SELF-INJURIOUS AND AGGRESSIVE BEHAVIOUR IN ANGELMAN, CRI DU CHAT AND CORNELIA DE LANGE SYNDROMES

by

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ABSTRACT

In a series of studies, the role of operant reinforcement of phenotypic problem behaviours in Angelman, Cri du Chat and Cornelia de Lange syndromes was explored. Firstly, a systematic review of the literature highlighted papers with robust experimental functional analytic designs; providing appropriate methodology for the subsequent studies. The review also showed a trend towards an increase in the number of published papers that linked facets of the behavioural phenotype to challenging behaviour (gene-environment interactions). Next, the phenomenology and correlates of self-injurious and aggressive behaviour in the syndromes were explored at a given level of behavioural specificity. Results showed that self-injury was more common in Cornelia de Lange syndrome and specific forms of aggressive behaviour were common in Angelman syndrome. Experimental functional analysis and structured descriptive assessments were utilised to examine gene-environment interactions in the syndromes and broadly, challenging behaviour in the Cornelia de Lange syndrome group evidenced a stronger association with pain, whereas challenging behaviour in the Angelman syndrome group evidenced a stronger association with positive social reinforcement. Overall, the studies provide evidence that challenging behaviour in genetic syndromes can be influenced by environmental factors. Implications for practice and for informing a comprehensive model of challenging behaviour are discussed.

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CHAPTER 1

General Introduction

1.1. Introduction

Recent advances in molecular genetics have significantly enhanced understanding of the structure and function of the human genome and the consequences of genetic difference and disorder. The explorations of genetic influences on typical development have relied on understanding both multi-allelic variability and atypical development caused by genetic disorder. Currently, over 1600 genetic causes of intellectual disability have been identified, and this has promoted research into gene-behaviour relationships, an endeavour encapsulated by the term behavioural phenotypes. The following sections will describe the development of the relevant literature in the field of genetics, the concept of behavioural phenotypes and the importance of further development of behavioural phenotype research.

1.2. The history of genetic research

After Darwin's evolutionary theory was published in 1859, the first work on the principles of genetics followed soon after in 1866. At this time, Gregor Mendel published the results of his investigations into the genetic traits of the pea plant. Now referred to as 'The father of modern genetics', Mendel found that statistical rules could be applied to the inheritance patterns of certain features of the plant. Although at the time Mendel's work received little attention, his principles were very influential and 50 years later Mendelian inheritance patterns were applied to a much wider variety of organisms. By the 1950's, inheritance patterns were established, thus, the focus of much research turned to the physical structure of units of inheritance, or genes. 1953

marked the discovery of DNA and a new era of genetic research in which genes began to be studied at a molecular level. Through the development of technologies, molecular genetic research surged and 1966 marked the discovery of the genetic code.

The last 20 years has seen rapid advances in the study of the human genome and the ways in which its structure may be altered. In particular, the study of genetic disorders in which gene expression or chromosomal number is very atypical, has provided information on the identification of the typical structure and function of the genome. In addition, the discovery of many genetic causes of intellectual disability has also helped to elucidate genetic pathways involved in typical development (Raymond, 2003). At present, there are over 1600 identified genetic causes of intellectual disability and research into behaviour in genetic disorders has increased significantly in recent years. Comparing the literature on genetic syndromes across two decades, Hodapp and Dykens (2001) noted that for some syndromes there was a fourteen fold increase in the number of articles published in the 1990's compared to the 1980's. Much of this research has sought to increase understanding of gene-behaviour relationships and has attempted to discover to what extent behaviour observed in genetic syndromes is attributable to an individual's genetic status. An area of research that helped us to address this issue and continues to guide the discovery of genes that contribute to behavioural and cognitive characteristics, is the study of behavioural phenotypes. Research into behavioural phenotypes aims to discover links between genotype and phenotype and is driven by the expectation of further characterising genetic syndromes. The study of behavioural phenotypes has led to the establishment of the Society for the Study of Behavioural Phenotypes (SSBP) (http://www.ssbp.co.uk/ssbp/pages/about-ssbp.php). According to the SSBP:

> "The concept of behavioural phenotypes is intended to form a basis for research into behavioural, emotional, and other aspects of biologically determined syndromes associated with intellectual disability or mental retardation".
> (http://www.ssbp.co.uk/ssbp/pages/about-ssbp.php)

1.3. The concept of behavioural phenotype

Broadly, a behavioural phenotype is a set of behavioural, cognitive and emotional characteristics that is associated with a particular genetic syndrome. In 1972, Nyhan first used the term behavioural phenotype after observing compulsive self mutilation in individuals with Lesch-Nyhan and Cornelia de Lange syndromes. In Nyhan's opinion, the behaviour that he observed was endogenous to the disorders and arose from the individual's genetic makeup. More specifically, Nyhan's observations articulated the view that the phenotypic outcome of a genotype includes, not only a physical description of the organism but also clearly observable behavioural patterns, traits and characteristics. Consequently, according to Nyhan, behavioural phenotypes indicated associations between genes and behaviour, and thus, different genetic disorders have varying effects on behaviour as they are each defined in a genetically unique way.

Since its introduction, there has been much disagreement with regard to the use of the term behavioural phenotype and some divergence in determining the specificity of behaviours that are associated with genetic disorders. That is to say, researchers have differed in how they classify behaviours as phenotypic. Flint and Yule (1994) cited by Rutter, Taylor and Hersov (1995) used the following definition:

> "A behavioural phenotype should consist of a distinctive behaviour that occurs in almost every case of a genetic or chromosomal disorder, and rarely (if at all) in other conditions. Secondly…this behaviour has a direct and specific relationship to the genetic or chromosomal anomaly" (p.666).

Flint and Yule's definition typifies the total specificity view identified by Hodapp (1997) that stipulates a single pathway from genes to behaviour. Flint and Yule's strict definition implies that a particular behaviour or behaviours will be specific to a genetic disorder and that behaviour will not be observed in any other genetic disorder. Adhering to such strict criteria, a behavioural phenotype can probably only be identified in three genetic syndromes. Firstly, it appears that extreme self-injury, in particular, that which is directed the lips, fingers and hands is unique to individuals with Lesch-Nyhan syndrome (Anderson & Ernst, 1994; Robey, Reck, Giacomini, Barabas & Eddey, 2003). Hyperphagia in Prader-Willi syndrome (Dykens & Cassidy, 1996) and stereotypic 'hand-to-mouth' movements in Rett syndrome are also judged to be unique behaviours; characteristic of the syndromes (Dykens, 2000).

Total specificity behavioural phenotypes are rare and the definition does not account for within syndrome differences that are often evident (Hodapp, 1997). For example, although the prevalence of a behaviour may be raised within a particular syndrome (e.g. self-injury in Cornelia de Lange syndrome: Hyman, Oliver & Hall, 2002), the behaviour is not seen in all individuals with the syndrome, nor is it only seen in that particular syndrome (self-injury is common to other behavioural phenotypes e.g. Lesch-Nyhan and Smith-Magenis syndromes). Further, in both young children and adults, levels of self-injurious behaviour (SIB) in Lesch-Nyhan and repetitive hand movements in Rett syndrome have been found to vary with environmental change (Bergen,

Holborn & Scott-Huyghebaert, 2002; Evans & Meyer, 1999; Hall, Oliver & Murphy, 2001; Wehmeyer, Bourland & Ingram, 1993). In contrast to Flint and Yule's somewhat restrictive definition, these findings reveal that even when behaviour is classified as part of a syndrome's behavioural phenotype, its effect may not always be direct and specifically related to a genetic anomaly. It may be more appropriate therefore, to take a more probabilistic definition of a behavioural phenotype. Dykens (1995) for example, defined 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" (p.523).

Dyken's conceptualisation of a behavioural phenotype follows the partial specificity viewpoint identified by Hodapp (1997). Partial specificity proposes that a few genetic disorders lead to unique behavioural characteristics and these characteristics differ from the total population of people with intellectual disabilities, but are not necessarily specific to a given syndrome. Rather, many genetic syndromes are likely to lead to similar behavioural characteristics. Hodapp (1997) argued that partial specificity is the most commonly occurring behavioural effect of genetic syndromes. Clarke and Boer (1998) provided direct support for partial specificity in their study of problem behaviours in Prader-Willi, Cri du Chat and Smith-Magenis syndromes. Clarke and Boer found that the three genetic syndromes had a relatively typical pattern of behaviours, with some of the behaviours being typical of more than one syndrome and not present in all individuals with a particular syndrome. The advantage of Dyken's less restrictive definition, in contrast to Flint and Yule (1994) is that, it recognises that there might be a heightened probability of a certain

behaviour occurring in a syndrome, whist still allowing for possible variability within and between syndromes. Importantly, the position also implies that behaviours are likely to be both genetically and environmentally determined.

1.4. Why is the study of behavioural phenotypes important?

For many years the primary aim of behavioural phenotype research has been to characterise the behavioural, emotional and cognitive profile for a particular syndrome. Although sometimes criticised as being a purely descriptive exercise, delineating syndrome specific behavioural and cognitive profiles is an essential first step in furthering knowledge about specific genetic syndromes. An appreciation of a syndrome's behavioural variability is important in order to understand within syndrome phenotypic expression, and may help to prevent generation of erroneous information. The last two decades have seen more comparisons made between syndrome groups, to permit understanding of similarities and differences between syndromes so that commonalities and unique features can be identified. In addition, there has been a focus on syndrome comparisons of syndrome groups which are known to demonstrate similar behaviours. This 'same-but-different' approach is concerned with taking the same behaviour in two or more syndrome groups and describing differences in form or cause. This enables more precise identification of phenomenology within and between syndrome groups, and lends itself towards more specific hypothesis testing than a purely descriptive exercise. Methodologies in behavioural phenotype research are discussed in further detail in Section 1.5.

Together with advances in molecular genetics, the identification of particular behaviours and cognitive abilities in syndromes has facilitated the isolation of specific genetic abnormalities (e.g. genetic microdeletions). In Cornelia de Lange syndrome for example, careful characterisation of the behavioural phenotype has led to the generation of hypotheses in relation to genotype-phenotype correlations. There is large variability in phenotypic expression in Cornelia de Lange syndrome, with both the physical and the behavioural phenotype of the syndrome falling onto a large continuum, from those showing subtle facial features, low frequency behaviours and a mild to moderate intellectual disability, through to more pronounced facial characteristics, severe self-injury and severe to profound intellectual disability (Berney, Ireland & Burn, 1999; Ireland, 1996; Jackson, Kline, Barr & Koch, 1993; Oliver, Arron, Sloneem & Hall, 2008).

Such substantial variability in phenotypic expression led clinical geneticists to assume that the aetiology of Cornelia de Lange syndrome must be genetically variable (i.e. accounted for by more than one genetic anomaly). Krantz *et al.* (2004) and Tonkin, Wang, Lisgo, Bamshad and Strachan (2004) found the genetic mutation of the NIPBL gene, located at chromosome 5p13.1 accounts for 50% of affected individuals. Recent research has located two other mutations (mutations of the SMC3 gene on chromosome 10 and X-linked SMC1A gene), which account for a further 5% of individuals affected (Deardorff *et al.,* 2007). Deardorff *et al.* found that individuals who have a SMC3 or SMC1A mutation tend to have milder phenotypes, typically characterised by less growth retardation, fewer upper limb abnormalities and a milder degree of intellectual disability.

The study of behavioural phenotypes has also contributed significantly to developmental theory. It has challenged traditional developmental approaches to cognitive development, which often assume that the presence of an intellectual disability has similar cognitive and behavioural consequences for all affected individuals (Burack, 1995). The identification of cognitive strengths and weaknesses, along with constellations of behaviours has been used to answer questions about individuals who do not have specific genetic anomalies. In this way, we are able to learn more about development in the broader intellectual disability population and the general population (Holland, 1999).

In spite of its benefits, the study of behavioural phenotypes has received much criticism. There have been particular concerns over individuals being labelled, once a discrete set of behavioural characteristics are linked to a syndrome. Labelling may lead to assumptions that individuals with similar genetic abnormalities have similar behavioural patterns, and individual difference may not be acknowledged. There is also the threat of creating self-fulfilling prophecies whereby, behaviours may develop in certain syndromes as they are anticipated and so others react in ways that may encourage the emergence of specific behaviours. Those citing this threat, express fears of a new 'eugenics' era and the danger of creating therapeutic nihilism (O'Brien, 2000). In defence of this criticism, Dykens, Hodapp and Finucane (2000) suggest that the behavioural effects of genetic syndromes are not inevitable and increasing knowledge of behavioural phenotypes can help to enlighten intervention services, which, in turn will lead to increased inclusion.

Prevailing over any criticism of behavioural phenotype research is the impact that research has had in the field of treatment. One of the most important implications of behavioural phenotype research is its clinical value and the impact that it has for individuals and their families. When carers are faced with a child who has a genetic disorder, many of the physical and behavioural manifestations of the condition can be difficult to understand and parents may blame themselves (Johnson, O'Reilly & Vostanis, 2006; Turk & Sales, 1998). It is likely to be reassuring for carers to know that many of these observable features are characteristic of the syndrome and therefore, self-blame for the child's condition is lessened (Skuse, 2000; Turk & Sales, 1998). In addition, being aware of a behavioural phenotype of a particular syndrome allows a child's behaviour to be anticipated and therapeutic opportunities are enhanced (O'Brien, 2000). In Rett syndrome, for example, development in the first twelve months is analogous to that of a typically developing child, although some subtle abnormalities may be present at birth. Between six and eighteen months there is a period of developmental stagnation where speech, facial expression and hand movements regress and the syndrome takes a progressive and degenerative course (Mount, Hastings, Reilly, Cass & Charman, 2003). In Rett syndrome, and indeed many other genetic syndromes, knowledge of the behavioural phenotype allows carers to be more aware and perhaps better prepared for their child's future behavioural development. Parents are likely to be more attentive to monitoring early signs of deviation from development. In turn, this allows more opportunities for early effective clinical intervention and parent counselling before the onset difficult behaviours (Finnegan, 1998; O'Brien, 2000; Turk & Sales, 1998).

1.5. Methodology in behavioural phenotype research

Historically, behaviours associated with genetic syndromes have been identified using case study descriptions. Hoddap and Dykens (2001) and Dykens et *al.* (2000) identify several methods for studying behavioural phenotypes, which advance the field using a more refined and systematic approach. More robust methodology typically includes the use of control or contrast groups and these include the use of typically developing individuals (matched on chronological age), individuals with intellectual disability of heterogeneous cause (matched on mental age) and individuals with other genetic syndromes. The use of chronological aged matched individuals fails to control for degree of intellectual disability and so inferences about the strength of association between syndrome and behaviour are compromised. Employing a comparison group of individuals with intellectual disability of heterogeneous cause allows one to assess whether behaviour can be accounted for by degree of disability (Dykens, 1995; Hodapp & Dykens, 2001). One problem with this method is the potential for including individuals with genetic syndromes who do not have known diagnoses. Researchers may be unaware of these individuals and they may unknowingly be influencing the profile of the comparison group. These methods may be modified to include across syndrome comparisons in which the groups are known to demonstrate similar behaviours. This 'same-but-different' approach permits a more precise understanding of phenomenology within and between syndromes so that commonalities and unique features can be identified. Oliver and Woodcock (2008) also note that there is a steady shift in the methods used to elucidate behavioural phenotypes. They argue that there is now a greater need for standardised measures and, if we are to be successful in understanding and intervening with behaviours, we need to generate multi-level models that reflect a diversity of disciplines and methods.

1.6. Research area of interest

There has been much interest in recent years in studying challenging behaviour within behavioural phenotypes. This is largely due to the fact that individuals with specific genetic syndromes are thought to be at greater risk of the development of challenging behaviour (e.g. Arron *et al.,* 2006; McClintock, Hall & Oliver, 2003). Consequently, although the examination of prevalence, phenomenology, function and correlates of challenging behaviour in genetic syndromes has merit in its own right, it is also likely to inform theoretical models for the total population of people with intellectual disabilities.

In comparison to prevalence rates for individuals with mixed aetiology intellectual disabilities, the rates for challenging behaviours such as self-injury and aggression have been found to be raised in a number of genetic syndromes such as Cri du Chat syndrome (Collins & Cornish, 2002; Dykens & Clarke, 1997), Cornelia de Lange syndrome (Berney *et al.,* 1999; Hyman *et al.,* 2002), Fragile-X syndrome (Symons, Clarke, Hatton, Skinner & Bailey, 2003), Lesch-Nyhan syndrome (Anderson & Ernst, 1994; Nyhan, 1972), Prader-Willi syndrome (Holland, Whittington, Webb, Boer & Clarke, 2003) and Smith-Magenis syndrome (Clake & Boer, 1998; Dykens & Smith, 1998). There may be highly specific features of each of these syndromes which promote challenging behaviour, or, the high number of correlates of challenging behaviour evidenced in the broader intellectual disability population associated with the syndromes may increase the probability of challenging behaviour. Other correlates or individual characteristics associated with challenging behaviour include age, level of ability, Autism Spectrum Disorder and communication deficits (McClintock *et al.,* 2003). The next section (1.7) gives an overview

of the term challenging behaviour, before operant theory to explain challenging behaviour is discussed (Section 1.8).

1.7. What is challenging behaviour?

Challenging behaviour is a widely used term in the field of intellectual disability and has been defined as:

> "culturally abnormal behaviour (s) of such an intensity, frequency or duration that the physical safety of the person or others is likely to be placed in serious jeopardy, or behaviour which is likely to seriously limit use of, or result in the person being denied access to, ordinary community facilities" (Emerson, 1995 p. 4-5).

Emerson and Bromley (1995) estimated that 8% of people with intellectual disabilities showed challenging behaviour. Similarly, Lowe *et al.* (2007) found a prevalence of five people with challenging behaviour per 10,000 of the total population, representing approximately 10% of the intellectual disability population. Challenging behaviour can have wide ranging detrimental effects. For the individual, it can limit social integration (Anderson, Lakin, Hill & Chen, 1992) and lead to a reduction in life satisfaction (Schwartz, 2003). Schwartz found a negative correlation between level of challenging behaviour and lifestyle satisfaction, i.e. those with more problematic behaviour expressed less lifestyle satisfaction. People with challenging behaviour are also more likely to be placed in institutionalised settings (Eyman & Call, 1977) and face exclusion from community-based services (Hill & Bruininks, 1984).

Challenging behaviour can also have an impact on the lives of others. For families, challenging behaviour is the strongest predictor of parents seeking a residential placement for their child (Tausig, 1987) and it can often place parents at increased risk for stress and depression when compared to parents of typically developing children (Olsson & Hwang, 2001). In addition, Wiegel, Langdon, Collins and O'Brien (2006) found that challenging behaviour often leads to attributions of blame from care staff. Staff working with patients who had an intellectual disability and challenging behaviour were more likely to attribute the causes of behaviour as internal to the person and controllable by them rather than external and uncontrollable. Staff were also more likely to make critical comments, compared to staff working with patients who had no challenging behaviour.

The term challenging behaviour is often regarded as an umbrella term that encompasses many different forms of behaviour such as noncompliance, physical and verbal aggression, outbursts and temper, self-injury and destructive behaviours. Perhaps the most commonly cited forms of challenging behaviour in the intellectual disability literature are self-injurious and aggressive behaviours. Prevalence estimates vary for self-injury from 4 to 10% (Kiernan & Kiernan, 1994 as cited by Emerson *et al.,* 2001; Oliver, Murphy & Corbett, 1987) and 7 to 25% for aggression (Emerson, 2001; Kiernan & Kiernan, 1994 as cited by Emerson *et al.,* 2001). Using a meta-analysis of published research, McClintock *et al.* (2003) showed that there are some risk factors for self-injury, such as degree of intellectual disability, communication deficits, autistic spectrum disorders and genetic syndrome, but these are less evident for aggression.

1.8. Operant theories of challenging behaviour

There are many theories that relate to the development and maintenance of challenging behaviour. Broadly, these theories will fall into either biological/physiological or behavioural domains. Biological theories have tended to focus on neurotransmitter dysfunction and thus have provided multiple possibilities regarding medication interventions. Although medical interventions have shown some success in individual trials, they have proved less successful when implemented on a broader scale (e.g. King, 2000). Perhaps the most highly cited and well established theory of challenging behaviour is the operant perspective which is outlined below.

Due to the experimentally sound methodologies employed in operant studies of challenging behaviour, the operant behaviour hypothesis is perhaps the most robust theory to explain the development and maintenance of challenging behaviour. Empirical research has also shown that operant models have been the basis for the most effective interventions over the past 30 years (Kahng, Iwata, Thompson & Hanley, 2002; Oliver, 1993). The theory distinguishes between the cause of the initial onset of the behaviour and the factors that maintain it. For example, SIB has been reported to initially appear in an individual's repertoire for a number of reasons such as, health conditions or the shaping of existing behaviours such as stereotypies (Guess & Carr, 1991; Oliver, 1993). Operant theory proposes that challenging behaviours such as self-injury and aggression are learned behaviours that are maintained by their consequences. The theory emphasises the importance of the relationship between the behaviour, discriminative stimuli, establishing operations and mutual reinforcement. An establishing operation is an antecedent variable that, in combination with a discriminative stimulus, occasions the occurrence of behaviour, whilst a reinforcer is a stimulus that occurs contingently on the behaviour, and

increases the likelihood that the behaviour will occur again. An establishing operation has been defined as a motivational state and refers to the level of deprivation and satiation at any given point in time, which increases the reinforcing properties of contingencies (Michael, 1982). When applying operant theory to challenging behaviour, a common establishing operation might be a low level of social attention from a parent or caregiver. The deprivation of attention establishes caregiver attention as a reinforcing stimulus and thus attention-eliciting behaviour may occur. This behaviour may take various forms, such as an appropriate verbal or non-verbal request or challenging behaviour such as self-injury or aggression. In this example, reinforcement would be attention from the caregiver contingent on challenging behaviour and so the likelihood that challenging behaviour will occur in the future is increased. Processes of reinforcement described in the literature commonly fall into the following three classes: positive reinforcement, negative reinforcement and automatic or sensory reinforcement.

The process of positive reinforcement can be defined as the increased possibility of the future occurrence of behaviour due to the contingent presentation of a reinforcer. Positive reinforcement can include reinforcers such as social attention or access to tangible items (preferred items such as activities or edibles; Carr & Durand, 1985; Durand & Crimmins, 1988). The process of negative reinforcement can be defined as the increased possibility of the future occurrence of behaviour due to the contingent removal of an aversive stimulus. Negative reinforcement may include escape from task demands or escape from social attention (Carr & Durand 1985; Iwata, Dorsey, Slifer, Bauman & Richman**,** 1982/1994a). Automatic reinforcement refers to behaviours that are maintained by their sensory consequences. Reinforcing consequences can be both positive and negative but the stimuli are internal to the person. For example, eye pressing in an

individual with visual impairments has been shown to be positively reinforced by the visual feedback it produces which is often in the form of apparent flashing light (e.g. Jan, Good, Freeman & Espezel, 1994).

Functional analysis

The 1960's marked the start of an era of research into the role of the operant reinforcement of challenging behaviour (Lovaas, Schreibman, Koegel & Rehm, 1965; Lovaas & Simmons, 1969). Although the studies were fairly elementary and tended to focus on single sources of reinforcement, they were considered to be very influential, particularly in the area of intervention which, until that point, had generally involved the use of positive punishment techniques. Perhaps the most significant advance in the empirical assessment of operant reinforcement of behaviours originates from the functional analysis procedure first described by Iwata *et al.* (1982, 1994a). Experimental functional analysis of behaviour involves the direct manipulation of antecedents and consequences that are hypothesised to occasion and maintain problem behaviour. Effects of manipulations are evaluated in highly controlled conditions in which behaviour is evoked. Elevated levels of behaviour in one condition are taken as evidence that the behaviour is reinforced and the operant functions of challenging behaviour can be established. If sources of reinforcement are identifiable, it is assumed that these will be used in the development of more specific and tailored interventions. Iwata et *al.* (1982) published a key paper that described 'analogue methodology' as a standardised experimental examination of the operant functions of self-injury. The analogue functional analysis comprised several experimental conditions in which establishing operations of levels of adult attention, task demands and tangibles and reinforcement contingencies of adult attention and escape were arranged in a multi-element design. An 'alone'

condition was also included which appraised automatic or sensory reinforcement processes. Iwata *et al.* (1982) reported differential responding in a specific condition for six out of the nine participants. Iwata *et al.* (1994a) extended the functional analysis of self-injury for 152 individuals to examine the epidemiology of function. The authors report that functions for SIB were identified in 95.4% of individuals. Social negative reinforcement accounted for the largest proportion of individuals (38.1%), whilst 26.3% were found to have challenging behaviour that was maintained by social positive reinforcement, 25.7% by automatic (sensory) reinforcement and 5.3% were found to have multiple functions. This methodology has since been refined and alternative techniques have been developed (e.g. Carr & Durand, 1985; Iwata, Duncan, Zarcone, Lerman, & Shore, 1994; Vollmer, Iwata, Duncan, & Lerman, 1993).

Functional communication training

Identification of operant behavioural functions has undoubtedly had a major impact on intervention. In particular, functional communication training (FCT) seeks to replace an aberrant behaviour with an alternative communicative response that is functionally equivalent. FCT was first introduced by Carr and Durand (1985) who developed intervention strategies based on the results of functional analysis on four children with intellectual disabilities. Carr and Durand argued that problem behaviours often serve a non-verbal pragmatic communicative function and thus, teaching an individual a functionally equivalent communicative response should lead to a reduction in problem behaviour. After functional analysis revealed that disruptive behaviour displayed by children in the classroom was maintained by access to adult attention and escape from task demands, Carr and Durand devised interventions that involved teaching children new phrases which would elicit attention or assistance from the teacher. In a reversal design, the

authors were able to demonstrate that only relevant new phrases were successful in reducing target behaviours, thus showing the importance of functional equivalence of the new response to the target behaviour.

To summarise, there is much empirical evidence to support the operant theory that suggests that challenging behaviour is learned and maintained by its consequences. Much of the evidence comes from research that demonstrates an association between environmental events and challenging behaviour, functional properties of challenging behaviour and behavioural interventions that have shown success in reducing challenging behaviour.

1.9. Overview of the thesis

In summary, evidence for the existence of behavioural phenotypes and their importance in the identification of pathways from genes to behaviour has been reviewed in this chapter. There is also a robust literature that describes the operant reinforcement of challenging behaviour in individuals with intellectual disabilities. These two theories of genetic predisposition and operant reinforcement remain quite distinct; neither theory on its own is sufficient to explain challenging behaviour in genetic syndromes and an integrated approach is required. One way of bringing the two approaches together is to explore the role of operant reinforcement of problem behaviours in genetic syndromes that are deemed to be part of the behavioural phenotype. More specifically, exploring these behaviours in syndromes and examining potential associations with another genetically predisposed facet of the behavioural phenotype will allude to gene-environment interactions; identifying plausible causal routes to problem behaviours.

Perhaps the most appropriate starting point for this research is to study operant reinforcement in syndromes in which there is known to be a raised prevalence of problem behaviours deemed phenotypic of the syndrome. Challenging behaviours such as self-injury and aggression are known to be prevalent, at varying levels, in Angelman, Cri du Chat and Cornelia de Lange syndromes. These syndromes are also comparable on a number of risk markers which are known to associate with the presence of challenging behaviour such as degree of intellectual disability, communication and mobility. Dykens *et al.* (2000) note that in behavioural phenotype research it is important to assess and control for the presence of these factors so that syndrome-specific patterns can be identified.

In a recent across syndrome comparison of self-injury and aggression, Arron, Oliver, Berg, Moss & Burbidge (in review) found that self-injury was significantly higher in the Cornelia de Lange (70% of sample) and Cri du Chat syndrome groups (76.8%) compared to the contrast group of intellectual disability of mixed aetiology (27%). Physical aggression was found to be significantly higher in the Angelman (73%) and Cri du Chat (70%) syndrome groups compared to 46% in the matched contrast group. Consequently, as well as offering an opportunity to integrate behavioral phenotype and operant literatures, there are also a number of pragmatic reasons why one would study these three syndromes. Such high rates of challenging behaviour in these syndromes place the individuals themselves at risk of injury, place others at risk of injury, increase exclusion from ordinary educational and community settings and place additional stress on family members (Anderson *et al.,* 1992; Eyman & Call, 1977; Hill & Bruininks, 1984; Olsson & Hwang, 2001; Schwartz, 2003; Tausig, 1987; Wiegel *et al.,* 2006).

The aim of this thesis is to study the causes of two 'same-but-different' behaviours (self-injury and aggression), which are of social significance and thought to be part of the behavioural phenotype of three genetic syndromes. Given the association between self-injury and aggression and other behaviours in the wider population of people with intellectual disability, and the between and within syndrome variability in the prevalence of self-injurious and aggressive behaviours, there is a need to generate causal models that can account for behaviour-behaviour associations and incorporate genetic vulnerability (Hodapp & Dykens, 2001). The thesis aims to examine the influence of the environment on self-injury and aggression and interactions between other parts of the phenotype to generate causal models. The elucidation of some of the gene-behaviour pathways in a comprehensive model of challenging behaviour would help to inform effective early intervention strategies. In order to realise these aims, a number of separate studies will be undertaken. These are:

1. Systematically reviewing the literature to identify studies that describe an environmental influence on problem behaviours associated with genetic syndromes. Attention will be paid to studies that associate problem behaviours to some other aspect of the behavioural phenotype (gene-environment interactions). The review will also appraise the current status of research and methodologies in order to identify appropriate methodology. (Chapter 2).

2. Examining the behavioural phenotypes of Angelman, Cri du Chat and Cornelia de Lange syndromes using observations and measures with sound psychometric properties. Particular attention will be paid to delineating the phenomenology of challenging

behaviour and the relationship between specific participant characteristics and challenging behaviour. (Chapter 3).

3. Utilising experimental functional analysis (identified in Chapter 2) to examine the gene-environment interactions on self-injurious and aggressive behaviour in Angelman, Cri du Chat and Cornelia de Lange syndromes. (Chapter 4).

4. Utilising structured descriptive assessments to identify idiosyncratic functions in individuals where conventional experimental functional analysis in Chapter 4 had demonstrated no social function to challenging behaviour. (Chapter 5).

5. Providing an assimilation of the studies in the thesis and a focus on the discussion of gene-environment interactions within genetic syndromes and the need for an integrated approach. (Chapter 6).

The studies presented in this thesis are part of a wider project carried out in collaboration with the Institute of Psychiatry, King's College London and Bangor University, Wales. In addition to exploring behaviour within the three syndrome groups, other aims of the project included exploring family adjustment and parental well-being. It is only the behavioural aspects of the project that are presented in this thesis.

CHAPTER 2

Literature Review: Gene-environment interactions in genetic syndromes

----------Preface to Chapter 2----------

Evidence for the existence of behavioural phenotypes and the operant reinforcement of challenging behaviour were considered in Chapter 1. One strategy to integrate the two approaches is to explore the role of operant reinforcement of problem behaviours in genetic syndromes. This systematic review will identify studies in the literature that reveal this integration with a focus on studies that demonstrate gene-environment interactions. It is anticipated that a review of this literature will evaluate the current status of research and the methods typically employed. Following this, future research directions will be identified.

2.1. Introduction

The term challenging behaviour is an umbrella term which encompasses many different forms of behaviour such as noncompliance, physical and verbal aggression, temper outbursts, self-injury and destructive behaviours (Emerson, 1995). Challenging behaviour is a significant problem that can have an impact on the lives of those displaying such behaviours, as well as those who care for them (Hassiotis, Parkes, Jones, Fitzgerald & Romeo; 2008; Hastings, 2002; Olsson & Hwang, 2001; Schwartz & Rabinovitz; 2003).

The focus of this systematic review is the interaction between environmental influences on challenging behaviour and characteristics of the behavioural phenotype of genetic syndromes. A review of this empirical research is important in order to evaluate the current status of empirical research and highlight potentially productive areas for further work. There is emerging evidence in the literature to suggest that problem behaviours associated with genetic syndromes could be influenced by an interaction between a genetically predisposed aspect of the behavioural phenotype and operant processes (e.g. O' Reilly, 1997; Oliver, Murphy, Crayton & Corbett, 1993; Taylor & Oliver, 2008). Examination of specific forms of gene-environment interactions within syndromes will promote understanding of the aetiology of problem behaviours within both genetic syndromes and, ultimately, the wider population of individuals with severe intellectual disabilities and extend existing causal models.

Prior to the review, the seemingly opposing biological and environmental theories are described briefly to give context to the studies that are described. A systematic review follows with critique of methodology used in the study of problem behaviour associated with genetic syndromes.

Environmental influences on behaviours within genetic syndrome research are detailed and relationships between behavioural phenotypes and features of syndromes are discussed.

Finally, the review will highlight the importance of functional analytic studies that incorporate facets of behavioural phenotypes to further understand the behaviour of children and adults with genetic syndromes. Future research is discussed with particular reference to effective early intervention strategies.

2.1.1. Opposing theories as explanations of challenging behaviour

There is robust evidence from cohort studies that challenging behaviour in people with intellectual disabilities is associated with a number of characteristics or risk markers such as a greater degree of intellectual disability, communication impairments, Autism Spectrum Disorder and the presence of stereotyped, compulsive and impulsive behaviours (Bodfish *et al.,* 1995; Brylewski & Wiggs, 1999; Deb, Thomas, & Bright, 2001; McClintock, Oliver & Hall, 2003; Powell, Bodfish, Parker, Crawford, & Lewis, 1996; Rojahn, Matson, Naglieri, & Mayville, 2004). In addition, genetic syndromes are a significant risk marker for the development of challenging behaviour (McClintock *et al.,* 2003; Arron *et al.,* 2006). This highlights the importance of studying genetic syndromes in which the prevalence of challenging behaviour is raised, and other aspects of the behavioural phenotypes as a means of understanding aetiology in the broader intellectual disability population.

A behavioural phenotype is defined by an increased probability of behavioural characteristics compared with individuals without the syndrome (Dykens, 1995; See Chapter 1, Sections 1.3 to

1.5 for overview of behavioral phenotypes). Evidence suggests that certain forms of self-injurious and aggressive behaviour may constitute part of the behavioural phenotype of a number of genetic syndromes. Gene-behavior associations of varying specificity have been repeatedly demonstrated across a number of syndromes, for example, Cri du Chat, Cornelia de Lange, Lesch-Nyhan, Fragile-X, Smith-Magenis and Angelman syndromes (Finucane, Simon & Dirrigl, 2001; Horsler & Oliver, 2006b; Nyhan, 1972; Symons, Clark, Hatton, Skinner, & Bailey, 2003).

In syndromes in which estimates of challenging behaviour are consistently high, it has often been assumed that the behaviour has strong biological determinants. One line of evidence in the literature concerns neurotransmitter systems, namely the dopamine, opioid and serotonin systems and how these may be disturbed. Much research over the last twenty years has focussed on the role of neurotransmitter imbalance in the expression of self-injury in some individuals. For example, in Lesch-Nyhan syndrome where self-injurious behaviour (SIB) is observed in approximately 90% of individuals with the syndrome (Christie *et al.,* 1982), the dopaminergic system has been widely implicated (Clarke, 1998). In brief, evidence arises from neuropathological, neuroimaging and neurochemical studies of individuals with Lesch-Nyhan syndrome (Schroeder *et al.,* 2001). Functional loss of dopamine terminals has been found in positron-emission tomography studies of healthy individuals with Lesch-Nyhan syndrome and in post mortem studies. It has also been suggested that there is a super-sensitivity of postsynaptic dopamine receptors that results from the loss of dopamine terminals and this dopamine loss acts to mediate the self-injury (Casas-Bruge *et al.,* 1985 cited by Ernst *et al.,* 1996; Clarke, 1998; Ernst *et al.,* 1996; Turner & Lewis, 2002). Van Acker (1991) also implicated abnormalities in the

dopamine system to the hand stereotypies and loss of purposeful hand movements that are associated with Rett syndrome.

Other studies have attempted to examine a broader range of potential biological factors and identify brain regions that may be centrally involved in the expression of SIB. Several researchers have identified the basal ganglia as a particularly strong candidate. The basal ganglia are made up of several structures, including the striatum and the globus pallidus. Lesions to the basal ganglia in humans have been associated with a variety of outcomes, including movement disorders, speech disorders, obsessive-compulsive behaviours and disinhibition (Bhatia & Marsden, 1994). Dysregulation of basal ganglia structures has been implicated in a range of disorders such as Tourette's syndrome, Parkinson's disease, Autism, Rett syndrome and Lesch-Nyhan syndrome (Albin & Mink, 2006; Cromwell & King, 2004; Holden, Wilman, Wieler & Martin, 2006; Sears *et al.,* 1999). What is striking is that SIB is commonly observed in the majority of these disorders.

There is also a robust literature focusing on the role of the environment in the development of challenging behaviour. More specifically there is substantial empirical evidence in support of the application of operant theory that considers challenging behaviour as a learned behaviour, shaped and maintained by reinforcing consequences (Carr and Durand, 1985; Iwata, Dorsey, Slifer, Bauman & Richman, 1982/1994; Oliver, 1995). In this way, challenging behaviour is viewed as being functional and, perhaps most importantly, changeable via effective environmental intervention.

2.1.2. Models of integration

The biological and operant studies of challenging behaviour remain quite distinct and, arguably, compete. The emerging literature exploring environmental factors influencing challenging behaviour in genetic syndromes offers an opportunity to integrate the two models. Biological theories alone are insufficient to account for challenging behaviour within genetic syndromes, as they would predict no within-syndrome variability and no effect on behaviour of operant processes. Operant theory alone is also insufficient to account for challenging behaviour across syndromes, as it would predict that prevalence rates would be equal as environmental influences are, presumably, randomly distributed across groups. Within and between syndrome variability of the prevalence of broad classes and specific forms of behaviour indicates that, whilst associations between genetic disorders and behaviour are robust, within syndrome variability suggests other aetiological factors. At present, in most behavioural phenotype research, investigators have yet to go beyond the demonstration of simple gene–behaviour associations (Hodapp & Dykens, 2001) to elucidate pathways from gene to behaviour. This systematic review will examine studies in which the influence of environmental factors on problem behaviours in genetic syndromes has been explored. There is particular attention paid to studies that link problem behaviours that are considered to be phenotypic with some other aspect of the behavioural phenotype.

Studies that link phenotypic problem behaviours to other aspects of the behavioural phenotype allude to gene-environment interactions as plausible causal routes to problem behaviours, in which a genetically predisposed facet of the behavioural phenotype interacts with operant reinforcement of challenging behaviour. A recent study examining aggression in Angelman syndrome by Strachan *et al.* (2009) is an example of such an interaction. The results of their

study, which utilised experimental functional analysis, suggested that a genetic predisposition to find social contact rewarding may account for the high levels of aggressive behaviour observed in the syndrome; if social contact from adults is presented contingent on the occurrence of aggressive behaviour. This association may then account for the comparatively high levels of aggression observed in Angelman syndrome. Examination of operant influences on behaviours of social importance within genetic syndromes, in which there is a high prevalence of these behaviours would provide a useful starting point for building comprehensive aetiological models of challenging behaviour.

2.2. Aims

This literature review has two aims. First, a systematic review of the literature will be conducted and studies describing an environmental influence on problem behaviours associated with genetic syndromes will be identified. An initial hand search will identify syndromes of interest, which will then be searched for electronically. Studies will then be divided into three categories:

1. Studies in which the influence of the environment on a problem behaviour in a genetic syndrome has been appraised. However, the behaviour is not widely documented as part of the behavioural phenotype for that syndrome. The decision about whether or not behaviour is phenotypic will be made after key papers studying the syndrome identified are reviewed. If no evidence is found to suggest that the behaviour is part of the phenotype the paper will be included in this category.

2. Studies in which the influence of the environment on a problem behaviour in a genetic syndrome has been appraised and the behaviour is documented as part of the behavioural phenotype for that syndrome.

3. Studies in which the influence of the environment on a problem behaviour in a genetic syndrome has been appraised and the behaviour is documented as part of the behavioural phenotype for that syndrome. In addition, the target behaviour is associated with another aspect of the behavioural phenotype or feature of the syndrome.

The second aim of this systematic review is to appraise the status of current research and the methodologies used and identify future directions for research.

2.3. Method

The first stage of identifying potential studies involved hand searching all issues of the following journals from January 1993 to December 2008:

- American Journal on Mental Retardation (AJMR)
- Behavioral Interventions (BI)
- Behavior Modification (BM)
- Journal of Applied Behavior Analysis (JABA)
- Journal of Applied Research in Intellectual Disabilities (JARID)
- Journal of Autism and Developmental Disorders (JADD)
- Journal of Intellectual Disability Research (JIDR)
- Research in Developmental Disabilities (RIDD)

These journals were selected as they are typically the journals that would report on problem behaviours in people with severe intellectual disability. Inclusion and exclusion criteria for

published studies can be found in Table 2.1. A limit of the previous fifteen years was set on the initial search as this is the period in which the importance of genetic aetiology has been increasingly recognised and growth in the research area is evident (Hodapp & Dykens, 2001).

Table 2.1: Inclusion and exclusion criteria for papers in the initial hand search of the systematic review.

Inclusion Criteria	Exclusion Criteria
The paper reports at least one participant that has a genetic syndrome	Review paper
The genetic syndrome reported is associated with moderate to severe intellectual disability	Paper reports prevalence data only
Environmental influences on a problem behaviour displayed by a participant (s) are appraised	If the paper concerns Autism or Down syndrome[1]
At least two phases of observational data collection with measurement of the dependent variable	

As Table 2.1 shows, papers in which at least one participant with a genetic syndrome associated with moderate to severe intellectual disability were identified. Of these, only those papers that reported on challenging or problem behaviours were taken forward. Finally, the influence of the environment on the problem behaviour must be appraised, through at least two phases of observational data collection in which there was measurement of the dependent variable.

From the initial hand search, 23 papers were identified which reported on ten different syndrome groups (Cornelia de Lange, Angelman, Rubinstein-Taybi, William's, Soto's, Prader-Willi, Lesch-Nyhan, Fragile-X, Smith-Magenis and Rett syndromes). Details of the number of papers

[1] Autism is not considered to be a genetic syndrome as no known genetic basis has been identified. Down syndrome is not typically related to challenging or problem behaviours.

identified and the syndromes reported from each journal are shown in Appendix A. The ten syndrome names identified were the then entered into Psycinfo and Web of Science electronic databases in order to identify further papers on these syndromes published after 1970. Alternative names for the syndromes were derived from the Online Mendelian Inheritance in Man database (OMIM) (all search terms are outlined in Table 2.2). The electronic database search found a further seventeen papers[1].

Table 2.2: Terms employed in the electronic literature search.

Search Term	Variation from OMIM database
Angelman, Angelman Syndrome	Happy puppet, Happy puppet syndrome
Cri du Chat, Cri du Chat Syndrome	Crying cat syndrome, 5-p, 5-p syndrome, 5-p deletion syndrome
Cornelia de Lange, Cornelia de Lange Syndrome	CdLS, CdL, Typus degenerativus amstelodamensis, de lange syndrome, Brachmann-de Lange, Brachmann-de Lange Syndrome, BdLS
Fragile- X, Fragile-X syndrome	Martin-Bell Syndrome, FXS, Marker X syndrome
Lesch-Nyhan, Lesch-Nyhan Syndrome	LNS
Prader-Willi, Prader-Willi Syndrome	PWS, Prader-Labhart-Willi syndrome
Rett, Rett Syndrome	RTS, RTT
Rubinstein-Taybi syndrome	Rubinstein syndrome, Broad-thumb halux syndrome
Smith-Magenis, Smith-Magenis Syndrome	SMS

[1] Details of the number of papers identified and syndromes reported from the electronic search can be found in Appendix B.

Search Term	Variation from OMIM database
Soto's, Soto's syndrome	-
Williams, Williams syndrome	WS, Williams-Beuren syndrome, WB

2.4. Results and discussion

2.4.1. *Tabulated papers*

Tables 2.3, 2.4 and 2.5 describe all of the studies identified from the hand and electronic search and divides these studies into the categories that were outlined in Section 2.2. Firstly, Table 2.3 outlines seven studies that show an appraisal of environmental influences on behaviours that are not typically classified as part of the behavioural phenotype for the syndromes reported.

Table 2.3: Studies in which the influence of the environment on a problem behaviour in a genetic syndrome has been appraised, however, the behaviour is not documented as part of the behavioural phenotype for that syndrome.

Authors	Participants				Study Design	Experimental method	Results	
	Syndrome	Age	Gender	Behaviour			Assessment outcome	Treatment outcome
Iwata *et al*. (1994a)	Rubinstein-Taybi syndrome	13yrs	Male	Self-injury	Alternating treatment design (A-B-C-D)	4 analogue conditions: social disapproval, demand, play and alone	Undifferentiated response pattern	-
Kern, Mauk, Marder & Mace (1995)	Cornelia de Lange syndrome	7yrs	Female	Breath holding	Multi-element baseline A-B-A-B reversal	Baseline: EFA: (Iwata *et al.,* 1984/ 1992). Treatment: extinction, scheduled attention and mand training	Breath holding maintained by attention	Breath holding reduced from 15.7% to 3.6% of time in attention condition
Piazza *et al*. (1998)	Cornelia de Lange syndrome	7yrs	Female	Pica	Multi-element baseline A-B-A-B reversal	Baseline: EFA: (Iwata *et al.,* 1984/ 1992). Treatment: Alone condition plus matched stimuli	Pica maintained by automatic reinforcement	Mean rate of pica reduced from 1.2 to 0.1 following treatment
O'Reilly, Lancioni, King, Lally & Dhomhnaill (2000)	Fragile-X syndrome	22yrs	Male	Aggression	Multi-element baseline A-B-C with follow-up	Baseline: EFA: (Iwata *et al.,* 1984/ 1992). Treatment: Diverted attention condition, with and without NCA	Aggression maintained by social attention	Rapid reduction in aggression following treatment. Maintained at follow-up
Kelley, Lerman & Camp (2002)	Cornelia de Lange syndrome	10yrs	Female	Destruction	Multiple baseline reversal	EFA: (Iwata *et al.,* 1984/ 1992). Treatment: FCT with and without extinction, plus blocking (holding arms)	Destruction maintained by access to attention and escape from demands	FCT produced most significant reduction in destruction when exposed to extinction and blocking

Authors	Participants				Study Design	Experimental method	Results	
	Syndrome	Age	Gender	Behaviour			Assessment outcome	Treatment outcome
O' Connor, Sorensen-Burnworth, Rush & Eidman (2003)	Fragile-X syndrome	14yrs	Male	Destruction (included aggression, self-injury and destruction)	Multi-element baseline A-B-A-B reversal and follow-up	Baseline: EFA: (Iwata *et al.,* 1984/ 1992) and mand analysis Treatment: Individual system intervention (Hagopian *et al.,* 2002)	Behaviour maintained by adult compliance with his mands	98.1% reduction in behaviour from baseline. Successful transference to home and school and 6 & 9 month follow-up
Saloviita & Pennanen (2003)	Fragile-X	11yrs	Male	Thumb sucking	ABABA reversal and follow-up	Baseline: Nat obs Treatment: Verbal prompts, praise and chewing gum	Behaviour maintained by automatic reinforcement	Reduction from baseline to treatment of 53% to 1% (mean time engaging). Follow up at 22% time

EFA: *Experimental functional analysis,* FCT: *Functional communication training,* Nat obs: *Naturalistic observations*, NCA: *Non-contingent attention.*

Table 2.3 shows that all studies report on single cases and the syndromes identified in these studies are: Cornelia de Lange (n=3), Rubinstein-Taybi (n=1) and Fragile-X (n=3) syndromes. Problem behaviours studied include self-injury, aggression, pica, destruction and thumb sucking, and all of the studies use experimental designs with robust internal validity to appraise environmental effects on these behaviours. Six out of the seven studies identified used experimental functional analysis as a baseline assessment technique (Iwata *et al.,* 1982/1994a), which is widely regarded as one of the best assessment techniques for determining operant modes of reinforcement for behaviour. The seventh study used natural observations at baseline followed by ABABA reversal and follow-up. Six out of seven of the studies employed interventions and of these, five used a reversal design. Interventions included mand training[1], functional communication training (FCT) and extinction, and all interventions produced significant decreases in target behaviours. Iwata *et al.* (1994a) is the only study not employing an intervention, and assessment results following analogue experimental functional analysis revealed an undifferentiated response pattern in a thirteen-year-old male with Rubinstein-Taybi syndrome. The remaining six studies *did* identify social function to the behaviours reported and these generally fell into the categories of attention maintenance, automatic or sensory reinforcement and escape from demands.

These studies demonstrate that problem behaviours in syndromes can be subject to standard applied behaviour analysis methods to show an influence of the environment. Although worthy of note, these studies are unable to contribute to causal models of problem behaviours in genetic syndromes because the studies describe behaviours which are not syndrome

[1] Mand training involves teaching a child to bring about desired changes i.e. allowing a child to acquire something that they want at the time that it is wanted. Mand training can decrease negative behaviours that serve the same mand function.

specific. In addition, no known facet of the behavioural phenotype of the syndromes was deemed to be influential.

Table 2.4 reports on 23 papers in which the influence of the environment on a problem behaviour associated with the behavioural phenotype of a given syndrome has been evaluated.

Table 2.4: Studies in which the influence of the environment on a problem behaviour in a genetic syndrome has been appraised and the behaviour is documented as part of the behavioural phenotype for that syndrome.

Authors	Participants				Study Design	Experimental method	Results	
	Syndrome	Age	Gender	Behaviour			Assessment outcome	Treatment outcome
Duker (1975)	Lesch-Nyhan	13	Male	Self-injury	Descriptive analysis and treatment	Baseline: Recreation of high-risk situations (e.g. car) Treatment: Extinction	Behaviour occurring in car when stationary	Self-injury extinguished
Anderson, Dancis & Alpert (1978)	5 ppts with Lesch-Nyhan syndrome	3, 5, 11, 12 and 13yrs	Male	Self-injury	Alternating treatment and 24 month follow up	Baseline: No restraint, response prevention Treatments: Punishment, positive reinforcement of self-injury or non self-injury and timeout	Consistently high levels of self-injury in baseline	Positive reinforcement of non self-injury and timeout rapidly reduced behaviour. Maintenance at 24months
Bull & LaVecchio (1978)	Lesch-Nyhan syndrome	10yrs	Male	Self-injury and physical restraint	Baseline followed by repeated treatment design and follow-up	Baseline: Physical attention Treatment: Systematic desensitisation with extinction (15 trials)	Anecdotal reports from parents that self-injury maintained by attention and phobic reaction in response to restraint removal	Self-injury extinguished and all physical restraints removed. Maintained at 18 month follow-up
Singh and Pulman (1978)	Cornelia de Lange syndrome	13yrs	Male	Self-injury	A-B-A-B	Baseline: Nat obs Treatment: DRO and punishment	Mean of 43 occurrences of self-injury per hour	Self-injury significantly reduced by DRO (mean of 43 to 4 responses per hour). Addition of punishment reduced to zero

Authors	Participants				Study Design	Experimental method	Results	
	Syndrome	Age	Gender	Behaviour			Assessment outcome	Treatment outcome
Gilbert, Spellacy & Watts (1979)	Lesch-Nyhan syndrome	4yrs	Male	Self-injury and physical restraint	Baseline followed by repeated treatment design	Baseline: Nat obs Treatment: Extinction of self-injury and DRO	Self-injury maintained by attention	Marked decrease in behaviour during treatment. Failed to generalise to home environment
Menolascino, McGee & Swanson (1982)	Cornelia de Lange syndrome	14yrs	Male	Self-injury	Repeated intervention	Extinction of non-compliance with task demands and positive reinforcement	-	Behaviour extinguished following intervention
Iwata, Pace, Willis, Gamach & Hyman (1986)	Rett Syndrome	2ppts No age reported	Female	Self-in jury	Multi-element baseline and treatment	EFA (Iwata *et al.,* 1984) Treatment: Guided compliance with reinforcement, response interruption, DRO	Self-stimulatory outcome	Ppt 1: Reduction in self-injury from 15% to 4% of time. Ppt 2: Reduction in self-injury from 69% to 3%
McGreevy & Arthur (1987)	Lesch-Nyhan syndrome	2yrs	Male	Self-injury	A-BC-A-BC	Baseline: Play with restraint Treatment: DRI (B) and punishment (C) with no restraint	Observations revealed self-injury occurred immediately after restraint removed	Elimination of behaviour
Dosseter, Couryer and Nicol (1991)	Cornelia de Lange syndrome	14yrs	Female	Self-injury	Treatment only	Massage for 30mins twice daily	-	Elimination of self-injury
Grace, Cowart & Matson (1988)	Lesch-Nyhan syndrome	14yrs	Male	Self-injury	Multiple baseline across different settings and 19 week follow-up	Self-evaluation of self-injury Treatment: Timeout and positive reinforcement	High rates of self-injury in baselines	Elimination of self-injury. Maintained at follow-up

Authors	Participants				Study Design	Experimental method	Results	
	Syndrome	Age	Gender	Behaviour			Assessment outcome	Treatment outcome
Bay, Mauk, Radcliffe & Kaplan (1993)	Cornelia de Lange syndrome	6yrs	Male	Self-injury, aggression, destruction	Multi-element baseline and treatment	EFA (Mace *et al.,* 1991) Intervention: scheduled attention, extinction and DRO	Behaviour maintained by access to attention	Decrease in self-injury during the attention-related conditions
Paisey, Whitney & Wainczak (1993)	Rett syndrome	3yrs	Female	Self-injury	Multiple baseline	Baseline: Nat obs Intervention: Physical interruption and DRI	50-60% mean occurrence of behaviour	Contingent interruption and DRI had most significant reduction on behaviour. 50-60% of time in baseline to near zero
Wehmeyer, Bourland & Ingram (1993)	Rett syndrome	19 and 23yrs	Female	Stereotyped hand movements	Alternating treatment design	EFA: Alone, demand, attention and leisure	Behaviour maintained by escape from demands and automatic reinforcement	-
Lerman, Iwata, Shore & DeLeon (1997)	Cornelia de Lange syndrome	25yrs	Female	Self-injury	Multi-element baseline Repeated treatments in a reversal design	Baseline: EFA: (Iwata *et al.,* 1984/ 1992). Treatment: Punishment (contingent restraint)	Self-injury maintained by automatic reinforcement	Thinned punishment procedure produced decrease in self-injury. 25.6% of the time to 3.3% from baseline
Obi (1997)	Lesch-Nyhan syndrome	24yrs	Male	Self-injury and physical restraint	Functional assessment and repeated intervention	Assessment: Questionnaire and interview. Intervention: Restraint fading, skills-shaping and relaxation	Self-injury, fear and anxiety when out of restraints	50% reduction in self-injury and restraint from baseline

Authors	Participants				Study Design	Experimental method	Results	
	Syndrome	**Age**	**Gender**	**Behaviour**			**Assessment outcome**	**Treatment outcome**
Evans and Meyer (1999)	Rett Syndrome	5yrs	Female	Stereotyped hand movements	Multiple baseline longitudinal study	Observations of behaviour over 3yr period Treatment: FCT, DRI, tactile stimulation	Undifferentiated pattern of flicking and rubbing hands in baseline. Anecdotal reports of attention maintenance	Reductions in behaviour related to positive interactions but teaching alternative behaviour was unsuccessful
Berg *et al.,* (2000)	Rett syndrome	4yrs	Female	Self-injury	Alternating treatment	EFA: (Iwata *et al.,* 1984/ 1992) preceded by non-contingent attention or contingent escape	Undifferentiated analogues unless preceded by a pre-test condition	-
Maglieri, DeLeon, Rodriguez-Catter & Sevin (2000)	Prader-Willi syndrome	14yrs	Female	Food stealing	A-B-A-B reversal and stimulus control assessment	Baseline: Free access to food Intervention: Reprimands contingent on stealing	Food consumption high in baseline	No food consumed following reprimands and stimulus control (prohibited foods labelled)
Hall, Oliver & Murphy (2001)	3 ppts with Lesch-Nyhan syndrome	17, 25 and 30 months	Male	Self-injury	Descriptive analysis	Nat obs at 3 monthly intervals for 18 months	Sequential analysis revealed that self-injury was more likely to occur during periods of low social interaction	-
Harding *et al.* (2001)	Soto's syndrome	2yrs	Female	Tantrums, aggression and destruction	Multi-element baseline A-B-A reversal	Baseline :EFA: (Iwata *et al.,* 1984/ 1992). A : All behaviours reinforced B : Severe behaviours reinforced	Behaviours maintained by attention and access to tangibles. Mild behaviours always preceded severe	-

Authors	Participants				Study Design	Experimental method	Results	
	Syndrome	**Age**	**Gender**	**Behaviour**			**Assessment outcome**	**Treatment outcome**
Roane, Piazza, Sgro, Volkert & Anderson (2001)	Rett syndrome	14 and 23yrs	Female	Hand wringing and hand mouthing	Multi-element baseline Intervention: Combined alternating treatment and reversal	Baseline:EFA: (Iwata *et al.,* 1984/ 1992). Treatment: Interruption of behaviour and DRI	Behaviour maintained by automatic reinforcement	Both interventions produced dramatic reduction in behaviours e.g. ppt 1: 97.5% of time to 4.7% following intervention
Bergen, Holborn & Scott-Huyghebaert (2002)	Lesch-Nyhan syndrome	28yrs	Male	Self-injury	Alternating treatment	4 analogue conditions in which levels of adult attention were manipulated	Behaviour most frequent in continuous attention condition	-
Wales, Charman & Mount (2004)	8 ppts with Rett syndrome	13-17yrs	Female	Repetitive and movements	Alternating treatment design (A-B-C-D)	EFA: (Iwata *et al.,* 1986): Attention, no stimulation, stimulation and demand	Behaviour occurring at very high levels in all conditions. Undifferentiated response patterns	-

DRI: *Differential reinforcement of incompatible behaviour,* DRO: *Differential reinforcement of other behaviour*, EFA: *Experimental functional analysis,* FCT: *Functional communication training,* Nat obs: *Naturalistic observations,* ppts: *participants*.

Table 2.4 shows that nine of the 23 papers report on SIB in Lesch-Nyhan syndrome (documented as phenotypic by Christie *et al.,* 1982). Seven papers report on Rett syndrome; three of these describing SIB and four describing stereotyped or repetitive hand movements, both of which are deemed phenotypic (Hagberg, Aicardi, Dias & Ramos, 1983; Mount, Hastings, Reilly, Cass & Charman, 2001). Five papers report on SIB in Cornelia de Lange syndrome (documented as phenotypic by Hyman, Oliver & Hall, 2002), one paper reports on food stealing in Prader-Willi syndrome (documented as phenotypic by Holland, Treasure, Coskeran & Dallow, 1995) and one paper reports on aggression, destruction and temper tantrums in Soto's syndrome, which are commonly regarded as phenotypic problem behaviours (Finnegan *et al.,* 1994).

Seventeen of the papers employed intervention and although two papers utilised a descriptive analysis (Duker, 1975; Hall *et al.,* 2001), all others use robust experimental techniques such as reversal, alternating treatment and multiple baseline designs. Assessment outcome found behaviours to be maintained by attention, escape from demands, access to tangibles, automatic reinforcement and more idiosyncratic situations such as being in the car and having restraints removed. All interventions produced a favourable outcome (reductions in target behaviours).

These studies demonstrate that the environment can influence problem behaviours that are phenotypic. Although the majority of studies show changes in behaviour with changes in the environment, some of the studies utilising experimental functional analysis show undifferentiated patterns of behavioural responding across conditions. This is evident for behaviours that are extremely high rate such as SIB in Lesch-Nyhan syndrome (e.g. Anderson

et al., 1978; Grace *et al.,* 1988; McGreevy *et al.,* 1987) and stereotyped hand movements in Rett syndrome (Berg *et al.,* 2000; Evans & Meyer, 1999; Iwata *et al.,* 1986; Roane *et al.,* 2001; Wales *et al.,* 2001; Wehmeyer *et al.,* 1993). In these studies, the assumption is that behaviour is maintained by automatic reinforcement. It is therefore, more accurate to refer to these studies as showing no influence of social variables. The studies in Table 2.4 reveal that there is some support for the view that problem behaviours associated with the behavioural phenotype of genetic syndromes are operantly reinforced. For example, in Rett syndrome where the majority of studies have assumed automatic reinforcement of repetitive hand movements, Wehmeyer *et al.* (1993) found evidence for behaviour maintained by escape from demands in a 19-year-old woman. In addition, interventions such as differential reinforcement of other behaviour (DRO), differential reinforcement of incompatible behaviour (DRI) and FCT have been successful at reducing stereotyped behaviour in Rett syndrome (Evans & Meyer, 1999; Iwata *et al.,* 1986; Roane *et al.,* 2001). Although the studies in Table 2.4 show how the environment may influence phenotypic behaviours, they do not provide evidence for gene-environment interactions, as the target behaviours are not linked to any other aspects of the behavioural phenotype.

Table 2.5 reports on ten papers that outline an environmental influence on problem behaviours in genetic syndromes. The behaviours are known to be associated with the behavioural phenotype of that syndrome and the behaviour can also be linked to another characteristic of the syndrome, therefore providing support for gene-environment interactions.

Table 2.5: Studies in which the influence of the environment on a problem behaviour in a genetic syndrome has been appraised and the behaviour is documented as part of the behavioural phenotype for that syndrome. In addition, the target behaviour is associated with another aspect of the behavioural phenotype or feature of the syndrome.

Authors	Participants				Study Design	Experimental method	Results	
	Syndrome	Age	Gender	Behaviour			Assessment outcome	Treatment outcome
Oliver *et al.* (1993)	Rett syndrome	3yrs	Female	Stereotyped behaviour and Self-injury	Alternating treatment	EFA: Continuous attention, non-stimulation, stimulation and demand.	Stereotyped behaviour maintained by automatic reinforcement and self-injury maintained by escape from social interactions.	-
O'Reilly (1997)	Williams syndrome	26 months	Female	Self-injury	Alternating treatment	EFA: 6 conditions conducted in presence and absence of otitis media	Self-injury only occurring when otitis media present.	-
Vollmer, Borrero, Lalli & Daniel (1999)	Soto's syndrome	9yrs	Male	Aggression	Multi-element baseline A-B-A-B-C-A reversal	Baseline: EFA: (Iwata *et al.,* 1984/ 1992 Treatment: FCT with and without delay	Aggression maintained by access to food and TV.	Aggression occurred when it produced immediate small reinforcers (mands produced larger delayed). Linked to impulsivity
Kahng, Iwata, Thompson & Hanley (2000)	Angelman syndrome	31yrs	Female	Self-injury and aggression	Multi-element baseline Multiple baseline between ppts treatment	Baseline: EFA: (Iwata *et al.,* 1984/ 1992. Treatment: NCR and extinction	Behaviours maintained by attention	Little or no target behaviour following extinction.

Authors	Participants				Study Design	Experimental method	Results	
	Syndrome	Age	Gender	Behaviour			Assessment outcome	Treatment outcome
O'Reilly, Lacey & Lancioni (2000)	Williams syndrome	5yrs	Female	Aggression and destruction	Alternating treatment in reversal design	EFA: Attention, demand and play conditions evaluated under different contexts: no noise, noise, noise with earplugs	Escape maintained behaviour in noise condition.	-
Bass & Speak (2005)	Smith-Magenis syndrome	26yrs	Female	Self-injury	A-B	Assessment. ABC charts, MAS, semi-structured interviews Treatment: DRO, self-monitoring and extinction	Behaviour maintained by attention	Marked reduction in behaviour post intervention
Moss *et al.* (2005)	8 ppts with Cornelia de Lange syndrome	4-14yrs	5 male, 3 female	Self-injury	Descriptive analysis	4 hrs nat obs per ppt	7/8 ppts showed self-injury associated with a particular setting event. One ppt showed undifferentiated pattern with no link to setting events	-
Hall, DeBernardis & Reiss (2006)	114 ppts with Fragile-X syndrome	6-17yrs	74 male, 40 female	Social escape behaviours including self-injury	A-B-C-D descriptive analysis	4 conditions: Interview, silent reading, oral reading and singing	Behaviour higher in singing and interview conditions. Higher cortisol levels predictive of lower levels of eye contact	-
Arron *et al.* (2006)	16 ppts with Cornelia de Lange syndrome	1-16yrs	7 male, 9 female	Self-injury	A-B-A-B reversal	No attention and attention conditions	9 ppt's behaviour was related to level of attention. No association for other 7 ppts	-

Authors	Participants				Study Design	Experimental method	Results	
	Syndrome	Age	Gender	Behaviour			Assessment outcome	Treatment outcome
Taylor & Oliver (2008)	5 ppts with Smith-Magenis syndrome	3-13 yrs	3 male, 2 female	Self-injury, aggression and destruction	Descriptive analysis	9-12 hrs of nat obs per ppts	Behaviours evoked in response to low levels of adult contact	-

DRO: *Differential reinforcement of other behaviour*, EFA: *Experimental functional analysis*, FCT: *Functional communication training,* Nat obs: *Naturalistic observations,* NCR: *Non-contingent reinforcement*, ppts: *participants.*

Table 2.5 shows that two papers report on SIB in Cornelia de Lange syndrome (documented as phenotypic by Hyman *et al.,* 2002), two report on phenotypic SIB in Smith-Magenis syndrome (Allanson, Greenberg & Smith, 1999; Colley, Leversha, Voullaire & Rogers, 1990) and two papers report on SIB, aggression and destruction in Williams syndrome (documented as phenotypic by Semel & Rosner, 2003). Single papers were found describing SIB in Rett syndrome, aggression in Soto's syndrome, social avoidance and SIB in Fragile-X syndrome and aggression in Angelman syndrome; all of which are behaviours deemed to be phenotypic (Finnegan *et al.,* 1994; Hagberg *et al.,* 1983; Horsler & Oliver, 2006a; Mount *et al.,* 2001; Symons *et al.,* 2003).

Three papers employed interventions which all produced reductions in target behaviours. Five papers utilised experimental functional analysis (Iwata *et al.,* 1982/1994a), which successfully identified the functions of problem behaviours. One study used an A-B design and three used descriptive analysis, methods that are arguably less experimentally robust when appraising environmental influences on behaviour. Assessment outcomes included attention maintenance, social escape, noisy environments, tangibles and the presence of health conditions.

Two of the papers in Table 2.5 are studies demonstrating that behaviours that are in the behavioural repertoire of a syndrome may become operantly reinforced. For example, Oliver *et al.* (1993) showed that phenotypic stereotyped hand to mouth movements in Rett syndrome were maintained by automatic or sensory reinforcement. Interestingly, harder hits to the mouth were found to be associated with continuous adult attention, suggesting a social escape function to the behaviour. The authors proposed that the period of social withdrawal documented in early life in

Rett syndrome produce an increased vulnerability and susceptibility to operant reinforcement by escape, such that the phenotypic behaviour of hand flicks was differentially negatively reinforced by escape from social interaction and eventually become injurious. Similarly, in Cornelia de Lange syndrome, SIB may appear in an individual's repertoire in response to painful health conditions. An association between challenging behaviour and gastroesophageal reflux in Cornelia de Lange syndrome has been noted in previous research (Luzzani, Macchini, Valade, Milani & Selicorni, 2003) suggesting that, pain and discomfort may be a contributing factor to the development and maintenance of challenging behaviour in some individuals. Once in the behavioural repertoire, SIB may then become operantly reinforced and associate with particular environmental events (Arron *et al.,* 2006; Moss *et al.,* 2005). In addition, reduced sensitivity to pain in Cornelia de Lange syndrome may prevent the establishment of a contingency between injurious behaviour and painful consequences (Johnson, Ekman, Freisen, Nyhan & Shear, 1976).

Table 2.5 also outlines papers that describe challenging behaviour in syndromes resulting from a predisposition to find particular stimuli aversive. Hyperacusis or hypersensitivity to sound is reported to be present in approximately 95% of individuals with Williams syndrome (Van Borsel, Curfs & Fryns, 1997). O'Reilly *et al.* (2000a) showed the potential for hyperacusis to alter the reinforcing effectiveness of particular environmental events. More specifically, using experimental functional analysis, O'Reilly *et al.* found that background noise was associated with an increase in escape maintained aggressive behaviour in a five year old girl with Williams syndrome, thus showing the ability of a genetic predisposition to alter the reinforcing properties of environmental events. In addition, O'Reilly (1997) found that otitis media (a commonly observed health condition in Williams syndrome) could act as an establishing operation that

lowered the threshold at which sound is experienced as aversive. O'Reilly found that SIB in a 26 month old girl with Williams syndrome was highest when there was noise in the environment in the presence of otitis media.

There is some evidence to suggest that the Hypothalamo- Pituitary- Adrenal (HPA) axis might be dysfunctional in individuals with Fragile-X syndrome and this may explain why behavioural anxiety is present during social situations (Hessl *et al.,* 2001). Hall *et al.* (2006) found evidence to suggest that this biological predisposition may interact with environmental events such that, certain social situations evoke more social escape behaviours. Using a series of experimental conditions, Hall *et al.* found that interview and singing conditions produced more social escape behaviours which included gaze aversion, physical dissent, face hiding, fidgeting and SIB than did a silent or oral reading condition. In Soto's syndrome, symptoms of Attention Deficit Hyperactivity Disorder (ADHD), such as impulsivity and overactivity (Finnegan *et al.,* 1994; Sarimiski, 2003) may result in more immediate, smaller reinforcers being preferred to larger, more delayed reinforcers and this may be linked to difficulties with self-control and inhibition. Vollmer *et al.* (1999) showed that impulsivity might be directly linked to aggressive behaviour maintained by access to tangible items in Soto's syndrome. For two young boys, aggressive behaviour was more likely to occur if it produced immediate and small reinforcers. Lastly, the social escape function of SIB in Rett syndrome provides further evidence for challenging behaviour in syndromes resulting from a predisposition to find particular stimuli aversive. In this example, the degenerative nature of Rett syndrome often leads to an increase in autistic characteristics and social withdrawal, leading to social interactions becoming aversive for individuals (Oliver *et al.,* 1993).

Finally, Table 2.5 presents papers that describe challenging behaviour in syndromes resulting from a predisposition to find particular stimuli rewarding. For example, in Angelman syndrome high levels of laughing and smiling and pro-social behaviours that are considered to be part of the behavioural phenotype (Horsler & Oliver, 2006a) have been proposed to arise through the phenomenon of genomic imprinting (Brown & Consedine, 2003; Oliver *et al.,* 2007). Individuals with Angelman syndrome typically have a genetic propensity to find social contact very rewarding and thus, studies examining the functions of self-injurious and aggressive behaviour have found it to be maintained by access to social attention (Kahng *et al.,* 2000). Individuals with Smith-Magenis syndrome have also been found to engage in more self-injurious, aggressive and disruptive behaviour at times of low social attention (Bass & Speak, 2005; Taylor & Oliver, 2008). In both Angelman and Smith-Magenis syndromes, the genetic predisposition to find social contact rewarding may act as an accelerator for the mutual social reinforcement of challenging behaviour. In Smith-Magenis syndrome, the additional facet of reduced pain perception may result in increased response efficiency for engaging in the behaviour as the cost (injury to self) is reduced (Greenberg *et al.,* 1991).

2.4.2. Summary of the results

In summary, the literature shows that behaviour in syndromes can be influenced by environmental factors (see Table 2.3) and often these behaviours are phenotypic problem behaviours (see Table 2.4). This research supports the potential role of an operant conceptualisation of challenging behaviour in genetic syndromes and supports the view that phenotypic behaviours can be subject to change through environmental interventions. There is also growing evidence to suggest that gene-environment interactions may govern the presentation

of these behaviours through a number of different pathways (see Table 2.5). Namely, behaviours may enter the repertoire and then become operantly reinforced or there may be particular aspects of the syndrome that drive operant reinforcement and influence the likelihood of problem behaviours being shown. The next sections describe the implications of these findings and directions for future research.

2.4.3. Implications for a comprehensive model of challenging behaviour

Given the evidence for the, arguably, distinct behavioural phenotype and operant reinforcement of challenging behaviour theories that were presented in Chapter 1, the aim of this systematic literature review was to identify studies which demonstrated an integration of the two approaches. More specifically, the review sought to identify studies in which the influence of the environment on phenotypic problem behaviour had been appraised, and the target behaviour was associated with another aspect of the syndrome (gene-environment interactions). Through the identification of single case experimental designs, the results of the literature review have shown that there are a number of gene-environment interactions that can be identified in syndromes. These are clearly extremely important for building syndrome specific models of challenging behaviour in which different weight is given to different child characteristics. Such syndrome specific models have important implications for interventions and this is discussed later in section 2.4.5.

In addition to syndrome specific models, more broadly, each gene-environment interaction that has been identified delineates a potential causal route to problem behaviour. These routes could inform a comprehensive aetiological model of challenging behaviour for the total population of

people with intellectual disabilities. This integration of behavioural phenotype and operant theories in order to inform causal models has started to emerge in the literature and to date; Oliver (1993; 1995) and Langthorne and McGill (2008) have proposed conceptual models to explain the development of SIB. In each model individual characteristics of genetic origin interacts with environmental characteristics to drive the development of self-injury.

With regard to delineating specific causal pathways from genetic characteristics to behaviour in order to inform a comprehensive model, the results of this review have revealed that one plausible pathway to challenging behaviour might be through an attenuated or accentuated specific motivation. For example, a heightened motivation to seek out social attention in Angelman and Smith-Magenis syndrome may result in challenging behaviour that is maintained by access to attention (Kahng *et al.,* 2000; Taylor & Oliver, 2008). In addition, for self-injury in Smith-Magenis syndrome, one must also be aware of the pathway from genetics to central and peripheral nervous system development that may result in reduced pain perception. In this way, there may be a reduced cost for the individual when engaging in the behaviour (Greenberg *et al.,* 1991). Conversely, the review has highlighted syndromes where there may be attenuated motivations and predispositions to find particular stimuli aversive. Evidence for this pathway is provided by the finding that social performance situations result in more social anxiety and challenging behaviour in Fragile-X syndrome (Hall *et al.,* 2006), and the finding that the period of social withdrawal documented in early life in Rett syndrome produces an increased vulnerability and susceptibility to operant reinforcement by escape (Oliver *et al.,* 1993).

A comprehensive model might also consider the pathway from genes to accentuated or attenuated sensory input given the findings related to hyperacusis in Williams syndrome. The review has highlighted the potential of hyperacusis to alter the reinforcing effectiveness of particular environmental events in Williams syndrome leading to challenging behaviour (O'Reilly *et al.,* 2000a). In addition, the review has drawn attention to the importance of health conditions and how these may offer a plausible route to challenging behaviour. For example, SIB in a young girl with Williams syndrome was only found to occur during periods of otitis media. Otitis media may have acted as an establishing operation related to escape from ambient noise (O'Reilly, 1997), whilst pain and discomfort in Cornelia de Lange syndrome may result in SIB entering an individual's behavioural repertoire. Once in the repertoire there is then the potential for the behaviour to become operantly reinforced and associate with particular environmental events (Arron *et al.,* 2006; Moss *et al.,* 2005).

Finally evidence from Soto's syndrome has drawn attention to specific cognitive impairments that may drive the development of challenging behaviour. Impulsivity and overactivity, which are common in Soto's syndrome, may be linked to difficulties with self-control and inhibition such that challenging behaviour may become operantly reinforced by access to immediate rewards (Vollmer *et al.,* 1999). Woodcock, Oliver and Humphreys (2009) also proposed a gene-environment interaction in Prader-Willi syndrome in which deficits in task switching (proposed as part of the cognitive endophenotype of Prader-Willi syndrome) result in temper tantrums when there is a decrease in predictability in the environment and thus, there is high demand placed upon cognitive resources needed for attention switching. There is then the potential for temper tantrums to be subject to operant reinforcement via social contingencies. Although evidence in

support of specific causal pathways to challenging behaviour has been identified through a number of single cases, a comprehensive model still needs to be developed. The next section outlines potential avenues for future research that would be likely to be productive in this process.

2.4.4. Future research directions

Now that the potential for causal pathways has been identified, future research might usefully examine these syndrome specific models via empirical study. In particular, specific predictions regarding challenging behaviour that is regarded as phenotypic within a given syndrome can be tested. For example, given the results of the single case studies in this literature review, predictions about challenging behaviour in Williams syndrome might be made. Specifically, it might be predicted that hyperacusis and the presence of otitis media might alter the reinforcing properties of environmental events, to drive the expression of self-injury and aggression or functionally similar escape maintained behaviours. For Angelman and Smith-Magenis syndromes, it might be predicted that given the genetic predisposition to find social contact rewarding, challenging behaviour would evidence stronger maintenance by positive social reinforcement. Such predictions need to be assessed in large scale, cross-syndrome comparison studies and the utilisation of experimental functional analysis would offer a robust assessment of environmental influences on behaviours.

It is also notable that the pathways proposed have been described as single points in time and the way that these pathways *develop* has not been discussed. Advantages have been highlighted with respect to the study of the developmental trajectories of language and cognitive capacities within

neurodevelopmental disorders such as Williams and Down syndrome (Thomas *et al.,* 2009). It is important to emphasise investigation of hypotheses from a developmental perspective given that, in some syndromes there are known changes in aspects of the behavioural phenotype. For example, behavioural characteristics demonstrated in individuals with Williams syndrome include hypersociability characterised by social disinhibition and increased empathy (Bellugi *et al.,* 2007; Martens, Wilson & Reutens, 2008). However, over time there appears to be a change in the profile of sociability within Williams syndrome with some decrease in sociability and increase in behavioural and emotional problems, communication disturbance and anxiety as individuals get older (Einfield, Tonge & Rees, 2001; Gosch & Pankau, 1997). In addition, SIB in Rett syndrome has been shown to have different social functions (functions to escape and to obtain social attention) depending on the stage of a child's development. Specifically, the profile of Rett syndrome causes social interaction to be reinforcing and punishing at different developmental stages (Oliver *et al*., 1993). An important avenue for future research is the consideration that over time certain motivations and facets of the syndrome may change, and this may have implications for variability in challenging behaviour at different stages of development.

Future research also needs to examine whether the potential causal pathways are applicable to intellectual disability that is not genetically determined, for example, in foetal alcohol syndrome or in ASD and ADHD, which are behaviourally defined conditions. In addition, there are other risk markers for the development of challenging behaviour such as ASD and impulsivity (McClintock *et al.,* 2003) that have not been outlined in the review that may be implicated in the development of challenging behaviour for some individuals. Such factors need to be explored within a larger group design and incorporated into a comprehensive model.

2.4.5. Implications for intervention

The findings of the systematic review provide important implications for early intervention of challenging behaviour at a syndrome level. Early intervention in children with intellectual disabilities may be more effective at reducing challenging behaviour and enhancing other adaptive skills and abilities than a reactive approach (See Richman, 2008 for overview). Preparing families and professionals with knowledge and information enhances intervention opportunities, allows behaviour to be anticipated and responses to challenging behaviour to be monitored. As challenging behaviour develops and dyadic reinforcement takes place, the behaviour will become more established in an individual's behavioural repertoire (Oliver, 1995; Oliver, Hall & Murphy, 2005). Although prevention of the behaviour entering a behavioural repertoire is perhaps only realistic or possible for a subset of individuals, pre-emptive and early intervention strategies may be beneficial. In Cornelia de Lange syndrome for example, SIB may appear in an individual's repertoire in response to painful health conditions. Ensuring that health conditions commonly seen in Cornelia de Lange syndrome (e.g. gastroesophageal reflux, otitis media) are immediately and effectively treated may help to prevent potentially injurious responses.

Early intervention strategies may also shift the focus from behaviour and move more towards managing motivation and increasing awareness of syndrome specific vulnerability and susceptibility to operant reinforcement. In Angelman syndrome for example, awareness of aspects of the behavioural phenotype such as the excessive motivation to gain social attention and its possible link with aggressive behaviour, offers significant implications for early intervention. Knowledge of this underlying motivation may have wider reaching implications for individuals

with Angelman syndrome and their families. It is probable that this drive for social attention is likely to affect a host of other behaviours in addition to challenging behaviour, particularly those behaviours which are linked to increased allocation of social resources (Brown & Consedine, 2004). Sleep disturbances are commonly reported in the syndrome (Chertkoff-Waltz, Beebe & Byars, 2005; Didden, Korzilius, Smits & Curfs*,* 2004; Miano *et al.,* 2004; Pelc, Cheron, Boyd & Dan, 2008) and the drive for social attention may result in children waking other people at night. Anecdotally there are also reports of stranger approach and sibling relationship difficulties as an individual competes for social resources. The findings may also provide an opportunity to minimise conditions known to mediate operant conditioning. For example in Rett and Fragile-X syndromes, knowledge of the predisposition to find high levels of social interaction aversive at certain points in development and particular situations may help to minimise the reinforcement of challenging behaviour. FCT (Carr & Durand, 1985) has proven to be particularly effective for challenging behaviour maintained by social consequences. The main target of FCT is to replace an aberrant behaviour with an alternative communicative response that is functionally equivalent (Carr and Durand, 1985). In syndromes, knowledge of operant vulnerability and susceptibility could inform FCT so that alternative functionally equivalent responses could be reinforced before the development of challenging behaviour.

The findings also provide potential implications for assessment, and emphasise the importance of assessment to intervention designs that determine the functions of challenging behaviour and manipulate operant determinants in intervention. The results of the review provide some evidence for syndrome specific models in which there may be causal pathways from genetic cause to behaviour. Within any given syndrome, many pathways may be operational, however, syndrome

specific gene-environment interactions provide us with information on which pathway might be most significant. In turn, this provides information on which particular assessments should be prioritised in which syndromes. For example in Cornelia de Lange syndrome, a pain assessment may be prioritised given the link between health conditions and SIB (Luzzani *et al.,* 2003). In Soto's syndrome levels of impulsivity may be assessed first, or in Smith-Magenis syndrome a motivational assessment for challenging behaviour may be foremost.

Demonstrations that behaviour in genetic syndromes can be influenced by environmental factors are important as they counter determinist positions which suggest that behaviours are wholly accounted for by an underlying biological aetiology (Deb, 1997, Harris, 1987) and thus are unchangeable. An operant conceptualisation of challenging behaviour that is part of the behavioural phenotype of a syndrome negates therapeutic nihilism. This review has shown the role of the environment may be instrumental in shaping and maintaining behaviours in genetic syndromes and thus, it is not inevitable that challenging behaviour will develop. In this way, responsive intervention for already established challenging behaviour is very important. The review has identified high risk and vulnerable groups for the development of challenging behaviour that need to be targeted with intervention.

The findings presented also highlight the need for dissemination of information. As Oliver (1993) indicates, important questions around the process of dissemination include: What will be disseminated, by whom and how? Academics and researchers most commonly undertake active dissemination; however, the role of syndrome support groups in the research process has been evolving in recent years. Support groups have been successful in developing working

partnerships with researchers from many disciplines. The groups have now become more proactive in determining the research agenda, and have taken advantage of new technologies for dissemination that gives a role for support groups to commission and disseminate research. A collaborative approach between parent groups and researchers is likely to prove important to ensuring that research focuses on the most pressing problems of those who have syndromes and their families. Furthermore, such collaborations promote rapid dissemination of robust findings to shortcut the typical delays of research moving to influence practice.

CHAPTER 3

The Phenomenology and Correlates of Challenging Behaviour in Angelman, Cri du chat and Cornelia de Lange Syndromes

----------Preface to Chapter 3----------

Evidence for the effects of gene-environment interactions on problem behaviours in genetic syndromes was considered in Chapter 2. A number of single case experimental designs showed that gene-environment interactions might be conceivable causal pathways within a comprehensive model of challenging behaviour. The current status of research was also appraised in Chapter 2 and it was suggested that future research might usefully examine these syndrome specific gene-environment interactions in larger scale, cross-syndrome comparison studies that utilise experimental functional analysis. This study examines the behavioural phenotypes of three syndromes known to be associated with a high prevalence of challenging behaviours: Angelman, Cri du Chat and Cornelia de Lange syndromes. It is anticipated that a comparison of the phenomenology and correlates of challenging behaviour within these syndromes will help to inform the causes of challenging behaviour within each syndrome and across the different syndromes with subsequent implications for interventions.

3.1. Introduction

Contemporary research designs for the study of behavioural phenotypes have primarily employed empirical description of behavioural phenomenology in a syndrome relative to chronological aged matched controls or mental-aged matched controls (Dykens, 1995; Hodapp & Dykens, 2001). More recently there has been a focus on syndrome comparisons in which syndrome groups are known to demonstrate similar behaviours. This 'same-but-different' approach promotes a more precise delineation of phenomenology within and between syndromes so that commonalities and unique features can be identified and causal mechanisms described. In this study, the aim is to generate these data on the phenomenology and correlates of challenging behaviour for Angelman, Cornelia de Lange and Cri du Chat syndromes. These three syndrome groups have been chosen as they are groups in which high rates of challenging behaviours such as self-injury and aggression are known to occur. In addition, given previous research identifying risk markers for challenging behaviour and the benefits of using comparison groups in behavioural phenotype studies, the groups are comparable on characteristics such as degree of intellectual disability, communication and mobility. The groups will also be matched on a number of other characteristics such as gender and age. This will be the first study to examine the phenomenology and correlates of challenging behaviour within these syndromes at a fine grained observational level, as well as employing a number of questionnaire and interview measures with robust psychometric properties. It is anticipated that comparisons of the phenomenology of challenging behavior across syndromes will provide valuable data for informing the causes of challenging behaviour within and across syndrome groups with subsequent implications for interventions. The next sections (3.2-3.4) will describe the existing literature on the behavioural phenotypes of Angelman, Cri du Chat and Cornelia de Lange syndromes.

3.2. Angelman Syndrome

3.2.1. *Cause, prevalence and physical characteristics of Angelman syndrome*

Harry Angelman first identified Angelman syndrome in 1965. Dr Angelman described the children as 'Happy Puppets' because of their happy character and stiff jerky movements. The syndrome is rarely referred to by this name now, with professionals and families preferring to adopt the name 'Angelman syndrome'. The prevalence estimates for Angelman syndrome range from 1 in 10,000 to 1 in 40,000 live births (Buckley, Dinno & Weber, 1998; Clayton-Smith, 1993; Peterson, Brondum-Neilsen, Hansen & Wulff, 1995). The genetic cause of Angelman syndrome is a loss of genetic information at 15q11-q13 (Cassidy, Dykens & Williams, 2000; Kaplan *et al.,* 1987; Knoll *et al.,* 1989) which affects the expression of the UBE3A gene at this locus. Deletions in this region are also associated with Prader-Willi syndrome; however, Prader-Willi syndrome is caused by a loss of information on the paternal chromosome, whilst Angelman syndrome arises from a loss of information on the maternal chromosome (Knoll *et al.,* 1989). The observation that the same genetic cause could give rise to different phenotypes, led to Angelman and Prader-Willi syndromes being the first syndromes to be identified which result from abnormalities within a chromosomal region that is subject to genomic imprinting (Knoll *et al.,* 1989). Genomic imprinting refers to a parent-of-origin specific process of genotypic expression whereby, either the paternally or maternally inherited allele of a gene is rendered inactive (Clayton-Smith, 1992; Reik & Walter, 2001).

There are four main genetic mechanisms that can lead to the loss of information at the critical genetic locus and these are referred to as subtypes of the syndrome. Approximately 70% of

affected individuals have a maternal deletion of chromosome 15q11-q13 (deletion subtype), between 2 and 5% have a unipaternal disomy (UPD subtype) in which both copies of chromosome 15 are inherited from the father, and 3 to 5% of individuals have an imprinting defect resulting in a loss of function of 15q11-q13 on the maternally derived chromosome (imprinting subtype). Between 5 and 10% of individuals with Angelman syndrome show a mutation of the UBEA3 gene (UBEA3 subtype; Clayton-Smith & Laan, 2003). UBE3A encodes for the production of the enzyme Ubiquitin Protein Ligase in the brain, which is involved in the degradation of other proteins within cells. In most bodily tissue, both the maternal and paternal copies of the UBE3A gene are active. In the brain, however, only the maternal copy is active and thus any lack of expression of the maternal copy prevents the enzyme from being produced in the brain. This loss of enzyme function causes the characteristic features of Angelman syndrome which are outlined below (Clayton-Smith & Laan, 2003). Clayton-Smith and Laan also report a fifth subtype of individuals with Angelman syndrome, which refers to individuals who have received a clinical diagnosis but have no demonstrable cytogenetic or molecular abnormality of chromosome 15q11-13. This suggests that there may be other genes involved in the syndrome.

There are a number of physical characteristics associated with Angelman syndrome; most notably individuals often have a movement or balance disorder which can be characterised by ataxic gait (Beckung, 2004). Individuals with the syndrome often lack coordination whilst performing voluntary movements such as walking and these can appear to be clumsy, inaccurate or unstable. Some individuals may walk with their arms raised and their wrists and elbows flexed in an attempt to maintain balance (Clayton-Smith, 2001; Dykens, Hodapp & Finucane, 2000). From birth, individuals with Angelman syndrome have axial hypotonia and from infancy, limb

hypertonia develops which predominates at the lower extremities. Mobility can decrease with age due to hypertonicity of the limbs, which can make movement very difficult. Scoliosis occurs in approximately 10% of individuals, particularly those who are less mobile (Clayton-Smith, 2001).

A distinctive pattern of resting brain activity (as measured using an electroencephalogram) is seen in almost all individuals with Angelman syndrome, and seizure disorder occurs in approximately 80% to 90% of individuals (Boyd, Harden & Pattern, 1988; Pelc, Boyd, Cheron & Dan, 2008). Many different types of seizures have been reported in Angelman Syndrome with atypical absences and myclonic seizures being particularly common. There is some evidence to suggest that seizures are often more severe in individuals who have a chromosome 15q11-13 deletion subtype (Pelc *et al.,* 2008a). Recurrent seizures often lead to a diagnosis of epilepsy and this is usually most severe throughout childhood. Most seizure activity can be controlled by medication (Boyd et *al.,* 1988; Clayton-Smith, 2001).

Dysmorphic facial features of the syndrome include a pointed chin, long face, flat occiput, widely spaced teeth, wide jaw, protruding tongue, microenchephaly, deep set eyes and a short nose. Hypopigmented skin, blond hair and blue eyes relative to an individual's family members are also common (Clayton-Smith, 2001; Dykens *et al.,* 2000).

3.2.2. *Cognitive and behavioural characteristics of Angelman syndrome*

Almost all individuals with Angelman syndrome have a severe to profound intellectual disability and an absence of expressive speech (Clarke & Marston, 2000; Peters *et al.,* 2004; Smith *et al.,* 1996). However, slight variation in development has been found between genetic subtypes, specifically those with a typical deletion have been found to have a more severe developmental delay, have less expressive communication (Jolleff, Emmerson, Ryan & McConachie, 2006) and walk later (Lossie *et al.,* 2001) than those with unipaternal disomy or imprinting defects. Steffenburg, Gillberg, Steffenburg and Kyllerman (1996) suggested that Autism may be common in Angelman syndrome, after their sample of four children all met full diagnostic criteria. However, it is important to note that the characteristics of Autism Spectrum Disorder (ASD) can look very similar to those identified in individuals with severe and profound levels of intellectual disability. Trillingsgaard and Østergaard (2004) found that individuals with Angelman Syndrome demonstrated greater skills than individuals with ASD in particular areas including social smile, facial expression directed to others, response to name, shared enjoyment and unusual interests and repetitive behaviour. These skills are less reliant upon the person having achieved a particular developmental level than other diagnostic characteristics of ASD.

One of the most salient and commonly reported behavioural features of Angelman syndrome includes an 'excitable' personality, 'happy demeanour' and pro-social behaviours such as frequent bouts of laughing and smiling (e.g. Horsler & Oliver, 2006a; Richman, Gernat & Teichman, 2006). There has been much debate about the causes and the appropriateness of laughing and smiling within Angelman syndrome. Early reports viewed the behaviour as being caused by a neurological impairment (Williams & Frias, 1982) and case reports have often

described the behaviour as unprovoked, excessive and inappropriate (Fridman *et al.,* 2003). One case study even reported prolonged laughter after vomiting (Magenis, Brown, Lacey, Budden & LaFrach, 1987). More recent, robust and systematic observational studies have found that although laughing and smiling behaviour is heightened in Angelman syndrome, it is appropriately associated with environmental events and cues such as adult speech, touch, eye contact and laughing and smiling of others (Oliver, Demetriades & Hall, 2002; Horsler & Oliver, 2006b; Oliver *et al.,* 2007; although for negative results in a small (n=2) sample of very young (18-42 months) children see Richman *et al.,* 2006).

Kinship theory (also see maternal investment theory) by Haig and Westerby (1989) proposes a framework which attempts to account for the phenomenon of genomic imprinting from an evolutionary perspective. The authors propose that maternal and paternal alleles are expressed differently in order to favour the propagation of maternal or paternal genes. This occurs because whilst it is certain that alleles of maternal origin will be propagated to present and all future maternal offspring, it is only certain that alleles of paternal origin will be propagated to present maternal offspring (future maternal offspring may have different fathers). As such, imprinted genes should influence maternal resource allocation to the offspring, with paternally expressed alleles increasing the maternal resources allocated to an offspring, whilst maternally expressed alleles have the opposite effect (the maternal genome would benefit from balancing maternal resources across all of her offspring). Isles, Davis and Wilkinson (2006) provide support for this theory in their work with imprinted genes in mice on placental function and neonate suckling. Brown and Consedine (2004) suggest that some of the behavioural characteristics of Angelman syndrome function to gain maternal resources. One behaviour that is common in Angelman

syndrome is excessive laughing and smiling and Brown and Consedine use emotional signalling theory to explain how behaviour such as laughing and smiling has the capacity to command maternal resources (social attention).

Other behavioural characteristics of Angelman syndrome include excessive chewing and mouthing (Buckley *et al.,* 1998, Smith *et al.,* 1996) hyperactivity (Clarke & Marston, 2000) and attention problems (Chertkoff-Waltz & Benson, 2002) which are usually coupled with sleep disturbance (Chertkoff- Waltz, Beebe & Byars, 2005; Didden, Korzilius, Smits & Curfs, 2004; Miano *et al.,* 2004; Pelc, Cheron, Boyd & Dan, 2008). Oliver, Berg, Moss, Arron and Burbidge (in review) found greater levels of hyperactivity and impulsivity within Angelman syndrome and this behaviour has also been linked to physical aggression within the syndrome (Arron, Oliver, Berg, Moss & Burbidge*,* in review). There are also reports that individuals with Angelman syndrome are fascinated by water (Didden *et al.,* 2006; Ishmael, Begleiter & Butler, 2002; Clarke & Marston, 2000) and tend to be captivated by reflective surfaces (Clayton-Smith & Laan, 2003). Progression into adulthood usually sees an increase in attention span and a decrease in hyperactivity and challenging behaviours, although the sociable disposition and easily provoked laughter is thought to remain (Clayton-Smith, 2001).

3.2.3. *Challenging behaviour in Angelman syndrome*

There are many anecdotal case reports in the literature which make reference to aggressive behaviour within Angelman syndrome (Clayton-Smith, 2001; Hersh et *al.,* 1981; Moore & Jeavons, 1973; Sandanam *et al.,* 1997; Steffenburg *et al.,* 1996; Thompson & Bolton, 2003; Williams and Frias, 1981). There have been very few empirical studies examining aggressive

behaviour in Angelman syndrome. However, when reviewing the literature, Horsler and Oliver (2006a) found that 15% of 64 studies made reference to aggression. Similarly, in a review of behavioural problems in Angelman syndrome, Summers, Allison, Lynch and Sandler (1995) found that 10% of case reports (n=108) indicated the presence of aggressive behaviour. In the second part of their study, Summers *et al.* conducted a small questionnaire based survey (n=11) and found that all parents reported children to engage in aggression, namely hair pulling and grabbing. More recently, Arron *et al.* (in review) examined the prevalence of self-injury and aggression in seven genetic syndromes and found that the prevalence of physical aggression was significantly higher in Angelman syndrome (73%) than a matched comparison group (46%) and five other genetic syndromes associated with intellectual disability. Strachan *et al.* (2009) provide the only known experimental study into aggressive behaviour in Angelman syndrome in which they utilised experimental functional analysis. Strachan *et al.* used experimentally manipulated conditions in which levels of adult attention and demand were manipulated for twelve children with Angelman syndrome. They found that ten out of twelve participants displayed aggressive behaviour (hair pulling, spitting, biting, smacking, grabbing and pinching) and environmental influences over aggressive behaviour were found for the majority of participants. The results of the study suggest the need for further observational studies to examine the phenomenology of aggressive behaviour in Angelman syndrome using a larger sample of individuals and matched contrast group.

Self-injurious behaviour (SIB) in Angelman syndrome has only been reported in a handful of studies (Clarke & Marston, 2000; Hou, Wang & Wang, 1997), and Horsler and Oliver (2006a) found that only 3% of the 64 studies reviewed made reference to self-injury in Angelman

syndrome. In a recent across-syndrome questionnaire study, Arron *et al.* (in review) found that 45% of individuals with Angelman syndrome showed SIB against 27% of the comparison group (mixed aetiology intellectual disability). Topographies of SIB were quite variable, however they included hitting self (with body or object), biting self, pulling self and rubbing and scratching self. Out of seven genetic syndromes studied, Angelman syndrome was the only syndrome in which individuals were not significantly more likely than the comparison group to display SIB (as calculated by odds ratios). These findings clearly warrant further clarification and to date, no observational studies examining SIB in Angelman syndrome have been conducted.

From the review of Angelman syndrome, it is important to note that there are a number of risk markers present in the syndrome which have been described in the literature as being associated with challenging behaviour. Although correlates of challenging behaviour have not been explored in Angelman syndrome, the literature shows that the syndrome is associated with a severe to profound level of intellectual disability, a deficit in communication and possible ASD characteristics (Deb, Thomas & Bright, 2001; McClintock, Hall & Oliver, 2003; Rojahn, Matson, Naglieri & Mayville, 2004).

3.3. Cri du Chat Syndrome

3.3.1. *Cause, prevalence and physical characteristics of Cri du Chat syndrome*

First described by Lejeune in 1963, Cri du Chat syndrome is often referred to as Deletion 5p-syndrome and chromosome five short arm deletion. The prevalence of Cri du Chat has been

estimated at 1 in 50,000 live births and although the exact gender ratio is unknown, the syndrome is thought to be approximately twice as prevalent in females as in males (Niebuhr, 1978).

Cri du chat syndrome results from a deletion of chromatin from the short arm of chromosome five (5p). The size of the deletion ranges from the entire short arm to the region 5p15 (Overhauser *et al.,* 1994). A de novo deletion is present in 85% of cases; 10 to 15% are familial with more than 90% due to a parental translocation and 5% due to an inversion of 5p (Van Buggenhout *et al.,* 2000). Neibuhr was the first researcher to identify the specific chromosomal region implicated in the syndrome as 5p15.1-5p15.3, using cytogenetic analysis (Niebuhr, 1978). More recent work has mapped specific critical areas within this region as being responsible for the expression of the core clinical features of the syndrome. For example, the characteristic high pitched 'cat-like' cry from which the syndrome derives its name has been mapped to the proximal part of 5p15.3 (Gersh *et al.,* 1995), the speech delay to the distal part of 5p15.3 and severe intellectual impairment to 5p15.2 (Overhauser *et al.,* 1994).

The distinctive cat-cry is a core feature of the syndrome and is still regarded as an important early clinical diagnostic feature in most but not all individuals. The cry is thought to be due to anomalies of the larynx (small, narrow and diamond shaped) and of the epiglottis that is usually small and hypotonic (Neibuhr, 1978). Many infants tend to be of low birth weight and low weight usually persists in the first two years of life for both sexes (Marinescu et *al.,* 2000). Feeding difficulties are common and the associated failure to thrive may be the initial clinical presentation. Some infants may require tube feeding, a process which may have to continue for several years. Gastroesophageal reflux is also reported to be common in Cri du Chat syndrome

during the first years of life (Collins & Eaton-Evans, 2001). Other health problems include respiratory tract infections, otitis media and dental problems. Many individuals with Cri du Chat syndrome are prone to developing a curvature of the spine (congenital scoliosis) and this can become more apparent with advancing age. Some of the most frequently cited physically defining features of Cri du Chat syndrome are facial characteristics including microcephaly, rounded face, widely spaced eyes, downward slanting of palpebral fissures, low set ears, broad nasal ridge and short neck (Dykens *et al.,* 2000; Goodart *et al.,* 1994; Gersh *et al.,* 1995; Marinescu *et al.,* 1999).

3.3.2. *Cognitive and behavioural characteristics of Cri du Chat syndrome*

Early reports on Cri du Chat syndrome suggested that profound intellectual disability was a feature of the syndrome (Niebuhr, 1978). More recent, albeit limited research data, indicates that there is a wider range of cognitive ability in Cri du Chat syndrome (Cornish, 1996; Cornish, Bramble, Munir & Pigram, 1999). Progression in motor development is delayed and adaptive behaviour within the domains of socialisation, communication, daily living skills and motor skills does not appear to show any significant strengths or weakness, although no contrast groups have been employed (Cornish, Munir & Bramble, 1998). Interestingly, strengths seem to be evident within domains, particularly in the communication domain. Most individuals with Cri du Chat syndrome have minimal or no speech (Cornish *et al.,* 1999) and receptive language skills tend to be significantly more developed than expressive and written skills. Receptive language skills are considered a marked strength within the cognitive profile of Cri du Chat syndrome (Cornish *et al,* 1998; Cornish & Munir, 1998). Marinescu *et al.* (1999) found no association between the size of the genetic deletion on 5p and scores on the Vineland Adaptive Behavior Scales (Sparrow, David & Cicchetti*,* 1985); however, individuals with translocations as opposed to deletions have been

found to have a more severe developmental delay, heightened social withdrawal and more autistic-like features (Dykens & Clarke, 1997).

3.3.3. *Challenging behaviour in Cri du Chat syndrome*

Although self-injurious and aggressive behaviour appear to be common behavioural features of Cri du Chat syndrome (Collins & Cornish, 2002; Cornish *et al.,* 1998; Cornish & Pigram, 1996; Dykens & Clarke, 1997), there are very few studies examining prevalence and phenomenology. Using a questionnaire study to examine the prevalence of stereotypy, self-injury and aggressive behaviour in children and young adults, Collins and Cornish (2002) found that 92% of the sample (n=66) exhibited some form of SIB. Other questionnaire studies have found prevalence rates of self-injury to be approximately 70% (Cornish & Pigram, 1996; Dykens & Clarke, 1997). Collins and Cornish (2002) found the most common forms of SIB to be head banging, hitting the head against body parts and self-biting. In a recent questionnaire study, Arron *et al.* (in review) found SIB to be present in 76.8% of the sample and common topographies included pulling self, hitting self with objects, hitting self with body and rubbing or scratching self.

Cornish and Pigram (1996) found the prevalence of aggressive behaviour in a sample of 27 individuals with Cri du Chat syndrome to be 52%. Collins and Cornish (2002), found a higher occurrence with 88% of the sample exhibiting aggressive behaviour and the most common topographies were hitting, pulling hair, biting and pinching. Arron *et al.* (in review) found aggressive behaviour to be present in 70% of the sample, with an odds ratio of 2.7 compared to a matched contrast group. Currently, there are no observational studies that have examined challenging behaviour in Cri du Chat syndrome. In addition, there are no studies that have

examined the correlates of challenging behaviour in Cri du Chat syndrome even though the syndrome is known to be associated with some risk markers for the development of challenging behaviour (e.g. severe level of intellectual disability, expressive communication impairments).

3.4. Cornelia de Lange Syndrome

3.4.1. *Cause, prevalence and physical characteristics of Cornelia de Lange syndrome*

Cornelia de Lange syndrome is a rare congenital syndrome that was first described by Brachmann in 1916 and the Dutch paediatrician, de Lange in 1933. Prevalence estimates for the syndrome range from between 1 in 10,000 and 1 in 50,000 live births (Beck, 1987; Optiz, 1985). To date, three genetic mutations have been identified as causing Cornelia de Lange syndrome. It is estimated that approximately half of all affected individuals have a mutation in the NIPBL gene located at located at 5p13.1 (Tonkin, Wang, Lisgo, Bamshad & Strachan, 2004). In addition, Deardorff *et al.* (2007) have found that mutations of the SMC3 gene on chromosome 10 and X-linked SMC1A gene account for a further 5% of affected individuals. Mutations in the SMC1A and SMC3 genes result in a milder phenotype than mutations in the NIPBL gene (Deardoff *et al.,* 2007). Genetic causes of Cornelia de Lange syndrome have only recently begun to be understood, so most diagnoses of the syndrome are made based on its clinical features which are typically quite distinctive.

There are a number of distinct facial features associated with Cornelia de Lange syndrome which include a long and prominent philtrum, arched and confluent eyebrows, long eyelashes, widely spaced teeth, thin lips, a broad nasal bridge, low set ears and anteverted nostrils (Ireland, Donnai

& Burn, 1993; Jackson, Kline, Barr & Koch, 1993; Kline *et al.,* 2007). Three-dimensional facial imaging has shown that the facial characteristics and facial profile present in individuals with a known NIPBL mutation ('classic Cornelia de Lange syndrome') are different to both a comparison group of individuals without the syndrome and individuals who have a diagnosis Cornelia de Lange syndrome due to a different genetic mutation (Bhuiyan *et al.,* 2007). Other physical characteristics include low birth weight, delayed growth and short stature, microcephaly, excessive hair growth and small hands and feet (Kline *et al.,* 2007; Jackson *et al.,* 1993). Severe limb abnormalities are also present in approximately 25-30% of individuals affected (Jackson *et al.,* 1993).

There are many health problem associated with Cornelia de Lange syndrome and gastrointestinal problems are the most commonly reported. Difficulties with the upper gastrointestinal tract, including the oesophagus, stomach and upper small intestine are common. The most prevalent gastrointestinal problem is gastroesophageal reflux, which is thought to be present in 65% of individuals with the syndrome (Hall, Arron, Sloneem & Oliver, 2008; Luzzani, Macchini, Valade, Milani & Selicorni, 2003). Other common health problems include ocular abnormalities, nasal problems, cardiac abnormalities, bone and joint problems, hearing loss and chronic otitis media (Berg, Arron, Burbidge, Moss & Oliver, 2007; Hall *et al.,* 2008; Hawley, Jackson & Kurnit, 1985; Jackson *et al.,* 1993; Kline *et al.,* 2007)

3.4.2. *Cognitive and behavioural characteristics of Cornelia de Lange syndrome*

Most individuals with Cornelia de Lange syndrome have a moderate to profound level of intellectual disability (Kline *et al.,* 1993; 2007), however, there have been some reports of

individuals with Cornelia de Lange syndrome who have cognitive abilities within the normal range (Cameron & Kelly, 1988; Gadoth, Lerman, Garty & Shmuelewitz, 1982). Communication deficits are common, all individuals have delayed speech development and many never develop verbal communication (Sarimski, 1997; Goodban, 1993). Using a questionnaire study to investigate communication in Cornelia de Lange syndrome, Sarimski (1997) found that 85% of children in the sample (N=27) were non-verbal, however, many of the older children were able to utilise non-verbal communication. More recently, Basile, Villa, Selicorni and Molteni (2007) found that fourteen out of 56 individuals with Cornelia de Lange syndrome aged between one and 31 years showed no verbal or non-verbal acts of intentional communication. After evaluating 116 individuals with Cornelia de Lange syndrome, Goodban (1993) noted that the observed delay in language and communication development was a specific feature of the syndrome and was independent from level of intellectual disability.

There is substantial variability in behaviour in Cornelia de Lange syndrome, however, a number of behavioural characteristics have been associated with the syndrome, including hyperactivity, autistic features and stereotyped and repetitive behaviours (Berney, Ireland & Burn, 1999; Hyman & Oliver, 2001; Hyman, Oliver & Hall, 2002; Moss *et al.,* 2008; Moss, Oliver, Arron, Burbidge & Berg, 2009). Using standardised diagnostic assessments for Autism, Moss *et al.* (2008) found that more individuals with Cornelia de Lange syndrome (61.8%) reached the diagnostic cut-off for ASD compared to a matched comparison group of individuals with Cri du Chat syndrome (39.2%). Examining in detail the specific impairments, the authors suggested that impairments in communication and socialisation were most common. Difficulties with socialisation might be accounted for by social anxiety which suggests a more atypical autistic

profile in the syndrome. Oliver, Arron, Sloneem and Hall (2008) also found that individuals in their sample demonstrated an increased likelihood of showing autistic-like behaviours and according to the Childhood Autism Rating Scale (CARS), were more likely to be classified as 'severely autistic' (32%) than a matched comparison group (7%). Bhuiyan *et al.* (2007) found 89% (n=17) of their sample met criteria for ASD, whilst 37% (n=7) met the criteria for Autism. Autistic traits were more common in participants with the lowest levels of adaptive functioning and so it remains uncertain whether autistic features in Cornelia de Lange syndrome are confounded by low levels of adaptive functioning. There is also some recent evidence to suggest that autistic characteristics in the syndrome are associated with SIB (Oliver *et al.,* in review). Further examination of the this association is needed due to concerns around the psychometric properties of the Gilliam Autism Rating Scale (GARS; Gilliam, 1995) which was used to measure ASD. In addition, the literature reveals further risk markers in the syndrome that have been found to be associated with the development of challenging behaviour such as communication deficits and poor mobility (Deb *et al.,* 2001; McClintock *et al.,* 2003; Rojahn *et al.,* 2004) which warrant further investigation.

3.4.3. *Challenging behaviour in Cornelia de Lange syndrome*

SIB is commonly regarded as being part of the behavioural phenotype of Cornelia de Lange syndrome and since the 1970's has been reported as a clinically significant problem (Bryson, Sakati, Nyhan & Fish, 1970; Johnson, Ekman, Friesen, Nyhan & Shear, 1976). Prevalence rates for SIB from questionnaire studies range from sixteen (Beck, 1987) to 63% (Hyman *et al.,* 2002). The highest reported prevalence rate by Gualtieri (1990, as cited by Basile *et al.,* 2007) indicated that 75% of their sample (n=88) displayed self-injury (however these findings have not been peer

reviewed). Arron *et al.* (in review) found that SIB was significantly higher in individuals with Cornelia de Lange syndrome (70% of sample) compared to a comparison group of individuals with intellectual disability of mixed aetiology (27%). However, a recent study by Oliver, Sloneem, Hall and Arron (2009) found that clinically significant self-injury was not more prevalent in Cornelia de Lange syndrome when compared to a matched comparison group. Oliver *et al.* found that mild or proto-injurious behaviours directed towards the hands, body and head were more prevalent in the Cornelia de Lange syndrome group.

The first study to report topographies of self-injury by Shear and colleagues (1971) noted that the two boys studied both bit their lower lip and picked at their chest, chin and face. Beck (1987) found very similar topographies in another six participants. More recent questionnaire studies suggest that individuals with Cornelia de Lange syndrome manifest a variety of self-injurious behaviours. However, biting and scratching tend to be the most prevalent forms (Berney *et al.,* 1999; Sarimski, 1997). In an observational study using a sample of 56 participants, Basile *et al.* (2007) found that those individuals with a 'classical' phenotype were more likely to display SIB, as were older participants and those with a lower cognitive level.

Observations of individuals with Cornelia de Lange syndrome have shown that individuals who self-injure may seek restraint and there is distress evident when physical restraints are removed (Dosseter *et al.,* 2001; Shear, Nyhan, Kirman & Stern, 1971). There is also evidence to suggest that individuals with severe intellectual disability and SIB may show self-restraint behaviours in an attempt to resist compulsive SIB (Basile *et al.,* 2007; King, 1993; Powell, Bodfish, Parker, Crawford & Lewis, 1996). Hyman *et al.* found that 53% of individuals with Cornelia de Lange

syndrome showed at least one form of self-restraint. The most common forms included holding onto other people to seek restraint, holding or squeezing objects, wrapping oneself in clothing and holding hands together. The association between SIB and self-restraint was significant and those individuals showing SIB and self-restraint were significantly more likely to display compulsions. This was the first study to examine the phenomenon of self-restraint within the syndrome and suggests that for some individuals with Cornelia de Lange syndrome, SIB may have taken on a compulsive-like quality which may lead to self-restraint as a method of bringing the behaviour under control.

The literature reveals compulsive behaviours, repetitive behaviours, proto-self-injurious behaviour and self-restraint to be common in Cornelia de Lange syndrome; this alludes to the potential role of the basal ganglia in regulation of these behaviours. Compulsive behaviours which are typically defined as repetitive, intentional behaviours have been linked to alterations in basal ganglia function (Lewis & Bodfish, 1998; Lewis, Tanimura, Lee & Bodfish, 2007) and specifically in basal ganglia dopamine levels (Schroeder *et al.,* 2001). Reduced basal ganglia volumes have been reported in patients with compulsive self-injury, and neurochemical studies have indicated reduced levels dopamine in Lesch-Nyhan syndrome, a syndrome commonly associated with high rates of SIB (O'Sullivan, *et al.,* 1997).

There are few studies examining the prevalence of aggression in Cornelia de Lange syndrome and the findings from these studies lack consistency. Hyman *et al.* (2002) found that 43% of their sample of 88 individuals had displayed physical aggression in the last month and Berney *et al.* (1999) found that 49% of their sample (N=49) showed one form of aggression (either vocal or

physical) on a daily basis, and this was strongly associated with the presence of autistic behaviours. In contrast, Basile *et al.* (2007) found that only 20% of their sample displayed aggressive behaviour, a similar prevalence to that found in the total population of people with intellectual disabilities (Emerson *et al.,* 2001). Oliver *et al.* (2009) also found the prevalence of aggression in Cornelia de Lange syndrome group (40% of the sample) to be lower than a matched contrast group of individuals with intellectual disability of mixed aetiology.

3.5. Individual characteristics associated with challenging behaviour

As discussed in the syndrome reviews (Sections 3.2-3.4), in addition to the prevalence of challenging behaviour being raised in many genetic syndromes, there are a number of individual characteristics that correlate with the presence of challenging behaviour. These are commonly referred to as risk markers and include increasing levels of intellectual disability and age (Deb *et al.,* 2001; McClintock *et al.,* 2003; Rojahn *et al.,* 2004). These factors are also common in people with genetic syndromes (Dykens *et al.,* 2000) and so it is important in behavioural phenotype research to assess and control for these factors so that syndrome specific patterns can be identified. The three syndrome groups in this study will be comparable on level of intellectual disability, age, mobility and speech. The study will investigate the association between challenging behaviour and level of intellectual disability and age, as well as exploring the association between challenging behaviour and a number of risk marker that have been previously identified in the literature such as repetitive behaviour and autistic characteristics (Arron *et al.,* in review; Hyman *et al.,* 2002). The relationship between positive and negative affect and challenging behaviour is also of interest given the differing profiles of sociability within the syndromes.

Of additional interest is the positive association between pain and health problems and rates of challenging behaviour (Breau *et al.,* 2003; Carr & Blakeley-Smith, 2006; Carr & Owen-DeSchryver, 2007; Carr, Smith, Giacin, Whelan & Pancari, 2003; O'Reilly, 1997; Oberlander & Symons, 2006). For example, Carr and Owen-DeSchryver (2007) showed that the level of problem behaviour (SIB, aggression, property destruction, stereotypic behaviour and tantrums) in a group of children with moderate to severe intellectual disabilities was significantly higher on 'sick days' rather than 'well days'. The 'sick days' indicated a time in which the individual was experiencing pain. Further, the higher the level of pain, the greater the frequency and intensity of problem behaviour. As pain is a subjective experience, reliance is often placed on self-report to identify its presence. For individuals with an intellectual disability, dependence on self report is problematic as many individuals may be unable to identify and verbally communicate the pain that they are experiencing. Breau, McGrath, Camfield & Finley (2002) developed the Non-Communicating Child Pain Checklist (NCCPC) in an attempt to overcome the problem of self-report. The NCCPC is an observational checklist of items generated through semi-structured interviews with primary caregivers.

One health issue known to cause pain and discomfort is gastroesophageal reflux (Locke, Talley & Fett, 1997) and as noted in the syndrome reviews, gastroesophageal reflux is known to be common in Cornelia de Lange syndrome and during infancy in Cri du Chat syndrome (Collins & Eaton-Evans, 2001; Luzzani *et al.,* 2003). In Cornelia de Lange syndrome, an association between gastroesophageal reflux and SIB has been demonstrated (Luzzani *et al.,* 2003). For this reason the associations between challenging behaviour and pain, health and gastroesophageal reflux will be explored. Further understanding about the nature of, and influences on challenging

behaviour in genetic syndromes may provide information about causal mechanisms underlying challenging behaviour.

3.6. Summary

From reviewing the literature it is clear that challenging behaviour within in Angelman, Cri du Chat and Cornelia de Lange syndromes warrants further investigation. Although the syndromes are comparable on level of intellectual disability, it is interesting that the profile of challenging behaviour in the groups is somewhat different. In Angelman syndrome, many studies have made reference to aggressive behaviour however there have been very few empirical studies. Studies by Summers *et al.* (1995) and Strachan *et al.* (2009), suggest that hair pulling and grabbing may be common topographies of aggressive behaviour in Angelman syndrome. However, neither of the studies utilised a comparison group and the findings warrant clarification with a larger sample of individuals. Given that heightened sociability has been frequently reported in Angelman syndrome (Horsler & Oliver, 2006a; Richman *et al.,* 2006) and there is evidence that aggressive behaviour may be maintained by social attention (Strachan *et al.,* 2009), the relationship between affect and challenging behaviour will be explored. SIB does not appear to be more common in Angelman syndrome than in the intellectual disabled population as a whole. In Cri du Chat syndrome, the data on the prevalence and phenomenology of SIB and aggression have been generated from a small number of questionnaire studies. From these studies, prevalence rates of SIB in Cri du Chat have been estimated to be between 70% and 92% and commonly reported topographies include head banging, hitting the head against body parts and self-biting. The prevalence of aggressive behaviour has been estimated at between 52% and 88% and common topographies include hitting, hair pulling, biting and pinching. Therefore, it appears that both

self-injurious and aggressive behaviour may be common in Cri du Chat syndrome. In Cornelia de Lange syndrome, SIB has commonly been reported as being part of the behavioural phenotype and the literature suggests that a range of topographies may be observed. A recent study by Oliver *et al.* (2009) found no difference between a Cornelia de Lange syndrome group and a matched control group on the prevalence of clinically significant SIB. However, the Cornelia de Lange syndrome group displayed more potentially injurious behaviours. The more rare forms of proto-injurious behaviour need to be further studied to examine the distinctiveness in the expression of SIB in Cornelia de Lange syndrome relative to other syndromes. Although there is some lack of consistency in the literature regarding aggressive behaviour in Cornelia de Lange syndrome, it would appear that it is less common than in the total population of people with intellectual disabilities.

3.7. Aims

Despite the increased prevalence of challenging behaviour in Angelman, Cri du Chat and Cornelia de Lange syndromes, there is a paucity of research that delineates the phenomenology using comparisons across syndromes. In addition, there are very few robust direct observational studies using operationally defined behaviours. Therefore, the first aim of this chapter is to conduct a comparison of the phenomenology of challenging behaviour within Cornelia de Lange, Cri du Chat and Angelman syndromes. It is also important to note that all three syndromes are associated with risk markers for the development of challenging behaviour. Individual characteristics such as level of ability, age and communication deficits have been found to be predictive of challenging behaviour (McClintock *et al.,* 2003; Oliver, Murphy & Corbett, 1987; Powell *et al.,* 1996), as have other more syndrome specific factors such as repetitive behaviour,

autistic characteristics, affect, health conditions, pain, discomfort and gastroesophageal reflux. For this reason, the second aim of this chapter is to study the relationship between these participant characteristics and challenging behaviour in the syndromes.

3.8. Hypotheses

The study has two specific hypotheses:

1. The proportion of participants displaying SIB will be greater in the Cornelia de Lange syndrome groups than in the Cri du Chat or Angelman syndrome groups.
2. The proportion of participants displaying aggressive behaviour will be greater in the Angelman syndrome group than in the Cri du Chat or Cornelia de Lange syndrome groups.

3.9. Method

3.9.1. Context of the study

The study was conducted as part of a wider project carried out in collaboration with the Institute of Psychiatry, King's College London and Bangor University, Wales. The project was funded by the Big Lottery. In addition to exploring behaviour within the three syndrome groups, other aims of the project included exploring family adjustment and parental well-being.

3.9.2. Ethical Review

The project was reviewed by the School of Psychology Human Research Ethics Committee at all three research bases: The University of Birmingham, King's College London and Bangor University, Wales (Ethical approval letters can be found in Appendix C).

3.9.3. Recruitment

Families that were recruited for this study had previously agreed to have their details held on password protected databases, managed by Prof. Chris Oliver at the University of Birmingham and to be contacted directly by the research team with information about future research studies conducted by members of the team. From these databases, individuals with Cornelia de Lange syndrome (database N = 186), Cri du Chat syndrome (database N = 68), and Angelman syndrome (database N = 124) aged between two and nineteen years were identified based on informant responses to two items on the Challenging Behaviour Questionnaire (CBQ; Hyman *et al.,* 2002) that were completed as part of a previous research study (Oliver *et al.*, in review). The CBQ is a brief informant based questionnaire evaluating the presence or absence of self-injury, physical aggression, verbal aggression, destruction of property and inappropriate vocalisations over the last month. Previous examination of the psychometric properties of the questionnaire has demonstrated good inter-rater reliability with reliability coefficients ranging from .61 to .89 (Hyman *et al*., 2002). Identification of potential participants required endorsement of either or both of the following questions:

1) Has the person shown self-injurious behaviour in the last month? (e.g. head banging, head-punching or slapping, removing hair, self-scratching, body hitting, eye poking or pressing).
2) Has the person shown physical aggression in the last month? (e.g. punching, pushing, kicking, pulling hair, grabbing other's clothing).

In total 136 potential participants were identified (Cornelia de Lange syndrome (N=45), Angelman syndrome (N= 58) and Cri du Chat syndrome (N=33)). Of these, seventeen were

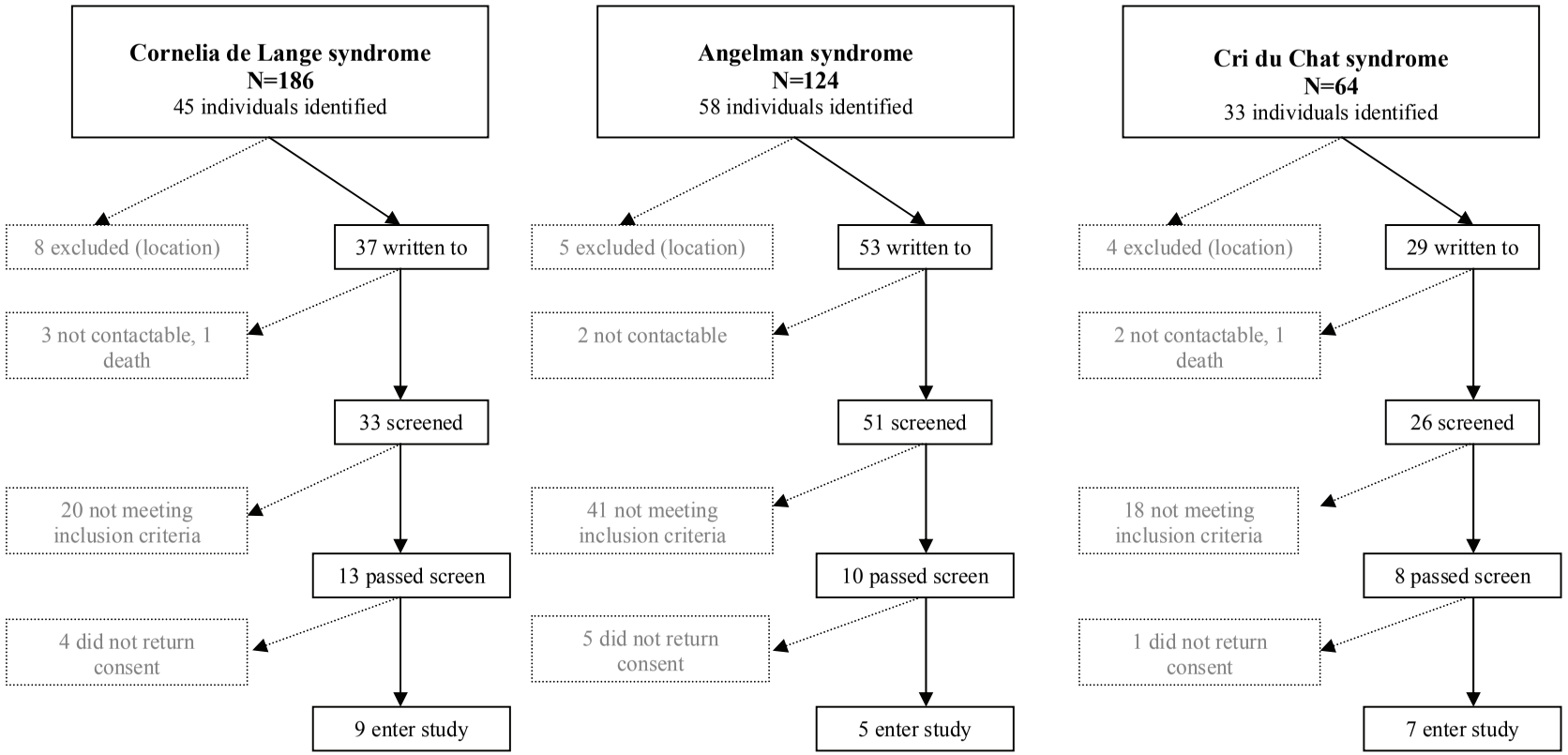
excluded due to distance from the three research bases and thus 119 potential families were contacted directly with information about the study (initial contact letters and information sheets are shown in Appendix D). Telephone contact to the selected parents and caregivers was made within seven days of sending initial information sheets and potential participants were screened over the phone. Telephone screening was conducted in order to ensure that families received all necessary information about the study and that potential participants met criteria for inclusion into the study. Inclusion criteria were as follows:

1) The participant had a confirmed clinical or genetic diagnosis of Angelman, Cri du Chat or Cornelia de Lange syndrome.
2) The participant was aged between two and nineteen years.
3) The participant was reported to engage in self-injurious behaviour and/or aggression at least once a day.

Seven families could not be contacted due to incorrect address details and two individuals had died. Of the 110 participants that were screened, 31 (28%) met inclusion criteria for the study and these families were sent a background questionnaire, information and consent forms to return (Appendix E). Separate consent forms and information sheets were sent to families depending upon whether their child or person they cared for was aged between two and fifteen or sixteen and over. For children aged up to and including fifteen years, parental/ guardian consent was received, however for individuals over the age of sixteen, consent forms comprised of two sections: one for children over the age of sixteen who were unable to provide consent and a section for those children who were over sixteen and able to consent themselves (Appendix E).

Of the 31 families who were sent information following the screening procedure, 21 (68%) returned consent and entered the study. Families that were not on the research database or who had not previously taken part in research were invited to take part via flyers (Appendix F) which were mailed to them by the syndrome support groups. The flyers were also posted on the syndrome support groups' websites, in newsletters and were distributed at family conferences. There were 37 families who contacted the research team directly after having seen the flyer and of these, 26 (70%) potential participants met inclusion criteria following the screen. Of these, 23 (88%) returned consent and entered the study. In addition, fourteen participants were recruited at family conferences and two were recruited from Ireland due to the location of a family conference. Figure 3.1 provides a summary of the recruitment procedure.

Active recruitment: Direct contact following identification of participants from database



Indirect recruitment	**Cornelia de Lange**	**Angelman**	**Cri du Chat**
• Response to leaflets	7	12	4
• Recruitment at conferences	4	3	7
• Ireland recruitment	0	0	2
TOTAL	**20**	**20**	**20**

Figure 3.1: Summary of recruitment procedure

3.9.4. Procedure

After having received consent forms and background questionnaires, a phone call was made to each family to arrange the following stages of the study. The participant's main caregiver was asked to inform their child's/ person they care for's teacher or key worker that the child was taking part in the study, and letters and information sheets were sent to teachers introducing them to the project. Following this, a series of phone calls were made to both teachers and main caregivers to arrange a mutually convenient date to visit the participant for two consecutive days in school and to conduct a home visit after the school day. Visits were typically organised two to four weeks prior to the visit date to give main caregivers time to complete the questionnaire pack that was mailed to them along with the visit confirmation letter. The Vineland Adaptive Behavior second edition (VABS II, Sparrow, Cicchetti & Balla, 2005) was administered via a telephone interview with parents/ carers prior to the research visit.

Out of the total of 60 participants, 57 were visited in school by two researchers. For three participants, home visits were made as they had not yet reached school age. Direct observations were carried out in an empty room in the participant's school and two researchers were present at all times. After the school day, researchers made a visit to the participant's home to conduct the Challenging Behaviour Interview (CBI; Oliver *et al.,* 2003a; Section 3.9.6.3) with main caregivers. For five participants, interviews were not conducted due to limitations on time on the day of the visit. For these five participants, attempts were made to conduct the interview by phone but with no response. Questionnaire packs were also collected at this point. If the questionnaires had not been completed by the date of the visit, stamp-addressed envelopes were left with families so that they could return them via post. If the questionnaires were not returned

within two weeks of the research visit, prompt phone calls were made. A maximum of four prompt attempts were made to obtain the questionnaires. Despite the researcher's best efforts, questionnaire packs were not returned for nine participants. Following the coding of the observational data (Section 3.6.7.1), detailed feedback reports were sent to each family within eight weeks of the final research visit. The feedback reports outlined observations from the research visits as well as recommendations around managing challenging behaviour (an anonymous feedback report can be found in Appendix G).

3.9.5. Participants

Table 3.1 presents information regarding the age, gender, speech and mobility of participants within each syndrome group. This demographic information was collected via the background questionnaire (Background questionnaire is shown in Appendix E). Statistical comparison of the groups using ANOVAs and chi-square tests showed that there were no significant differences between the groups for age, gender, speech and mobility.

Table 3.1: Information regarding the age, gender, speech and mobility of participants.

		Cornelia de Lange n=20	**Cri du Chat n=20**	**Angelman n=20**	**F/ χ^2 (df)**	***p***
Age (in years)	Mean	12.09	9.00	10.43	2.56 (2)	.087
	(SD)	(3.39)	(4.75)	(4.72)		
	Range	*6.13-18.52*	*2.09-16.78*	*3.04-18.54*		
Gender	n (male)	10	4	10	5.00 (2)	.082
	% male	(50)	(20)	(50)		
Speech	n (verbal)	4	11	2	10.88 (2)	.486
	% verbal	(20)	(55)	(10)		
Mobility	n (mobile)	9	13	13	2.91 (4)	.572
	% mobile	(45)	(65)	(65)		

Table 3.2 presents information regarding adaptive behaviour within each syndrome group (calculated from the VABS II, Sparrow *et al.,* 2005). A series of one-way ANOVAs assessing group differences in adaptive behaviour revealed significant main effects of group (at a level of $p < .05$) on all three domains (communication, daily living skills and socialisation) and on the Adaptive Behavior Composite score. Post-hoc comparisons indicated that individuals with Cri du Chat syndrome scored significantly higher than individuals with Cornelia de Lange syndrome on all domains and on the Adaptive Behaviour Composite. The Cri du Chat syndrome group scored significantly higher than Angelman syndrome group on the communication domain total score and the Adaptive Behavior Composite. All 60 participants were classified as having a low level of adaptive functioning as calculated from the Adaptive Behavior Composite score.

Table 3.2: Information regarding adaptive behaviour of participants.

	Cornelia de Lange n=20	Cri du Chat n=20	Angelman n=20	F (df)	*p*	Post-hoc
Adaptive behaviour Communication[1]	38.68 (11.31)	54.25 (10.25)	40.95 (10.46)	12.26 (2)	<.001	CdC> CdLS, AS
Receptive[2]	3.90 (3.21)	7.70 (2.27)	5.55 (3.0)	8.80 (2)	<.001	CdC> CdLS
Expressive[2]	6.42 (17.17)	5.96 (2.28)	3.44 (1.95)	.47 (2)	630	-
Written[2]	5.0 (1.45)	6.67 (2.06)	5.61 (2.36)	3.33 (2)	.044	CdC> CdLS
Daily living skills[1]	37.70 (9.96)	49.15 (8.65)	39.95 (11.37)	7.28 (2)	.002	CdC> CdLS
Personal[2]	2.58 (2.22)	4.4 (2.09)	3.39 (2.26)	3.46 (2)	.039	CdC> CdLS
Domestic[2]	4.42 (2.17)	6.6 (2.52)	5.28 (2.63)	3.99 (2)	.024	CdC> CdLS
Community[2]	3.47 (1.68)	6.10 (2.49)	4.61 (2.40)	6.86 (2)	.002	CdC> CdLS
Socialisation[1]	44.25 (10.97)	57.60 (9.24)	47.85 (10.64)	8.98 (2)	<.001	CdC> CdLS
Interpersonal[2]	3.74 (1.94)	7.05 (1.93)	5.17 (2.0)	14.06 (2)	<.001	CdC> CdLS
Play and Leisure[2]	4.32 (3.29)	6.55 (2.24)	4.67 (2.59)	3.78 (2)	.029	CdC> CdLS
Coping[2]	6.21 (1.44)	7.90 (1.90)	6.44 (1.38)	6.53 (2)	.003	CdC> CdLS
Adaptive Behaviour Composite[1]	36.65 (10.23)	47.90 (9.24)	36.95 (8.91)	9.15 (2)	<.001	CdC> CdLS, AS

[1] Standard scores from VABS II (Sparrow, Cicchetti & Balla, 2005). [2] V-Scale scores from VABS II (Sparrow *et al.,* 2005).

3.9.6. Measures

3.9.6.1. Measure of Ability: The Vineland Adaptive Behavior Scales Second Edition (VABS II; Sparrow *et al.,* 2005).

The VABS II was conducted over the phone with parents or legal guardians in order to assess each participant's personal and social adaptive behaviour levels and level of intellectual disability. The VABS-II is a semi-structured interview that is suitable for use with individuals with or without intellectual disability. The interview comprises 261 items divided into four domains (Communication, Daily Living Skills, Socialisation and Motor skills). Each domain is divided into three sub domains. The optional maladaptive behaviour domain was excluded from this study as these behaviours were being assessed by other measures. The interviewer asks open-ended questions to obtain information about the individual being rated. Scores are based on what a person habitually does, not what he or she can do and an overall Adaptive Behavior Composite score may be derived. The Adaptive Behavior Composite score for the current study was based on three domains (motor domain was excluded) for all participants. As the motor domain is only calculated for children under the age of seven, the domain was excluded so that composite scores for those groups with more children under seven years were not over-inflated. Sparrow *et al.* (2005) report internal consistency ranges from .83-.94 for each of the domains and .69-.89 for the sub domains. The measure is also associated with high test-retest reliability with levels of agreement ranging from .80 to .95.

3.9.6.2. Questionnaire Measures:

Two questionnaire booklets were completed by the participant's main caregiver. The first questionnaire was a background booklet (Appendix E) that consisted of demographic questions.

Demographic information was collected regarding the participant's chronological age, gender, mobility (able to walk unaided), verbal ability (more than 30 signs or words) and diagnostic status (the precise diagnosis made, when and by whom).

The second questionnaire booklet comprised measures to assess challenging behaviour, repetitive behaviour, health, pain and gastroesophageal reflux and was completed by the participant's main caregiver. Although the content of the questionnaire pack was the same, it was made syndrome specific and the Angelman syndrome pack is shown in Appendix H.

3.9.6.2.1. Assessment of Autistic phenomenology: Social Communication Questionnaire (SCQ; Rutter, Bailey, Berument, Lord & Pickles, 2003).

The SCQ is a 40-item informant questionnaire that screens for the behaviours and features of communication and social interaction that are associated with ASD. The SCQ provides a dimensional measure of ASD symptomatology with a cut-off score that can be used to indicate the likelihood that an individual has Autism or ASD. Items relate to three different domains: the Reciprocal Social Interaction Domain, the Communication Domain and the Restricted, Repetitive and Stereotyped Patterns of Behavior Domain. Total scores range from 0 to 39 (the item on current language level is not included in the summary score); the maximum possible score on the Communication, Social Interaction, and Repetitive Behavior domains are twelve, fifteen and eight respectively. Rutter *et al.* suggested a cut-off of fifteen for ASD and 22 for Autism. Only the current form of the SCQ, which is completed with reference to the individual's behaviour during the most recent three month period, was employed in this study. All items on the SCQ require a yes/no response. A score of one is given for the presence of abnormal behaviour and a

score of 0 for its absence. The internal consistency of the SCQ is good with an alpha coefficient of .90 for the total scale.

3.9.6.2.2. Assessment of Health: The Health Questionnaire (Hall *et al.,* 2008).

The Health Questionnaire measures the presence and severity of fifteen health problems. Informants are asked to rate the presence and severity (0= never occurred to 3= severe problem) of health problems that have ever occurred in the person's life and those that have occurred 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.

Inter-rater reliability for The Health Questionnaire has been obtained with a sample of 24 individuals (Hall *et al.,* 2008). 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 Score and for the total number of health problems, over the last month or during the persons life, were .65 and .73, and .71 and .68 respectively.

3.9.6.2.3. Assessment of Gastroesophageal Reflux: The Gastroesophageal Distress Questionnaire (GDQ; Oliver & Wilkie, 2005).

The Gastroesophageal Distress Questionnaire (GDQ) is a questionnaire that has been developed to measure behavioural correlates of gastroesophageal reflux in children and adults with a range of intellectual disabilities. The GDQ consists of seventeen items that assess whether an individual has showed specific behaviours indicative of reflux in the last two weeks. Items one to twelve

require that the informant rate how often each of the behaviours has occurred in the last two weeks on a five-point Likert scale ranging from 'not occurred' (0) to 'occurred more than once an hour' (4). Three additional items are answered using a four point Likert scale ranging from 'never' to 'every night / all day everyday' and two items are answered on a yes/no basis. Indicators of reflux are deemed clinically significant if they occur at least once daily and thus a total number of clinical indicators can be calculated from items 1-17. Preliminary data on the psychometric properties suggest that inter-rater reliability is good at item level, ranging from .24 to .82, with a mean range of .58 (Oliver & Wilkie, 2005).

3.9.6.2.4. Assessment of pain: Non-Communicating Children's Pain Checklist-Revised (NCCPC-R, Breau *et al.,* 2002).

In order to examine the presence of pain and discomfort across the three groups the Non-Communicating Children's Pain Checklist (NCCPC-R, Breau *et al.,* 2002) was completed. The NCCPC-R contains 30 items across seven subscales reflecting different indicators of pain: vocal, social, facial, activity, body and limbs, physiological and eating and sleeping. Items require the informant to rate on a four-point Likert scale ('not at all' (0) to 'very often' (3)), how often the child has shown the behaviours in the last week. Items one to 30 are summed to give a total pain score. The authors report good internal consistency (Alpha= .93), test-retest reliability (no significant difference in items endorsed across two assessments), significant discriminant validity between 'pain' and 'no pain' assessments and good concurrent validity (Pearson's correlation values: .2 to .5). The checklist asks caregivers to rate the presence of the 30 indicators over the previous week.

3.9.6.3. Interviews

Interviews assessing challenging behaviour were conducted at home with the participant's main caregiver.

Challenging Behaviour Interview (CBI; Oliver *et al.,* 2003a)

The Challenging Behaviour Interview (CBI) was administered to main caregivers. The CBI assesses the form and severity of challenging behaviours displayed by people with intellectual disabilities. Part one identifies the topographies of challenging behaviour that have been displayed in the last month. In part two, for each behaviour identified, fourteen questions are asked about the characteristics of the behaviour such as frequency, duration, response necessary to manage the behaviour and the effects of the behaviour on others. Items in part two are summed to obtain a total severity score. If self-injury or aggression for a given participant was identified in part one of the CBI, part two was completed for the relevant behaviour and a severity score obtained. For those participants who scored 'present' for both self-injurious and aggressive behaviour in part one, part two of the CBI was completed twice (once for each behaviour). Where behaviour was identified as 'absent' in part one, a severity score of zero was recorded. Inter-rater reliability for the overall severity is reported to be .69 with a Pearson's correlation coefficient of .90 for test-retest (Oliver *et al.,* 2003a).

3.9.6.4. Direct observations

For each participant, direct observations were made through experimental functional analyses. Section 4.4.2.3 gives details of the experimental functional analysis conditions[1]. All sessions were video-recorded and subsequently coded in real time using the behaviours and operational definitions described in Table 3.3.

3.9.7. Observational data

3.9.7.1. Coding

Observational data were coded using Obswin 32 software (Martin, Oliver & Hall, 2000). Obswin 32 enables behaviours to be recorded as real-time 'durations' in which onset and offset times are recorded. Participant behaviours coded included: self-injury, aggression, destruction and repetitive and communicative behaviours. Environmental variables included adult attention, demands, denials and prompts. Each topography of self-injury and aggression was coded separately to allow fine-grained analysis of phenomenology to be undertaken. Table 3.3 shows a complete list of behaviours coded with operational definitions. Any individual topographies occurring in less than ten participants were not included in the analysis, however, definitions and the number of participants displaying each of these behaviours is shown in Table 3.3.

3.9.7.2. Reliability

A second observer coded 25% of each participant's analogue functional analysis sessions in order to obtain a measurement of inter-observer reliability. Inter-observer reliability was calculated in ten-second intervals using Cohen's Kappa. The mean Kappa value was .68 (range .43-1)

[1] The reader is referred to Chapter 4 in order to avoid repetition of the method.

suggesting that overall reliability was good (Landis & Koch, 1977). It should be noted that not all topographies of behaviour were observed within the inter-observer period, thus Kappa values could not be generated for very infrequent behaviours. Kappa values for all participant and environmental variables can be seen in Table 3.3.

Table 3.3: Direct observation behavioural codes with operational definitions and Kappa reliability values.

Variable	Code	Operational definition of behaviour	Number of participants displaying[1]	Kappa
Challenging behaviours	**Aggressive behaviour**	Physical aggression directed towards another person. Defined specifically for each participant. Variable includes a total of all of the following topographies:	35	.75
	Biting others	Enclosure and clamping down of the teeth onto another person's body.	12	.76
	Eye poking	Abrupt thrust of finger (s) into another person's eye.	1	.89
	Grabbing others	A sudden grasping or clutching motion at another person's body or clothing.	24	.70
	Pulling hair	Grasping and then applying force to another person's hair in order to pull it towards oneself.	21	.73
	Head butting	To strike the forehead against another person.	3	.71
	Hitting others	Quick and forceful movement of the hand to make contact with another person's body.	16	.70
	Kicking others	To strike another person using the foot.	14	.61
	Poking	Abrupt thrust of finger (s) into another person's body. Note, not eye.	1	1.0
	Pulling others	Applying force in order to move another person towards oneself.	2	.67
	Pushing others	Applying force in order to move another person away.	3	.78
	Scratching others	Rapid sweeping movement of the finger nails across another person's body.	9	.76
	Self-injurious behaviour	Non-accidental behaviours that may result in tissue damage. Defined specifically for each participant. Variable includes all of the following topographies:	39	.75

[1] Behaviours occurring in less than ten participants were excluded from analyses.
- indicates where a Kappa value has been unable to be calculated. This occurred for behaviours which were infrequent and thus did not occur in the inter-observer period.

Variable	Code	Operational definition of behaviour	Number of participants displaying	Kappa
Self-injurious behaviours	Arm banging	Forceful movement of the arm to make contact with a surface.	1	.65
	Arm hitting	Forceful movement of hand to make contact with the arm.	1	-
	Back slamming	Forceful movement of the back to make contact with a surface.	6	.50
	Biting self	Enclosure and clamping of the teeth onto one's own body.	9	.79
	Body hitting	Forceful movement of hand to make contact with the body.	2	.69
	Chest hitting	Forceful movement of hand to make contact with the chest.	3	.70
	Face hitting	Forceful movement of hand to make contact with the face.	8	.69
	Finger picking	Removing and scratching at skin on the fingers.	1	.86
	Hair pulling	Grasping and then applying force to one's own hair.	21	1.0
	Hand biting	Enclosure and clamping of the teeth onto one's own hand.	1	-
	Head banging	Movement of head towards and making contact with surface (e.g. tables, wall, floor).	14	.72
	Head hitting	Forceful movement of hand to make contact with the head.	5	.83
	Hitting self	Forceful movement of hand to make contact with one's own body.	3	.80
	Hitting self with object	Forceful movement of an object to make contact with one's own body.	4	.55
	Leg hitting	Forceful movement of hand to make contact with one's leg.	1	.46
	Leg banging	Forceful movement of the leg to make contact with a surface.	1	-
	Lip biting	Enclosure and clamping of the teeth onto one's own lip.	1	.70
	Picking self	Removing and scratching at skin on one's own body.	6	.73
	Pinching self	Squeezing one's own skin tightly with the fingers.	5	.78
	Punching self	Driving of the fist forcibly to make contact with the face or body.	2	.78
	Scratching self	Rapid sweeping movement of the finger nails across another one's own body.	1	-
	Destructive behaviour	Destructive behaviour i.e. tearing, tipping furniture, pulling items off walls, throwing/ swiping items.	52	.67

Variable	Code	Operational definition of behaviour	Number of participants displaying	Kappa
	Combined Challenging behaviour	Combined percentage occurrence of aggressive, self-injurious and destructive behaviour global variables.	53	.72
Stereotyped and repetitive behaviours	Contact stereotypy	Any repetitive movements that involve contact with the body (e.g. chin tapping, hand clapping).	37	.72
	Non-contact stereotypy	Any repetitive movements that do not involve contact with the body (e.g. hand flapping, body rocking and spinning).	42	.71
	Object stereotypy	Non-functional repetitive manipulation of object or surface (e.g. twiddling and twirling objects).	35	.60
	Mouthing	Insertion of any fingers or objects into the mouth (e.g. hand mouth, object mouth, chewing clothing).	36	.74
Affect	Positive affect	Includes laughing and smiling: Any horizontal stretching of the lips, upturning of the corners of the mouth followed by a parting of the lips and viewing of the teeth, this may be accompanied by an inarticulate voiced noise.	58	.61
	Negative affect	Includes negative vocalisations such as crying, moaning and whining. Usually accompanied by a facial expression which includes a lowered mouth and arched eyebrows.	35	.63
Communication	Communication	The conveyance of information from participant to adult. This includes verbal communication (spoken word) and non-verbal communication (signing, pecs, pointing).	34	.61
	Vocalisations	Any inarticulate voiced noise that is not clearly a recognisable word. Non-communicative	53	.63

3.9.7.3. Data reduction

Following coding, individual topographies of self-injurious and aggressive behaviour were combined to form overall categories of global self-injurious and aggressive behaviour. A category of combined challenging behaviour was also created which included all individual topographies of self-injury, aggression and destruction. Similarly, communication, mouthing and negative affect variables were created.

3.10. Data analysis

Observational data

The first approach to data analysis included examining the total percentage duration of participant behaviours in the direct observations across syndrome groups. Statistical analyses were only conducted on behaviours that occurred in ten or more participants. All observational data were checked for normality and homogeneity of variance using box-plots, histograms and Kolmogorov-Smirnov tests prior to analyses. All data were found to be not normally distributed and so Kruskal-Wallis tests were employed when comparing the percentage time that the three independent samples (Angelman, Cri du Chat and Cornelia de Lange syndrome groups) engaged in particular types of behaviour during the direct observations. Where significant differences were identified, pairwise Mann Whitney-U tests were employed for post-hoc comparison. Spearman's correlations were conducted to explore relationships between variables. Alpha levels were set at .05 for exploratory analyses and one-tailed tests were employed for directional hypotheses. All analyses were conducted using the statistical computer package SPSS for windows version 14.

Interview data: *Challenging behaviour interview (CBI; Oliver et al., 2003a)*

The CBI data were found to be not normally distributed and so Kruskal-Wallis non-parametric tests were used to examine challenging behaviour severity across participant groups. Where significant differences were identified, pairwise Mann Whitney-U tests were employed for post-hoc comparison.

Questionnaire data

All questionnaire data were checked for normality and homogeneity of variance. Where data were normally distributed, a series of ANOVAs were used to explore scores across groups. Kruskal-Wallis tests were employed across groups where data was non-normally distributed. Categorical data such as the presence of self-injury and aggression (CBQ) was determined by chi-squared tests.

3.11. Results

3.11.1. Challenging behaviour in the total sample

Participants were recruited for the study based on the presence of self-injury and/or aggressive behaviour. The proportion figures that are presented are therefore relevant to those participants who show one or both of these behaviours. Across the total sample of 60, 54 (90%) participants met inclusion criteria for SIB, whilst 51 (85%) participants met criteria for aggression. In the direct observations, SIB was observed in 39 (72%) of those participants who met initial screening criterion for SIB and the mean percentage duration was 2.88% (SD=6.02) of the time (range: .08-33.91 %). Aggression was observed in 35 (69%) participants of those participants who met initial screening criterion for aggression and the mean percentage duration was 1.9% (SD= 3.68) of the

time (range: .06-18.42%). Mean severity of aggression as assessed by the CBI was 17.56 (SD= 9.54), whilst the mean severity of SIB was 14.90 (SD= 6.49). Combined challenging behaviour, which included SIB, aggression and destruction was observed in 53 (88%) participants and the mean percentage duration was 5.8% (SD= 7.61) of the time (range: .06- 36.32).

3.11.2. The proportion of participants displaying SIB will be greater in the Cornelia de Lange syndrome groups than in the Cri du Chat or Angelman syndrome groups

The first hypothesis predicted that the proportion of participants displaying SIB would be greater in the Cornelia de Lange syndrome groups than in the Cri du Chat or Angelman syndrome groups**.** The first test of this hypothesis was to compare the observational data on challenging behaviour across the three syndrome groups. Table 3.4 shows the number of participants within each syndrome group who displayed aggression, self-injury, destruction and combined challenging behaviour in the direct observations. Table 3.4 also reports median and interquartile ranges for each syndrome group based on the total percentage time spent engaging in the behaviours across the whole observational period. A Kruskal-Wallis test revealed a significant difference between groups on the total percentage time engaged in SIB. Post-hoc analyses revealed that as predicted, the Cornelia de Lange syndrome group engaged in significantly more SIB than the Angelman syndrome group.

Table 3.4: Comparison of challenging behaviour across syndrome groups (total % time from observational data).[1]

		Cornelia de Lange		**Cri du Chat**		**Angelman**		**Kruskal Wallis χ^2**	***p***	**Post-hoc**
		Total % time		Total % time		Total % time				
	Total n displaying behaviour	n	Median *(IQ range)*	n	Median *(IQ range)*	n	Median *(IQ range)*			
Aggression	35	6	0 *(.13)*	12	.46 *(1.91)*	17	1.44 *(5.92)*	16.52	<.001	AS> CdLS
Self-injury	39	16	1.91 *(6.99)*	14	.27 *(1.72)*	9	.04 *(.62)*	10.49	.005	CdLS> AS
Destruction	52	10	.02 *(.23)*	15	.28 *(.41)*	17	.63 *(1.89)*	7.99	.018	AS> CdLS
Combined CB	53	18	2.32 *(6.58)*	17	1.31 *(4.57)*	18	4.01 *(8.73)*	1.68	.430	-

CB= Challenging behaviour

The second test of this hypothesis was to compare the presence of SIB that was reported using the CBQ (Hyman *et al.,* 2002). The CBQ was completed prior to visiting participants to ascertain suitability for the study (Section 3.9.3). The CBQ determines whether self-injury or aggression has occurred in the last month. Table 3.5 shows the proportion of participants within each syndrome group who were reported to engage in self-injurious and aggressive behaviour in the last month. A chi-square test revealed that the proportion of participants who engaged in SIB was significantly higher in the Cornelia de Lange syndrome group than the Angelman syndrome group.

[1] Data in table 3.4 includes scores of zero for those participants who did not display the behaviour. Analysis was also conducted on the data when the zero scores were removed and the same results were generated.

Table 3.5: Presence of challenging behaviour (CBQ definition) across syndrome groups.

Presence		**Cornelia de Lange n=20**	**Cri du Chat n=20**	**Angelman n=20**	χ^2	*p*	**Post-hoc**
	Total N	Present	Present	Present			
Aggression	51	13 (65%)	18 (90%)	20 (100%)	10.19	.006	AS >CdLS
Self-injury	54	20 (100%)	19 (95%)	15 (75%)	7.78	.020	CdLS> AS

3.11.3. The proportion of participants displaying aggressive behaviour will be greater in the Angelman syndrome group than in the Cri du Chat or Cornelia de Lange syndrome groups.

The second hypothesis predicted that the proportion of participants displaying aggressive behaviour would be greater in the Angelman syndrome group than in the Cri du Chat or Cornelia de Lange syndrome groups. The first test of this hypothesis was to compare the total percentage time spent engaging in aggressive behaviour during the direct observations across the groups. A Kruskal-Wallis test revealed a significant difference between groups on total percentage time engaging in aggressive behaviour during the direct observations (Table 3.4). Post-hoc tests revealed that the Angelman syndrome group engaged in significantly more aggressive behaviour than the Cornelia de Lange syndrome group. A Kruskal-Wallis test (Table 3.4) also showed that there was a significant difference between groups on total percentage of time engaging in destructive behaviour with the Angelman syndrome group engaging in significantly more destructive behaviour, than the Cornelia de Lange syndrome group. There were no differences between the groups on combined challenging behaviour.

Eleven forms of aggressive behaviour were coded and of these, five were included in statistical analyses as these were shown by ten or more participants. Table 3.6 shows the most commonly observed forms of aggressive behaviour were biting others, grabbing others, pulling hair, hitting others and kicking others. Table 3.6 shows the number of participants within each group who displayed these forms of aggression as well as the mean and standard deviation for each form of aggression in each syndrome group. A series of Kruskal-Wallis tests revealed significant differences between syndrome groups for the total percentage time engaging in grabbing others and hair pulling. For both behaviours post-hoc comparisons revealed that the Angelman syndrome group engaged in significantly more grabbing and hair pulling than the Cornelia de Lange syndrome group.

Table 3.6: Comparison of topographies of aggressive behaviour across syndrome groups (total % time from observational data).

		Cornelia de Lange		**Cri du Chat**		**Angelman**		**Kruskal Wallis χ^2**	***p***	**Post-hoc**
		Total % time		Total % time		Total % time				
	Total N observed	N	Mean (SD)	n	Mean (SD)	n	Mean (SD)			
Biting others	12	2	.02 (.05)	5	.15 (.33)	5	.29 (.86)	2.02	.363	-
Grabbing others	24	3	.03 (.07)	7	.80 (2.28)	14	1.14 (1.81)	13.05	<.001	AS> CdLS
Pulling hair	21	1	.22 (1.0)	7	.38 (.99)	13	1.14 (1.89)	14.91	<.001	AS> CdLS
Hitting others	16	2	.01 (.05)	6	.15 (.52)	8	.42 (.91)	5.78	.055	-
Kicking others	14	2	.01 (.05)	4	.22 (.77)	8	.54 (1.55)	5.94	.064	-

The second test of this hypothesis was to compare the presence of aggressive behaviour using the CBQ (Hyman *et al.,* 2002). Table 3.5 shows that the proportion of participants displaying aggressive behaviour in the Angelman syndrome group was significantly higher than in the Cornelia de Lange syndrome group.

3.11.4. Severity of challenging behaviour

In addition to the presence of self-injury and aggression, the severity of these behaviours was assessed using the CBI (Oliver *et al.,* 2003a). Those participants who were not reported to display the behaviour received a severity score of zero. Table 3.7 describes the severity scores of each of the groups. A Kruskal-Wallis test revealed that the severity of aggressive behaviour was significantly higher in the Angelman syndrome group than the Cri du Chat and Cornelia de Lange syndrome groups. The severity of SIB was found to be higher in the Cri du Chat syndrome group than the Angelman syndrome group. Following this initial analysis of severity, severity of self-injury and aggression was also examined amongst *only* those participants who were reported to display the target behaviours. In this analysis, there was no difference in the severity of self-injury across the groups; however, the severity of aggressive behaviour was significantly higher in the Angelman syndrome group than in the Cornelia de Lange syndrome group (see Appendix I for this analysis).

Table 3.7: Severity of challenging behaviour assessed by the CBI across syndrome groups.

Severity		**Cornelia de Lange n=17**	**Cri du Chat n=20**	**Angelman n=17**	**Kruskal-Wallis χ^2**	***p***	**Post-hoc**
Aggression	Mean	12.0	17.3	23.44	11.67	.002	AS>CdLS, CdC
	(SD)	(10.55)	(8.34)	(6.13)			
Self-injury	Mean	15.53	17.15	11.65	6.23	.047	CdC>AS
	(SD)	(4.40)	(5.86)	(7.85)			

3.11.5. The relationship between challenging behaviour and participant characteristics across the syndrome groups

The second aim of the study was exploratory in nature and sought to explore the relationship between challenging behaviour and a number of participant characteristics, namely autistic phenomenology, stereotyped and repetitive behaviour, pain, health and gastroeosophageal reflux. Prior to conducting this analysis the participant characteristics were examined across the syndrome groups. Firstly the groups were compared on autistic phenomenology. Table 3.8 presents information regarding autistic phenomenology measured by the Social Communication Questionnaire (SCQ: Rutter *et al.,* 2003).

Table 3.8: Information regarding autistic phenomenology across syndrome groups.

		Cornelia de Lange n=17	Cri du Chat n=17	Angelman n=16	F (df)	*p*	Post-hoc
Communication	Mean	5.88	4.53	5.69	2.67(2)	.08	-
	(SD)	1.69	1.81	1.79			
	Range	*1.0-7.0*	*2.0-8.0*	*1.0-7.58*			
Social Interaction		10.18	6.25	7.69	5.58 (2)	.007	CdLS> CdC
		3.78	3.35	2.91			
		2.0-15.0	*1.0-15.0*	*1.0-13.0*			
Repetitive behaviour		4.53	3.93	4.81	1.28 (2)	.289	-
		1.81	2.05	1.76			
		1.0-7.0	*0-7.0*	*1.0-7.0*			
Total Score		22.47	16.65	19.82	4.87 (2)	.012	CdLS> CdC
		4.65	5.86	5.29			
		15.0-31.0	*10.0-30.0*	*6.0-7.0*			
		Cornelia de Lange	**Cri du Chat**	**Angelman**	**χ^2 (df)**	**p**	**Post-hoc**
ASD cut off	%	100.0	53.3	93.8	12.24 (2)	<.00	CdLS, AS>
	n	20	8	15		1	CdC
Autism cut off	%	52.9	13.3	43.8	5.73	.06	-
	n	8	2	7			

ASD: Autism Spectrum Disorder

As expected, a one way ANOVA revealed a statistically significant difference across syndrome groups on the social interaction domain, with the Cornelia de Lange syndrome group scoring significantly higher than the Cri du Chat syndrome group. There was also a significant difference across groups on the total score, again the Cornelia de Lange syndrome group scored higher than the Cri du Chat syndrome group. There was no significant difference across groups in the number of participants reaching a cut off score for Autism, however, as expected, significantly more individuals in the Cornelia de Lange and Angelman syndrome groups reached a cut off for ASD in comparison to the Cri du Chat syndrome group.

Secondly, stereotyped and repetitive behaviours were compared across groups using the observational data. Table 3.9 presents data from the direct observations on different forms of stereotyped and repetitive behaviour across syndrome groups.

Table 3.9: Comparison of stereotyped and repetitive behaviours across syndrome groups (total % time from observational data).

		Cornelia de Lange		**Cri du Chat**		**Angelman**		**Kruskal-Wallis χ^2**	***p***	**Post-hoc**
		Total % time		Total % time		Total % time				
	Total N observed	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)			
Contact stereotypy	37	11	.70 (1.20)	16	1.03 (2.12)	10	2.79 (10.62)	1.14	.565	-
Object stereotypy	35	8	.46 (1.27)	13	1.17 (2.07)	14	2.79 (4.96)	7.21	.027	AS> CdLS
Non-contact stereotypy	42	14	6.26 (10.70)	14	2.09 (3.12)	14	2.50 (2.97)	.98	6.14	-
Mouthing	36	10	5.04 (8.08)	17	7.19 (7.72)	9	1.18 (2.71)	10.22	.006	CdC> AS

A Kruskal-Wallis test revealed a significant difference across the groups on total percentage time spent engaging in object stereotypy, with the Angelman syndrome group engaging in significantly more object stereotypy than the Cornelia de Lange syndrome group. There was also a difference between groups on total percentage time spent engaging in mouthing, with the Cri du Chat syndrome group engaging in significantly more mouthing than the Angelman syndrome group. There were no significant differences found between the groups on total percentage time spent engaging in contact stereotypy and non-contact stereotypy.

The syndrome groups were next compared on positive and negative affect which had been displayed during the direct observations. Table 3.10 shows data on positive and negative affect across the syndrome groups (based on total percentage time spent engaging during the direct observations).

Table 3.10: Comparison of positive and negative affect across syndrome groups (total % time from observational data).

		Cornelia de Lange		**Cri du Chat**		**Angelman**		**Kruskal Wallis χ^2**	***p***	**Post-hoc**
		Total % time		Total % time		Total % time				
	Total N observed	N	Median *(IQ range)*	n	Median *(IQ range)*	n	Median *(IQ range)*			
Positive affect	58	18	3.98 *(4.90)*	20	4.59 *(10.90)*	20	17.46 *(21.37)*	15.13	.001	AS> CdLS, CdC
Negative affect	35	14	1.51 *(5.64)*	11	.25 *(1.97)*	10	.14 *(1.77)*	2.33	.311	-

A Kruskal-Wallis test found that as predicted, there was a significant difference across the syndrome groups for positive affect, with the Angelman syndrome group spending a significantly longer percentage of time engaging in laughing and smiling (positive affect) than the Cornelia de Lange and Cri du Chat syndrome groups. No differences were found for negative affect.

Table 3.11 shows data on communication across the groups during the direct observations (based on the total percentage time spent engaging during the direct observations). A comparison of communicative behaviours with a Kruskal-Wallis test revealed that there was a significant difference in communication across the groups with the Cri du Chat group spending significantly

more time engaging in communicative behaviours than the Angelman and Cornelia de Lange syndrome groups.

Table 3.11: Comparison of communication across syndrome groups (total % time from observational data).

		Cornelia de Lange		**Cri du Chat**		**Angelman**		**Kruskal Wallis χ^2**	***p***	**Post-hoc**
			Total % time		Total % time		Total % time			
	Total N observed	n	Median *(IQ range)*	n	Median *(IQ range)*	n	Median *(IQ range)*			
Communication	34	6	0 *(3.49)*	16	4.82 *(23.75)*	12	.35 *(4.28)*	10.73	.005	CdC> CdLS, AS

Table 3.12 describes the total pain scores from the NCCPC of each of the groups. A Kruskal-Wallis test showed that there were no significant differences in total pain scores across the groups.

Table 3.12: Comparison of pain across the syndrome groups (total pain score from NCCPC, Breau, *et al.,* 2002).

	Cornelia de Lange n=17	**Cri du Chat n=18**	**Angelman n=16**	**Kruskal Wallis χ^2**	***p***	**Post-hoc**
	Median *(IQ range)*	Median *(IQ range)*	Median *(IQ range)*			
Total pain score	9.0 *(18.5)*	9.0 *(5.50)*	8.5 *(10.25)*	.037	.981	-

Table 3.13 describes the total number of current and lifetime health conditions of each of the syndrome groups. A One-way ANOVA revealed that there were differences across the groups on total number of lifetime and current health conditions. As expected, the Cornelia de Lange

syndrome group had more lifetime and current health conditions than the Cri du Chat or Angelman syndrome groups.

Table 3.13: Comparison of lifetime and current health conditions across the syndrome groups (Health Questionnaire, Hall *et al.,* 2008).

	Cornelia de Lange n=17 Mean (SD)	**Cri du Chat n=18** Mean (SD)	**Angelman n=16** Mean (SD)	**F**	***p***	**Post-hoc**
Lifetime health conditions	17.7 (6.34)	10.05 (4.43)	8.31 (4.21)	16.41	<.001	CdLS> CdC, AS
Current health conditions	7.52 (3.66)	3.78 (2.36)	2.67 (2.94)	11.64	<.001	CdLS> CdC, AS

Lastly, Table 3.14 shows the mean total number of clinical/ behavioural signs of gastroeosophageal reflux for each of the groups. A one-way ANOVA showed that there was no difference across groups in the total number of clinical/behavioural signs of gastroesophageal reflux.

Table 3.14: Comparison of clinical/ behavioural signs of gastroeosophageal reflux across the syndrome groups (GDQ, Oliver & Wilkie, 2006).

	Cornelia de Lange n=17 Mean (SD)	**Cri du Chat n=18** Mean (SD)	**Angelman n=16** Mean (SD)	**F**	***p***	**Post-hoc**
GDQ total score	7.18 (2.94)	7.55 (3.94)	7.6 (1.76)	.095	.910	-

In order to explore the relationship between challenging behaviour and participant characteristics, correlations were conducted within syndrome groups. Table 3.15 shows the correlation matrix for Cornelia de Lange syndrome. Table 3.15 shows that level of intellectual disability was negatively

correlated with both lifetime health problems and current health, such that, a greater degree of intellectual disability in Cornelia de Lange syndrome was associated with more health problems. Both self-injury and aggression were positively correlated with lifetime health conditions, such that individuals with more health conditions displayed more self and aggression. Self-injury was also positively correlated with total SCQ score, which suggests that those individuals with more autistic characteristics were more likely to display self-injury.

Table 3.16 shows the correlation matrix for Cri du Chat syndrome. Table 3.16 shows that a higher number of current health problems was positively associated with a greater number of gastroesophageal reflux signs. Higher pain scores were also correlated with a greater number gastroesophageal reflux signs in Cri du Chat syndrome. There was a negative association between age and the total number of gastroesophageal reflux signs, such that older individuals have less gastroesophageal reflux signs. The severity of self-injury in Cri du Chat syndrome was associated with total SCQ score suggesting that the greater the impairment in social communication, the more severe the level of self-injury. Table 3.17 shows a correlation matrix for Angelman syndrome. Table 3.17 shows that there was a negative association between age and aggression severity suggesting that with increasing age, the severity of aggression decreases in Angelman syndrome.

Table 3.15: Spearman's correlation matrix to show the relationship between challenging behaviour and participant characteristics in Cornelia de Lange syndrome.

	Level of ID	Age	Aggression	Self-injury	Destruction	SIB severity	Aggression severity	Positive affect	Negative affect	Repetitive behaviour	Total SCQ	Lifetime health	Current health	Pain6
Level of ID[1]														
Age	-.49*													
Aggression[2]	-19	.07												
Self-injury[2]	-.49*	.42	.07											
Destruction[2]	.10	-.51*	.44	-.24										
SIB severity[3]	.31	-.05	.18	.44	.16									
Aggression severity[3]	.20	-.35	-.15	-.38	.21	-.09								
Positive affect[2]	.28	-.01	.22	-.25	.05	.14	-.09							
Negative affect[2]	-.53*	.15	.09	.17	-.02	-.12	-.14	-.11						
Repetitive behaviour[4]	.08	-.06	-.21	-.30	-.04	.01	.15	.07	-.32					
Total SCQ[4]	-.50	.07	.29	.52*	.48	.47	-.27	-.23	.24	.13				
Lifetime health[5]	-.52*	.12	.56*	.55*	.22	.21	-.23	-.04	.16	-.49*	.53*			
Current health[5]	-.54*	.06	.28	.12	-.04	-.19	.05	-.03	-.06	-.35	-.07	.51*		
Pain[6]	-.36	-.18	-.11	.06	.18	-.00	.17	-.19	.24	.00	.53*	.29	.24	
GRQ[7]	-.53*	.09	.29	.16	.07	-.22	-.30	-.06	.21	-.46	.20	.42	.34	.46

*$p<.05$, ** $p<.001$

[1] Adaptive behaviour composite standard score from VABS II (Sparrow *et al.,* 2005)
[2] Total mean percentage time from observational data
[3] Severity score obtained from CBI (Oliver *et al.,* 2003a)
[4] Scores from SCQ (Rutter *et al.,* 2003)
[5] Total scores for current and lifetime health problems from Health Questionnaire (Hall *et al.,* 2008)
[6] Total pain score from NCCPC (Breau *et al.,* 2002)
[7] Total reflux score from GDQ (Oliver & Wilkie, 2005)

Table 3.16: Spearman's correlation matrix to show the relationship between challenging behaviour and participant characteristics in Cri du Chat syndrome.

	Level of ID	Age	Aggression	Self-injury	Destruction	SIB severity	Aggression severity	Positive affect	Negative affect	Repetitive behaviour	Total SCQ	Lifetime health	Current health	Pain6
Level of ID[1]														
Age	-.22													
Aggression[2]	-.22	-.22												
Self-injury[2]	-.23	-.13	.45*											
Destruction[2]	-.10	-.46*	.41	.22										
SIB severity[3]	-.06	-.03	-.16	-.25	-.19									
Aggression severity[3]	.19	-.14	.09	.17	-.09	.23								
Positive affect[2]	-.19	.07	-.10	.42	-.08	.32	-.09							
Negative affect[2]	-.18	-.50*	.37	-.03	.41	.07	.31	.04						
Repetitive[4] behaviour	.15	-.14	.03	.01	-.28	.28	-.14	.06	-.28					
Total SCQ[4]	-.26	-.31	.17	.30	.05	.54*	-.06	.35	-.04	.70**				
Lifetime health[5]	.39	-.01	-.27	.23	.04	.16	-.01	.39	-.44	-.03	.10			
Current health[5]	.24	-.24	.03	.22	-.28	.24	-.12	.39	-.07	.46	.39	.27		
Pain[6]	.21	-.32	-.02	.03	-.25	.36	-.33	.39	.03	.35	.42	-.06	.48	
GRQ[7]	.43	-.73**	.14	.06	.24	.32	-.03	.17	.38	.45	.51	-.01	.48*	.55*

*$p<.05$, ** $p<.001$

[1] Adaptive behaviour composite standard score from VABS II (Sparrow *et al.,* 2005)
[2] Total mean percentage time from observational data
[3] Severity score obtained from CBI (Oliver *et al.,* 2003a)
[4] Scores from SCQ (Rutter *et al.,* 2003)
[5] Total scores for current and lifetime health problems from Health Questionnaire (Hall *et al.,* 2008)
[6] Total pain score from NCCPC (Breau *et al.,* 2002)
[7] Total reflux score from GDQ (Oliver & Wilkie, 2005)

Table 3.17: Spearman's correlation matrix to show the relationship between challenging behaviour and participant characteristics in Angelman syndrome.

	Level of ID	Age	Aggression	Self-injury	Destruction	SIB severity	Aggression severity	Positive affect	Negative affect	Repetitive behaviour	Total SCQ	Lifetime health	Current health	Pain6
Level of ID[1]														
Age	-.35													
Aggression[2]	-.35	.05												
Self-injury[2]	-.39	-.21	.09											
Destruction[2]	-.57*	.15	.40	.28										
SIB severity[3]	-.43	-.04	.11	.50*	-.03									
Aggression severity[3]	.20	-.74**	.09	.16	.17	.18								
Positive affect[2]	-.33	-.04	.39	.42	.22	.43	.26							
Negative affect[2]	-.06	-.24	.03	-.28	.19	-.02	.45	.05						
Repetitive behaviour[4]	.24	.11	-.12	.10	.30	.16	.16	-.05	.15					
Total SCQ[4]	-.35	.23	.03	.16	.62*	.21	-.09	-.17	.16	.67**				
Lifetime health[5]	.04	.08	04	-.41	.03	.03	.24	-.16	.61*	.44	.41			
Current health[5]	.02	-.39	-.12	-.19	-.37	-.06	.36	.02	.35	-.38	-.51	.37		
Pain[6]	.64*	.04	-.31	-.60*	-.09	-.63*	.05	-.46	.05	.48	.10	.32	.02	
GRQ[7]	-.25	-.24	.34	.24	.05	.48	.23	.42	.22	.40	.27	.48	.29	-0.6

*$p<.05$, ** $p<.001$

[1] Adaptive behaviour composite standard score from VABS II (Sparrow *et al.,* 2005)
[2] Total mean percentage time from observational data
[3] Severity score obtained from CBI (Oliver *et al.,* 2003a)
[4] Scores from SCQ (Rutter *et al.,* 2003)
[5] Total scores for current and lifetime health problems from Health Questionnaire (Hall *et al.,* 2008)
[6] Total pain score from NCCPC (Breau *et al.,* 2002)
[7] Total reflux score from GDQ (Oliver & Wilkie, 2005)

3.12. Discussion

This is the first study that has examined the phenomenology and correlates of challenging behaviour in Angelman, Cri du Chat and Cornelia de Lange syndromes. Observational data collection was conducted under experimentally controlled conditions with robust inter-observer reliability, and questionnaire measures with sound psychometric properties were utilised providing a robust design and a fine-grained analysis of behaviour. The design allowed the comparison of the phenomenology and correlates of challenging behaviour to be made across three genetic syndromes. These syndromes were selected for their reported high rates of self-injury and aggression. In addition, in line with previous research identifying risk markers for challenging behaviour and the importance of using comparison groups in studies of behavioural phenotypes, the groups were comparable on characteristics such age, communication, speech and mobility.

Analysis of demographic characteristics in the current study revealed that the Cri du Chat syndrome group scored significantly higher than the Cornelia de Lange and Angelman syndrome groups on all domains of adaptive behaviour. A greater number of individuals with Cri du Chat syndrome were also reported to have speech (more than 30 words or signs) and were found to engage in more communication (both verbal and non-verbal) than the Cornelia de Lange and Angelman syndrome groups during the observation period. This presents as a possible confound to the results of the study. Although increasing levels of intellectual disability are typically associated with higher levels of challenging behaviour (McClintock *et al.,* 2003), the results of this study show that there were no difference in overall levels of challenging behaviour across groups and SIB severity was actually highest in the Cri du Chat syndrome group in spite of a

higher level of adaptive behaviour. This therefore suggests that a higher level of adaptive behaviour, speech and communication in the Cri du Chat syndrome group is unlikely to present a confound in the current study.

Analysis of challenging behaviours revealed that there was a higher proportion of participants in the Angelman syndrome group that displayed physical aggression than in the Cornelia de Lange or Cri du Chat groups. This is consistent with the findings of Arron *et al.* (in review). Results also showed that there was a higher proportion of participants in the Cornelia de Lange syndrome group that displayed SIB than in the Angelman syndrome group which supports suggestions that Cornelia de Lange syndrome is associated with self-injury (Berney *et al.,* 1999; Hyman *et al.,* 2002). However, it should be noted that Oliver *et al.* (2009) found that self-injury was not more prevalent in Cornelia de Lange syndrome in comparison to a matched contrast group of individuals with intellectual disability of mixed aetiology. Oliver *et al.* (2009) found that proto-SIB or potentially injurious behaviours were more common in the Cornelia de Lange syndrome group. The current study employed broad operational definitions that encompassed both SIB and proto-SIB so this distinction could not be made.

Although the literature describing destructive behaviour in the syndromes is limited, the results from this study are consistent with previous research in noting more destructive behaviour in Angelman and Cri du Chat syndromes than in Cornelia de Lange syndrome (Horsler & Oliver, 2006a; Van Buggenhout *et al.,* 2000). Interview data indicated that the severity of aggressive behaviour was higher in the Angelman syndrome group than the Cri du Chat and Cornelia de Lange syndrome groups, whilst more severe self-injury was common in the Cri du Chat group

compared to the Angelman syndrome group. Results also indicated that age was negatively associated with aggression severity in Angelman syndrome suggesting that severity of aggression decreases as individuals get older. There has yet to be any systematic study of the effects of aging on behaviour in Angelman syndrome, however, limited research and anecdotal reports from parents suggested that there may be a gradual reduction in challenging behaviour with progressing age (Clayton-Smith, 2001).

Comparisons of topographies of aggressive behaviour indicated that forms differed across syndrome groups and specific topographies were associated with Angelman syndrome. Consistent with previous research, grabbing and hair pulling were the most common topographies of aggression in Angelman syndrome (Summers *et al.,* 1995). Hair pulling and grabbing were observed in 70% and 65% of the Angelman syndrome group respectively. This is a notable finding as these topographies differ from those topographies reported to be most common in the broader population of people with intellectual disabilities, namely hitting others with hands, hitting others with objects and scratching others (Emerson *et al.,* 2001). In addition, these forms of aggressive behaviour were observed in a much smaller proportion of individuals in both the Cornelia de Lange and the Cri du Chat groups, which suggests that these behaviours may represent syndrome specific topographies of Angelman syndrome. This highlights the importance of conducting more detailed study of behavioural characteristics across syndrome groups rather than broad behavioural phenomenology. In Angelman syndrome, the finding that hair pulling and grabbing are particularly prevalent may be indirectly linked to the heightened levels of sociability and behaviours that access social attention that are reported to be characteristic of the syndrome (Brown & Consedine, 2004; Oliver *et al.,* 2007; Strachan *et al.,* 2009). Under conditions of

deprivation of social attention, hair pulling and grabbing are typically forms of aggression that would be most effective as attempts at regaining eye contact, thus briefly prolonging social interaction.

Due to only small numbers of people displaying certain topographies of SIB, an analysis of specific forms of SIB in the syndromes could not be conducted. This is unfortunate as literature links genetic syndromes such as Prader-Willi, Lesch-Nyhan and Smith-Magenis with particular forms of self-injury (Anderson & Ernst, 1994; Dykens & Kasari, 1997; Smith *et al.,* 1986), suggesting that certain topographies of SIB may be specific to certain syndromes (Arron *et al.,* in review).

More individuals with Angelman syndrome reached the ASD cut-off than individuals with Cri du Chat syndrome. This finding is consistent with reports in the literature that indicate ASD in the syndrome (Steffenburg *et al.,* 1996). However, it is important to note that the presence of ASD characteristics in Angelman syndrome may be confounded by the presence of severe to profound levels of intellectual disability. Trillingsgaard and Østergaard (2004) found that individuals with Angelman syndrome demonstrated greater skills than individuals with ASD in particular areas including social smile, facial expression directed to others, response to name, shared enjoyment and unusual interests and repetitive behaviour. This highlights the importance of considering levels of intellectual disability when assessing ASD in Angelman syndrome.

The study also found that more individuals with Cornelia de Lange syndrome reached the ASD cut off than individuals with Cri du Chat syndrome, which is consistent with previous literature

indicating an increased prevalence of autistic characteristics in the syndrome (Bhuiyan *et al.,* 2007; Moss *et al.,* 2009; Oliver *et al.,* 2008). In addition, the Cornelia de Lange syndrome group was also found to have more impairment in the social interaction domain than the Cri du Chat syndrome group. Moss *et al.* (2008) found a similar profile of impairment in their study and suggested that difficulties in social interaction may be due to the presence of social anxiety in the syndrome, suggesting an atypical ASD profile in Cornelia de Lange syndrome. The current study also found an association between total SCQ score and SIB such that those individuals with more autistic traits were more likely to display SIB. This supports recent findings, which link autistic characteristics in Cornelia de Lange syndrome with SIB (Oliver *et al.,* in review). The lack of association between ASD and Cri du Chat syndrome supports the findings of Moss *et al.* (2008) and provides further support that an autism spectrum-like profile is unlikely to be associated with the syndrome.

As expected, both recent and lifetime heath problems were found to be more common in the Cornelia de Lange syndrome group than the Cri du Chat or Angelman syndrome groups. In addition, recent and lifetime health conditions were negatively associated with level of intellectual disability such that the greater the level of intellectual disability, the more health problems were present. This is consistent with the literature that documents many health problems associated with Cornelia de Lange syndrome and gastrointestinal problems are the most commonly reported (Hall *et al.,* 2008; Luzzani *et al.,* 2003). The most prevalent of gastrointestinal problems is gastroesophageal reflux which is thought to be present in 65% of individuals with the syndrome (Hall *et al.,* 2008; Luzzani *et al.,* 2003). Interestingly, lifetime health conditions were also associated with both self-injury and aggression in Cornelia de Lange

syndrome. This is consistent with the findings of Luzzani *et al.* who linked SIB and gastroesophageal reflux in Cornelia de Lange syndrome and suggested that individuals may engage in self-injury in response to painful health conditions. This highlights the need to monitor health conditions in the syndrome to avoid potentially injurious responses from entering an individual's repertoire. It was surprising that no difference in pain or signs of gastroesophageal reflux were found across the groups. Given the prevalence of gastrointestinal problems in Cornelia de Lange syndrome it was expected that there would be more signs of gastroesophageal reflux in this group. One explanation for the lack of association may be that the groups are confounded by a severe degree of intellectual disability and it is known that there is a positive association between degree of intellectual disability and health problems (Jansen, Krol, Groothoff & Post, 2004).

In Cri du Chat syndrome, health problems were positively correlated with gastroesophageal reflux signs and clinical signs of gastroesophageal reflux were associated with pain scores. This suggests that gastroesophageal reflux may be a problematic and painful health condition in Cri du Chat syndrome. Feeding difficulties, failure to thrive and reflux have been noted to be common in the first two years of life (Collins & Eaton-Evans, 2001) and this study shows an association between gastroesophageal reflux signs and age such that, the number of signs decreases with increasing age. The association between gastroesophageal reflux and Cri du Chat syndrome warrants further research and this is particularly important given the link between gastroesophageal reflux and self-injury in Cornelia de Lange syndrome (Luzzani *et al.,* 2003).

High levels of positive affect in Angelman syndrome compared to Cornelia de Lange and Cri du Chat syndrome groups is consistent with a wealth of research indicating heightened sociability and laughing and smiling in the syndrome (e.g. Horsler & Oliver, 2006a; Richman *et al.,* 2006). The comparison of laughing and smiling to two other genetic syndromes supports the view that the behaviour is part of the behavioural phenotype of Angelman syndrome (Horsler & Oliver, 2006a). Although the result did not reach significance, negative affect was found to be highest in the Cornelia de Lange syndrome group which is consistent with Collis, Moss, Jutley, Cornish and Oliver (2008). Collis *et al.* found a significantly lower ratio of positive to negative affect in a group of individuals with Cornelia de Lange syndrome compared to a group with Cri du Chat syndrome and a group of individuals with intellectual disability of mixed aetiology.

Given previous case reports and a questionnaire study that indicates excessive mouthing and chewing in Angelman syndrome (Buckley *et al.,* 1998; Steffenburg *et al.,* 1996; Summers *et al.,* 1995), it was surprising that the present study did not support this finding. Rather, the Cri du Chat syndrome group were found to have higher levels of mouthing than the Angelman syndrome group. High levels of mouthing in the syndromes may result from gastroesophageal reflux and Oliver and Wilkie (2005) note mouthing as an indicator of gastroesophageal reflux in the GDQ, as it is thought that mouthing acts to increases the production of saliva. It is important to note that although signs of gastroesophageal reflux were found to be comparatively lower in the Angelman syndrome group, this does not mean that it did not occur in this group and thus some mouthing behaviour may be linked to this health condition. Object stereotypy was found to be higher in the Angelman syndrome group than the Cornelia de Lange syndrome group and this is consistent

with reports in the literature of increased repetitive and stereotyped behaviour (Horsler & Oliver, 2006a, Moss *et al.,* 2009).

All findings of the study should be considered in relation to the methodology adopted. It is possible that the sample for the study is biased by recruiting from syndrome support groups. Families in need of more support because of the severity of the child's behaviour may be more likely to be members of a support group and so this may mean that children with greater problems are overrepresented in this sample. However, given the selective nature of the sampling method (i.e. children were recruited into the study for the presence of challenging behaviour) it is not felt that this is an issue. In addition, if this bias is evident, it is likely to be comparable across groups and therefore comparisons of challenging behaviour and correlates of challenging behaviour within the groups should still be valid. It is also notable that the percentage duration of challenging behaviour during the direct observations did not correlate with severity of challenging behaviour as measured by the CBI. Although this appears somewhat surprising, the lack of association is likely to be due to the fact that observational data is only concerned with duration of time spent engaging in challenging behaviour. The interview data (CBI), however, is concerned with more dimensions of the behaviour such as frequency, duration, response necessary to manage the behaviour and the effects of the behaviour on others. The CBI is also concerned with challenging behaviour within the previous month whilst the observational data collected is immediate.

In spite of the limitations, the study is the first to use observational methods to examine the phenomenology and correlates of challenging behaviour in Angelman, Cri du Chat and Cornelia

de Lange syndromes which have allowed sensitive measurement of the behaviours. A difference between some of the challenging behaviour variables and predictors alludes to the importance of syndrome specific models.

CHAPTER 4

Examination of the Function of Challenging Behaviour in Angelman, Cri du Chat and Cornelia de Lange Syndromes

----------Preface to Chapter 4----------

The study in Chapter 3 used direct observations to examine the phenomenology and correlates of challenging behaviour within Angelman, Cri du Chat and Cornelia de Lange syndromes. Operationally defined behaviours permitted a fine-grained analysis of behaviour across syndrome groups rather than broad behavioural phenomenology. The study elucidated specific topographies and correlates of challenging behaviour within the syndrome groups that are potentially important to consider within gene-environment interactions. Using experimental functional analysis methods that were identified in Chapter 2, this study examines the gene-environment interactions on self-injurious and aggressive behaviour in Angelman, Cri du Chat and Cornelia de Lange syndromes.

4.1. Introduction

Prevalence estimates vary for self-injury in people with intellectual disability from 4 to 10% (Kiernan & Kiernan, 1994; Oliver, Murphy & Corbett, 1987) and 7 to 25% for aggression (Emerson *et al.*, 2001; Kiernan & Kiernan, 1994). These behaviours impinge significantly on the quality of life of people with severe intellectual disabilities and their families, and can lead to exclusion and the need for costly services (Hassiotis, Parkes, Jones, Fitzgerald & Romeo; 2008; Hastings, 2002; Schwartz & Rabinovitz, 2003). There is robust evidence from cohort studies that self-injurious behaviour (SIB) and aggression in people with intellectual disabilities is associated with a greater degree of intellectual disability, Autism Spectrum Disorder (ASD) and the presence of stereotyped, compulsive and impulsive behaviours (Bodfish *et al.,* 1995; Brylewski & Wiggs, 1999; Deb, Thomas, & Bright, 2001; McClintock, Hall & Oliver, 2003; Powell, Bodfish, Parker, Crawford, & Lewis, 1996; Rojahn, Matson, Naglieri, & Mayville, 2004). In addition, the literature reveals that some forms of challenging behaviour are prominent in some genetic disorders. For example, SIB is seen in a substantial proportion of people with Lesch-Nyhan, Fragile-X, Cornelia de Lange, Cri du Chat and Smith-Magenis syndromes (Christie *et al.,* 1982; Collins & Cornish, 2002; Finucane, Simon & Dirrigl, 2001; Nyhan, 1972; Oliver, Arron, Sloneem & Hall, 2008; Symons, Clark, Hatton, Skinner, & Bailey, 2003). Interestingly, there is comparatively less research into aggression in genetic syndromes but it is noted in Angelman and Smith-Magenis syndromes (Arron *et al.,* 2006; Oliver, Berg, Moss, Arron & Burbidge, in review; Summers, Allison, Lynch & Sandler, 1995; Strachan *et al.,* 2008). The association between self-injury and aggression and other behaviours in the wider population of people with intellectual disability, and between and within syndrome variability in the prevalence of self-injurious and

aggressive behaviours, indicate the need for causal models that can account for behaviour-behaviour associations and incorporate genetic vulnerability (Hodapp & Dykens, 2001).

An extensive and robust literature on the aetiology of challenging behaviours shows that within and between person variability in the behaviour can, in part, be explained by the application of operant theories (Carr & Durand 1985; Hanley, Iwata & McCord, 2003; Iwata, Dorsey, Slifer, Bauman & Richman, 1982/1994; Oliver, 1995; Oliver, Hall & Murphy, 2005; Chapter 1: Section1.8). Operant theories suggest that behaviours such as self-injury and aggression are maintained by reinforcing consequences with supportive evidence coming from the study of the relationship between behaviour, discriminative stimuli and establishing operations in the context of mutual reinforcement (Oliver, 1995; Oliver *et al.,* 2005). An establishing operation is an antecedent variable that occasions the occurrence of behaviour, and it can be usefully defined as a motivational state which increases the reinforcing properties of contingencies (Michael, 1982). A reinforcer is a stimulus that occurs contingently on the behaviour and increases the likelihood that the behaviour will occur again in the future.

The conclusions that might be drawn from the empirical literature on behaviour-behaviour associations, genetic predisposition and operant reinforcement are, arguably, inconsistent, as each gives different emphasis to the role played by biological and environmental determinants. However, given the strength of the empirical evidence, the conclusion that either influence is sufficient cannot be supported and an integrated approach is needed to account for the available empirical data. In this study, the focus is on gene-environment interactions for self-injurious and aggressive behaviour.

Anastasi (1958) proposed that no behaviour could exist without both genes and environment and authors have subsequently proposed various models of gene-environment interactions contributing to individual variation and traits (Hodapp, 1997; Kendler & Eaves, 1986; Plomin, 1995; Plomin, DeFries & Loehlin, 1977; Scarr & McCartney, 1983). For example, genetic and environmental factors have been shown to interact and influence the development of psychosis and schizophrenia (Caspi *et al.,* 2005; Tsuang, Stone & Faraone, 2001), adolescent depression (Eaves, Silberg & Erkanli, 2003) and Attention Deficit Hyperactivity Disorder (ADHD) symptoms (Brookes *et al.,* 2006). Rutter, Moffitt and Capsi (2006) have also shown gene-environment interactions to have powerful effects on the development of several physical and mental health conditions. Rutter *et al.* propose that genetic factors confer susceptibility or insensitivity in a particular environment. For example, Capsi and Moffit (2006) have investigated why only some children who are maltreated develop antisocial behaviour. They found that functional polymorphism in the monoamine oxidase (MAOA), a gene promoter, can moderate the association between early life trauma and increased risk for antisocial behaviour. Individuals who were abused as children and had a genotype conferring low levels of MAOA expression, were more likely to develop symptoms of antisocial behaviour and aggression than those with high levels of MAOA.

A particularly pertinent model is that proposed by Scarr and McCartney (1983) who described three genotype-environment effects: passive, active and evocative. They proposed a probabilistic model, in which people with certain genotypes will receive certain kinds of parenting (passive), will select certain environments (active), and evoke certain responses (evocative). In the field of genetic disorders an evocative genotype-environment effect may be of particular interest as,

different behavioural phenotypes related to different genetic disorders could evoke particular environmental responses. At a broad level for example, Hodapp, Dykens & Masino (1997) found that levels of maladaptive behaviour in children with Prader-Willi syndrome, such as overeating and skin picking, were significantly correlated with levels of familial stress. Thus, it is probable that problem behaviours associated with this syndrome had evoked a response.

In the intellectual disability field, there is growing recognition of gene-environment interactions as plausible accounts for the differing prevalence of self-injury across syndromes and evidence for operant conditioning. Oliver (1993; 1995), Taylor and Oliver (2008) and Langthorne and McGill (2008) have proposed conceptual models to explain the development of SIB. In each model, individual characteristics of genetic origin interacts with environmental characteristics to drive the development of self-injury. However, to date there are few empirical studies of these models.

One strategy for testing these models is to explore challenging behaviour deemed to be phenotypic of given genetic syndromes. Operant learning theory alone would predict no differences in prevalence or phenomenology of challenging behaviour across syndromes because environmental influences would, presumably, be randomly distributed across groups. In addition, a purely genetic determinist approach would expect no influence of the environment given that the syndromes are defined by a specific genetic abnormality. To date, there is a growing body of research providing evidence that environmental determinants can maintain and exacerbate self-injury and aggression in genetic syndromes such as Angelman, Cornelia de Lange, Rett and Smith-Magenis syndromes (e.g. Arron *et al.,* 2006; Moss *et al.,* 2005; Oliver, Murphy, Crayton &

Corbett, 1993; Strachan *et al.,* 2009; Taylor & Oliver, 2008. Also see Chapter 2 for a review of possible gene-environment interactions in syndromes). These studies have tended to be case reports or small group comparisons and there is a lack of larger scale group designs.

In these studies there are a number of potential gene-environment interactions proposed. For example, in Rett syndrome, hand to mouth SIB may initially enter a behavioural repertoire as a stereotyped behaviour and subsequently be subject to operant reinforcement. Oliver *et al.* (1993) found that SIB in young girl with Rett syndrome was evoked by high levels of antecedent social demands, which were linked to a predisposition in the syndrome to find high levels of social contact aversive. In this example two phenotypic characteristics of Rett syndrome (repetitive hand to mouth movements and a period of experiencing social interaction as aversive) interact with operant contingencies to drive the development of self-injury. Similarly, SIB may enter a behavioural repertoire in response to pain or discomfort, for example in Cornelia de Lange syndrome (Luzanni, Macchini, Valade, Milani & Selciorni, 2003; Moss *et al.,* 2005). Additionally, if pain perception is compromised and the individual has a predisposition to find social stimuli particularly rewarding, SIB may become operantly reinforced by access to social contact with response cost reduced by the higher pain threshold. This model has been proposed for Smith-Magenis syndrome with some empirical support (Taylor & Oliver, 2008). Finally, many genetic syndromes are also associated with generic risk markers for the development of self-injury and aggression, such as severe intellectual disability and expressive communication deficits (McClintock *et al.,* 2003).

The empirical functional assessment of operant reinforcement of behaviours has its roots in the procedure first described by Iwata *et al.* (1982). This methodology has since been refined and alternative techniques developed (e.g. Carr & Durand, 1985; Iwata *et al.,* 1994a; Iwata, Duncan, Zarcone, Lerman, & Shore, 1994; Vollmer, Iwata, Duncan, & Lerman, 1993; Oliver, Hall & Nixon, 1999). Experimental functional analysis is now widely accepted as one of the best procedures for ascertaining if operant social reinforcement influences a given behaviour. However, to date, the functional analysis methods that have been used in genetic syndrome research have either employed only very brief analogues (Arron *et al.,* 2006; Strachan *et al.,* 2009) or experimentally weak descriptive analyses (Moss *et al.*, 2005; Sloneem, Arron, Hall & Oliver*,* 2009). Given the lack of directly comparable data, exploration of the social reinforcement of SIB and aggression across different genetic syndromes is needed. These data would be informative for developing models of the causes of these behaviours within and between syndrome groups with implications for intervention. This chapter seeks to generate these data for Angelman, Cornelia de Lange and Cri du Chat syndromes. These three syndrome groups have been chosen as they are groups in which high rates of challenging behaviours of interest such as self-injury and aggression are known to occur. Further, given previous research identifying risk markers for challenging behaviour and the importance of using matched groups in behavioural phenotype studies, these syndromes have been chosen as they are broadly comparable on level of intellectual disability, communication and mobility; the groups will also be comparable on age and gender. Although complete overviews of the syndromes are provided in Chapter 3 (Sections 3.2-3.4), the focus of the following section is on challenging behaviour within these syndromes.

4.1.1. Challenging behaviour within Angelman, Cri du Chat and Cornelia de Lange syndromes

Angelman syndrome

Numerous case reports in the literature make reference to aggression in Angelman syndrome (Clayton-Smith, 2001; Hersh et *al.,* 1981; Moore & Jeavons, 1973; Sandanam *et al.,* 1997; Steffenburg, Gillberg, Steffenburg & Kyllerman, 1996; Thompson & Bolton, 2003; Williams & Frias, 1981). Reviewing the literature on Angelman syndrome, Horsler and Oliver (2006a) found that 15% of 64 studies made reference to aggression. Similarly, in a review of behavioural problems in Angelman syndrome, Summers *et al.* (1995) found that 10% of case reports (n=108) indicated the presence of aggressive behaviour. In the second part of their study, Summers *et al.* conducted a small questionnaire based survey (n=11) and found that all parents reported children to engage in aggression, namely hair pulling and grabbing. More recently, Strachan *et al.* (2009) have utilised experimental functional analysis to determine the frequency of aggressive behaviour in Angelman syndrome and to explore environmental influences on the behaviour. Strachan *et al.* used experimentally manipulated conditions in which levels of adult attention and demand were manipulated for twelve children with Angelman syndrome. They found that ten out of twelve participants displayed aggressive behaviour (hair pulling, spitting, biting, smacking, grabbing and pinching) and eight out of ten that showed aggression, did so in the high attention condition. A further three displayed aggression in the low attention condition and four out of ten exhibited the behaviour in the demand condition. The pattern of increased aggression at times of high social contact did not meet Strachan *et al's.* original hypothesis which, predicted more aggression at times of low social contact in accordance with an attention maintenance hypothesis. However, the authors suggest that aggression at times of high social contact may serve to maintain and initiate social contact. This is supported by the finding that the children had high levels of positive affect

during this condition and well documented reports of heightened sociability within the syndrome. Oliver *et al.* (2007) and Strachan *et al.* argue that problem behaviours such as aggression may be indirectly related to the heightened sociability and high prevalence of pro-social behaviours in Angelman syndrome. Using operant learning theory, Oliver *et al.* (2007) and Strachan *et al.* (2009) postulate that aggression may be maintained by access to social attention, as it is a potent reinforcer for individuals with Angelman syndrome. Under conditions of deprivation of social attention, physical contact (hair pulling, grabbing) may serve as attempts at regaining eye contact, thus briefly prolonging social interaction. It is also important to note the high proportion of participants in the study by Strachan *et al.* demonstrating a demand escape function, this is an interesting finding that warrants further exploration within a larger sample.

SIB in Angelman syndrome has only been reported in a handful of studies (Clarke & Marston, 2000; Hou, Wang & Wang, 1997). Horsler and Oliver (2006a) found that only 3% of the 64 studies reviewed made reference to SIB in Angelman syndrome. In a recent review of self-injury and aggression in genetic syndromes, Arron, Oliver, Berg, Moss and Burbidge (in review) found that 45% of the sample of individuals with Angelman syndrome showed SIB compared to 27% of the comparison group who had intellectual disabilities of mixed aetiology. Topographies of SIB were variable and included hitting self (with body or object), biting self, pulling self and rubbing and scratching self. Out of seven genetic syndromes studied, Angelman syndrome was the only syndrome in which individuals were not significantly more likely to display SIB (as calculated by odds ratios).

Cri du Chat syndrome

Self-injurious and aggressive behaviour appear to be common behavioural features of Cri du Chat syndrome (Collins & Cornish, 2002; Cornish, Munir & Bramble, 1998; Cornish & Pigram, 1996; Dykens & Clarke, 1997). In a prevalence study of stereotypy, self-injury and aggressive behaviour in children and young adults, Collins and Cornish (2002) found that 92% of the sample (n=66) exhibited some form of SIB. Other prevalence studies have found rates of self-injury to be approximately 70% (Cornish & Pigram, 1996; Dykens & Clarke, 1997). Collins and Cornish (2002) found the most common forms of SIB to be head banging, hitting the head against body parts and self-biting. Collins and Cornish also classified vomiting as a common topography of SIB; however it is unclear to what extent this may be related to the gastro-intestinal problems that are often present in the syndrome. In addition, studies have found high correlations between the prevalence of SIB and stereotypic behaviour in Cri du Chat syndrome (Collins & Cornish, 2002; Cornish & Pigram, 1996; Dykens & Clarke, 1997) and thus it has been suggested that stereotypic behaviour may be subject to operant reinforcement (Oliver, 1995)

Cornish and Pigram (1996) found the prevalence of aggressive behaviour in a sample of 27 individuals with Cri du Chat syndrome to be 52%. Other studies have indicated that the prevalence of aggression is higher at 88% and common topographies include hitting, pulling hair, biting and pinching (Collins & Cornish, 2002).

It is has been suggested that the challenging behaviours observed in Cri du Chat syndrome may often serve a communicative function. Given the disparity between receptive and expressive language skills (receptive skills exceed expressive), behaviours may be maintained as they serve

a communication need (Collins & Cornish, 2002; Cornish *et al.,* 1998). There is also tentative evidence in the literature to suggest a decline in self-injurious and aggressive behaviour with age (Van Buggenhout *et al.*, 2000). A reduction in challenging behaviour with age may reflect an improvement in communication and socialisation skills, however, further research is needed to clarify the nature of this association (Collins & Cornish, 2002).

Cornelia de Lange syndrome

Self-injury is commonly regarded as being part of the behavioural phenotype and since the 1970's has been reported as a clinically significant problem in the syndrome (Bryson, Sakati, Nyhan & Fish, 1970; Johnson, Ekman, Friesen, Nyhan & Shear, 1976). Prevalence rates for SIB range from 16 (Beck, 1987) to 63.6 % (Hyman, Oliver & Hall*.,* 2002). The highest reported prevalence rate by Gualtieri (1990, as cited by Basile, Villa, Selicorni & Molteni, 2007) indicated that 75% of their sample (n=88) displayed self-injury, however, these findings have not been peer reviewed.

The first study to report topographies of self-injury by Shear and colleagues (1971) noted that two boys studied both bit their lower lip and picked at their chest, chin and face. Beck (1987) found very similar topographies in another six participants. More recent studies suggest that individuals with Cornelia de Lange syndrome manifest a variety of self-injurious behaviours, however biting and scratching tend to be the most prevalent forms (Berney, Ireland & Burn, 1999; Sarimski, 1997). Basile *et al.* (2007) found that those individuals with a 'classical' phenotype were more likely to display SIB, as were older participants and those with a lower cognitive level. Using a fine-grained observational study of 54 individuals with Cornelia de

Lange syndrome compared to a comparison group of 46 individuals matched on age, gender, level of intellectual disability and mobility, Oliver *et al.* (2009) found that clinically significant self-injury was *not* more prevalent in Cornelia de Lange syndrome. This finding contests the view that SIB is part of the behavioural phenotype. Interestingly, Oliver *et al.* found that mild or proto-injurious behaviours directed towards the hands, body and head were more prevalent in the Cornelia de Lange syndrome group.

The serotonergic system has been implicated in SIB in Cornelia de Lange syndrome. For example, Greenberg and Coleman (1973) reported that Cornelia de Lange syndrome participants who had low blood levels of serotonin were more likely to self-injure. Serotonin has been implicated in a range of behavioural problems such as aggression, impulse control and obsessive-compulsive disorders (Bond, 2005; Olivier & Van Oorschot, 2005) and selective serotonin reuptake inhibitors have been shown to reduce challenging behaviour in clinical populations. For example, Lewis, Bodfish, Powell, Parker & Golden (1996) found that Clomipramine had significant reductions on self-injury in six out of eight individuals with intellectual disability. As mentioned previously, serotonin has been implicated in compulsive behaviours and studies show that there are high rates of compulsive behaviours associated with Cornelia de Lange syndrome (Bryson *et al.,* 1970; Hyman *et al.,* 2002; Oliver *et al.,* 2008). A recent questionnaire study by Oliver *et al.* (2008) found that over 85% of the participants with Cornelia de Lange syndrome displayed compulsive behaviours and this prevalence was significantly higher than that found in a matched comparison group.

A number of observations of individuals with Cornelia de Lange syndrome have noted that individuals who self-injure may seek restraint and distress may be evident when physical restraints are removed (Dossetor, Couryer & Nichol, 1991; Shear, Nyhan, Kirman & Stern, 1971). There is also evidence to suggest that individuals with severe intellectual disability and SIB may show self-restraint behaviours in an attempt to resist compulsive SIB (Basile *et al.,* 2007; King, 1993; Powell *et al.,* 1996). Hyman *et al.* found that 53% of their sample of individuals with Cornelia de Lange syndrome showed at least one form of self-restraint. The most common forms included holding onto other people to seek restraint, holding or squeezing objects, wrapping oneself in clothing and holding hands together. Hyman *et al.* also found a significant association between SIB and self-restraint and those individuals were significantly more likely to display compulsions. This is the first study to examine the phenomenon of self-restraint within the syndrome and suggests that for some individuals with Cornelia de Lange syndrome, SIB may have taken on a compulsive-like quality that may lead to self-restraint as a method of bringing the behaviour under control.

Although early reports allude to the fact that self-injury in Cornelia de Lange syndrome may be biologically determined (Nyhan, 1972), there is increasing evidence to suggest an environmental influence on the behaviour. In a questionnaire study, Berney *et al.* (1999) reported that 76% of the sample exhibited self-injury in response to a recognisable trigger such as anxiety or fear, boredom and demand avoidance. Dossetor *et al.* (1991) also found that the frequency of self-injury and aggression was related to the moods of the woman that they observed. Intervention studies using behavioural techniques such as differential reinforcement of other behaviour (DRO), extinction and massage has been shown to successfully reduce SIB in individuals with

Cornelia de Lange syndrome (Dossetor *et al.,* 1991; Menolascino, McGee & Swanson, 1982; Singh & Pullman, 1979). These studies provide preliminary evidence that SIB in Cornelia de Lange syndrome may be affected by environmental factors and is not exclusively related to the biology of the syndrome.

More recent and robust studies have utilised experimental functional analysis in order to evaluate environmental effects on behaviour in Cornelia de Lange syndrome (Arron *et al.,* 2006). Systematic environmental manipulations led the authors to find that for three out of nine individuals who displayed SIB, social attention significantly affected rates of behaviour. One participant displayed more SIB at times of high social interaction, whilst two showed more SIB at time of low social interaction, suggesting that environmental variables do influence the expression of self-injury in Cornelia de Lange syndrome. In a recent descriptive analysis, Sloneem *et al.* (2009) observed SIB in 27 individuals with Cornelia de Lange syndrome to a matched contrast group of seventeen individuals who did not have the syndrome. The proportion of individuals showing an association between SIB and environmental events was just under a third, which is comparable to the results of Arron *et al.* (2006). However, there was no difference between the two groups on number or degree of environmental associations. Similarly, another descriptive analysis by Moss *et al.* (2005) found that seven out of eight participants in the sample showed self-injury that was associated with a particular setting event (group, one-to-one, play or transition). Interestingly, one participant's self-injury showed no association with any setting event with high levels being observed across all settings. Anecdotal reports suggested that following intervention to remedy gastroesophageal reflux, the individual's SIB ceased. Indeed, the self-injury observed in Cornelia de Lange syndrome has been linked to physical health

problems such as gastroesophageal reflux (Luzzani *et al.,* 2003). A high pain threshold has also been reported in Cornelia de Lange syndrome and has been correlated with SIB (Basile *et al.,* 2007) and this is particularly important when thinking of SIB as being operantly reinforced. The efficiency of behaviour is determined by the difference between the gain and cost that accrue from its occurrence, and it is the efficiency of self-injury that is central to its survival in a behavioural repertoire (Oliver, 1995). Pain from engaging in SIB is clearly a cost, however, if individuals with Cornelia de Lange syndrome do have compromised pain perception, it potentially means that there is decreased cost to engaging in the behaviour.

There are few studies examining the prevalence of aggression in Cornelia de Lange syndrome and the findings from these studies lack consistency. Hyman *et al.* (2002) found that 43% of the sample of 88 individuals had displayed physical aggression in the last month and Berney *et al.* (1999) found that 49% of the sample (N=49) showed one form of aggression (either vocal or physical) on a daily basis, and this was strongly associated with the presence of autistic behaviours. In contrast, Basile *et al.* (2007) found that only 20% of their sample displayed aggressive behaviour, a similar prevalence to that found in the total population of people with intellectual disabilities.

4.2. Aims

From reviewing the literature (also see Chapter 2) it is clear that problem behaviours within genetic syndromes could be influenced by gene-environment interactions. The aim of this chapter is to examine the gene-environment interactions on SIB and aggression in Angelman, Cri du Chat and Cornelia de Lange syndromes by utilising experimental functional analysis. Previous research provides evidence of heightened sociability, positive affect and aggression as being part of the behavioural phenotype of Angelman syndrome. Given recent research that indicates the occurrence of physical aggression at times of low adult attention, there is good reason to suspect that aggressive behaviour in Angelman syndrome is maintained by social contact. In Cornelia de Lange syndrome, research indicates a link between SIB and painful health conditions, SIB of a compulsive-like quality and the presence of self-restraint and physical restraint. Given this evidence, it is anticipated that SIB will be less functional in this group. The influence of the environment on problem behaviours in Cri du Chat syndrome has yet to be studied; however, the marked expressive/receptive language discrepancy and anecdotal reports of heightened sociability might indicate a communicative function to both self-injurious and aggressive behaviour. Thus, the study will offer an initial exploration as well as providing an appropriate group for comparison with the other two syndromes studied. The three syndrome groups will allow a comparison of environmental influences on challenging behaviour, whilst providing control over a number of characteristics known to be associated with high levels of challenging behaviour.

4.3. Hypotheses

There are three specific hypotheses:

1. Challenging behaviours in the Cornelia de Lange syndrome group will evidence a stronger association with pain than challenging behaviours in the Angelman syndrome and Cri du Chat syndrome groups.
2. Self-injurious behaviour in the Cornelia de Lange syndrome group will be influenced less by social operant reinforcement than self-injurious behaviour in the Angelman syndrome and Cri du Chat syndrome groups.
3. Aggressive behaviour in the Angelman syndrome group will evidence stronger maintenance by positive social reinforcement than aggressive behaviours in the Cornelia de Lange syndrome and Cri du Chat groups.

4.4. Method

4.4.1. Recruitment and participants

The present study used the same participants as those reported in Chapter 3. Refer to Sections 3.9.3 and Figure 3.1 for recruitment and Section 3.9.5 and Tables 3.1 and 3.2 for participant information.

4.4.2. Measures

4.4.2.1. Measure of Ability: See section 3.9.6.1

4.4.2.2. Questionnaire Measures:

Questionnaire booklets are identical to those described in Section 3.9.6.2. The only additional questionnaire information collected regarded the assessment of challenging behaviour and sociability:

4.4.2.2.1. Assessment of challenging behaviour: Questions about behavioral function (QABF; Matson & Vollmer, 1995).

The QABF was used in order to assess factors that maintain aberrant behaviour. It is comprised of 25 questions related to the possible function of the behaviour in five subscales (social attention, escape from demands, physical discomfort, tangible and escape from social attention). Each item is rated on a four point Likert scale, from 'never' (0) to 'often' (3). For example, questions 25 asks 'Does he/she seem to be saying "give me that (toy item, food item)" when engaging in the behaviour?' When interpreting the QABF, a clear function is considered when there is an endorsement of four or five items within one subscale with no other subscales containing significant endorsements. Internal consistency for the total scale ranges from .79-.99 and test-retest reliability is reported to be good with correlations between raters ranging from .64 to 1.0 (Paclawskyj, Matson, Rush, Smalls & Vollmer, 2000).

4.4.2.2.2 Assessment of sociability: Sociability questionnaire for people with intellectual disabilities (SQID; Collis, Moss & Oliver, Unpublished)

The SQID is an informant-based questionnaire developed to examine behaviours indicative of sociability and social anxiety in children and adults with a range of intellectual disabilities. This 24-item questionnaire focuses on how individuals have behaved in specific social settings over

the past two months. Twenty items are rated using a seven point Likert scale ranging from 'very shy' to 'very sociable' and four items are answered on a yes/no basis. The items form two subscales: Social Interaction and Social Performance. The psychometric properties of the SQID are currently being examined but preliminary analysis indicates that the subscales have good inter-rater reliability. Inter-rater reliability for the Social Interaction subscale and the Social Performance subscale are .87 and .86, respectively.

4.4.2.3. Observational measures

Experimental functional analysis conditions

For each participant, experimental functional analyses based on those by Iwata *et al.* (1982/1994a), Carr and Durand (1985) and Strachan *et al.* (2009) were employed. Three conditions were used in an alternating treatment design (ABAC) to evaluate the influence of social reinforcement on self-injurious and aggressive behaviour. Each condition lasted five minutes and each ABAC session was repeated four times resulting in a total of 20 trials.

Condition A: High attention. This condition was analogous to Carr and Durand's (1985) 'Easy 100' condition and involved the researcher maintaining high levels of verbal attention with the participant without issuing any demands. This condition acted as a control condition for the presence of the researcher and the presence of attention. The researcher maintained proximity to the participant throughout the condition and this included moving around the room with the participant if they were mobile. If the participant spoke to or approached the other researcher in the room the high level of verbal attention was maintained. The rooms in which the sessions were carried out were always as distraction-free as possible. However, there were times when

participants would comment on or pick up objects in the room. At these times, the researcher would remark briefly on the object without introducing the object into the session. Any challenging or inappropriate behaviours shown by the participant were not responded to in any way. High levels of target behaviour in this condition would suggest that the behaviour was occasioned by aversive social contact and maintained by escape from that contact.

Condition B: Low attention. This condition was analogous to Carr and Durand's (1985) 'Easy 33' condition and began with the researcher in close proximity to the participant. The researcher then removed attention from the participant by saying "I'm going to talk to X now" and then talking to the other researcher in the room. In this condition it was not necessary for the researcher to maintain proximity with the participant and so mobile participants were free to move around the room. This was to ensure that any approaches directed toward the researcher could be observed. For less mobile participants the researcher remained close enough to the participant so that they were able to make physical contact, however, the researcher turned away from the participant to provide the cue that their attention was no longer available. All behaviours except for self-injurious and aggressive behaviour displayed by the participant were ignored; this included any attempts by the participant to initiate interaction. Verbal and physical attention was given contingent on self-injurious or aggressive behaviour. The attention was a standard verbal statement of concern for self-injury ("Don't do that, you'll hurt yourself") and aggression ("Don't do that, it hurts") accompanied by physical attention, such as rubbing the participants arm or removing their hand. After five seconds of attention, the researcher withdrew their attention again. This condition allows the positive reinforcement through attention delivery hypothesis to be tested when compared with the results from Condition A. Higher levels of target behaviour in

this condition would be indicative of behaviour occasioned by low levels of adult attention and maintained by contingent attention.

Condition C: Task demand. This condition was analogous to Carr and Durand's (1985) 'Difficult 100' condition and involved the researcher prompting the participant through a task that their teacher or parent had identified as being difficult. Tasks varied considerably depending on the ability of the participant; however, commonly used tasks included shape sorters, jigsaw puzzles and matching tasks. Three-point prompting procedures of verbal, verbal and gestural (or model) and physical prompt was used throughout. Each stage of the prompt occurred approximately three seconds after the previous prompt if the participant had not completed the task. Completion of the task for both independent and prompted responding lead to verbal praise and physical attention (mostly rubbing of the participant's arm or back). The task and the researcher's attention were removed for ten seconds contingent on self-injurious or aggressive behaviour but all other behaviours were ignored. If the self-injurious or aggressive behaviour continued longer than the ten second 'time-out' period, the task was not reinstated until there had been five seconds with no self-injury or aggression. This condition allowed a negative reinforcement through escape from demands hypothesis to be tested. High levels of target behaviour in this condition compared to Condition A would suggest behaviour occasioned by an aversive task and maintained by contingent removal (escape) of that task. All sessions were video-recorded and subsequently coded in real time using the behaviours and operational definitions described in Chapter 3, Section 3.9.7 and Table 3.3.

4.4.3. Procedure and data collection

Procedure and data collection is the same as that detailed in Chapter 3 (Section 3.9.4). As outlined in Section 3.9.3, all participants were screened using two items from the CBQ (Hyman *et al.,* 2002) prior to the study to ensure that they met inclusion criteria (i.e. self-injury and/or aggressive behaviour was reported by the main caregiver to be observed on a daily basis). The information gained from the CBQ was then used as criteria for observing either self-injurious and/or aggressive behaviour within the experimental functional analysis conditions. In other words it was necessary to know which form/s of challenging behaviour was expected to be observed in the experimental functional analysis conditions. For example, if a participant were reported by the main caregiver to display SIB on a daily basis but never displays aggressive behaviour, the participant would meet the criterion for analysis of SIB.

4.5. Data analysis

4.5.1. Observational data

The analysis to explore social function in challenging behaviour across the groups was conducted at two levels. Firstly, in order to consider the social function of self-injurious and aggressive behaviour on an individual participant level, the mean percentage duration of self-injurious and aggressive behaviour across experimental functional analysis conditions for each participant was plotted in a multi element graph (see Appendix J for each participant's graph and Figure 4.1 for an example). Each datum point on the graph in Figure 4.1 represents the mean percentage of time the participant spent engaging in self-injurious behaviour during that trial of the experimental functional analysis.

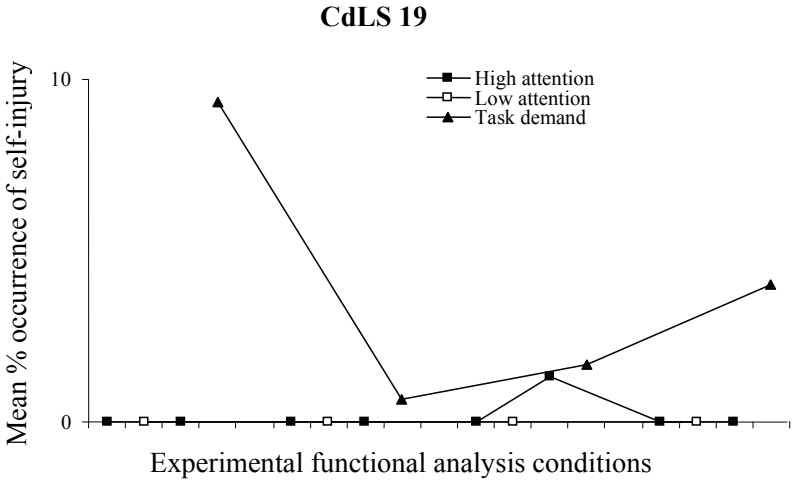


Figure 4.1: A graph to show the mean percentage occurrence of self-injurious behaviour across experimental functional analysis trials for Cornelia de Lange syndrome participant 19.

Secondly, the dominance statistic (*d;* Cliff, 1993) was calculated for each participant's self-injurious and aggressive behaviour across the experimental functional analysis conditions. The *d* statistic is a measure of how much one sample distribution lies above another and this is determined by comparing all scores in one condition to all scores in another using a dominance matrix. In order to calculate whether self-injury or aggression had an attention maintained function, each datum point (datum point = mean percentage time per trial) from the low attention condition was compared to every datum point from the high attention condition. Demand escape function was determined by comparing each task demand condition datum point to every datum point from the high attention condition. An example of a calculated dominance matrix is shown in Table 4.1. The cells in Table 4.1 are calculated by endorsing a value of +1 if the row value (demand datum point) is greater than the column value (high attention datum point), -1 if the row value is less than the column value and zero if the two values are identical. The sample value *d* is

the mean value of the elements in the dominance matrix. A *d* value of +1 would indicate that every datum point in a series is greater than every other datum point in another series. A *d* value of -1 would indicate that every datum point in a series is less than every other datum point in another series.

Table 4.1: Example of a dominance matrix from Cornelia de Lange syndrome participant 19.

	High attention							
Demand	0	0	0	0	0	1.33	0	0
9.33	1	1	1	1	1	1	1	1
0.67	1	1	1	1	1	-1	1	1
1.67	1	1	1	1	1	1	1	1
4	1	1	1	1	1	1	1	1

Calculation: 31/32= .97
d= .97 Strong social function

In order to compare the *d* statistic for social function at a categorical level, a cut-off value was arbitrarily nominated. A *d* value of between 0 and .33 indicates no social function, whilst any *d* value of .33 or above would suggest functional behaviour.

For each participant, *d* values were calculated for SIB and/or aggression and the highest absolute *d* value for each individual participant was taken and compared across syndrome groups. This analysis permits the identification of *any* environmental influence on challenging behaviour. Behaviour was classified as not having a social function if its *d* value was below .33 or, if no behaviour was observed in the experimental functional analysis conditions when that participant met the inclusion criterion of reportedly showing the behaviour when formally assessed using the

CBQ. When self-injurious or aggressive behaviour was observed within the experimental functional analysis conditions, a *d* value would be calculated. Social function in the experimental functional analysis conditions was determined at a participant level and not a behavioural level, i.e. if a participant was reported by carers to be showing both self-injurious and aggressive behaviour and social function was identified for one of the behaviours then the participant was classed as 'functional'. One-tailed tests were employed when directional hypotheses were stated.

4.5.2. Questionnaires

Functions to challenging behaviour were also explored using the QABF. The results of the Kolmogorov-Smirnov tests revealed that the data were normally distributed so a mixed design ANOVA was conducted. The five subscales of the QABF were the within-subjects factor and syndrome group was the between subjects factor.

4.6. Results

4.6.1. *Challenging behaviour function in the total sample*

Across the total sample of 60, 54 (90%) participants met inclusion criterion for SIB, whilst 51 (85%) participants met criterion for aggression. 45 (75%) participants met inclusion criteria for both SIB and aggression. SIB was observed in 39 (72%) out of the 54 participants who met criterion and the mean percentage duration of SIB during the experimental functional analyses was 2.88% of the time (SD=6.02; range: .08-33.91 %). Aggression was observed in 35 (69%) out of 51 participants who met criterion and the mean percentage occurrence was 1.9% of the time (SD=3.68; range:.06-18.42%). Combined challenging behaviour included all individual topographies of self-injury and aggression and this was observed in 50 participants (83% of total

sample of 60) and the mean percentage occurrence was 4.7% of the time (SD= 6.87; range: .08-35.94). The mean percentage duration of self-injurious and aggressive responding across experimental functional analysis conditions was plotted for each participant and is shown in Appendix J. Social function (attention maintenance or demand escape) of SIB was identified in 16 participants (30% of those meeting criterion), whilst functional aggressive behaviour was identified in 18 participants (35% of those meeting criterion). Four participants were found to have social function to both self-injury and aggression. In addition, unexpectedly six (11%) participants meeting criterion displayed more SIB in the high attention condition and ten (18%) participants meeting criterion for aggression displayed more aggressive behaviour in the high attention condition. This behaviour was found to be functional in this condition (i.e. *d* value was -.33 or below) and seven participants were found to have this unexpected function to both self-injury and aggression. Since function was identified at a participant level and not a behavioural level, this results in social function (attention maintenance or demand escape) being identified in 30 (50%) out of 60 participants. With the addition of the participants who were found to have behaviour that was functional in the high attention condition, the number of participants that were classed as functional rose to 39 (65%).

4.6.2. *Examination of any environmental influence on challenging behaviour across the syndrome groups*

Observational experimental functional analysis

Prior to testing the first hypothesis, the data were analysed to explore whether there was any difference in environmental influences on challenging behaviour between the three syndrome groups. Table 4.2 shows the means and standard deviations for the highest absolute *d* values

across the syndrome groups. Highest absolute *d* values were obtained for each participant and the 60 *d* values included: 25 *d* values for aggression, 23 *d* values for SIB and twelve *d* values of zero. A one-way ANOVA revealed that there were no significant differences between the groups with regard to the highest participant *d* value calculated for self-injurious or aggressive behaviour in the experimental functional analysis conditions. Consequently there was no difference in environmental influences on challenging across the groups.

Table 4.2: Comparison of highest absolute *d* value across syndrome groups in the experimental functional analysis conditions.

	Cornelia de Lange n=20		**Cri du Chat n=20**		**Angelman n=20**		**ANOVA F (df)**	***p***	**Post-hoc**
	n	Mean (SD)	N	Mean (SD)	N	Mean (SD)			
Highest absolute *d*	20	.45 (.36)	20	.45 (.29)	20	.49 (.30)	.13 (2)	.881	-

4.6.3. Challenging behaviours in the Cornelia de Lange syndrome group will evidence a stronger association with pain than challenging behaviours in the Angelman syndrome and Cri du Chat syndrome groups

The first hypothesis predicted that challenging behaviour in the Cornelia de Lange syndrome group would evidence a stronger association with pain than challenging behaviours in the Angelman and Cri du Chat syndrome groups. To test this hypothesis, environmental influences on challenging behaviour were explored using the QABF. Mean scores and standard deviations for the QABF broken down by subscale and syndrome group are presented in Table 4.3. Using

the five subscales from the QABF (attention, escape, pain, self-stimulatory and tangible) as the within-subjects factor and syndrome group as the between-subjects factor, a mixed ANOVA revealed a significant interaction between QABF subscale and syndrome group ($F(2,4) = 34.30$, p=.028). Post-hoc pair-wise *t*-test comparisons (see Table 4.3) revealed significant differences between the groups on the attention and pain subscales. In accordance with the first hypothesis, the Cornelia de Lange syndrome group scored significantly higher than both the Angelman and Cri du Chat syndrome groups on the pain subscale. These results indicate that challenging behaviour in the Cornelia de Lange syndrome group evidences a stronger association with pain than challenging behaviours in the Angelman and Cri du Chat syndrome groups.

Table 4.3: Comparison of QABF subscales across syndrome groups**.**

	Cornelia de Lange n=17	**Cri du Chat n=16**	**Angelman n=16**	**Post-hoc *t* values**	***p***	**Post-hoc**
	Mean (SD)	Mean (SD)	Mean (SD)	-	-	-
Attention	5.94 (4.31)	6.60 (3.70)	8.63 (3.61)	-1.93	.03	AS>CdLS
Escape	6.65 (4.76)	7.44 (3.24)	8.0 (3.96)	-	-	-
Self-stimulation	7.88 (4.04)	6.88 (4.96)	6.0 (3.5)	-	-	-
Pain	9.11 (4.11)	6.50 (4.0)	6.25 (3.04)	2.26 1.84	.02 .04	CdLS> AS, CdLS> CdC
Tangible	6.71 (5.30)	7.81 (4.86)	8.94 (4.93)	-	-	-

AS= Angelman syndrome, CdC= Cri du Chat syndrome, CdLS= Cornelia de Lange syndrome.

4.6.4. *Self-injurious behaviour in the Cornelia de Lange syndrome group will be influenced less by social operant reinforcement than for the Angelman syndrome and Cri du Chat syndrome groups*

The second hypothesis predicted that SIB in the Cornelia de Lange syndrome group would be influenced less by social operant reinforcement than in the Angelman and Cri du Chat syndrome groups. Table 4.4 shows the number and percentage of participants within each syndrome group who displayed functional self-injurious behaviour in the experimental functional analysis. Social functions are defined as attention maintained, demand escape, 'either function' which refers to attention maintained *or* demand escape and neither of the two functions. Table 4.4 also shows an unexpected result (other function) that is not consistent with the hypothesis. 'Other function' refers to those individuals who showed more self-injury during the high attention condition than the low attention or demand conditions and when the *d* value for the high attention condition was less than -.33.

Table 4.4: Comparison of functional self-injurious behaviour across syndrome groups (functional = *d* value of .33 and above).

	Cornelia de Lange n=20	**Cri du Chat n=20**	**Angelman n=20**	**χ^2 (df)**	***p***	**Post-hoc**
SIB reported (n)	20[1]	19	15	-	-	-
SIB observed (n)	16	14	9	-	-	-
Function:						
Attention maintained	4 (20%)[2]	6 (32%)	1 (6.5%)	3.18 (2)	.10	-
Demand escape	6 (30%)	1 (5%)	2 (13%)	4.85 (2)	.05	-
Either function	8 (40%)	6 (32%)	2 (13%)	3.33 (2)	.09	-
Neither function[3]	12 (60%)	13 (68%)	13 (87%)	3.33 (2)	.09	-
Other function	2 (10%)	4 (22%)	0 (0%)	3.73 (2)	.155	-

The first test of this hypothesis was to compare the number of participants within each syndrome group who were found to have attention maintained SIB as evidenced by a *d* value of .33 or above. Of the 54 participants in the study reported to display SIB, an attention maintained function of SIB was found in eleven (20%) of participants. Table 4.4 shows that a chi-square test revealed no difference in the proportion of participants across the groups who displayed attention maintained SIB. The second test of this hypothesis was to compare the number of participants within each syndrome group who were found to have demand escape SIB. In total, nine (17%) participants were found to have a demand escape function to their SIB. A chi-square test showed that there was no difference in the proportion of participants displaying demand escape SIB

[1] Note that percentages in the columns may total more than 100%. This is due to some participants having more than one function or participants for whom SIB was observed even though it had not been reported.
[2] As a percentage of those reported to display SIB (meeting inclusion criterion).
[3] 'Neither function' refers to participants who displayed SIB in the experimental functional analysis conditions and no social function was found by the *d* statistic and those participants who did not engage in SIB even though it was reported to occur.

across the groups; however, the result is approaching significance with the Cornelia de Lange syndrome group having a greater proportion of participants with a demand escape function to SIB. Finally, the proportion of participants within each group shown to have either attention maintained or demand escape function was compared to the proportion of participants within each group who showed neither of these two modes of operant social function (i.e. no function). Sixteen (30%) participants were found to have either social function whilst 38 (70%) participants were found to have neither attention maintained nor demand escape SIB. Chi-square tests showed that there were no differences in functional SIB across the groups, nor were there any differences in the number of participants across the groups displaying neither social function. There were also no differences across the groups in the proportion of participants showing SIB that demonstrated 'other function'.

In addition to exploring differences in the number of participants within each group who displayed functional or non-functional SIB, an alternative method of exploring the social function of SIB was to compare the *d* values of SIB for both attention maintenance and demand escape function across the groups (Table 4.5). A Kruskal-Wallis revealed that there was no significant difference across the groups for the *d* value for either attention maintained function or demand escape function calculated for SIB within the experimental functional analysis conditions. Consequently there was no difference in overall SIB function across the groups when comparing *d* values.

Table 4.5: Comparison of *d* values for SIB across syndrome groups in the experimental functional analysis conditions.

	Cornelia de Lange n=20 Median *(IQ range)*	**Cri du Chat n=20** Median *(IQ range)*	**Angelman n=20** Median *(IQ range)*	**Kruskal-Wallis χ^2 (df)**	***p***	**Post-hoc**
Attention	0 *(.18)*	.17 *(.50)*	.07 *(.13)*	.84 (2)	.66	-
Demand	.09 *(.78)*	.04 *(.30)*	.07 *(0)*	2.62 (2)	.27	-

4.6.5. ***Aggressive behaviour in the Angelman syndrome group will evidence stronger maintenance by positive social reinforcement than aggressive behaviours in the Cornelia de Lange syndrome and Cri du Chat groups.***

The third hypothesis predicted that aggressive behaviour in the Angelman syndrome group would evidence stronger maintenance by positive social reinforcement than aggressive behaviours in the Cornelia de Lange and Cri du Chat syndrome groups. Prior to testing the third hypothesis, the data on sociability were examined across syndrome groups. Table 4.6 shows the results of a one-way ANOVA on the total sociability scores on the SQID for both familiar and unfamiliar adults.

Table 4.6: Comparison of total sociability with familiar and unfamiliar adults across syndrome groups (SQID).

SQID subscale	**Cornelia de Lange n=17** Mean (SD)	**Cri du Chat n=18** Mean (SD)	**Angelman n=16** Mean (SD)	**F (df)**	***p***	**Post-hoc**
Familiar total	42.59 (7.23)	48.22 (8.15)	53.25 (2.91)	10.77 (2)	<.001	AS>CdCS, CdLS CdCS>CdLS
Unfamiliar total	31.41 (9.89)	35.17 (11.86)	44.56 (6.11)	8.0 (2)	.001	AS>CdCS, CdLS

AS= Angelman syndrome, CdC= Cri du Chat syndrome, CdLS= Cornelia de Lange syndrome.

As predicted, the ANOVAs revealed that there was a difference across groups in sociability with both familiar and unfamiliar adults. Post-hoc comparisons revealed that the Angelman syndrome group were more sociable than the Cri du Chat and Cornelia de Lange syndrome groups with both familiar and unfamiliar adults whilst, the Cri du Chat syndrome group was more sociable than the Cornelia de Lange syndrome group on the familiar subscale only. Secondly, differences on the subscales scores on the SQID were examined using Kruskal-Wallis tests. Table 4.7 shows the medians and interquartile ranges for the subscales of the SQID across syndrome groups.

Table 4.7: Comparison of sociability with familiar and unfamiliar adults across syndrome groups (SQID).

		Cornelia de Lange n=17	**Cri du Chat n=18**	**Angelman n=16**	**Kruskal-Wallis χ^2 (df)**	***p***	**Post-hoc**
SQID subscale		Median *(IQ range)*	Median *(IQ range)*	Median *(IQ range)*			
Familiar	Receive interaction	11.0 *(10.0)*	13.0 *(9.0)*	14.0 *(5.0)*	12.97	.002	AS>CdLS
	Interaction	12.0 *(6.0)*	13.0 *(5.0)*	14.0 *(3.0)*	9.56	.008	AS>CdLS
	Approach	8.0 *(10.0)*	13.0 *(8.0)*	8.0 *(6.0)*	16.45	<.001	AS, CdCS>CdLS
	Performance	12.0 *(6.0)*	13.0 *(6.0)*	14.0 *(2.0)*	10.67	.005	AS>CdLS
Unfamiliar	Receive interaction	8.0 *(8.0)*	9.0 *(11.0)*	11.5 *8.0)*	8.03	.018	AS>CdLS
	Interaction	9.0 *(10.0)*	9.0 *(10.0)*	11.5 *(8.0)*	5.17	.075	-
	Approach	6.0 *(6.0)*	8.50 *(12.0)*	11.5 *(8.0)*	14.05	.001	AS>CdLS
	Performance	8.0 *(10.0)*	7.5 *(11.0)*	12.0 *(8.0)*	14.15	.001	AS>CdLS, CdCS

AS= Angelman syndrome, CdC= Cri du Chat syndrome, CdLS= Cornelia de Lange syndrome.

After having explored differences in sociability across the syndrome groups, the first test of the

third hypothesis was to explore environmental influences on challenging behaviour using the QABF. As Table 4.3 showed, the Angelman syndrome group scored significantly higher than the Cornelia de Lange syndrome group on the attention subscale of the QABF. This provides some support for the prediction made in hypothesis three that aggressive behaviour in the Angelman syndrome group would evidence stronger maintenance by positive social reinforcement than aggressive behaviour in the Cornelia de Lange syndrome and Cri du Chat groups. The second test of this hypothesis was to compare the number of participants within each syndrome group who were found to have attention maintained aggressive behaviour. Table 4.8 shows the number and percentage of participants within each syndrome group who displayed functional aggressive behaviour in the experimental functional analysis.

Table 4.8: Comparison of functional aggressive behaviour across syndrome groups (functional=*d* value of .33 and above).

	Cornelia de Lange n=20	**Cri du Chat n=20**	**Angelman n=20**	**χ^2(df)**	***p***	**Post-hoc**
Aggression reported (n)	13[1]	18	20			
Aggression observed (n)	6	12	17			
Function:						
Attention maintained	1 (8%)[2]	5 (28%)	11 (55%)	8.35 (2)	.007	AS> CdLS
Demand escape	0 (0%)	1 (5.5%)	6 (30%)	7.84 (2)	.010	AS> CdLS
Either function	1 (8%)	5 (28%)	12 (60%)	10.05 (2)	.007	AS> CdLS
Neither function	13 (100%)	2 (11%)	8 (40%)	10.05 (2)	.003	CdLS>AS
Other function	2 (15%)	3 (17%)	5 (25%)	.73 (2)	.696	-

[1] Note that columns may total more than total n for aggression reported. This is due to some participants having more than one function or participants for whom aggression was observed even though it had not been reported.
[2] As a percentage of those reported to display aggression.

Table 4.8 shows that a chi-square test revealed that there were a greater proportion of individuals in the Angelman syndrome group who had attention maintained aggressive behaviour than the Cornelia de Lange syndrome group, which is in line with the hypothesis. The third test of this hypothesis was to compare the number of participants within each syndrome group who were found to have demand escape aggression. A chi square test revealed that there was significantly more demand escape aggressive behaviour observed in the Angelman syndrome group than in the Cornelia de Lange syndrome group. When comparing the groups on the number of participants found to have either attention maintained or demand escape aggression, as predicted, there was a significant difference between the Angelman and Cornelia de Lange syndrome groups, with the Angelman syndrome group having a greater proportion of participants with social function to their aggression. Finally when comparing the number of participants across the groups who have neither attention maintained nor demand escape aggressive behaviour, there was a significant difference between the groups with less influence of social function on aggression being observed the Cornelia de Lange syndrome group in comparison to the Angelman syndrome group. Across all syndrome groups, out of the 51 participants reported to display aggression, eighteen (35%) were found to have an attention maintained function, seven (14%) a demand escape function, eighteen (35%) were found to have one or other of these social functions, 23 (45%) were found to have neither function and 10 (20%) were found to have 'other function'. 'Other function' was not accounted for in the original hypothesis and refers to those participants who were functional in the high attention condition (i.e. had a *d* value of -.33 or below). There was no difference in the proportion of participants across syndrome groups that were found to have aggressive behaviour that was classified as 'other function'. To summarise, aggressive behaviour in the Angelman syndrome group evidenced stronger maintenance by positive social reinforcement in the form of

attention maintained and demand escape aggression than the Cornelia de Lange syndrome group. Aggression in the Cornelia de Lange syndrome group was influenced less by positive social reinforcement than for the Angelman and Cri du Chat syndrome groups.

Function of aggressive behaviour was also explored by comparing the *d* value of aggression for both attention maintenance and demand escape function across the groups. Table 4.9 shows medians and inter-quartile ranges for the *d* values for aggression on attention maintained and demand escape function. A Kruskal-Wallis test revealed that there was no significant difference across the groups for the *d* values for either attention maintained function or demand escape function, calculated for aggression within the experimental functional analysis conditions. Consequently there was no difference in overall aggression function across the groups using this method of analysis.

Table 4.9: Comparison of *d* values for aggression across syndrome groups in the experimental functional analysis conditions.

	Cornelia de Lange n=20 Median *(IQ range)*	**Cri du Chat n=20** Median *(IQ range)*	**Angelman n=20** Median *(IQ range)*	**Kruskal-Wallis χ^2 (df)**	***p***	**Post-hoc**
Attention	.02 (0)	.12 *(.43)*	.23 *(.55)*	4.80	.09	-
Demand	0 *(0)*	0 *(0)*	.12 *(.46)*	.36	.83	-

4.7. Discussion

This is the first empirical study that has examined operant theory applied to self-injurious and aggressive behaviour in Angelman, Cri du Chat and Cornelia de Lange syndromes. The broad aim of the study was to examine the gene-environment interactions on self-injury and aggression in these genetic syndromes and this has been appraised by utilising robust experimental functional analysis. Experimental functional analysis was carried out under controlled conditions with systematic environmental manipulations that were based on previously published methodology (Iwata *et al.*, 1982/1994a; Carr and Durand, 1985; Strachan *et al.,* 2009). The observation of operationally defined behaviours was rigorous and inter-observer reliability for the coding of these behaviours was good. The statistical method (Cliff's *d* statistic, 1993) used for allocating function to behaviour extends previous research which has typically relied on visual inspection of the graphed percentage duration of challenging behaviour across conditions. The *d* statistic offers a more systematic and robust approach to determining the function of challenging behaviour and is both applicable and appropriate for a small, non-parametric data set (Cliff, 1993). When comparing challenging behaviour across the three syndrome groups, the results broadly demonstrate that challenging behaviour in Cornelia de Lange syndrome may be associated with pain, whilst aggression in the Angelman syndrome group evidences stronger maintenance by positive social reinforcement.

The proportion of individuals with Cornelia de Lange syndrome reported by main caregivers to display self-injury was 20 (100%) and self-injury was observed in sixteen (80%) participants during the experimental functional analysis. Participants were selected for the study if they were reported to display either self-injury and/or aggression on a daily basis and so, although these

high proportions of reported and observed self-injury are unsurprising, it is interesting to note that all 20 participants (100%) in the Cornelia de Lange syndrome group were recruited based on the presence of self-injury rather than the presence of aggressive behaviour. This is consistent with studies in the literature that report SIB as a clinically significant problem in Cornelia de Lange syndrome (e.g. Bryson *et al.,* 1970; Hyman *et al.,* 2002; Johnson *et al.,* 1976) and that rates of aggressive behaviour are relatively low in the syndrome (Oliver *et al.,* in review).

As predicted, challenging behaviour in the Cornelia de Lange syndrome group evidenced a stronger association with pain and discomfort than the same behaviours in the Angelman and Cri du Chat syndrome groups. This is consistent with previous research that has linked SIB in Cornelia de Lange syndrome to physical health problems and suggests that SIB may enter an individual's behavioural repertoire in response to pain or discomfort (Luzzani *et al.,* 2003; Moss *et al.,* 2005; Oliver *et al.,* 2003b). Cornelia de Lange syndrome is associated with many health problems and gastrointestinal problems are the most commonly reported (Hall *et al.,* 2008). Health problems affecting the upper gastrointestinal tract, including the oesophagus, stomach and upper small intestine are common and gastroesophageal reflux is thought to be present in 65% of individuals with Cornelia de Lange syndrome (Hall *et al.,* 2008, Luzzani *et al.,* 2003). Luzzani *et al.* (2003) suggested that pain resulting from gastroesophageal reflux may be linked to self-injury. Although this study provides some support for the role of pain and discomfort and its association with self-injury in Cornelia de Lange syndrome, it should be noted that the questionnaire measure used to determine environmental influences on behaviour was not specific about the form of challenging behaviour. In this way, informants may have answered questions relevant to either self-injury or aggression and so firm conclusions that self-injury specifically is linked to pain in

Cornelia de Lange syndrome can not be made. Of course this issue is also true across for the Angelman and Cri du Chat syndrome groups. In addition, the study relied on an informant-based questionnaire in order to assess pain in the sample. The QABF has been a useful measure in this study for a group of individuals who are unable to self-report feelings of pain; however, reliance on informant-based questionnaires is not as reliable as direct observational techniques. Voepel-Lewis, Mekrel, Tait, Trzcinka and Malviya (2002) note that questionnaire ratings of pain are susceptible to observer bias as well as being affected by the expression of other emotions in addition to pain. Future research exploring pain in Cornelia de Lange syndrome would benefit from the inclusion of behavioural measures of pain such as the Child Facing Coding System (CFCS, Chambers, Cassidy, McGrath, Gilbert & Craig, 1996).

It was also predicted that SIB in the Cornelia de Lange syndrome group would be influenced less by operant reinforcement than the Angelman syndrome and Cri du Chat syndrome groups. No support for this hypothesis was found and there were no differences across the syndrome groups in the proportions of participants found to have functional self-injury. This result seems somewhat surprising given previous research which links self-injury to painful health conditions (Luzzani *et al.,* 2003; Oliver *et al.,* 2003b), SIB of a compulsive-like quality (Hyman *et al.,* 2002) and the presence of self-restraint and physical restraint in Cornelia de Lange syndrome (Basile *et al.,* 2007; Dosseter *et al.,* 2001; Hyman *et al.,* 2002; King, 1993; Powell *et al.,* 1996; Shear *et al.,* 1971). However, it is possible that once SIB becomes part of an individual's repertoire (i.e. in response to pain and discomfort: Luzanni *et al.,* 2003; Moss *et al.,* 2005), it may then become operantly reinforced and associate with particular environmental events (Arron *et al.,* 2006; Moss *et al.,* 2005). In fact, the proportion of Cornelia de Lange syndrome participants showing

functional SIB was 40%, which is similar to that reported by Arron *et al.* (2006) and Sloneem *et al.* (2009). There appears to be a consensus emerging in the literature in the proportion of individuals with Cornelia de Lange syndrome who are showing SIB that is related to an environmental event and this seems to be at approximately 30-40%. For the remaining 60-70% of individuals with Cornelia de Lange syndrome, environmental influences on SIB tend not be identified through conventional experimental functional analysis (Arron *et al.,* 2006; Sloneem *et al.,* 2009).

A result that was surprising and not accounted for in the original hypotheses was those participants who displayed more self-injury during the high attention condition (classed as 'other function'). Although there were no significant differences across the groups, 10% of participants in the Cornelia de Lange syndrome group and 22% of the Cri du Chat group were found to have self-injury that demonstrated this function. It is not entirely clear what this function demonstrates, however, higher levels of self-injury at times of high social contact may suggest a social escape function. This may be a plausible explanation for individuals with Cornelia de Lange syndrome given the high prevalence of autistic-like characteristics in the syndrome and particular difficulties in the areas of sociability, communication and increased rates of social anxiety (Moss *et al.,* 2008; Chapter 3, Section 3.11.5 and Table 3.8). However, given anecdotal reports of heightened sociability in Cri du Chat syndrome, escape from social interaction does not seem an appropriate explanation. Another possible explanation for the unexpected result may be that the presence of the researcher in close proximity during the high attention condition acted as a discriminative stimulus. The presence of the researcher may have 'signalled' to some of the

participants that attention was available and therefore they were more likely to show challenging behaviour at these times to ensure that social interaction was maintained.

Aggressive behaviour was reported by parents and carers to occur in all 20 (100%) participants with Angelman syndrome and observed in seventeen participants (85%) during the experimental functional analysis. This is a similar proportion of individuals to that observed by Strachan *et al.* (2008). In line with the hypotheses, aggressive behaviour in the Angelman syndrome group evidenced stronger maintenance by positive social reinforcement than the aggressive behaviours in the Cornelia de Lange syndrome group, however, there were no differences in functional aggressive behaviour between the Angelman and Cri du Chat syndrome groups. Specifically, more individuals in the Angelman syndrome group were found to have an attention maintained function of aggressive behaviour than the Cornelia de Lange syndrome group. This result is similar to the findings of Strachan *et al.* (2009) in their study of twelve children with Angelman syndrome, in which experimental functional analysis was also employed.

The finding that more of the Angelman syndrome group engaged in aggressive behaviour at times of low social contact suggests that they may be engaging in the behaviour in order to reinstate social attention. This is indirectly relevant to the heightened sociability in Angelman syndrome that was both found in the previous study (Chapter 3, Section 3.11.5 and Table 3.10) and is reported in the literature (e.g. Horsler & Oliver, 2006a; Oliver *et al.,* 2002; Oliver *et al.,* 2007). For example, Oliver *et al.* (2007) found that children with Angelman syndrome showed increased laughing and smiling in response to social interaction and actively sought social interaction with adults more than the comparison group. Oliver *et al.* and Strachan *et al.* use

operant learning theory to suggest that aggression may be maintained by access to social attention, as it is a potent reinforcer for individuals with Angelman syndrome. Under conditions of deprivation of social attention, physical aggression may serve as attempts at regaining eye contact, thus briefly prolonging social interaction. This is directly relevant to the findings of the study in Chapter 3 in which specific topographies of aggressive behaviour were found to be more common in Angelman syndrome. Specifically, hair pulling and grabbing were observed in 70% and 65% of the Angelman syndrome group respectively, and these topographies differ from those reported to be most common in the broader intellectual disability population. This suggests that these topographies may be specific to Angelman syndrome and under conditions of low social contact, hair pulling and grabbing are aggressive behaviours that act to re-establish social contact and evoke eye contact. This reveals an interesting evocative gene-environment interaction in Angelman syndrome in which an aspect of the behavioural phenotype is able to evoke particular environmental responses. Oliver *et al.* (2007) found that higher levels of smiling in adults were observed in response to the smiling of the children and this was not evident for a comparison group. In this study, results have shown that individuals with Angelman syndrome are more sociable with both familiar and unfamiliar adults in comparison to individuals with Cornelia de Lange and Cri du Chat syndromes. The present study provides evidence that a genetic predisposition to find social contact rewarding may account for the high levels of aggressive behaviour observed in the syndrome; if social contact from adults is presented contingent on the occurrence of aggressive behaviour.

It is also notable that 25% of the Angelman syndrome sample also showed the highest levels of aggressive behaviour in the high attention condition of the experimental functional analysis. In

the literature this pattern typically represents a social escape function; however this seems unlikely given the evidence of positive affect throughout the observational period (See Chapter 3, Section 3.11.5). Strachan *et al.* (2009) also found this pattern in 30% of their sample and indicated that it may reflect a motivation in Angelman syndrome to maintain, rather than initiate social interaction. In the Cornelia de Lange syndrome group, 15% of participants demonstrated this 'other function' as well as 17% of participants in the Cri du Chat syndrome group.

No specific predictions were made about demand escape behaviour in the Angelman syndrome group, however six participants (30% of sample) were found to have aggressive behaviour that evidenced a demand escape function and this proportion was higher than in the Cornelia de Lange syndrome group. Hyperactivity, impulsivity and difficulties with attention are commonly reported in Angelman syndrome (Chertkoff-Waltz & Benson, 2002; Clarke & Marston, 2000; Oliver *et al.,* in review) and so keeping on task in the demand conditions may have been difficult or aversive for some individuals. Another explanation for aggression maintained by escape from demands is that demands themselves may provide an opportunity for reward when the adult engages with the child. Aggression at the time that the demand is placed may not indicate an escape function but may be, as discussed previously, an attempt by the child to maintain social contact. In order to prevent behavioural extinction in the experimental functional analysis, the demand was removed and the adult turned away from the participant contingent on challenging behaviour. The demand was then not reinstated until there had been five seconds without challenging behaviour. Anecdotal observations of some of the Angelman syndrome participants showed that once the demand was removed, it was unable to be reinstated as aggressive behaviour was persistent. It was felt that much of the aggressive behaviour observed at these

times (predominantly hair pulling and grabbing) may have been attempts by the individual to regain the researcher's attention, rather than to prevent the presentation of the task. This explanation is plausible given the results of this study and previous research that indicates aggression at times of low social contact. Although demand escape function was found to be higher in the Angelman syndrome, it should be borne in mind that the proportion of the group that displayed this function (30%) is not dissimilar to the proportions found in the wider population of people with intellectual disabilities. For example, Iwata *et al.* (1994) found that social negative reinforcement function accounted for 38.1% of the 152 participants with which experimental functional analysis was conducted.

Although there were no statistically significant differences between the groups, the Cri du Chat group had the highest proportion of individuals who showed attention maintained self-injury (32%) compared to 20% and 6.5% in the Cornelia de Lange and Angelman syndrome groups respectively. The proportion of individuals who were found to have aggression maintained by attention in the Cri du Chat group was at a similar level to SIB (33%), which was higher than the Cornelia de Lange group (8%) but not as high as the Angelman syndrome group (55%). Self-injury and aggression maintained by escape from task demands in the Cri du Chat group was low: 5 and 10% respectively. Social reinforcement of challenging behaviour in Cri du Chat syndrome is consistent with anecdotal reports of heightened sociability in the syndrome, although to date there are no reports of empirical studies. Anecdotally, it is also notable that challenging behaviour resulting from communication difficulties was observed in four individuals in the Cri du Chat syndrome group. Instances of self-injury and aggression were mainly in response to the experimenter failing to understand what the participant was saying. These anecdotal observations

are consistent with the marked expressive/receptive language discrepancy that was found in Chapter 3 (Section 3.9.5) and is commonly reported in the syndrome (Cornish & Munir, 1998; Cornish *et al.,* 1999). Communication impairments have been argued to be a risk marker for problem behaviours such as self-injury and aggression in other individuals with intellectual disability (Carr & Durand, 1985: McClintock *et al.,* 2003). Future research should aim to explore the link between communication impairments and challenging behaviour in Cri du Chat syndrome in more detail.

All findings of the study should be considered in relation to the limitations. Firstly, there may have been a bias in recruitment where parents and carers may have opted in to the study if they were unable to identify triggers to their child's behaviour; whilst for those families where triggers were more easily identifiable they may have chosen not to take part. These families may have felt that their child's behaviour was already predictable and high-risk situations were clear, in this way they may already have had useful management strategies in place and thus felt that the study may not offer any novel information. Conversely, for parents and carers who were not able to identify triggers to behaviour, the study may have provided them with the opportunity to identify function to their child's behaviour and recommendations to help with management. In order to avoid such a bias and take the focus away from identifying function and behaviour management, measures were taken to title information sheets, flyers and letters with more general headings such 'Understanding Challenging Behaviour in X syndrome'. Secondly, this study had an age range of two to nineteen years. Given that there is some evidence to suggest that aggressive behaviour in Angelman syndrome may decrease with progression into adulthood (Clayton-Smith, 2001), it would be interesting in future work to study challenging behaviour in an older sample to

see whether modes of operant reinforcement of challenging behaviour are subject to change over time also.

Overall, the results of this study add to an emerging literature showing that problem behaviours in syndromes can be influenced by an interaction between a genetically predisposed aspect of the behavioural phenotype and operant processes. Studies which demonstrate that challenging behaviour in genetic syndromes can be influenced by environmental factors are important in highlighting the point that behaviours in these syndromes should not be considered as immutable and thus negate therapeutic nihilism. Aggressive behaviour in Angelman syndrome has been found to have a stronger maintenance by positive social reinforcement, whilst challenging behaviour in Cornelia de Lange syndrome is more likely to be associated with pain and discomfort from health problems arising from the syndrome. In both syndromes, individual characteristics of genetic origin interact with environmental factors to drive the development of challenging behaviour. Examples of gene-environment interactions have also been demonstrated in a number of other genetic syndromes. For example, Taylor and Oliver (2008) found that SIB in Smith-Magenis syndrome was linked to low levels of adult contact and additionally, response cost of the behaviour may be reduced due to dampened pain sensitivity. Oliver *et al.* (1993) found that phenotypic stereotyped hand-to-mouth movements in Rett syndrome were operantly reinforced, and harder hits to the mouth became functional by escape from social attention. Examinations of specific forms of gene-environment interactions within syndromes is important in order to promote understanding of the aetiology of problem behaviours both within genetic syndromes and the wider population of individuals with severe intellectual disabilities (see

Chapter 2). The results of the study also suggest that there is a growing need for functional analytic studies in order to understand and delineate these gene-environment interactions.

What appears to be most important is that this study has highlighted the need to progress from assessing the functions of challenging behaviour and move towards considering how specific modes of reinforcement may be linked to specific motivations. The study has shown support for a difference in motivation between Angelman and Cornelia de Lange syndromes. In Angelman syndrome, aggressive behaviour for over half of the sample was maintained by access to social attention which is linked to the genetic predisposition to find social contact rewarding. Having knowledge of this underlying motivation may have wider reaching implications for individuals with Angelman syndrome and their families. It is probable that this drive for social attention is likely to affect a host of other behaviours in addition to challenging behaviour, particularly those behaviours which are linked to gaining maternal resources (Brown & Consedine, 2004). Examples of such behaviours are sleep disturbance (particularly waking others at nighttime), which is commonly reported in the syndrome (Chertkoff- Waltz *et al.,* 2005; Didden *et al.,* 2004; Miano *et al.,* 2004; Pelc *et al.,* 2008) and anecdotally the reports of stranger approach and sibling relationship difficulties as an individual competes for maternal resources.

In Cornelia de Lange syndrome there seems to be less evidence of operant reinforcement. However, there is support for the notion that SIB may arise in response to painful health conditions. This is consistent with empirical evidence showing an association between gastroesophageal reflux related pain specifically and self-injury in Cornelia de Lange syndrome (Luzzani *et al.*, 2003). As many individuals with Cornelia de Lange syndrome have limited

expressive communication they may not always be able to indicate to others that they are in pain. Having knowledge of the link between pain and self-injury may help carers to be attentive of the early signs of self-injury and be aware of health conditions which may arise. This issue is directly relevant to the quality of life of individuals with Cornelia de Lange syndrome.

The study also has important implications for assessment and intervention. Assessment of challenging behaviour may take similar forms for all individuals, however, the study highlights the importance of prioritising assessments. For example, ensuring that illnesses commonly seen in Cornelia de Lange (e.g. gastroesophageal reflux, otitis media) are assessed and treated immediately and effectively may help to prevent potentially injurious responses. In Angelman syndrome the influence of the environment on aggressive behaviour alludes to the potential for intervention to utilise operant reinforcement.

CHAPTER 5

Beyond Conventional Experimental Functional Analysis to Examine Challenging Behaviour in Angelman, Cri du Chat and Cornelia de Lange Syndromes

----------Preface to Chapter 5----------

The study in Chapter 4 used experimental functional analysis to examine gene-environment interactions on self-injurious and aggressive behaviour in Cornelia de Lange, Cri du Chat and Angelman syndromes. Although social function to these behaviours was identified in 65% of the sample, there were still a number of participants who either, demonstrated no behaviour within the assessments, or the pattern of behaviour observed was not functional in any specific condition. This study utilises structured descriptive assessments to identify idiosyncratic functions in individuals where conventional experimental functional analysis in Chapter 4 had demonstrated no social function to challenging behaviour.

5.1. Introduction

Experimental methods of functional assessment (Carr & Durand, 1985; Iwata, Dorsey, Slifer, Bauman & Richman, 1982/1994) have been important in the identification of sources of reinforcement that maintain problem behaviour. The main advantage of this methodology, in comparison to other methods of functional assessment, is the degree of control that is exerted over environmental variables, which allows for inferences to be made regarding the functions of behaviour. However, one shortcoming that results from strict adherence to an established manipulation of environmental events in conventional experimental functional analysis is, whether the range of potential is sufficiently large enough to identify idiosyncratic or unusual functions.

Conventional experimental functional analysis typically only tests a specific set of establishing operations and these are usually levels of social attention, demand and access to tangible items (Carr & Durand, 1985, Iwata *et al.,* 1982/1994a). There is also good evidence that challenging behaviours may be maintained by idiosyncratic factors, for example, avoidance of termination of ritualistic behaviours, transitions, individuals being in non-preferred locations (i.e. in and out of wheelchair) and the presence of a caregiver (Adelinis, Piazza, Fisher & Hanley, 1997; English & Anderson, 2004; McCord, Thomson & Iwata, 2001; Murphy, Macdonald, Hall & Oliver, 2000).

In contrast to conventional experimental functional analysis, descriptive assessments involve observations of the individual and their behaviour in the natural environment. Variables are not manipulated and instances of target behaviour and environmental events that precede or follow the behaviour are recorded and are subjected to probabilistic analyses (Hall & Oliver, 1992;

Oliver, Hall & Murphy, 2005). Descriptive assessments confer the advantage of potentially identifying idiosyncratic variables associated with problem behaviour, as well as exerting significantly less control over environmental factors and this may be useful in documenting the mutual reinforcement process (e.g. Tiger, Hanley & Bessette, 2006). Descriptive assessments may also be useful in situations where conventional experimental functional analysis is difficult to conduct and they may inform on which specific establishing operations to assess in conventional experimental functional analysis. In addition, they may provide information when conventional experimental functional analysis has proven inconclusive (Borrero, Vollmer & Borrero, 2006; Mace & Lalli, 1991). In spite of the benefits to descriptive assessments, they are only able to yield correlational information about behaviour-environment relations, and reinforcing consequences may not be identified if behaviour is only reinforced occasionally (Mace, Lalli & Shea, 1992 as cited by Anderson & Long, 2002).

Anderson and Long (2002) developed the structured descriptive assessment (SDA), which is designed to capitalise on the strengths of both conventional experimental functional analysis and descriptive assessments. The SDA is conducted in the environment in which the target behaviour typically occurs and is usually conducted by the individual's main caregiver. The SDA is designed based on situations that caregivers report to be influential in triggering challenging behaviour and is similar to conventional experimental functional analysis in that, specific antecedent conditions believed to evoke problem behaviour are delivered in a systematic way. However, unlike conventional experimental functional analysis, consequences are not manipulated. Anderson and Long (2002) developed the SDA for four children with developmental disabilities and severe challenging behaviour including self-injurious behaviour

(SIB), aggression and destruction. Results from the SDA were compared to the results of conventional experimental functional analysis and for three of the children, both assessments produced similar hypotheses regarding the environmental variables maintaining their behaviour. For the fourth participant, different hypotheses were identified by the two assessments. However, an intervention based on the results of the SDA was successful at significantly reducing target behaviour. An intervention based on the conventional experimental functional analysis results was not implemented and so unfortunately the authors were unable to establish whether this would have been more or less effective than the intervention based on the SDA.

English and Anderson (2006) evaluated interventions based on conventional experimental functional analysis and SDA results in three children with mild intellectual disability, and found that interventions based on the SDA were more effective at reducing problem behaviours. The authors suggested that the efficacy of interventions based on the SDA came from the ability of the SDA to test a much broader range of reinforcing consequences, whereas conventional experimental functional analysis provides specifically manipulated consequences. The SDA has also been found to be useful in developing hypotheses about environment-behaviour relations in typically developing children (Anderson, English & Hedrick, 2006).

The present study follows on from the study in Chapter 4, which utilised conventional experimental functional analysis for self-injury and aggression with 60 participants with Angelman (N=20), Cri du Chat (N=20) and Cornelia de Lange (N=20) syndromes. The study was the first to examine operant theory of self-injury and aggression in these syndromes and the study explored the effects of the establishing operations of low levels of adult attention and high levels

of task demand on levels of self-injurious and aggressive responding. In Cornelia de Lange syndrome, eight participants (40% of the sample) were found to have SIB that demonstrated a social function (either attention maintained or demand escape), whilst only one participant (8%) had aggressive behaviour that had a social function. In Cri du Chat syndrome, six participants (32%) were found to have SIB with a social function and five participants (28%) had aggression with a social function. Finally, in Angelman syndrome, two participants (13%) were found to have SIB that demonstrated a social function and twelve (60%) had functional aggression. Unexpectedly, there were also two (10%) participants in the Cornelia de Lange syndrome group and four (22%) participants in the Cri du Chat syndrome group who had self-injury that was functional in the high attention condition. With regards to aggressive behaviour, there were two (15%) participants in the Cornelia de Lange syndrome group, three (17%) participants in the Cri du Chat syndrome group and five participants (25%) in the Angelman syndrome group who were found to have behaviour that was functional in the high attention condition.

Although clearly conventional functional analysis was useful in this study for identifying function for a number of participants (social function in the experimental functional analysis conditions was determined at a participant level and not a behavioural level and was identified in 65% of the sample of 60), the method may have failed to identify idiosyncratic social function that was not tested. This is a an important issue in the field of functional assessment as failure to identify function in conventional functional assessment does not necessarily mean that there is no social function to an individual's challenging behaviour. It may simply mean that specific, unusual or idiosyncratic antecedents have not been tested.

In summary, research suggests that the SDA is a useful addition to functional analysis methods. The SDA may be particularly useful at identifying idiosyncratic variables maintaining problem behaviour that would otherwise not be tested in conventional experimental functional analysis. In addition, environment-behaviour relations that are identified by conventional experimental functional analysis may differ from those identified by the SDA and interventions based on the SDA may be more effective than those derived from conventional experimental functional analysis. This study follows on from a previous study described in Chapter 4 in which conventional experimental functional analysis was carried out with individuals with Angelman, Cri du Chat and Cornelia de Lange syndromes. For those participants where social function was not identified through conventional experimental functional analysis, the SDA may be useful in determining some idiosyncratic functions that would otherwise be overlooked in conventional experimental functional analysis.

5.2. Aims

The general aim of this chapter is to assess whether structured descriptive assessments (based on caregivers reports of high-risk situations for challenging behaviour) are able to identify environmental influences on targeted challenging behaviour in Angelman, Cri du Chat and Cornelia de Lange syndromes when conventional experimental functional analysis methods have not demonstrated a social function.

5.3. Method

5.3.1. Recruitment

All participants for this study had been part of the larger studies described in Chapters 3 and 4. The initial recruitment procedure is described in section 3.9.3. Following the study in Chapter 4 in which conventional experimental functional analysis was carried out with 60 participants; potential participants for this study were those for whom social function for challenging behaviour had not been identified. Social function in the conventional experimental functional analysis was determined at a participant level and not a behaviour level, i.e. if a participant was reported by carers to be showing both self-injurious and aggressive behaviour and social function was identified for one of the behaviours in the conventional functional analysis conditions then they were classed as 'functional'. However, if no social function to self-injury or aggression was identified or the experimental functional analysis had proved inconclusive, participants and their carers were approached for inclusion in the current study. A summary of how participants were recruited for the current study from the previous study is shown in Figure 5.1.

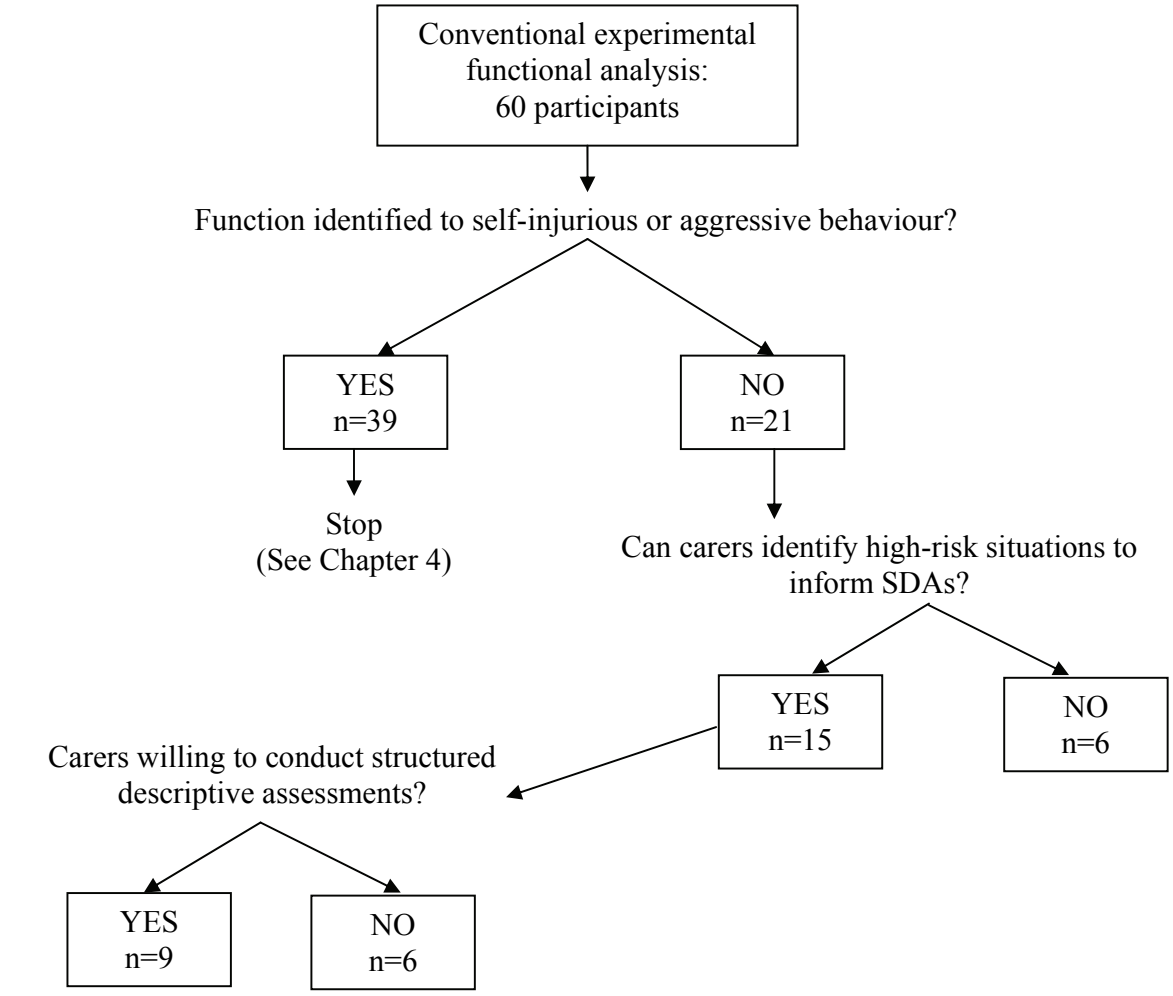


Figure 5.1: Summary of recruitment for the structured descriptive assessments.

As Figure 5.1 shows, function was not identified for 21 (35%) participants. In the current study, participants were only included if the main caregiver could identify a specific, high-risk situation for the occurrence of challenging behaviour. This is because the construction of the SDA relies on the manipulation of a known antecedent variable. Six caregivers were unable to identify high-

risk situations for challenging behaviour. All six of these participants had Cornelia de Lange syndrome and for five of these participants, SIB was observed during the conventional functional analysis, however, the behaviour was not found to have a social function. For the remaining participant, although SIB was reported to occur it was not observed during conventional functional analysis. Of the fifteen participants for whom high-risk situations for challenging behaviour had been identified by carers, six participants were not recruited for the current study due to carers not agreeing to take part[1]. This resulted in nine participants and their carers taking part in the current study.

5.3.2. Participants

There were nine participants in the study (three from each of the syndrome groups) and participant characteristics are shown in Table 5.1. Participants were aged between three years and eight months and fourteen years and one month and six participants were male. Adaptive Behavior Standard Scores from the VABS II (Sparrow, Cicchetti & Balla, 2005) are also shown in Table 5.1. The VABS II classified all nine participants as having a *low* level of adaptive behaviour.

[1] For one participant parents did not agree to take part due to time commitments. For the remaining five participants, parents were not willing to participate because of ethical concerns about evoking challenging behaviour.

Table 5.1. Participant characteristics.

Participantβ	Gender	Chronological age[1]	Adaptive behaviour standard scores[2]	Physical disability[3]
AS 1	M	10.5	24	Ambulant Normal vision Normal hearing
AS 2	M	11.0	57	Ambulant Normal vision Normal hearing
AS 10	F	10.6	46	Ambulant Normal vision Normal hearing
CdC 14	M	7.9	58	Ambulant Poor vision Normal hearing
CdC 17	M	3.8	36	Non-ambulant Normal vision Normal hearing
CdC 18	F	3.9	46	Non-ambulant Normal vision Normal hearing
CdLS 3	M	6.1	29	Ambulant Normal vision Poor hearing
CdLS 17	M	14.1	50	Ambulant Normal vision Normal hearing
CdLS 18	F	6.9	37	Ambulant Normal vision Normal hearing

[1] In years and months
[2] Standard scores of the Adaptive Behavior Composite on three domains of the VABS II (Sparrow *et al.,* 2005)
[3] Data derived from the demographic background questionnaire.
β AS= Angelman syndrome. CdC= Cri du Chat syndrome. CdLS= Cornelia de Lange syndrome.

5.3.3. Measures and procedure

Structured Descriptive Assessments (SDA)

An SDA was designed on an individual basis for all nine participants. Where conventional experimental functional analysis had proved inconclusive, high-risk situations for the occurrence

of challenging behaviour were identified through the functional analytic interview. The interview had been conducted as part of the original functional analytic study with both main caregivers and teachers (Chapter 4). The functional analytic interview is a semi-structured interview that seeks to assess the functions of challenging behaviour and the variables that maintain it. The interview was created by the researchers to provide descriptive information for the feedback reports (An anonymous feedback report is shown in Appendix G). Pertinent questions from the functional analytic interview which were used to inform the SDA were as follows:

1) What event or situation would always or almost always lead to an episode of the behaviour?
2) In this situation what would always or almost always stop the behaviour?
3) Are there any other high-risk situations for the behaviour?
4) What event or situation would never or almost never lead to an episode of the behaviour?
5) Are there any situations that you avoid because they lead to the behaviour occurring?

Main caregivers were telephoned approximately two weeks after the initial home visit to discuss a follow-up visit to conduct an SDA. High-risk times for challenging behaviour were verified and main caregivers were asked about their willingness to conduct an SDA. If they agreed to take part and a high-risk situation for the occurrence of challenging behaviour was identified, a follow-up home visit was arranged within the next month.

For eight participants, an SDA was conducted with parents at home and for one participant (CdLS 18) the SDA was carried out at school as this was identified as the highest-risk situation

for challenging behaviour. Sessions were conducted during the times of the day when certain activities pertaining to each SDA condition normally occurred (e.g. a demand session was conducted at times of the day when the carer was most likely to place a demand upon the participant, such as meal times). The highest risk situation for challenging behaviour formed the test condition and each SDA also included a control condition. For some participants additional conditions were included which acted as further controls for the effects of any confounding variables.

Prior to each session, carers were given instructions about the antecedent condition, for example, if restricted access to tangibles had been identified as a high-risk situation, the carer would systematically manipulate access to tangibles at a time of day that this was most likely to naturally occur. They were then asked to leave consequences free to vary and respond to challenging behaviour as they typically would. Condition length across participants varied from 30 seconds to ten minutes and sessions were repeated in a multi-element design. Conditions were repeated up to ten times in order to make the SDA robust. The number of repetitions was variable across participants, however this decision was based on the individual, as avoidance of unnecessary challenging behaviour was the main concern. Table 5.2 outlines all nine structured descriptive assessments, including the design, description of conditions, variables manipulated and target behaviours. As Table 5.2 shows, seven out of the nine participants displayed challenging behaviour during the SDA.

Table 5.2: Structured descriptive assessment methodology.

Participant	Variable(s) manipulated	Design	Conditions	Condition length	Outcome variable	Target behaviours
AS 1	Parental attention and eye contact	ABACABACA and ACCABACABA.	-Attention, no eye contact **(Test)** -Attention and eye contact *(Control A)* -Low attention, no eye contact (Controlling for attention: *Control B*)	30 secs	Aggression	Grabbing Hair pulling Biting
AS 2	Level of parental attention and proximity of parent	ABC x 3	-Low attention, adult approachable **(Test)** -High attention *(Control A)* -Low attention, adult unapproachable (Controlling for adult proximity: *Control B*)	10 mins	Aggression	Grabbing Hitting Kicking
AS 10	Demands	ABCD x 3	- Hair brushing **(Test)** - Picture matching *(Control A)* - Teeth brushing (Controlling for form of personal care activity: *Control B*) - Putting on shoes and coat (Controlling for form of personal care activity: *Control C*)	2 mins	Self-injury	Head hitting
CdC 14	Interruption of activities	ABCB x 5	- Preferred activity *(Control A)* -Interruption **(Test)** - Neutral activity (Controlling for activity preference: *Control B*)	2 mins	Aggression	Biting Hitting Kicking Pushing
CdC 17	Demands	ABCD x 6	- Bathing **(Test)** - Playpen *(Control A)* - Teeth brushing (Controlling for personal care activity: *Control B*) - Washing in sink (Controlling for location of personal care activity: *Control C*)	2 mins	Aggression	Biting Hitting

Participant	Variable manipulated	Design	Conditions	Condition length	Outcome variable	Target behaviours
CdC 18	Levels of parental attention and time in feeding chair	ABCD x 4	- Low attention, in chair **(Test)** - High attention, out of chair *(Control A)* - Low attention, out of chair (Controlling for location: *Control B*) - High attention, in chair (Controlling for attention: *Control C*)	3 mins	Self-injury	Hair pulling
CdLS 3	Interruption of routine and of preferred activities	SDA 1: AB x 10 SDA 2: AB x 6	SDA 1: - Free play *(Control)* - Interruption **(Test)** SDA 2 - Preferred activity *(Control)* - Non-preferred activity **(Test)**	30 secs	No behaviour observed	-
CdLS 17	Levels of parental attention and access to activities	ABCD x 3	- Low attention and no toys **(Test)** - High attention and toys *(Control A)* - Low attention and toys (Control for presence of toys: *Control B*)	10 mins	Aggression	Hair pulling Hitting
CdLS 18	Access to tangibles	AB x 8	- Restricted access to tangibles **(Test)** - Access to tangibles *(Control)*	2 mins	No behaviour observed	-

Table 5.3: Structured descriptive assessment behavioural codes with operational definitions and Kappa reliability values.

Variable	Code	Operational definition of behaviour	Kappa
Challenging behaviours	Aggressive behaviour	Physical aggression directed towards another person. Defined specifically for each participant. Variable includes a total of all of the following topographies:	.80
	Biting others	Enclosure and clamping down of the teeth onto another person's body.	.75
	Grabbing others	A sudden grasping or clutching motion at another person's body or clothing.	.56
	Pulling hair	Grasping and then applying force to another person's hair in order to pull it towards.	.93
	Hitting others	Quick and forceful movement of the hand to make contact with another person's body.	.78
	Kicking others	To strike another person using the foot.	.54
	Pushing others	Applying force in order to move another person away.	.44
	Self-injurious behaviour	Non-accidental behaviours that may result in tissue damage. Defined specifically for each participant. Variable includes a total of all of the following topographies:	.78
	Hair pulling	Grasping and then applying force to one's own hair.	.93
	Head banging	Movement of head towards and making contact with surface (e.g. tables, wall, floor).	1.0
	Picking self	Removing and scratching at skin on one's own body.	1.0

5.3.4. Coding

All sessions were video-recorded and subsequently coded in real time using the same method as described in section 3.9.7.1. A second observer coded 25% of the sessions for each participant to provide inter-observer reliability. Behavioural variables with their definitions and Kappa values can be found in Table 5.3. The mean Kappa value was .70 (range= .44-1). Following coding, individual topographies of self-injurious and aggressive behaviour were combined to form overall categories of global self-injurious and aggressive behaviour.

5.3.5. Data analysis

The analysis strategy to explore social function in challenging behaviour was the same as that outlined in section 4.5.1. Graphed mean percentage duration of self-injurious and aggressive responding in the SDA was produced and the dominance statistic (*d,* Cliff; 1993, see section 4.5.1) was calculated for the seven participants who displayed SIB or aggression. *d* values were calculated by comparing all 'Test' condition data points to all 'Control A' condition data points. Effects of confounding variables were explored by comparing all 'Test' condition data points to all the data points of the extra control condition. Any *d* value above .33 indicated social function to behaviour.

5.4. Results

Figure 5.2 shows multi-element graphs for the seven participants who displayed challenging behaviour during the SDA. Each graph displays the mean percentage of time that each participant engaged in SIB and aggression during the SDA conditions. For two participants (CdLS 3 and CdLS 18), no self-injurious or aggressive behaviour was observed in the SDA.

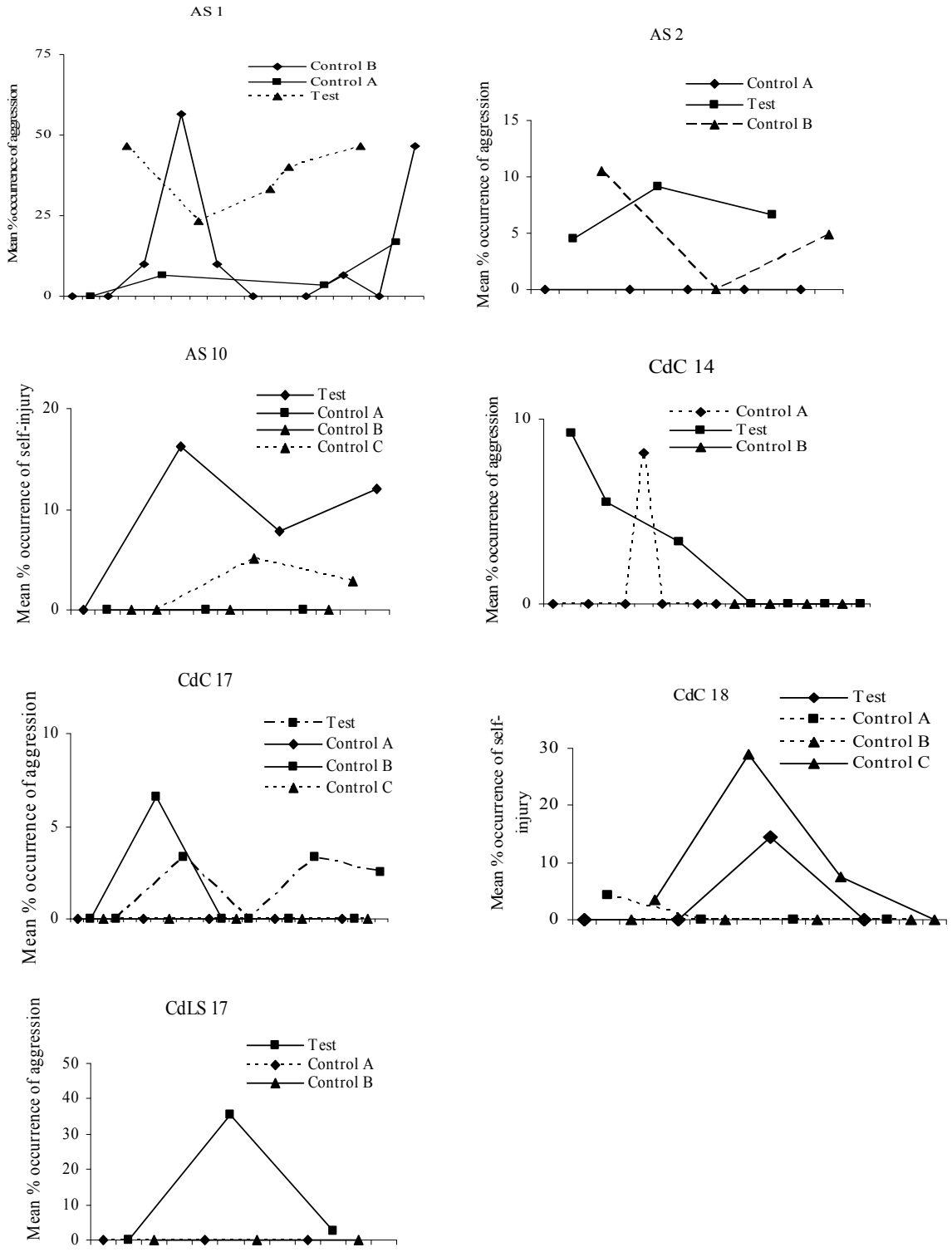


Figure 5.2: Multi-element graphs to show the mean percentage of time that each participant engaged in SIB and aggression during the structured descriptive assessments.

Table 5.4 shows the *d* values that were obtained when comparing the 'Test' condition with the control conditions. The results of the SDAs are summarised within Table 5.4.

Table 5.4. Structured descriptive assessment results with *d* values.

Participant	Variable (s) manipulated	Conditions	*d* stat value Test condition effects (Test compared to control)	*d* stat value Confounding variables effects (Test compared to additional control conditions)	Conclusions
AS 1	Parental attention and eye contact	-Attention, no eye contact **(Test)** -Attention and eye contact *(Control A)* -Low attention, no eye contact (Controlling for attention: *Control B*)	*d*=.64 Function in test condition	*d*=.01 No function in test condition	Lack of eye contact resulted in aggressive behaviour. No effect of levels of parental attention
AS 2	Level of parental attention and proximity of parent	-Low attention, adult approachable **(Test)** -High attention *(Control A)* -Low attention, adult unapproachable (Controlling for adult proximity: *Control B*)	*d*=1 Function in test condition	*d*=.65 Function in test condition	Combination of parent being approachable at times of low attention resulted in aggressive behaviour
AS 10	Demands	- Hair brushing **(Test)** - Picture matching *(Control A)* - Teeth brushing (Controlling for form of personal care activity: *Control B*) - Putting on shoes and coat (Controlling for form of personal care activity: *Control C*)	*d*=1 Function in test condition	*d*=1 and *d*=1 Function in test condition	Hair brushing resulted in more SIB than other demands

Participant	Variable (s) manipulated	Conditions	*d* stat value Test condition effects (Test compared to control)	*d* stat value Confounding variables effects (Test compared to additional control conditions)	Conclusions
CdC 14	Interruption of activities	- Preferred activity *(Control A)* -Interruption **(Test)** - Neutral activity (Controlling for activity preference: *Control B*)	*d*=.75 Function in test condition	*d*=1 Function in test condition	Interruption of any activity resulted in aggressive behaviour
CdC 17	Demands	- Bathing **(Test)** - Playpen *(Control A)* - Teeth brushing (Controlling for personal care activity: *Control B*) - Washing in sink (Controlling for location of personal care activity: *Control C*)	*d*=.6 Function in test condition	*d*=.6 and *d*=.52 Function in test condition	Bathing resulted in more aggressive behaviour than other demands
CdC 18	Levels of parental attention and time in feeding chair	- Low attention, in chair **(Test)** - High attention, out of chair *(Control A)* - Low attention, out of chair (Controlling for location: *Control B*) - High attention, in chair (Controlling for attention: *Control C*	*d*= 0 No function in test condition	*d*= .25 (Control B) *d*= -.44 (Control C)	Being in feeding chair results in more self-injury. No impact of levels of parental attention
CdLS 17	Levels of parental attention and access to activities	- Low attention and no toys **(Test)** - High attention and toys *(Control A)* - Low attention and toys (Control for presence of toys: *Control B*)	*d*=1 Function in test condition	*d*=.65 Function in test condition	Low levels of parental attention in combination with a lack of activities resulted in more aggression

As Table 5.4 shows, an SDA identified a social function to challenging behaviour for seven out of nine participants where function had not been identified by conventional experimental functional analysis. For one participant (AS 2) challenging behaviour was found to be maintained by adult attention. Although levels of attention were manipulated in the original conventional functional analysis, what seems to be important in the SDA is that the establishing operation for challenging behaviour is low levels of *parental* attention specifically. In addition, for this participant it seems that the combination of low levels of parental attention at times when the parent is approachable or is in close proximity, is more difficult than if the parent is unapproachable. For CdLS participant 17, it appears to be the combination of low levels of parental attention *combined* with a lack of activities or toys that is maintaining aggressive behaviour. During the test condition, in which there was a low level of adult attention and no toys available, aggressive behaviour occurred at mean duration of 13% of the time, whilst the high attention control condition and the low attention with toys condition resulted in no aggressive behaviour being observed. For participant AS 1, even when controlling for levels of parental attention, aggressive behaviour was observed only when parental eye contact was withheld. In fact, very high rates of aggressive behaviour occurred in the high attention, no eye contact condition (mean duration of 38% of time) compared to the control condition of high attention with eye contact (mean duration of 6% of the time). For this participant, aggressive behaviour was consistently more frequent and strongly associated with situations in which there was a lack of eye contact. For two participants (AS 10 and CdC 17) challenging behaviour was found to be maintained by escape from personal care activities such as hair brushing and bathing; activities that would not be tested in conventional experimental functional analysis. For participant CdC 18, more self-injury occurred when in the feeding chair and the inclusion of the control

conditions found levels of parental attention to have no impact (i.e. self-injury occurred more in the feeding chair, regardless of whether levels of parental attention were high or low). Finally, for participant CdC 14, challenging behaviour was found to be maintained by avoidance of termination of activities and activity preference was not found to have any effect on levels of challenging behaviour. As Figure 5.2 shows, what is particularly worthy of note for this participant is the decrease in aggressive behaviour with repeated presentation of the test condition (interruption).

To summarise, the SDA identified social function to challenging behaviour in seven participants (12% of the original sample of 60, Chapter 4) who were found to have no social function to challenging behaviour during conventional functional analysis.

5.4.1. Examination of environmental influences on challenging behaviour

In the previous conventional functional analytic study (Chapter 4), data were explored to see if there was any difference in environmental influences on challenging behaviour across syndrome groups. For each participant, *d* values were calculated for SIB and/or aggression and the highest absolute *d* value for each participant was taken and compared across syndrome groups using a one-way ANOVA. Table 5.5 presents the means and standard deviations for the highest absolute *d* value attained in the conventional experimental functional analysis *or* in the SDA for either self-injury or aggression. With the addition of the SDA, the highest *d* value included 30 *d* values for aggression, 25 for self-injury and five *d* values of zero where no behaviour in either the conventional functional analysis or the SDA was observed. The ANOVA revealed that with the

addition of the SDA, there was still no significant difference across the groups on highest absolute *d* value.

Table 5.5: Comparison of highest absolute *d* values across syndrome groups in the conventional experimental functional analysis and structured descriptive assessments.

	Cornelia de Lange **n=20** Mean (SD)	**Cri du Chat** **n=20** Mean (SD)	**Angelman** **n=20** Mean (SD)	**ANOVA F (df)**	***p***	**Post-hoc**
Highest absolute *d* from conventional functional analysis	.45 (.36)	.45 (.29)	.49 (.30)	.13 (2)	.881	-
Highest absolute *d* from conventional functional analysis and addition of the SDA	.49 (.38)	.51 (.39)	.62 (.27)	1.02 (2)	.366	-

Functional challenging behaviour in the conventional functional analysis study (Chapter 4) included behaviour that was found to either have an attention maintained, demand escape or function in the high attention condition. From the conventional functional analysis, social function to challenging behaviour was identified in 65% of the sample and with the addition of the SDA this rose to 77% of the sample. Figure 5.3 displays the percentage of participants within each syndrome group that displayed self-injurious or aggressive behaviour that was found to have a social function. This includes behaviour that was found to have a social function in the conventional experimental functional analysis and that which was found to have a social function in the SDA.

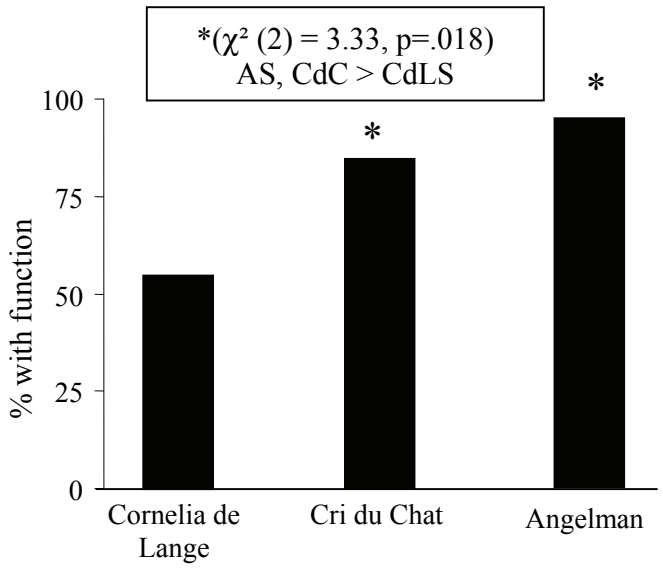


Figure 5.3: Percentage of participants in each syndrome group displaying either functional aggressive or self-injurious behaviour in the conventional experimental functional analysis or SDA (overall behavioural function).

As Figure 5.3 shows, 18 participants (90%) in the Angelman syndrome group, 17 participants (85%) in the Cri du Chat syndrome group and eleven participants (55%) in the Cornelia de Lange syndrome group were found to have a social function to their challenging behaviour. These proportion figures for each syndrome group were the analysed with a chi-square test to see if there were any differences in the proportion of participants displaying *any* social function to challenging behaviour (includes participants found to have social function within the conventional experimental functional analysis or the SDA). A chi square test revealed that there was a significant difference across the groups with regard to the proportion of participants who were found to have challenging behaviour which demonstrated social function (χ^2 (2) = 3.33, *p*=.018). Post-hoc chi square tests revealed that the Angelman and Cri du Chat syndrome groups were found to have more functional behaviour than the Cornelia de Lange syndrome group.

5.5. Discussion

This study was an extension of the conventional functional analytic study described in Chapter 4. The study assessed whether an SDA was able to identify environmental influences on targeted challenging behaviour in Angelman, Cri du Chat and Cornelia de Lange syndromes when conventional experimental functional analysis had not demonstrated a social function. Nine participants took part in the study and the SDA was designed on an individual basis to capitalise on the strengths of both conventional experimental functional analysis and descriptive assessments and to identify unusual or idiosyncratic function to challenging behaviour (Anderson & Long, 2002). The SDA always included at least one control condition against which the test condition could be evaluated. Operationally defined behaviours provided a rigorous methodology and inter-observer reliability on the coding of the behaviours was good. The same statistical method that was used in Chapter 4 of allocating function was utilised in this study (Cliff's *d* statistic, 1993).

Challenging behaviour which demonstrated social function was identified in seven out of the nine participants and idiosyncratic functions included low levels of parental attention, low levels of parental attention in combination with a lack of activity, personal care demands and activity interruption. Two of the participants (CdLS 3 and CdLS 18) who took part in the current study displayed no self-injurious or aggressive behaviour in either the conventional functional analysis or the SDA, despite the SDA being devised based on the highest-risk situation for challenging behaviour. However, CdLS participant 18 did display destructive behaviour (which in addition to SIB and aggression was reported by parents to be problematic) only in the test condition of the SDA, resulting in a *d* value of 1 for destruction. For participant CdLS 3, the SDA was designed

twice in order to try and maximise differential responding. Anecdotally the participant's mother noted that the participant appeared to be very aware of the researcher's presence and thus at one point the research team left the home in order to make the SDA as comparable to natural circumstances as possible. The participant's mother noted that the participant still appeared to be very aware of the camera. This is an interesting finding as it questions the applicability of the SDA, or indeed other methods of functional assessment for more able participants, or participants that have the ability to predict environmental changes.

For one participant (AS 1), results showed that aggressive behaviour was consistently more frequent and strongly associated with situations in which there was a lack of eye contact. Anecdotal reports from the participant's parents suggest that the presence of eye contact during interaction seems to be extremely motivating. This is consistent with the behavioural phenotype of Angelman syndrome which typically includes high levels of sociability and aggressive behaviour (Arron, Oliver, Berg, Moss & Burbidge, in review; Horsler & Oliver, 2006a; Richman, Gernat & Teichman, 2006; Chapter 3, Section 3.11). The previous studies in Chapters 3 and 4 reports on aggressive behaviours in Angelman syndrome, which have the ability to gain social attention from adults. The study in Chapter 3 reports on comparisons of topographies of aggressive behaviour across genetic syndromes. Results of this study showed that grabbing and hair pulling were common topographies of aggressive behaviour in Angelman syndrome. These forms of aggression are forms that typically function to maintain adult attention and gain eye contact. Similarly, the results of Chapter 4 showed that eleven (55%) participants in the Angelman syndrome group had challenging behaviour that was maintained by positive social reinforcement.

It is also interesting to note that for participant CdC 14, whose challenging behaviour was found to be maintained by avoidance of termination of activities, there was a decrease in aggressive behaviour with repeated presentation of the test condition (interruption). This may suggest that as the assessment progressed, the participant learned to anticipate the interruption and thus began to predict environmental changes and alter behaviour accordingly. Anecdotal reports from the participant's parents suggested that this altering of behaviour was specific to the SDA and did not suggest that the challenging behaviour had extinguished. In fact, the participant's parents felt that the change in the child's behaviour may have been partly due to the presence of the researcher and the child being aware that his behaviour was being subject to an assessment. This is an important finding for the design of the SDA in that, researchers need to be aware of their own presence at the assessment and the effect that this may have on the participant's behaviour. With this in mind, it is also important to consider a participant's level of ability when conducting an SDA and how this may impact on repeated exposure to a specific establishing operation.

The previous study in Chapter 4 utilised conventional functional analysis with individuals with Angelman (n=20), Cri du Chat (n=20) and Cornelia de Lange syndromes (n=20). The study identified a social function to challenging behaviour in 39 out 60 participants (65% of the sample). The previous study only tested the establishing operations of low levels of social attention and high levels of task demand on the occurrence of challenging behaviour. The current study was a direct follow on from the study in Chapter 4 and found that the SDA was able to identify social function to challenging behaviour in a further seven participants, resulting in a total of 46 (77%) out of 60 participants with an identified social function to challenging

behaviour. Taken as a whole, the wide range of establishing operations that were found to maintain challenging behaviour in this study extends previous research, which has shown that the inclusion of idiosyncratic variables can maintain challenging behaviour (e.g. Adelinis *et al.,* 1997; English & Anderson, 2004; Kennedy & Meyer, 1996; McCord *et al.,* 2001; Murphy *et al.,* 2000). For the remaining fourteen participants where social function to challenging behaviour was not identified, there were six participants whose carers could not identify high-risk situations for challenging behaviour, a further six who could identify triggers but did not wish to take part and two participants took part in both studies, however, conventional experimental functional analysis and the SDA failed to identify any environmental influences on behaviour.

With the addition of the SDA to conventional functional analysis, the current study has found that challenging behaviour in the Angelman and Cri du Chat syndrome groups evidences stronger maintenance by positive social reinforcement than the same behaviours in the Cornelia de Lange syndrome. This supports the original hypotheses made in Chapter 4 which was based on a review of the literature on challenging behaviour within these syndromes (see Sections 4.1-4.3 in Chapter 4). Given previous research which links self-injury in Cornelia de Lange syndrome to painful health conditions (Luzzani, Macchini, Valade, Milani & Selicorni, 2003; Oliver *et al.,* 2003b), SIB of a compulsive-like quality (Hyman, Oliver & Hall, 2002) and the presence of self-restraint and physical restraint (Basile, Villa, Selicorni & Molteni, 2007; Hyman *et al.,* 2002; King, 1993; Powell, Bodfish, Parker, Crawford & Lewis, 1996; Shear, Nyhan, Kirman, & Stern, 1971) it was predicted that challenging behaviour in Cornelia de Lange syndrome would be influenced less by social reinforcement. In Angelman syndrome, the results of this study and the study in Chapter 4 indicate physical aggression that is maintained by social contact, and this is

consistent with previous research (Strachan *et al.,* 2009). The current study and the study in Chapter 4 are the first empirical studies to examine the social reinforcement of challenging behaviour in Cri du Chat syndrome. Results have shown that challenging behaviour is influenced by social reinforcement in a greater proportion of individuals with Cri du Chat syndrome than those with Cornelia de Lange syndrome and this is consistent with the findings that these individuals are sociable, particularly with people who are familiar (Chapter 4, Section 4.6.5).

The current study has shown the ability of the SDA to identify environmental influences to challenging behaviour that are not ordinarily tested in conventional functional analysis studies. The current study was able to identify idiosyncratic environmental influences to challenging behaviour in a further seven (12%) participants where functional analysis had not demonstrated a social function. This is particularly important as if the SDA had not been included, following no identified function in conventional functional analysis, it may have been assumed that the behaviours had no social function. Indeed this is not the case and the study highlights the importance of the SDA as an addition to conventional functional analysis. Demonstrating the influences of environmental factors on challenging behaviour within genetic syndromes is important as it highlights the potential utility of experimental studies to explore how these factors might be utilised effectively in behavioural interventions. Given the high prevalence of self-injurious and aggressive behaviour within Angelman, Cri du Chat and Cornelia de Lange syndromes and the often early age of onset, early intervention would be appropriate and this has been shown to be effective at reducing challenging behaviour and enhancing adaptive skills in the wider intellectual disability population (Richman, 2008).

In summary, research suggests that the SDA is a useful addition to functional analytic methods. The study has shown that despite genetic factors in syndromes, the environment does have an effect on the development and maintenance of challenging behaviour. The SDA may be particularly useful at identifying idiosyncratic variables maintaining problem behaviour that would otherwise not be tested in conventional experimental functional analysis. The study has shown proof of principle i.e. there are environmental influences on challenging behaviour within Angelman, Cri du Chat and Cornelia de Lange syndromes. Although the influence of the environment has been demonstrated, it is still unclear to what extent these influences are representative of the participant's behaviour and it can not be assumed that all behaviour is explicable in this way.

CHAPTER 6

General Discussion

6.1. Introduction

The empirical studies (Chapters 3, 4 and 5) presented in this thesis are the first to employ experimental analysis to examine problem behaviours in Cornelia de Lange, Cri du Chat and Angelman syndromes. The studies adopted a 'same but different' approach to challenging behaviour in which these three genetic syndromes were compared. As described in Chapters 3 and 4, experimental functional analysis was carried out under controlled conditions with systematic environmental manipulations which were based on previously published methodology, identified through a review of the research literature (Chapter 2; Iwata, Dorsey, Slifer, Bauman & Richman, 1982/1994; Carr & Durand, 1985; Oliver, Hall & Nixon, 1999; Strachan *et al.,* 2008). All behaviours were coded in real time (yielding results with greater ecological validity than time based sampling), operational definitions were employed and inter-observer reliability was ascertained for each behaviour coded. The use of observations was considered a necessity in order to conduct a fine-grained analysis that would not have been possible from informant-based questionnaires. Such methodology also prevents the omission of any important syndrome-specific behaviours, which are less likely to be included in standardised measures. The groups were matched on age, speech, gender and mobility and the samples were relatively large given the low incidence of the syndromes.

Using this design, it was possible to compare the phenomenology and correlates of challenging behaviour (outlined in Chapter 3) and to appraise the influence of the environment and social

reinforcement on phenotypic problem behaviours (Chapter 4). Chapter 4 provides the first study to examine operant theory applied to self-injurious and aggressive behaviour in a between group design, with the broad aim of identifying gene-environment interactions within the three syndromes. Chapter 5 presented an extension of the work described in Chapter 4 by applying structured descriptive assessments (Anderson & Long, 2002) to test a wider range of idiosyncratic establishing operations that had been identified by carers as influential. Across studies, when determining the social function of challenging behaviour, Cliff's *d* statistic (1993) provided a systematic and robust approach for a non-parametric data set.

6.2. Main findings

Evidence for the existence of behavioural phenotypes and the operant reinforcement of challenging behaviour generally, was considered in Chapter 1, and it was found that the two approaches were seemingly distinct from each other. Neither approach was sufficient to explain challenging behaviour in genetic syndromes. Exploring the role of operant reinforcement of problem behaviours in genetic syndromes was highlighted as a strategy that would allow integration between the two approaches. As a starting point, the systematic literature review in Chapter 2 aimed to identify studies that described an environmental influence on problem behaviours associated with genetic syndromes. The review highlighted a number of papers with robust experimental functional analytic designs, and there was a trend towards an increase in the number of published papers that linked facets of the behavioural phenotype to challenging behaviour (gene-environment interactions). Potential gene to challenging behaviour pathways identified in the literature review included accentuated or attenuated motivations, accentuated sensory input, the influence of painful health conditions and specific cognitive processes. The

review showed that this was an area of study that was worth exploring in order to extend existing causal models of challenging behaviour. Chapters 3, 4 and 5 aimed to elucidate gene-environment interactions within three genetic syndromes in order to inform a comprehensive model that would be applicable to the wider population of individuals with intellectual disability. It should be noted that although the term gene-environment interaction has been used throughout the thesis, some caution needs to be applied when using the term. Gene-environment interaction may suggest that behaviours can be linked to the genetic basis of a syndrome. Given that the genotypes of particular syndromes are not always known, perhaps a more appropriate term would be syndrome-environment interaction. In the thesis the term gene-environment interaction has been used for ease of reading.

There are numerous methodologies that might be adopted when studying behavioural phenotypes (see Chapter 1, Section 1.5) and one of these, the 'same-but-different' approach, involves a comparison of genetic syndromes in which individuals are known to demonstrate apparently similar behaviours. In comparison to prevalence rates for individuals with mixed aetiology intellectual disabilities, the rates for challenging behaviours such as self-injury and aggression have been found to be raised in a number of genetic syndromes. The examination of prevalence, phenomenology, function and correlates of challenging behaviour in genetic syndromes therefore, has merit in its own right. Additionally, it was a good starting point for identifying potentially important causal pathways to challenging behaviour in the total population of people with intellectual disabilities. In pursuit of this goal, Chapter 3 involved a comparison of three genetic syndromes (Angelman, Cri du Chat and Cornelia de Lange syndromes), which, are known to be associated with high rates of challenging behaviour. Furthermore, the existing

literature suggested that the prevalence, form and causes of these behaviours differed across the syndrome groups. The aim of Chapter 3 was to conduct the first large-scale study to compare the phenomenology of challenging behaviour in these three syndrome groups at a fine-grained level. In addition, features of the syndromes that might increase the probability of an individual displaying challenging behaviour were explored.

Broadly, the results of Chapter 3 showed that SIB was more common in the Cornelia de Lange syndrome group, whilst aggression was more common in the Angelman syndrome group. These findings were in line with the hypotheses and support previous research suggesting that these forms of challenging behaviour are part of the behavioural phenotype of the syndromes (Chapter 3, Section 3.11; Arron, Oliver, Berg, Moss & Burbidge, in review; Berney, Ireland & Burn, 1999; Hyman, Oliver & Hall, 2002). Interestingly, SIB was not found to be associated with Angelman syndrome which is surprising given that the syndrome is associated with many risk factors for its development such as severe level of intellectual disability, communication deficits, overactivity and ASD (McClintock, Hall & Oliver, 2003; Petty & Oliver, 2005; Steffenburg, Gillberg, Steffenburg & Kyllerman, 1996). Further research into why individuals with Angelman syndrome appear to show lower than expected levels of SIB would have important implications for a comprehensive model of self-injury. Results supported the notion that there is a decrease in aggressive behaviour with age in the Angelman syndrome group (Clayton-Smith, 2001). However, this result was based on correlational data and thus warrants further empirical study, preferably using longitudinal methods. Nonetheless, this finding highlights the need to study gene-behaviour pathways within a developmental context and this issue was discussed in more detail in Chapter 2, Section 2.4.4 in relation to other syndrome-specific developmental changes.

Importantly, Chapter 3 highlighted the need for research into behavioural phenotypes to conduct more detailed study of behavioural characteristics across syndrome groups, with particular attention being paid to describing behaviour at a greater level of specificity rather than broad behavioural phenomenology. The results of the study in Chapter 3 found important differences in the forms of challenging behaviour between the syndrome groups, for example, grabbing and hair pulling were found to be highly prevalent in the Angelman syndrome group and this alludes to an evocative gene-environment interaction. Hair pulling and grabbing may be indirectly linked to the heightened levels of sociability and behaviours that access social attention that are reported to be characteristic of Angelman syndrome, as they are likely to prolong rather than terminate social interaction (Oliver *et al.,* 2007; Strachan *et al.,* 2009). This level of specificity regarding forms of challenging behaviour seems to be increasingly important in order to associate particular topographies with given genetic syndromes. For example, a form of self-injury that is rarely described elsewhere in the literature is nail removal and this appears to be common to Smith-Magenis syndrome (Smith *et al.,* 1986; Lockwood *et al.,* 1988), whilst skin picking is commonly reported in Prader-Willi syndrome (Greenswag, 1987; Dykens, Hodapp, Wash & Nash, 1992; Dykens & Kasari, 1997).

Having explored the phenomenology of challenging behaviour within the syndrome groups, the aim of the study in Chapter 4 was to examine the gene-environment interactions as causes of self-injury and aggression in these genetic syndromes. Given the literature describing other aspects of the behavioural phenotypes of these syndromes and the findings of Chapter 3, specific hypotheses were made regarding operant reinforcement of self-injury and aggression. Predictions were largely supported and evidence for specific gene-environment interactions in the syndromes

was found. Firstly, the finding that challenging behaviour in the Cornelia de Lange syndrome group evidenced a stronger association with pain than the challenging behaviours in the Angelman syndrome and Cri du Chat syndrome groups provides support for an important casual pathway in a comprehensive model of challenging behaviour. Cornelia de Lange syndrome is known to be associated with many health problems (Berg, Arron, Burbidge, Moss & Oliver, 2007; Hall, Arron, Sloneem & Oliver, 2008; Hawley, Jackson & Kurnit, 1985; Kline *et al.,* 2007; Jackson, Kline, Barr & Koch*,* 1993; Luzzani, Macchini, Valade, Milani & Selicorni, 2003) and the literature notes a positive association between pain and health problems and challenging behaviour in individuals with intellectual disability (Breau *et al.,* 2003; Carr & Blakeley-Smith, 2006; Carr & Owen-DeSchryver, 2007; Carr, Smith, Giacin, Whelan & Pancari, 2003; Oberlander & Symons, 2006). Although the association between pain and challenging behaviour is derived from informant-based questionnaires, The results of the study in Chapter 4 raise the possibility that challenging behaviour, particularly SIB, may enter an individual's behavioural repertoire in response to pain or discomfort. Once in the behavioural repertoire, the SIB may be associated with particular environmental contingencies (Arron *et al.,* 2006; Moss *et al.,* 2005). Similarly, one of the single case experimental designs that was reported in Chapter 2 noted that SIB in Williams syndrome was more likely to be displayed in the presence of otitis media (O'Reilly, 1997). This is a significant pathway in a model of challenging behaviour as painful health conditions are commonly reported in individuals with intellectual disabilities (e.g. Jansen, Krol, Groothoof & Post, 2004; van Schrojenstein Lantman-de Valk *et al.,* 1999) and thus the finding is pertinent for a much wider population. This is clearly not only relevant to challenging behaviour but to quality of life more generally.

The literature review in Chapter 2 revealed that one plausible pathway to challenging behaviour might be through an accentuated specific motivation. Kahng, Iwata, Thompson and Hanley (2000) and Taylor and Oliver (2008) described studies of self-injury and aggression in Angelman and Smith-Magenis syndromes respectively. The papers provided some evidence for a gene-environment interaction as the heightened motivation to seek out social attention in these syndromes may result in challenging behaviour that is maintained by access to attention. This reveals an interesting evocative gene-environment interaction in Angelman and Smith-Magenis syndromes in which an aspect of the behavioural phenotype evokes particular environmental responses. In Chapter 4, the aim was to further elucidate this pathway by employing a larger group of individuals with Angelman syndrome and robust methodology. The results of the functional analytic study provided support for the proposed gene-environment interaction and it was found that aggressive behaviour in the Angelman syndrome group evidenced stronger maintenance by positive social reinforcement than aggressive behaviours in the Cornelia de Lange syndrome group. In addition, it was also notable that 25% of the Angelman syndrome group showed the highest levels of aggressive behaviour in the high attention condition of the experimental functional analysis. Given previous research that has found similar proportions (30% of sample in Strachan *et al.*, 2009) this may reflect a motivation to maintain, rather than initiate social interaction. Anecdotally this explanation is in line with the researcher's experiences, however, further research is required to establish the function of aggressive behaviour at times of high social interaction in Angelman syndrome.

In order to propose accentuated motivational pathway in Angelman syndrome, it was necessary to confirm that the Angelman group did indeed have heightened sociability and this evidence was

provided by the study in Chapter 3 and is supported by previous literature (e.g. Brown & Consedine, 2003; Horsler & Oliver, 2006a; Oliver, Demetriades & Hall, 2002; Oliver *et al.,* 2007). In addition, the topographies of aggressive behaviour that were found to be common in the Angelman syndrome group in Chapter 3 (hair pulling and grabbing) further support this proposed gene-environment interaction, as under conditions of low social contact, hair pulling and grabbing are aggressive behaviours that act to re-establish social contact and evoke eye contact.

Conversely, challenging behaviour may also occur through attenuated motivation and predispositions to find particular stimuli aversive. Evidence for this gene-environment interaction is provided by the finding that social performance situations result in more social anxiety and challenging behaviour in Fragile-X syndrome (Hall, DeBernardis & Reiss, 2006), and the finding that the period of social withdrawal documented in early life in Rett syndrome produces an increased vulnerability and susceptibility to operant reinforcement by escape (Oliver, Murphy, Crayton & Corbett, 1993).

The finding that 30% of the Angelman syndrome group showed aggressive behaviour that demonstrated a demand escape function also suggests a gene-environment interaction in which short attention span, hyperactivity and impulsivity (commonly reported in Angelman syndrome; Chertkoff-Waltz & Benson, 2002; Clarke & Marston, 2000; Oliver, Berg, Moss, Arron & Burbidge, in review) result in challenging behaviour that is maintained by escape from task demands, because staying on task is particularly difficult or aversive for individuals who show these characteristics. This pathway may be relevant to any individual with an intellectual disability given that similar proportions of individuals are found to have demand escape function

in heterogeneous intellectual disability samples (Iwata *et al.,* 1994a). There are also other examples in the literature in which specific cognitive impairments may drive the development of challenging behaviour. For example, challenging behaviour in Soto's syndrome has been linked to difficulties in impulsivity and inhibition (Vollmer, Borrero, Lalli & Daniel, 1999), whilst temper tantrums in Prader-Willi syndrome have been linked to deficits in task switching which places high demands on cognitive resources if there is a decrease in predictability in the environment (Woodcock, Oliver & Humphreys, 2009).

Taken as a whole, the findings of the study in Chapter 4 reveal that applying operant learning theory alone is not a useful approach when explaining behaviour in syndromes. A purely operant perspective would predict no differences in challenging behaviour across syndromes because environmental influences are, presumably, randomly distributed across groups. Similarly, purely genetic determinist approaches alone are not useful, as they would predict no influence of the environment in determining behaviour, which should result directly from the specific genetic abnormalities associated with a syndrome. The studies here have shown that there are both differences in the prevalence, forms and causes of challenging behaviour across syndrome groups and these behaviours are subject to environmental change. Thus, the research has provided evidence for the integration between genetic predisposition and an influence of the environment in determining challenging behaviour in genetic syndromes.

Extending the findings reported in Chapter 4, the study in Chapter 5 revealed that challenging behaviour within the three syndromes could be maintained by a much wider set of social and environmental variables than those that were tested in Chapter 4. This supports previous

literature, which describes unusual and idiosyncratic function to challenging behaviour (e.g. Adelinis, Piazza, Fisher & Hanley, 1997; English & Anderson, 2004; Kennedy & Meyer, 1996; McCord, Thompson & Iwata, 2001; Murphy, Macdonald, Hall & Oliver, 2000). This also has important implications for the assessment of challenging behaviour in general and suggests that conventional experimental functional analysis may not always identify social function to challenging behaviour, as typically, only a discrete set of antecedent variables are studied. Therefore, following conventional experimental functional analysis, it may be erroneously assumed that the behaviour is without social function, when in fact, the behaviour may be maintained by idiosyncratic variables that were not tested. The study in Chapter 5 has shown that with the addition of structured descriptive assessments, behaviour in these syndromes has been found to be maintained by specific idiosyncratic variables and there is no reason to suspect that this would be different for individuals without a genetic syndrome.

6.3. Future research

Although the impact of pain on challenging behaviour in Cornelia de Lange syndrome has been demonstrated, future research needs to continue to explore this association in order to show proof of principle. The association between pain and challenging behaviour in this thesis is based on questionnaire data and future research should aim to explore this association with the use of robust experimental methods. Ideally, large-scale randomised control trials (RCTs) are needed to test the influence of painful health conditions on challenging behaviour in the syndrome. Due to relatively low numbers of individuals affected, RCTs are unlikely to be possible, thus the alternative option is to continue to demonstrate the gene-environment interaction in single case experimental designs with robust methodology. Given the link between pain and challenging

behaviour, the results of Chapter 3 also revealed an interesting finding in Cri du Chat syndrome. Although based on informant questionnaire data, health problems were positively associated with signs of gastroesophageal reflux and signs of gastroesophageal reflux were associated with pain scores. This suggests that gastroesophageal reflux may be a problematic and painful health condition in Cri du Chat syndrome. Feeding difficulties, failure to thrive and reflux have been noted to be common in the first two years of life (Collins & Eaton-Evans, 2001) and the current study shows an association between gastroesophageal reflux signs and age such that, the number of signs decreases with increasing age. Thus, the association between gastroesophageal reflux and Cri du Chat syndrome warrants further research.

For individuals with Angelman syndrome, the delineation of the evocative gene-environment pathway provides useful information to guide early intervention programmes. Specifically, early intervention strategies may shift the focus from behaviour and move towards managing the excessive motivation to gain social attention and its link with challenging behaviour. Functional communication training (FCT) may be a promising avenue for individuals with Angelman syndrome as it seeks to replace an aberrant behaviour with an alternative communicative response that is functionally equivalent and its efficacy has been demonstrated in the literature (Carr & Durand, 1985). Any intervention of this kind would need to be evaluated, however, FCT, specifically in relation to management of motivation, could potentially have much wider reaching implications than simply focussing on challenging behaviour. Indeed, a strong drive for social attention in Angelman syndrome may affect a host of other behaviours in addition to challenging behaviour, particularly those behaviours which are linked to increased allocation of social resources (Brown & Consedine, 2004). Sleep disturbances are commonly reported in the

syndrome (Chertkoff-Waltz, Beebe & Byars, 2005; Didden, Korzilius, Smits & Curfs, 2004; Miano *et al.,* 2004; Pelc, Cheron, Boyd & Dan, 2008) and the drive for social attention may result in children waking other people at night. Anecdotally there are also reports of stranger approach and sibling relationship difficulties. Sibling relationship difficulties would fit in with increased competition for social resources by individuals with Angelmans syndrome. Given the possible link between difficulties with attention, hyperactivity, impulsivity and demand escape behaviour in Angelman syndrome (Chertkoff-Waltz & Benson, 2002; Clarke & Marston, 2000; Oliver *et al.,* in review) future research should explore interventions targeting this interaction.

The results of Chapter 4 showed that the Cri du Chat group included a higher proportion of individuals who showed attention maintained self-injury compared to the Cornelia de Lange and Angelman syndrome groups (although this result did not reach statistical significance). Social reinforcement of challenging behaviour in Cri du Chat syndrome is consistent with anecdotal reports of heightened sociability in the syndrome, although to date there are no empirical studies. No specific hypotheses were made about the social function of challenging behaviour in Cri du Chat syndrome; however, the studies afforded an initial exploration and also provided an appropriate group for comparison with the other two syndromes studied. Anecdotally, it was notable that challenging behaviour in Cri du Chat syndrome often occurred at times of expressive communication difficulties. Instances of self-injury and aggression were mainly in response to the researcher failing to understand what the participant was saying. These anecdotal observations are consistent with the marked expressive/receptive language discrepancy (receptive language skills exceed expressive) that is commonly reported in the syndrome (Cornish & Munir, 1998; Cornish, Bramble, Munir & Pigram, 1999). Given that communication impairments are

thought to be a risk marker for problem behaviours such as self-injury and aggression (Carr & Durand, 1985: McClintock *et al.,* 2003), future research should explore this association in more detail for individuals with Cri du Chat syndrome. In addition, future research should aim to gather more information regarding participant's level and method of communication (e.g. speech, signs, Makaton or PECS) to explore the relationship between communication and challenging behaviour.

6.4. Limitations

Various limitations have been addressed in previous chapters but following the conclusions discussed above, limitations pertinent to the issues raised by these conclusions are highlighted below.

The design of the present study led to limitations concerning the degree to which the participants were representative of the populations from which they were drawn, which may limit the generalisability of the results. Participants were recruited from syndrome support groups, which may comprise a bias of members towards families of higher social economic status, families who cannot identify triggers to their child's challenging behaviour, families caring for individuals at home (not in residential care) and families caring for individuals with more challenging behaviour (families may therefore draw more on external support). Given the selective nature of the sampling method (i.e. the presence of challenging behaviour was a criterion for inclusion in the study) it is unlikely the final point relating to more severe challenging behaviour being shown by individuals whose families are members of a support group would impact on the present results. The principle aims of the study were to delineate gene-environment interactions on self-

injury and aggression and the most appropriate way to do this was to study individuals who were known to demonstrate these behaviours, as such it was necessary that the sample be selective. It should also be noted that any bias due to syndrome group recruitment is likely to be comparable across groups, and therefore comparisons of challenging behaviour and correlates of challenging behaviour within the groups should still be valid.

Although for the purposes of the studies described in the thesis the sampling method was selective, it must be borne in mind that this does raise some important considerations when interpreting the results. Firstly, it must be remembered that the results of Chapter 3 indicate a descriptive profile of a highly selective sample of individuals who display challenging behaviour. Participants were recruited based on the presence of challenging behaviour and thus the results in Chapter 3 are not representative of the total population of individuals with Angelman,Cri du Chat and Cornelia de Lange syndrome; the data indicates proportions, not prevalence. In addition, it must be noted that the direct observations reported in Chapter 3 are amalgamations of the analogue conditions that are described within Chapter 4. The degree of experimental control applied within these conditions is important and may have resulted in higher rates of challenging behaviour than would have been observed in natural observations.

A second potential problem with the study was the lack of a heterogeneous or non-specific intellectual disability comparison group. Comparisons to groups with mixed aetiologies directly tests whether a behavioural feature characterises persons with intellectual disability in general or, instead, the specific syndrome group under study (Dykens, 1995; Hodapp & Dykens, 2001). However, although the inclusion of a mixed or non-specific group is common within the

behavioural phenotype literature, it does present difficulties. Firstly, finding a group of participants with mixed intellectual disability involves recruiting from a number of different services (e.g. schools, residential setting, day centres etc.) and it is difficult to know the degree to which participants of these services represent the total population of individuals with intellectual disability. Secondly, the profile of the heterogeneous group might be unknown and include a large proportion of people with particular disorders; Autism Spectrum Disorder, for example, or individuals with genetic syndromes who do not have diagnoses. The 'same but different' approach that was adopted in the present studies ensured comparisons of relatively homogeneous groups and thus, avoided the potential problems that would arise with the inclusion of a mixed aetiology group.

A third criticism of the study is that although carers were asked a number of questions about the diagnostic status of the person they care for (which syndrome, which genetic abnormality, when diagnosed and by whom), specific details on genetic diagnosis were not collected. This means that although participants may have been diagnosed clinically, a genetic diagnosis via a clinical geneticist may not have been made. In order to obtain this level of information, it would have been necessary to ask carers to send a copy of the original report from the clinical geneticist or genetics laboratory which details information about the precise location of the genetic abnormality. For many carers this would have involved approaching the GP and then for the GP to contact the genetics laboratory. If would have been the carer's responsibility to follow up the GP if the information was not obtained and the responsibility of the research team to prompt carers to do this. For these reason, it was felt that this was too much to ask of carers given the commitment that they had already given to the research. Also, many individuals with Cornelia de

Lange Syndrome and a proportion of those with Angelman syndrome would not have a genetic diagnosis, as there is ongoing research to identify other implicated genes. For example, in Cornelia de Lange syndrome, genetic mutations associated have only been identified for approximately 50% of individuals, and thus many participants would have a diagnosis made based only on the clinical features of the syndrome that are typically quite distinctive.

Additionally, a lack of genetic status meant that in Angelman and Cornelia de Lange syndromes, information on genetic subtypes was unknown and in Cri du Chat syndrome, information on the size of the deletion on chromosome five was missing. Given the literature describing variability in phenotypic expression in the syndromes resulting from genetic variability, this information may have been useful in the interpretation of the results. In Angelman syndrome there is some evidence to suggest that those individuals with a deletion subtype may have a more severe developmental delay and less expressive communication (Jolleff, Emmerson, Ryan & McConachie, 2006) than those individuals with unipaternal disomy, imprinting or UBEA3 mutation subtypes. In Cornelia de Lange syndrome, mutations in the SMC1S and SMC3 genes result in a milder phenotype than mutations in the NIPBL gene (Deardorff *et al.,* 2007) and in Cri du Chat syndrome, the size of the deletion ranges from the entire short arm of chromosome five to the region 5p15, which results in huge phenotypic variability in the syndrome (Overhauser *et al.,* 1994).

6.5. Implications for practice

Overall, the research has provided evidence that challenging behaviour in genetic syndromes can be influenced by environmental factors. This finding is important clinically as it highlights that

behaviours in these syndromes are not inevitable and should not be considered immutable thus challenging therapeutic nihilism. Further, examinations of specific forms of gene-environment interactions within syndromes are important in order to promote understanding of the aetiology of problem behaviours both within genetic syndromes and the wider population of individuals with severe intellectual disabilities. As the discussion sections in each chapter have considered, identification of gene-environment interactions is extremely important, not only for building syndrome-specific models but also in the construction of a comprehensive aetiological model of challenging behaviour in individuals with intellectual disability. The results have shown that there are many pathways that may be implicated in such a model including abnormal motivation, sensory impairments, health conditions and cognitive factors. These pathways have clear implications for intervention at a syndrome level. Firstly they provide an opportunity to minimise conditions known to mediate operant conditioning with the possible use of FCT (Carr & Durand, 1985). As mentioned, FCT has proven to be particularly effective for challenging behaviour maintained by social consequences and seeks to replace an aberrant behaviour with an alternative communicative response that is functionally equivalent (Carr & Durand, 1985). In syndromes, knowledge of operant vulnerability and susceptibility could inform FCT so that alternative functionally equivalent responses could be reinforced before the development of challenging behaviour.

The findings also have potential implications for clinical assessment and emphasise the importance of assessment to intervention designs that determine the functions of challenging behaviour and manipulate operant determinants in intervention. Within any given syndrome, many causal pathways may operate. However, syndrome specific gene-environment interactions

provide information on which pathway might be most significant. In turn, this provides information on which particular assessments should be prioritised in which syndromes. For example in Cornelia de Lange syndrome, a pain assessment may be prioritised given the link between health conditions and SIB (Luzzani *et al.,* 2003). In Soto's syndrome, levels of impulsivity may be assessed first or in Smith-Magenis syndrome a motivational assessment for challenging behaviour may be foremost.

Finally, the findings have important implications for early intervention in challenging behaviour. Early intervention in children with intellectual disabilities may be more effective at reducing challenging behaviour and enhancing other adaptive skills and abilities than a reactive approach (See Richman, 2008 for overview). Preparing families and professionals with knowledge and information enhances intervention opportunities and allows behaviour to be anticipated and responses to challenging behaviour to be monitored. As challenging behaviour develops and dyadic reinforcement takes place, the behaviour will become more established in an individual's behavioural repertoire (Oliver, 1995; Oliver, Hall & Murphy, 2005). Although prevention of the behaviour entering a behavioural repertoire is perhaps only realistic or possible for a subset of individuals, pre-emptive and early intervention strategies may be beneficial. In Cornelia de Lange syndrome for example, SIB may appear in an individual's repertoire in response to painful health conditions. Ensuring that health conditions commonly seen in Cornelia de Lange syndrome (e.g. gastroesophageal reflux, otitis media) are immediately and effectively treated may help to prevent potentially injurious responses.

The question is: how we disseminate the research findings quickly to the health service to affect change in practice? In order to shortcut the typical delays of research influencing practice, collaborations with syndrome support groups may be effective. Support groups have been successful in developing working partnerships with researchers from many disciplines. The groups have now become more proactive in determining the research agenda, and have taken advantage of new technologies for dissemination that gives a role for support groups to commission and disseminate research. Further, a collaborative approach between parent groups and researchers is likely to prove important in ensuring that research focuses on the most pressing problems of those who have syndromes and their families.

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APPENDIX A

The number of papers identified from journals and details of the syndromes reported: Results from the initial hand search of the literature review

Journal	Number of papers	Syndrome (s) reported
Journal of Applied Behavior Analysis	12	Cornelia de Lange syndrome (4), Soto's syndrome (2), Prader-Willi syndrome (1), Fragile-X syndrome (1), Williams syndrome (2), Angelman syndrome (1), Rubinstein-Taybi syndrome (1), Rett syndrome (1)
American Journal on Mental Retardation	0	-
Behavioral Interventions	3	Fragile-X syndrome (1), Lesch-Nyhan syndrome (1), Rett syndrome (1)
Journal of Autism and Developmental Disorders	2	Fragile-X syndrome and Rett syndrome
Journal of Applied Research in Intellectual Disabilities	0	-
Journal of Intellectual Disability Research	5	Rett syndrome (3), Cornelia de Lange syndrome, Smith-Magenis syndrome
Research in Developmental Disabilities	0	-
Behavior Modification	1	Lesch-Nyhan syndrome

APPENDIX B

Details of the number of papers identified and the syndromes reported: Results from the electronic search of the literature review

Journal	Number of papers	Syndrome (s) reported
American Journal of Medical Genetics	2	Cornelia de Lange and Rett syndromes
Behavioural and Cognitive Psychotherapy	1	Smith-Magenis syndrome
Developmental Disabilities Bulletin	1	Fragile-X syndrome
Developmental Medicine and Child Neurology	5	Lesch-Nyhan syndrome (4) and Cornelia de Lange syndrome
Disability and Rehabilitation	2	Lesch-Nyahn and Rett syndromes
Journal of Consulting and Clinical Psychology	1	Lesch-Nyhan syndrome
Journal of Mental Deficiency Research	3	Lesch-Nyhan Cornelia de Lange (2)
Journal of the Mulithandicapped Person	1	Lesch-Nyhan syndrome
The British Journal of Psychiatry	1	Cornelia de Lange syndrome

Brackets indicate the number of papers.

APPENDIX C

Ethical approval letters

APPENDIX D

Initial contact letters and information sheets sent to potential participants

The Three Syndromes Study
The Angelman, Cri du Chat and Cornelia de Lange Syndrome Support Groups
Funded by The Big Lottery to tackle behaviour problems and support families

Ref: PC/01/ CREC/06/07-190

Dear X,

We are writing to inform you of a new research project that is being conducted at the University of Birmingham in collaboration with the University of Wales, Bangor and the Institute of Psychiatry, King's College London. The research project is being conducted in association with the Cornelia de Lange Syndrome Foundation (UK & Ireland), Cri du Chat Syndrome Support Group and the Angelman Syndrome Support, Research and Education trust and is supported by the Big Lottery Fund.

The research aims to improve our understanding of the role of factors within the environment that may impact on self injurious and aggressive behaviours commonly associated with Cornelia de Lange, Cri du Chat and Angelman syndromes. The study will also consider factors that are related to family well-being and adjustment. This is an important area of study but has rarely been attended to within the literature.

We have selected individuals from our database of families who we feel may be well suited to participate in this research project. We would like to make telephone contact with you in the next seven days to discuss further the possibility of you and your son/daughter X taking part in this study.

There is an information sheet enclosed that gives you some more detailed information about why the research is being carried out and what it will involve. If you feel it is appropriate you may wish to discuss the research with the person that you care for.

Please take the time to read the enclosed information sheet. If you are unclear about any aspect of the study of have any queries then please contact Professor Chris Oliver by telephone: [redacted], email: [redacted] or at the above address.

Thank you for your time and continued support for our research at the University of Birmingham. We look forward to speaking to you in the next 7 days. .

Yours sincerely,

Professor Chris Oliver (Project Director)

Supported by The National Lottery® through the Big Lottery Fund

BEHAVIOUR DISORDER AND FAMILY ADJUSTMENT IN CRI DU CHAT, CORNELIA DE LANGE AND ANGELMAN SYNDROMES:
INFORMATION SHEET FOR PARENTS AND CARERS

Introduction to the research and invitation to take part:
We have selected you and your child/person you care for as potential participants in a study being conducted at the University of Birmingham, in collaboration with the University of Wales, Bangor and the Institute of Psychiatry, King's College London.

The research project is being conducted in association with the Cornelia de Lange Syndrome Foundation (UK & Ireland), Cri du Chat Syndrome Support group and the Angelman Syndrome Support, Research and Education Trust and is supported by the Big Lottery Fund.

The study aims to improve our understanding of the role of factors within the environment that may impact on self injurious and aggressive behaviours commonly associated with Cornelia de Lange, Cri du Chat and Angelman syndromes. We will also examine the factors that are related to family well-being within these syndrome groups and the impact that having a child with a genetic syndrome has on the family. We hope that greater understanding of the behaviours associated with these syndrome groups will help to support social inclusion, develop better intervention and management strategies for families and improve the health and well-being of affected individuals and their families.

What does it involve?
Participation in the research project will involve the following:

- You will be asked to complete three brief questionnaire packs in order to provide us with some background information about your child/person you care for and their behaviour. Some of these questionnaires will also ask you some questions about your wellbeing and the impact that having a child with a genetic syndrome has on the family

- We would like to take some time to discuss with you about your child's/person you care for's behaviour and to ask you some questions concerning your wellbeing and the impact that having a child with a genetic syndrome has on the family. Some of this will be done over the phone and some will be done during a home visit. The phone interviews will take approximately 30-45 minutes and will be recorded (with your permission) in order to assist accurate data collection. The tapes will be filed anonymously and will only be available to researchers working on the project.

- We will visit your child/person you care for at their school or day centre for the day. During this time, we will carry out short observations of your child/person you care for in different social situations and during a series of games and activities. These different social situations and activities will be presented to your child/person you care for by two members of the research team.

- We would like to talk to your child's/person you care for's teacher/key worker to ask them about your child's/person you care for's behaviour at school.

An example of the timetable for collecting the above information from you, your child/person you care for and their teacher is shown below:

Stage One:	Return consent form
Stage Two:	Complete questionnaire pack.
Stage Three:	Complete phone interview
Stage Four:	Two research workers will visit you at home to talk about your child's/person you care for's behaviour.
Stage Five:	Two research workers will visit your child/person you care for at school for the day.
Stage Six:	You will receive a detailed individual feedback form about your child's/person you care for's assessments.

How will behaviours be observed and recorded?

- When we visit your child/person you care for at school/day centre, we will carry out short observations with them in different social situations and during a series of games and activities. Video recordings of your child/person you care for during these situations and activities will be made and stored. This allows us to return to the video recordings for detailed analysis of information and means that we can check the accuracy of our observations.

- When videotapes are not used they will be stored in a locked filing cabinet.

- The privacy and dignity of your child/person you care for will be respected at all times and video recordings will not take place if there is evidence that the observations are causing distress.

- You may ask to see a copy of the video recordings of your child/person you care for.

- Video recordings may only be viewed by legal guardians or individuals providing a service to the person you care for and members of the research team working on this project.

- Information identifying your child/ person you care for will not be stored on or with the tape.

- The University of Birmingham will hold the copyright for the video recordings in order that the confidentiality of the recordings of your child/person you care for be protected. However, this does not mean that the University of Birmingham will have the right to edit, copy or use the videos for teaching purposes without your written permission.

- We may contact you again in the future to ask your permission to use the video recordings for teaching purposes. At that stage you will be able to decide whether or not you are happy for the videos to be used for these purposes. However, agreeing to participate in this study does not mean that you will be obliged to give your permission for the use of these video recordings in the future.

Consent:

After our phone call, if you decide to become involved in the project then you will be required to complete a consent form and return this us.

Withdrawal:

Should you or the person you care for decide that you no longer wish to be involved in the research; you are free to withdraw your participation at anytime during the study and for a period of three months after

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

Confidentiality:
All information collected will be kept on a confidential database that is only accessible to those working on the project. In the unlikely event of any evidence of abuse being identified, this information will be disclosed by the research workers. All personal details will be kept separately from the information collected and your child/person you care for will be identifiable by a code throughout the study to ensure anonymity. If published, information will be presented without reference to any identifying information. Information will be held in accordance with the Data Protection Act principles.

At the end of the study:
Each parent/carer will receive a personalised feedback report on their child/the person they care for. A summary of the project's findings will be circulated to anyone involved who wishes to see a copy. Any requests for advice concerning your child/person you care for will be referred to Professor Chris Oliver, Clinical Psychologist. It is possible that you may be invited to participate in further research after the study. However, consenting to participate in this study does not mean that you are obliged to do so.

Who has reviewed the study?
This research project has been reviewed and approved by the University of Birmingham, School of Psychology Research Ethics Committee (4), the University of Wales, Bangor Ethics Committee (ext) and the King's College London Ethics Committee ; ref: CREC/06/07-190).

Any concerns of queries?
If you are unclear about any aspect of the study or have any questions, please do not hesitate to contact Professor Chris Oliver by telephone: , by email: or at the following address:

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

Thank you very much for taking the time to read this information

APPENDIX E

Background questionnaire, information sheet and consent forms sent to main caregivers after meeting inclusion criteria for the study

UNIVERSITY OF BIRMINGHAM

The Three Syndromes Study

The Angelman, Cri du Chat and Cornelia de Lange Syndrome Support Groups Funded by The Big Lottery to tackle behaviour problems and support families

Booklet 1: Background Information

Instructions for Completing Questionnaire:

1. The questionnaires should be completed by the **main caregiver.**

2. When you have completed the questionnaire, please check that you have answered every question. We will collect at the visit.

Thank you for supporting our research

Supported by The National Lottery® through the Big Lottery Fund

ID _____

DEMOGRAPHIC QUESTIONNAIRE

Today's date: _____

Your relationship to your child/person you care for?

_____

SECTION A: The following questions tell us about the person you care for:

1. **Gender:** Male ☐ Female ☐

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

3. **Is the person you care for verbal?** (i.e. more than 30 signs/ words in their vocabulary) *Yes/ No (delete as appropriate)*

4. **Is the person you care for able to walk by themselves? Please tick where appropriate**

1 = not at all ☐ **2** = not up stairs ☐ **3** = up stairs and elsewhere ☐

5. **Vision:**

1 = blind or almost ☐ **2** = poor ☐ **3** = normal ☐

6. **Hearing:**

1 = deaf or almost ☐ **2** = poor ☐ **3** = normal ☐

7. **Has the person you care for been diagnosed with a syndrome?**

Yes/ No (delete as appropriate)

If yes, please indicate which of the following syndromes have they been diagnosed with?

7a. Cornelia de Lange syndrome ☐ Cri du Chat syndrome ☐

Angelman syndrome ☐

8. **What is the genetic mechanism causing the syndrome in the person you care for?**

Uni-parental disomy	☐	Sequence repetition	☐
Deletion	☐	Translocation	☐
Unknown	☐	Other _____	

9. **When was the person you care for diagnosed?** _____

10. **Who diagnosed the person you care for?**

Paediatrician	☐	Clinical Geneticist	☐
GP	☐	Other _____	

11. **Has your child/person you care for had any medical / health difficulties in the last six months? If yes, please give details:**

_____

_____

_____

SECTION B: The following questions tell us about you and your family

1. **Are you male or female?** Male ☐ Female ☐

2. **What was your age in years on your last birthday?** _____years

3. **Please tick the highest level of your educational qualifications.**

No formal educational qualifications	☐
Fewer than 5 GCSE's or O Level's (grades A-C), NVQ 1, or BTECH First Diploma	☐
5 or more GCSE's or O Level's (grades A-C), NVQ 2, or equivalent	☐
3 or more 'A' Levels, NVQ 3, BTECH National, or equivalent	☐
Polytechnic/University degree, NVQ 4, or equivalent	☐
Masters/ Doctoral degree, NVQ 5, or equivalent	☐

4. **What is your relationship to your child/person you care for (e.g., mother, father, stepmother, grandmother, adoptive parent, carer)?** _____

5. **In total how many people currently live in your home?** _____Adults ____ Children

6. **Does your child/person you care for normally live with you?** Yes ☐ No ☐

If no, then where do they live? _____

7. What is your current marital status? ***(please tick)***

Married, and living with spouse ☐

Living with partner ☐

Divorced/Separated/Widowed/Single and NOT living with a partner ☐

If living with partner/spouse, please answer the following questions. If not, please go on to question 12.

8. Is your partner male or female? Male ☐ Female ☐

9. What was their age in years on their last birthday? _____years

10. Please tick the highest level of your partner/spouses educational qualifications.

No formal educational qualifications ☐

Fewer than 5 GCSE's or O Level's (grades A-C), NVQ 1, or BTECH First Diploma ☐

5 or more GCSE's or O Level's (grades A-C), NVQ 2, or equivalent ☐

3 or more 'A' Levels, NVQ 3, BTECH National, or equivalent ☐

Polytechnic/University degree, NVQ 4, or equivalent ☐

Masters/ Doctoral degree, NVQ 5, or equivalent ☐

11. What is your partner/spouses relationship to your child/person you care for (e.g., mother, father, stepmother, adoptive parent, carer)? _____

12. Recent data from research with families of children with special needs has shown that a family's financial resources are important in understanding family member's views and experiences. With this in mind, we would be very grateful if you could answer the additional question below. We are not interested in exactly what your family income is, but we would like to be able to look at whether those with high versus lower levels of financial resources have different experiences.

What is your current total annual family income? Please include a rough estimate of total salaries and other income (including benefits) before tax and national insurance/pensions

Please tick one box only:

Less than £15,000 ☐ £15,001 to £25,000 ☐

£25,001 to £35,000 ☐ £35,001 to £45,000 ☐

£45,001 to £55,000 ☐ £55,001 to £65,000 ☐

£65,001 or more ☐

13. Is respite care available to you for your child/person you care for?

Yes ☐ No ☐

If yes, please continue but skip question 15. If no, please go on to question 15.

14. How often do you use respite care? Please tick the box that is the closest approximation

Don't use	Weekly	Every two weeks	Once a month	Once every two months	Once every three months	Twice a year	Once a year

15. Would you use respite care if it were available? Yes ☐ No ☐

Please answer the following question regardless of whether or not you currently have access to respite care:

16. Ideally, how often would you like to have access to respite care? Please tick the box that is the closest approximation

Weekly	Every two weeks	Once a month	Once every two months	Once every three months	Twice a year	Once a year

Thank you very much for completing this questionnaire

Consent Information Sheet

BEHAVIOUR AND FAMILY WELL-BEING IN CORNELIA DE LANGE, CRI DU CHAT AND ANGELMAN SYNDROMES.

INFORMATION SHEET FOR PARENTS AND CARERS

You and the person you care for are being asked to take part in a research study. Before you decide if you both wish to take part it is important that you understand why we are doing the research and what it will involve. Please take time to read the following information carefully and if it is appropriate, explain and discuss it with the person you care for. If there is anything that is unclear, or if you would like more information please contact us using the details provided at the end of the sheet.

What is research and what is the purpose?

This study is being conducted at the University of Birmingham in collaboration with the University of Wales, Bangor and the Institute of Psychiatry, King's College London.

The research project is being conducted in association with the Cornelia de Lange Syndrome Foundation (UK & Ireland), Cri du Chat Syndrome Support group and the Angelman Syndrome Support, Research and Education Trust and is supported by the National Lottery, Community Fund.

The study aims to improve our understanding of the role of factors within the environment that may impact on self injurious and aggressive behaviours commonly associated with Cornelia de Lange, Cri du Chat and Angelman syndromes. The study will also examine the factors that are related to family well-being within these syndrome groups and the impact that having a child with a genetic syndrome has on the family. We hope that greater understanding of the behaviours associated with these syndrome groups will help to support social inclusion, develop better intervention and behaviour management strategies and improve the health and well-being of affected individuals and their families.

Do we have to take part?

It is up to you and the person you care for whether or not you decide to take part, the decision you come to will not affect any services you receive, support from the syndrome groups or the availability of clinical consultations from Chris Oliver and his team at support group meetings. If you and the person you care for do decide to take part you will be asked to sign a consent form.

Will I be able to withdraw from the research?

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

Will our information be confidential?
All information collected will be kept on a confidential database that is only accessible to those working on the project. In the unlikely event of any evidence of abuse being identified, this information will be disclosed by the research workers. All personal details will be kept separately from the information collected and your child/person you care for will be identifiable by a code throughout the study to ensure anonymity. If published, information will be presented without reference to any identifying information. Information will be held in accordance with the Data Protection Act principles.

What does it involve?

Participation in the research project will involve the following:

- You will be asked to complete three questionnaire packs for this study. The first questionnaire pack will provide us with general information about your child/ person you care for and their abilities, it will also ask you (parent or legal guardian) for some information about yourself. The second questionnaire pack will ask questions regarding your child's/ person you care for's behaviour, sleep, communication and health. Finally, a third questionnaire pack will ask you questions concerning your wellbeing, and the impact that having a child with a genetic syndrome has on the family.

- We would like to take some time to discuss with you about your child's/person you care for's behaviour and to ask you some questions concerning your wellbeing and the impact that having a child with a genetic syndrome has on the family. Some of this will be done over the phone and some will be done during a home visit. The phone interviews will take approximately 30-45 minutes and will be recorded (with your permission) in order to assist accurate data collection. The tapes will be filed anonymously and will only be available to researchers working on the project.

- We will ask your child's/person you care for's teacher/key worker to complete a questionnaire pack. These will be questions concerning your child's/ person you care for's behaviour and communication at school. We will also ask them to take some time to discuss your child's/person you care for's behaviour at school.

- We will visit your child/person you care for at their school, day centre or college for the day on two consecutive days. During this time, we will carry out short observations of your child/person you care for in different social situations and during a series of games and activities. Video recordings of the observation sessions will be made, as it is necessary for another psychologist at the University of Birmingham/King's College London, to check the accuracy of the observations (additional information on videoing is provided further on in this information sheet). The different social situations and activities will be presented to your child/person you care for by two members of the research team. We will use three different social situations which will last 10 minutes each. The first situation will provide your child/ person you care for with lots of attention and we will play games with them. In the second situation we will not initiate any interaction with your child but we will

interact if the child attempts to initiate interaction. In the third condition we aim to see how your child responds if we do not interact with them socially.

- During our time at your child/person you care for's school, day centre or college we will also carry out some observations to help understand what triggers certain problem behaviours. We will carry out observations as your child takes part in situations where levels are adult attention and demands are varied. The situations include three different conditions (5 minutes each), which your child will experience regularly in their normal school environment. The first situation is a "high attention" in which the teacher or researcher will interact with your child while they play with a preferred toy or game. The second condition is a "high demand" condition in which the teacher or researcher will ask your child to take part in a less preferred task and will continue to prompt and guide your child throughout the task. The final condition is a "low attention" condition in which your child will again have access to a preferred game or toy but this time the teacher or researcher will move their attention away from your child and will talk to the researcher. It is possible that these situations will cause an increase or decrease in particular behaviours. If your child becomes extremely distressed or is at excessive risk of injuring themselves we will immediately stop the session.

- During the home visit, we may also conduct some short observations of your child/ person you care for within the home. This will be very similar to the method described above, only this time we will ask *you* to interact with your child/person you care for. The situations will be very natural and will be situations that are part of your childs'/person you care for's regular routine. The situations will be similar to the high attention, low attention, and demand conditions conducted during the school assessments (see above) and we will ask you to think of a time in your daily routine where this situation may occur (e.g. high attention may occur when you play a game at a certain point during the day). We will then ask you to run through this situation so that we can observe any changes in behaviour that might occur during that time. In some cases it may be necessary to ask you to think of more specific situations in which self-injurious or aggressive behaviour usually occur and include this situation in the observations (for example it may be the case that you observe higher rates of these behaviours when a preferred activity is terminated. Therefore, we would include this situation in the observations). There may also be times when we ask you respond to your child/person you care for in a different way to that which you would normally do (e.g. during a low attention condition, we may ask you to turn around and talk to your child/person you care briefly when behaviour occurs, rather than not paying any attention to the behaviour). Again, this is to observe any changes in behaviour that occur as a result of these situations and responses. It is possible that these situations will cause an increase or decrease in particular behaviours. If your child becomes extremely distressed or is at excessive risk of injuring themselves we will immediately stop the session.

How video recordings will be made?

- Observations and video recordings will only take place during previously specified times that have been agreed by teachers and parents/ legal guardians.

- Video recordings will be kept and stored for further review by the Three Syndromes Project research team. When videotapes are not in use they will be stored in a locked cabinet in the School of Psychology, University of Birmingham/King's College London and will only be viewed by research workers from the University of Birmingham/King's College London. Information identifying your child will not be stored on or with the tape.

- Your child's privacy and dignity will be respected and video recordings will not take place if children are in a state of undress or when there is evidence that the observations are causing distress.
- Parents/ legal guardians and teachers can ask to see a copy of the videotape.

- The video recordings may only be viewed by legal guardians, individuals providing a service to the person, Professor Chris Oliver and research staff at the University of Birmingham. Any data that are derived from the tape will remain anonymous.

- The University of Birmingham will hold the copyright for the video recordings in order that the confidentiality of the recordings of your child/person you care for be protected. However, this does not mean that the University of Birmingham will have the right to edit, copy or use the videos for teaching purposes without your written permission.

- We may contact you again in the future to ask your permission to use the video recordings for teaching purposes. At that stage you will be able to decide whether or not you are happy for the videos to be used for these purposes. However, agreeing to participate in this study does not mean that you will be obliged to give your permission for the use of these video recordings in the future.

At the end of the study

Each parent/ legal guardian will receive a personalised feedback report on their child/the person they care for.
A summary of the overall project's findings will be circulated to anyone involved who wishes to see a copy. Any requests for advice concerning your child/person you care for will be referred to Professor Chris Oliver, Clinical Psychologist. It is possible that you may be invited to participate in further research after the study. However, consenting to participate in this study does not mean that you are obliged to do so.

Who has reviewed the study?

This research project has been reviewed and approved by the University of Birmingham, School of Psychology Research Ethics Committee ( ), the University of Wales, Bangor Ethics Committee ( ) and the King's College London Ethics Committee (; ref: CREC/06/07-190)

Consent:
It is up to you whether or not you would like your child/person you care for to take part in the study. If your child/person you care for is aged between 2 and 15 years and you would like them to participate in this study please complete the enclosed consent form and return it to us in the envelope provided. If you feel it is appropriate, you may wish to discuss the project with your child/person you care for.

If you decide to become involved in the project then please complete the appropriate consent form and return this in the envelope provided. After you have returned your consent form you will be contacted by your allocated project worker who will give you further information about the project.

Any concerns of queries?
If you are unclear about any aspect of the study or have any questions, please do not hesitate to contact Professor Chris Oliver by telephone: [redacted], by email: [redacted] or at the following address:

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

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

Consent Form for participants aged 2-15 years

Please initial the boxes

I confirm that I have read and understood the attached information sheet for the above study and have had the opportunity to ask questions. ☐

I understand that participation in the study is voluntary and that I am free to end my own involvement or that of my child / the person I care for at any time, or request that the data collected in the study be destroyed, without giving a reason. ☐

I consent to the processing of my personal information for the purposes of this research study. I understand that such information will be treated as strictly confidential and handled in accordance with the provisions of the Data Protection Act 1998. ☐

I understand that as part of the above study, video/voice recordings of myself and my child/person I care for will be made and stored for further review. ☐

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

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

I agree to participate in the above study. ☐

I agree to the participation of my child / the person I care for in the above study. ☐

Please complete the information below

Participant's name…….date of birth……

Parent or guardian's name……Mr/Mrs/Miss/Ms (please circle)

Parent or guardian's signature……Date……..

Please state relationship with participant…….

CREC/06/07-190
FOR OFFICE USE ONLY
Signature of researcher……..Date……...

Consent Form for participants aged 16 and over

<u>SECTION A:</u> For children who are over the age of 16 but who are unable to provide consent.

Please initial the boxes

I confirm that I have read and understood the attached information sheet for the above study and have had the opportunity to ask questions. ☐

I understand that participation in the study is voluntary and that I am free to end my own involvement or that of my child / the person I care for at any time, or request that the data collected in the study be destroyed, without giving a reason. ☐

I consent to the processing of my personal information for the purposes of this research study. I understand that such information will be treated as strictly confidential and handled in accordance with the provisions of the Data Protection Act 1998. ☐

I understand that as part of the above study, video/voice recordings of myself and my child/person I care for will be made and stored for further review. ☐

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

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

I am happy to be contacted in the future by the University of Birmingham with information about future research projects ☐

I agree to participate in the above study. ☐

I agree to the participation of my child / the person I care for in the above study. ☐

Please complete the information below

Participant's name…….date of birth……

Parent or guardian's name……Mr/Mrs/Miss/Ms (please circle)

Parent or guardian's signature……Date……..

Please state relationship with participant…….

FOR OFFICE USE ONLY

Signature of researcher……..Date……...

SECTION B: For children who are over 16 and are able to consent

Please initial the boxes

I confirm that I understood the information sheet for the study and have been able to ask any questions. ☐

I understand that participation in the study is voluntary and that I can stop it at any time, or request that the data collected in the study be destroyed, without giving a reason. ☐

I consent to the processing of my personal information for the purposes of this research study. I understand that such information will be treated as strictly confidential and handled in accordance with the provisions of the Data Protection Act 1998. ☐

I understand that as part of the above study, video recordings will be made of me during the assessments. ☐

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

I am happy to be contacted in the future about the use of video recordings for teaching purposes. ☐

I agree to participate in the study. ☐

Please complete the information below

Participant's name…….

Participant's signature……Date……..

FOR OFFICE USE ONLY

Signature of researcher……..Date……...

APPENDIX F

Study Flyer

The 3 Syndromes Study Research Team is looking for you!

The University of Birmingham research team has started a new research project about challenging behaviour and family wellbeing in children and adults with Cornelia de Lange, Angelman and Cri du Chat syndromes. Our research team has now expanded to include research teams in both London and North Wales so that we are now able to get in touch with more families and children around the UK.

In this project we are inviting children and adults aged between 2 *and 19* years who are showing aggressive or self-injurious behaviour *at least once a day* to take part in the study. At this stage we would simply like to inform you of the study and ask any families of children and adults who are engaging in these behaviours to get in touch with us.

- **How do we define aggressive behaviour?** Aggressive behaviour includes any behaviour which may cause physical discomfort or possible harm to another person including hair pulling, grabbing, scratching, pushing, kicking, biting, hitting etc. It may well be that the person doesn't mean to hurt others or is too small to hurt others. For this project we would still be interested in hearing from you.

- **How do we define self-injurious behaviour?** Self-injurious behaviour includes any behaviour which may cause physical discomfort (including reddening of the skin or bruising) or harm to the person such as picking, biting, tapping, hitting, banging, scratching etc.

If the person you care for shows either or both of the above behaviours at least once a day *or* they show something like self-injury or aggression but you're not sure if they could be included, then please contact Professor Chris Oliver at the University of Birmingham on: [redacted], via email: [redacted] or post: Professor Chris Oliver, School of Psychology, University of Birmingham, Edgbaston, B15 2TT. Alternatively, please contact Karen Kings (administrator) at the University on: [redacted] via e mail: [redacted] *Responding to this leaflet does not in any way commit you to participation in the study. We will give you some more information, you can discuss the project with us and then you can decide what to do in your own time.*

Supported by The National Lottery® through the Big Lottery Fund

UNIVERSITY OF BIRMINGHAM

UNIVERSITY OF WALES BANGOR

Institute of Psychiatry at The Maudsley

APPENDIX G

Anonymous Feedback Report

The Cerebra Centre for Neurodevelopmental Disorders

UNIVERSITY OF BIRMINGHAM

REPORT

Name: X
DOB: X
Date of assessments:
Assessments conducted by:
Reason for assessment: Research visit

Background information:
We visited X at School, where he has been attending since …. X was assessed as part of a research study investigating challenging behaviour in Angelman syndrome. X's mother contacted the University of Birmingham expressing interest in the study and with some concerns about his self-injurious and aggressive behaviour, which was occurring daily.

During the research visit to X at school on 5th and 6th November we observed X's behaviour across different environmental situations and conducted in depth interviews with his mother and teacher about his behaviour at home and school (See Appendix A for a summary of the information provided). While at school we conducted some informal observations of X's behaviour in the classroom during two situations in which his teacher had indicated that aggressive behaviour was likely to occur. We also conducted some assessments of X's social interaction skills, the results of this assessment are not discussed in detail here but a summary of the findings can be seen in Appendix B and E.

Adaptive Behaviour: Vineland Adaptive Behaviour Scales- Second Edition (VABS II; Balla *et al.*, 2005):
The VABS-II was conducted with X's Mother on 13th November 2007 via the telephone in order to assess his adaptive behaviour skills and to provide the research workers with some background information about X's general abilities. Adaptive behaviours are the day-to-day activities necessary to take care of one-self and to get along with others. Questions about adaptive behaviour in this assessment ask about the person's *typical* performance, rather than the potential ability of the individual – what a person **actually** does as opposed to what a person is capable of doing. The VABS-II interview measures personal and social ability in four areas: (a) Communication, (b) Daily Living Skills, (c) Socialisation, and (d) Motor Skills.

The table below shows what X's particular strengths are within the four domains assessed by the VABS-II.

Domain	X's strengths in each domain
Communication	*Receptive language*- X is able to point to both major and minor (e.g. teeth) body parts when asked, and able to listen to a story for at least 5 minutes, and is sometimes able to follow two-part instructions (e.g *bring me the apple and the banana*).
Daily Living Skills	*Personal* – X is able to eat finger foods independently, is able to take off a coat, and is able to sometimes pull up clothing

	with elastic waistbands. *Domestic* –if X sees laundry on the floor, he will often pick it up. *Community*- X demonstrates understanding of a telephone and will sometimes listen to familiar people on the phone, he is also able to turn on the T.V.
Socialisation	*Interpersonal Relationships* – X is affectionate towards familiar people, he also shows interest in other children of the same age and will independently approach other children in order to interact with them. *Play and Leisure time* –is able to play cooperatively with other children for quite a while, and will continue playing without fussing if his caregiver leaves. *Coping skills*- will change from one activity to another with little fuss.
Motor skills	*Gross Motor Skills* -. X can go up and down stairs unaided, can climb up high objects, and is very adept at using a bicycle with training wheels. *Fine Motor Skills* - is able to manipulate small objects using his thumb and fingers, is able to open and close doors, and is able to complete a puzzle with at least two pieces or shapes.

For more detailed information and scores from the VABS II, please see Appendix C.

General observations during the assessment period:

We visited X at school on two consecutive days and also at home, after the school day on 5th November. At school, X was very engaging and generally happy to work with the examiners during assessment period. At times, he became a little upset and distressed, particularly during the demand condition of the analogue assessments, but he was easily distracted from this and it did not interfere with the assessment in any way. X was generally very sociable and appeared to enjoy the interaction with the examiners. His concentration was poor at times and this often resulted in the examiners having to quickly re-engage him in activities or introduce novel activities to the assessment. His use of verbal communication was somewhat limited although he did use his vocalisations effectively to indicate his needs. His use of nonverbal communication skills was very good and he demonstrated good eye contact, use of facial expressions, pointing and gesturing to indicate his needs effectively. Although this was not directly assessed, X's receptive language skills seemed to be a relative strength and he was able to understand and follow instructions, direction and comments made by the examiners. It was noted that using visual cues used alongside verbal communication when giving instructions were also very helpful to X.

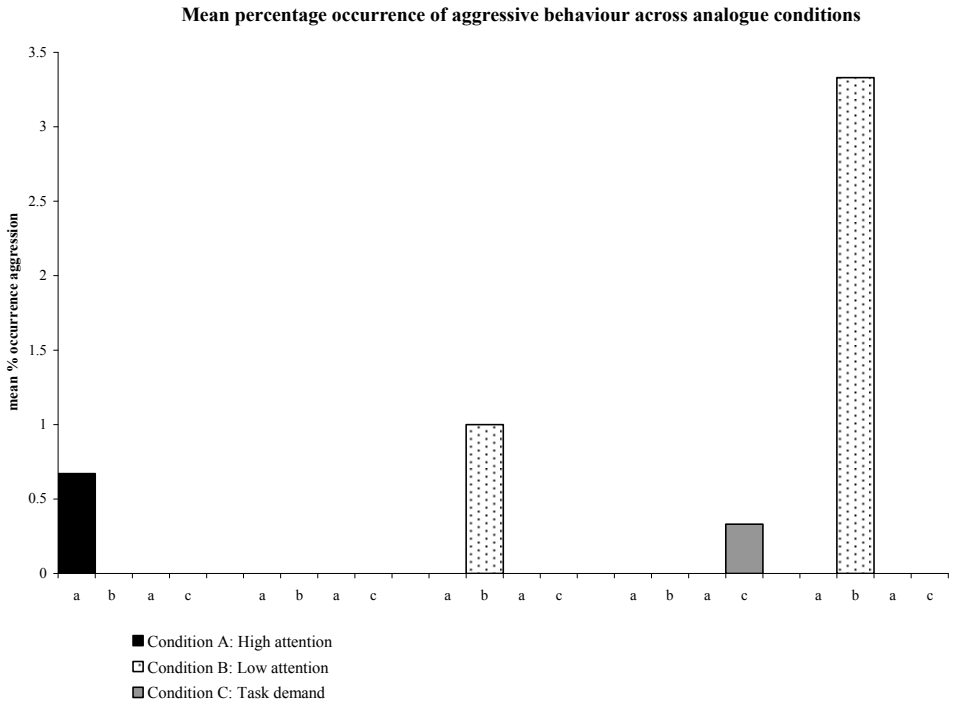
We observed some very brief episodes of aggressive behaviour during the analogue assessments at school. However, this was at a very low frequency and consequently, it was very difficult to be able gain a full understanding of the nature of these behaviours from these observations alone. We have therefore relied heavily on the interviews conducted with X's mother and teacher in order to gain a broader understanding of his behaviour. Although the terms 'aggression' and 'aggressive behaviour' are used throughout this report, they do not imply that X has intent to harm or injure others.

Summary of results:

Direct experimental observation of aggressive behaviour in different environmental situations:

- This assessment involved alternating different environmental situations in which the level of attention and demands placed upon X was varied in a similar way to the commonly employed method first described by Carr and Durand (1985). The level of attention available to X was varied in conditions A (high attention) and B (low attention). During condition C (demand), X was asked to engage in a task with the examiner for five minutes. This task was something that X could manage to complete but was somewhat of a challenge for him. The selected task involved X engaging in an inset puzzle which his teacher had identified to be challenging for him.

- The Graph in Figure 1 below shows the mean percentage of time that X spent engaging in aggressive behaviour across the different environmental situations.



- The above graph shows that X engaged in aggressive behaviour in 4 out of 16 trials.

- X displayed aggressive behaviour in 2 out of 4 low attention trials, 1 out 8 high attention trials (very low frequency) and 1 out of 4 demand trials (very low frequency). Whilst it is difficult to be certain due to the low frequency of observed behaviour, the results suggest that during the analogue assessments, X's aggressive behaviour was more likely to occur when the examiner was not available to engage with X. This finding is consistent with the fact that X is a very socially motivated little boy who enjoys interacting with both familiar and unfamiliar people (please see the results of the experimental social presses in Appendix B and the results from the ADOS assessment in Appendix E).

- This is also consistent with reports from his teacher that X is more likely to engage in aggressive behaviour during circle time at school and during the snack period. In both of these situations, she and other members of staff are present but their attention is shared between the

children rather than focusing on X. The examiners observed X informally during both of these situations. Although no aggressive behaviour was recorded during these particular sessions (X was very aware of the camera and the presence of the examiners in the room), it was noted that during the snack time observation, X was frequently seeking eye contact and interaction from other members of staff who were dealing with other children. Following this, X would touch or tug at other staff members clothing or hands and following this he would grab other children's food. At this point a member of staff would generally intervene, thus providing X with attention.

- Aggressive behaviour in situations where social contact is low or unavailable is commonly observed in children with Angelman syndrome. The reason that we think we observe this pattern of behaviour in Angelman syndrome is outlined below:

  - Children with Angelman syndrome are typically sociable children who find social contact very rewarding.
  - When social contact is unavailable (at times when attention towards the child is diverted away), the child would like to reinstate this social contact.
  - How does the child, with limited expressive language skills (a feature of Angelman syndrome) get the adult to attend to them again? ….by being aggressive!

- In addition to X's strong motivation for social interaction, his poor expressive language skills coupled with a relative strength in receptive language skills may be factors that increase the risk of aggressive behaviour occurring in situations where attention is diverted.

- However, the findings from this assessment are not consistent with the types of situations reported by X's mother to be predictable triggers of aggressive behaviour at home. The fact that X demonstrates aggressive behaviour for different reasons in different environments is not at all unusual to observe in children with intellectual disability. X's mother reported that at home, his aggressive behaviour is more likely to occur when he is asked to do something that he does not want to do such as get dressed, have dinner. She also reported that he is more likely to engage in aggressive behaviour when he is not able to have or do something that he wants. In line with this, his teacher also indicated that in addition to circle and snack time, X may be more likely to be aggressive when he is asked to do something that he does not want to do or when he is not able to have something that he wants. It is not unusual for children to engage in challenging behaviour for different reasons in different environments and therefore it is possible that X's aggressive behaviour may have two different functions. The first being to seek interaction from others (evidenced in the graph and descriptions above) and the second being to escape from demand situations. Given that we did no observe any challenging behaviour in the latter conditions, it is difficult to be certain about this.

General summary:

We observed X at school on two consecutive days in order to conduct some direct assessments of his aggressive behaviour. We also conducted some informal classroom observations and assessments of his social interaction skills. We observed some brief episodes of aggressive behaviour during our direct assessments which indicated that X was more likely to engage in aggressive behaviour during low attention situations. This is inline with reports from his teacher and our informal observations of X in the classroom. However, the frequency of observed behaviour during our assessment period was very low and it is therefore difficult to draw firm conclusions about X's behaviour. Both his mother and teacher reported that X is also more likely to engage in aggressive behaviour in situations when he is asked to do something that he does not want to do or when he is denied an activity or object that he

wants. We have provided some general recommendations for managing X's behaviour based on both our observations of X and the information provided from interviews with his mother and teacher.

Advice and recommendations for X:

Given that we did not observe many of the behaviours reported by X's mother and teacher during our assessment, the recommendations provided below are largely based upon reports from X's mother and teacher of his behaviour at home and at school. As a result, these recommendations provide some general guidelines for managing aggressive behaviour. For more specific advice on managing X's behavioural difficulties, or for help with implementing the suggested management strategies, it may be helpful to contact your local learning disability services or to seek a referral to your local clinical psychology services via your GP, who may be able to provide a more detailed assessment of these behaviours and work with X at home and at school to provide more specific behaviour management strategies.

General advice and recommendations for dealing with aggressive behaviour:

- When X engages in aggressive behaviour we would generally advise you to:

    1) Modify your response to the behaviour. If you need to respond to protect yourself or other people, be 'cool', do not give eye contact, do not speak to X (even to reprimand, as this can still be considered positive attention by some children) and do not show any change in your facial expression (e.g. do not laugh, smile).

    2) If safe to do so, terminate your contact with X or his contact with others (depending on who he has been aggressive towards) by taking his hands in yours and placing them by his side, then count for ten seconds. Within this 10 second period do not respond to any approaches that X makes towards you, do not speak and do not give eye contact. After 10 seconds has elapsed, any approaches made by X should be responded to in the manner that you usually would.

Advice and recommendations for aggression occurring at times when attention is diverted away from X.

- If X is displaying aggressive behaviour towards other children or individuals during periods of low or diverted attention, try to terminate contact between X and the individual for 10 seconds. Remember to keep 'cool' when you respond, do not give eye contact do not speak to X, and do not show any change in your facial expression (e.g. do not laugh, smile). If after 10 seconds X has not displayed any aggression praise him.

Advice and recommendations for aggression occurring at times of demand or during tasks

- Try not to remove the task when X shows aggressive behaviour. Be 'cool', do not give eye contact, do not speak to X and do not show any change in your facial expression (e.g. do not laugh, smile).

- Break the task of dressing for example into smaller steps and give big rewards for completion or tries of each step rather than just a reward at the end of the task (e.g. give reward or praise after he has tolerated (with no aggressive behaviour) you putting one leg in his trousers, then the other leg etc). Over time it may be possible to fade the steps so that X is rewarded for doing two steps rather than one, and with more time only rewarded at the end of the task. This 'task analysis' approach may help to make the task of dressing more fun for X.

- Find or teach a communicative response that can tell you that X wants the task to stop and respond to this. If the communicative response for 'stop' happens too frequently set a timer with X and only respond after the timer has gone off. Gradually increase the time.

Important notes

- When aggression **is not** occurring *do* present positive and fun attention, it might even be helpful to set a timer to remind you. Also reward X for playing with other children but not being aggressive.
- **Please note** it is very important that everyone is doing the same thing, this includes grandparents or any key workers/teachers that work closely with X.
- **Please be aware** that when you first start implementing the strategies, it is very likely that the behaviour may get worse before it gets better. It is important to persist until the behaviour decreases.

References:

Carr, E. G., & Durand, V. M. (1985b). The social communicative basis of severe behavior problems in children. In S. Reiss and R.R. Bootzin (Eds.) *Theoretical Issues in Behavior Therapy* (pp. 219-254). New York: Academic Press.

Mount, R. (2005).*Pro-social behaviour in Angelman and Williams syndromes.* Unpublished PhD Thesis, University of Birmingham.

Oliver, C., Horsler, K., Berg, K., Bellamy. G., Dick, K., & Griffiths, E. (2007). Genomic imprinting and the expression of affect in Angelman syndrome: what's in the smile? *Journal of Child Psychology and Psychiatry, 48,* 571-579.

Feedback report Appendix A:

Functional Analysis Interview – Oliver Unpublished:

This semi-structured interview was conducted with X's mother and X's teacher at school The interview provides information about the history of X's challenging behaviour and information about current difficulties. This interview has been developed by the researchers in order to gain a detailed understanding of the individual's self-injurious behaviour, aggression and use of restraints, either mechanical (i.e. helmet or splints) or any self-restraint that the individual might be showing.

X's mother reported that X engages in aggressive behaviour in the form of kicking, biting, hair pulling and grabbing clothes and skin. His aggressive behaviour occurs on a daily basis and can occur in moderate injury such as bruising and tissue damage. When he engages in aggressive behaviour X's mother reported that his facial expression may appear tense or stern for a moment but that he might also laugh and grin. When aggressive behaviour is occurring, his mother reported that he might sometimes be throwing objects or grabbing/pulling people towards him. She also indicated that he often pulls away from people and attempts to leave the room. X's mother was able to pinpoint specific situations in which X is most likely to engage in aggressive behaviour. These include: dressing, dinner time, when he is asked to do things he doesn't want to do and when he cannot have or do things that he wants. However, she also indicated that at times his behaviour can be unpredictable.

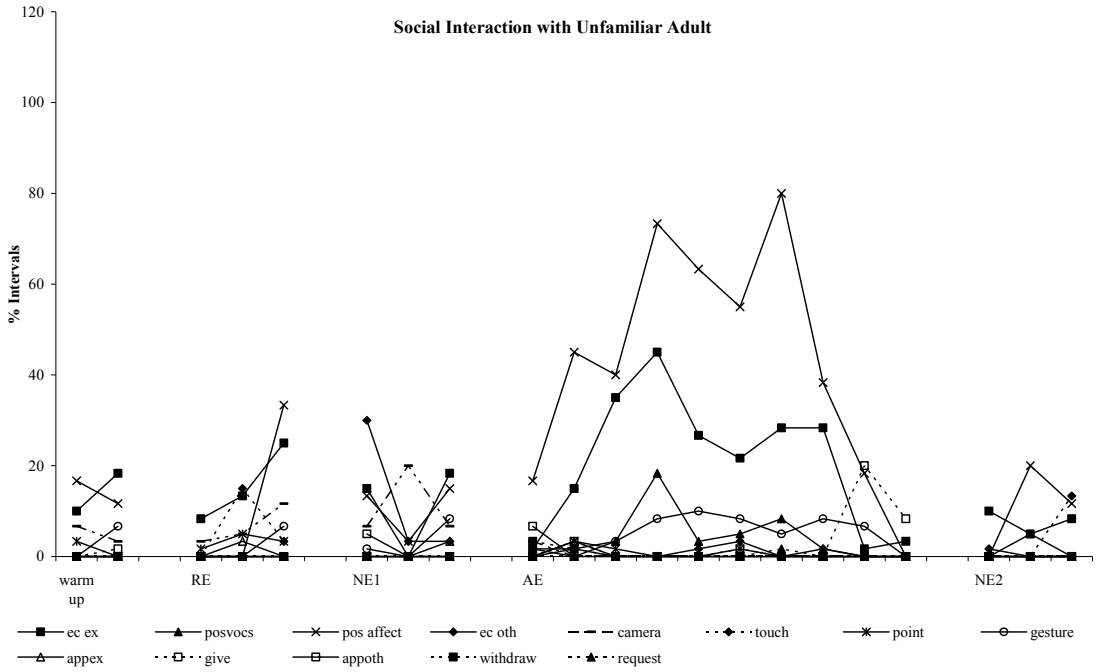
The above interview was also conducted with X's class teacher Y. Y reported that X also engages in aggressive behaviour at school. This is usually in the form of grabbing/pulling hair or skin and biting. She was particularly concerned about the fact that he bites other children and has caused moderate damage to several other children in the class. At school his aggressive behaviour occurs frequently and can require informal physical intervention from members of staff by removing X from the situation or moving other children away from him. When he engages in aggressive behaviour Y reported that he does not appear angry or distressed but tends to be tense or anxious. When engaging in aggressive behaviour Y reported that X often vocalises or signs, grabs or pulls people towards him, pushes or throws things or try to get something. Y was able to identify particular situations that she felt were most likely to trigger X's aggressive behaviour. This included circle and snack times at school or other situations in which staff members were present but dealing with other children, situations when he is asked to do something he doesn't want to do or when he is told he cannot have something that he wants.

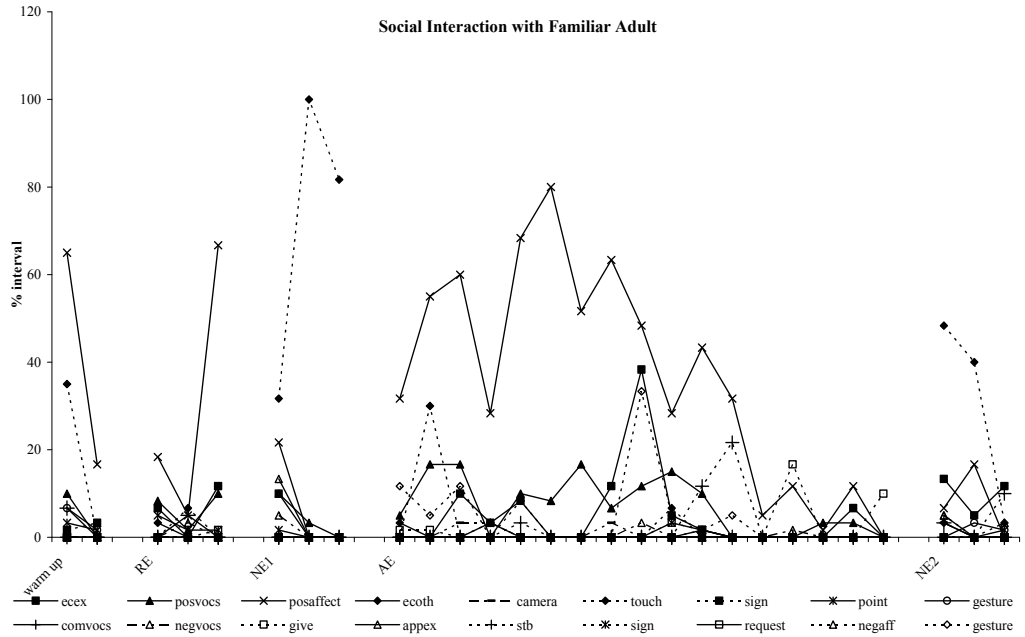
Y reported that X also engages in some brief self-injurious behaviour (biting arms) although this was less frequent than his aggressive behaviour and she could not pinpoint any particular situations in which the behaviour was more or less likely to occur.

In summary, X's aggressive behaviour is a concern for both his mother and teacher who both report that X engages in aggressive behaviour on a daily basis. They were both able to identify situations in which X's behaviour is more likely to occur. These included situations when he was asked to do something he doesn't want to do or is not able to have or do something that he wants. Y also indicated that X was more likely to engage in aggressive behaviour during situations in which staff members are present but dealing with other children, in particular, circle time and snack time were problematic.

Feedback report Appendix B:

Experimental Social Presses: This assessment involves systematically varying the social demands and availability for social interaction of familiar and unfamiliar adults using three different social conditions. There is a warm up period followed by four experimental conditions. Condition A is a response engagement condition (RE) in which social interaction is available but social demands are low. Condition B is a no engagement condition (NE 1) in which social interaction is not available and social demands are low. Condition C is an active engagement condition (AE) in which social interaction is available and social demands are high as the adult works through a series of interaction games. Condition D is a no engagement, no toys condition (NE 2) in which social interaction is not available but not toys are available to occupy the person. X's social interaction skills including his use of eye contact, positive facial expression, approach to the adult interacting with him and others were assessed and coded using real time coding in all four conditions.





During interaction with the unfamiliar adult (J.M) X generally engaged well with the examiner and enjoyed the activities and toys that were presented to him. He demonstrated good social interaction skills, using eye contact, positive facial expression and gestures to indicate his pleasure in the activities and engaged in some to and fro play with the ball and building blocks with the examiner. He also demonstrated good use of eye contact and use of nonverbal communication skills such as pointing and gesturing. At times, his ability to concentrate on the toys presented to him was limited and he was easily distracted by other objects in the room. At these times he was easily re-directed to the toys and tasks presented by offering him something novel to engage with. His concentration was far better during a more structured interaction condition (AE) when activities were led by the examiner. During the conditions when social interaction was less readily available to him (RE and NE conditions), X initially demonstrated some motivation to interact with the examiner and the other adult present in the room. However, he soon moved on to engage with the toys alone or to occupy himself in some other way.

During interaction with the familiar adult (X's mother) X demonstrated a great deal of positive facial expressions and positive vocalisations throughout the sessions, clearly enjoying the interaction with his mother. Generally, X made good, effective use of his eye contact and other nonverbal skills including signing and gesturing to indicate his needs and to express his enjoyment in the activities. As with the unfamiliar adult, X engaged in some to and fro play with his mother and engaged in some joint social play with her during the peek a boo task. When social interaction was less readily available to him (RE and NE conditions) X actively sought his mother's attention, approaching her in several different ways and clearly demonstrating a strong motivation to interact with her. As may be expected, X was more persistent in seeking social interaction during these conditions with his mother than with the unfamiliar adult.

In summary, X demonstrates a strong motivation to engage in social interaction with both familiar and unfamiliar adults. He uses good and well coordinated eye contact, facial expression and other nonverbal communication skills to express his needs effectively. He seeks out interaction when this is not readily available using appropriate means, although he is more likely to be persistent in seeking interaction with a familiar adult than with an unfamiliar adult. His concentration for toys and activities can be somewhat limited when left to occupy himself. He is able to attend for longer periods when the interaction is more structured for him and led by the adult.

Feedback report Appendix C:

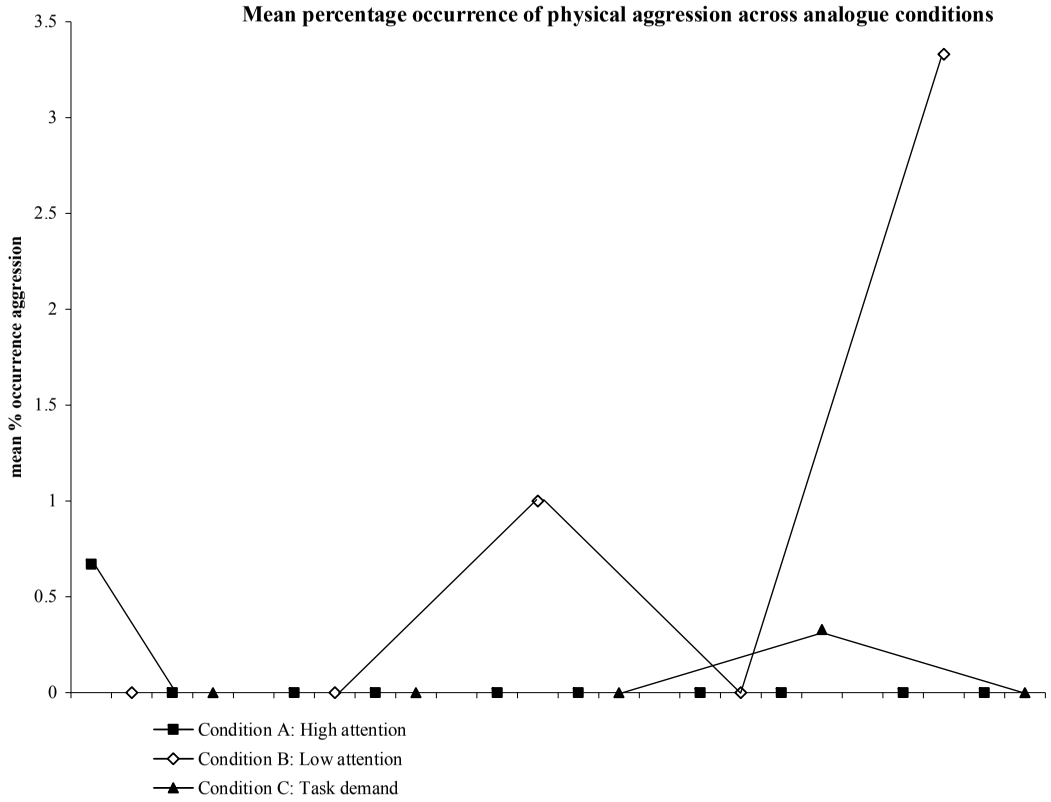
Vineland Adaptive Behavior Scales II

Domain	Standard Score	Age Equivalent
Communication	52	--
Receptive	--	1 yr 9 mo
Expressive	--	10 months
Written	--	Basal*
Daily Living Skills	46	--
Personal	--	1 yr 0 mo
Domestic	--	1 yr 2 mo
Community	--	1 yr 6 mo
Socialisation	55	--
Interpersonal Relationships	--	9 months
Play and Leisure Time	--	1 yr 6 mo
Coping Skills	--	1 yr 9 mo
Motor Skills	56	--
Gross		1 yr 8 mo
Fine		2 yrs 0 mo
Adaptive Behavior Composite	**50**	**--**

* X scores at a floor level, therefore he we are not able to provide a score for X on this subscale.

Feedback report Appendix D:

Experimental analogues: The graph below describes X's aggressive behaviour across three different experimental conditions. The behaviours recorded for X in these sessions include: biting, hair pulling and grabbing others clothes or skin. Condition A (high attention) involved presenting X with high levels of verbal attention Condition B (low attention) involved presenting X with very little attention while the examiner talked to the other researchers. Condition C (task demand) involved presenting X with a task that his teacher reported was somewhat of a challenge for him but could be completed with prompting. Each five minute condition was repeated 4 times across the day in the following format: ABAC



Feedback report Appendix E:

Autism Diagnostic Observation Schedule (ADOS; Lord *et al.*, 2001): The ADOS is a semi-structured observational assessment designed to assess impairments and characteristics associated with autism spectrum disorders during a series of behavioural 'presses' in which the participant is expected to engage in. A module 1 assessment was appropriate for X given his level of expressive language.
Although a little apprehensive at times and a little anxious at the beginning of the assessment, X engaged in all of the ADOS tasks well. He demonstrated good use of eye contact and facial expressions when interacting with the examiner. He rarely vocalised but was able to make his needs know through nonverbal communication skills such as pointing and gesturing. Generally, these nonverbal strategies were effective in helping him to indicate his needs clearly. He enjoyed interacting with the examiner, particularly the peek-a-boo task and the balloon activity. The table below describes X's scores on this assessment. A lower score on this measure indicates that there are fewer autism related characteristics present.

	Communication Domain	Social Interaction Domain	Total Communication & Social Interaction	Repetitive Behaviour Domain	Play Domain
X's score	0	4	4	1	4
Suggested ASD author cut off	2	4	7	-	-
Suggested Autism cut off	4	7	12	-	-

- cut off score not provided for repetitive behaviour and play domains

It is clear from X's scores on this assessment that he demonstrates very few autistic like characteristics and impairments on all areas assessed on this measure. His scores do not reach the suggested cut off criteria for autism on any domain although his social interaction score reaches the less conservative ASD cut off point. This is likely to be accounted for by his level of learning disability rather than the presence of an autistic like condition.

APPENDIX H

Main Caregiver Questionnaire Pack

UNIVERSITY OF BIRMINGHAM

The Three Syndromes Study

The Angelman, Cri du Chat and Cornelia de Lange Syndrome Support Groups
Funded by The Big Lottery to tackle behaviour problems and support families

Booklet 2: Family and Behaviour: Angelman Syndrome

Instructions for Completing Questionnaire:

3. **These questionnaires should be completed by the <u>main caregiver.</u>**

4. **When you have completed the questionnaire, please check that you have answered every question, and return them to us in the *freepost* envelope provided.**

Thank you for agreeing to participate in this research.

Supported by The National Lottery® through the Big Lottery Fund

ID _____

Today's date: _____

Your relationship to your child/person you care for with Angelman syndrome_____

SECTION A: The following questions ask about the behaviour of your child/person you care for with Angelman syndrome. Please read the instructions for each questionnaire carefully and complete as many of the questions as possible

THE QABF

Please think about your child's self-injurious behaviour or aggressive behaviour over the past month.

Please indicate which type self-injurious (skin picking, head banging etc) or aggressive behaviour (hitting or biting others) that you have been most concerned about in the last month_____

Rate how often the person you care for demonstrates the stated behaviour (above) in situations where they might occur. Be sure to rate how often each behaviour occurs, not what you think a good answer would be.

		Does not apply	Never	Rarely	Some	Often
1	Engages in the behaviour to get attention.	X	0	1	2	3
2	Engages in the behaviour to escape work or learning situations.	X	0	1	2	3
3	Engages in the behaviour as a form of 'self-stimulation'.	X	0	1	2	3
4	Engages in the behaviour because he/she is in pain.	X	0	1	2	3
5	Engages in the behaviour to get access to items such as preferred toys, food, or beverages.	X	0	1	2	3
6	Engages in the behaviour because he/she likes to be reprimanded	X	0	1	2	3
7	Engages in the behaviour when asked to do something (get dressed, brush teeth, work, etc).	X	0	1	2	3
8	Engages in the behaviour even if he/she thinks that no one is in the room.	X	0	1	2	3
9	Engages in the behaviour more frequently when he/she is ill.	X	0	1	2	3

10	Engages in the behaviour when you take something away from him/her	X	0	1	2	3
11	Engages in the behaviour to draw attention to him/herself.	X	0	1	2	3
12	Engages in the behaviour when he/she does not want to do something.	X	0	1	2	3
13	Engages in the behaviour because there is nothing else to do.	X	0	1	2	3
14	Engages in the behaviour when there is something bothering him/her physically.	X	0	1	2	3
15	Engages in the behaviour when you have something he/she wants.	X	0	1	2	3
16	Engages in the behaviour to try and get a reaction from you.	X	0	1	2	3
17	Engages in the behaviour to try to get people to leave him/her alone.	X	0	1	2	3
18	Engages in the behaviour in a highly repetitive manner, ignoring his/her surroundings.	X	0	1	2	3
19	Engages in the behaviour because he/she is physically uncomfortable.	X	0	1	2	3
		Does not apply	Never	Rarely	Some	Often
20	Engages in the behaviour when a peer has something he/she wants.	X	0	1	2	3
21	Does he/she seem to be saying ‘come see me’ or ‘look at me’ when engaging in the behaviour?	X	0	1	2	3
22	Does he/she seem to be saying ‘leave me alone’ or ‘stop asking me to do this’ when engaging in the behaviour?	X	0	1	2	3
23	Does he/she seem to enjoy the behaviour, even if no one is around?	X	0	1	2	3
24	Does the behaviour seem to indicate to you that he/she is not feeling well?	X	0	1	2	3
25	Does he/she seem to be saying ‘give me that (toy item, food item)’ when engaging in the behaviour?	X	0	1	2	3

SCQ

The following questions relate to the person you care for. Please answer each question by circling *yes* or *no*. A few questions ask about several related types of behaviour; please circle *yes* if *any* of these behaviours have ever been present. Although you may be uncertain about whether some behaviours were ever present or not, please answer *yes* or *no* to every question on the basis of what you think.

1.	Is she/he now able to talk using short phrases or sentences?	**Yes**	**No**
	If *No,* skip to question 8		
2.	Can you have a to and fro "conversation" with her/him that involves taking turns or building on what you have said?	**Yes**	**No**
3.	Has she/he ever used odd phrases or said the same thing over and over in almost exactly the same way (either phrases that she/he has heard other people use or ones that she/he has made up?	**Yes**	**No**
4.	Has she/he ever used socially inappropriate questions or statements? For example, has she/he ever regularly asked personal questions or made personal comments at awkward times?	**Yes**	**No**
5.	Has she/he ever got her/his pronouns mixed up (e.g., saying *you* or *she/he* for *I*)?	**Yes**	**No**
6.	Has she/he ever used words that she/he seemed to have invented or made up her/himself; put things in odd, indirect ways; or used metaphorical ways of saying things (e.g., saying *hot rain* for *steam*)?	**Yes**	**No**
7.	Has she/he ever said the same thing over and over in exactly the same way or insisted that you say the same thing over and over again?	**Yes**	**No**
8.	Has she/he ever had things that she/he seemed to have to do in a very particular way or order or rituals that she/he insisted that you go through?	**Yes**	**No**
9.	Has her/his facial expression usually seemed appropriate to the particular situation, as far as you could tell?	**Yes**	**No**
10.	Has she/he ever used your hand like a tool or as if it were part of her/his own body (e.g., pointing with your finger, putting your hand on a doorknob to get you to open the door)?	**Yes**	**No**
11.	Has she/he ever had any interests that preoccupy her/him and might seem odd to other people (e.g., traffic lights, drainpipes, or timetables)?	**Yes**	**No**
12.	Has she/he ever seemed to be more interested in parts of a toy or an object (e.g., spinning the wheels of a car), rather than using the object as it was intended?	**Yes**	**No**

13.	Has she/he ever had any special interests that were *unusual* in their intensity but otherwise appropriate for her/his age and peer group (e.g.,trains, dinosaurs)?	**Yes**	**No**
14.	Has she/he ever seemed to be *unusually* interested in the sight, feel, sound, taste, or smell of things or people?	**Yes**	**No**
15.	Has she/he ever had any mannerisms or odd ways of moving her/his hands or fingers, such as flapping or moving her/his fingers in front of her/his eyes?	**Yes**	**No**
16.	Has she/he ever had any complicated movements of her/his whole body, such as spinning or repeatedly bouncing up and down?	**Yes**	**No**
17.	Has she/he ever injured her/himself deliberately, such as by biting her/his arm or banging her/his head?	**Yes**	**No**
18.	Has she/he ever had any objects (*other* than a soft toy or comfort blanket) that she/he *had* to carry around?	**Yes**	**No**
19.	Does she/he have any particular friends or a best friend?	**Yes**	**No**
20a.	Have you known the person since they were 4 years old?	**Yes**	**No**

For the following questions, please focus on the time period between the person's fourth and fifth birthdays. You may find it easier to remember how things were at that time by focusing on key events, such as starting school, moving house, Christmas time, or other specific events that are particularly memorable for you as a family. If your child is not yet 4 years old, please consider her or his behaviour in the past 12 months.

If you have not known the person since they were 4 years old, please leave questions 20 to 40 blank and go on to the next questionnaire.

20.	When she/he was 4 to 5, did she/he ever talk with you just to be friendly (rather than to get something)?	**Yes**	**No**
21.	When she/he was 4 to 5, did she/he ever *spontaneously* copy you (or other people) or what you were doing (such as vacuuming, gardening, or mending things)?	**Yes**	**No**
22.	When she/he was 4 to 5, did she/he ever *spontaneously* point at things around her/him just to show you things (not because she/he wanted them)?	**Yes**	**No**
23.	When she/he was 4 to 5, did she/he ever use gestures, other than pointing or pulling your hand, to let you know what she/he wanted?	**Yes**	**No**
24.	When she/he was 4 to 5, did she/he nod her/his head to mean *yes*?	**Yes**	**No**
25.	When she/he was 4 to 5, did she/he shake her/his head to mean *no*?	**Yes**	**No**
26.	When she/he was 4 to 5, did she/he usually look at you directly in the face when doing things with you or talking with you?	**Yes**	**No**

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

Please check your answers and go on to the next questionnaire.

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**
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**
How would the person you care for appear if…	**Very shy**	**Moderately shy**	**A little shy**	**Neither**	**A little sociable**	**Moderately sociable**	**Very sociable**
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**
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?

……

……

……

.....

Please check your answers and go on to the next 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) **1b.** Corrective surgery / medication / treatment: **yes / no**	**0**	**1**	**2**	**3**
2a. Ear Problems (e.g. infections, glue ear) **2b.** Corrective surgery / medication / treatment (e.g. grommets): **yes / no**	**0**	**1**	**2**	**3**
3a. Dental Problems (e.g. toothache / gum problems / mouth ulcers / delayed eruption of teeth) **3b**.Dental surgery / treatment (e.g. teeth removal): **yes / no**	**0**	**1**	**2**	**3**
4a. Cleft Palate **4b.** Repaired: **yes / no**	**0**	**1**	**2**	**3**
5a. Gastrointestinal Difficulties (e.g. reflux / stomach problems) **5b.** Corrective surgery / medication / treatment (e.g. nissen fundoplication): **yes / no**	**0**	**1**	**2**	**3**
6a. Bowel Problems (e.g. obstruction) **6b.** Corrective surgery / treatment: **yes / no**	**0**	**1**	**2**	**3**
7a. Heart Abnormalities or Circulatory Problems (e.g. congenital heart lesions or murmur) **7b.** Corrective surgery / medication / treatment: **yes / no**	**0**	**1**	**2**	**3**
8a. Problems with Genitalia (e.g. prostate/ testicular problems i.e. undescended testes) **8b.** Corrective surgery / treatment: **yes / no**	**0**	**1**	**2**	**3**
9a. Hernia (e.g. inguinal or hiatal) **9b.** Repair / treatment: **yes / no**	**0**	**1**	**2**	**3**
10. Limb Abnormalities (e.g. malformed arm)	**0**	**1**	**2**	**3**
11a. Epilepsy / Seizures / Neurological Referrals. **11b.** Medication: **yes / no**	**0**	**1**	**2**	**3**
12a. Lung or Respiratory Problems (asthma/bronchitis) **12b.** Corrective surgery / medication / treatment: **yes / no**	**0**	**1**	**2**	**3**
13a. Liver or Kidney Problems **13b.** Corrective surgery / medication / treatment: **yes / no**	**0**	**1**	**2**	**3**
14a. Diabetes or Thyroid Function Problems **14b.** Corrective surgery / medication / treatment: **yes / no**	**0**	**1**	**2**	**3**

15a. Skin Problems (e.g. tinea, eczema, psoriasis, dry skin) **15b.** Medication / treatment: **yes / no**	**0**	**1**	**2**	**3**
16a. Other (please specify problem, severity from 0-3) **16b.** Corrective surgery / medication / treatment: **yes / no**	**0**	**1**	**2**	**3**

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**

The GDQ

Instructions:

- This questionnaire asks about behaviours sometimes shown by people with learning disabilities.
- Please read the questions and examples carefully and indicate how often each behaviour has occurred in the **last two weeks** by circling the appropriate answer.

Does the person you care for:	**More than once an hour**	**Once an hour**	**Once a day**	**Once a week**	**Not occurred**
1. Arch his/her back, lie over arms of chairs or people on his/her back?	**4**	**3**	**2**	**1**	**0**
2. Lie over an object on his/her stomach? e.g. a side of an arm chair.	**4**	**3**	**2**	**1**	**0**
3. Salivate excessively?	**4**	**3**	**2**	**1**	**0**
4. Fidget, wriggle or move their body a great deal?	**4**	**3**	**2**	**1**	**0**
5. Place their hands or fingers in back of their mouth?	**4**	**3**	**2**	**1**	**0**
6. Chew on his/her clothes, fingers, hands or other parts of the body, objects or material?	**4**	**3**	**2**	**1**	**0**
7. Grind their teeth?	**4**	**3**	**2**	**1**	**0**
8. Scratch, hit, press or rub around the upper chest or throat?	**4**	**3**	**2**	**1**	**0**
9. Drink, request or seek out an excessive amount of fluids?	**4**	**3**	**2**	**1**	**0**
10. Cough, gag or regurgitate?	**4**	**3**	**2**	**1**	**0**
11. Appear in pain or discomfort (cry, groan or moan)?	**4**	**3**	**2**	**1**	**0**
12. Refuse food even though they are probably hungry?	**4**	**3**	**2**	**1**	**0**

13. Does the person you care for appear indecisive about food (edging towards table or food then moving away repeatedly, taking food and putting it back)? *(please tick)* **Yes** ☐ **No** ☐

14. Does the person you care for wake during the night? **Never** **Once a week** **Most nights** **Every night**

15. Does the person you care for sleep sitting or propped up? **Never** **Once a week** **Most nights** **Every night**

16. Does the person you care for seem to have bad breath?

Never **Once a week** **At the same time everyday** **All day every day**

17. Has the person you care for prone to respiratory tract infections? *(please tick)* **Yes** ☐ **No** ☐

If 'yes' please indicate how often they occur:

Monthly **Quarterly** **Every six months** **Annually**

Other (please specify)_____

Please check your answers and go on to the next questionnaire

THE NCCPC-R: PAIN CHECKLIST

How often has your child shown these behaviours in the last week? Please circle a number for each item. If an item does not apply to your child (for example he/she does not eat solid food or cannot reach with his/her hands), then indicate 'not applicable' for that item.

		Not at all	Just a little	Fairly often	Very often	Not applicable
I. Vocal						
1.	Moaning, whining, whimpering (fairly softly)	0	1	2	3	NA
2.	Crying (moderately loud)	0	1	2	3	NA
3.	Screaming/yelling (very loud)	0	1	2	3	NA
4.	A specific sound or word for pain (e.g. a word, cry or type of laugh)	0	1	2	3	NA
II. Social						
5.	Not cooperating, cranky, irritable, unhappy.	0	1	2	3	NA
6.	Less interaction with others, withdrawn.	0	1	2	3	NA
7.	Seeking comfort or physical closeness	0	1	2	3	NA
8.	Being difficult to distract, not able to satisfy or pacify	0	1	2	3	NA
III. Facial						
9.	A furrowed brow	0	1	2	3	NA
10.	A change in eyes, including squinching of eyes, eyes opened wide, eyes frowning.	0	1	2	3	NA
11.	Turning of mouth, not smiling	0	1	2	3	NA
12.	Lips puckering up, tight, pouting or quivering.	0	1	2	3	NA
13.	Clenching or grinding teeth, chewing or thrusting tongue out.	0	1	2	3	NA
IV. Activity						
14.	Not moving, less active, quiet	0	1	2	3	NA
15.	Jumping around, agitated, fidgety	0	1	2	3	NA
V. Body and limbs						
16.	Floppy	0	1	2	3	NA
17.	Stiff, spastic, tense, rigid	0	1	2	3	NA

18.	Gesturing to or touching part of the body that hurts	0	1	2	3	NA
19.	Protecting, favouring or guarding part of the body that hurts	0	1	2	3	NA
20.	Flinching or moving the body part away, being sensitive to touch	0	1	2	3	NA
21.	Moving the body in a specific way to show pain (e.g. head back, arms down, curls up etc)	0	1	2	3	NA
VI. Physiological						
22.	Shivering	0	1	2	3	NA
23.	Change in colour, pallor	0	1	2	3	NA
24.	Sweating, perspiring	0	1	2	3	NA
25.	Tears	0	1	2	3	NA
26.	Sharp intake of breath, gasping	0	1	2	3	NA
27.	Breath holding	0	1	2	3	NA
VII. Eating/ Sleeping						
28.	Eating less, not interested in food.	0	1	2	3	NA
29.	Increase in sleep	0	1	2	3	NA
30.	Decrease in sleep.	0	1	2	3	NA

THANK YOU FOR TAKING THE TIME TO COMPLETE THIS QUESTIONNAIRE

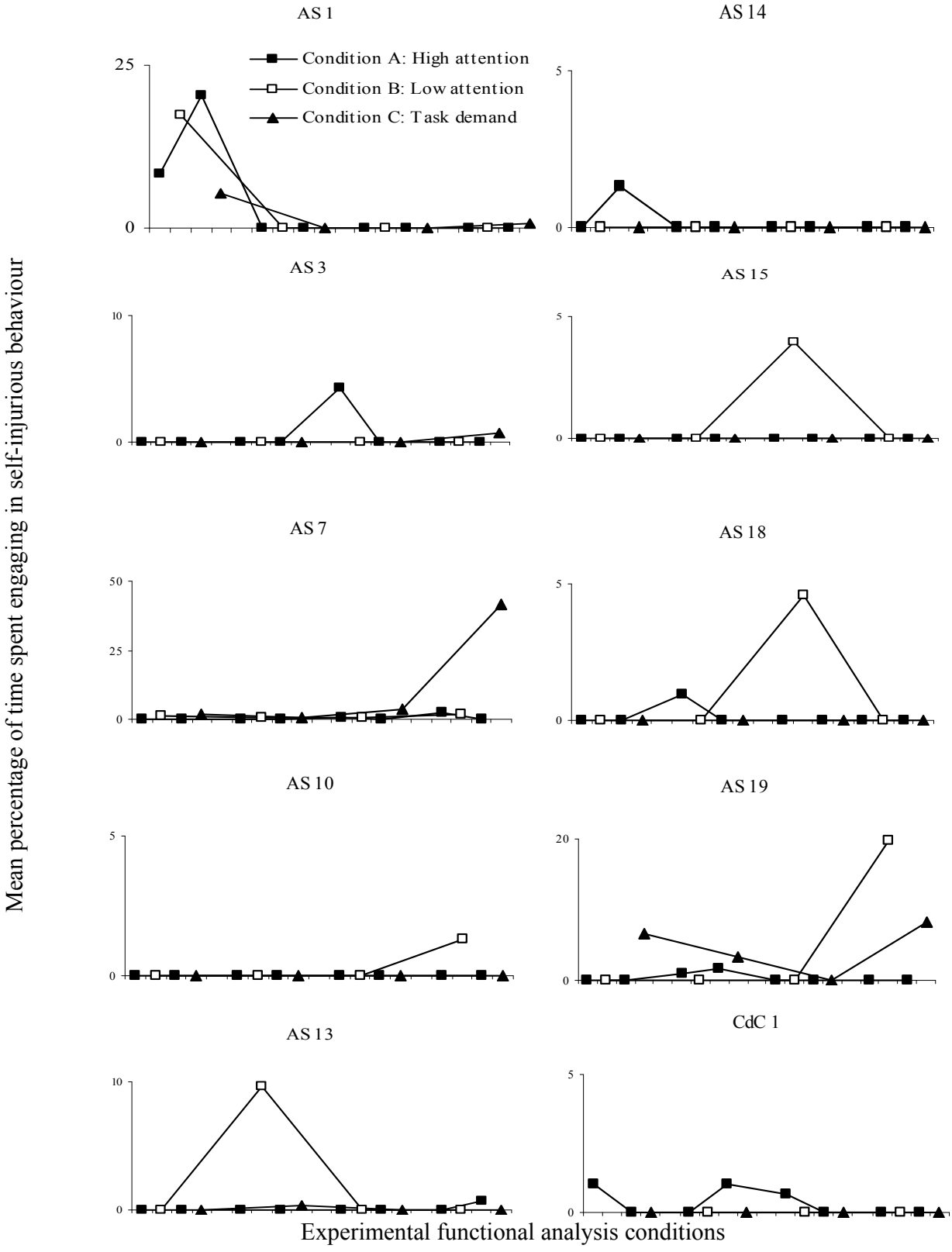
APPENDIX I

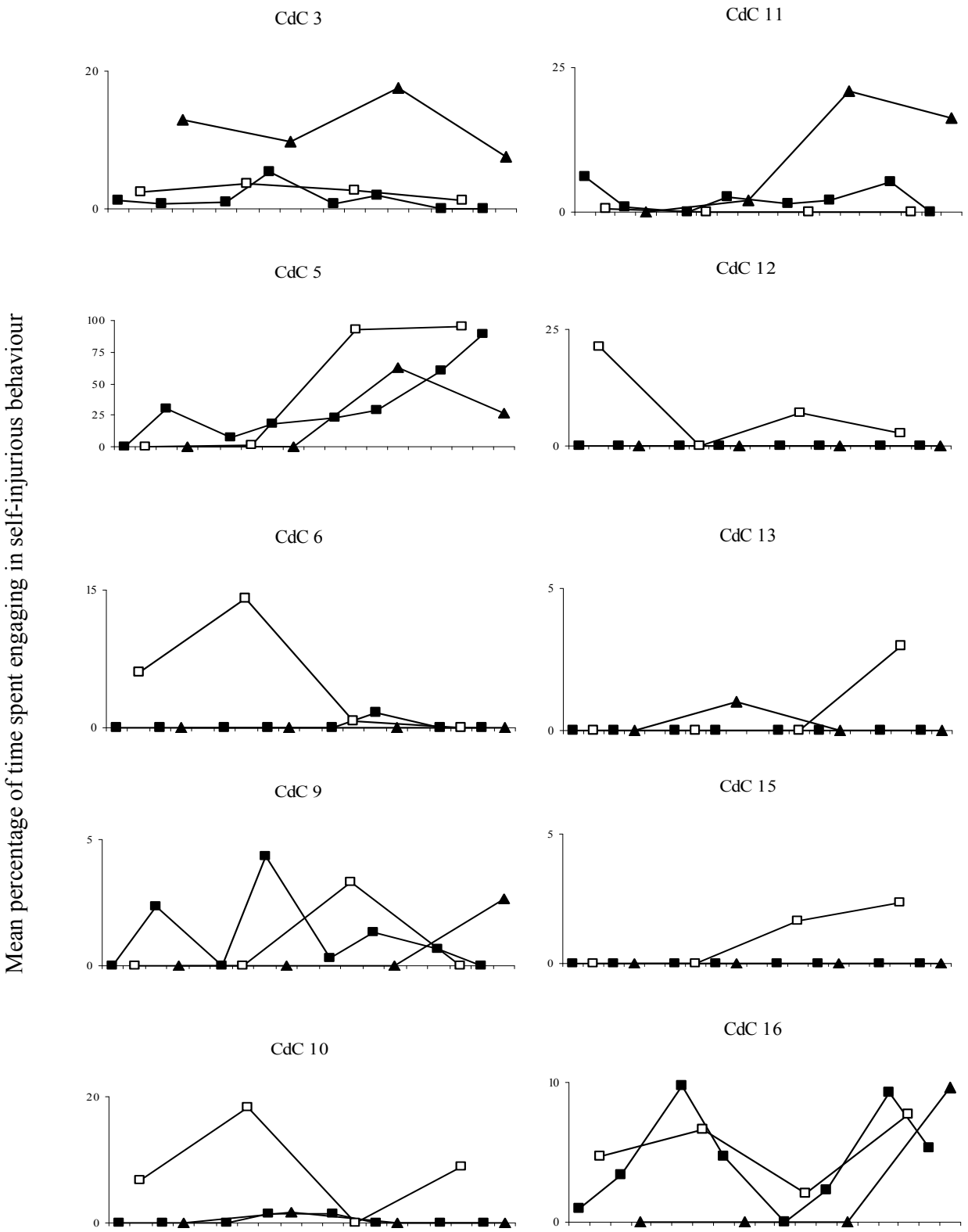
Severity of challenging behaviour across syndrome groups (assessed by the Challenging Behaviour Interview). Results based only on those participants reported to display self-injury and aggression

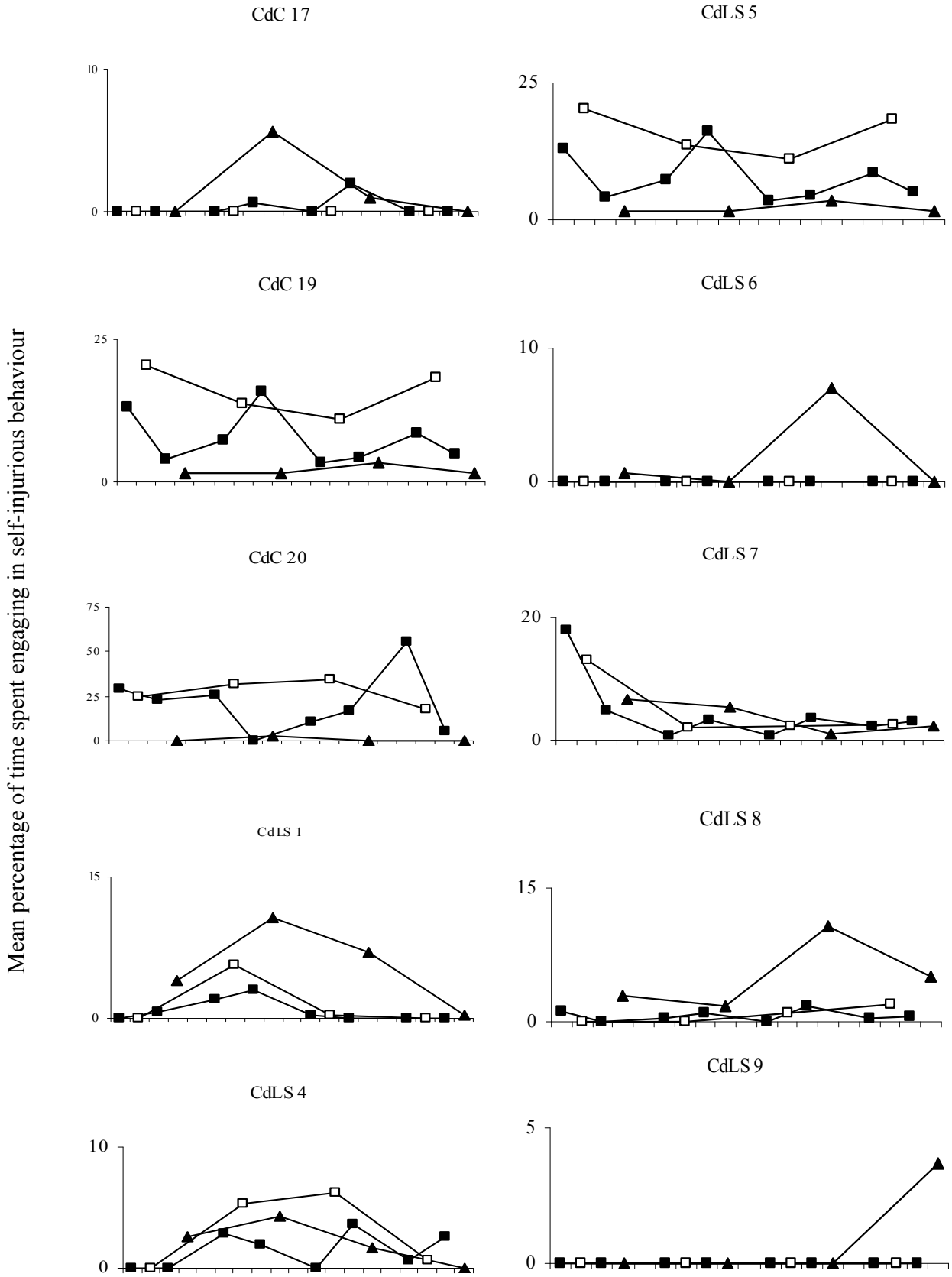
Severity		**Cornelia de Lange (n=12)**	**Cri du Chat (n=18)**	**Angelman (n=17)**	**Kruskal-Wallis χ^2**	**P**	**Post-hoc**
Aggression	Mean (SD)	17.0 (8.32)	18.8 (6.23)	23.6 (6.59)	6.06	.048	AS> CdLS
Self-injury	Mean (SD)	15.25 (4.59)	18.4 (3.95)	14.14 (6.15)	4.75	.093	-

APPENDIX J

Multi-element graphs to show the mean percentage of time that each participant spent engaging in self-injurious and aggressive behaviour across experimental functional analysis conditions


AS 1
AS 14
Condition A: High attention
Condition B: Low attention
Condition C: Task demand
25
0
5
0
AS 3
AS 15
10
0
5
0
AS 7
AS 18
50
25
0
5
0
AS 10
AS 19
5
0
20
0
AS 13
CdC 1
10
0
5
0
Mean percentage of time spent engaging in self-injurious behaviour
Experimental functional analysis conditions


CdC 3
CdC 11
CdC 5
CdC 12
CdC 6
CdC 13
CdC 9
CdC 15
CdC 10
CdC 16
Mean percentage of time spent engaging in self-injurious behaviour
Experimental functional analysis conditions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10
0
CdLS 5
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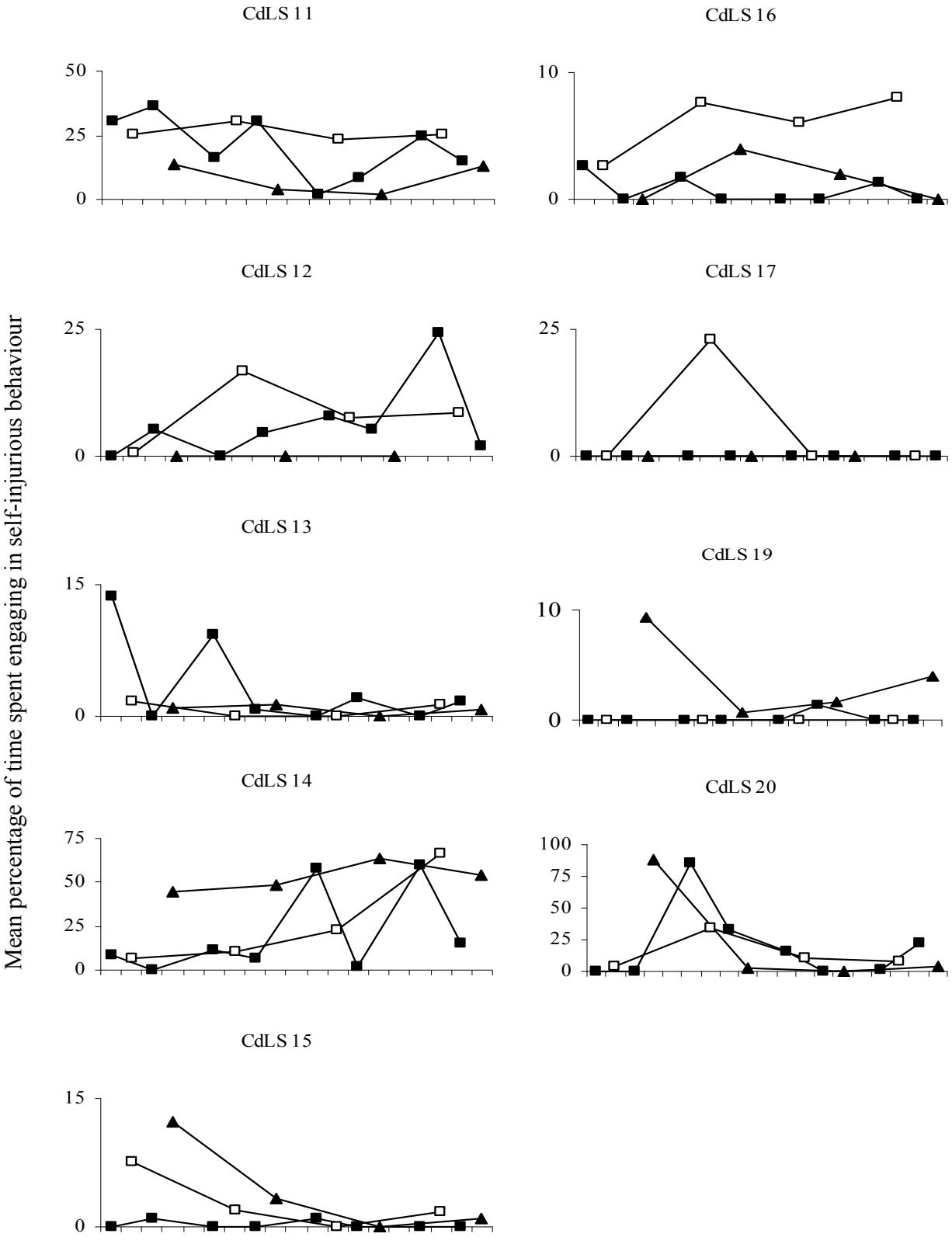
0
CdC 19
25
0
CdLS 6
10
0
CdC 20
75
50
25
0
CdLS 7
20
0
CdLS 1
15
0
CdLS 8
15
0
CdLS 4
10
0
CdLS 9
5
0
Mean percentage of time spent engaging in self-injurious behaviour
Experimental functional analysis conditions


CdLS 11
50
25
0
CdLS 16
10
0
CdLS 12
25
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CdLS 17
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0
CdLS 13
15
0
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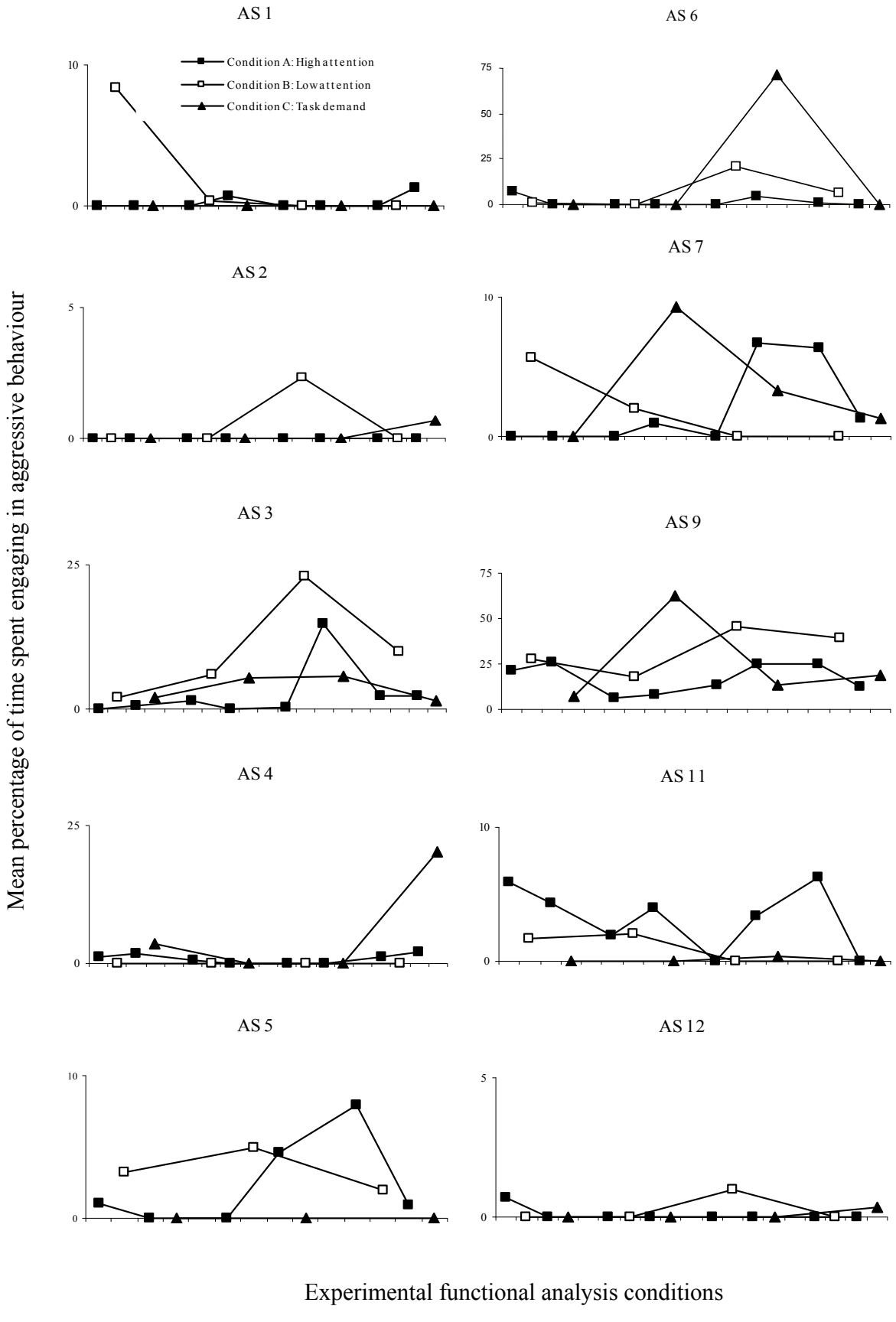
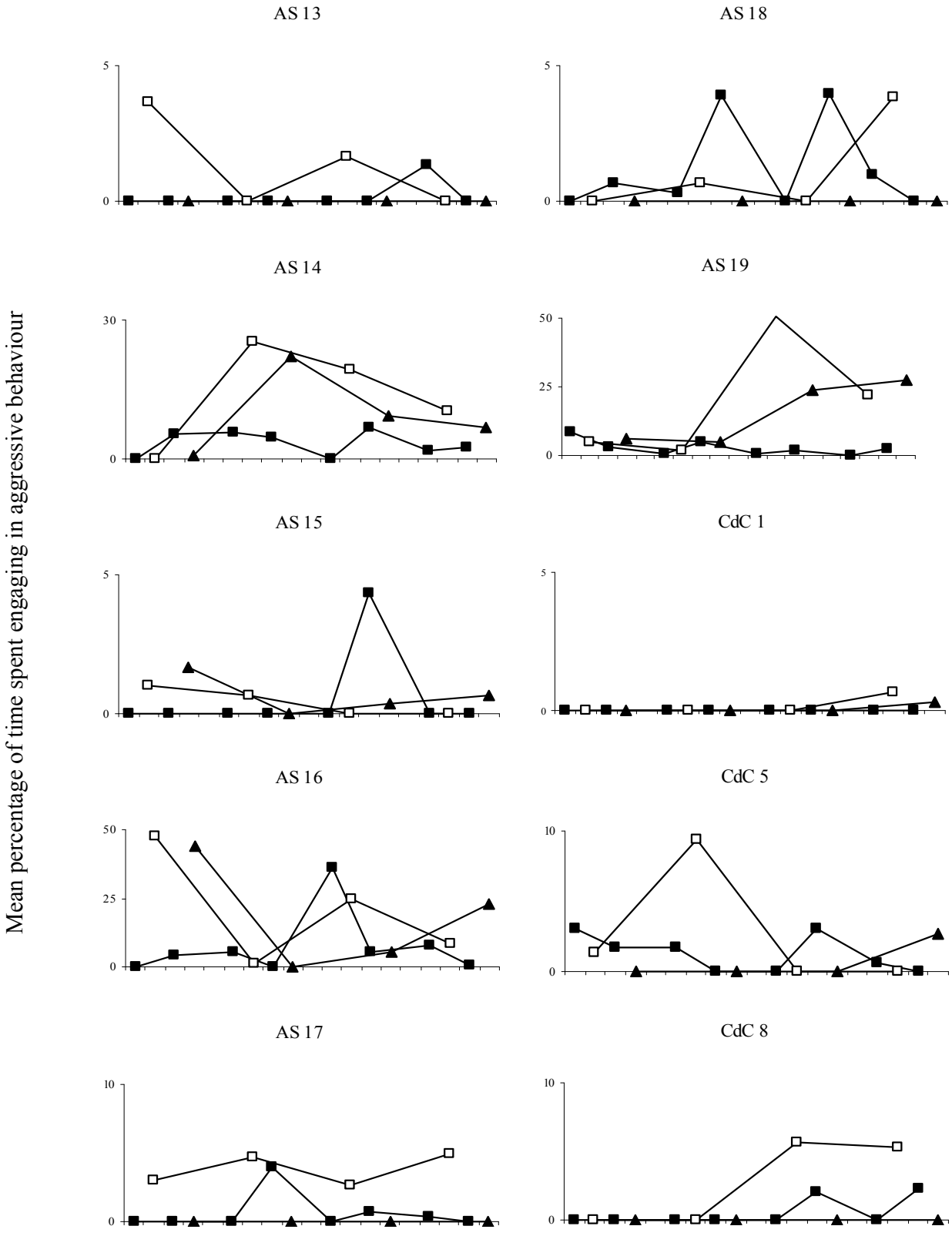
10
0
CdLS 14
75
50
25
0
CdLS 20
100
75
50
25
0
CdLS 15
15
0
Mean percentage of time spent engaging in self-injurious behaviour
Experimental functional analysis conditions


AS 1
AS 6
Condition A: High attention
Condition B: Low attention
Condition C: Task demand
AS 2
AS 7
AS 3
AS 9
AS 4
AS 11
AS 5
AS 12
Mean percentage of time spent engaging in aggressive behaviour
Experimental functional analysis conditions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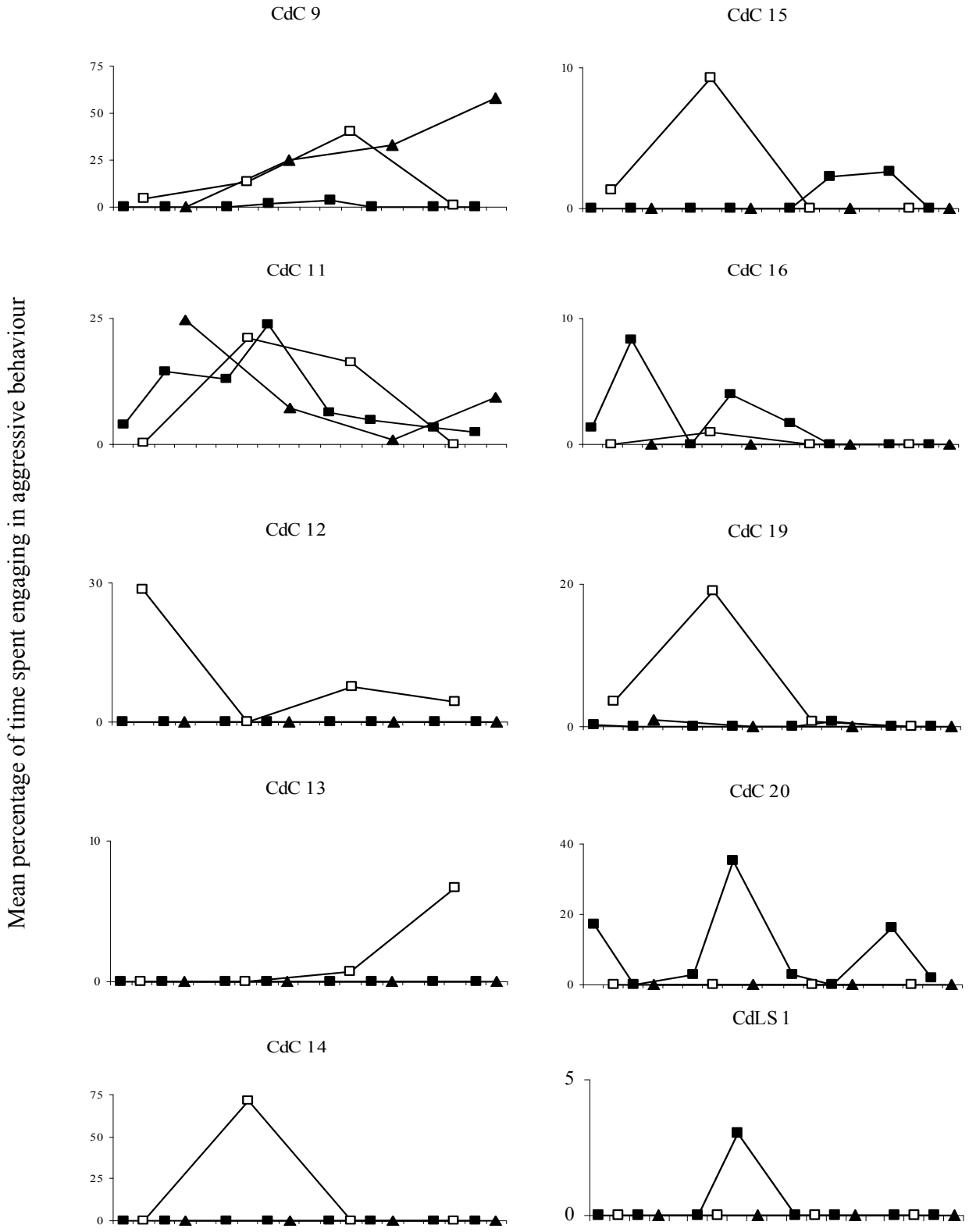
AS 18
AS 14
AS 19
AS 15
CdC 1
AS 16
CdC 5
AS 17
CdC 8
Mean percentage of time spent engaging in aggressive behaviour
Experimental functional analysis conditions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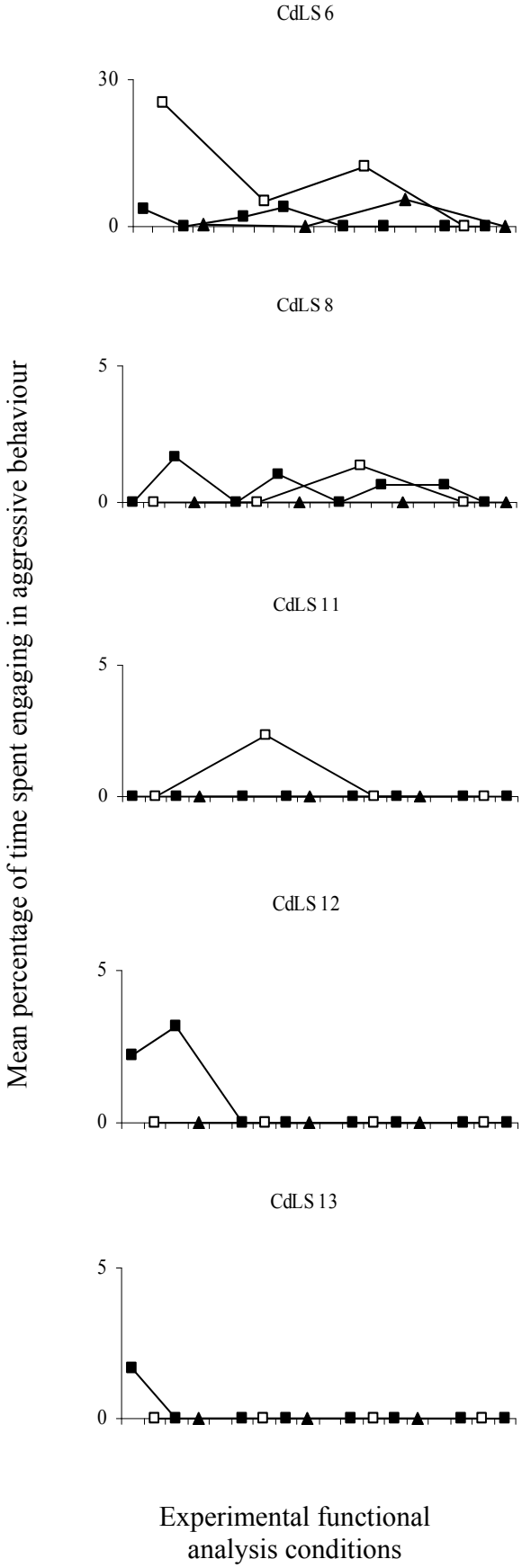
CdC 15
CdC 11
CdC 16
CdC 12
CdC 19
CdC 13
CdC 20
CdC 14
CdLS 1
Mean percentage of time spent engaging in aggressive behaviour
Experimental functional analysis conditions


CdLS 6
30
0
CdLS 8
5
0
CdLS 11
5
0
CdLS 12
5
0
CdLS 13
5
0
Mean percentage of time spent engaging in aggressive behaviour
Experimental functional analysis conditions