patterns of sociability in the five contrast groups, which is useful for groups that are less well-researched, such as Rubinstein Taybi syndrome. In addition to examining differences in sociability between the six groups, the study has also examined the proportion of individuals showing extreme sociability and extreme shyness in both familiar and unfamiliar situations in order to generate information about prevalence rates of those who may show hypersociability and those who may experience social anxiety in various social situations. Finally, the study has estimated the prevalence of selective mutism for each group and identify whether a heightened probability of selective mutism is characteristic of Cornelia de Lange syndrome.

A preliminary analysis of the psychometric properties of the SQID indicated good inter-rater reliability at subscale level. Furthermore, the face validity of the questionnaire appears good, with further support for heightened sociability in Down syndrome and Angelman syndrome and heightened social anxiety in Autism spectrum disorder and

Fragile X syndrome. Although, further analysis of psychometric properties is required, the SQID also appears useful because scores seem to be unrelated to degree of disability and severity of Autism spectrum related characteristics. This means that it is suitable for individuals with a range of intellectual disabilities and that the raised prevalence of Autism spectrum disorder reported in a number of genetic syndromes and in the intellectual disability population in general, will not influence the outcome of scores (e.g., Moss & Howlin, 2009).

An analysis of SQID total and subscale scores between the groups indicated that the Cornelia de Lange syndrome group showed social impairments, indicative of extreme shyness. The Cornelia de Lange syndrome group obtained significantly lower total familiar and unfamiliar scores than the Angelman, Down and Rubinstein Taybi syndrome groups indicating that individuals with Cornelia de Lange syndrome are significantly less sociable in familiar and unfamiliar situations than individuals with these syndromes. Furthermore, the levels of sociability shown by the Cornelia de Lange syndrome group in social situations were similar to those evidenced by the Autism spectrum disorder and Fragile X syndrome groups, two groups associated with an increased prevalence of social anxiety (e.g., Bellini, 2004; Bregmann et al., 1988; Hagerman & Sobesky, 1989; Lachiewicz, 1992; La Greca & Lopez, 1998; Lesniak-Karpiak, Mazzocco & Ross, 2003; see sections 1.6.3.1. and 1.6.3.2.). A more fine-grained analysis conducted at subscale level, indicated that the Cornelia de Lange syndrome group appeared to show extreme shyness in all unfamiliar social situations. The Cornelia de Lange syndrome group again were reported to be significantly less sociable than the Angelman, Down and Rubinstein Taybi syndrome groups in all unfamiliar situations examined, with similar levels of

shyness to the Autism spectrum disorder group, being reported in unfamiliar situations. The Fragile X syndrome group were reported to show significantly higher levels of shyness than the Cornelia de Lange syndrome group in three of the four unfamiliar social situations. These results may indicate that the shyness reported in Cornelia de Lange syndrome is not as extreme as that reported in Fragile X syndrome. In summary, it seems that a heightened probability of extreme shyness is characteristic of Cornelia de Lange syndrome, although the impairments do not appear as extreme as those seen in Fragile X syndrome. At this stage, it is difficult to determine whether the extreme shyness in Cornelia de Lange syndrome meets the diagnostic criteria for Social anxiety disorder.

These findings provide support for the literature published on social impairments in Cornelia de Lange syndrome. For example, anecdotal reports of extreme shyness and social anxiety in several participants with Cornelia de Lange syndrome were reported in Moss et al.'s (2008) study. Also, the first empirical case-control study examining social anxiety in Cornelia de Lange syndrome found that children with Cornelia de Lange syndrome showed significantly more hand movements and less eye contact (both indicators of anxiety) at times of social interaction than a comparable contrast group, indicating that social anxiety may be characteristic of individuals with the syndrome (Richards et al., 2009). The findings in the current study are consistent with previous research and suggest that extreme shyness with unfamiliar people appears characteristic of individuals with Cornelia de Lange syndrome. From the current study, it is difficult to determine whether individuals with Cornelia de Lange syndrome show extreme shyness or social anxiety, the clinically significant form of extreme shyness.

An examination of the cut-offs for extreme sociability and extreme shyness showed that the proportion of individuals with Cornelia de Lange syndrome showing extreme shyness with unfamiliar people was relatively high. The prevalence rates of extreme shyness across the unfamiliar social situations ranged from 14.4% to 24.5%. These prevalence rates were similar to those observed in the Autism spectrum disorder group, higher than those seen in the Angelman syndrome, Rubinstein Taybi syndrome and Down syndrome groups but lower than those reported for the Fragile X syndrome group. The Fragile X syndrome group showed the highest prevalence rate of extreme shyness across all unfamiliar social situations, providing further support for the high prevalence of social anxiety associated with the syndrome (e.g., Hall, DeBernardis & Reiss, 2006; Hessl et al., 2006; Lesniak-Karpiak, Mazzocco & Ross, 2003). The prevalence rates for extreme shyness in unfamiliar situations was still high for the Cornelia de Lange syndrome group with at least 20% of individuals reported to show extreme shyness in an unfamiliar ongoing interaction, when approached by an unfamiliar person and in an unfamiliar group situation. A report published on 49 individuals Cornelia de Lange syndrome found that 40% of individuals with the syndrome were quiet, shy and retiring (Kline et al., 2007a). Although the reported prevalence rates were lower in the current study, the current study in line with Kline et al.'s (2007a) findings, provide further support for a raised prevalence of extreme shyness and, perhaps, social anxiety in Cornelia de Lange syndrome.

On the basis of the findings from Chapter Two, it was also important to examine the age-related pattern for sociability in Cornelia de Lange syndrome. The analysis indicated that the *12 to 18 years* age group with Cornelia de Lange syndrome showed significantly lower levels of initiating behaviour with unfamiliar people than the *under 12 years* age group

with Cornelia de Lange syndrome. This finding suggests that a difficulty in initiating interactions with unfamiliar people may be a specific difficulty for adolescents and young adults with Cornelia de Lange syndrome and perhaps indicates a decline in initiating interactions with unfamiliar people during adolescence, although caution must be exercised when interpreting these results due to the cross-sectional nature of this analysis. This age-related pattern appears to be characteristic of the Cornelia de Lange syndrome group as these differences between the age bands were not evident in any of the five contrast groups. Furthermore, these results would suggest that this age-related pattern is atypical because it was only evident in the Cornelia de Lange syndrome group and warrants a closer investigation into determining why this may be happening. Furthermore, there may also be a general characteristic shyness with unfamiliar people in adolescents and young adults with Cornelia de Lange syndrome. Differences between the *under 12 years* and *12 to 18 years* age bands in the Cornelia de Lange syndrome group on the *Unfamiliar Ongoing Interaction* subscale and the *Unfamiliar Receive Interaction* subscale approached significance ($p < .05$) yet this difference was not apparent for the Cornelia de Lange syndrome group on any of the familiar subscales. Investigations into whether there is an age-related pattern of decreased general sociability with unfamiliar people with age would be helpful to determine the nature of the differences reported in this study. However, the fact that none of the contrast groups showed this profile of behaviour would indicate that this age-related pattern is characteristic of Cornelia de Lange syndrome.

These findings provide unique information about the age-related pattern of sociability shown by individuals with Cornelia de Lange syndrome because it provides the first empirical data indicating that individuals show significantly less initiating of interactions

with unfamiliar people during adolescence and early adulthood. The current literature does suggest that there are differences between older and younger individuals in sociability and so these findings do provide further support for this. Sarimski (1997) found that older children with Cornelia de Lange syndrome experienced significantly more social isolation than younger children with Cornelia de Lange syndrome. In a broader study, Basile et al. (2007) found a significant correlation between chronological age and behavioural problems, including communication disturbances and anxiety. Recently, Oliver et al. (in review) found that significantly more adults with Cornelia de Lange syndrome were reported to show impulsivity compared to children with the syndrome. This study, in line with these findings, perhaps suggest that the age-related pattern of a number of behaviours in Cornelia de Lange syndrome changes with age and this encompasses initiating interactions with unfamiliar people, however, further detailed research is needed to investigate this more closely.

The approximate prevalence rates of selective mutism were also examined across the groups in the present study. The approximate rate of selective mutism for verbal individuals with Cornelia de Lange syndrome was reported to be 40%, which was significantly higher than rates reported for the Fragile X, Down and the Rubinstein Taybi syndrome groups. These findings would indicate that selective mutism is characteristic of Cornelia de Lange syndrome. Very little information has been published about selective mutism in Cornelia de Lange syndrome, although anecdotal reports suggest that it is evident. For example, anecdotal reports from Moss et al.'s (2008) study indicated that selective mutism was shown by several participants. Also, the pilot study (Collis et al., 2006) conducted with caregivers of nine adolescents and young adults with Cornelia de

Lange syndrome found that 66.7% of individuals were reported to show selective mutism. The rate of selective mutism reported in the pilot study is higher than that found in the current study. This may be due to the fact that there was a sampling bias in the pilot study as only individuals reported to show behavioural changes with age were recruited for the pilot study, whereas a random sample of individuals with Cornelia de Lange syndrome was recruited for the current study. Although, it was not possible to determine in the current study whether rates of selective mutism were higher in older individuals (due to the small sample of verbal individuals with the syndrome), it may be that selective mutism forms part of the age-related change reported in Cornelia de Lange syndrome and so higher rates of selective mutism would be reported in the pilot study because the sample only consisted of adolescents and young adults. Whether selective mutism becomes more apparent with age needs to be determined.

It is interesting that an investigation into the relationship between selective mutism and social anxiety showed that individuals with selective mutism showed significantly higher levels of shyness in all unfamiliar social situations than those who did not show selective mutism. This supports previous literature on selective mutism which suggests that selective mutism is an extreme form of social anxiety. For example, Black & Uhde (1992) found that nearly all (97%) participants with selective mutism in their study experienced social anxiety, avoidant disorder, or both. The data from the current study contribute to the literature on selective mutism by providing information on an atypical population. This demonstrates that one of the strengths of research into behavioural phenotypes is that information can be used to also inform knowledge about disorders in the typically developing population.

It was interesting to find that the Cornelia de Lange syndrome group showed the highest prevalence of selective mutism. If selective mutism was simply an extreme form of social anxiety, it would have been expected that the Fragile X syndrome group showed the highest rate of selective mutism, given that they showed the highest rates of extreme shyness in all unfamiliar social situations and they obtained the lowest median total and subscale unfamiliar scores. This perhaps suggests that there may be other factors contributing to selective mutism in Cornelia de Lange syndrome. Recent research suggests that perhaps individuals with selective mutism have a phobia of their own speech (Omdal & Galloway, 2008). Omdal & Galloway (2008) also suggest that as a result of selective mutism, individuals may become socially isolated and then develop social anxiety as a secondary problem. This may be apparent in Cornelia de Lange syndrome, particularly given the number of studies demonstrating expressive communication problems in the syndrome (Goodban, 1993; Oliver et al., 2008). Also, findings from Manassis et al.'s (2007) study implicated specific executive functioning deficits in the cause of selective mutism, which may be important in Cornelia de Lange syndrome given the developmental age-related pattern of a number of behaviours in the syndrome. Therefore, it may be that in Cornelia de Lange syndrome selective mutism develops as a result of the expressive communication difficulty and / or executive functioning impairments and then social anxiety develops as a secondary problem to this. In Fragile X syndrome, however, it may be that social anxiety is the primary difficulty. Therefore, different causal pathways may underpin social anxiety in these syndromes.

Although this study focuses on research into the behavioural phenotype of Cornelia de Lange syndrome, some interesting findings were also found for the contrast groups in the current study, which will be briefly mentioned here. Firstly, given the limited information available about sociability in Rubinstein Taybi syndrome, the current study was able to provide further empirical evidence of a heightened level of sociability in this syndrome. This supports the current literature on sociability in Rubinstein Taybi syndrome. Hennekam et al. (1992) found that individuals with Rubinstein Taybi syndrome demonstrated better social communication and social competency skills than individuals with other causes of intellectual disability. A recent questionnaire study also showed that better social contact and social interest, such as, acceptance of physical contact and initiating play with other children, was demonstrated by individuals with Rubinstein Taybi syndrome than a comparable contrast group (Galéra et al, 2009). The current findings, in line with previous research, indicate that there is a heightened level of sociability in Rubinstein Taybi syndrome.

Another interesting finding related to the Angelman syndrome group. Significantly more initiating behaviour was reported for the Angelman syndrome group in both familiar and unfamiliar situations than all other groups participating in the current study. This indicates that high levels of initiating behaviour in social interactions is characteristic of individuals with Angelman syndrome. These findings provide further support for the literature published on sociability in Angelman syndrome. Individuals with Angelman syndrome have been found in previous studies to show high levels of social approach behaviours (Horsler & Oliver, 2006b; Strachan et al., 2009). The current findings provide further

support for the literature indicating that social approach behaviours are characteristic of individuals with Angelman syndrome.

The current study also provided further evidence for the social anxiety commonly reported in Fragile X syndrome (see section 1.6.3.1.). The current study found that rates of extreme shyness in unfamiliar situations ranged from 27.5% to 47.2%. The highest rate of extreme shyness was reported in an unfamiliar group situation, indicating that this situation is the most difficult for individuals with Fragile X syndrome. Interestingly, 4.9% of individuals with Fragile X syndrome were also reported to show extreme shyness in familiar group situations when a rate of 0% or almost 0% was expected. These results indicate that perhaps group situations are particularly difficult for individuals with Fragile X syndrome, which is compounded by the effect of familiarity. This information will provide additional information for the literature on social anxiety in Fragile X syndrome.

Interesting findings about the age-related pattern of sociability in Down syndrome was also identified in the current study. The youngest group (*Under 12yrs*) of individuals with Down syndrome showed significantly higher levels of initiating behaviour with familiar people than the oldest group of individuals with the syndrome (*Over 18yrs*). This suggests that adults with Down syndrome show a difficulty in initiating social interactions with familiar people. This age-related pattern is characteristic of the Down syndrome group and appears atypical, given that none of the other groups showed this difference in behaviour. It may be that this difference relates to the onset of dementia in Down syndrome, which is relatively common in the syndrome (Holland et al., 1998). However, this was not assessed

in the current study. It would be interesting to investigate this relationship further in a future study.

There are several limitations to the study that need to be taken into consideration when interpreting the current findings. Firstly, psychometric properties, including test-retest reliability and construct validity were *not* examined in the current study due to time constraints. Therefore, caution must remain when interpreting the data until a full investigation into all the psychometric properties of the SQID has been undertaken. However, the face validity and the inter-rater reliability are good, suggesting this is a promising screening measure of sociability for individuals with a range of intellectual disabilities. The informant-based nature of the assessment is a strength for research with individuals who have intellectual disabilities, however, the fact that it is a questionnaire and not a direct experimental assessment limits the amount of detailed information that can be drawn from the study. This study has been useful, however, in allowing a large group comparison study of sociability across relatively rare neurodevelopmental disorders and provides useful information about the age-related pattern of sociability in each group. The cross-sectional nature of the study was also a limitation when trying to draw inferences about the age-related pattern of sociability in Cornelia de Lange syndrome and the five contrast groups due to potential cohort effects. However, the inclusion of a number of contrast groups helped to indicate whether an age-related pattern of sociability appeared atypical. Finally, an interesting issue that became apparent was the interpretation of the results of the study. If a significant difference was found between two groups it was difficult to know whether this meant that one group showed a heightened level of sociability to that which would be expected or whether the other group showed a lower

level of sociability in comparison to that which would be expected. The use of cut-offs for examining extreme sociability and extreme shyness helped determine which groups showed a higher prevalence of extreme sociability and extreme shyness and also comparing the findings with other research helped to determine whether the results were consistent with research on other groups, such as, Fragile X and Angelman's syndromes (e.g., Freund et al., 1993; Hall et al., 2006; Hessl et al., 2006; Horsler & Oliver, 2006a; see sections 1.1.3.2. and 1.6.3.1.). The interpretation of results in cross-syndrome comparisons remains a challenge for this type of research.

This is the first study to develop an informant-based measure of sociability for individuals with a range of intellectual disabilities and use it in a large-scale study to compare sociability across groups of individuals with neurodevelopmental disorders and examine how the trajectories of sociability differ. The current study demonstrated that extreme shyness appears to be characteristic of individuals with Cornelia de Lange syndrome, providing further support for more recent evidence published on social impairments in the syndrome. Furthermore, this study is one of the first to provide information about the 'atypical' age-related pattern of sociability with unfamiliar people in Cornelia de Lange syndrome. It seems that initiating social interactions with unfamiliar people is problematic for individuals with Cornelia de Lange syndrome in adolescence and early adulthood and this difficulty may be part of a more general shyness with unfamiliar people at this time. Given that a number of other behavioural changes have been reported in Cornelia de Lange syndrome with age, it may be that these age-related differences are underpinned by a common causal pathway. Further investigations are needed to investigate this fully. The current study also demonstrated that high prevalence rates of selective mutism are apparent

in Cornelia de Lange syndrome and this appears characteristic of the syndrome. The causes of selective mutism in Cornelia de Lange syndrome warrant further investigation because it is likely that social anxiety is not the only cause of selective mutism in this syndrome. In summary, extreme shyness with unfamiliar people appears characteristic of Cornelia de Lange syndrome and this appears to become more apparent with age. Furthermore, individuals with Cornelia de Lange syndrome show a heightened probability of experiencing selective mutism, which may be due to causes other than solely social anxiety.

CHAPTER FOUR

An Experimental Study of Sociability in Cornelia de Lange syndrome

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4.1. PREFACE TO CHAPTER FOUR

The study conducted in Chapter Three has provided further support and empirical evidence for a heightened probability of extreme shyness being characteristic of individuals with Cornelia de Lange syndrome. Whether the extreme shyness reported in this group is consistent with a diagnosis of social anxiety is difficult to determine from a questionnaire-based study. A further complicating factor in determining whether individuals with Cornelia de Lange syndrome do experience social anxiety is that the diagnostic criteria for social anxiety are not readily applicable to those with a more severe degree of intellectual disability since this definition involves being able to access and express cognitions and emotions. Therefore, an experimental study employing behavioural indicators of social anxiety, similar to those reported in the Fragile X syndrome literature (see section 1.8.5.), will help identify in more detail, the phenomenology of the social impairments reported in Cornelia de Lange syndrome.

The developmental trajectory of sociability in Cornelia de Lange syndrome was examined in Chapter Three, based on findings from Chapter Two, which provided further evidence for differences in behaviour and emotion across age groups in Cornelia de Lange syndrome. The findings in Chapter Three also provided empirical evidence for differences across age groups in initiating social interactions with unfamiliar people; individuals in adolescence and early adulthood with Cornelia de Lange syndrome were reported to show significantly less initiating behaviour with unfamiliar people than younger individuals with the syndrome. Although, it is not fully clear from the results of the study in Chapter Three, this difference between younger and older individuals with the syndrome may be part a broader difference in sociability with unfamiliar people. A closer examination of the effect of the familiarity of people on interactions with individuals who have Cornelia de Lange syndrome is needed to fully understand how this affects individuals in social situations.

Chapter Three has provided useful empirical evidence suggesting that there are differences in levels of sociability in individuals of different ages with Cornelia de Lange syndrome. The advantage of initially conducting a questionnaire study is that it provided information about a large number of individuals who have a rare genetic syndrome in order to provide initial empirical evidence and an indication of the difficulties for individuals with Cornelia de Lange syndrome in social situations. Furthermore, it provided information about the probable developmental trajectory of sociability in Cornelia de Lange syndrome and determined a vulnerable time period for experiencing a decline in sociability with unfamiliar people, more specifically initiating interactions. Based on these findings, there is now a need to conduct an experimental assessment of social anxiety employing

behavioural indicators, to examine the phenomenology of social impairments in Cornelia de Lange syndrome.

When conducting a closer examination of the phenomenology of social impairments it is important to remain mindful of the extremely high rates of selective mutism reported in Cornelia de Lange syndrome. In Chapter Three, 40% of individuals with Cornelia de Lange syndrome were reported to show selective mutism and this rate was significantly higher than three contrast groups, including Fragile X syndrome a group reported to show the most extreme form of shyness in the questionnaire study. This indicates that there may be other important factors contributing to the social impairments reported in Cornelia de Lange syndrome, such as the expressive language difficulty or executive functioning impairments. As part of an examination of the phenomenology of social impairments in Cornelia de Lange syndrome, a closer examination of verbalisation is crucial if we are to fully understand the nature of social impairments in this group. Furthermore examining the relationship between social impairments and executive functioning will also be important to provide initial information about whether these impairments are perhaps underpinned by cognitive impairments.

4.2. ABSTRACT

4.2.1. Background: Evidence suggests that extreme shyness may be characteristic of adolescents and adults with Cornelia de Lange syndrome (see Chapter Three), however the phenomenology of these impairments is not well documented. The current study will develop and apply an experimental assessment of social anxiety in a group of adolescents and adults with Cornelia de Lange syndrome to determine the nature of the social impairments experienced by this group. The study will also examine whether social impairments identified in the Cornelia de Lange syndrome group are related to specific impairments in executive functioning.

4.2.2. Method: Social tasks compromising three experimental conditions were administered by both a familiar adult and an unfamiliar adult, separately, with a group of individuals with Cornelia de Lange syndrome (n = 25; % male = 44; mean age = 22.16; *SD* = 8.81) and a comparable group of individuals with Down syndrome (n = 20; % male = 35; mean age = 24.35; *SD* = 5.97). The BRIEF-P, an informant measure of executive function, was administered to participants' caregivers.

4.2.3. Results: The duration of verbalisation differed between the groups. Significantly less verbalisation was observed in the Cornelia de Lange syndrome group than the Down syndrome group in conditions requiring the initiation of speech. In the Cornelia de Lange syndrome group, impairments in verbalisation were not associated with a greater degree of intellectual disability but were significantly correlated with impairments in both planning

and working memory. This pattern of results was not evident in the Down syndrome group.

4.2.4. Conclusions: Adolescents and adults with Cornelia de Lange syndrome have a specific difficulty with the initiation of speech when social demands are placed upon them. This impairment in verbalisation may be underpinned by specific cognitive deficits, although further research is needed to investigate this fully.

4.3. INTRODUCTION

In Chapter Three it was noted that comparatively less research has been published on sociability in genetic syndromes compared to other aspects of behaviour. The research that is published has revealed a spectrum of profiles of sociability across genetic syndromes, which appears unrelated to degree of intellectual disability. This spectrum includes a heightened level of sociability evident in Angelman, Williams and Down syndromes, as well as social anxiety in Fragile X and Turner's syndromes (see section 3.3.).

In Chapter Three, the limited literature on social impairments in Cornelia de Lange syndrome was reviewed and this provided the basis for the quantitative questionnaire-based study undertaken (see section 3.3.). The results from the questionnaire study revealed that the prevalence rate of 'extreme shyness' in Cornelia de Lange syndrome was relatively high, ranging from 14.4% to 24.5%, in four types of unfamiliar social situations. This rate was similar to that seen in an Autism spectrum disorder group, in which an increased prevalence of social anxiety is evident (Bellini, 2004). The results also indicated that the developmental trajectory of shyness may change with age in Cornelia de Lange syndrome. Individuals with Cornelia de Lange syndrome aged between 12-18yrs were reported to initiate significantly less social interactions with unfamiliar people than those aged under 12 years. Differences between these age bands approached significance on two other unfamiliar interaction subscales (ongoing interaction with an unfamiliar person and being approached by an unfamiliar person), indicating that interactions with unfamiliar people in general may become more problematic for individuals with Cornelia de Lange syndrome when they reach adolescence. These findings should be interpreted with caution

because a cross-sectional design was employed so the results may be due to cohort effects. However, given that none of the five contrast groups showed a relationship between sociability and age in interactions with unfamiliar people, it is *less* likely that a cohort effect may account for the results found in the Cornelia de Lange syndrome group. It is therefore *more* likely that there is a specific change with age in Cornelia de Lange syndrome around adolescence, evidenced by a marked decline in sociability with unfamiliar people, with particular difficulties in initiating interactions.

In Chapter Three it was also shown that there is a high rate of selective mutism reported in Cornelia de Lange syndrome, with approximately 40% of verbal individuals being reported to experience selective mutism. This is a rate of at least double that of all four contrast groups utilised in the analysis. Selective mutism was initially conceptualised as an extreme form of social anxiety but more recent research alludes to a phobia of expressive language (Omdal & Galloway, 2008). Another recent study has also found that children with selective mutism had significant deficits in visual memory in comparison to two contrast groups and in nonverbal working memory in comparison to one of the contrast groups, although this was not consistent across all the non-verbal measures (Manassis et al., 2007). This evidence may indicate that specific executive functioning deficits are implicated in the cause of selective mutism and shows that it may be important to investigate this relationship in Cornelia de Lange syndrome. Given that the Cornelia de Lange syndrome group were reported to show a significantly higher rate of selective mutism than individuals with Fragile X syndrome, a group known to experience social anxiety, it suggests that perhaps other factors, apart from social anxiety, are important in the cause of selective mutism in Cornelia de Lange syndrome.

In keeping with the findings from Omdal & Galloway's (2008) study, the high rates of selective mutism in Cornelia de Lange syndrome may be associated with the expressive communication difficulties commonly reported in the syndrome. The majority of individuals with Cornelia de Lange syndrome show a discrepancy between expressive and receptive language, with marked difficulties in expressive language (Oliver et al., 2003; Oliver et al., 2008). Goodban (1993) found that 33% of participants with Cornelia de Lange syndrome had no or only one or two words, 67% of participants aged four years or over had an expressive vocabulary of at least three to ten words and 53% of individuals aged four and over were able to combine two or more words. Interestingly, Goodban (1993) also reported anecdotally that those individuals who have speech are often reluctant to use it. It may be that there is a specific problem in expressive communication even for those individuals with Cornelia de Lange syndrome who develop speech. Given that the data in Chapter Three indicated that extreme shyness is characteristic of individuals with Cornelia de Lange syndrome, it is possible that an expressive communication problem interacts with anxiety so that anxiety causes further problems with communication.

The evidence so far suggests that individuals with Cornelia de Lange syndrome do show social impairments in the form of extreme shyness and perhaps social anxiety. These social impairments appear to be particularly evident in adolescents and adults with the syndrome, who appear to show difficulties in social interactions with unfamiliar people, with particular problems in initiating interactions. Individuals with Cornelia de Lange syndrome also show extremely high levels of selective mutism, which may be related to a specific expressive communication problem and / cognitive impairments. An experimental

study focusing on verbal adolescents and adults with Cornelia de Lange syndrome would be able to detail the phenomenology of these social impairments in Cornelia de Lange syndrome and examine the effect of aspects of social interactions on speech initiation.

Although one experimental study on social anxiety in Cornelia de Lange syndrome has been published to date, the conclusions that can be drawn from the study are limited by the experimental design and methods (Richards, Oliver, Moss, O'Farrell & Kaur, 2009). In the study, three behavioural indicators of social anxiety were examined in response to two sets of social interaction with an unfamiliar adult for twelve children with Cornelia de Lange syndrome (mean age of 11 years) and twelve matched children with Cri du Chat syndrome. No control for the effect of familiarity of the other person in the interaction and no comparison for the high attention condition (i.e. a low attention condition) were incorporated into the design of the study. Also, the use of only three behavioural indicators of social anxiety excluded other important indicators, such as facial expression. Another major limiting factor was the inclusion of only children in the study because research suggests it is older individuals with Cornelia de Lange syndrome who experience extreme shyness (see section 3.3.). This perhaps explains why no significant differences were found between the groups in the overall frequency or duration of the behavioural indicators used. A more refined experimental design targeting the appropriate age group is needed to examine the phenomenology of social impairments in Cornelia de Lange syndrome.

The use of experimental assessments to examine social anxiety is not unusual in the typically developing population. Experimental assessments have been utilised for both

typically developing children and adults to assess social anxiety (e.g., Beidel et al., 1989; Harb et al., 2003; Norton & Hope, 2001; Rao et al., 2007; Thompson & Rapee, 2002) (see section 1.8.3.5.). However, there is still no 'gold-standard' experimental measure of social anxiety because experimental designs are typically constructed to test hypotheses about the nature of social anxiety. Experimental assessments of social anxiety either comprise a general assessment of social anxiety, examining both performance and interaction anxiety, or, if the person reports experiencing difficulty in a particular social situation, an experimental condition will be constructed to examine that situation, e.g., speaking to someone in authority (e.g., Norton & Hope, 2001; Thompson & Rappe, 2002; Trower, 1980).

There has been a move towards the experimental assessment of social impairments in the intellectual disability research literature (see section 1.8.5.). The move towards an experimental assessment of social impairments has been most notable in the Fragile X syndrome literature (e.g., Lesniak-Karpiak, Mazzocco & Ross, 2003). Several studies on Fragile X syndrome have employed experimental conditions to provide a more detailed picture of the behavioural responses to specific social situations. It has also allowed researchers to determine if there are specific social situations (antecedents) which evoke anxiety-behaviours.

Cohen et al. (1988) constructed two conditions in which individuals with Fragile X syndrome interacted with both a familiar and unfamiliar person and this interaction was compared to individuals with autism. Eye contact was examined because it has been well documented that gaze aversion is one of the most characteristic features of individuals with

Fragile X syndrome (Garrett et al., 2004; Wolff et al., 1989). The experimental study showed that individuals with Fragile X syndrome evidenced different levels of eye contact between familiar and unfamiliar adults, whilst individuals with autism did not.

Lesniak-Karpiak et al. (2003) published data on one experimental condition in which females with Fragile X syndrome, females with Turner Syndrome and females who had neither syndrome were asked to participate in a role-play. Participants assumed the role of a neighbour and were instructed to initiate and maintain a conversation with a confederate who assumed the role of a new person that had just moved into their area. A series of analyses revealed that females with Fragile X syndrome took significantly longer to initiate conversation and showed significantly more hand wringing during the conversation than females in both contrast groups. Confounding factors in the study may to some extent explain why some differences were not identified between the groups. The duration of the experimental condition was only 105 seconds, which may not have been long enough to provide enough data to detect significant differences between the groups. The scenario itself involved a very specific situation, which may not be a relevant anxiety-provoking situation for all females with Fragile X syndrome. Despite these confounding factors, the experimental design was a novel way of assessing anxiety in females with Fragile X syndrome.

Two studies have been published that have incorporated similar methodologies (Hall et al., 2006; Hessl et al., 2006). Both studies employed four social challenge tasks: an interview with the experimenter, reading silently, reading aloud and singing aloud. Hall et al. (2006) carried out the social challenges with females and males with Fragile X syndrome. They

examined several indicators of anxiety and found that the three most prevalent problem behaviours across all conditions for males and females with Fragile X syndrome were face hiding, fidgeting and refusals. The researchers used this methodology to demonstrate that specific social demands evoked escape behaviours. However, the study did not employ a contrast group thus it could not be determined whether these behaviours were specific to the syndrome or due to more general impairments, such as, degree of disability. Conversely, Hessl et al. (2006) employed a contrast group of the participants' siblings. The researchers were then able to determine whether or not there was any relationship between behaviour in families or whether it was independent of this. However, by not employing a group matched for mental age, it was still not possible to determine whether the differences were just an effect of cognitive impairments associated with the syndrome. Furthermore, there were specific problems with the Social Challenge tasks, which meant that they may not mimic realistic social situations for individuals with intellectual disabilities.

On the basis of published research, it is clear that experimental methodology involving manipulations of social demand is an effective way to gain a detailed picture of social impairments in individuals who have an intellectual disability. However, careful consideration about the nature of the social tasks is important due to the limitations of previous experimental designs utilised in the literature. One important consideration is the examination of the behaviour of the other person in the interaction, which has not been examined in the Fragile X syndrome literature on social anxiety. Research in other genetic syndromes, such as, Down and Angelman's syndromes, have considered the importance of the inter-play between participant and adult behaviour (e.g., de Falco et al., 2009; Horsler

and Oliver, 2006b; Oliver, Demetriades and Hall, 2002; Venuti et al., 2009). Oliver, Demetriades, and Hall (2002), for example, demonstrated that three children with Angelman syndrome laughed and smiled more in an ongoing social interaction than in control conditions. Horsler and Oliver (2006b) extended this finding further, in a study of thirteen children with Angelman syndrome, by demonstrating that smiling, touch, eye contact and speech from adults were important in eliciting smiling and laughing in participants. Considering the behaviour of the other person in the interaction, is an important consideration for the current study because a reduction in verbalisation by individuals with Cornelia de Lange syndrome may have an impact upon the vebalisation of the other person in the interaction, e.g., the other person may use more prompts. The current study will also examine the behaviour of the other person in the social interaction.

The studies which have employed experimental methods demonstrate the importance of employing an appropriate contrast group so that any impairments identified are not related to degree of disability. Individuals with Down syndrome are one of the most widely used contrast groups in the behavioural phenotype literature because Down syndrome is a well described group. In the current study a group of individuals with Down syndrome will be employed as the contrast group. An examination of the social profile of individuals with Down syndrome suggests that sociability in this group is not impaired and individuals with Down syndrome may show heightened levels of sociability (e.g., Gibbs & Thorpe, 1983; Kasari & Freeman, 2001; Kasari & Sigman, 1996). Although, this may have an impact on the way in which the results of the current study can be interpreted, individuals with Down syndrome also show significant impairments in expressive language, which affects their ability to initiate and maintain conversation (e.g., Chapman & Hesketh, 2000). Given that

one focus for this study is the impact of social interaction on speech in Cornelia de Lange syndrome, it is important to include a group with comparable difficulties in language.

In addition to comparing the phenomenology of sociability in these two groups, it is also important to consider the processes that may be underpinning the social impairments in Cornelia de Lange syndrome. Recent literature on a number of disorders suggests that specific social impairments are associated with specific executive function processes. The literature on schizophrenia, for example, has identified a relationship between social impairments and executive functioning. Addington and Addington (1999) found a relationship between cognitive flexibility and interpersonal problem solving skills in individuals with schizophrenia. The literature on Autism spectrum disorder has generated a wealth of information implicating theory of mind deficits in underpinning social impairments characteristics of the disorder (e.g., Baron-Cohen et al., 1985). Interestingly, research into theory of mind deficits in Fragile X syndrome has demonstrated that theory of mind deficits associated with the syndrome, are likely to be underpinned by impairments in working memory (Grant, Apperly & Oliver, 2007). More recent research has also identified that specific executive processes may underpin the social impairments reported in the disorder. For example, a study examining the relationship between executive functioning and joint attention impairments in children with Autism spectrum disorder found that ventromedial test performance was related to joint attention (Dawson, Meltzoff, Osterling, Rinaldi & Brown, 1998). These studies demonstrate that social impairments may be related to and underpinned by impairments in executive functioning.

In the current study, the relationship between executive functioning and social impairments will be examined in order to identify whether impairments in social interactions in Cornelia de Lange syndrome may be underpinned by specific cognitive impairments. Although, theory of mind deficits may also be important due to the strong association found between theory of mind deficits and social impairments in Autism spectrum disorder, theory of mind abilities *will not* be considered in the current study. This is mainly due to the different phenomenology of social impairments seen in Cornelia de Lange syndrome compared to idiopathic autism. Also, the evidence suggests that social impairments in Cornelia de Lange syndrome may form part of a broader age-related change in behaviour and emotion, meaning that it is more likely that there are cognitive changes with age, leading to broader behavioural changes, and so examining cognition in relation to social impairments may be more important in Cornelia de Lange syndrome.

The current study was conducted as part of a larger study examining behaviour and cognition in more able adolescents and adults with Cornelia de Lange syndrome and only some of the data will be reported here. This part of the study aimed to examine the phenomenology of social impairments in verbal adolescents and adults with Cornelia de Lange syndrome. The study will focus on more able individuals with Cornelia de Lange syndrome who are verbal so that the effect of social demands on speech can be examined, particularly given the evidence of these problems identified in previous research. The study will employ a contrast group of individuals with Down syndrome to control for the effect of degree of disability and expressive language problems. As no 'gold-standard' assessment of social anxiety exists for this population, the study will employ novel experimental conditions which systematically manipulate both the *level of social demand*

and the *familiarity of the other person in the interaction*, so these effects on participants' social behaviour, including expressive language can be examined. The behaviour of the other person in the interaction will also be examined. A preliminary investigation into the association between any specific social impairments identified in the Cornelia de Lange syndrome group and cognitive impairments associated with executive function will finally be conducted.

In summary, there are two main aims to the current study:

1. To detail the phenomenology of the social impairments in adolescents and adults with Cornelia de Lange syndrome and examine the effect of both social demands and the familiarity of the other person in the interaction on these behaviours.

2. To examine the association between any social impairments identified in the Cornelia de Lange syndrome group and executive functioning.

4.4. METHOD

4.4.1. Participants

The current study was undertaken as part of a larger project on behaviour and cognition in more able people with Cornelia de Lange syndrome. 25 participants with Cornelia de Lange syndrome (11 males and 14 females) aged between 13 and 42 years (mean age = 22.16; *SD* = 8.81) and 20 participants with Down syndrome (7 males and 13 females) aged between 15 and 33 years (mean age = 24.35; *SD* = 5.97) took part in this study. All participants were verbal and mobile. Individuals with Cornelia de Lange syndrome were recruited both directly through a research database held at the University of Birmingham and indirectly through the Cornelia de Lange syndrome Foundation (UK & Ireland), the parent support group. Participants with Down syndrome were recruited through the research database.

Individuals with Cornelia de Lange syndrome and Down syndrome were recruited directly through the database if they had provided consent to take part in future research and met inclusion criteria which indicated they would be able enough to participate. The inclusion criteria were as follows: a diagnosis of the relevant syndrome from an appropriate professional, aged 12 years or over, able to speak more than 30 words, mobile and a self help score on the Wessex Scale (Kushlick, Blunden & Cox, 1973) of seven or more (maximum score is 9), indicating that they were able or at the upper end of partly able in terms of self help skills or had a receptive vocabulary age equivalent score on the Vineland

Adaptive Behavior Scale (VABS; Sparrow, Balla & Cicchetti, 1984) of 40 months or more.

Individuals with Cornelia de Lange syndrome were also recruited indirectly via the Cornelia de Lange Syndrome Foundation (UK & Ireland). Two methods of recruitment were used. First, an advert about the study was published in the magazine produced by the parent support group. Secondly, the Cornelia de Lange syndrome Foundation sent flyers to all families for whom they had contact details and who had not already been approached directly. In total, 325 flyers were sent to families living in England, Scotland and Wales (Ireland was deemed to be too far away, given the limited resources that were available). Both the advert in the magazine and the flyer provided families with information about the study, who would be eligible for the study and contact details. To be eligible for the study, the person with Cornelia de Lange syndrome was required to have a diagnosis of Cornelia de Lange syndrome from an appropriate professional, be aged 12 years and over, be mobile and speak in two to three word phrases or in sentences. It was made clear that individuals with Cornelia de Lange syndrome who had speech but only used it in certain situations (selective mutism) were still eligible for the study. Families who responded to the flyer or the advert in the magazine were screened over the phone to ensure the participants were able enough to take part.

In total, 34 families of individuals with Cornelia de Lange syndrome were interested in taking part. From these, five did not take part in the study for various reasons (one was too far away, two were due to illness, one was not able enough after screening and one showed significant behavioural deterioration before the research visit), two individuals with

Cornelia de Lange syndrome withdrew their consent to take part in the study because they felt so anxious about being visited by someone they did not know and two individuals with Cornelia de Lange syndrome took part in the study but did not sit down long enough to complete the Social tasks. In total 25 participants with Cornelia de Lange syndrome took part in the study.

24 families of individuals with Down syndrome showed interest in taking part in the study. Three did not take part for various reasons; one had moved to another country, one was on holiday and one could not be contacted. 21 individuals with Down syndrome took part in the research visits but the Social tasks did not record for one participant due to an error with the camera so observational data are only available for 20 participants with Down syndrome.

A comparison of the group demographics, demonstrated that the two groups did not differ in terms of age, gender, receptive language and adaptive behaviour (see Table 4.1).

Table 4.1: A comparison of demographic information between the Cornelia de Lange and Down syndrome groups.

			CdLS	DS	T / χ^2	df	*P*
N			25	20			
Age (years)		Mean	22.16	24.35	-.95	43	.35
		(SD)	8.81	5.97			
		Range	13-42	15-33			
Gender		% Male	44	35	.38	1	.54
Speech		% Verbal	100	100			
Mobility		% Mobile	100	100			
BPVS							
	Raw score	Mean	67.12	69.25	-.34	43	.74
		(SD)	19.96	22.30			
	Age equivalence (yrs)	Mean	6.16	6.45	-.41	43	.69
		(SD)	2.12	2.68			
VABS	Communication domain standard score	Mean	50.44	50.80	-.06	38	.96
		(SD)	17.58	24.01			
	Daily Living Skills Domain standard score	Mean	56.56	57.20	-.15	38	.88
		(SD)	14.18	10.36			
	Socialisation Domain standard score	Mean	57.52	53.40	.55	22.38	.59
		(SD)	18.00	25.61			
	ABC standard score	Mean	54.64	51.33	.58	38	.56
		(SD)	16.58	18.68			

4.4.2. Measures

4.4.2.1. Demographic Questionnaire

The Demographic Questionnaire was used to obtain background information regarding age, gender and diagnostic status (whether a diagnosis had been made and by whom the diagnosis was made by).

4.4.2.2. The British Picture Vocabulary Scale – Second Edition (BPVS II; Dunn, Dunn, Whetton & Burley, 1997)

The BPVS II is used to assess receptive vocabulary for standard English in typically developing children aged between 3 years and 16 years. The assessment comprises 168 items which are presented as fourteen sets of twelve items. The administration of the test allows basal and ceiling levels to be established without needing to administer the entire test. For each item, a participant is presented with four alternative pictures in a stimulus book. The examiner orally presents a word to the individual and the person is asked to select the picture which most accurately represents the meaning of the word. The test has been standardised on individuals who are typically developing and it has been reported to be psychometrically robust with good validity and reliability. The median of the split-half values for the raw scores is .86.

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

The EOWPVT is used to assess the verbal expression of language in children aged between two and eighteen years. The test comprises 100 pictures of objects. Participants are presented with a picture and asked to name the object shown. The test is discontinued when a participant makes six continuous errors. The test does not require a participant to be able to read or write. It has been standardised using a sample of US children. The internal consistency is reported to range from .84 to .92 with a median coefficient of .90.

4.4.2.4. The Vineland Adaptive Behavior Scale-II (VABS-II; Sparrow, et al., 2005)

The VABS-II is a semi-structured interview divided into four domains: Communication, Daily Living Skills, Socialisation and Motor Skills. Each domain is divided into three further subdomains. An overall Adaptive Behavior Composite Score may also be derived. Scores are based on how a person typical behaves, not on what they are able to do. Sparrow et al. (2005) found that internal consistency ranged from .83-.94 across the domains and it ranged from .69-.89 across the subdomains.

4.4.2.5. Behaviour Rating Inventory of Executive Function-Preschool version (BRIEF-P; Gioia, Espy & Isquith, 2003)

The BRIEF-P is an informant based questionnaire used to examine potential deficits in several areas of executive function. The questionnaire consists of 86 items. For each item, an informant rates whether a specific behaviour has been a problem for their child over the last six months using a three-point Likert scale (never, sometimes and always). The BRIEF-P is comprised of two domains: Behavioural Regulation Index (BRI) and Metacognition Index (MI). The BRI consists of three sub-domains: inhibit, shift and emotional control and the MI consists of five sub-domains: initiate, working memory, plan / organise, organisation of materials and monitor. The sum of the BRI and MI produces a Global Executive Composite score (GEC). Higher scores on the BRIEF are suggestive of greater perceived deficits. The psychometric properties of the BRIEF appear robust. Studies conducted with the BRIEF have demonstrated that it "captures profiles" of executive functioning that differ across various disorders, including Attention-Deficit

Hyperactivity Disorder and Autism spectrum disorder (Gioia, Isquith, Kenworthy, & Barton, 2002).

4.4.2.6. Social tasks

The Social tasks are designed to assess experimentally whether behaviours indicative of anxiety are evoked by various social situations. The Social tasks are comprised of four conditions. See Table 4.2 for a full description of each condition. One condition is a *Control condition* and three conditions are *Experimental conditions*. The Experimental conditions are designed so that they systematically place increasingly more social demands upon the participant by manipulating the level of demand in each condition. The Experimental conditions are *Low demand*, *High demand* and *Very high demand*.

The *Control condition* is a modified version of the 'Break' condition from modules three and four of the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2000). During this condition, the participant and adult are sat at a table. The participant is given some items (paper and pens, newspaper, magazine and some puzzles) to engage with, whilst the adult either does some work or reads a magazine. At no point during the condition does the adult put any social demands upon the participant. However, the adult is still in close proximity to the participant during this condition to control for the presence of the adult in the experimental conditions. The *Control condition* lasts for approximately four minutes.

Table 4.2: Detailed description of Social tasks.

		Description of Social tasks
CONTROL	**Unfamiliar**	The unfamiliar adult and the participant are sat at a table. The unfamiliar adult says, "*Let's take a break. I need to make some notes to remember what has happened so far during the morning. Whilst, I am making notes, I have brought some items that may interest you. Feel free to use any of them*". The unfamiliar adult shows the participant the 'Break' materials. If the participant is unfamiliar with any of the 'Break' objects, the unfamiliar adult then demonstrates how they work. If nothing interests the participant, the adult asks the participant if there is anything else they would like to do. Once the participant appears settled, the unfamiliar adult starts the stop watch and appears to be making notes at the table. If the participant tries to engage with the adult, the adult should respond briefly but positively and tell the participant that they need to finish their work before carrying on. The condition is timed so that it lasts for approximately four minutes.
	Familiar	The condition is very similar to the unfamiliar control condition. However, rather than needing to make some notes, the familiar adult says that they are going to read a magazine. If the participant tries to engage with the adult during the condition, the familiar adult should say that they want to finish reading the article before carrying on.
LOW DEMAND	**Unfamiliar**	The unfamiliar adult and the participant are sat at a table. The unfamiliar adult says, "*I've brought some holiday photos with me today. They are from my holiday last year. I thought it would be nice to show them to you*". The unfamiliar adult proceeds to show the participant a series of twenty photographs, presenting each photograph for approximately three seconds (adult estimates time). After every other photograph, the unfamiliar adult makes a pre-determined bold statement about the scene in the photograph so in total ten statements (an equal number of positive and negative statements) are made by the adult. Each statement is written on the back of the corresponding photograph so the unfamiliar adult can refer to it subtly without having to memorise the statements (see *Appendix C* for the list of statements used in this condition). The statements used in this condition would naturally elicit someone to ask a question about the holiday and so provide the participant with an opportunity to initiate a conversation with the adult. However, there is *no* expectation upon the participant to do this, which reduces the social demand of the condition. The participant also has the opportunity to make comments about the photographs, which the adult does not comment on. If the participant initiates a conversation with the adult about the holiday, the adult makes up an appropriate answer to the question and then carries on showing the photographs. This condition is not timed and finishes when the unfamiliar adult shows the participant the last photograph and has given the participant chance to comment if they wish to do so.
	Familiar	The condition is very to the unfamiliar Low demand condition apart from the fact that the familiar adult tells the participant that they have found some old holiday photographs that they have not shown them before. The familiar adult pretends that they went on holiday to Thailand a long time ago. The photographs and the statements used in this condition are different to those used by the unfamiliar adult (see *Appendix C* for the list of statements used in this condition). The principal of the statements is the same as those used in the unfamiliar condition.
HIGH DEMAND	**Unfamiliar**	The unfamiliar adult and the participant are sat at a table. The unfamiliar adult says, "*Today, I just wanted to have a chat with you so we can get to know each other a bit better. I wondered whether it would be ok if I ask you a few questions? [Wait for response]. Feel free to ask me any questions if you want to*". Three suggested topics of conversation, with questions are provided for the unfamiliar adult so that they may use it during the conversation, however, there is no expectation that they have to use these topics given that it is not always appropriate for each participant and the topic of conversation may change depending on what the participant says. See *Appendix C* for list of topics and questions. The main point is that the conversation remains as natural as possible. When the unfamiliar adult asks the participant a question, he / she should remain neutral in expression. However, when the participant is speaking, the unfamiliar adult should show positive facial expressions,

		such as smiling and use supportive non-verbal gestures, such as nodding, when it is appropriate to do so. For example, the adult may smile in response to a smile shown by the participant when he / she is talking. If the person asks the adult a question, the adult should responds as they would normally. The unfamiliar adult should try to incorporate both open-ended and closed-ended questions being conscientious about incorporating as many open-ended questions as possible. If the adult asks a question and the person *does not* respond after approximately ten seconds (adult estimates time), the adult should prompt the participant with a 'yes/no' question. For example, if the adult asks, "What is your favourite TV programme?" and the participant *does not* respond after 10 seconds, the adult could then ask, "Is it Eastenders?", "Is it Coronation Street?" etc. The adult should try not to ask more than three prompt questions together. If the participant still does not respond to the prompts, the adult should just move onto another question. If the participant is asked a closed-ended question and *does not* respond after approximately ten seconds (adult estimates time), the unfamiliar adult should say, "*It is ok to nod and shake you head in response to the questions, if that's easier for you*". The examiner should ask the question again and then wait for approximately another ten seconds (adult estimates time) for a response (verbal or non-verbal) before moving onto another closed-ended or open-ended question.
	Familiar	The condition is similar to that conducted with the unfamiliar adult apart from the suggested topics and questions are different. See *Appendix C* for list of topics and questions.
VERY HIGH DEMAND	**Unfamiliar**	The unfamiliar adult and the participant are sat at a table. The unfamiliar adult says, "*You will see a cartoon, which tells a story. I want you to have a look at the cartoon and then stand up and retell the story to me*". The unfamiliar adult places the first cartoon in front of the participant. The adult provides an explanation of the cartoon (see *Appendix C* for explanations of both cartoons). After the adult provides the explanation, they should ask the participant to stand up and retell the story. The person *must* leave the cartoon on the table so their hands are free. If the participant *does not* say anything after thirty seconds of being stood up (estimate time with watch), the unfamiliar adult prompts the participant with the story and then asks the participant to retell it. If the participant doesn't say anything after another minute (estimate time with watch), the unfamiliar adult should move onto the next cartoon. If the participant has a period of silence during the cartoon lasting for thirty seconds or more, the adult should prompt the participant with the relevant bit of the story. After the first cartoon has been presented the unfamiliar adult should say, *"I am going to show you another cartoon, which tells story. Once you have looked at the cartoon, I want you to stand up again and retell the story to me"*. The same procedure should then be used with the second cartoon. This condition is not timed and finishes once the second cartoon is completed.
	Familiar	This condition is carried out in the same way by the familiar adult.

The *Low demand condition* involves the adult showing the participant a series of twenty holiday photographs reported to be from the participant's own holiday and making pre-determined comments about every other photograph. In total, ten comments are made by the adult during this condition. The condition places very little social demand on the participant because although the adult and participant are engaging in a social interaction, there is *no* expectation on the participant to respond to the adult or initiate a verbal interaction. The participant is, however, provided with the opportunity to make a comment about the photographs or respond to a comment made by the adult. This condition is not timed and finishes after the last photograph has been shown to the participant.

The *High demand condition* involves a conversation between the adult and participant, whereby the adult asks the participant a series of questions and the participant *is* expected to respond to them. The conversation also provides the participant with the opportunity to initiate conversation with the adult by asking the adult questions. This condition is predominantly led by the adult because they ask the participant questions in order to maintain the conversation. The *High demand condition* lasts for approximately four minutes.

The *Very high demand condition* is a performance condition in which the participant is expected to present two stories to the adult. It is a modified version of the 'Cartoons' condition from the ADOS (Lord et al., 2000) and utilises both sets of cartoons from the ADOS (one cartoon is about two monkeys and one cartoon is about a fisherman and a cat). The adult tells the participant the story in one of the cartoons and then asks the participant to stand up and tell them the story back. This procedure is then repeated for the second

cartoon. The participant is expected to stand up and re-tell or 'perform' a story on their own without being guided through it. Only if the participant shows difficulty with retelling the story are they prompted through it by the adult. This condition is different to the *High demand condition*, which is an interaction predominantly led by the adult. This condition is not timed and finishes after the participant has presented both cartoons.

The four tasks are carried out separately by a familiar adult and an unfamiliar adult, in order to identify whether there is an effect of familiarity on the Social tasks. The familiar adult is someone the participant knows very well and has regular contact with, seeing them *at least* three times a week, e.g., their main caregiver, their teacher, their support worker etc. The unfamiliar adult is a trained confederate involved in the project who has never met the participant.

4.4.2.6.1. Behavioural measures of anxiety

The literature on observational indicators of social anxiety in both typically developing children and individuals with intellectual disabilities, was examined to identify indicators of social anxiety (Cohen *et al*., 1988; Conger & Farrell, 1981; Fydrich et al., 1998; Glass & Arnkoff, 1989; Glennon & Weisz, 1978; Hall et al., 2006; Hessl et al., 2006; Lesniak-Kapiak et al., 2003; Millbrook et al., 1986; Monti et al., 1984; Trower et al., 1978). Behaviours previously identified as indicators of social anxiety are coded during each condition. Some behaviours were chosen because the deficit in that behaviour would be indicative of anxiety, e.g., *not* looking in the direction of the adult. Other behaviours were chosen because it is the presence of that behaviour which is indicative of anxiety, e.g., the

presence of fidgeting. Several adult behaviours are also coded during the conditions and used in the analysis to provide a more detailed picture of the nature of the interaction between the adult and the participant. All behaviours are operationally defined. *Appendix D* lists all behaviours coded during the Social tasks. It is important to note that *not* all of these behaviors coded were used in the analysis section because some behaviours were of such a low frequency (median was zero in at least half of the conditions) that they could not be analysed. Table 4.3 shows all the behaviours which were included in the analysis.

Table 4.3: Operationalised Definitions of Behaviours coded as control variables; and Participant and Adult Behaviours used in the analysis.

PARTICIPANT VERBALISATION	OPERATIONALISED DEFINITIONS
Participant verbalisation (duration)	The participant's speech; These may be utterances (e.g. 'erm'), words, phrases or sentences. The person may use speech for the purpose of communication with someone else, e.g., asking a question, making a comment, answering a question or the speech may be used when the person is talking to themselves. The participant's speech may be intelligible or unintelligible.
Participant Question (event)	The participant asks the adult a question. For example, 'Did you drive here?'
Participant Offers information (event)	The participant spontaneously (not in response to a question) offers information. The information may or may not be about themselves. For example, 'I went to the beach on holiday' or 'the cartoon is funny'.
Participant Verbal Response (event)	The participant responds verbally to a question, statement, comment, prompt or request made by the adult by providing information. N.b. this code also includes the participant's description of the cartoons in the Cartoon condition.
PARTICIPANT NON-VERBAL BEHAVIOUR	
Participant Positive Facial Expression (duration)	The participant demonstrates a positive facial expression, for example, laughing or smiling. Facial expression must clearly indicate expression of pleasure in activity or conversation. Facial expression may or may not be directed towards the examiner.
Participant Looks at adult (duration)	The participant looks in the direction of the adult's eyes or face.
Participant Nod / shake (event)	The participant responds to a question, statement, comment or prompt made by the examiner, by nodding their head to indicate 'yes' or shaking their head to indicate 'no'. This *does not* include use of Makaton or British Sign Language.
Participant Descriptive Gestures (duration)	The participant uses movements of their arms or hands to help them describe something.
Participant Fidget (duration)	The participant displays restless, repetitive, non-rhythmic, non-functional motor movements, such as, moving their hands, touching their face or hair or moving an object, or wriggling in their seat. This code *does not* include stereotyped behaviours, which are *rhythmic*, unusual seemingly purposeless movements of their body or objects (based on Lesniak-Karpiak, Mazzocco & Ross, 2003).
ADULT VERBALISATION	
Adult Verbalisation (duration)	The adult's speech; These may be utterances (e.g. 'erm'), words, phrases or sentences. The person may use speech for the purpose of communication with someone else, e.g., asking a question, making a comment, answering a question or the speech may be used when the person is talking to themselves. The adult's speech may be intelligible or unintelligible.
Adult Question (event)	The adult asks the participant a question, which requires a response from the participant. For example' What books do you like?'
Adult Prompt (event)	The adult prompts the participant to respond by repeating or slightly paraphrasing the original question, request, comment or piece of information.
Adult Verbal response	The adult responds to the participant's verbal question, comment, statement or

(event)	offering of information using verbal communication to give the appropriate information.
Adult Offers information (event)	The adult spontaneously (not in response to a question) offers information. The information may or may not be about themselves. For example 'I came from Birmingham'. N.b. this code also includes the adult's description of the cartoons in the Cartoon condition.
BEHAVIOURS CODED AS CONTROL VARIABLES	
Participant Engage with task (duration)	The participant looks at and/or touches an object allocated for a condition. This may be reading a magazine / newspaper, colouring with felt tips, listening to the radio in the 'Break' condition; looking at or touching the photographs in the 'Photograph' condition; looking at or touching the cartoon in the 'Cartoon' condition. Objects which have not been incorporated as part of the social presses, *should not* be coded, e.g., if the person is drinking from a cup or mug which is on the table. This code *does not* apply to the 'Conversation' condition because no objects are required for this condition.
Adult Looks at participant (duration)	The adult is looking in the direction of the participant's eyes or face.

4.4.3. Procedure

All participants were visited at home by one or two researchers. Approximately two weeks before the research visit took place the participant's caregiver was sent a letter of confirmation about the visit, a questionnaire pack and an information sheet for the person acting as the familiar adult in the Social tasks. Caregivers were asked to complete the questionnaire pack before the research visit day so that it could be collected by the researcher(s) during the visit. The research visits took place over one or two days. Typically, the visits to the Cornelia de Lange syndrome participants took place over two days, whilst the visits to the Down syndrome participants took place in one day. This was due to the fact that an extra two assessments were completed with the Cornelia de Lange syndrome participants (Expressive One Word Picture Vocabulary Test (Brownell, 2000) and the Wechsler Pre-school & Primary Scale of Intelligence - Third UK Edition (WPPSI-

III^{UK}; Weschler, 2004) or the Wechsler Abbreviated Scale of Intelligence (WASI; Weschler, 1999), depending on ability).

The first assessment to be conducted on all research visits was the Social tasks so that the researcher acting as the unfamiliar adult would have had minimal contact with the participant. The Social tasks were always conducted in a room with a table and only the participant and familiar or unfamiliar adult were present. All Social tasks were recorded with a digital camera so that they could be transferred to DVD afterwards for coding. The Social Task conditions were counterbalanced so that there were no order effects across the groups. See *Appendix C* for more information on counterbalancing of conditions. The Social tasks took approximately an hour to complete.

After the Social tasks were completed, the BPVS-II (Dunn et al., 1997) was administered. The VABS-II (Sparrow, et al., 2005) was administered to either the participant's main caregiver or key worker at a convenient time for them, during the research visit day. A number of other assessments which examined Theory of Mind and Executive functioning were also completed with the participant afterwards but the results of these are not included in the current study. As mentioned previously the EOPVT (Brownell, 2000) and the WPPSI-III^{UK} (Weschler, 2004) or WASI (Weschler, 1999) was completed with participants with Cornelia de Lange syndrome. During the research visit day(s), it was ensured that all participants were given regular breaks.

After the research visits had taken place, the Social tasks were coded using Obswin 3.2 (Martin, Oliver & Hall, 1998). The *Low demand* and *Very high demand conditions* were

coded for the full length of time that they had been recorded for because these conditions were dependent on other factors i.e. the *Low demand condition* finished once all twenty photographs had been shown to the participant and the *Very high demand condition* finished once the participant had explained the story in both cartoons. The *Control condition* and the *High demand condition* were however edited so that the duration of these conditions were matched across the groups. If the duration of either of these conditions exceeded four minutes then the rest of the condition was *not* coded. Some behaviours were coded as *durations* (i.e. behaviours with an onset and an offset) and some were coded as *events* (i.e. behaviours of such short duration that only their occurrence is recorded). Table 4.3 shows whether behaviours were coded as events or durations.

The following three variables were coded in addition to the participant and adult outcome behaviours: *adult off camera*, *participant off camera* and *participant's hands off camera*. These variables affected whether several outcome variables could be coded during a condition, e.g., if the participant was off camera, *participant looks at adult* could *not* be coded. For the purpose of calculating more accurate durations and frequencies of outcome behaviours, if any of these three variables occurred for 10% or more of the time in a condition then the outcome behaviours affected by these variables were recalculated to only take into account the time when these behaviours could be coded, e.g., if a participant's hands were off the camera for 15% of time during a condition, then *participant fidgets* was only coded during the 85% of time during which the participant's hands could be seen.

Inter-rater reliability was conducted on all behaviours coded in the Social tasks for 26.67% of participants (25% of Down syndrome participants and 28% of Cornelia de Lange syndrome participants). Participants were selected for inter-rater reliability so that the range of behaviours was demonstrated across the groups. Two raters independently coded the Social tasks. Agreement was calculated using Cohen's Kappa co-efficient (Hartmann, 1977) based on 5-s interval by interval basis. The mean level of agreement across the participant behaviours was .64 (range: .48 to .82). The mean level of agreement across the adult behaviours was .59 (range: .44 to .85) (see *Appendix E* for detailed information of inter-reliability). This reliability was considered to be good.

4.5. DATA ANALYSIS

A preliminary analysis was conducted to ensure that the conditions did not differ between the groups (i.e. that the Social tasks were administered in a uniform way across both groups). The *duration of the condition*, the *duration of the participant engaging in the task* and the *duration of the adult looking at the participant* were examined. See Table 4.4 for differences on these variables. A less conservative alpha level was used for this analysis so that marginal differences would be identified ($p < .05$). The majority of differences were *not* significant. The differences that were significant were differences which could not be controlled for given the need to keep the conditions as representative of naturalistic social situations as possible. Given that the majority of comparisons were *not* significant and that any significant differences were only marginally significant, it shows that the conditions were well matched between the Cornelia de Lange syndrome and Down syndrome groups.

In summary, these analyses show that any significant differences identified between the groups in any of the behavioural outcome variables are *not* due to differences in the administration of the Social tasks.

Table 4.4: Differences between the Cornelia de Lange syndrome and Down syndrome groups on control variables.

Behaviour	Condition	CdLS (median)	DS (median)	U	*Z*	*P*
DURATION OF CONDITION	Familiar Low Demand	341	355	236.5	-.02	.98
	Unfamiliar Low Demand	225	228.5	217	-.75	.45
	Familiar High Demand	240	240	218	-.59	.56
	Unfamiliar High Demand	240	240	236	-.74	.46
	Familiar Very High Demand	151	109	173	-1.53	.13
	Unfamiliar Very High Demand	142	125	150.5	-2.06	**< .05**
PARTICIPANT ENGAGE IN TASK	Familiar Low Demand	89.67	97.97	89	-3.52	**< .001**
	Unfamiliar Low Demand	96.15	96.63	180.5	-1.59	.11
	Familiar High Demand	N/A	N/A			
	Unfamiliar High Demand	N/A	N/A			
	Familiar Very High Demand	87.5	97.16	145.5	-2.18	**< .05**
	Unfamiliar Very High Demand	92.91	95.49	192.5	-1.07	.29
ADULT LOOKS AT PARTICIPANT	Familiar Low Demand	27.05	22.04	186	-1.22	.22
	Unfamiliar Low Demand	21.36	37.27	134	-2.65	**< .01**
	Familiar High Demand	94.58	97.5	181	-1.34	.18
	Unfamiliar High Demand	95.83	94.79	248.5	-.03	.97
	Familiar Very High Demand	0	0	233	-.14	.89
	Unfamiliar Very High Demand	0	0	149	-2.48	**< .05**

The following variables were coded as outcome participant variables: *Participant verbalisation*, *participant positive facial expression*, *participant looks at adult*, *participant fidget* and *participant non-verbal communicative behaviour* (sum of *participant gestures* and *participant nod/shake*). The categorisation of *participant verbalisation* was also examined by analysing *participant response*, *participant question* and *participant offers information*. *Adult verbalisation* and its categorisation into *adult response*, *adult question*, *adult prompt* and *adult offers information*, were also examined to provide more information about the nature of the verbal interaction between the adults and participants. See Table 4.3 for operationalised definitions.

When conducting the analysis, the categorisation of verbalisation was only examined, if significant differences were identified between the groups in the duration of participant or adult verbalisation. Not all categorisations of *participant verbalisation* were analysed for each condition because they were not all applicable. *Participant offers information* was not analysed for the *Very high demand* condition. For adult verbalisation, *adult question* and *adult offers information* was not analysed in the *Very high demand* condition.

The distribution of the outcome variables was examined via visual inspection of Q-Q plots and utilising the Kolmogrov-Smirnov test. The data for almost all the outcome variables were *not* normally distributed across all conditions ($p < .05$) and consequently non-parametric tests were employed throughout the analysis. Mann-Whitney tests were employed for between-group analyses and Wilcoxon rank-sum tests were employed for within-group analyses. The analyses examined the effect of *group*, *level of demand* and *familiarity* on the outcome variables. An effect of all three independent variables on an

outcome variable would indicate a three-way interaction. An effect of two of these variables would indicate a two-way interaction and an effect of only one of these variables would indicate a main effect of that variable only.

The Results section is divided into a preliminary section and then two main sections. The preliminary section will compare the outcome variables between the Control condition and the Experimental conditions to demonstrate that the outcome variables are specifically evoked by the demands of the Experimental conditions. Part One of the results section will then address the first aim of the study which was to compare behavioural indicators of social anxiety between the two groups, in response to the Social tasks and also examine the difference in adult verbalisation. A more conservative alpha level ($p < .005$) will be employed for this set of analyses. Part Two will address the second aim of the study, which was to examine the association between any social impairments identified in the Cornelia de Lange syndrome group and executive functioning. This comparison will also be conducted for the Down syndrome group to examine whether the relationship appears to be specific to the Cornelia de Lange syndrome group. As an informant-based measure of executive functioning was used, caution must be exercised when interpreting the results.

4.6. RESULTS

4.6.1. Preliminary analysis: Comparison between the Control condition and Experimental conditions

An analysis was conducted initially for each group to ensure that participant outcome variables examined in the Experimental conditions were evoked by social demands. Consequently, pairwise Wilcoxon Rank sum tests were conducted separately for each group to compare each participant outcome variable between the *Control condition* and the *Experimental conditions*[1] (*Appendix F* shows results of comparisons). All but one[2] of the analyses were significant with all the outcome variables being observed for significantly longer in the *Experimental conditions* than the *Control condition*, demonstrating that the outcome variables being examined in the current study were evoked by the social demands of the *Experimental conditions*. In summary, any behaviours evoked in the *Experimental conditions* for either the Cornelia de Lange syndrome or Down syndrome group are due to the social demands associated with those conditions.

[1] A mean score was taken across the three Experimental conditions.
[2] A significant difference was *not* found in positive facial expression ($p = .02$) for the Down syndrome group between the familiar Control condition and the mean of the Experimental conditions. This was due to the low level of positive facial expression shown by the group in the Experimental conditions.

4.6.2. Part one: Comparison of outcome variables on Social tasks

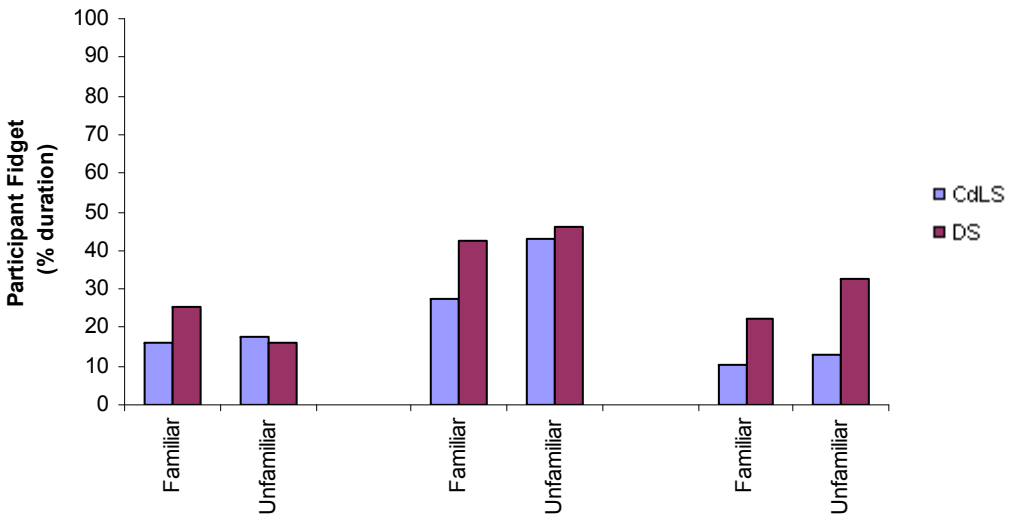
4.6.2.1. Participant Behaviour

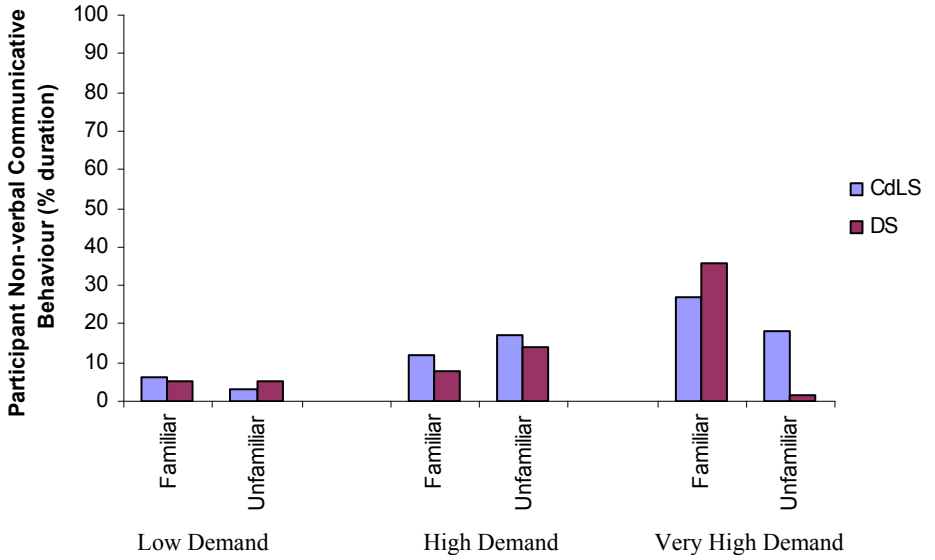
Table 4.5 shows the median duration/ frequency for each outcome variable. In order to address the first aim of the study, a series of Mann-Whitney tests were conducted to compare the Cornelia de Lange syndrome and Down syndrome groups on each outcome variable (participant verbalisation, etc) in each condition (e.g., *familiar Low demand condition*), and a series of Wilcoxon Rank sum tests were conducted to compare outcome variables for equivalent familiar and unfamiliar conditions in each group (e.g., comparison of each outcome variable for the *familiar Low demand condition* and *unfamiliar Low demand condition* in the Cornelia de Lange syndrome group). Figure 4.1 shows median duration/ frequency of the participant outcome variables for both the Cornelia de Lange syndrome and Down syndrome groups.

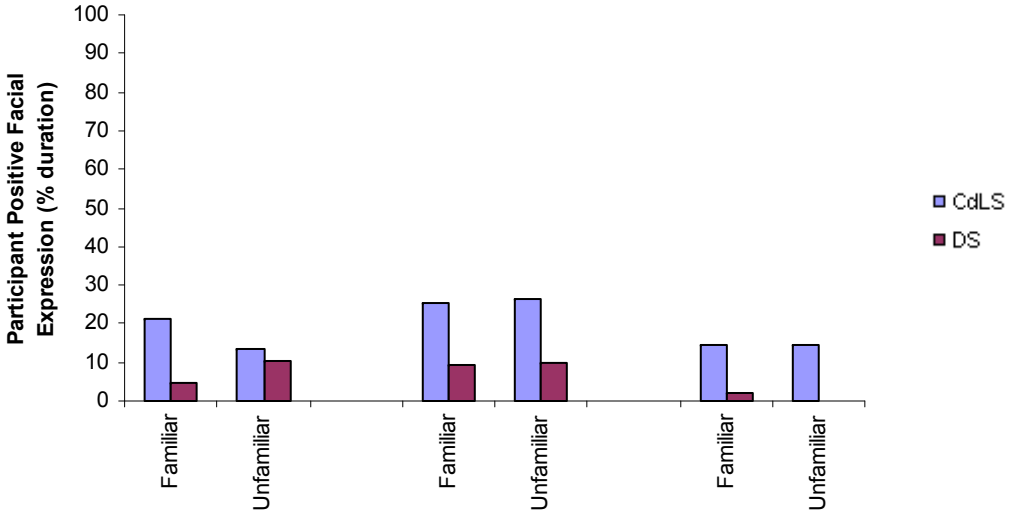
Table 4.5: Median frequency / duration of the behavioural outcomes for the Cornelia de Lange syndrome and Down syndrome groups.

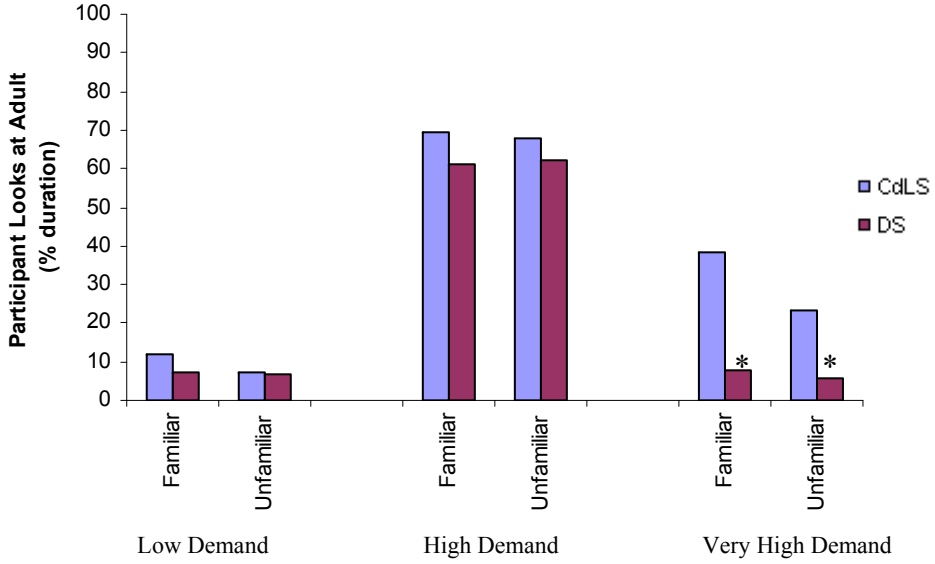
		Median (Inter-quartile range)		U	Z	*P*
		CdLS	**DS**			
VERBALISATION	Familiar Low Demand	14.52 (3.02-25.83)	35.00 (16.88-39.55)	108	-3.07	.002
	Unfamiliar Low Demand	4.80 (0.00-15.49)	32.48 (23.43-47.99)	65	-4.23	.000
	Familiar High Demand	37.92 (23.13-56.04)	55.42 (42.08-67.50)	134	-2.45	.014
	Unfamiliar High Demand	46.67 (6.46-68.34)	66.67 (58.23-80.11)	130	-2.74	.006
	Familiar Very High Demand	44.81 (30.25-78.97)	90.40 (74.04-96.15)	77.5	-3.79	.000
	Unfamiliar Very High Demand	32.93 (21.48-91.72)	93.88 (70.49-95.38)	109	-3.05	.002
NON-VERBAL COMMUNICATIVE BEHAVIOUR	Familiar Low Demand	6.29 (1.70-10.88)	5.28 (1.55-14.58)	210	-.65	.52
	Unfamiliar Low Demand	2.87 (0.00-10.21)	5.13 (1.75-10.62)	193	-1.31	.19
	Familiar High Demand	11.67 (5.00-22.25)	7.92 (2.60-12.08)	197.5	-.95	.34
	Unfamiliar High Demand	17.08 (10.00-28.67)	13.78 (6.04-26.99)	222	-.64	.52
	Familiar Very High Demand	26.98 (5.64-59.08)	35.90 (0.00-69.44)	212	-.61	.54
	Unfamiliar Very High Demand	18.07 (3.37-75.75)	1.32 (0.00-52.75)	155	-2.00	.05
LOOKING AT ADULT	Familiar Low Demand	11.76 (4.38-28.06)	7.50 (1.49-18.61)	174	-1.5	.13
	Unfamiliar Low Demand	7.03 (1.52-22.78)	6.60 (1.69-13.71)	243	-.16	.87
	Familiar High Demand	69.58 (35.42-84.80)	61.25 (35.42-72.92)	207.5	-.71	.48
	Unfamiliar High Demand	67.92 (16.46-86.46)	62.09 (43.64-73.44)	212.5	-.86	.39
	Familiar Very High Demand	38.24 (14.24-55.17)	7.80 (2.36-22.39)	99	-3.3	.001
	Unfamiliar Very High Demand	23.45 (4.37-46.23)	5.52 (.77-15.15)	135	-2.43	.015

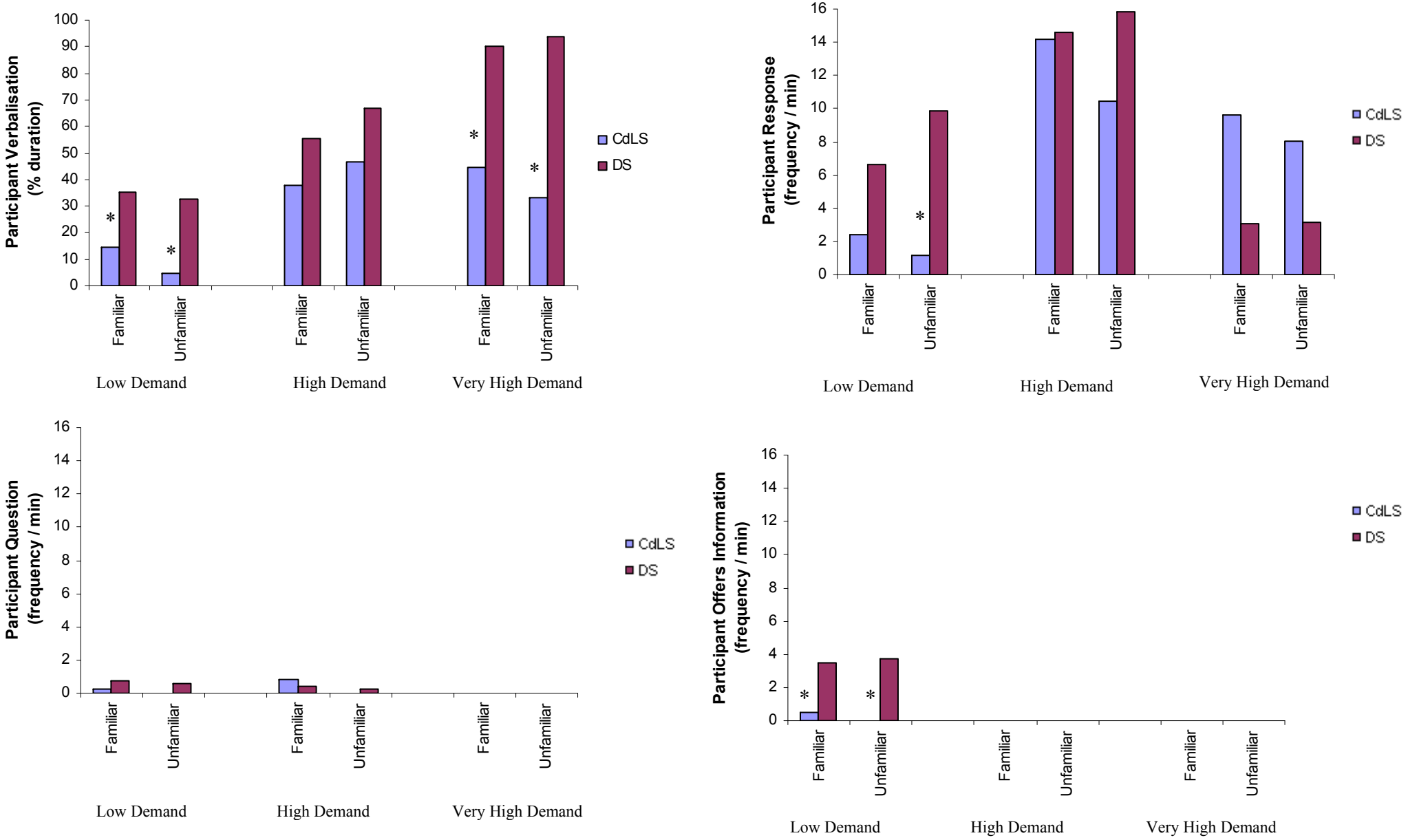
		Median (Inter-quartile range)		U	Z	*P*
		CdLS	**DS**			
POSITIVE FACIAL EXPRESSION	Familiar Low Demand	21.28 (5.93-44.32)	4.80 (2.64-9.60)	141	-2.29	.022
	Unfamiliar Low Demand	13.59 (1.22-19.79)	10.54 (5.65-17.22)	238.5	-.26	.79
	Familiar High Demand	25.42 (7.71-48.96)	9.17 (2.92-13.75)	128	-2.60	.009
	Unfamiliar High Demand	26.25 (.65-49.58)	9.79 (3.96-16.56)	193.5	-1.29	.196
	Familiar Very High Demand	14.56 (1.42-72.44)	1.98 (0.00-6.58)	113	-2.96	.003
	Unfamiliar Very High Demand	14.46 (2.69-57.99)	0.00 (0.00-2.60)	75	-3.97	.000
FIDGETING	Familiar Low Demand	16.19 (7.40-24.90)	25.24 (5.28-37.43)	210	-.65	.52
	Unfamiliar Low Demand	17.58 (.80-31.14)	16.05 (7.05-37.71)	227	-.53	.60
	Familiar High Demand	27.59 (20.38-47.08)	42.50 (14.17-80.83)	189.5	-1.14	.26
	Unfamiliar High Demand	42.92 (6.88-62.50)	46.04 (16.46-66.89)	229	-.48	.63
	Familiar Very High Demand	10.24 (2.16-30.74)	22.06 (0.00-29.17)	222	-.37	.71
	Unfamiliar Very High Demand	13.03 (1.09-24.90)	32.89 (15.15-48.99)	143	-2.24	.025


Participant Fidget (% duration)
100
90
80
70
60
50
40
30
20
10
0
Familiar
Unfamiliar
Familiar
Unfamiliar
Familiar
Unfamiliar
CdLS
DS


Participant Non-verbal Communicative Behaviour (% duration)
100
90
80
70
60
50
40
30
20
10
0
Familiar
Unfamiliar
Familiar
Unfamiliar
Familiar
Unfamiliar
Low Demand
High Demand
Very High Demand
CdLS
DS


Participant Positive Facial Expression (% duration)
100
90
80
70
60
50
40
30
20
10
0
Familiar
Unfamiliar
Familiar
Unfamiliar
Familiar
Unfamiliar
CdLS
DS


Participant Looks at Adult (% duration)
100
90
80
70
60
50
40
30
20
10
0
Familiar
Unfamiliar
Familiar
Unfamiliar
Familiar
Unfamiliar
*
*
Low Demand
High Demand
Very High Demand
CdLS
DS



* Significant difference between the Cornelia de Lange syndrome and Down syndrome groups ($P < .005$).

Figure 4.1: Graphs of participant outcome variables for the Down syndrome and Cornelia de Lange syndrome groups.

The analysis revealed a two-way interaction between *group* and *level of demand* for *participant verbalisation*. The Cornelia de Lange syndrome group showed significantly less verbalisation than the Down syndrome group in both the *familiar* ($U = 108$, $p < .005$) and *unfamiliar* ($U = 65$, $p < .001$) *Low demand conditions* and both the *familiar* ($U = 77.5$, $p < .001$) and *unfamiliar* ($U = 109$, $p < .005$) *Very high demand conditions*. No significant difference, however, was observed for *verbalisation* between the Cornelia de Lange syndrome and Down syndrome groups in either the familiar or unfamiliar *High demand conditions*. The difference in verbalisation between the groups in the *unfamiliar High demand condition*, approached significance ($p = .006$).

An analysis of the type of *participant verbalisation* shown in the *Low demand* and *Very high demand conditions* revealed that there was a significant difference between the groups in the type of verbalisation shown in the *Low demand condition* only. The Down syndrome group demonstrated significantly more *offering of information* than the Cornelia de Lange syndrome group in both the *familiar* ($U = 62$, $p < .001$) and *unfamiliar Low demand conditions* ($U = 46$, $p < .001$) and also *responded* significantly more often than the Cornelia de Lange syndrome group in the *unfamiliar Low demand condition* ($U = 73$, $p < .001$).

The analyses also revealed a main effect of familiarity for *participant verbalisation* in the *High demand condition* for the Down syndrome group. The Down syndrome group actually showed significantly more verbalisation in the *unfamiliar High demand condition* than in the *familiar High demand condition* ($z = -3.14$, $p < .005$), which was the opposite pattern to that expected. Although no significant effect of familiarity was found for the

Cornelia de Lange syndrome group in the *High demand condition*, this group also showed more verbalisation in the *unfamiliar High demand condition* compared to the *familiar High demand condition*.

Surprisingly, the analysis also showed significantly more positive facial expression by the Cornelia de Lange syndrome group in comparison to the Down syndrome group in the *familiar Very high demand condition* ($U = 113$, $p < .005$) and the *unfamiliar Very high demand condition* ($U = 75$, $p < .001$). The analysis also revealed that the Cornelia de Lange syndrome group looked at the adult for a significantly longer duration than the Down syndrome group in the *familiar Very high demand condition* ($U = 99$, $p = .001$). Although the Cornelia de Lange syndrome group also looked at the adult for a longer period of time in the *unfamiliar Very high demand* condition, this difference did not reach significance. It seems that the differences between the groups in looking at the adult and the duration of positive facial expression in the *Very high demand condition*, showed a similar trend and this trend was opposite to that expected.

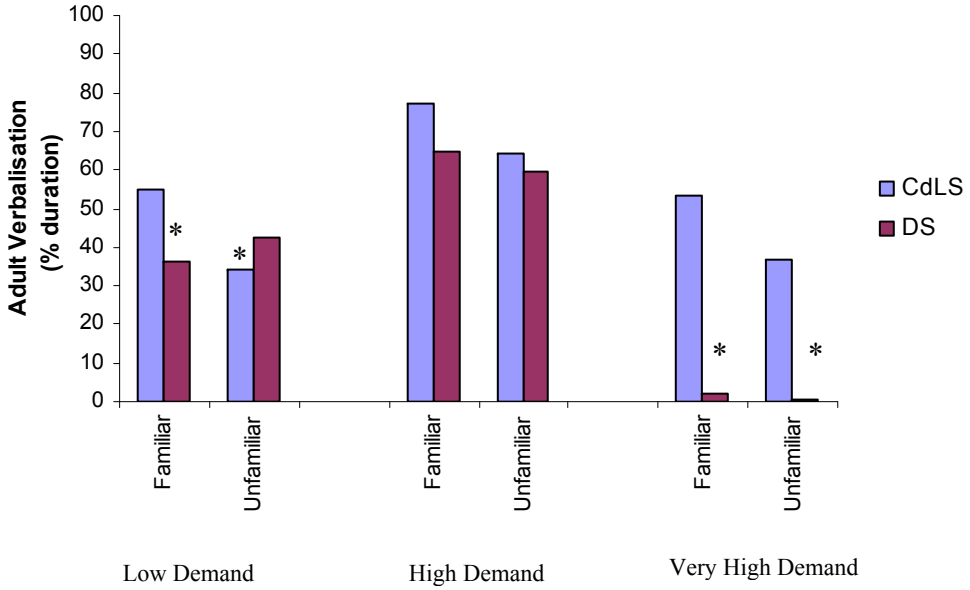
Finally, the analysis demonstrated that there was no significant difference in fidgeting or non-verbal communicative behaviour between the two groups, in any condition.

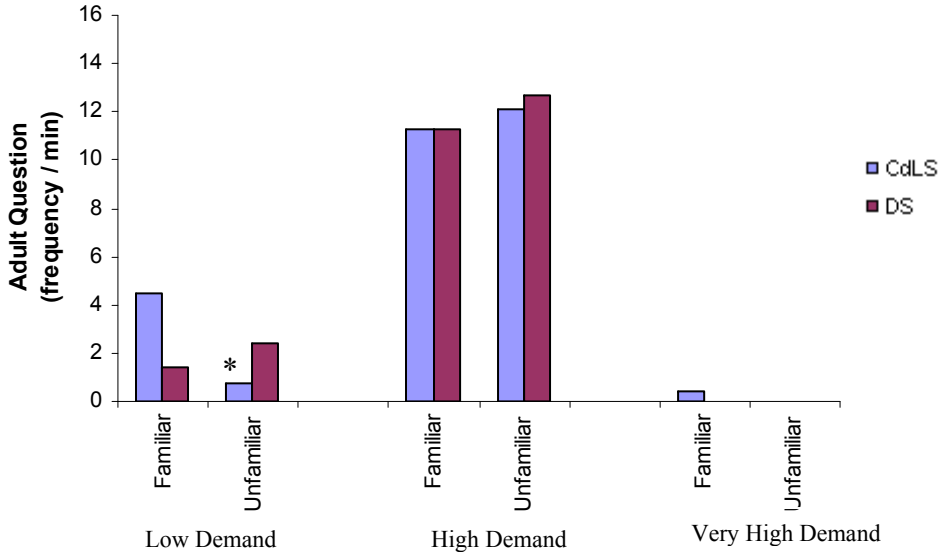
In summary, significantly less verbalisation was shown by the Cornelia de Lange syndrome group in comparison to the Down syndrome group in the *familiar* and *unfamiliar Low demand* and *Very high demand conditions*. An analysis of the type of participant verbalisation shown in these conditions, revealed that the Down syndrome group showed significantly more offering of information than the Cornelia de Lange syndrome group in

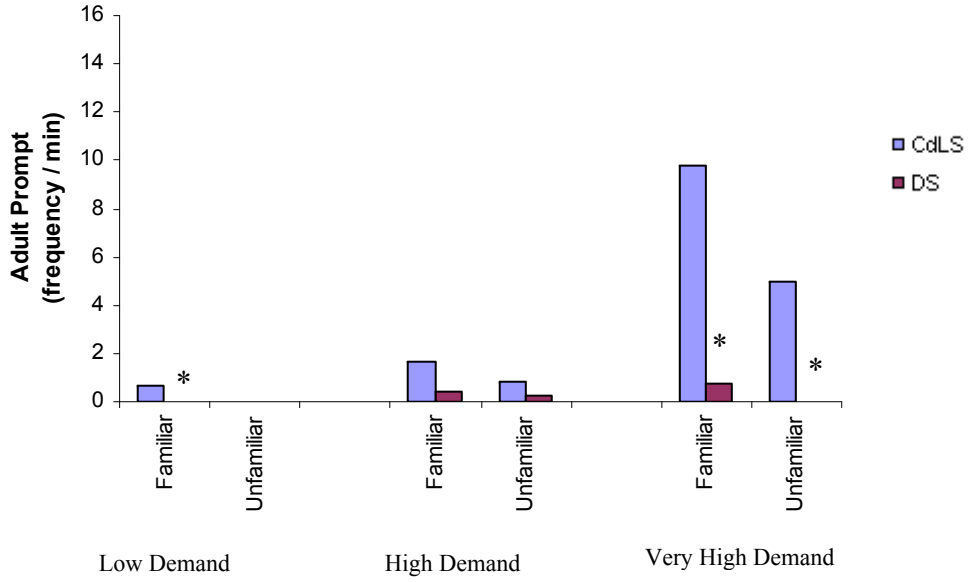
the *familiar Low demand condition* and showed significantly more offering of information and responded significantly more often than the Cornelia de Lange syndrome group in the *unfamiliar Low demand condition*. Unsurprisingly, no significant difference in the type of verbalisation was observed between the two groups in the *Very high demand conditions*. Significantly more positive facial expression was demonstrated by the Cornelia de Lange syndrome group in the *familiar* and *unfamiliar Very high demand conditions* and significantly more looking at the adult was also shown by the Cornelia de Lange syndrome group in the *familiar Very high demand* condition. No significant differences were found between the two groups in fidgeting and non-verbal communicative behaviour.

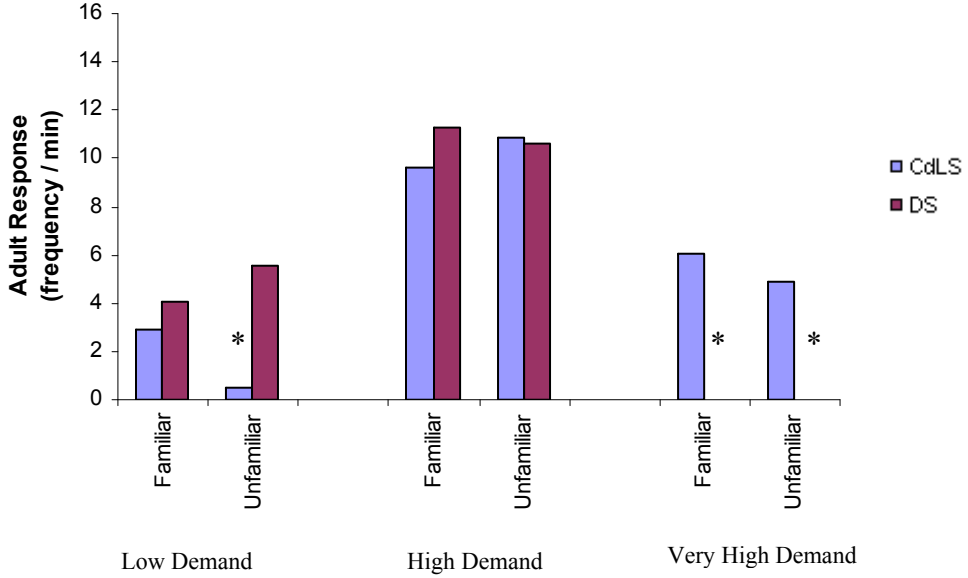
4.6.2.2. Adult Behaviour

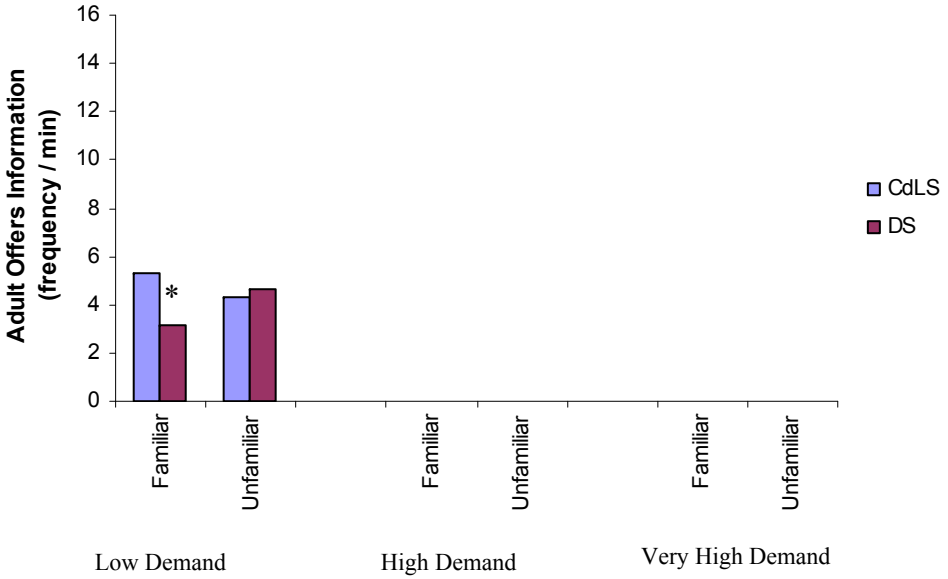
Figure 4.2 shows the median duration/ frequency of the adult outcome variables for both the Cornelia de Lange syndrome and Down syndrome groups. An analysis of *adult verbalisation* revealed a two-way interaction between *group* and *level of demand* as significant differences were found between the two groups in the *Low demand condition* and the *Very high demand condition* but not in the *High demand condition* (see Figure 5.1). Significantly more verbalisation was shown by the familiar (U = 23, p < .001) and unfamiliar (U = 43, p < .001) adults when interacting with the Cornelia de Lange syndrome group in the *Very high demand* condition, when compared to the Down syndrome group. Significantly more verbalisation was also shown by the familiar adults in the *Low demand condition* (U = 112, p < .005) with the Cornelia de Lange syndrome group in comparison to the Down syndrome group. The unfamiliar adults, however, showed significantly more verbalisation with the Down syndrome participants than the Cornelia de Lange syndrome participants in the *Low demand condition* (U = 119, p < .005). It is interesting that the opposite pattern of *verbalisation* was shown by the familiar and unfamiliar adults with the two groups in the *Low demand condition* (see discussion).


Adult Verbalisation (% duration)
100
90
80
70
60
50
40
30
20
10
0
CdLS
DS
Familiar
Unfamiliar
Low Demand
High Demand
Very High Demand


Adult Question (frequency / min)
16
14
12
10
8
6
4
2
0
CdLS
DS
Familiar
Unfamiliar
Low Demand
High Demand
Very High Demand


Adult Prompt (frequency / min)
16
14
12
10
8
6
4
2
0
CdLS
DS
Familiar
Unfamiliar
Low Demand
High Demand
Very High Demand


Adult Response (frequency / min)
16
14
12
10
8
6
4
2
0
CdLS
DS
Familiar
Unfamiliar
Low Demand
High Demand
Very High Demand



* Significant difference between the Cornelia de Lange syndrome and Down syndrome groups ($P < .005$).

Figure 4.2: Graphs of adult outcome variables for the Down syndrome and Cornelia de Lange syndrome groups.

An analysis of the type of adult verbalisation shown in the *Low demand* and *Very high demand conditions* revealed that the familiar adults used significantly more *prompts* (U = 70, $p < .001$) and *responses* ($U = 32$, $p < .001$) with the Cornelia de Lange syndrome group than the Down syndrome group in the *Very high demand condition*. The unfamiliar adults also used significantly more *prompts* ($U = 85.5$, $p < .001$) and *responses* ($U = 67$, $p < .001$) with the Cornelia de Lange syndrome group than the Down syndrome group in the *Very high demand condition*. The familiar adults gave significantly more *prompts* ($U = 107.5$, $p < .005$) and *offering of information* ($U = 100$, $p < .005$) to the Cornelia de Lange syndrome group than the Down syndrome group in the *Low demand condition*, whilst the unfamiliar adults gave significantly more *questions* ($U = 106$, $p < .005$) and *responses* ($U = 97$, $p < .001$) to the Down syndrome group than the Cornelia de Lange syndrome group in the *Low demand condition*

In summary, the familiar adults showed significantly more verbalisation with the Cornelia de Lange syndrome group in the *Very high demand condition* and in the *Low demand condition*. The familiar adults used significantly more prompts and responses with the Cornelia de Lange syndrome group in the *Very high demand condition* and significantly more prompts and offering of information to the Cornelia de Lange syndrome group in the *Low demand condition*. The unfamiliar adults showed significantly more verbalisation with the Cornelia de Lange syndrome group in the *Very high demand condition* but showed significantly more verbalisation with the Down syndrome group in the *Low demand condition*. The unfamiliar adults used significantly more prompts and responses with the Cornelia de Lange syndrome group in the *Very high demand condition* and used

significantly more questions and responses to the Down syndrome group in the *Low demand condition*.

4.6.3. Part Two: Relationship between Social Impairments and Cognitive Functioning in Cornelia de Lange syndrome

Part Two of the analysis was used to address the second aim of the study which was to examine the relationship between any social impairments identified in the Social tasks for the Cornelia de Lange syndrome group and cognitive functioning. As a specific impairment in verbalisation has been identified for the Cornelia de Lange syndrome group, this was correlated with a measure of executive functioning. For the purpose of this analysis, the mean duration of *participant verbalisation* across the familiar and unfamiliar *Very high demand conditions* was used for examining the relationship between *verbalisation* and executive functioning because this condition placed the highest social (and thus cognitive) demands on participants. The analysis was also conducted for the Down syndrome group to identify whether any relationships between verbalisation and cognitive impairments, were specific to the Cornelia de Lange syndrome group.

Before conducting the main analysis, mean *participant verbalisation* across the *Very high demand conditions* was correlated with age, receptive and expressive language and adaptive behaviour in order to examine whether these broader developmental variables were also related to verbalisation in either group. A series of Spearman's correlations were conducted for this analysis. Table 4.6 shows the results for these correlations.

Table 4.6: Correlations between mean participant verbalisation across the Very high demand conditions and age, receptive and expressive language and adaptive behaviour for the Cornelia de Lange syndrome and Down syndrome groups.

	age (years)	BPVS raw score	EOPVT raw score	VABS communication domain standard score	VABS daily living skills domain standard score	VABS socialization domain standard score
CdLS mean Participant Verbalisation	.30	.53**	.51*	-.16	.30	.27
DS mean Participant Verbalisation	.16	.81**	N/A[3]	.76**	.75**	.59*

* $P < .05$
** $P < .01$

The analysis revealed that only receptive language (measured by the BPVS) was significantly, positively correlated with *verbalisation* in the Cornelia de Lange syndrome group with the relationship between expressive language (measured by the EOPVT) and *verbalisation* approaching significance. In the Down syndrome group, both language and adaptive behaviour were significantly correlated with *verbalisation*. The pattern of correlations observed for the Down syndrome group is expected given that as verbalisation increases, adaptive behaviour would also be expected to increase. The dissociation of the relationship between verbalisation and adaptive behaviour in the Cornelia de Lange syndrome group suggests that these individuals may have a specific cognitive impairment that is related to language and is independent of global development of adaptive behaviour.

[3] The EOPVT was not administered to participants with Down syndrome due to time contstraints.

Table 4.7 shows the correlations between mean *verbalisation* and the BRIEF-P subscales, for the Cornelia de Lange and Down syndrome groups. A series of Spearman's correlations[4] between mean *verbalisation* across the *Very high demand conditions* and subscale scores on the BRIEF-P revealed that there were significant associations between the duration of verbalisation and working memory, and the duration of verbalisation and planning in the Cornelia de Lange syndrome group but these associations were not evident in the Down syndrome group. The correlation between the Inhibit subscale and verbalisation approached significance in the Cornelia de Lange syndrome group. No significant correlations between any of the BRIEF-P subscales and the duration of verbalisation, was found in the Down syndrome group. The significant correlations found for the Cornelia de Lange syndrome group indicate that *less* verbalisation in the *Very high demand condition* is associated with poorer performance on working memory and planning assessments.

Table 4.7: Correlations between Mean Participant verbalisation across the Very high demand conditions and BRIEF-P subscales for both the Cornelia de Lange syndrome and Down syndrome groups.

	BRIEF-P Inhibit subscale	BRIEF-P Shift subscale	BRIEF-P Emotional control subscale	BRIEF-P Working memory subscale	BRIEF-P Plan/Organise subscale
CdLS mean Participant Verbalisation	-.41*	-.26	-.31	-.57**	-.62**
DS mean Participant Verbalisation	-.24	.07	-.12	.10	-.07

* $P < .05$
** $P < .01$

[4] Pearson's Partial correlations between mean participant verbalisation and the BRIEF-P subscales, whilst controlling for BPVS scores in the Cornelia de Lange syndrome group and BPVS and VABS in the Down syndrome group, showed the same findings as the Pearson's correlations.

4.7. DISCUSSION

This novel experimental study assessed the phenomenology of social impairments in verbal adolescents and adults with Cornelia de Lange syndrome in contrast to a group of adolescents and adults with Down syndrome. This is the first study on social anxiety in Cornelia de Lange syndrome to employ a robust factorial, experimental design, placing an increasing level of social demand on participants whilst varying familiarity, in order to examine which factors evoked behaviours indicative of social anxiety. The study examined the relationship between any social impairments identified in the Cornelia de Lange syndrome group and cognitive functioning in order to identify whether there was preliminary evidence for specific cognitive impairments underpinning specific social impairments in this group.

The most striking difference identified between the two groups was in the duration of participant verbalisation. The Cornelia de Lange syndrome group showed significantly *less* verbalisation than the Down syndrome group in the *familiar* and *unfamiliar Low demand* and *Very high demand conditions*, whilst no significant difference was observed between the groups in the *High demand condition*. It appears that there are specific social demands in the *Low demand* and *Very high demand conditions* which evoke a reduction in verbalisation in the Cornelia de Lange syndrome group; these are different to those expected to be problematic given that a difference was found between the groups in the *Low demand* and *Very high demand conditions* but *not* in the *High demand condition*. The two conditions which showed group differences in verbalisation rely more heavily on participants being able to initiate speech, so it may be that this is a particular difficulty for

the Cornelia de Lange syndrome group. The *Very high demand condition* relies almost totally upon the individual being able to initiate speech because the participant is expected to re-tell a story to the adult, with as little help as possible. Also, verbalisation in the *Low demand condition* relies on participants being able to comment (offering information) on photographs or respond to a comment made by the adult on a photograph (response). The ability to comment on a photograph depends on being able to *initiate* speech and the analysis demonstrated that this was a specific difficulty for the Cornelia de Lange syndrome group in the *familiar* and *unfamiliar Low demand condition* (the Cornelia de Lange syndrome group commented significantly less on photographs than the Down syndrome group). Taken together, these findings suggest that individuals with Cornelia de Lange syndrome have a specific difficulty with the initiation of speech and when social demands involving the initiation of speech are placed upon individuals with Cornelia de Lange syndrome, it causes individuals to show a marked reduction in verbalisation.

This is the first empirical evidence showing a reduction in speech, in adolescents and adults with Cornelia de Lange syndrome that may be due to a specific difficulty in the initiation of speech. These findings contribute to the sparse literature on social impairments in Cornelia de Lange syndrome. To date, only one study has been published on the phenomenology of social anxiety in Cornelia de Lange syndrome and this study found no significant difference in communication (included both verbal and non-verbal communication) between children with Cornelia de Lange syndrome and children in a comparable contrast group (Richards et al., 2009). Although, Richards et al.'s (2009) findings appear to contrast with those found in the current study, both of these results may be valid if the developmental trajectory of sociability in Cornelia de Lange syndrome

changes with age because children were recruited for Richards et al.'s (2009) study, whilst adolescents and adults were recruited for the current study.

The findings in the current study therefore indicate that specific social demands reduce verbalisation in individuals with Cornelia de Lange syndrome group, with the familiarity of the other person being relatively unimportant. Although this may be true, previous research indicates that this is *not* the case (Collis et al., 2006; Kline et al., 2007a) and that the familiarity of the other person in the interaction does affect sociability in adolescents and adults with Cornelia de Lange syndrome. For example, the pilot study found that all participants with Cornelia de Lange syndrome were reluctant to interact with unfamiliar people (Collis et al., 2006) and the findings from Chapter Three demonstrated that adolescents and young adults initiated significantly less social interactions with unfamiliar people than younger individuals with the syndrome. It may be that the effect of familiarity was not fully captured by the Social tasks in the current study due to limitations in the administration of the Social tasks, most notably, having an unfamiliar adult present in their home. Some findings from the current study do support this position. Firstly, anecdotal reports from many familiar adults indicated that participants with Cornelia de Lange syndrome were much less sociable with them during the Social tasks than would typically be expected. It is possible that there was a performance effect of being filmed. Also, familiar adults felt that the effect of having an unfamiliar person present in their home during the research visit caused participants anxiety throughout the day affecting sociability even with familiar people. This was further supported by the fact that two individuals with Cornelia de Lange syndrome withdrew from the study because they felt so anxious about having an unfamiliar person present in their home.

The findings for participant verbalisation in the *High demand condition* also provide support for these anecdotal reports. This condition involved a conversation between the adult and the participant and it would typically be expected that both groups would verbalise more with a familiar adult than with an unfamiliar adult. Both the Cornelia de Lange syndrome group and the Down syndrome group, however, showed more verbalisation with the unfamiliar adult than with the familiar adult during this condition. This suggests that the effect of familiarity had been mitigated in the *High demand condition* and so participant verbalisation in this condition was dependent on the ability of the adult to help the participant provide the most complete answers to their questions. The confederates acting as the unfamiliar adults were experienced in administering the condition so perhaps were able to probe the participant into providing longer answers to their questions and therefore lead to both groups verbalising more with the unfamiliar adult.

There was also some empirical evidence for the effect of familiarity in the *Low demand condition*. The Cornelia de Lange syndrome group responded significantly less to comments made by the unfamiliar adult than the Down syndrome group yet no significant difference was found between the groups in responding to the familiar adult in this condition. This suggests that the presence of an unfamiliar adult caused a significant reduction in responses by the Cornelia de Lange syndrome group, providing support for the effect of familiarity on social interactions in Cornelia de Lange syndrome. In summary, there may be an effect of familiarity on verbalisation in Cornelia de Lange syndrome with individuals showing a specific difficulty initiating speech with unfamiliar people, however,

the way in which the Social tasks were administered (i.e. the unfamiliar adult being present in the home whilst the Social tasks were conducted with the familiar adult and using a camera to record the Social tasks) means that this is still difficult to determine in the current study. Future research is needed to examine this.

The analysis also revealed that there were significant differences in the duration of positive facial expression and the duration of looking in the direction of the adult, between the two groups. Contrary to expectations, the Cornelia de Lange syndrome group actually showed significantly more positive facial expression with the familiar and unfamiliar adults in the *Very high demand condition* and looked significantly longer at the familiar adult in the *Very high demand condition*, than the Down syndrome group. The Cornelia de Lange syndrome group also looked at the unfamiliar adult longer than the Down syndrome group in the *Very high demand condition*, although significance was not reached. These are unexpected findings given that a longer duration of positive facial expression and a longer duration of looking in the direction of the adult, would *not* be expected if social anxiety was evident in the Cornelia de Lange syndrome group.

It may be that participants with Cornelia de Lange syndrome do not experience social anxiety and in fact it is a specific communication problem affecting the initiation of speech that makes it appear that individuals with Cornelia de Lange syndrome show anxiety in social situations. This would also support the fact that no significant differences were found between the groups in fidgeting and non-verbal communicative behaviour. Although this is possible, the reported effect of the presence of unfamiliar people on levels of sociability in the literature for individuals with Cornelia de Lange syndrome, would

suggest that there is some anxiety-related difficulty, in this group. It may be that there is a communication problem which is enhanced by anxiety caused by the presence of unfamiliar people. A positive facial expression and looking in the direction of the adult may then serve to compensate for the lack of verbalisation in demanding conditions or act as a coping strategy. This is supported by the fact that these behaviours were shown in the *Very high demand condition* where the most difficulties in verbalisation were evident. A positive facial expression and looking in the direction of the adult may also prompt the adult to speak on their behalf, although it is not possible to determine at this stage. A future study involving the sequential analysis of behaviour in social interactions would be helpful to identify whether participant behaviours do affect adult behaviour and vice versa.

This is the first study to show that reduced verbalisation appears to be the main impairment in adolescents and adults with Cornelia de Lange syndrome in social interactions. This is interesting given that it seems there is a communication impairment which is affected by social demands. Interestingly, Basile, Villa, Selicorni & Molteni (2007) found a significant correlation between chronological age and behavioural problems, including communication disturbances and anxiety. The current study provides some support for Basile et al.'s (2007) study, as verbalisation impairments were found in adolescents and adults with Cornelia de Lange syndrome and there was some evidence indicating that verbalisation was affected by anxiety. The trajectory of verbalisation impairments in Cornelia de Lange syndrome is yet to be examined as this study only focused on a specific age range of individuals but it would be interesting to explore further whether the differences in sociability between the age groups, identified in Chapter Three, is related to changes in the ability to initiate speech with age.

Group differences were found in the duration of adult verbalisation in the *Low demand* and *Very high demand conditions*. Familiar and unfamiliar adults showed significantly more verbalisation with the Cornelia de Lange syndrome group in the *Very high demand condition*, with significantly more prompts and responses being used for the Cornelia de Lange syndrome participants. It appears that the adults tried to help the Cornelia de Lange syndrome participants, although, the increase in verbalisation by adults may have further increased the demands on the Cornelia de Lange syndrome participants. This pattern of behaviour was also demonstrated by the familiar adults in the *Low demand condition* as familiar adults used significantly more comments and prompts with the Cornelia de Lange syndrome group. Interestingly, the *Low demand condition* does not involve adults prompting participants because participants should verbalise *only* if they wish to do so. Perhaps this shows that the familiar adults will try to prompt individuals with Cornelia de Lange syndrome to verbalise whenever they can, to encourage individuals to verbalise.

There is currently no study to date on Cornelia de Lange syndrome which examines how participant and adult behaviour affect one another in social interactions. Therefore, this is the first study to contribute to the literature in this way. Further research examining the inter-play between participant and adult behaviours would be useful to determine how these may affect one another. Research in other genetic syndromes has already demonstrated the inter-play between participant and adult behaviour. For example, increased laughing and smiling by individuals with Angelman's syndrome has been found to be evoked by increased social interactions with adults and increases social contact from adults (Oliver, et al., 2007). This type of research is important in Cornelia de Lange

syndrome because it may also help when devising intervention strategies, e.g., asking adults not to prompt the person if it increases further demands on them.

The second aim of the study was to examine whether social impairments observed in the Cornelia de Lange syndrome group was related to specific cognitive impairments. The results indicated that reduction of verbalisations in the Cornelia de Lange syndrome group were associated with impairments in both planning and working memory. This was further supported by the fact that this relationship was *not* evident in the Down syndrome group and the fact that verbalisation was not related to adaptive behaviour in the Cornelia de Lange syndrome group. It cannot be assumed that the relationship between verbalisation and cognitive impairments is causal from the correlational analysis and the use of an informant-based measure of executive functioning. However, the fact that a significant association between these domains was present in the Cornelia de Lange syndrome group but not in the Down syndrome group, suggests that further investigations examining the relationship between planning, working memory and verbalisation in Cornelia de Lange syndrome are needed to understand whether deficits in working memory and planning underpin the difficulties observed in verbalisation in this group. A direct measure of executive functioning is needed to fully examine the relationship between social impairments and verbal impairments in this group.

These findings are similar to a recent study on selective mutism which found that children with selective mutism had significant deficits in visual memory in comparison to two contrast groups and in nonverbal working memory in comparison to one of the contrast groups, although this was not consistent across all the non-verbal measures (Manassis et

al., 2007). This evidence may indicate that specific executive functioning deficits are implicated in the cause of selective mutism, which may be important when considering the causes of reduced verbalisation in Cornelia de Lange syndrome. Further research is needed into both areas to identify whether there are similar pathways from cognition to verbalisation.

Although, there have been no studies published to date on executive functioning in Cornelia de Lange syndrome, the current literature on other disorders has shown that specific social impairments may be underpinned by cognitive impairments. For example, a study examining the relationship between executive functioning and joint attention impairments in children with Autism spectrum disorder found that ventromedial test performance was related to joint attention (Dawson, Meltzoff, Osterling, Rinaldi & Brown, 1998). Also, Grant et al. (2007) reported that the theory of mind deficits associated with Fragile X syndrome were likely to be underpinned by working memory deficits. A further investigation is needed to fully examine the relationship between impairments in verbalisation and impairments in executive functioning in Cornelia de Lange syndrome due to the limitations of the analysis in the current study, in order to develop useful prevention and intervention strategies for these individuals.

There were several limitations to the current study which may affect the interpretation of the findings. Only behavioural indicators of social anxiety were employed in the current study, which meant that it was difficult to fully determine whether a reduction in verbalisation in the Cornelia de Lange syndrome group was due to or affected by anxiety caused by the presence of unfamiliar people. Physiological measures have been used in

combination with behavioural indicators of social anxiety in the Fragile X syndrome literature (Hall et al., 2006; Hessl et al., 2002; Hessl et al., 2006), to provide a more accurate picture about whether the behaviours shown in this group are anxiety-related. Any future research on social anxiety in Cornelia de Lange syndrome should try to incorporate physiological measures as well as behavioural indicators of social anxiety. Another limitation to the current study was the way in which the Social tasks were administered. Many caregivers of participants with Cornelia de Lange syndrome reported that the anxiety caused by having an unfamiliar person present in their home throughout the research visit meant that they were less sociable even with familiar people. Therefore, the effect of familiarity may not be accurately represented in this study. If this study were to be conducted again, the administration of the Social tasks by the familiar person without the unfamiliar person being present in the home would provide a more accurate picture about the effect of familiarity on social impairments in Cornelia de Lange syndrome. Also, it is possible that the *Very high demand condition* placed demands on working memory because although the participant was given the cartoon pictures whilst retelling the story, they may have been trying to remember the story as it was told to them by the adult. This potential confound however was negated by the similar group differences found in verbalisation in the *Low demand condition*. Another drawback to the current study is that the levels of social anxiety in adolescents and adults with Cornelia de Lange syndrome may be under-reported. Two individuals with Cornelia de Lange syndrome were recruited for the current study but withdrew before the research visits were about to take place because parents reported that both individuals were experiencing significant anxiety about being visited by an unfamiliar person. One individual was even reported to have stopped eating due to the anxiety. The fact that these and other individuals with Cornelia de Lange

syndrome may not have taken part in the current study due to anxiety about being visited by an unfamiliar person indicates that the effect of unfamiliar people on levels of anxiety may be under-reported in this study.

Despite the limitations, this study has still provided several important findings that contribute to the literature on social impairments in Cornelia de Lange syndrome. The results suggest that adolescents and adults with Cornelia de Lange syndrome have a specific difficulty with the initiation of speech that leads to a reduction in verbalisation when social demands involving the initiation of speech are placed upon individuals. Although, the evidence was not conclusive in the current study, adolescents and adults with Cornelia de Lange syndrome seem to show increased anxiety in the presence of unfamiliar people, which causes a further reduction in speech. It is likely that these impairments in verbalisation are underpinning the general reports of social impairments in the group. The results from the current study also indicate that there is a syndrome-environment interaction between verbalisation in adolescents and adults with Cornelia de Lange syndrome and verbalisation in adults interacting with them. It seems that a reduction in verbalisation in adolescents and adults with Cornelia de Lange syndrome is related to increased verbalisation in adults interacting with them. It may be that this increased adult verbalisation causes further demands on verbalisation in people with Cornelia de Lange syndrome and increases the cognitive and social demand. The study also provided some preliminary evidence for a relationship between verbalisation, working memory and planning in Cornelia de Lange syndrome. Research is needed to examine the pathway from cognition to behaviour in Cornelia de Lange syndrome in order to identify the cause of the verbal impairment and use this to develop helpful prevention and

intervention strategies. Furthermore, a clearer understanding of the association between anxiety and verbalisation in this group is needed to understand how these factors impact upon each other.

CHAPTER FIVE

General Discussion

5.1. BACKGROUND

Nyhan first observed compulsive self-mutilation in individuals with Cornelia de Lange syndrome in 1972. Since this first observation of self-injurious behaviour in Cornelia de Lange syndrome, the focus of research on the behavioural phenotype of Cornelia de Lange syndrome has changed and developed over time. Early research tended to focus on the increased level of self-injurious behaviour in the syndrome, whilst more recent research has taken a new course, with studies conducted on the prevalence and phenomenology of Autism spectrum disorder in the syndrome (Berney et al., 1999; Gualtieri, 1990; Hyman et al., 2002; Moss et al., 2008; Nyhan, 1972; Sarimski, 1997). Research has demonstrated that there is an atypical profile of Autism spectrum disorder in Cornelia de Lange syndrome comprising, impaired communication and the presence of specific repetitive behaviours (Moss et al., 2008; Moss et al., 2009).

There has also been some research conducted on age-related changes in Cornelia de Lange syndrome. The available evidence to date indicates that there may be a number of behavioural and emotional changes evident in this group, with age (Basile et al., 2007;

Collis et al., 2006; Kline et al., 2007a; Kline et al., 2007b). However, the lack of robust experimental methodology (e.g., the absence of contrast groups and appropriate measures) in the majority of these studies means that the evidence for age-related changes in Cornelia de Lange syndrome is relatively weak and the changes themselves have not been well documented.

There is therefore a need to carefully characterise the age-related changes reported in Cornelia de Lange syndrome and use a more robust methodology when conducting research, to increase the construct, internal and external validity of any findings reported. The areas focused upon in this thesis were mood and social anxiety. It was important to investigate mood because findings from Oliver et al.'s (in review) study indicated that low mood, interest and pleasure was characteristic of older individuals with Cornelia de Lange syndrome. The first study in this thesis therefore involved a two-year follow-up of mood, interest and pleasure in individuals with Cornelia de Lange syndrome from Oliver et al.'s (in review; Arron et al., in review; Moss et al., 2009) study.

In addition to investigating changes in mood, interest and pleasure, with age, the findings from the pilot study also indicated that an increase in behaviours indicative of social anxiety may be evident in Cornelia de Lange syndrome with age, although no study to date has effectively demonstrated this (Collis et al., 2006). Therefore, two studies examining sociability in Cornelia de Lange syndrome were conducted. The first study examined the age-related pattern of sociability in Cornelia de Lange syndrome using a questionnaire-based design. The second study, improved on the design by using experimental, observational methods to document the precise phenomenology of social impairments in

adolescents and adults with Cornelia de Lange syndrome. The relationship between any social impairments identified in the Cornelia de Lange syndrome group and cognition was also investigated to provide preliminary information about the relationship between cognition and behaviour in this syndrome. This relationship has *not* been considered previously in the literature on Cornelia de Lange syndrome.

The studies conducted in this thesis employed more robust, quantitative methodologies than previous research on ageing in Cornelia de Lange syndrome. For example, appropriate contrast groups were selected for each study so it was possible to determine whether any findings were phenotypic of the syndrome rather than a consequence of the associated intellectual disability (Dykens and Hodapp, 2001). By employing contrast groups, it was also possible to document the trajectory of mood and sociability in the contrast groups as well, further contributing to the literature on other genetic syndromes. The design of the first study conducted in this thesis was also strengthened by incorporating a longitudinal design so that changes (without potential cohort effects) in mood, interest and pleasure could be examined over time. This was the first study on age-related changes in Cornelia de Lange syndrome to employ a longitudinal approach. Psychometrically sound assessments were also employed where possible throughout the studies. Measures were only developed when there was an absence of an appropriate tool for the research being conducted but it was hoped that the measures developed (i.e. the SQID and the Social tasks) would be useful for other researchers in this field. A final, major strength of all three research studies was the number of participants with Cornelia de Lange syndrome recruited for each study, given the rarity of the syndrome. This means that

any findings from this thesis are more generalisable to the Cornelia de Lange syndrome population.

5.2. AIMS OF THE THESIS

The first aim of the thesis was to document the age-related pattern of mood and sociability in Cornelia de Lange syndrome and determine whether the trajectory appeared to be atypical in comparison to other contrast groups. The second aim of the thesis was to determine whether low mood and social anxiety is characteristic of adolescents and adults with Cornelia de Lange syndrome and identify the time period when individuals with Cornelia de Lange syndrome experience the lowest levels of mood, interest and pleasure and sociability with unfamiliar people. The third aim of the thesis was to document more precisely the impairments in mood and sociability in older individuals with the syndrome. The final aim of the thesis was to conduct a preliminary investigation into the relationship between behaviour and cognition in adolescents and adults with Cornelia de Lange syndrome so that hypotheses about the pathways from gene to behavioural change with age could be developed.

5.3. FINDINGS FROM RESEARCH STUDIES

5.3.1. Chapter Two: A Longitudinal Study on Mood, Interest and Pleasure in Cornelia de Lange syndrome

The first empirical study examined changes in mood, interest and pleasure with age, in Cornelia de Lange syndrome. Using a quantitative methodology, the study identified a number of important findings. Firstly, low mood, interest and pleasure was found to be characteristic of older adolescents and adults (over 15 years) with the syndrome. A more fine-grained analysis showed that individuals with Cornelia de Lange syndrome aged between 19 and 22 years were reported to experience the lowest levels of mood, interest and pleasure and these low levels were particularly pronounced for interest and pleasure. The longitudinal analysis showed that both older and younger individuals with Cornelia de Lange syndrome showed no change in mood, interest and pleasure over a two-year period. An examination of factors predicting mood, interest and pleasure in Cornelia de Lange syndrome showed that insistence on sameness was a significant predictor of mood, interest and pleasure in Cornelia de Lange syndrome and that age was also an important factor when considering mood, interest and pleasure in Cornelia de Lange syndrome.

It seems therefore that low mood, interest and pleasure is characteristic of late adolescence and early adulthood (19-22 years) in Cornelia de Lange syndrome, with the lowest levels being evident in interest and pleasure compared to mood. This perhaps indicates a change in the trajectory of mood, interest and pleasure with age in Cornelia de Lange syndrome with the trajectory of interest and pleasure being slightly different from the trajectory of

mood. These conclusions are based on findings from the cross-sectional analysis so it is important to remain cautious about the validity of these results. Although, these findings were not fully supported by the longitudinal analysis, it is important to remain mindful that the longitudinal follow-up was only conducted over a two-year period and perhaps a longer follow-up is necessary to demonstrate significant changes. Furthermore, the use of two broad age bands (15 years and below; and above 15 years) may have meant that significant changes for some individuals within an age band were masked by other individuals who showed no change.

This was the first study to show that insistence on sameness predicted mood, interest and pleasure in Cornelia de Lange syndrome. Given the relationship with this second variable and evidence of other changes with age in the literature, it may be that there are biological and cognitive changes with age in Cornelia de Lange syndrome causing these behavioural changes (Basile et al., 2007; Collis et al., 2006; Kline et al., 2007a; Kline et al., 2007b; Oliver et al., in review). It may also be that there is a syndrome-environment interaction in Cornelia de Lange syndrome around adulthood, accounting for the lowest levels of mood, interest and pleasure at this time, particularly as higher levels of mood, interest and pleasure were reported between 23 and 28 years. Perhaps, the environmental effect of change and / or increased demands around the time of late adolescence / early adulthood (e.g., transition from school to college or increased demands of being an adult) leads to even lower levels of mood, interest and pleasure in Cornelia de Lange syndrome, at this time. The idea of a syndrome-environment interaction in Cornelia de Lange syndrome, gives rise to the possibility that interventions involving modifications to the environment

may help prevent such pronounced low levels of mood, interest and pleasure, during this time period.

These age-related differences reported in Cornelia de Lange syndrome add to the growing literature on developmental trajectories that have been documented in other genetic syndromes, including, Fragile X, Down and Williams syndromes (Einfeld et al., 1999; Fisch et al., 1996; Hernandez et al., 2009; Howlin et al., 2010). Documenting age-related differences across a number of genetic syndromes will facilitate the identification of atypical trajectories and help in the identification of individuals who may be at risk of showing a decline in behaviour and thus enable targeting of prevention and intervention strategies.

This study has helped to further pave the way in investigating the age-related pattern of behaviour and emotion in Cornelia de Lange syndrome. A strong quantitative methodology has strengthened the validity of the findings and the results provide further support for the need for research on age-related changes in Cornelia de Lange syndrome. The questionnaire design also allowed for the collection of a large amount of information on a relatively rare syndrome group. A major drawback of the study was the inclusion of only two very broad age bands during the analysis. This meant that some of the longitudinal effects may have been masked because only some individuals in a given age band may have showed changes over a two-year period. A longer follow-up, with a more fine-grained analysis across the groups is important in future research. This study also demonstrated the problem of using a questionnaire-based study because it was not possible

to understand in detail the phenomenology of low mood, interest and pleasure in adolescents and adults with Cornelia de Lange syndrome.

5.3.2. Chapter Three: Sociability in Cornelia de Lange syndrome: A comparative study

The second questionnaire study examined the trajectory of sociability in Cornelia de Lange syndrome in comparison to five contrast groups. In accordance with the findings in Chapter Two, the results suggested that there was an age-related difference in sociability in individuals with Cornelia de Lange syndrome. Individuals with Cornelia de Lange syndrome aged between 12 and 18 years were reported to show significantly less initiating behaviour with unfamiliar people than those aged under 12 years. Differences between these two age groups also approached significance in two other unfamiliar situations (*Unfamiliar Ongoing Interaction* and *Unfamiliar Receive Interaction*). These differences were not evident in any of the five contrast groups. The prevalence rate of 'extreme shyness' with unfamiliar people was high for the Cornelia de Lange syndrome group, with rates of 'extreme shyness' ranging from 14.4% to 24.5% in four types of unfamiliar social situation. The reported prevalence rate of selective mutism was found to be highest in the Cornelia de Lange syndrome group, with around 40% of individuals with Cornelia de Lange syndrome being reported to show selective mutism. These rates were significantly higher than those found for individuals with Fragile X, Down and Rubinstein Taybi syndromes. A relationship was also demonstrated between selective mutism and social anxiety with those reported to show selective mutism experiencing significantly higher levels of shyness in unfamiliar social situations.

The results suggest that there is a characteristic difficulty in initiating interactions with unfamiliar people in adolescents and young adults with Cornelia de Lange syndrome and this may be part of a more general characteristic shyness with unfamiliar people. It may be that the difficulty in initiating interactions with unfamiliar people is the most pronounced social difficulty for adolescents and adults with Cornelia de Lange syndrome. These differences between age groups are similar to the differences reported between the age groups in Chapter Two but a different phenomenology is reported here. The high rates of 'extreme shyness' with unfamiliar people shown by the Cornelia de Lange syndrome group across all social situations provides support for a characteristic shyness with unfamiliar people in the syndrome. These rates were examined across the group as a whole but given the previous evidence it may be that the prevalence rates of extreme shyness are higher in older individuals with the syndrome. The reported rate of selective mutism was also high in Cornelia de Lange syndrome. Given that the rate of selective mutism in Cornelia de Lange syndrome was significantly higher than in Fragile X syndrome, it suggests that something other than social anxiety is important in causing selective mutism in Cornelia de Lange syndrome. It may be that the expressive communication impairment typically associated with Cornelia de Lange syndrome or cognitive impairments also contributed to the high rate of selective mutism. The rate of selective mutism was again examined for the group as a whole but it may be that the rate of selective mutism increases with age. Research is needed to investigate this further.

This study was the first to examine different aspects of sociability in six neurodevelopmental disorders. Due to the lack of appropriate tools for this type of

research, the study involved the development of an informant-based measure of sociability for individuals with a range of intellectual disabilities (SQID). Although, the validity of the questionnaire was not examined in the study, the findings from the study are consistent with reports on sociability in the contrast groups, for example, the high level of initiating behaviour reported in Angelman syndrome (Oliver et al., 2007). Using the SQID demonstrated the importance of examining different aspects of sociability in neurodevelopmental disorders because different aspects of sociability showed different developmental trajectories across the different neurodevelopmental disorders.

This study has further demonstrated the importance of the age-related pattern of behaviour in Cornelia de Lange syndrome. These results, in combination with the results from Chapter Two, suggest that the trajectory of a number of behaviours may be atypical in Cornelia de Lange syndrome, perhaps suggesting that there are cognitive changes in the syndrome underpinning these difficulties in adolescence and adulthood. Similarly, with the findings from Chapter Two, there may also be an age-related, syndrome-environment interaction associated with sociability in Cornelia de Lange syndrome. The interaction involves the environmental effect of the presence of unfamiliar people on sociability in adolescents and adults with Cornelia de Lange syndrome. The idea of a syndrome-environment interaction provides the possibility for interventions in which a person's environment can be adjusted, e.g., a graded exposure programme focusing on unfamiliar people, to help reduce shyness with unfamiliar people in adolescents and adults with the syndrome.

This study was the first to compare sociability across several groups of individuals with neurodevelopmental disorders. This is a strength of the study as it allowed for the documentation of the age-related pattern of sociability across six groups of individuals with neurodevelopmental disorders. This means that it is possible to document with more confidence trajectories which appear to be atypical in a syndrome given the associated intellectual disability. In addition, the development of a measure to examine different aspects of sociability in individuals with a range of intellectual disabilities is also a strength of the study because it allowed for the inclusion of genetic syndromes associated with a more severe degree of intellectual disability. The findings from this study demonstrated the need for an experimental observational study to detail the precise phenomenology of social impairments in adolescents and adults with Cornelia de Lange syndrome group because detailing the phenomenology was limited by the questionnaire-based nature of the study.

5.3.3. Chapter Four: An Experimental Study of Sociability in Cornelia de Lange syndrome

An experimental, observational study was conducted to explore the phenomenology of social impairments in more detail, in adolescents and adults with Cornelia de Lange syndrome. The results showed that adolescents and adults with Cornelia de Lange syndrome showed significantly less verbalisation than adolescents and adults with Down syndrome in situations where there was a need to initiate speech in a social setting. No effect of familiarity was demonstrated for the duration of verbalisation in these conditions. However, further analysis of the type of verbalisation shown in these conditions and

anecdotal reports indicated that there was an effect of familiarity on verbalisation in individuals with Cornelia de Lange syndrome, with less verbalisation being shown in the presence of unfamiliar people. Contrary to expectations, the Cornelia de Lange syndrome group demonstrated significantly more eye contact and positive facial expression in the condition which involved solely the initiation of speech (*very high demand condition*). Verbalisation of adults differed between the two groups. Familiar and unfamiliar adults prompted the Cornelia de Lange syndrome participants more often in the condition involving solely the initiation of speech (*very high demand condition*). Interestingly, familiar adults still prompted Cornelia de Lange syndrome participants even when instructed not to do so (*low demand condition*). The impairment in verbalisation in the Cornelia de Lange syndrome group was significantly associated with impairments in both working memory and planning, a relationship that was not evident in the Down syndrome group. Also, no relationship was found between verbalisation and adaptive behaviour in Cornelia de Lange syndrome, which was evident in Down syndrome.

The results demonstrated that there were strong group differences in the duration of verbalisation in conditions which involved the initiation of speech. This perhaps suggests that adolescents and adults with Cornelia de Lange syndrome are impaired in the initiation of speech in comparison to the Down syndrome group. There may also be an effect of familiarity on verbalisation but the mixed results made it difficult to determine the impact of familiarity at this stage. Individuals with Cornelia de Lange syndrome may compensate for the reduction in verbalisation with increased eye contact and a positive facial expression because these behaviours were evident in the condition which showed the largest reduction in verbalisation for the Cornelia de Lange syndrome participants. The

lack of verbalisation shown by individuals with Cornelia de Lange syndrome may also affect adults' verbalisation as increased adult verbalisation was reported in conditions where participants with Cornelia de Lange syndrome showed a decrease in verbalisation. This suggests that there may be an inter-play between participant verbalisation and verbalisation by the other person in the interaction in Cornelia de Lange syndrome and investigations are needed to explore this further. The relationship between verbalisation and impairments in planning and working memory in Cornelia de Lange syndrome indicate that specific cognitive impairments may account for the lack of verbalisation in adolescents and adults with Cornelia de Lange syndrome, although caution must be exercised when interpreting the results because only a correlational analysis was conducted.

It may be therefore that individuals with Cornelia de Lange syndrome experience increased impairments in working memory and planning during adolescence or adulthood. These cognitive impairments may then give rise to impairments in the initiation of verbalisation. Individuals with Cornelia de Lange syndrome may also experience more difficulty in interacting with unfamiliar people with age. It may be therefore that the difficulty in the initiation of verbalisation is more pronounced with unfamiliar people and this difficulty accounts at a fine-grained level for the reports of increased social anxiety with age, in Cornelia de Lange syndrome.

The main strength of this study was the improvement on experimental designs used in previous studies because the design allowed for the systematic assessment of the impact of both familiarity and social demand on indicators of social anxiety in Cornelia de Lange syndrome. Also, the use of operationally defined indicators of social anxiety increased the

objectivity of the study. Another strength of the study was the examination of social impairments in Cornelia de Lange syndrome at a fine-grained level because it allowed for a specific difficulty in verbalisation to be identified in this group. The study was limited mainly by the administration of the Social tasks i.e. having an unfamiliar person present in the person's home whilst the tasks were administered by a familiar person. Another limitation of the study was the difficulty in choosing an appropriate contrast group. It may be that with a different contrast group different findings would have resulted. This makes the interpretation difficult when there is only one contrast group. The inclusion of a second contrast group would have been helpful.

5.3.4. Summary of Main Findings

In summary, the findings from the research conducted suggest that individuals with Cornelia de Lange syndrome show age-related differences in both sociability, and mood, interest and pleasure. Specifically, individuals in adolescence and adulthood show characteristic low levels of mood, interest and pleasure with the most pronounced low levels being evident in early adulthood. Adolescents and adults with Cornelia de Lange syndrome also show a difficulty in the initiation of social interactions with unfamiliar people, which may form part of a more general shyness with unfamiliar people. Reduced verbalisation is also evident in this group when there is a demand on these individuals to initiate speech and this may be affected by the familiarity of the other person in the social interaction. Adolescents and adults with Cornelia de Lange syndrome also show an increase in positive facial expressions and eye contact in social interactions which place demands on speech initiation. These behaviours may serve to compensate for the lack of

verbalisation seen in these individuals when there is a demand on speech initiation. Difficulties in working memory and planning are associated with difficulties in verbalisation in adolescents and adults with Cornelia de Lange syndrome perhaps suggesting that impairments in verbalisation are underpinned by cognitive causes. There may also be an age-related, syndrome-environment interaction (change from school environment or increased social demands) evident in late adolescence or early adulthood in Cornelia de Lange syndrome which leads to more pronounced low levels of mood, interest and pleasure and increased shyness with unfamiliar people. The prevalence of selective mutism is also high in Cornelia de Lange syndrome, although it is not known at this stage whether this is age-related.

5.4. A HYPOTHETICAL MODEL OF CORNELIA DE LANGE SYNDROME

The studies conducted in this thesis have provided further information about age-related differences in Cornelia de Lange syndrome. Findings from Chapter Four also indicate a relationship between behaviour and cognition in adolescents and adults with Cornelia de Lange syndrome. The findings also provide some evidence of an age-related effect of the environment upon behaviour in this syndrome and thus suggest there is a syndrome-environment interaction in late adolescence or early adulthood. The model described in Figure 5.1 provides a hypothetical model for the relationship between genes, cognition and behaviour in adolescents and adults with Cornelia de Lange syndrome and is based on Morton's model (2004). Some of the pathways have been demonstrated by evidence collected in this thesis, whilst other pathways are purely hypothetical and need further research to investigate whether they are correct.

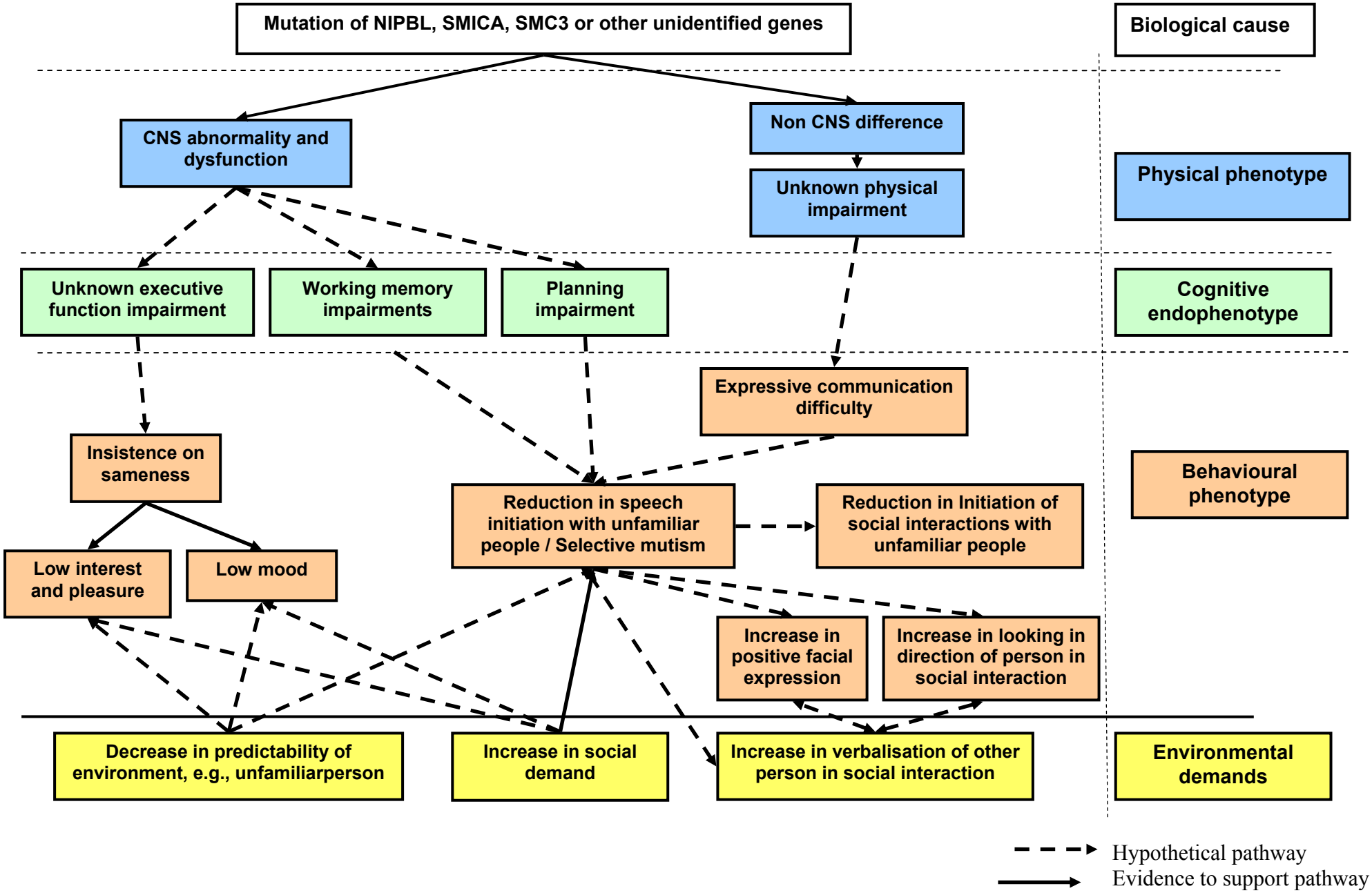


Figure 5.1: A hypothetical model of the pathway from genes to behaviour during late adolescence to early adulthood in Cornelia de Lange syndrome.

The findings from Chapter Two showed that low mood and low interest and pleasure are characteristic of older adolescents and young adults with Cornelia de Lange syndrome. Hence, *low mood* and *low interest and pleasure* are presented in the model as part of the behavioural phenotype for these individuals. Mood and interest and pleasure have been separated into two separate constructs as the findings from Chapter Two showed that mood and interest and pleasure have slightly different developmental trajectories. The findings from Chapter Two also showed that insistence on sameness predicts mood, interest and pleasure in Cornelia de Lange syndrome. Hence, there is evidence to support the pathway from *insistence on sameness* to *low mood* and *low interest and pleasure* in the model. It is currently unknown what causes increased insistence on sameness in this group of individuals so there is a hypothetical pathway from *unknown executive function impairment* to *insistence on sameness* in the model.

From the information gathered in the pilot interview (Collis et al., 2006) it appears that there may also be an effect of the environment on mood, interest and pleasure in older adolescents and young adults with Cornelia de Lange syndrome leading to a more pronounced decline in mood, interest and pleasure at this time. The environmental effect may be changing from a school environment to a college or work environment, it may be due to the unstructured nature of the new college or work environment, or it may be due to the increased social demands without adult support, such as increased social demands at college. Hence, there are hypothetical pathways in the model from a *decrease in predictability of environment* and *increase in social demand* to *low mood* and *low interest and pleasure*.

The findings in Chapter Three showed that older adolescents and young adults with Cornelia de Lange syndrome showed a difficulty in initiating social interactions with unfamiliar people. Hence, *reduction in initiation of social interactions with unfamiliar people* is shown in the model as part of the behavioural phenotype for this group of individuals. The findings in Chapter Three also showed a raised prevalence of selective mutism in individuals with Cornelia de Lange syndrome. Although, it was not possible to determine at this stage whether this was age-related, it is represented as part of the model because there is further support for selective mutism in older adolescents and young adults with Cornelia de Lange syndrome from the findings in Chapter Four and the findings from the pilot study (Collis et al., 2006). Hence, *selective mutism* is presented as part of the behavioural phenotype. Given that the levels of selective mutism were higher in this group than would be expected if it were solely a manifestation of social anxiety, it was hypothesised that the expressive language difficulty commonly reported in the syndrome may be a contributing factor to selective mutism in older adolescents and young adults with the syndrome. Hence, there is a hypothetical pathway from *expressive communication difficulty* to *selective mutism*. It is unknown at a physical level what leads to the expressive communication difficulty so there is a hypothetical pathway from *unknown physical impairment* to *expressive communication difficulty*.

The findings in Chapter Four demonstrated that adolescents and adults with Cornelia de Lange syndrome showed a reduction in the initiation of speech. Although it was difficult to determine the exact effect of familiarity on the initiation of speech, there was evidence from both Chapter Three and the pilot study (Collis et al., 2006) which supported the effect

of familiarity on sociability and speech, so *reduction speech initiation with unfamiliar people* is presented in the model as part of the behavioural phenotype for older adolescents and young adults with Cornelia de Lange syndrome. *Reduction speech initiation with unfamiliar people* and *selective mutism* are presented in the same box because it is hypothesised that they both have the same causes because selective mutism is just a more extreme form of a reduction in verbalisation with an unfamiliar person.

Chapter Four also demonstrated the environmental effect of increasing social demands on reduced speech so there is evidence to support the pathway from *social demand* to a *reduction in speech initiation with unfamiliar people / selective mutism*. Also, findings from the pilot study suggested that selective mutism was evident during early adulthood when there was change in the environment, hence there is a hypothetical pathway from *decrease in predictability of environment* to *reduction in speech initiation with unfamiliar people / selective mutism*.

In Chapter Four, a relationship was also demonstrated between reduced verbalisation and working memory and planning impairments. At this stage we cannot assume causality so there is a hypothetical pathway from *working memory impairments* and *planning impairments* to *reduction in speech initiation with unfamiliar people / selective mutism* in the model. It is hypothesised that the reduction in speech intitiation with unfamiliar people may cause a reduction in the initiation of social interactions with unfamiliar people, hence there is a hypothetical pathway from *reduction in speech initiation with unfamiliar people / selective mutism* to *decrease in initiating social interactions with unfamiliar people*.

Further analysis in Chapter Four showed that in situations where there was the most demand for individuals with Cornelia de Lange syndrome to initiate speech, that they would show an increase in positive facial expression and an increase in looking in the direction of the adult. It was hypothesised that these non-verbal behaviours serve a function of compensating for the absence of speech. Therefore, there is a hypothetical pathway from *reduction in the initiation of speech with unfamiliar people / selective mutism* to an *increase in positive facial expression* and *increase in looking in direction of person in social interaction*.

The findings from Chapter Four also demonstrated an increase in the verbalisation of the other person in the social interaction, through prompting and comments. It was hypothesised that the reduction in verbalisation and the non-verbal behaviours (i.e. increase in positive facial expression and looking in direction of other person) evoke speech from the other person in the interaction. It was also hypothesised that the speech from the other person in the interaction may increase non-verbal behaviours (i.e. increase in positive facial expression and looking in direction of other person) and also place increasing demands on the person leading to a further reduction in their speech. Hence, there is a hypothetical two-way pathway shown between an *increase in verbalisation of other person in interactio*n and *increase in positive facial expression* and *increase in looking in direction of person in social interaction* and between *increase in verbalisation of other person in interactio*n and *reduction in the initiation of speech with unfamiliar people / selective mutism*.

5.5. DIRECTIONS FOR FUTURE RESEARCH

The research findings from this thesis have provided the basis for a number of possible avenues to be explored further in the future. First, it is important to carefully characterise and document the behavioural and emotional changes with age in Cornelia de Lange syndrome. A long-term follow-up of these changes in individuals with Cornelia de Lange syndrome is needed to provide information about the trajectory of behaviour and emotion in this group over time. The examination of executive functioning is also important so that the association between behaviour and executive functioning can be examined in any follow-up assessments. The inclusion of younger individuals will be important so that changes in behaviour, emotion and cognition can be monitored across the life span in Cornelia de Lange syndrome.

In any follow-up conducted, the use of detailed, refined measures is important to ensure that a comprehensive assessment of change is undertaken in Cornelia de Lange syndrome. The use of Social tasks, for example, will enable researchers to identify at a fine-grained level the changes in social impairments with age. Also, the comprehensive assessment of executive functioning will ensure that any changes in this domain can also be carefully monitored over time. By using comprehensive assessments it will be possible to determine whether there is a common cognitive cause to these behavioural and emotional changes with age or whether there are a number of different pathways involved.

Research also needs to be conducted at a biological level to understand the pathway from genes to behaviour via cognition. Neuroimaging studies of individuals with Cornelia de

Lange syndrome will help to provide a detailed understanding of this. By examining the results of the neuroimaging studies in relation to age, cognition and behaviour, it will be possible to gain an understanding of the biological changes that may be occurring with age in Cornelia de Lange syndrome and understand whether these biological changes lead to cognitive, behavioural and emotional changes in the syndrome. In Cornelia de Lange syndrome it will also be important to consider the effect of the genetic subtypes on the pathways from genes to behaviour because three different genes have been identified to date in the cause of Cornelia de Lange syndrome (Deardorff et al., 2007; Krantz et al., 2004; Tonkin et al., 2004). It may be that there are different pathways from genes to behaviour for each gene disorder in Cornelia de Lange syndrome and it may be that the changes with age are related to specific subtypes. An understanding of the difference between the subtypes in Cornelia de Lange syndrome will be important in future research.

Research examining the syndrome-environment interaction in adolescents and young adults with Cornelia de Lange syndrome is also important because this information may provide the basis for developing effective interventions for this age group based upon manipulations of the environment. For example, it will be important to understand the effect of changes in the environment on an individual's behaviour during this time, e.g., visiting an unfamiliar place or moving from school to college. Once the syndrome-environment interaction is fully understood, it will be important to conduct intervention studies to examine whether specific changes to a person's environment will help to decrease the impact of the environment upon their behaviour. This part of the research is crucial for parents and carers as well as the individual.

Finally, given the extremely high prevalence rate of selective mutism reported in Cornelia de Lange syndrome, it is also important to conduct research into understanding the cause of selective mutism in the syndrome. The results from the thesis suggest that there may be other important pathways, other than social anxiety, leading to selective mutism in the syndrome. A comprehensive study examining the factors underpinning selective mutism in the syndrome is important so that appropriate interventions can be designed particularly as selective mutism has such a profound effect on people's everyday lives. This research may also demonstrate that the pathways causing selective mutism differ between genetic syndromes (e.g., Cornelia de Lange syndrome and Fragile X syndrome) and thus help to inform theories of selective mutsim in the typically developing population. As a final note, it will also be important to understand the trajectory of selective mutism with age in Cornelia de Lange syndrome because it may be that selective mutism increases with age when impairments in planning and working memory become more evident.

5.6. BROADER IMPLICATIONS OF RESEARCH

This thesis demonstrates the importance of understanding genetic syndromes from a developmental perspective and understanding how the trajectory of behaviour and emotion changes with age. Understanding age-related changes across the life span in neurodevelopmental disorders will help to identify individuals at risk for psychological disorder and help to inform effective prevention and intervention strategies.

This thesis also demonstrates that syndrome-environment interactions in genetic syndromes may also be age-related. It may be that there are ages at which individuals with

a given genetic syndrome are more likely to show a given behaviour. This behaviour may then interact with the environment at this time in a person's life leading to an age-related, syndrome-environment interaction. For example, individuals with Angelman syndrome show the highest levels of laughing and smiling when they are younger so it may be that the syndrome-environment interaction demonstrated for this behaviour in the literature is more evident when individuals are younger (Horsler & Oliver, 2007b). The effect of age on syndrome-environment interactions has *not* been considered in the literature on genetic syndromes and this is important in future research.

This research also demonstrates the importance of examining behaviour at a fine-grained level in genetic syndromes. Solely relying upon questionnaire information may not provide an accurate picture of the phenomenology of behaviour in a given genetic syndrome. It is important that researchers also use experimental, observational studies to gain a detailed understanding of the phenomenology of behaviour in genetic syndromes. This will then lead to the refinement of the phenomenology of the behavioural phenotype of genetic syndromes.

This thesis also shows the importance of understanding the pathway from genes to behaviour via cognition and understanding how changes in cognition with age may underpin behavioural changes with age. Conducting follow-ups of executive functioning in addition to behaviour in genetic syndromes, will allow a clearer understanding of why changes may be occurring with age in neurodevelopmental disorders. Furthermore, it will mean that intervention strategies for age-related changes in syndromes can be targeted at a cognitive level as well as a behavioural level.

5.7. CLINICAL IMPLICATIONS OF RESEARCH

It is important to raise awareness with both parents and professionals about the increased probability of age-related changes in Cornelia de Lange syndrome. There will be an ethical dilemma about the type of information given to parents if these changes in behaviour seem to be underpinned by biological causes because it may give parents a sense of hopelessness about their child's future. When providing parents with information it will be important to emphasise that these changes are *not* necessarily inevitable and that some people with the syndrome have lives without these difficulties. Furthermore, when giving this information to families, it will also be essential to provide them with useful intervention strategies so that any decline in behaviour and emotion may be minimised for their child. This will allow parents to feel that even if their child experiences changes with age, modifications to their environment will help to minimise the impact upon their behaviour and well-being.

Useful intervention strategies, for example, may take into account the environmental impact upon adolescents' and adults' behaviour. For example, careful, advanced planning around transition periods for these individuals and the identification of appropriate environments for individuals once finishing school may be crucial for these individuals. It may be that small, structured, relatively low-demand environments are more likely to be suitable for adults with Cornelia de Lange syndrome rather than environments that are large and unstructured. These recommendations are also supported by anecdotal parental reports on young adults with Cornelia de Lange syndrome (Collis et al., 2006).

It will also be important to consider teaching individuals with Cornelia de Lange syndrome coping strategies for potentially difficult social situations, for example using social skills training. Also, it may be that preparing individuals with Cornelia de Lange syndrome for unfamiliar social situations where possible, may be a useful intervention strategy. For example, providing individuals with a picture-schedule for unfamiliar situations which are planned ahead may mean that new, unpredictable events become more predictable and thus reduce a person's anxiety about the event. Strategies already proven to be effective in the Autism spectrum disorder literature on transition planning and social skills may also prove to be useful for individuals with Cornelia de Lange syndrome.

It will also be important to provide interventions for individuals with Cornelia de Lange syndrome who show selective mutism. Research in the typically developing population has already demonstrated the effectiveness of behavioural interventions for treating selective mutism (Cohan et al., 2006; Pinonek Stone et al., 2002). Perhaps utilising similar operant behavioural principles will be effective in increasing verbalisation in individuals with Cornelia de Lange syndrome. However, it will also be important to take into consideration the cause of selective mutism in Cornelia de Lange syndrome. For example, if it is related to impairments in working memory and planning, work around these cognitive difficulties will be important.

The notion of age-related changes in Cornelia de Lange syndrome perhaps indicates that the introduction of serial assessments of behaviour and cognition in individuals with Cornelia de Lange syndrome, from birth through the life time, will be useful to detect any changes with age. If individuals were monitored at regular intervals (once a year) then any

changes in individuals' cognition or behaviour can be identified and appropriate interventions can be implemented early and thus reduce the chance of such a pronounced change in behaviour with age.

Finally, these clinical implications demonstrate the importance of increasing the debate about individual difference in mass-produced services. It seems that individuals with Cornelia de Lange syndrome have specific needs and it is important that services take this into consideration to ensure that the well-being of the person is maintained, e.g., providing appropriate adult learning and residential environments.

5.8. CONCLUDING REMARKS

This thesis provides some of the first quantitative data for age-related differences in behaviour in Cornelia de Lange syndrome. This thesis demonstrates the importance of understanding behavioural phenotypes in genetic syndromes from a developmental perspective, so that effective prevention and intervention strategies may be developed if there is a risk for associated psychological difficulties. This thesis has provided the first preliminary evidence for the relationship between behaviour and cognition in Cornelia de Lange syndrome and alludes to implications for a change in cognition with age, thus accounting for the changes in behaviour. Evidence for a syndrome-environment interaction with age has also been provided which thus provides a basis for environmental strategies when providing interventions for a decline in behaviour with age in Cornelia de Lange syndrome.

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APPENDIX A1

Demographic Questionnaire

BACKGROUND INFORMATION

Please tick or write your response to these questions concerning background details:

1. Today's date: _____

2. Your name: _____

Your address: _____

_____

Your phone number: _____

3. Would you be happy to be contacted for future research? Yes ☐ No ☐

*The following questions regard information about the **person you care for**:*

1. Name of person: _____ **Gender:** Male ☐ Female ☐

2. Date of Birth: ___/___/____ **Age:**_____

3. Is the person verbal? (i.e. speaks / signs more than 30 words) Yes ☐ No ☐

4. Is the person able to walk unaided? Yes ☐ No ☐

5. Has the person been diagnosed with a syndrome? Yes ☐ No ☐

If yes, please answer the rest of this questionnaire. If no, please move on to question 10.

6. Which syndrome has the person been diagnosed with?

Sotos syndrome ☐ Rubinstein-Taybi syndrome ☐
Down's syndrome ☐ Other _____

7. When was the person diagnosed? _____

8. Who diagnosed the person?

Paediatrician ☐ Clinical Geneticist ☐
GP ☐ Other _____

9. If the person has had a blood test to determine the cause of their genetic syndrome, please answer the rest of question 9. If not, please move on to question 10.

9a. When was the blood test carried out? _____

9b. Where was the blood test carried out? _____

9c. Who carried out the blood test? _____

9d. Can we contact the person to request the test results? Yes ☐ No ☐

If yes, please sign to provide consent _____

10. Has the person experienced any of the following life events in the *past twelve months*:-

	Yes	No	N/A
10a. Significant change of staff or friends at residential unit? ……...	☐	☐	☐
10b. Significant change of staff or friends at day provision? ……....	☐	☐	☐
10c. Significant change in day provision, e.g. school, college or job placement? ……	☐	☐	☐
10d. Significant change in place of residence? ……..	☐	☐	
10e. Serious illness and / or hospitalisation? ……..……	☐	☐	
10f. Serious illness of a close relative, close friend or close member of staff? …….	☐	☐	
10g. Death of a close relative, close friend or close member of staff? ……...	☐	☐	
10h. Parents divorced or separated? ……...	☐	☐	

Other (please give details) _____

_____

APPENDIX A2

The Mood, Interest and Pleasure Questionnaire – Short Version

THE MOOD, INTEREST AND PLEASURE QUESTIONNAIRE – SHORT FORM (MIPQ-S)

Instructions:

- This questionnaire contains 12 questions – you should complete all 12 questions.
- Each question will ask for your opinion about particular behaviours, which you have observed in the last 2 weeks. For every question you should circle the most appropriate response e.g.

6) In the last two weeks, how interested did the person appear to be in his/her surroundings?

interested all of the time	*interested most of the time*	*interested about half of the time*	*interested some of the time*	*never interested*

The Mood, Interest and Pleasure Questionnaire - Short Form

1) In the last two weeks, did the person seem…

sad all of the time	sad most of the time	sad about half of the time	sad some of the time	never sad

Please comment if anything has happened in the last two weeks which you feel might explain sadness if it has been observed (e.g. a bereavement):

2) In the last two weeks, how often did you hear positive vocalizations* when the person was engaged in activities*?

all of the time	most of the the time	about half of the time	some of the time	never

*positive vocalizations: e.g. laughing, giggling, "excited sounds" etc.
*engaged in activities: i.e. when someone is actively involved in any activity such as a mealtime, a social interaction, a self-care task or social outing etc.

3) In the last two weeks, do you think the facial expression of the person looked "flat"*…

all of the time	most of the the time	about half of the time	some of the time	never

*flat expression: expression seems lifeless; lacks emotional expression; seems unresponsive.

4) In the last two weeks, would you say the person…

cried every day	cried nearly every day	cried 3-4 times each week	cried once or twice each week	cried less than once each week

5) In the last two weeks, how interested did the person appear to be in his/her surroundings?

interested all of the time	interested most of the time	interested about half of the time	interested some of the time	never interested

6) In the last two weeks, did the person seem to have been enjoying life…

all of the time	most of the the time	about half of the time	some of the time	never

Please comment if there are any reasons why this person might not have been enjoying him/herself e.g. illness, being in pain, experiencing a loss etc.:

7) In the last two weeks, would you say the person smiled…

at least once every day	at least once nearly every day	3-4 times each week	once or twice each week	less than once each week

8) In the last two weeks, how disinterested did the person seem to be in his/her surroundings?

disinterested all of the time	disinterested most of the time	disinterested about half of the time	disinterested some of the time	never disinterested

9) In the last two weeks, when the person was engaged in activities*, to what extent did his/her facial expressions* suggest that s/he was interested in the activity?

interested all of the time	interested most of the time	interested about half of the time	interested some of the time	never interested

*engaged in activities: i.e. when someone is actively involved in any activity such as a mealtime, social interaction, self-care task or social outing etc.
*facial expressions: interest might be indicated by the degree to which the person's gaze is being directed at the person/things involved in an activity.

10) In the last two weeks, would you say that the person…

laughed every day	laughed nearly every day	laughed 3-4 times each week	laughed once or twice each week	laughed less than once each week

11) In the last two weeks, how often did you see gestures which appeared to demonstrate enjoyment* when the person was engaged in activities*?

all of the time	most of the the time	about half of the time	some of the time	never

*gestures which appear to demonstrate enjoyment: e.g. clapping, waving hands in excitement etc.
*engaged in activities: i.e. when someone is actively involved in any activity such as a meal time, social interaction, self-care task or social outing etc.

12) In the last two weeks, did the person's vocalizations* sound distressed…

all of the time	most of the the time	about half of the time	some of the time	never

*vocalizations: any words, noises or utterances.

Please feel free to make any additional comments about the behaviour of the person over the last two weeks (continue overleaf if necessary):

APPENDIX A3

The Health Questionnaire

Health Questionnaire

PART A

Instructions:

- Have these problems **EVER** affected your child or person you care for?
- Please rate as **0** – if the problem has never affected the person you care for, **1** – if it has been a mild problem, **2** - if the problem has been moderately serious, or **3** – if the problem has been severe.
- If the person you care for has had these problems please state whether any treatment has been implemented by circling **yes** or **no**.

	Never	Mild	Moderate	Severe
1a. Eye Problems (e.g. glaucoma / blocked tear duct/s).....	**0**	**1**	**2**	**3**
1b. Corrective surgery / medication / treatment: **yes / no**				
2a. Ear Problems (e.g. infections, glue ear)	**0**	**1**	**2**	**3**
2b. Corrective surgery / medication / treatment (e.g. grommets): **yes / no**				
3a. Dental Problems (e.g. toothache / gum problems / mouth ulcers / delayed eruption of teeth).....	**0**	**1**	**2**	**3**
3b.Dental surgery / treatment (e.g. teeth removal): **yes / no**				
4a. Cleft Palate.....	**0**	**1**	**2**	**3**
4b. Repaired: **yes / no**				
5a. Gastrointestinal Difficulties (e.g. reflux / stomach problems).....	**0**	**1**	**2**	**3**
5b. Corrective surgery / medication / treatment (e.g. nissen fundoplication): **yes / no**				
6a. Bowel Problems (e.g. obstruction).....	**0**	**1**	**2**	**3**
6b. Corrective surgery / treatment: **yes / no**				
7a. Heart Abnormalities or Circulatory Problems (e.g. congenital heart lesions or murmur).....	**0**	**1**	**2**	**3**
7b. Corrective surgery / medication / treatment: **yes / no**				
8a. Problems with Genitalia (e.g. prostate/ testicular problems i.e. undescended testes) ……	**0**	**1**	**2**	**3**
8b. Corrective surgery / treatment: **yes / no**				
9a. Hernia (e.g. inguinal or hiatal).....	**0**	**1**	**2**	**3**
9b. Repair / treatment: **yes / no**				
10. Limb Abnormalities (e.g. malformed arm).....	**0**	**1**	**2**	**3**
11a. Epilepsy / Seizures / Neurological Referrals.....	**0**	**1**	**2**	**3**
11b. Medication: **yes / no**				
12a. Lung or Respiratory Problems (asthma/bronchitis).....	**0**	**1**	**2**	**3**
12b. Corrective surgery / medication / treatment: **yes / no**				
13a. Liver or Kidney Problems.....	**0**	**1**	**2**	**3**
13b. Corrective surgery / medication / treatment: **yes / no**				
14a. Diabetes or Thyroid Function Problems.....	**0**	**1**	**2**	**3**
14b. Corrective surgery / medication / treatment: **yes / no**				
15a. Skin Problems (e.g. tinea, eczema, psoriasis, dry skin)……....	**0**	**1**	**2**	**3**
15b. Medication / treatment: **yes / no**				
16a. Other (please specify problem, severity from 0-3).....	**0**	**1**	**2**	**3**
16b. Corrective surgery / medication / treatment: **yes / no**				

PART B

Instructions:

- Have these medical problems affected the person you care for in the past **MONTH**

- Please rate as **0** – if your child has not been affected by this problem in the past month, **1** - if they have been mildly affected, **2** – if the problem has moderately affected your child and **3** - if your child has been severely affected by the problem.

	No	Mild	Moderate	Severe
17. Eye Problems (e.g. glaucoma / blocked tear duct/s).....	**0**	**1**	**2**	**3**
18. Ear Problems (e.g. infections, glue ear).....	**0**	**1**	**2**	**3**
19. Dental Problems (e.g. toothache / gum problems / mouth ulcers / delayed eruption of teeth).....	**0**	**1**	**2**	**3**
20. Cleft Palate.....	**0**	**1**	**2**	**3**
21. Gastrointestinal Difficulties (e.g. reflux / stomach problems).....	**0**	**1**	**2**	**3**
22. Bowel Problems (e.g. obstruction).....	**0**	**1**	**2**	**3**
23. Heart Abnormalities or Circulatory Problems (e.g. congenital heart lesions or murmur)……	**0**	**1**	**2**	**3**
24. Problems with Genitalia (e.g. prostate / testicular problems i.e. undescended testes).....	**0**	**1**	**2**	**3**
25. Hernia (e.g. inguinal or hiatal).....	**0**	**1**	**2**	**3**
26. Limb Abnormalities (e.g. malformed arm).....	**0**	**1**	**2**	**3**
27. Epilepsy / Seizures / Neurological Referrals.....	**0**	**1**	**2**	**3**
28. Lung or Respiratory Problems (asthma / bronchitis).....	**0**	**1**	**2**	**3**
29. Liver or Kidney Problems.....	**0**	**1**	**2**	**3**
30. Diabetes or Thyroid Function Problems.....	**0**	**1**	**2**	**3**
31. Skin Problems (e.g. tinea, eczema, psoriasis, dry skin).....	**0**	**1**	**2**	**3**
32. Other (please specify problem and severity from 0-3) ……....	**0**	**1**	**2**	**3**

APPENDIX A4

The Repetitive Behaviour Questionnaire

THE RBQ

INSTRUCTIONS:

1. The questionnaire asks about 19 different behaviours.

2. Each behaviour is accompanied by a brief definition and examples. The examples given for each behaviour are not necessarily a complete list but may help you to understand the definitions more fully.

3. Please read the definitions and examples carefully and circle the appropriate number on the scale to indicate how frequently the person you care for has engaged in each of the behaviours **within the last month**.

4. If a particular behaviour does not apply to the person you care for because they are not mobile or verbal please circle the number 0 on the scale

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

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

APPENDIX A5

The Social Communication Questionnaire

APPENDIX A6

The Sociability Questionnaire for People with Intellectual Disabilities

THE SOCIABILITY QUESTIONNAIRE FOR PEOPLE WITH INTELLECTUAL DISABILITIES (SQID)

Instructions:

This questionnaire asks you how the person you care for typically behaved in social situations over the last two months. Each situation will involve one of the following:

1. *The person's main caregiver*: Someone that provides the main support and care for the person, e.g. a parent or carer.

2. *A familiar adult or someone familiar of the same age*: Someone that knows the person relatively well but does *not* provide the main care for the person, e.g. a relative *not* in the immediate family, a friend of the family, a support worker at school / college, a friend at school / college etc.

3. *An adult or someone of the same age that the person does not know*: Someone the person has *never* met before, e.g. a stranger, a new teacher, a new support worker at school / college, someone new of the same age at school / college etc.

The person may appear 'sociable', 'shy' or somewhere in between in the situations given below.

- If the person is 'sociable' (s)he may show one or more of the following behaviours: looks pleased; starts to speak or sign to others; turns face and / or body towards others; or tries to gain other people's attention in someway.

- If the person is 'shy' (s)he may show one or more of the following behaviours: looks a little sad or distressed; reluctant to speak or sign to others; turns head and / or body away from others; tries to avoid or remove himself / herself from situations when other people are present.

Read each question and circle the response that best describes the behaviour of the person in the situation described.

For example, for question 4 if you think that when the person is spending time with a familiar adult (s)he would be 'very sociable' then your answer would look like this:-

4. (S)he is spending time with a familiar adult? 1 2 3 4 5 6 (7)

How would the person you care for appear if…	**Very shy**	**Moderately shy**	**A little shy**	**Neither**	**A little sociable**	**Moderately sociable**	**Very sociable**
1. Her / his main caregiver walks up to her / him?	**1**	**2**	**3**	**4**	**5**	**6**	**7**
2. (S)he is spending time with an adult (s)he does *not* know?…….....	**1**	**2**	**3**	**4**	**5**	**6**	**7**
3. Someone (s)he does *not* know that is her / his own age walks up to her /him? ……...	**1**	**2**	**3**	**4**	**5**	**6**	**7**
4. (S)he is spending time with a familiar adult? ……	**1**	**2**	**3**	**4**	**5**	**6**	**7**
5. (S)he is the focus of attention in a group of adults (s)he knows? ……...	**1**	**2**	**3**	**4**	**5**	**6**	**7**
6. (S)he is spending time with someone (s)he does *not* know that her / his own age? …….	**1**	**2**	**3**	**4**	**5**	**6**	**7**
7. Someone familiar that is her / his own age walks up to her /him? …….	**1**	**2**	**3**	**4**	**5**	**6**	**7**
8. (S)he has just been separated from her / his main caregiver to be with an adult (s)he does *not* know? ….....	**1**	**2**	**3**	**4**	**5**	**6**	**7**

How would the person you care for appear if…	**Very shy**	**Moderately shy**	**A little shy**	**Neither**	**A little sociable**	**Moderately sociable**	**Very sociable**
9. An adult (s)he does *not* know walks up to her / him? ……	**1**	**2**	**3**	**4**	**5**	**6**	**7**
10. (S)he is the focus of attention in a group of people her / his own age that (s)he does *not* know? …….....	**1**	**2**	**3**	**4**	**5**	**6**	**7**
11. (S)he is spending time with someone familiar that is her / his own age? …	**1**	**2**	**3**	**4**	**5**	**6**	**7**
12. (S)he is the focus of attention in a group of people her / his own age that (s)he knows? ……..	**1**	**2**	**3**	**4**	**5**	**6**	**7**
13. (S)he is with her / his main caregiver and then someone her / his own age that (s)he does *not* know starts to talk to her / him? …….....	**1**	**2**	**3**	**4**	**5**	**6**	**7**
14. A familiar adult walks up to her / him? ……	**1**	**2**	**3**	**4**	**5**	**6**	**7**
15. (S)he is with her / his main caregiver and then an adult (s)he does *not* know starts to talk to her / him? …….	**1**	**2**	**3**	**4**	**5**	**6**	**7**
16. (S)he is spending time with her / his main caregiver? …….	**1**	**2**	**3**	**4**	**5**	**6**	**7**
17. (S)he is the focus of attention in a group of adults (s)he does *not* know?...	**1**	**2**	**3**	**4**	**5**	**6**	**7**

	Never or very rarely	**Rarely**	**Sometimes**	**About half the time**	**Often**	**Very often**	**Nearly Always**
18. When there are only familiar people around, how often does (s)he try to make contact with them in any way (by talking, signing, vocalising, using gestures, moving towards them in any way etc.)? …….	**1**	**2**	**3**	**4**	**5**	**6**	**7**
19. When familiar people and people are around who (s)he does *not* know, how often does (s)he try to make contact with the people (s)he does *not* know in any way (by talking, signing, vocalising, using gestures, moving towards them in any way etc.)? ……..	**1**	**2**	**3**	**4**	**5**	**6**	**7**
20. When familiar people and people are around who (s)he does *not* know, how often does (s)he try to make contact with the familiar people in any way (by talking, signing, vocalising, using gestures, moving towards them in any way etc.)? …….	**1**	**2**	**3**	**4**	**5**	**6**	**7**
21. When there are only people around who (s)he does *not* know, how often does (s)he try to make contact with them in any way (by talking, signing, vocalising, using gestures, moving towards them in any way etc.)? ……	**1**	**2**	**3**	**4**	**5**	**6**	**7**

	YES	NO
22. Does the person you care for speak or sign **more** than 30 words?	☐	☐

If you answered **'yes'** to this question, please complete the rest of the questionnaire. If you answered **'no'**, please complete the box at the end of the questionnaire if there is anything else you think we should know.

23. Does the person speak *less* than (s)he used to?	☐	☐
24. Does the person *only* speak or sign in some settings and not others?	☐	☐

If 'yes' please describe

.....
.....
.....

25. Does the person *only* speak or sign to some people and not others?	☐	☐

If 'yes' please describe

……
……
……

Is there anything else you want to tell us about how the person you care for appears in social situations with other people (s)he knows or doesn't know, when separated from you, in a group setting or is the centre of attention in a group of people?

……
……
……
.....

APPENDIX B

Inter-rater reliability of SQID scores at item-level

Inter-rater reliability of SQID scores at item level		
Item no	**Spearman's correlation co-efficient**	***P*-value**
Q1	.537	<.0001
Q2	.741	<.0001
Q3	.656	<.0001
Q4	.656	<.0001
Q5	.536	<.0001
Q6	.753	<.0001
Q7	.740	<.0001
Q8	.681	<.0001
Q9	.687	<.0001
Q10	.689	<.0001
Q11	.627	<.0001
Q12	.508	<.0001
Q13	.715	<.0001
Q14	.628	<.0001
Q15	.684	<.0001
Q16	.428	<.005
Q17	.703	<.0001
Q18	.569	<.0001
Q19	.711	<.0001
Q20	.733	<.0001
Q21	.799	<.0001

APPENDIX C

Information on Social tasks

LIST OF STATEMENTS USED BY THE FAMILIAR AND UNFAMILIAR ADULTS IN THE LOW DEMAND CONDITION

Statements used by the unfamiliar adult

1. The weather was terrible. I had to wait at the airport for ages! (Photograph 1).
2. This is the hotel I stayed at. It was amazing! (Photograph 3).
3. This beach was really near the hotel. The cliffs were really dramatic! (Photograph 5).
4. I was shown around the local town. Some of the buildings were beautiful! (Photograph 7).
5. It was nice to relax at a café. This drink was really tasty! (Photograph 9).
6. I saw lots of animals at the zoo. This camel made me laugh! (Photograph 11).
7. These masks were very pretty. It was fun to look around the shops! (Photograph 13).
8. We went on a day trip to a Spanish village. It was awful! (Photograph 15).
9. The hotel had some entertainment in the evening. I loved the dancing! (Photograph 17).
10. This is the hotel at night. It looks like it's on fire!! (Photograph 19).

Statements used by the familiar adult

1. The flight was really long and the food on the plane was disgusting! (photograph 1).
2. There were lots of people, cars and motorbikes in the town – it was far too busy! (photograph 3).
3. There were lots of interesting buildings. Some of them were beautiful! (photograph 5).
4. These houses were built on stilts in the water. This person had lots of washing on their balcony! (photograph 7).
5. The countryside was very different from the busy towns! (photograph 9).
6. I went in a canoe. I nearly fell in the water! (photograph 11).
7. I had a ride on an elephant. It was really bouncy! (photograph 13).
8. It was really sunny, and I thought it was far too hot! (photograph 15).
9. I think this baby elephant had got lost! (photograph 17).
10. The food was really tasty! (photograph 19).

LIST OF SUGGESTED TOPICS AND QUESTIONS FOR THE UNFAMILIAR AND FAMILIAR ADULTS IN THE HIGH DEMAND CONDITION

Suggested topics for the unfamiliar adult

1. Weekday placement

What do you do during the week?
Do you attend school / college / work / stay at home?

If the person goes to school / college:-
How many days a week do you go to school / college?
How do you get to and from school / college?
What activities you do at school / college?
What is your favourite activity at school / college?
Do you have friends at school?
Who are they?
Do you like attending school / college?
What do you like most about going to school / college?
Is there anything you don't like about school / college?
What is it?

Do you go on any trips with school / college?
Can you tell me about a trip you have been on with school / college?

If the person goes to work:-
Where do you work?
How many days do you work?
Which days do you go to work?
What does your job involve?
Do you like your job?
What do you like about your job?
What don't like about your job?
Do you work with other people?
Do you like the people you work with?
How do you get to and from work?

If the person is based at home:-
What do you do at home during the week?
What is your favourite thing to do at home?
Do you like being at home during the week?
Do you go out to any places during the week?
Where do you go?
How do you get there?
Do you go with other people?
Who are they?

2. Family
Can you tell me about your family? Who is in it?
Who do you spend time with from your family?
Do you like to spend to with your parents?
What do you like to do with them?
Do you have any brothers or sisters?
Can you tell me about them?
What are their names?
How old are they?
Do you live with them?
Do you get on with them?
Do you spend time with them?
What do you do with them?
Do you have any pets?
What are they?
What are their names?
Do you look after them?
How do you look after them?
Do you have any grandparents?
Do you see them often?
What do you like to do with them?
Have you been to a family celebration / party recently?
Can you tell me about it?

3. Holidays
Have you ever been on holiday?
Can you tell me about a holiday you've really enjoyed?
Did you go on any day trips?
What were they?
Was the weather nice?
What did you enjoy most about the holiday?
What didn't you like about the holiday?
Would you like to go back to that place?
Have you been on holiday this year?
Where did you go?
Can you tell me about it?
Are you going on holiday next year?
Where are you going?

Suggested topics for the familiar adult

1. Hobbies and interests
Do you watch TV in your spare time?
What is your favourite TV programme?
Why do you like that TV programme?
Are there TV programmes you don't like?
Which TV programmes don't you like?
Why don't you like them?
Do you listen to music in your spare time?
What are your favourite music bands or signers at the moment?
Why are they your favourite music bands or singers?
What is your favourite type of music?
Do you buy many CDs?
What CDs have you bought most recently?
Is there anything else you like to do in your spare time?
What are they?
How often do you do them?
How did you become interested in them?

2. Friends
Do you have some friends?
What are the names of your friends?
Can you tell me about them?
How did you become friends?
What do you like to do with your friends?
Do you enjoy spending time with your friends?
Do your friends come over to your house?
What do you do when they come over?
Do you have a best friend?
Who is your best/closest friend?
Why is that person your best/closest friend?

3. Weekends
What do you like to do at the weekend?
Do you prefer to go out or stay in at the weekends? Why?

What do you like best about the weekends?
What do you like least about the weekends?
What did you do last weekend?
Did you enjoy last weekend?
What will you do next weekend?
Are you looking forward to next weekend?
Are there any weekend that you are particularly looking forward to? Why?
Has there been a weekend you have really enjoyed over the summer? Can you tell me about it?

DESCRIPTION OF CARTOONS GIVEN BY THE ADULT IN THE VERY HIGH DEMAND CONDITION

Story about the two monkeys

"Lets look at the pictures together. You can see that the first monkey has climbed up a tree to pick some coconuts. When he picks a coconut he throws it to the ground. There is a second monkey sat relaxing at the bottom of the tree. The coconut that the first monkey throws on the ground lands in front of him. The second monkey picks up the coconut, looking really pleased with himself and then runs away with it! As the first monkey picks another coconut and is about to throw it to the ground he can see that the first coconut has disappeared. He looks really confused because he doesn't know where it has gone! He then continues to pick some more coconuts and throw them to the ground. The second monkey is greedy and comes back to look for some more coconuts. The first monkey then catches him trying to steal his coconuts and gets his revenge by throwing one of them on his head! The second monkey is so dizzy he isn't able to steal anymore coconuts!"

Story about the fisherman, the cat and the pelican

"Lets look at the pictures together. You can see that there is a man sat on the harbour fishing. He catches a fish and looks really pleased with himself. Meanwhile, the man doesn't know that there is a cat sat behind him. The cat has seen him catch the fish and is planning to steal it. The man then places the fish in a bucket behind him but because he doesn't turn around fully, he doesn't notice that the cat is there. The greedy cat then moves towards the bucket as the man places his fish in it. The cat then sneakily steals the man's fish from the bucket without him noticing. He holds out the fish as he is about to escape. The cat then places it in a pelican's beak without realising! The pelican is very happy because he has just been given a fish to eat. The cat then realises what he has done and looks scared when he sees the pelican. The pelican then flies off very happy with the fish and the cat is left on the harbour looking really angry because the pelican has taken the fish that he was going to have for his dinner!

COUNTERBALANCING CONDITIONS FOR SOCIAL TASKS

The eight conditions were counterbalanced in four different ways. Equal numbers of participants in each group experienced each order, e.g. 25% of participants in the Cornelia de Lange syndrome group received the conditions in order one.

The cartoons were counterbalanced so that half the participants received the fisherman cartoon first and half received the monkey cartoon first.

	Condition 1	**Condition 2**	**Condition 3**	**Condition 4**	**Condition 5**	**Condition 6**	**Condition 7**	**Condition 8**
Order 1	Unfamiliar adult: high demand	Unfamiliar adult: low demand	Unfamiliar adult: very high demand	Unfamiliar adult: control	Familiar adult: high demand	Familiar adult: low demand	Familiar adult: very high demand	Familiar adult: control
Order 2	Unfamiliar adult: control	Unfamiliar adult: very high demand	Unfamiliar adult: low demand	Unfamiliar adult: high demand	Familiar adult: control	Familiar adult: very high demand	Familiar adult: low demand	Familiar adult: high demand
Order 3	Familiar adult: low demand	Familiar adult: high demand	Familiar adult: control	Familiar adult: very high demand	Unfamiliar adult: low demand	Unfamiliar adult: high demand	Unfamiliar adult: control	Unfamiliar adult: very high demand
Order 4	Familiar adult: very high demand	Familiar adult: control	Familiar adult: high demand	Familiar adult: low demand	Unfamiliar adult: very high demand	Unfamiliar adult: control	Unfamiliar adult: high demand	Unfamiliar adult: low demand

APPENDIX D

All behaviours coded in the Social tasks

PARTICIPANT BEHAVIOUR	OPERATIONALISED DEFINITIONS
Verbalisation	
Participant verbalisation (duration)	The participant's speech; These may be utterances (e.g. 'erm'), words, phrases or sentences. The person may use speech for the purpose of communication with someone else, e.g., asking a question, making a comment, answering a question or the speech may be used when the person is talking to themselves. The participant's speech may be intelligible or unintelligible.
Participant Question (event)	The participant asks the adult a question. For example, 'Did you drive here?'
Participant Prompt (event)	The participant prompts the examiner to respond by repeating or slightly paraphrasing the original question, request, comment or piece of information.
Participant Offers information (event)	The participant spontaneously (not in response to a question) offers information. The information may or may not be about themselves. For example, 'I went to the beach on holiday' or 'the cartoon is funny'.
Participant Verbal Response (event)	The participant responds verbally to a question, statement, comment, prompt or request made by the adult by providing information. N.b. this code also includes the participant's description of the cartoons in the Cartoon condition.
Participant verbal Uncertain response (event)	The participant responds verbally to a question made by the adult, by indicating that they do not know the answer to the question, e.g., 'don't know', 'can't remember', 'not sure'.
Participant verbal Termination of condition (event)	A vocalisation by the participant to terminate the task or leave the situation, e.g., 'I have to go', 'I don't want to', 'no', 'go away', 'bye bye', 'I can't' (based on Hall, Marie DeBernardis & Allan Reiss, 2006).
Facial Expression	
Participant Positive Facial Expression (duration)	The participant demonstrates a positive facial expression, for example, laughing or smiling. Facial expression must clearly indicate expression of pleasure in activity or conversation. Facial expression may or may not be directed towards the examiner.
Participant Negative Facial Expression (duration)	The participant demonstrates a negative facial expression, for example, frowning or crying. Facial expression must clearly express a lack of enjoyment in activity or conversation. May also include expression of pain or discomfort. Facial expression may or may not be directed towards the examiner.
Eye Gaze	
Participant Looking at adult (duration)	The participant looks in the direction of the adult's eyes or face.
Participant Active Avoidance (duration)	The participant moves their head away from the direction of the adult so that the participant and the adult can no longer make eye contact. For example, the participant bows their head down and looks at the floor; or the participant turns their head away from the adult and looks in the opposite direction, e.g., looking at the door of the room.
Other non-verbal behaviours	
Participant Sign (event)	The participant uses Makaton or British Sign Language for the purpose of communicating (i.e. to get help, make a request or to comment on an object or activity).

Participant Nod / shake (event)	The participant responds to a question, statement, comment or prompt made by the examiner, by nodding their head to indicate 'yes' or shaking their head to indicate 'no'. This *does not* include use of Makaton or British Sign Language.
Participant Uncertain non-verbal response (event)	The participant responds non-verbally to a question made by the adult, by shrugging their shoulders to indicate they don't know the answer to the question.
Participant non-verbal Termination of condition (event)	The participant uses body movements / gestures to try to terminate the current activity or conversation, such as, shaking their head from side to side repeatedly or crossing and uncrossing their hands in front of their body repetitively.
Participant Descriptive Gestures (duration)	The participant uses movements of their arms or hands to help them describe something.
Participant Touches adult (duration)	The participant spontaneously touches the adult with any part of their body e.g. taking the adult's hand, sitting on the adult's lap. This must be initiated by the participant and not the examiner.
Participant Fidget (duration)	The participant displays restless, repetitive, non-rhythmic, non-functional motor movements, such as, moving their hands, touching their face or hair or moving an object, or wriggling in their seat. This code *does not* include stereotyped behaviours, which are *rhythmic*, unusual seemingly purposeless movements of their body or objects (based on Lesniak-Karpiak, Mazzocco & Ross, 2003).
Participant Distracted by equipment (duration)	The participant looks at and/or touches the equipment used to examine physiological responses. The equipment includes the actiwatch, the heart monitor strap and the heart rate monitor watch.
Participant SIB (duration)	The participant engages in non-accidental self-directed injurious behaviours which produce temporary marks or reddening of the skin or cause bruising, bleeding or other temporary or permanent tissue including hair pulling, picking, biting, tapping, hitting, banging, scratching.
ADULT BEHAVIOUR	
Adult Verbalisation (duration)	The adult's speech; These may be utterances (e.g. 'erm'), words, phrases or sentences. The person may use speech for the purpose of communication with someone else, e.g., asking a question, making a comment, answering a question or the speech may be used when the person is talking to themselves. The adult's speech may be intelligible or unintelligible.
Adult Question (event)	The adult asks the participant a question, which requires a response from the participant. For example' What books do you like?'
Adult Prompt (event)	The adult prompts the participant to respond by repeating or slightly paraphrasing the original question, request, comment or piece of information.
Adult Verbal response (event)	The adult responds to the participant's verbal question, comment, statement or offering of information using verbal communication to give the appropriate information.
Adult Offers information (event)	The adult spontaneously (not in response to a question) offers information. The information may or may not be about themselves. For example 'I came from Birmingham'. N.b. this code also includes the adult's description of the cartoons in the Cartoon condition.
BEHAVIOURS CODED AS CONTROL VARIABLES	

Participant Engage with task (duration)	The participant looks at and/or touches an object allocated for a condition. This may be reading a magazine / newspaper, colouring with felt tips, listening to the radio in the 'Break' condition; looking at or touching the photographs in the 'Photograph' condition; looking at or touching the cartoon in the 'Cartoon' condition. Objects which have not been incorporated as part of the social presses, *should not* be coded, e.g., if the person is drinking from a cup or mug which is on the table. This code *does not* apply to the 'Conversation' condition because no objects are required for this condition.
Participant's face not on camera (duration)	The participant's face cannot be seen on camera.
Participant's hands not on camera (duration)	Both of the participant's hands *cannot* be seen on the camera.
Adult Eye contact (duration)	The adult is looking in the direction of the participant's eyes or face.
Adult's face not on camera (duration)	The adult's face can not be seen on camera.

APPENDIX E

Inter-rater reliability of behaviours coded in the Social tasks

Variable	Rtot	Range	Rocc	Rnonocc	Range	Kappa	Range
AComment	95.39	38.89-100.00	42.26	94.9	38.89-100.00	0.46	-0.22-1.00 (94/165 files)
AErm	99.27	75.93-100.00	45.78	99.26	75.93-100.00	0.5	-0.02-1.00 (46/165 files)
AEye	94.93	10.94-100.00	76.95	90.22	10.94-100.00	0.76	0.00-1.00 (128/165 files)
AOffCamera	97.55	48.19-100.00	68.48	96.61	5.88-100.00	0.68	0.00-1.00 (54/165 files)
APrompt	98.08	78.95-100.00	40.58	97.79	71.43-100.00	0.44	-0.03-1.00 (76/165 files)
AQuestion	95.75	62.50-100.00	48.64	94.06	52.63-100.00	0.5	-0.20-1.00 (88/165 files)
AResponse	94.52	67.80-100.00	48.01	92.74	50.00-100.00	0.51	-0.02-1.00 (96/165 files)
AVerbal	97.69	83.33-100.00	88.81	91.29	0.00-100.00	0.85	0.00-1.00 (146/165 files)
Avoidance	99.31	40.00-100.00	74.44	99.01	40.00-100.00	0.75	0.00-1.00 (18/165 files)
DistEquip	98.68	66.67-100.00	58.74	98.1	38.10-100.00	0.62	-0.02-1.00 (62/165 files)
EngageTask	94.27	0.00-100.00	84.01	90.41	0.00-100.00	0.82	0.00-1.00 (135/165 files)
Fidget	91.09	38.71-100.00	59.16	85.95	18.18-100.00	0.59	-0.06-1.00 (134/165 files)
Gestures	97.97	80.00-100.00	64.41	97.54	77.55-100.00	0.69	0.00-1.00 (79/165 files)
HandsOffCa	96.51	10.00-100.00	66.01	94.61	10.00-100.00	0.67	-0.02-1.00 (76/165 files)
NegAffect	98.78	40.35-100.00	80.26	97.3	33.33-100.00	0.78	0.00-1.00 (33/165 files)
NodShake	97.72	76.56-100.00	45.01	97.51	72.22-100.00	0.5	-0.09-1.00 (68/165 files)
PComment	98.45	77.78-100.00	43.01	98.24	66.67-100.00	0.48	-0.03-1.00 (46/165 files)
PErm	99.11	85.71-100.00	55.93	99.05	84.62-100.00	0.6	-0.03-1.00 (49/165 files)
PEye	95.82	46.67-100.00	73.59	90.82	0.00-100.00	0.73	-0.04-1.00 (126/165 files)

Photo	98.58	66.67-100.00	72.21	98.16	61.40-100.00	0.75	0.21-1.00 (24/165 files)
POffCamera	99.36	80.00-100.00	51.83	99.31	73.33-100.00	0.56	0.00-1.00 (26/165 files)
PosAffect	90.94	45.00-100.00	51.13	86.39	26.92-100.00	0.52	0.00-1.00 (129/165 files)
PPrompt	99.89	82.72-100.00	77.78	99.89	82.72-100.00	0.78	0.00-1.00 (9/165 files)
PQuestion	98.87	84.72-100.00	45.65	98.76	81.97-100.00	0.52	-0.06-1.00 (35/165 files)
PResponse	94.66	33.33-100.00	58.56	92.18	33.33-100.00	0.6	-0.14-1.00 (104/165 files)
PUncertVer	99.84	94.92-100.00	66.26	99.83	94.23-100.00	0.7	0.00-1.00 (21/165 files)
PVerbal	97.6	85.71-100.00	83.18	93.36	50.00-100.00	0.82	0.00-1.00 (115/165 files)
SIB	99.9	91.23-100.00	69.91	99.87	88.10-100.00	0.7	0.00-1.00 (7/165 files)
Signing	99.75	89.83-100.00	70.65	99.71	88.00-100.00	0.77	0.00-1.00 (13/165 files)
StopCondit	99.67	86.54-100.00	53.05	99.63	84.44-100.00	0.62	0.28-0.93 (7/165 files)
TouchAdult	99.98	97.06-100.00	75	99.98	97.06-100.00	0.75	0.00-1.00 (4/165 files)
UncertNV	99.96	95.65-100.00	60	99.96	95.65-100.00	0.6	0.00-1.00 (5/165 files)

APPENDIX F

Comparison between the control condition and the experimental conditions in the Social tasks

Comparison between the control condition and the experimental conditions for the Cornelia de Lange syndrome group

Test Statistics[b,c]

	MeanFamPVerbalExperCondit - Familiar Adult Break Condition: Participant Verbalisation (duration)	MeanFamFidgetExperCondit - Familiar Adult Break Condition: Fidget (duration)	MeanFamPosAffectExperCondit - Familiar Adult Break Condition: Positive Affect (duration)	MeanFamPEyeExperCondit - Familiar Adult Break Condition: Participant Eye Contact (duration)	MeanUnfamPVerbalExperCondit - Unfamiliar Adult Break Condition: Participant Verbalisation (duration)	MeanUnfamFidgetExperCondit - Unfamiliar Adult Break Condition: Fidget (duration)	MeanUnfamPosAffectExperCondit - Unfamiliar Adult Break Condition: Positive Affect (duration)	MeanUnfamPEyeExperCondit - Unfamiliar Adult Break Condition: Participant Eye Contact (duration)
Z	-4.197[a]	-3.834[a]	-3.915[a]	-4.076[a]	-4.015[a]	-3.646[a]	-3.717[a]	-3.592[a]
Asymp. Sig. (2-tailed)	.000	.000	.000	.000	.000	.000	.000	.000

a. Based on negative ranks.

b. Group = CdLS

c. Wilcoxon Signed Ranks Test

Comparison between the control condition and the experimental conditions for the Down syndrome group

Test Statistics[b,c]

	MeanFamPVerbalExperCondit - Familiar Adult Break Condition: Participant Verbalisation (duration)	MeanFamFidgetExperCondit - Familiar Adult Break Condition: Fidget (duration)	MeanFamPosAffectExperCondit - Familiar Adult Break Condition: Positive Affect (duration)	MeanFamPEyeExperCondit - Familiar Adult Break Condition: Participant Eye Contact (duration)	MeanUnfamPVerbalExperCondit - Unfamiliar Adult Break Condition: Participant Verbalisation (duration)	MeanUnfamFidgetExperCondit - Unfamiliar Adult Break Condition: Fidget (duration)	MeanUnfamPosAffectExperCondit - Unfamiliar Adult Break Condition: Positive Affect (duration)	MeanUnfamPEyeExperCondit - Unfamiliar Adult Break Condition: Participant Eye Contact (duration)
Z	-3.724[a]	-3.549[a]	-2.330[a]	-3.724[a]	-3.783[a]	-3.783[a]	-2.857[a]	-3.662[a]
Asymp. Sig. (2-tailed)	.000	.000	.020	.000	.000	.000	.004	.000

a. Based on negative ranks.

b. Group = DS

c. Wilcoxon Signed Ranks Test