SOCIAL COGNITION IN GENETIC SYNDROMES

by

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ABSTRACT

The distinct profiles of sociability and the development of social cognitive abilities was investigated in Cornelia de Lange (CdLS), Fragile X (FXS) and Rubinstein-Taybi (RTS) syndromes. An observational study demonstrated differences in the quality of broad social interaction skills and behaviours during a semi-structured social interaction with an examiner between individuals with CdLS, FXS and RTS. Individuals with FXS and RTS showed lower quality of eye contact, and individuals with FXS showed less person-focused attention, than those with CdLS. Associations between specific behaviours with age and autism spectrum disorder (ASD) symptomatology differed across groups. A second study assessing participant's performance on two scaled batteries of tasks assessing early (intentionality abilities) and later developing (ToM abilities) social cognitive abilities indicated that these groups do not develop these abilities in the same order as typically developing children. Different strengths and weaknesses observed between groups highlighted factors that may lead to disrupted social cognitive development in these groups. A third study showed that intentionality abilities predicted social enjoyment and social motivation, whereas ToM abilities predicted social enjoyment and ASD symptomatology in all groups. These findings were synthesised with previous literature to develop a preliminary model of sociability in CdLS, FXS and RTS.

DEDICATION

This thesis is dedicated to my Grandpa David Ellis and my family.

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CHAPTER ONE

BUILDING MODELS OF BEHAVIOURAL PHENOTYPES AND THE LINK BETWEEN SOCIAL COGNITION AND SOCIABILITY IN CORNELIA DE LANGE, FRAGILE X AND RUBINSTEIN-TAYBI SYNDROMES

1.1 Preface

In this thesis, I will investigate sociability and the development of social cognitive abilities within three genetic syndromes: Cornelia de Lange (CdLS), Fragile X (FXS) and Rubinstein-Taybi (RTS) syndromes. This introductory chapter comprises of an overview of relevant literature and themes that are key to the empirical work outlined in this thesis. The concepts 'behavioural phenotype' and 'sociability' are outlined and the empirical investigation of behavioural phenotypes in genetic syndromes and the aetiological and environmental mechanisms that may be associated with them is justified. The importance of investigating these mechanisms across development is also illustrated. The three genetic syndromes of interest, CdLS, FXS and RTS which have been chosen due to their heterogeneous profiles of behaviours characterising sociability, are described. Subsequently, social cognition and its development is outlined. Current research investigating: 1) the

influence of individual differences of social cognitive abilities on sociability in typically developing (TD) individuals, 2) social cognition in autism spectrum disorders (ASD) and 3) social cognition in genetic syndromes is reviewed. The rationale for investigating the association between social cognition and sociability in CdLS, FXS and RTS is then outlined.

1.2 Behavioural phenotypes

A behavioural phenotype refers to observable characteristics that individuals with a specific genetic syndrome are more likely to show compared to individuals without that syndrome (Dykens, Hodapp & Finucane, 2000). These characteristics may be unique to a syndrome, or may be observed across several syndromes. For example, excessive smiling and laughing (Adams, Horsler, Mount & Oliver, 2015) and a fascination with water (Didden, Korzilius, Sturmey, Lancioni & Curfs, 2008) are behavioural phenotypes observed in individuals with Angelman syndrome, but are not characteristic of other genetic syndromes. In contrast, self-injurious, aggressive and repetitive behaviours, as well as differences in processing sensory and perceptual information, have been observed in many syndromes. However, fine-grained investigation has shown differences in the profiles and topographies of these broadly defined behaviours between genetic syndromes. For example, specific topographies of self-injury such as onychotillomania (pulling out finger and toe nails) and polyembolokoilamania (inserting objects into bodily orifices) are thought to be frequent in individuals with Smith-Magenis syndrome but are rarely observed in other syndromes (Moss, Oliver, Arron, Burbidge, & Berg, 2009; Arron, Oliver, Moss, Berg & Burbidge, 2011; Waite et al., 2014). These findings indicate the need for detailed descriptions of behavioural phenotypes within each syndrome.

More broadly, behavioural phenotype research is important for the care and management of many individuals with genetic syndromes associated with intellectual disability (ID). It has been estimated that between 350,000 and 750,000 of individuals with an intellectual disability also have a genetic syndrome (Oliver & Woodcock, 2008) and around 60% of cases of profound/severe intellectual disability have a known genetic cause (Battaglia & Carey, 2003). Therefore, many individuals with ID are likely to show characteristic

behavioural phenotypes associated with a specific genetic abnormality. Understanding the pathways from this genetic abnormality up to behaviour is vital for developing successful and stratified interventions to predict and target the characteristics that may challenge an individual's quality of life.

1.2.1 Definition of sociability

Many behavioural phenotypes are observed specifically within social contexts and influence whether an individual's social interactions with others are successful or not. Examples include a wide range of behaviours such as social difficulties associated with ASD, social anxiety and social and communication skills (van Rijn et al., 2014; Galéra et al., 2009; Crawford et al., in prep; Lesniak-Karpiak, Mazzocco & Ross, 2003). Whilst there has clearly been interest in these behaviours, the literature has lacked consistent definitions and operationalisation of these behaviours and the key concepts that they are associated with.

Following a literature search on studies including typically developing (TD) and children with ID, Cook and Oliver (2011) identified four concepts (social cognition, social competence, social skills and social behaviour) associated with "sociability". All four concepts lacked consistent definitions across the literature and attempts to create working definitions to distinguish between these constructs identified the overlap between them. Social competence lacked a consistent definition within the literature, leading the authors to propose a broader theme of an ability to interact with others and achieve successful outcomes. Social cognition was defined as a broad concept that encompasses a range of "mind-reading" abilities and knowledge of other's social and emotional cues and information, the consequences and reasons underlying other's actions as well as their mental states across a range of social contexts. Although no agreed definitions emerged for social skills, many

conceptualised these skills as observable behaviours that can be defined as appropriate or inappropriate within their relevant social setting. Finally, a working definition was not provided for social behaviour as no definition could be given for a behaviour that can be defined as being purely "social". To best unify these working definitions, Cook and Oliver suggested conceptualising social competence as "an overarching concept that includes facets of social cognition, social skills and social behaviour", as each facet contributes to an individual becoming socially competent. It is evident that further work is required to better define these concepts.

This thesis will focus on 'sociability' in genetic syndromes, defined as an umbrella term that encompasses a broad range of social skills and behaviours that contribute to an individual's social competence (Cook & Oliver, 2011). Social interaction skills and behaviours considered to contribute to profiles of sociability will be investigated in individuals with CdLS, FXS and RTS in Chapter Three.

Many genetic syndromes can be positioned across a continuum of sociability, from extreme social withdrawal or shyness (e.g. FXS and CdLS) to "hyper-sociability" (e.g. RTS, Down, and Williams syndromes; Moss et al., 2016; Jawaid et al., 2012). Individuals with behavioural phenotypes at both the lower and upper ends of the continuum have difficulties that lead to atypical social interaction and increased social vulnerability, including social isolation, bullying, unstable relationships, employment difficulties and abuse above and beyond their level of ID (Karmiloff-Smith, 2012; Jawaid et al., 2012). More subtle difficulties are likely to have more nuanced but important negative consequences upon an individual's well-being as well. However, there are few successful evidence-based interventions that improve outcomes related to sociability in clinical populations, with many programmes failing to systematically match intervention strategies with specific skills deficits (Wang &

Spillane, 2009; Quinn, Kavale, Mathur, Rutherford & Forness, 1999; Bellini, Peters, Benner, & Hopf, 2007). Therefore, understanding and modelling the profiles of behaviours associated with sociability within syndromes is vital in developing better refined interventions and subsequently improving the lives of individuals with atypical profiles across the spectrum of sociability.

1.3 Developing explanatory models of behavioural phenotypes

In this thesis, I aim to contribute to explanatory models of profiles of sociability in three syndromes that can be distinguished by their unique behavioural phenotypes, i.e. CdLS, FXS and RTS. Understanding and explaining behavioural phenotypes entails creating causal multilevel models of the behaviour that include different mechanistic influences. The genetic abnormalities that cause syndromes are likely to influence a range of cortical networks and have a widespread and dynamic influence across numerous functions and behaviours (Karmiloff-Smith, 2012). Comprehensive explanatory models of behaviour in syndromes must delineate the route and impact from the genetic abnormality, to the central nervous system, to subsequent and cumulative impact upon cognitive, emotional and motivational endophenotypes, that subsequently drive or influence the behaviour (Oliver & Hagerman, 2007; Oliver & Woodcock, 2008; Waite et al., 2014). In addition, models must describe and explain: 1) how these internal factors interact with external environmental influences to determine the situations a behaviour may emerge in (McGill & Langthorne, 2011) and 2) the dynamic changes in behaviour across age and development (Karmiloff-Smith, 2012). These factors may explain why a behaviour is observed in some individuals within a syndrome and not others and why behaviours emerge within certain environmental contexts or developmental stages.

Creating explanatory models requires detailed phenomenological descriptions of behavioural phenotypes. These descriptions highlight potential aetiological pathways that drive subtle but important differences in behaviour across syndromes (Hodapp & Dykens, 2001). Whilst previous literature has described behavioural phenotypes across a range of syndromes, the field currently lacks empirical studies that explicitly delineate the causal pathways between the genes and the behaviour (Oliver & Woodcock, 2008). Understanding the development of mechanistic aetiological pathways is vital for developing interventions that target complex behaviour issues by focusing on: 1) the underlying aetiology or the environmental triggers that is most likely to lead to a change in the behaviour and 2) the appropriate developmental point in which the intervention will have the most impact.

Notation systems provide useful structures to illustrate these complex causal relationships. 'Causal modelling' provides a framework for visually conceptualising theories of the causal relationships amongst the biological, cognitive, behavioural and environmental factors that contribute to the emergence of behavioural phenotypes in developmental disorders (Morton, 2004; figure 1.1). This approach explicitly identifies intermediate factors between genes and behaviour (e.g. biological/neurological and cognitive factors) to create stronger explanatory accounts of behaviour by describing the cascading influence of a genetic abnormality from neurobiology, to cognition and up to behaviour. The influence of the environment upon each level is also explicitly outlined. However, whilst it provides a useful tool to outline these relationships, it is a static model. The framework neither accounts for the dynamic nature of behavioural phenotypes nor the transactional relationships between variables either between or within levels.

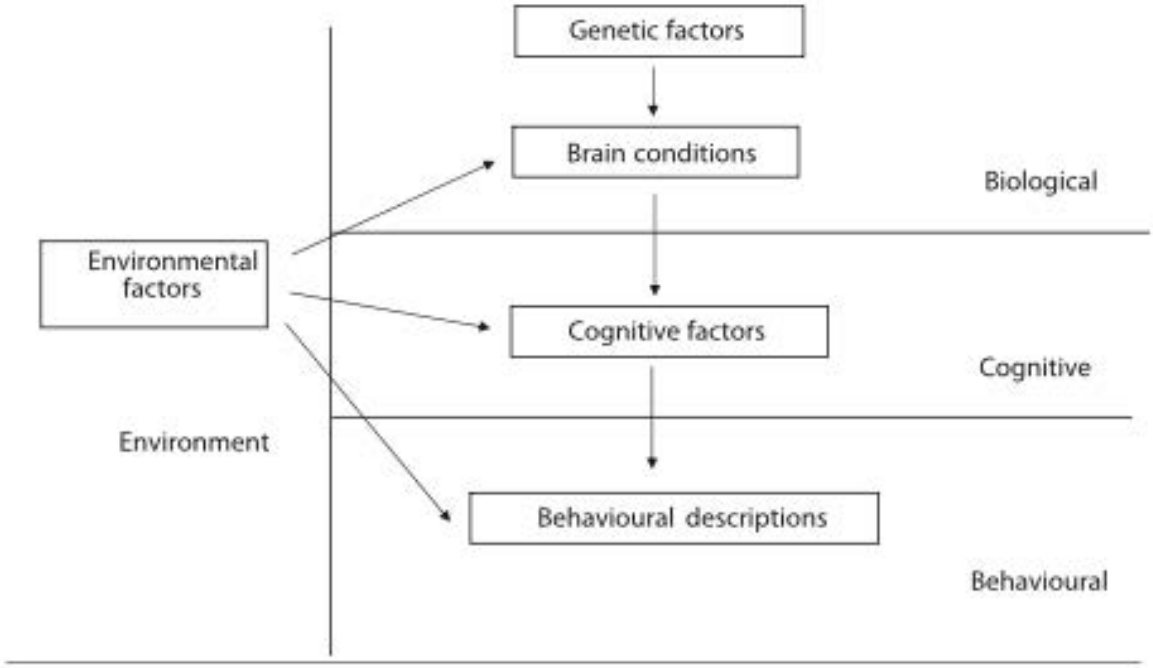

Figure 1.1. *The 'casual modelling approach' framework (Morton, 2004).*

To address these issues, Moore & George (2011) extended Morton's framework by developing the Accessible Cause-Outcome Representation and Notation system (ACORNS) (Figure 1.2). The ACORNS provides a tool to visually represent how associations between aetiological mechanisms and behaviours change over time by including an arrow at the bottom of the model that represents changes with time and development. In addition, causal relationships can be visualised both between and within aetiological levels (i.e. within neurobiological, cognitive, behavioural or environmental levels). Vertical arrows link factors across different levels, whereas diagonal arrows represent causal relationships within levels. Unlike Morton's framework, these causal relationships can be bi-directional. Finally, the ACORNS further refined aetiological levels included in Morton's framework. The environment is represented as an equivalent rather than a separate level to internal factors and physical and social environments are differentiated. The cognitive level is differentiated by

two sub-levels separated by a dashed line, cognitive and social-affective levels. Overall, the ACORN's model provides a comprehensive framework that captures the dynamic causal relationships between factors across multiple levels that may lead to behavioural phenotypes across time.

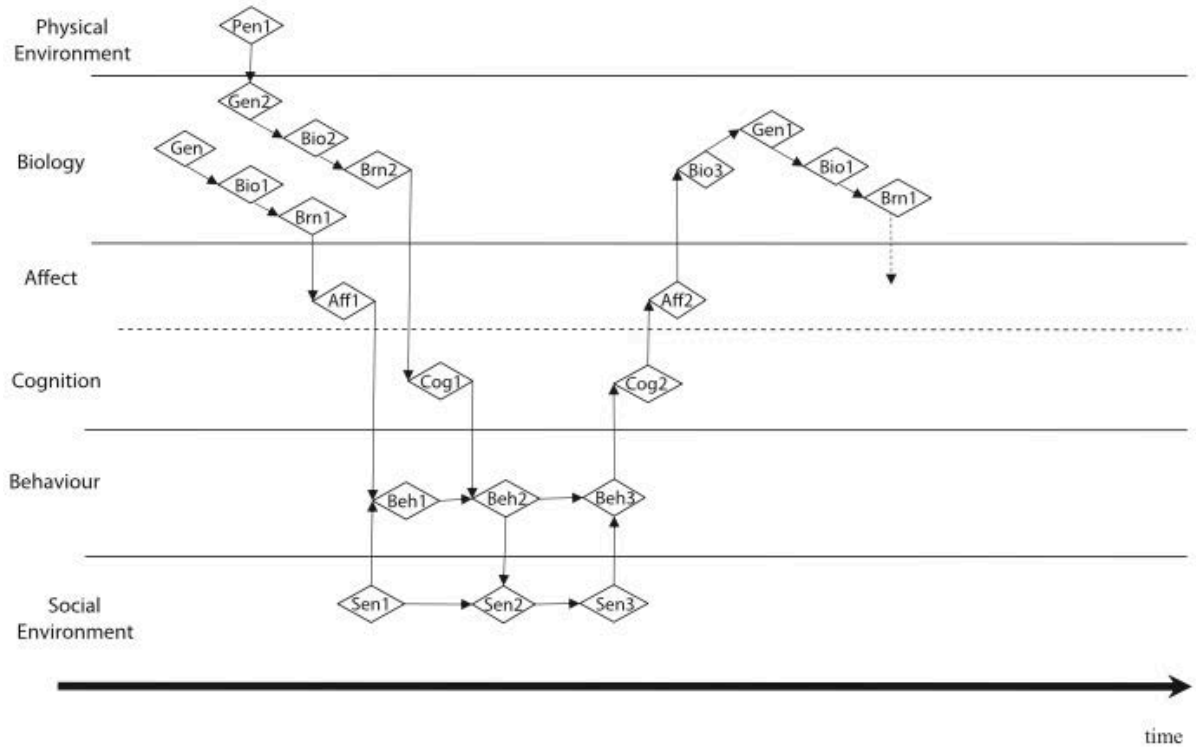

Figure 1.2. *An example of the ACORNS model (Moore & George, 201**1**).*

This thesis includes investigation into several components of the ACORNS model likely to contribute to profiles of sociability observed in CdLS, FXS and RTS. The following sections will outline the major mechanistic components that will be investigated in this thesis.

1.3.1 Endophenotypes

The 'affect' and 'cognition' levels of the ACORNS are examples of endophenotypes i.e. characteristics that are not directly observable, such as thoughts, cognitions, emotions and motivational states (Waite et al., 2014). The most commonly studied are cognitive endophenotypes, with many syndromes showing uneven but distinct cognitive profiles in which certain abilities may be spared or impaired compared to their general level of cognitive ability. For example, individuals with Williams syndrome have relatively spared verbal but impaired spatial abilities relative to cognitive ability, whereas individuals with Down syndrome show the opposite profile (Jarrold, Baddeley & Hewes, 1998; Chapman & Hesketh, 2000; Wang & Bellugi, 1994).

In contrast, some syndromes show similarities in cognitive profiles despite their differing genetic causes (Fung, Quintin, Haas & Reiss, 2012), which may lead to similarities in motivational states. Individuals with Prader-Willi syndrome (PWS) and FXS show attention switching difficulties, which are associated with aversion to changes in routine. However, whereas changes in routine are related to increased temper outbursts in children and adolescents with PWS, they are more likely to be related to heightened levels of anxiety in boys with FXS (Woodcock, Oliver & Humphreys, 2009a; 2009b). These findings demonstrate that different pathways contribute to the emergence of each syndrome's behaviour via neurobiological differences that: 1) may lead to certain cognitive profiles that make specific stimuli within the environment aversive or favourable and lead to motivational states and 2) determine their response to the stimulus (Woodcock et al., 2009a; 2009b).

These findings highlight the importance of identifying the similarities and differences across multiple aetiological pathways between syndromes to create comprehensive models of endo- and behavioural phenotypes specific to each syndrome. This thesis focuses on the

endophenotypic profile of social cognition in syndromes with distinct profiles of sociability i.e. CdLS, FXS and RTS. Social cognition is described and discussed in further detail below in section 1.6.

1.3.2 Environmental influences on behavioural phenotypes

Understanding the environmental influences on behavioural phenotypes may help explain within syndrome variation (Oliver & Woodcock, 2008). Behaviours phenotypic to an individual's syndrome may only be observed in the presence of a specific environmental stimulus that triggers that behaviour. These models of behaviour incorporate principles from operant conditioning (McGill & Langthorne, 2011; Oliver et al., 2013), in which phenotypic behaviours within a syndrome may become reinforced if the behaviour leads to a desirable outcome.

Whether and which environmental stimuli trigger behavioural responses may differ depending on an individual's syndrome. Woodcock and colleagues (2009a; 2009b) demonstrated how differences in the central nervous system may lead to certain environmental contexts to be rewarding or aversive (section 1.3.1). Studies that have systematically manipulated the environment, such as level of adult attention, lead to different behaviours depending on an individual's syndromes. Individuals with FXS show high levels of social avoidance behaviour (Cohen et al., 1988) and children with CdLS show behaviours indicative of social anxiety (Richards, Moss, O'Farrell, Kaur & Oliver, 2009) during conditions of high social demand. In contrast, individuals with Smith-Magenis syndrome frequently initiate social interaction when the level of adult attention they are receiving is low (Wilde, Mitchel & Oliver, 2016) and children with Angelman syndrome show more laughing and smiling in conditions of high adult attention involving adult speech, touch, smiling,

laughing and eye contact. These findings suggest that whereas individuals with CdLS and FXS find social contact aversive, those with Angelman and Smith-Magenis syndromes find social contact rewarding.

Understanding the influence of environmental factors on behavioural phenotypes aids intervention development as: 1) changing the environment or developing an individual's coping skills to help them adapt to an environment is easier than making changes to an individual's genetic or neurobiological make-up and 2) it increases specificity by enabling interventions to target specific environments that trigger behaviours within a certain syndrome. Therefore, in Chapter Three, I will investigate the influence of an environmental variable, i.e. the time spent interacting with someone, on components of sociability observed in individuals with CdLS, FXS and RTS.

1.3.3 Trajectories of behavioural phenotypes

Studies show that behavioural phenotypes are dynamic and change with both age and development (Adams et al., 2011; 2015; Oliver, Berg, Moss, Arron and Burbidge, 2011, Moss et al., 2016; Moss et al., 2017; Thomas et al., 2009; Karmiloff-Smith, 2012). Examples include a decline in laughing and smiling in children and adolescents with Angelman syndrome (Adams et al., 2011; 2015) and a decline in mood and sociability with increasing age in CdLS (Oliver et al., 2010, Moss et al., 2016; Moss et al., 2017). Understanding these changes is becoming more important as life expectancy increases in individuals with ID (Oliver & Hagerman, 2007). Changes in behaviour reflect the dynamic nature of cortical development, in which the brain becomes increasingly specialised and defined both by an individual's genetic expression and their interactions with dynamic environments throughout the lifespan (Karmiloff-Smith, 2012). However, the pathways from the aetiological changes in

neurobiology and cognition leading to dynamic behavioural phenotypes has yet to be explicitly delineated in many genetic syndromes.

The most investigated change with age in a genetic syndrome has been the cognitive and behavioural deterioration observed in individuals with Down syndrome. People with Down syndrome have intact social skills (Kasari & Freeman, 2001; Kasari, Freeman, Mundy & Sigman, 1995) and show high levels of sociability (Moss et al., 2016). However, they are at risk of developing Alzheimer's disease at an earlier age (around 55 years) than the typical population (65 years or above), due to having three copies of the amyloid precursor protein gene and subsequently greater amyloid-beta plaque deposition throughout their lifetime (Hithersay, Hamburg, Knight & Strydom, 2017). Alzheimer's disease leads to a deterioration in cognitive abilities and subsequently behavioural changes such as irritability, social withdrawal and aggression in individuals with Down syndrome (Esbenson, Johnson, Amaral, Tan & Macks, 2016). Outlining the trajectory of behaviour changes identified preclinical markers that marked critical points for early treatment. Changes in personality and behaviour associated with deterioration in executive function in individuals with Down syndrome were reported by care-givers five years before these individuals received a diagnosis of Alzheimer's disease (Ball et al., 2006). In addition, the cognitive profile of individuals with and without Down syndrome who have Alzheimer's disease are similar (Dick, Doran, Phelan & Lott, 2016), suggesting individuals with Down syndrome with Alzheimer's would benefit from early interventions targeting the same aetiology as those used in the general population. Chapter Three will explore the association between sociability and chronological age to identify changes with age that may have clinical implications (e.g. behavioural deterioration).

Previous research has shown unique profiles of developmental trajectories across cognitive skills in genetic syndromes. Whereas individuals with Williams syndrome's verbal

and nonverbal IQ scores remain consistent throughout childhood (Fisch et al., 2012), adolescence and adulthood (Fisher, Lense & Dykens, 2016), children and adolescents with FXS show a widening gap relative to TD children in verbal comprehension, perceptual organisation and processing speed with age. Individuals with FXS also showed different strengths and weaknesses at different developmental points: verbal skills become a strength relative to visuo-spatial constructive skills in adolescence, whereas a strength in processing speed relative to working memory observed in childhood diminishes with age (Quintin et al., 2015). Some syndromes show dissociations between abilities that are under the same overarching domain. A cross-sectional trajectory analysis revealed that whilst verbal working memory span increased with an individual's mental age in those with RTS, their visuo-spatial working span skills did not and instead show a flat trajectory (Waite, Beck, Heald, Powis & Oliver, 2016).

These findings have clinical implications for learning in individuals with RTS (Waite et al., 2015) and identifies the abnormal brain morphology that may underpin these differences in those with FXS for future study (Quintin et al., 2015). However, it is unclear what influence that the developmental trajectories have upon specific aspects of their behavioural phenotypes. Therefore, Chapter Four aims to outline the developmental trajectory of abilities in CdLS, FXS and RTS that are explicitly theorised to underpin sociability in both typical and atypical populations i.e. social cognitive abilities.

1.4 Comparing behavioural phenotypes across genetic syndromes.

Cross-syndrome comparisons distinguish the similarities and differences between behavioural phenotypes and their relevant aetiological mechanisms, providing greater detail beyond whether individuals in a syndrome simply shows a delay relative to TD individuals

(Hodapp & Dykens, 2001; Cebula, Moore & Wishart, 2010). I will investigate the profiles of sociability and development of social cognitive abilities within three genetic syndromes: CdLS, FXS and RTS. These syndromes have a similar range of ID (most ranging between mild to moderate; Oliver, Arron, Sloneem & Hall, 2008; Bennetto & Pennington, 2002; Hennekam, 2006), yet show differences in their behavioural phenotypes. Individuals with RTS are considered to have greater sociability (Moss et al., 2016) and social competence (Galéra et al., 2009; Hennekam, 2006) in comparison to individuals with CdLS and FXS, who are characterised by social anxiety (Nelson, Crawford, Reid, Moss & Oliver, 2017; Richards et al., 2009; Hall & Venema, 2017) and ASD symptomatology (Oliver et al., 2011). Comparing potential underlying mechanisms of behaviours (i.e. social cognition) between syndromes that show broad differences in sociability (i.e. RTS vs CdLS/FXS) can help identify whether these mechanisms lead to contrasting behavioural phenotypes.

Investigating "same-but-different" behaviours (Hodapp & Dykens, 2001) involves investigating behaviours that look similar between genetic syndromes but show subtle differences with detailed investigation. Although both individuals with FXS and CdLS show behaviours indicative of social anxiety (Nelson et al., 2017; Richards et al., 2009; Hall & Venema, 2017), the contexts in which these behaviours emerge differ across groups. Whereas adolescents and adults with FXS show social anxiety across a range of social contexts with both familiar and unfamiliar individuals, those with CdLS show significantly more social anxiety in contexts where individuals are expected to initiate interaction but are not required to do so and when interacting with an unfamiliar rather than a familiar examiner (Crawford et al., in prep). These differences may be indicative of differences in the aetiological pathways, as well as differences in the environments that lead to these behaviours. Therefore, the profiles of sociability and social cognition will also be refined in two groups who show global

similarities in sociability i.e. CdLS and FXS (Moss et al., 2016) in Chapter Three and Chapter Four respectively.

Section 1.2.3 outlined the dynamic nature of behavioural phenotypes across time. Therefore, a novel scaling approach is used in Chapter Four to investigate the developmental sequence of social cognitive abilities in individuals with CdLS, FXS and RTS across development, all of whom have reported to show changes of behaviour with age (Moss et al., 2017; Cochran, Moss, Nelson & Oliver, 2015; Hennekam, 2006).

The following sections will outline the genetic, physical, cognitive and behavioural characteristics associated with CdLS, FXS and RTS.

1.4.1 Cornelia de Lange syndrome

CdLS is a rare autosomal dominant genetic disorder, with a prevalence of 1 per 50,000 births (Oliver, Arron, Powis & Tunnicliffe, 2011; Whitehead, Nagaraj & Pearl, 2015). CdLS has heterogeneous genetic causes, including abnormalities on chromosomes 5 (Gillis et al., 2004), 10 (Deardorff et al., 2007) or X (Musio et al., 2006). These abnormalities disrupt the action of genes that encode cohesion complex proteins, which are vital for normal mitosis and meiosis throughout the body that affects the growth of multiple organs. Approximately 65% of cases of CdLS are caused by mutations in the *NIPBL* gene*,* although other potentially affected genes include *SMC1a, SMC3, RAD21* and *HDAC8* genes (Yuan et al., 2015; Whitehead et al., 2015). Deletion of genes that have a greater effect on exons within the cohesion complex leads to more severe forms of disability and behaviours (Grados, Alvi & Srivastava, 2017).

CdLS is a multi-systemic disorder that is characterised by many physical characteristics and medical issues related to growth impairment that range in prevalence and severity across individuals. Although most affected individuals show severe/profound levels of disability

(Mulder et al., 2016), some individuals can be mildly affected and subsequently underdiagnosed (Kline et al., 2007; Whitehead et al., 2015). Clinical diagnostic features include distinctive facial characteristics (including arched eye brows, upper limb defects) and delayed growth (Oliver et al 2010; Whitehead et al., 2015). Many also experience vision, hearing, gastroesophageal and mobility problems (Mulder et al., 2016). Distinct features identified through neuroimaging include skull based dysplasia, cerebral and brainstem volume loss, and gyral simplification, which vary in severity across individuals and may contribute to level of disability and prevalence of epilepsy (Whitehead et al., 2015).

These neurological consequences are likely to contribute to the cognitive and behavioural characteristics observed in those with CdLS, which include repetitive behaviours and self-injurious behaviour, with biting, head banging and skin picking being most prevalent. Many individuals show difficulties in expressive communication (Mulder et al., 2016; Grados et al., 2017) including difficulties utilising pronouns in communicative contexts, complex sentences (Lorusso et al., 2007) and understanding non-verbal communication (Hoddell, Moss, Woodcock & Oliver, 2011).

Social behaviour in a subset of individuals with CdLS is characterised by social anxiety, particularly in social environments that require them to speak, indicating that social anxiety may be related to expressive language difficulties. These difficulties appear to emerge as individuals begin to reach adolescence and adulthood (Nelson et al., 2017; Richards et al., 2009; Moss et al., 2016). Selective mutism has been observed in some individuals, (Nelson et al., 2017), suggesting that the reduced verbal interaction may be used by some individuals to avoid social interaction. Clinical reports have indicated extreme anxiety may occur when there are changes in routine or if an individual is prevented from completing a ritualistic behaviour (Grados et al., 2017).

ASD symptomatology has been reported within those with CdLS, although the occurrence of individuals reaching clinical cut-off scores on measures of ASD have ranged between 27 to 82% (Mulder et al., 2016). However, fine-grained comparisons between individuals with CdLS and idiopathic ASD (iASD) indicate different profiles of ASD-related impairments (Moss, Oliver, Nelson, Richards & Hall, 2013). Some reviews indicate individuals with CdLS who reach cut-off scores of clinical assessments of ASD show greater occurrence of repetitive behaviours (Grados et al., 2017), with another study using the *Social Communication Questionnaire* (Rutter, Bailey & Lord, 2003) suggesting that scores are driven more by communication difficulties in CdLS in comparison to those with iASD (Moss et al., 2013). These differences suggest that ASD-related behaviours may be driven by the different aetiological mechanisms in individuals with iASD compared to CdLS.

1.4.2 Fragile X syndrome

FXS is the leading inherited cause of ID, caused by repeats of the sequence of cytosine-guanine-guanine (CGG) trinucleotide on the Fragile X Mental retardation-1 (FMR1) gene on the X chromosome. The full mutation is defined by >200 CGG repeats, whereas the premutation is defined by repeats between 55-200. The full mutation is more prevalent in males compared to females. In addition, compared to males with the full mutation, females are overall less impaired due to the protective effect of an unaffected X chromosome that females have but males do not (Davenport, Schaefer, Friedmann, Fitzpatrick & Erickson, 2016). The greater number of repeats an individual has, the greater the level of disability that individual will have. Current clinical trials typically aim to evaluate pharmacological intervention that target pathways affected by the loss of Fragile X Mental Retardation Protein (FMRP), a product of the FMR1 gene, which leads to excitatory/inhibitory imbalance in

GABAergic signalling (Davenport et al., 2016) and considered key in pre- and post-natal brain development (Dykens & Hodapp, 2001). Those with the pre-mutation generate some FMRP, whereas the full mutation leads to hypermethylation and silences the FMR1 gene (Cornish et al., 2005).

FXS is associated with mild to moderate ID, with delays observed from as early as six months of age and increase with age when compared to TD infants and infants at high risk of ASD (Roberts, McCary, Shinakareva & Bailey Jr, 2016), with difficulties in language development (Abbeduto, Brady & Kover, 2007). As with those with CdLS, FXS is characterised by high levels of repetitive behaviours (Waite et al., 2015; Moss et al., 2009) and impulsivity (Powis, 2014) and are at heightened risk of ADHD (Grefer, Flory, Cornish, Hatton & Roberts, 2016). Many individuals with FXS show challenging behaviour, including self-injury such as biting and aggressive behaviours including hitting. These behaviours most commonly function to escape from demands placed by another person (Hardiman & McGill, 2017).

Individuals with FXS experience a range of social difficulties. One of the most characteristic behaviours in FXS is gaze avoidance, especially with others who are unfamiliar to the individual and in individuals with lower communication abilities. Gaze avoidance is hypothesised to be driven by social anxiety and hyperarousal in social situations (Hall & Venema, 2017). Many aspects of the FXS behavioural phenotype overlap with core diagnostic features of ASD. These include social communication difficulties, difficulties maintaining eye contact with other people (Hogan et al., 2017) and repetitive behaviour (Waite et al., 2015; Moss et al., 2009; Hogen et al., 2017). These difficulties appear to emerge within the first year of life, with social communication deficits such as eye contact, limited social interest, lack of social smiling and no social babbling, being the most prominent and earliest ASD risk

markers (Hogan et al., 2017). Those with a comorbid diagnosis of FXS and ASD (FXS+ASD) have greater social impairments compared to individuals with FXS without an ASD diagnosis (Hall & Venema, 2017; Hogan et al., 2017). In comparison, stereotyped behaviours appear to be unrelated to ASD diagnosis at an early age, suggesting that lower order repetitive motor behaviours are part of the broader FXS phenotype separate from ASD (Hogen et al., 2017).

Although the developmental trajectories of social communication difficulties appear similar between those with FXS+ASD and other groups at high risk of ASD (e.g. children with a sibling with iASD; Hogan et al., 2017), contrasts between individuals with FXS+ASD and those with iASD have shown differences in profiles of social interaction and communication skills. When controlling for receptive language and non-verbal ability, verbal children and adolescents with FXS+ASD made fewer signals of non-comprehension of purposefully confusing messages made by another person, an important pragmatic language skill for repairing breakdowns in social communication, compared to those with iASD (Martin et al., 2017). In addition, the profile of receptive-expressive language differs across the two groups, with boys with iASD showing lower receptive-expressive language impairments than boys with FXS+ASD, as well as greater discrepancies between these two domains (Haebig & Sterling, 2017). Differences have been found between boys with FXS and those with iASD on items in assessments of ASD symptomatology, which were previously masked by domain level scores. In particular, boys with FXS have shown significantly less impairment in social smiling, facial expressions, response to joint attention, gaze integration and quality of social interactions (McDuffie, Thurman, Hagerman & Abbeduto, 2015; Wolff et al., 2012).

1.4.3 Rubinstein-Taybi syndrome

RTS is a congenital neurodevelopmental disorder and affects between 100,000 and 720,000 newborns (Park et al., 2014). Most cases are caused by heterozygous de novo mutations encoding the cyclic adenosine monophosphate response element binding protein (CREBBP) (Petrij et al., 1995; Park et al., 2014) or the E1A binding protein (p300), although other causes include microdeletions on chromosome 16p.13.3 in which p300 is located (Lacombe, Suara, Taine & Battin, 1992; Hennakam, 2006; Milani et al., 2015). These abnormalities act on the CREBBP locus, which has numerous functions including regulating the tumour suppressor pathway (p53) and regulating gene expression and transcription through histone acetyltransferase activity (Park et al., 2014). Genetic abnormalities associated with RTS have been shown to lead to deficits in histone acetylation in both animal models and cell lines from RTS patients (Lopez-Atalaya et al., 2011), which has been implicated in some of the consequences of the disorder such as deficits in long-term memory (Park et al., 2014), motor learning (Oliveira, Abel, Brindle & Wood, 2006; Galéra et al., 2009) and more recently potential influences on short-term memory (Chen, Zou, Watanabe, van Deursen & Shen, 2010). As these causes are de novo mutations, there is a very low recurrence risk after an unaffected individual having a first child with RTS, but a person with the syndrome themselves have an estimated 50% recurrence risk (Hennekam, 2006; Milani et al., 2015).

Currently, a genetic diagnosis of RTS is possible in only 55% of cases (Hennekam, 2006) and thus diagnosis is often based on characteristic clinical features, such as mild to severe intellectual disability, characteristic facial features (full arched brows, long eyelashes, down slanting palpebral fissures, broad nasal bridge and beaked nose, and a grimacing smile), broad thumbs and toes, and microcephaly. Typical medical problems include congenital heart defects, eye and dental problems, respiratory problems, gastroesophageal reflux and feeding

difficulties at birth leading to difficulties in early growth, followed by weight gain in childhood (Stevens, Carey & Blackburn, 1990; Galéra et al., 2009; Milani et al., 2015). Many of these medical issues, such as short stature, obesity, visual difficulties and eating problems persist into adulthood, along with other issues such as keloids, spine curvature, joint problems and hypohidrosis (Stevens, Pouncey & Knowles, 2011). Due to the CREBBP locus' role in the tumour suppression pathway, individuals with RTS are at a heightened risk of developing tumours (Hennekam, 2006).

Recent studies have begun identifying the cognitive and behavioural characteristics specific to the syndrome. Care-giver reports suggest that children and adults with RTS show specific behavioural problems related to a short attention span and poor coordination (Galéra et al., 2009; Stevens et al., 2011). Formal IQ assessments suggest that overall the non-verbal ability of individuals is greater than verbal ability. Speech difficulties are common and parent reports suggest these abilities become more limited with age (Stevens et al., 1990; 2011). In addition, individuals with RTS show working memory impairments relative to their overall level of ability (Waite et al., 2016). Although not as heightened as observed in those with FXS, moderate levels of repetitive behaviours in those with RTS have been reported in several studies, characterised by motor stereotypies and repetitive questioning (Galéra et al., 2009; Stevens et al., 1990; Waite et al., 2015).

Despite these difficulties, previous research suggests that the social skills and social behaviour in those with RTS are intact. Many reports describe individuals with RTS as "loving, friendly and happy" (Stevens et al., 1990), with a considerable ability to "establish social contact" (Hennekam, 2006). Caregiver questionnaires suggest that individuals with RTS show better contact, more social interest and low levels of behaviours associated with ASD compared to groups of children with a similar level of ability and age (Galéra et al.,

2009) and higher rates of "extreme sociability", defined as motivation for social contact, compared to other genetic syndromes such as CdLS and FXS when interacting with both familiar and unfamiliar adults (Moss et al., 2016). However, caregiver reports have indicated changes in age, with some adults reported as showing decreased social interaction and more limited speech over time (Stevens et al., 2011), with sudden mood changes, anxiety, uncertain behaviour and aggression developing as individuals go into adulthood (Hennekam, 2006; Milani et al., 2015). In addition, Crawford and colleagues (in prep) reported similar levels of anxiety in adolescents and adults with RTS as those with CdLS and FXS. Overall, these studies suggest that individuals with RTS are very socially motivated but difficulties may emerge over time. Except for the Crawford and colleagues (in prep) study, evidence to demonstrate sociability in this population has largely relied on caregiver questionnaire reports and anecdotal descriptions, with little or no direct empirical and observational investigation of social skills and social behaviour in those with RTS.

1.5 Interim summary

In this section, the rationale for building models of behavioural phenotypes and profiles of sociability in individuals with genetic syndromes was described. Previous literature has demonstrated the influence of an individual's motivational and cognitive profiles (i.e. their endophenotype), the influence of environmental context and the importance and relationship of dynamic developmental trajectories of behavioural phenotypes and related underlying aetiological mechanisms across genetic syndromes. The behavioural phenotypes of three syndromes with distinct profiles of sociability (CdLS, FXS and RTS) was outlined and the rationale for investigating these syndromes was described. The following section will define social cognition and its constructs, describe recent literature outlining the development

of social cognitive abilities and outline evidence demonstrating the influence of social cognition on social behaviour in the typical and atypically developing literature.

1.6 Social cognition

There have been many definitions used to describe social cognition and a universally accepted and definitive definition appears to be absent from the literature. Cook & Oliver (2011) suggested that social cognition is not a unitary concept, but instead an "approach or philosophy". They proposed to view social cognition as a broad concept that encompasses a range of "mind-reading" knowledge and abilities of other's social and emotional cues and information, the consequences and reasons underlying other's actions as well as their mental states across a range of social contexts. These may include a wide range of abilities including theory of mind (ToM), intentionality, affective empathy, social perception, amongst other examples (Henry, von Hippel, Molenberghs, Lee & Sachdev, 2016; Schaller & Rauh, 2017). Due to the breadth of abilities this definition covers, Cook & Oliver (2011) advise researchers to further define the specific social cognitive construct that is under investigation.

In this thesis, a broad approach is taken in which social cognition is used as an umbrella term to refer to a range of cognitive processes that lead to understanding of another's thoughts and behaviours within a social context. This understanding is used to interpret and predict other people's behaviour, including someone's reaction to our own behaviour, making social cognition vital for successful and reciprocal social interactions (Frith, 2008; Frith & Frith, 2012; Schaller & Rauh, 2017; Tomasello, Carpenter, Call, Behne & Moll, 2005).

Social cognitive abilities have been further broken down into implicit and explicit processes. Implicit processes are automatic and unconscious (e.g. gaze following, imitation),

whereas explicit processes involve conscious mentalising, tracking and reasoning about other's mental states, including other's intentions, beliefs, knowledge and emotions. However, it has been argued that social cognitive abilities typically described as 'explicit' can be investigated in tasks that assess automatic behaviours (Frith & Frith, 2012; Baillargeon, Scott & He, 2010). Contributing to this debate is beyond the scope of this thesis and tasks are described as assessing 'explicit' only because they evaluate an individual's ability to explicitly reason about mental states and require a verbal response.

The focus of this thesis is upon the development of social cognitive abilities in CdLS, FXS and RTS relative to one another and against a normative TD benchmark from infancy to adulthood and how and/or whether these abilities contribute to their profiles of sociability.

1.6.1 The development of social cognition

In this thesis, an approach that conceptualises social cognition as a developmental sequence of abilities that emerge from infancy into childhood is used (Powis, 2014; Powis, Ellis, Oliver, Waite, Heald & Apperly., in revision; Wellman & Liu, 2004; Peterson, Wellman & Liu, 2005; Peterson, Wellman & Slaughter, 2012). ToM abilities, which enable individuals to explicitly reason and understand a range of other people's types of mental states, have received the most attention within the social cognition literature. These studies consist of a narrow range of experimental tasks assessing a small number of ToM abilities within a narrow age range (Apperly, 2012). The most common task is the false belief task, in which an individual must understand that an agent may hold a belief that is both different from the participants and contradictory from reality, to correctly predict that agent's behaviour. Once considered as the 'litmus' test of whether an individual does or does not have a ToM, most children pass this task around the age of four years (Wellman, 2014) and has been used to

demonstrate relative delay in acquiring these skills in a range of neurodevelopmental disorders associated with social difficulties including ASD (Baron-Cohen, Leslie & Frith, 1985), CdLS (Collis, Oliver, Moss, Gorniak & Apperly, 2008), FXS (Grant, Apperly & Oliver, 2007) and RTS (Powis, 2014). Recent research using scaling analysis provides evidence that the development of a range of distinct social cognitive concepts or abilities in TD children conform to a cumulative unidimensional statistical pattern (Wellman & Liu, 2004; Powis 2014, Powis, et al., in revision). It has been proposed that the natural emergence of such a stringent pattern suggests that these concepts are intrinsically related to one another (Gutman, 1994; 1950; Guttman & Greenbaum, 1998). These abilities will be outlined below, beginning with the development of early understanding of other's intentions and then later developing ToM abilities.

1.6.1.1 The development of early social cognitive skills: Intentionality abilities

A large body of literature indicates that some of the earliest developing social cognitive abilities enable infants to form a shared intentionality with others to cooperate and coordinate their interactions and achieve joint goals with others (Tomasello et al., 2005; Powis, 2014; Powis et al., in revision). These abilities are hypothesised to provide the foundations for later, more sophisticated abilities such as explicit understanding of other people's mental states. Throughout this thesis, abilities that contribute to the development of shared intentionality are referred to as 'intentionality' abilities.

Two developmental streams are hypothesised to be required to lead to shared intentionality (Tomasello et al., 2005). The first consists of an understanding of other's intentional states and actions, a basic ability shared with great apes. This basic understanding requires infants to: 1) understand that the acting person is an independent agent and

subsequently different from objects (Frith, 2008), 2) interpret the acting person's behaviour as an action plan to achieve a goal and subsequently 3) an understanding of what that individual's goal is based on their actions (Tomasello et al., 2005). The second developmental stream consists of a unique species specific motivation to share their own psychological states with another, to cognitively represent these shared states and to communicate to focus one another's attention on the same object of interest (Moll & Tomasello, 2007; Frith, 2008). These abilities are vital in fostering reciprocal communication and coordination during cooperative activities.

Recent literature suggests that intentionality abilities emerge in a reliable cumulative sequence in TD infants. Powis and colleagues (Powis, 2014; Powis et al., in revision) developed the *Early Social Cognition Scale*, a battery of tasks taken from the literature that assess a range of different types of intention understanding that emerge at different ages. Validation of the battery of tasks on a sample of infants across a range of ages indicated that infants typically acquire the abilities to pass these tasks in a reliable progression. These abilities ranged from understanding of basic goal directed actions, such as the intention behind an individual's reach towards an out-of-reach object, to more sophisticated cooperative and joint problem-solving abilities that requires a 'shared intentionality' and the formation of joint goals with others.

1.6.1.2 The development of later social cognitive skills: Theory of Mind abilities

ToM is the meta-representational ability to explicitly reason about other's mental states, such as beliefs, desires and knowledge and the ability to use this knowledge to predict that individual's behaviour (Apperly, 2012). Children aged between two and seven years old passed tasks assessing different ToM concepts in a scalable and cumulative fashion (Wellman

and Liu, 2004), ranging from a basic understanding that others can have different desires from their own, to sophisticated understanding that others can experience an emotion that is different to the one they are showing. These findings are robust and have been replicated in different cohorts of children (Peterson et al., 2005; 2012). This 'Theory of Mind Scale' (*ToMS*) has been extended to include a more advanced task assessing children's understanding of sarcasm, i.e. when someone makes a nonliteral comment (Peterson et al., 2012). The stringent, cumulative order that these tasks emerge within children suggest that these abilities may develop as a process of moderation (later developing abilities develop through broadening of earlier understanding) or mediation (later abilities develop from scaffolding of earlier abilities) (Wellman & Liu, 2004; Flavell, 1972).

1.6.2 The link between social cognition and social behaviour

Social cognition is considered fundamental for successful social communication and social interaction with others. Frith (2008) conceptualises the relationship between social cognition and behaviour within an information processing account. Within this framework, the way in which an individual behaves (i.e. their response) within social contexts and interactions with others will depend on the social cognitive processes that individual uses to interpret the causes of another's behaviour (i.e. the social stimuli).

Social cognitive processes enable individuals to learn about the world by observing other's reactions and behaviours. For example, around 18 months, infants can distinguish another person's communicative use of a pointing gesture intended to direct the infant's attention to stimuli of interest in the environment (Behne, Carpenter & Tomasello, 2005), teaching the infant what is relevant to their immediate social context (Frith, 2008). In turn, being able to reason about another's emotional state based on their reaction (e.g. disgust or

delight) to that environmental stimulus helps identify whether something is good or bad, inform our own behavioural response, as well as understanding the other person's behaviour (i.e. avoid or approach an object/individual respectively). Being able to interpret an individual's response to a stimulus enables individuals to learn who they may or may not be able to trust and learn about what may or may not be safe in an environment. The complexity of interactions an individual can successfully engage in increases with the development of more sophisticated social cognitive skills.

Social cognitive abilities predict social behaviour in typical populations (e.g. Caputi, Lecce, Pagnin & Banerjee, 2012) and a range of psychiatric, developmental and neurodegenerative disorders and brain damaged patients (Henry et al., 2016). Social cognition is named as one of the six core components that can be affected by a neurocognitive disorder in the most recent Diagnostic Manual (American Psychological Association, 2013). Impairments in social cognition lead to a range of impairments in social behaviour, such as lack of manners, abnormal eye contact, lack of understanding of personal boundaries and poor conversational turn-taking (Henry et al., 2016), many of which are core clinical features of ASD (Lord et al., 2012). However, disorders characterised by hyper-sociability, such as Williams syndrome (Karmiliff-Smith, 2012; Santos & Deruelle, 2009) and Rubinstein-Taybi syndrome (Powis, 2014; Moss et al., 2016) have shown mixed profiles on social cognitive assessments. The variety of conditions affected is likely due to the wide range of brain areas that interact with one another in social cognition, and therefore may be disrupted in individuals with CdLS, FXS and RTS due to their genetic origins.

The following sections outline evidence of a mechanistic influence of social cognition upon social behaviour. The following will be outlined: 1) the influence of individual differences in performance on social cognitive tasks on social outcomes in typical

development, 2) the social cognition hypothesis of social impairments in ASD and 3) social cognitive profiles in genetic syndromes with unique profiles of sociability.

1.6.2.1 The link between social cognition and social behaviour in typically developing populations

Previous research suggests that social cognition influences social behaviours in TD children. A meta-analysis including 6,432 children aged between 2 and 12 years found that children's scores on a range of ToM tasks were positively associated with scores of measures of a range of prosocial behaviours, including helping, cooperating and comforting (Imuta, Henry, Slaughter, Selcuk & Ruffman, 2016). Fink, Begeer, Peterson, Slaughter and de Rosnay (2014) found that higher performance on first-order and advanced FB tests at the age of five significantly predicted a greater likelihood of children having a mutual friendship at age seven. In addition, Jervis & Baker (2004) found that children and adolescent's performance on ToM tasks were positively associated with parent reported social adaptive abilities within everyday contexts.

Social behaviours can be influenced by targeting social cognitive abilities. Prosocial behaviours in four-year-olds were enhanced when children participated in cooperative tasks requiring developing a shared intentionality and joint goals with others, such as a music making (Kirschner & Tomasello, 2010). The authors hypothesised that forming stronger cognitive representations of shared goals increases a sense of acting as a unit, which encourages children to help and cooperate with others. These findings have important implications for developing interventions to improve prosocial behaviour in typical and atypical populations by identifying a mechanism that can be targeted.

Evidence suggests that lower social cognitive ability is associated with antisocial behaviour. A range of studies have shown an association between faulty judgements on mental state understanding of peer behaviours and aggression in children and adolescents (Hudley & Novac, 2007). However, Korucu, Selcuk & Harma (2017) found that when age and receptive language ability were controlled for, the number of tasks that children passed on the *ToMS* was associated with social competence, but not aggressive behaviour, in preschool children.

The differences between these studies may reflect a developmental difference in which ToM skills influence different behaviours at different ages depending on a child's social context. As children age, peer relationships become more important (Caputi et al., 2012) and children may be at increased competition with one another both academically and socially. Alternatively, ToM skills may be associated with certain topographies of aggressive behaviour (Korucu et al., 2017). These hypotheses support the need for: 1) investigating the influence of social cognition on social behaviour across development and 2) refined investigation into which specific behaviours are influenced by social cognition. In this thesis, both aspects will be investigated in individuals with CdLS, FXS and RTS by assessing a range of social cognitive abilities across development in Chapter Four, and exploring the influence of early and later developing social cognitive abilities on specific social outcomes in Chapter Five.

Mixed findings may also reflect the difference between *having* social cognitive abilities and *using* them. Whilst children may have the knowledge to pass social cognitive tasks, they may not apply them to every day social interaction (Caputi et al., 2012). Therefore, social cognitive abilities may be a necessary but not sufficient component of good social outcomes. ToM may influence social behaviour indirectly through moderation or mediation of

other variables. Even when controlling for level of ability, Caputi and colleagues (2012) found that children's overall performance on a range of ToM assessments at five years of age led to greater peer acceptance two years later by improving prosocial behaviour. Song, Volling, Lane and Wellman (2016) found that the association between high levels of aggression in first-born toddler's and high sibling antagonism one year after the birth of their sibling was mediated by poorer ToM at baseline. The influence of poor ToM abilities upon aggressive behaviour may be mediated by faulty attributions. Kinderman, Dunbar and Bentall (1998) found that undergraduate students who performed poorly on ToM tasks were more likely to attribute others as responsible for negative social situations. These findings elucidate mechanistic interactions between a range of variables that are unique to each behavioural outcome, highlighting the importance of detailed mechanistic models of behaviour.

1.6.2.2 The theory of social cognitive impairment in ASD

The social cognition theory of ASD suggests that a domain specific impairment in a ToM module (ToMM) leads to the social and communication difficulties experienced by those with the condition (Varga, 2011; Baron-Cohen, 1994). Since the 1980s, a wealth of literature has demonstrated that individuals with iASD show a weakness in explicitly reasoning and understanding other's false beliefs relative to control groups matched on age and IQ, in both children who are high functioning or have an ID (Baron-Cohen et al., 1985; Hughes, Soares-Boucaud, Hochmann, & Frith, 1997; Li, Zhu, Liu & Li, 2014; Tager-Flusberg, 2007).

Recent investigation of ToM deficits in ASD has progressed from a single task paradigm to utilising a range of mentalising tasks in line with literature outlining the different ToM abilities (Wellman & Liu, 2004). Although many high functioning adolescents and

adults pass traditional false belief tasks, many show difficulties understanding mental states in more complex social situations. Although their performance on the false belief task was comparable to TD adolescents matched on age and IQ, adolescents with high functioning iASD showed lower accuracy in identifying character's mental states after watching videos of a complex social situation, such as friends having a dinner party (Schaller & Rauh, 2017). In addition, adults with iASD demonstrate more inaccuracies in more advanced ToM abilities, tending to over-detect 'faux pas' compared to TD adults (Thiébaut et al., 2016). These tasks have extended investigation into ToM difficulties in those with iASD into adolescence and adulthood.

These studies highlight the need to investigate social cognitive abilities throughout development. Using the *ToMS*, Peterson and colleagues (2005; 2012) demonstrated that children with iASD show distinct atypicalities in the order that they develop ToM abilities. Both late-signing deaf children and children with iASD demonstrate delayed scale progression, possibly due to both groups experiencing divergent social experiences, limited scaffolding and little conversational exposure to others mental states throughout development. However, individuals with iASD also displayed a divergent developmental trajectory, in which they pass *Hidden Emotion* before passing *Contents False Belief*. In other words, these two tasks switch in terms of the sequence of developmental attainment. The authors hypothesised that this atypical order may be due to: 1) genetic and neurobiological differences in individuals with iASD that make processing others hidden emotion easier than their false beliefs, and/or 2) abnormal socialisation and peer experiences (e.g. teasing) that may make the *Hidden Emotion* task relevant to their daily experiences, leading to development of alternative strategies to partially succeed in these situations. Thus, findings led to the identification of biological and environmental variables that may influence individual's social cognitive development and

social behaviour. The same approach will be used in Chapter Four to investigate the developmental sequence of social cognitive abilities in individuals with CdLS, FXS and RTS.

More recent work has attempted to outline the relationship between social cognitive deficits and specific social and communication difficulties in the ASD phenotype. Sasson, Nowlin and Pinkham (2012) found that the relationship between scores on a questionnaire assessing the broad autism phenotype in the general population that was associated with 'social abnormalities' and reduced social skills, such as clarity and fluency of speech, involvement in conversation, appropriate facial expressions and eye contact during interaction with a research assistant, was mediated by performance on a range of explicit ToM tasks in a group of 74 undergraduate volunteers with no known clinical diagnoses. Several studies have reported an association between children's performance on ToM tasks and parent and teacher reported social skills considered to require mentalising skills observed in everyday life (Frith, Happé, & Siddons, 1994; Jervis & Baker, 2004; Peterson, Garnett, Kelly & Attwood, 2009), which have also been replicated cross-culturally (Hughes et al., 1997).

Whilst, most studies have focused upon performance on ToM tasks in those with iASD, Varga (2011) argues that shared intentionality may better account for social difficulties in these individuals, as social interactions are not solitary processes that occur following an individual's inference of another's mental states in isolation. Instead it is an intersubjective experience between two people that requires both individuals to coordinate and share attention. Although children with iASD have shown to understand some basic intentions of other people, such as helping a person reaching for an out-of-reach item, they have shown difficulties in some intention reading tasks that typically emerge throughout development: from distinguishing between another's intentional and accidental actions, to developing a shared intentionality (Liebal, Colombi, Rogers, Warneken & Tomasello, 2008; D'Entremont

& Yazbek, 2007). These findings suggest that children with iASD may show difficulties or a delay with some aspects of intention reading, which may contribute to difficulties in ToM skills later in development (Tomasello et al., 2005; Baron-Cohen, 1994).

1.6.2.3 Social cognition in genetic syndromes

Social cognitive abilities in Williams syndrome has received the most attention within the genetic syndromes literature (Cebula et al., 2010). These individuals are characterised by hyper-sociability and ease with strangers and have been compared against individuals with iASD as groups with polarising behavioural phenotypes. The pervasive view is that ToM is preserved in individuals with Williams syndrome (Karmiloff-Smith, Klima, Bellugi, Grant & Baron-Cohen., 1995). However, many individuals show difficulties in social interactions and social vulnerability (Karmiloff-Smith, 2012; Jawaid et al., 2012) and research investigating their performance on ToM tasks have shown impairments in some capacities (e.g. judging when another person is mistrusting; Hanley, Riby, Caswell, Rooney & Back, 2013), and spared abilities in others (e.g. understanding other's false beliefs and sarcasm; Sparaci, Stefanini, Marotta, Vicari & Rizzolatti, 2012; Karmiloff-Smith et al., 1995).

Individuals with Williams syndrome show relatively good performance on tasks assessing other's intentions (Santos & Deruelle, 2009), such as others non-inferential intentions behind their motor acts (Sparaci et al., 2012) and other's intentional use of gaze (Karmiloff-Smith et al., 1995). Individuals with Williams syndrome have good verbal abilities but relatively poor visuo-spatial skills (Jarrold et al., 1998). Santos and Deruelle (2008) found that children with Williams syndrome showed difficulties relative to TD children matched on mental age in interpreting a character's intentions when the task included visual but not verbal

cues. These findings demonstrate how cognitive strengths and weaknesses can influence social cognitive abilities within different contexts.

Performance in social cognitive assessments have shown to have different relationships with social behaviour dependent on an individual's syndrome. Despite their sociable phenotype and relatively intact success on false belief tasks (Baron-Cohen, 1989), individuals with Down syndrome show subtle difficulties in understanding other's intentions relative to their overall ability (Cebula et al., 2010). Higher rates of affect sharing were associated with poorer performance on a task assessing their ability to understand the intention behind another person's failed act in young children with Down syndrome. This association was not identified in a group of children with other developmental disabilities who were matched on developmental ability (Hahn, Fidler, Hepburn & Rogers, 2013). Although these findings may appear counter-intuitive, individuals with Down syndrome have been shown to overuse social behaviours (Kasari & Freeman, 2001). These findings suggest frequently used social behaviours in those with Down syndrome may be abnormally excessive, inappropriate and associated with poor social cognition. Therefore, in this thesis I will investigate both the quality and appropriateness of social skills and behaviours (Chapter Three) and a range of social cognitive abilities (Chapter Four) and the relationship between these constructs (Chapter Five) in syndromes that vary across the spectrum of sociability (i.e. CdLS, FXS and RTS).

Beyond Williams and Down syndromes, social cognition in genetic syndromes has received very little attention and has mostly utilised false belief tasks (e.g. Wingbermühle, Egger, Verhoeven, der Burgt & Kessels, 2012; Collis et al., 2008; Grant et al., 2007) or cross-sectional comparisons comparing overall performance on batteries of social cognitive tasks (e.g. Losh, Martin, Klusek, Hogan-Brown & Sideris, 2012). However, literature reviewed in

the previous sections suggest that social cognition may be an unexplored mechanism that contributes to different profiles of sociability between genetic syndromes. In addition, whilst the ASD literature (section 1.6.2.2) demonstrated the importance of examining a range of social cognitive abilities throughout development (Peterson et al., 2005; 2012), there has been little investigation into the development of social cognition within genetic syndromes. Therefore, this thesis will build upon previous work by providing the first study to use behavioural tasks to investigate a range of social cognitive abilities that emerge across development, from intentionality to ToM abilities across genetic syndromes with distinct profiles of sociability i.e. CdLS, FXS and RTS (Chapter Four). This thesis will be the first to investigate proof of principle that social cognition may underpin components of sociability in these syndromes (Chapter Five).

1.7 Summary and main aims

In this thesis, I aim to contribute to models of behavioural phenotypes in genetic syndromes by describing the profile of sociability in three distinct genetic disorders with unique social and behavioural profiles, CdLS, FXS and RTS. I will also describe the development of social cognitive abilities, a potential causal mechanism that may influence sociability in these syndromes, and explore the association between social cognition and sociability in individuals with CdLS, FXS and RTS.

CdLS, FXS and RTS are associated with unique behavioural phenotypes that range from hypersociability to extreme social withdrawal (Moss et al., 2016; Jawaid et al., 2012). These characteristics have been shown to have important implications on the wellbeing of individuals with profiles at both ends of the spectrum of sociability (Karmiloff-Smith, 2012;

Jawaid et al., 2012). Building explanatory models of behavioural phenotypes are vital for the development of better stratified interventions aiming to improve social skills and behaviours in those with a specific genetic syndrome. To build such a model, descriptions of the profile of sociability across syndromes, the environmental contexts and developmental points in which they emerge must be outlined. In Chapter Three, the social interaction skills and behaviours that contribute to profiles of sociability in individuals with CdLS, FXS and RTS will be evaluated using a behavioural rating scale (Child Sociability Rating Scale, Moss et al., 2013) during a standardised semi-structured social interaction with an examiner (Autism Diagnostic Observation Schedule, 2nd edition; Lord et al., 2012). The associations between components of sociability and duration of time spent interacting with an examiner, participant's chronological age, and ASD symptomatology within each syndrome will also be investigated.

The next steps towards building an explanatory model of sociability in CdLS, FXS and RTS is to describe the aetiological mechanisms that may underpin sociability in these syndromes. A wealth of literature suggests that differences in social cognitive abilities predict differences in social behaviours throughout typical (Imuta et al., 2016; Fink et al., 2014; Caputi et al., 2012; Kinderman et al., 1998) and atypical development (Peterson et al., 2005; 2009; 2012; Frith et al., 1994; Hahn et al., 2013). Differences in the development of social cognitive abilities may underpin differences in sociability in CdLS, FXS and RTS. Therefore, the development of a range of social cognitive abilities will be investigated in these groups in Chapter Four by utilising two scalable batteries of task: 1) the *Early Social Cognition Scale* (Powis, 2014; Powis et al., in revision) to assess the development of early developing intentionality abilities and 2) the *Theory-of-Mind Scale* (Peterson et al., 2012) to assess the development of later developing ToM abilities. In this chapter, I will explore whether these

abilities are advanced, preserved or delayed in these groups, as well as whether the sequence that individuals with CdLS, FXS and RTS develop social cognitive abilities diverges from the sequence observed in typical development.

The final stage of establishing models of behavioural phenotypes is to explicitly delineate the causal pathways between the genetic disorder, cognition and behaviour. Chapter Five is as a proof of principle study to directly explore the pathway between social cognitive ability and components of sociability for the first time in individuals CdLS, FXS and RTS.

Chapter Six will synthesise findings from this thesis with previous literature and to present visual models of sociability in individuals with CdLS, FXS and RTS. Hypothesised and tested associations between genetic, neurobiological, cognitive and behavioural factors and the role of the environment upon sociability will be described.

CHAPTER TWO

METHODOLOGY

2.1 Preface

In Chapter One, the literature investigating behavioural phenotypes, sociability and social cognition was reviewed and the rationale for investigating sociability and social cognition in individuals with CdLS, FXS and RTS was outlined. Chapters Three, Four and Five describe empirical studies investigating the profile of sociability, the development of social cognition and the influence of social cognitive abilities on components of sociability in CdLS, FXS and RTS. As data from these studies were collected within the same participants within the same timeframe and utilise many of the same assessments, this chapter will describe the methodology used across studies. The rationale for each study will be outlined in further detail in their respective chapters.

2.2. Method

2.2.1 Recruitment and Participants

The studies outlined in this thesis were part of a broader investigation of social cognition in CdLS, FXS and RTS. Participants were individuals with CdLS (N = 39; 22 females; M_{age} = 13.31 years, SD = 10.92), FXS (N = 38, no females; M_{age} = 15.09, SD = 12.45), and RTS (N = 32, 16 females; M_{age} = 16.72, SD = 13.54) between the age of two to 59 years. Cohorts included a wide range of ages and abilities to investigate sociability and social cognition across development. Participants were recruited via a participant database held by the Cerebra Centre of Neurodevelopmental Disorders (CNDD) at the University of Birmingham and via syndrome support groups. Table 2.1 outlines the number of families that were recruited via each method.

Individuals recruited through the CNDD database had taken part in previous research and had consented to be contacted with information about future studies. These individuals were initially sent information about the study via post. Within the following week, caregivers were contacted via telephone and asked whether they were interested in taking part. Participants recruited via syndrome support groups either contacted researchers in response to an advert placed in a newsletter or filled in an expression of interest form at family conferences.

Table 2.1.
Number of participants per syndrome who were recruited via each recruitment method

Syndrome	CdLS (*n* = 39)	FXS (*n* = 38)	RTS (*n* = 31)
CNDD database	10	18	5
Syndrome support group conference	22	11	24
Response to syndrome support group adverts	5	9	2
Referral from previous participants	2	0	0

Participants were included in the study if they had received a clinical diagnosis of their given syndrome by a paediatrician or a clinical geneticist. Participants older than 30 months were required to have a minimum communication and motor age equivalence of 15 months on the Vineland Adaptive Behavior Scales-II (Sparrow, Cicchetti & Balla, 2005; see section 2.2.2.2). Participants younger than 30 months were required to have a minimum non-verbal mental age of 12 months. Informed consent was collected from participants aged 16 years old or over and capable of consent, or from caregivers for participants under 16 years' olds. Individuals aged 16 years or older without the capacity to consent were not included as this study did not have approval from the ethical review board to include these individuals.

Table 2.2 shows that the overall sample of individuals with CdLS, FXS and RTS did not significantly differ in chronological or non-verbal mental age. Groups were not comparable on gender, due to girls with FXS being excluded from main analyses of this thesis for reasons outlined below. However, CdLS and RTS did not significantly differ on gender. As different participants were included in different analyses in Chapters Three to Five, participant characteristics included in each analysis will be reported separately in each chapter.

Table 2.2.
Participant characteristics for all participants with CdLS, FXS and RTS included in this thesis

	CdLS (n = 39)	FXS (n = 38)	RTS (n = 32)	p	Post-hoc tests (p<.05)
Mean chronological age in years (SD)	13.31 (10.92)	15.09 (12.45)	16.72 (13.54)	0.37	
Gender % female	56%	0%	52%	**<.001**	FXS < CdlS, RTS
Non-verbal mental age in years (SD)	3.80 (2.13)*	3.46 (1.10)**	3.40 (1.23)***	0.92	

* Information not available for three participants due to non-completion of the relevant measure

** Information not available for three participants due either to floor/ceiling performance (one participant)

*** Information not available for four participants due either to 1) floor/ceiling performance (one participant) or 2) non-completion of non-verbal scales of a cognitive assessment.

In addition to the sample included in table 2.2, data from six girls with FXS was collected. However, evidence of gender differences has been found in the typography and prevalence of social and behavioural difficulties and characteristics associated with ASD in individuals with Fragile X full mutation across the lifespan, as well as the genetic and environmental factors that influence these difficulties (Clifford et al., 2007; Hartley et al., 2011; Hessl et al., 2001; Hall et al., 2009). Differences were found in results when analyses were run with and without girls with FXS, suggesting it is inappropriate to analyse males and females with FXS in this study as a homogenous group. Therefore, results in the main body of text include only males with FXS. Summary tables of analyses including girls with FXS can be found in Appendix A.

2.2.2 Measures

2.2.2.1 Demographic Questionnaire.

A demographic questionnaire (Appendix B) was used to gain information on participant's characteristics such as age, gender, verbal ability, walking ability, diagnosis, living circumstances and socio-economic status.

2.2.2.2 Vineland Adaptive Behavior Scales-II (VABS-II, Survey Form; Sparrow et al., 2005).

The VABS-II (Appendix C) is a semi-structured interview conducted with caregivers, which assesses each participant's adaptive abilities in four main domains: communication, daily living skills, socialisation and motor skills. Age equivalent scores on the communication and motor scales were used to determine whether participant's verbal and non-verbal ability were high enough to participate in the study and contributed to the decision of which cognitive assessment was appropriate for that participant to take part in (see section 2.2.2.3).

2.2.2.3 Cognitive assessments.

As cohorts included individuals with a wide range of ages and ability, each participant's cognitive ability was assessed using either the Mullen Scales of Early Learning (MSEL: Mullen, 1995; suitable from birth to five years, eight months) or the British Ability Scales-III (BAS-III; Elliot & Smith, 2011; three years to 17 years, 11 months). These are standardised developmental assessments that evaluate verbal and non-verbal abilities.

There is a lack of cognitive assessments that have been normed and validated within populations with ID, or groups of participants' that include a wide range of ages and abilities. The *MSEL* and *BAS-III* were considered the most appropriate considering findings from Bishop, Guthrie, Coffing and Lord (2011), who demonstrated that the MSEL and the preschool form of the Differential Ability Scales (DAS; Elliot, 1990, 2007; the US normed version of the early year's form of the BAS) had good convergent validity on both verbal and non-verbal subscales in a sample of young children with iASD and those with non-spectrum conditions with ID. When the study began, these findings were the most recent data demonstrating convergent validity between cognitive assessments that span a range of abilities in populations associated with ID.

The *MSEL* consists of four subscales. The two subscales that assess verbal abilities include: 1) the receptive language subscale, which measures language comprehension and auditory memory and 2) the expressive language subscale, which measures speaking ability and language formation. The two subscales that assess non-verbal abilities are: 1) the visual reception subscale, which measures visual discrimination, memory and visual spatial awareness skills and 2) the fine motor subscale, which measures visual-motor skills and motor planning.

The *BAS-III* consists of two batteries: 1) *Early Years BAS-III* for children aged between 3:0 to 8:11 and 2) *School Age BAS-III* for children aged 6:0 to 17:11. Both batteries include a verbal ability, non-verbal reasoning ability and spatial domain. Participants only took part in the verbal and non-verbal domains. In the *Early Years* battery, the subscales that assessed verbal ability were: 1) *Verbal Comprehension*, measuring participant's receptive language through their understanding of basic concepts and spoken language and 2) *Naming Vocabulary*, measuring participant's expressive language by asking participants to identify

the names of pictures. The subscales that assessed non-verbal ability were: 1) *Picture Similarities*, measuring participant's ability to recognise similarities and relationships between pictures using non-verbal reasoning skills and 2) *Matrices*, measuring participant's ability to use rules and problem solving skills to recognise similarities and relationships between shapes. In the *School Age* battery, the subscales that assessed verbal ability were: 1) *Verbal Similarities*, measuring participant's receptive language ability by assessing their verbal reasoning and verbal knowledge and 2) *Word Definitions*, assessing participant's expressive language by assessing their ability to use expressive language to explain word meanings. The subscales that assessed non-verbal ability were: 1) *Quantitative Reasoning*, measuring the ability to recognise sequential patterns and relationships between number pairs using non-verbal reasoning skills and 2) *Matrices* (as outlined above).

The cognitive assessment a participant took part in was based on age equivalent scores on the communication and motor domains of the VABS-II and clinical judgement after meeting the participant. If a participant achieved floor or ceiling in a subscale in a domain, if time permitted, the participant was not too tired and (for individuals over 16 years) gave verbal consent, participants took part in the assessment that was appropriate for less/more able individuals respectively for the domain in which floor or ceiling effects occurred.

There are several ways to estimate and describe a participant's cognitive ability based on their scores from a cognitive assessment. Mervis and Klein-Tasman (2004) summarised three commonly used techniques researchers use when matching participants, including the use of: 1) standard scores, 2) raw scores or 3) age equivalents. The gold standard consists of calculating standard scores, in which t-scores are derived from each subscale's raw scores based upon a normed sample of individuals similarly aged to the participant. Standard scores are advantageous as they are measured on an interval scale, making them appropriate for

statistical comparisons and account for the influence of chronological age (Mervis & Klein-Tasman, 2004). However, many individuals included in the following studies had an ID and were often not able to succeed on tasks in the cognitive assessment appropriate for their chronological age. Normative data and t-scores were not available for individuals with a chronological age above five years, eight months who participated in the MSEL, or with a chronological age above 17 years, 11 months who participated in the BAS-III. However, mental age scores were used to compare overall ability between syndrome groups as this data was available in the greatest number of participants.

Due to practical and theoretical issues, non-verbal mental age equivalents are used in the following studies to capture participant's cognitive ability. Whilst data on both participant's verbal and non-verbal ability were assessed, many participant's performance showed ceiling and floor effects in a subscale. Some who participated in the BAS-III showed a pattern of ceiling effects on the *Early Years Naming Vocabulary* subscale (indicating a mental age of nine years or above) and floor effects on *School Age Word Definitions* (indicating a mental age of five years or below). This pattern of performance reflects differences in how these subscales measure expressive language. Whereas *Naming Vocabulary* assesses knowledge and memory of single words, *School Age Word Definitions* requires a greater level of verbal fluency and the ability to speak in sentences to describe the meaning of words. Participant's performance suggests these tasks assess dissociated abilities that fit under the umbrella of expressive language. In addition, many individuals with genetic syndromes show abnormal profiles of language ability relative to their overall cognitive ability dependent on their genetic syndrome, including individuals with CdLS, FXS and RTS (Fung et al., 2012; Mulder et al., 2016; Grados et al., 2017; Lorusso et al., 2007; Stevens et al., 1990; 2011), suggesting that non-verbal ability may provide a better estimate of overall

ability in comparison to verbal ability. Therefore, an overall non-verbal mental age was calculated from the mean of participant's age equivalents on the two non-verbal subscales of the cognitive assessment they participated in.

2.2.2.4 Behavioural assessments.

2.2.2.4.1 Autism Diagnostic Observation Schedule, 2nd edition (ADOS-II; Lord et al., 2012).

The ADOS-II is a semi-structured standardised observational assessment of communication, social and play skills for a range of ages and developmental abilities. It is considered the 'gold standard' observational assessment for autism spectrum disorders. Participants partake in one of five modules (toddler/T to module four), each with a different set of standardised social presses that are appropriate for each participant's expressive language ability and chronological age. These activities press for behaviours associated with ASD and were administered and scored by a research reliable trained examiner. Item scores range from 0 (no abnormalities) to 3 (pronounced abnormality). Specified items contribute to an algorithm which provides overall scores for *Social Affect* and *Restricted and Repetitive Behaviours* subscores. These subscales correspond with the two diagnostic domains of ASD (American Psychiatric Association, 2013) and the subscale scores are added together to make a total score. For each module, there are two cut off scores (autism spectrum and autism). Each subscale score and the total score can be used to calculate a severity score (CSS), providing a comparison of severity of autism symptoms relative to a sample of individuals with autism and the same chronological age as the participant. CSS range from scores of 1 (indicating a low level of ASD symptomatology) to 10 (indicating a high level of symptomatology). As the focus of this thesis is social behaviour in individuals with CdLS, FXS and RTS, any reference to 'severity scores' refer to *Social Affect* subscale CSS. In

addition, the terms 'ASD symptomatology' refers to behaviours that fall under the *Social Affect* subscale. ADOS-II footage was also coded with the *Child Sociability Rating Scale*.

2.2.2.4.2. The Child Sociability Rating Scale (CSRS; Moss et al., 2013).

The *CSRS* is an observational rating scale consisting of items assessing operationalised social interaction skills and behaviours indicative of frequency and quality of social enjoyment, social interaction skills and social motivation in children with ID, during social interactions with either a familiar or unfamiliar adult (Appendix D). The *Social Enjoymen*t domain includes three items (*Positive Emotional Affect, Social Responsiveness,* and *Negative Emotional Affect*). The *Social Motivation* domain includes five items (*Motivation for Adult Engagement, Spontaneous Initiation of Interaction, Focus of Attention, Frequency of Spontaneous Physical Contact,* and *Nature of Spontaneous Physical Contact)*. The *Social Interaction Skills* domain includes four items (*Frequency of Eye Contact, Nature of Eye Contact, Social Communication Style,* and *Quality of Social Communication*). Finally, the *Social Discomfort* domain includes two items (*Avoidance of Social Interaction* and *Social Anxiety*). Each item was rated using a five-point Likert scale ranging from zero (very low instances of the behaviour) to four (very high instances). Participants' behaviour was coded for each ten-minute segment of their ADOS-II footage. Paired items describing either the frequency or nature of a behaviour, such as *Frequency of Eye Contact* and *Nature of Eye Contact*, as well as *Social Communication Style* and *Quality of Social Communication Style* were combined and rescaled to make a composite item (*Social Communication Style* and *Social Communication Skills* respectively) scoring between 0-4. Combined items were rescaled using the following criteria: 0 = 0, 1-4 = 1, 6-8 = 2, 9-12 = 3, 13-16 = 4.

2.2.2.4.2.1. Concurrent validity for higher functioning participants.

Although the *CSRS* was originally designed for children, the items were considered appropriate for older and higher functioning individuals. To test this assumption, concurrent validity was explored between *CSRS* item scores and the duration of operationalised social interaction skills and behaviours coded from a previous sample of 37 verbal and mobile adults and adolescents with CdLS and Down syndromes during interaction with a familiar and unfamiliar adult (Nelson et al., 2017). The following items from the *CSRS* and corresponding behaviours respectively included: *Positive Emotional Affect* (against duration of positive affect) *Eye Contact (*against duration participants looks at adult) and *Quality of Social Communication Style* (against duration of verbalisation). Pearson's and Kendall-Tau correlations revealed moderate to strong correlations (.53-.70) between the relevant *CSRS* and observational items, which were all significant at a $p < .01$ level (table 2.3).

Table 2.3
Pearson's and Kendall-Tau coefficients between items on the CSRS and duration of observable behaviours during interaction with a familiar and unfamiliar adult

CSRS item	Observable behaviour	Familiar	Unfamiliar
Positive Emotional Affect	Duration of positive affect	.55	.53
Eye contact	Duration participant looks at adult	.65	.56
Quality of social communication style	Duration of verbalisation	.61*	.70*

* Run with Pearson's correlations as these data were normally distributed

2.2.2.4.2.2. CSRS inter-rater reliability.

Inter-rater reliability between two raters was calculated for 20% of the sample using intra-class correlations on each item. The mean level of agreement across behaviours was .89

(range: .76 to .98) indicating a good level of inter-rater reliability. All items reached a .60 cut-off point.

2.2.2.4.3. Social cognitive batteries

Social cognitive development was assessed by two batteries which evaluate the range of abilities across development as outlined in section 1.6.1 (Figure 2.1). These tasks are practical for research involving individuals with genetic syndromes and in common with similar validated test batteries (e.g. Mullen Scales of Early Learning) (Mullen, 1995) they include simple transportable materials that require only two experimenters (Powis, 2014; Powis et al., in revision). These useful properties have advantages over more technical methodologies (e.g. eye tracking or reaction time tasks) by: 1) enabling families to participate even if they could not visit the University as the researchers could visit them at their homes and 2) not requiring participants to remain still or pay attention for long periods of time per task. The latter is important considering the attention difficulties observed in these syndromes and in individuals with ID more broadly (Powis, 2014; Grefer et al., 2016; Scerif, Cornish, Wilding, Driver & Karmiloff-Smith, 2006).

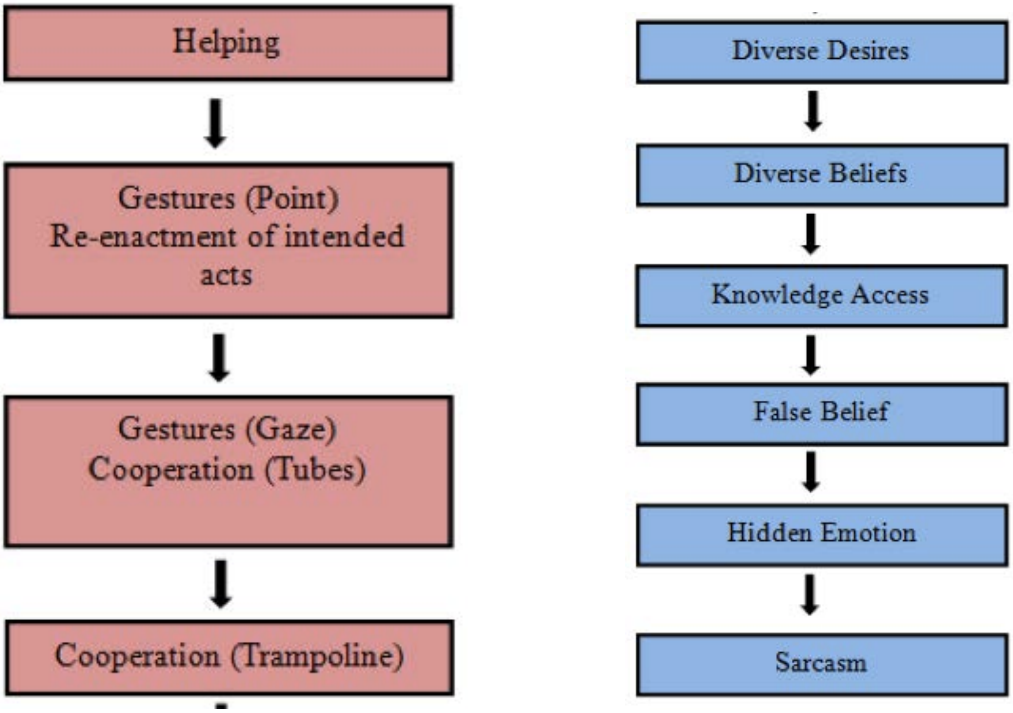

Figure 2.1. *Developmental order of tasks included in the ESCS and the ToMS.*

2.2.2.4.3.1 The Early Social Cognition Scale (ESCS; Powis, 2014; Powis et al., in revision).

The *ESCS* is a battery of tasks administered by two experimenters that assess intentionality abilities that typically emerge between the ages 14 to >24 months. Powis and colleagues (2014; in revision) found that TD infants pass six non-verbal tasks that assess different intentionality abilities taken from previous literature in a stringent and cumulative developmental order (figure 2.1). These findings provide a normative benchmark that the performance of children with CdLS, FXS and RTS can be compared against. Tasks include (in order of TD attainment): *'Helping'*, *'Re-enactment of Intended Acts'* and *'Gestures-Pointing'*, *'Gestures-Gaze'* and *'Cooperation – Tubes'* and *'Cooperation – Trampoline'*. Abilities assessed in the *ESCS* range from understanding of basic goal directed actions

(*Helping*), up to tasks assessing whether children have developed a 'shared intentionality' that enables them to cooperate with another person (*Cooperation* tasks).

Participants are coded either a 'pass' or 'fail' for each task. Three tasks (*Helping* and both *Gestures* tasks) include control trials that are analysed separately from experimental trials in Chapter Four to check participants produced target behaviours following interpretations of an experimenter's intention rather than reinstating the original situation (*Helping*) or due to low level attentional cues (*Gestures*). Table 2.4 summarises the ability assessed, passing criteria and any corresponding control trials for each task. Full descriptions of tasks can be seen in Appendix E.

Table 2.4

Ability assessed, passing criteria and control trials for each task in the ESCS (Powis, 2014; Powis et al., in revision)

Task	Ability assessed	Passing criteria	Corresponding control trial procedure
Helping	Whether the participant understands another person's basic intention and unachieved goals and show motivation to help that person achieve that goal	The infant picks up an item (either a pen or a polystyrene cone) that the experimenter reaches towards, which is close to the participant but out of reach from the experimenter and gives it to the experimenter, without any explicit prompts, in at least one out of two experimental trials.	Control trials follow the same procedure for each corresponding experimental trial, except the examiner does not reach for the item.
Re-enactment of Intended Acts	Whether the participant understands another person's intentions by interpreting that person's goal-oriented, but unsuccessful action	The infant must carry out the examiner's intended act, rather than imitating the examiner's failed actions, in two out of three trials.	
Gestures – Point	Whether the participant understands that a communicative pointing gesture from experimenter two that indicates where experimenter one has hidden an object is intentionally directed towards the participant and is relevant to the current context.	The infant must choose the correct box with the toy hidden inside in both experimental trials, in which the second examiner indicates the location of the toy with a communicative and intentional pointing gesture.	Control trials follow the same procedure as experimental trials, except experimenter two does not indicate where the toy is hidden and instead experimenter one directs a non-intentionally, non-communicative distracted point towards where the object is hidden.

Gestures – Gaze	Whether the participant understands that a communicative gaze gesture from experimenter two that indicates where experimenter one has hidden an object is intentionally directed towards the participant and is relevant to the current context.	The infant must choose the correct box with the toy hidden inside in both experimental trials, in which the second examiner indicates the location of the toy with a communicative and intentional gaze gesture.	Control trials follow the same procedure as experimental trials, except experimenter two does not indicate where the toy is hidden and instead experimenter one looks towards where the object is hidden in a non-intentional, non-communicative way.
Cooperation – Tubes	Whether an infant can form a shared intentionality and cooperate with another person to achieve a joint goal in a problem-solving game to retrieve an object from inside a tube with handles, in which both partners must pull a handle from one side each to open the tubes.	The infant must: 1) show sufficient coordination to open the tubes with the examiner across all four trials and 2) show at least one attempt to reengage the examiner to complete the task during two interruption periods in which the examiner stops performing their role.	
Cooperation – Trampoline	Whether an infant can form a shared intentionality and cooperate with another person to achieve a joint goal in a social game, in which both partners must hold onto one side of a trampoline and bounce a block together.	The infant must: 1) be sufficiently engaged and successfully bounce the block on the trampoline with the examiner across all four trials and 2) show at least one attempt to reengage the examiner to complete the task during two interruption periods in which the examiner stops performing their role.	

2.2.2.4.3.2 The Theory of Mind Scale (ToMS; Peterson et al., 2012).

The *ToMS* includes tasks that assess children's abilities to explicitly reason and understand a range of other people's mental states and use this understanding to predict that person's behaviour. Children aged between three to 11 years old passed in a stringent cumulative developmental order. Tasks include (in order of TD attainment) '*Diverse Desires', 'Diverse Beliefs', 'Knowledge Access', 'Contents False Belief', 'Hidden Emotion'* and *'Sarcasm'* (figure 2.1). Abilities assessed in the *ToMS* range from basic understanding that others can have different desires from their own (*Diverse Desires)* to the complex ability of identifying when someone is making a nonliteral comment (*Sarcasm*). All tasks followed a similar format and used similar materials, but differed in the type of mental state the task assessed. In each task, participants were told a story about an agent that provided some information about that agent's mental state, using figurines and pictures. Participants were then asked a target question that required participants to use their understanding about that agent's mental state. Some tasks (*Knowledge Access, Contents False Belief, Hidden Emotion* and *Sarcasm*) included control questions to assess participant's overall comprehension of the task. Participants are coded either a 'pass' or 'fail' for each task. To pass each task, participants had to answer target and (if applicable) control questions correctly. Table 2.5 summarises the ability assessed, passing criteria and any corresponding control trials for each task. Full descriptions of tasks can be seen in Appendix F.

Table 2.5

Ability assessed, passing criteria and control questions for each task in the ToMS (Peterson et al., 2012)

Task	Ability assessed	Target question passing criteria	Corresponding control question
Diverse Desires	Whether a participant can predict an agent's actions by inferring that agent's desire based upon previous knowledge of that agent's preferences and understand that the agent's desire about an object differs to their own	Correctly identify which snack (between two options) that the agent would choose, after learning about that agent's preference.	
Diverse Beliefs	Whether a participant can predict an agent's actions based on knowledge about that agent's belief of the location of something, when the participant has no knowledge of the true location themselves and the participant's belief conflicts with the agent's	Correctly identify where an agent will 'look for their cat' based on information about where that agent believes the cat is.	
Knowledge Access	Whether a participant can assess an agent's knowledge and/or ignorance about an object based on information about that agent's previous experiences with the object	Correctly identify that an agent doesn't know what is in a drawer based on information that the agent has never seen inside the drawer before	To check whether participants remembered key components of the story, they were asked a memory question ("did Polly see inside the draw?")

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Contents False Belief	Whether a participant can predict an agent's beliefs about the contents of a container based on knowledge about that agent's experience with the container, even when that agent's belief conflicts with reality and the participant's own belief	Correctly identify that the agent will think there are smarties in a smarties tube, even when the participant has seen there are instead pencils inside, based on knowledge that the agent has not seen inside the box before.	To check whether participants remembered key component of the story, they were asked a memory question ("did Peter see inside the box?")
Hidden Emotion	Whether a participant can distinguish between the emotion an agent is experiencing (real) and the emotion which they are outwardly expressing (apparent) even when those emotions contrast to one another.	Correctly identify the real emotion the agent is experiencing (sad) and the emotion that the agent is outwardly expressing (happy or 'just ok').	To check whether participants remembered key component of the story, they were asked two memory questions ("what did the other children do when Rosie told a mean joke about Matt?" and "In the story, what would the other children do if they knew about Matt felt?")
Sarcasm	Whether a participant can understand social inference i.e. the communicative intent behind another individual's non-literal statement	Correctly identify that an agent was being sarcastic (e.g. "was being sarcastic", "she didn't mean it", "was joking") when commenting "it was a lovely day for a picnic" when it was raining.	Participants comprehension of the story was assessed with a reality question ("was it true, what the girl said?") and a question about the girl's emotions about the scenario ("was the girl happy about the rain?")

2.2.2.4.3.3 Social cognitive scales inter-rater reliability

All *ESCS* and *ToMS* tasks that each participant took part in were coded in vivo at the time of the session. 46% of video recordings of the *ESCS* and 23% of video recordings from the *ToMS* were also coded by an examiner who was blind to the participant's diagnoses. Cohen's Kappa was used to determine level of agreement on each item between scores coded in vivo and those coded from video recordings. The mean level of agreement for the *ESCS* was .9 (ranging .71 – 1.0). Kappa levels of agreement for *ToMS* indicated a perfect level of agreement. As such, codes scored in vivo were considered reliable and were used in subsequent data analyses.

2.2.3 Procedure

Individuals were assessed either at the Cerebra Centre at the University of Birmingham, at their home and/or at syndrome family support group conferences. Prior visits to the University or at their home, questionnaires were mailed to caregivers to fill out and the VABS-II was administered with the caregiver via telephone one week before. During home and university visits, typically the cognitive assessment was first administered, followed by the social cognitive scales and finally the ADOS-II. Individuals who took part at conferences first participated in the social cognitive scales, followed by a University or home visit to complete the remaining assessments.

2.2.3.1 Social cognition batteries procedure.

As the social cognitive scales in combination covered tasks that spanned a wide range of abilities, the scale that each participant started on depended on their receptive verbal ability following the cognitive assessment. Individuals with a receptive language ability of below three years began on the *ESCS* (point A – outlined below) and those three years or above began on the *ToMS* (point B). The aim of these two starting points was to: 1) prevent

participants from becoming disengaged or frustrated due to tasks being too easy or difficult and 2) allow flexibility when participants either reach ceiling in the *ESCS* or floor on the *ToMS*, to get the most full and accurate description of participant's social cognitive development.

Participants starting at point A participated in all tasks in the *ESCS* in one of the orders displayed in table 2.6. The six tasks were split into two halves. The tasks within these groups were counterbalanced so that they were not in the same ordinal position and do not follow the same task more than twice. The first half was administered first and consisted of the three easiest tasks (i.e. *Helping*, *Re-enactment of Intended Acts* and *Gestures – Point*). The second half was then administered, consisting of the two more difficult tasks (i.e. both *Cooperation* tasks). The *Helping* experimental and control conditions were split between the two halves. The control was always administered in the first half, as it was considered that if administered first the experimental condition may prime helping behaviour in the control (Powis, 2014, Powis et al., in revision). Although *Gestures-Gaze* is typically considered the same difficulty as *Cooperation–Tubes*, it was placed in the first half because it could only be administered at the same time as *Gestures-Point*, which is easier. If participants passed two out of three of the most difficult tasks (i.e. *Gestures-Gaze*, *Cooperation – Tubes* and *Cooperation – Trampoline*), they continued onto point B and proceeded as outlined below.

Table 2.6

Counterbalanced orders of tasks in the Early Social Cognition Scale

Order 1	Order 2	Order 3	Order 4	Order 5	Order 6
Re-enactment of Intended acts	*Helping (control)*	*Helping (control)*	*Re-enactment of Intended acts*	*Gestures (Point & Gaze)*	*Gestures (Point & Gaze)*
Helping (control)	*Re-enactment of Intended acts*	*Gestures (Point & Gaze)*	*Gestures (Point & Gaze)*	*Re-enactment of Intended acts*	*Helping (control)*
Gestures (Point & Gaze)	*Gestures (Point & Gaze)*	*Re-enactment of Intended acts*	*Helping (control)*	*Helping (control)*	*Re-enactment of Intended acts*
Cooperation –Tubes	*Cooperation - Trampoline*	*Helping (experimental)*	*Cooperation –Tubes*	*Cooperation - Trampoline*	*Helping (experimental)*
Cooperation - Trampoline	*Cooperation –Tubes*	*Cooperation - Trampoline*	*Helping (experimental)*	*Helping (experimental)*	*Cooperation –Tubes*
Helping (experimental)	*Helping (experimental)*	*Cooperation –Tubes*	*Cooperation - Trampoline*	*Cooperation –Tubes*	*Cooperation - Trampoline*

Participants starting at point B followed one of the counterbalanced orders in table 2.7. The procedure and rationale of the counterbalancing was the same as for the *ESCS.* Whether participants carried out all tasks on the *ToMS* was contingent on their initial performance. Participants who passed two out of three of the first easiest tasks continued onto the second group of tasks of the *ToMS.* Those who did not continued onto point A and followed the procedure from this point up until they reached point B.

Table 2.7
Counterbalanced orders of tasks in the Theory of Mind Scale

Order 1	Order 2	Order 3	Order 4	Order 5	Order 6
Diverse Desires	*Diverse Desires*	*Diverse Beliefs*	*Diverse Beliefs*	*Knowledge Access*	*Knowledge Access*
Diverse Beliefs	*Knowledge Access*	*Knowledge Access*	*Diverse Desires*	*Diverse Desires*	*Diverse Beliefs*
Knowledge Access	*Diverse Beliefs*	*Diverse Desires*	*Knowledge Access*	*Diverse Beliefs*	*Diverse Desires*
Sarcasm	*Contents False Belief*	*Sarcasm*	*Contents False Belief*	*Hidden Emotion*	*Hidden Emotion*
Hidden Emotion	*Sarcasm*	*Contents False Belief*	*Hidden Emotion*	*Sarcasm*	*Contents False Belief*
Contents False Belief	*Hidden Emotion*	*Hidden Emotion*	*Sarcasm*	*Contents False Belief*	*Sarcasm*

Only one child with FXS who took part in the *ESCS* deviated from this pattern in which the *Cooperation* tasks, a task considered as more engaging than some of the easier tasks (Powis, 2014) was administered first due to the child showing a lot of anxiety when visiting the University. The alternative order they participated in was: *Cooperation-Trampoline, Cooperation-Tubes, Helping (Control), Gestures, Re-enactment of Intended Acts, Helping (experimental).*

CHAPTER THREE

AN EXPERIMENTAL STUDY OF SOCIABILITY IN CORNELIA DE LANGE, FRAGILE X AND RUBINSTEIN-TAYBI SYNDROMES

3.1. Preface

In Chapter One, the importance of phenomenological descriptions of behavioural phenotypes and sociability in genetic syndromes was outlined. Individuals with profiles at both ends of the continuum of sociability show atypical social interaction and are socially vulnerable. Previous research suggests that individuals with CdLS, FXS and RTS have distinct behavioural phenotypes characterised by differences in social functioning. The aim of this study is to directly assess and compare the broader profile of sociability in CdLS, FXS and RTS through direct observations of a broad range of operationalised social interaction skills and behaviours that are indicative of social enjoyment, social motivation, social interaction skills and social discomfort. I will compare sociability across syndromes on a broad level and describe the associations between components of sociability in CdLS, FXS and RTS and factors that previous literature indicates may influence sociability in these syndromes, including duration of time spent interacting with the examiner, participant's chronological age and ASD symptomatology. Describing these associations is important for developing more complete models of sociability in individuals with CdLS, FXS and RTS.

3.2. Introduction

3.2.1. Investigating profiles of sociability in genetic syndromes

Chapter One outlined how the term "sociability" has lacked a consistent definition in both the typically and atypically developing literature. This thesis adopts Cook and Oliver's (2011) framework, in which sociability is an umbrella term that encompasses a broad range of social skills and behaviours that contribute to an individual's social competence. To investigate sociability in CdLS, FXS and RTS, this study will assess observable behavioural responses that occur within social contexts (Moss et al., 2016) that are indicative of the frequency and *quality* of social interaction skills (i.e. eye contact and social communication skills) and social behaviours (indicative of social enjoyment, social motivation and social discomfort). These social interaction skills and behaviours are considered as the components of the profile of sociability in this thesis.

Most research investigating social interaction skills and behaviours in genetic syndromes has focused on ASD phenomenology in these groups and the consequent cognitive and neurobiological underpinnings that lead to difficulties in those with iASD (e.g. Mulder et al., 2016; Grados et al., 2017; Moss et al., 2013; Hogan et al., 2017; Waite et al., 2015; Davenport et al., 2016; Galéra et al., 2009; Powis, 2014; Davenport et al., 2016). Whilst understanding the presentation and nature of ASD in genetic syndromes has clinical implications, characteristics not diagnostic of ASD are nevertheless important for successful social interaction. Studies assessing social behaviour not specific to ASD in genetic syndromes have focused on individual behaviours. Examples include eye gaze in CdLS, FXS and RTS (Crawford, Moss, Anderson, Oliver & McCleery, 2015; Hall, Lightbody, Huffman, Lazzeroni & Reiss, 2009), frequency of social initiation in FXS, Angelman and Smith-Magenis syndromes (Roberts, Weisenfeld, Hatton, Heath & Kaufmann, 2007; Horsler &

Oliver, 2006; Wilde, Silva & Oliver, 2013; Crawford et al., in prep; Moss et al., 2013), frequency of social avoidance in FXS (Hall et al., 2009) and social anxiety in CdLS, FXS, RTS and Turner syndrome (Crawford et al., in prep; Richards et al., 2009; Lesniak-Karpiak et al., 2003). However, there has been little direct observational investigation into the broader profiles of sociability that characterise the nature and quality across a range of social interaction skills and behaviours in individuals with genetic syndromes.

Moss and colleagues (2016) describe the development of the Sociability Questionnaire for People with Intellectual Disability (SQID), a questionnaire that assesses sociability (defined by operationalised behaviours indicative of social motivation, social enjoyment and social anxiety) in different genetic syndromes across a range of defined social contexts. Based on these findings, syndromes were placed on a "continuum of sociability". Individuals with RTS, Angelman and Down syndromes scored significantly higher (indicating greater sociability) than individuals with iASD, CdLS and FXS with both familiar and unfamiliar adults and across a range of social contexts. However, carers' responses to questions regarding an individual's behaviour are subjective, and subject to bias and issues with retrospective recall. In addition, groups were not matched on several key variables that are likely to influence sociability including age and ability. Differences in these variables may have driven the reported differences in sociability instead of syndrome.

Therefore, in this study I aim to assess profiles of sociability in CdLS, FXS and RTS, genetic syndromes with unique social profiles, using robust observational assessments of operationalised behaviours indicative of social interaction skills and behaviours, who are comparable on age and ability. The *"Child Sociability Rating Scale"* (*CSRS*: Moss et al., 2013) is an observational behaviour rating scale that assesses the quality of behaviours indicative of social interaction skills, social enjoyment, social motivation and social

discomfort. Whereas other observational assessments have focused on a narrow range of behaviours such as social anxiety (Crawford et al., in prep; Lesniak-Karpiak et al., 2003), social approach (Roberts et al., 2007), eye contact (Hall & Venema, 2017) or joint attention (Mosconi, Reznick, Mesibov & Piven, 2009), the *CSRS* aims to capture the social profiles of syndromes more broadly, and has previously shown divergent profiles of sociability between individuals with CdLS, Angelman and Cri du Chat syndromes (Moss et al., 2013).

3.2.2. Investigating change in sociability when interacting with someone over time

In Chapter One, the importance of outlining environmental influences on behavioural phenotypes to better explain within syndrome variation (Oliver & Woodcock, 2008) and identifying the contexts in which behaviours occur for specific syndromes was described. Interventions can subsequently modify the specified environment or develop an individual's coping skills to help them adapt to that environment. I aim to compare the relatively unexplored effect of duration of time spent interacting with an examiner during social interaction on social interaction skills and behaviours between individuals with CdLS, FXS and RTS.

Behaviours shown by individuals with CdLS, FXS and RTS are influenced differentially across different environments. Crawford and colleagues (in prep) assessed observational behaviours indicative of social anxiety and social motivation in individuals with CdLS, FXS, RTS and Down syndrome across a range of social contexts whilst interacting with either a familiar or unfamiliar adult. Although overall levels of social anxiety were comparable between CdLS, FXS and RTS, only social anxiety in individuals with CdLS was mediated by the social situation and the familiarity of the adult they were interacting with. Individuals with CdLS showed more behavioural indicators of social anxiety when given

opportunities to initiate interaction, particularly when interacting with an unfamiliar adult. In comparison, the levels of social anxiety in individuals FXS and RTS were stable across contexts. Overall participant's level of social motivation did not differ across syndrome groups and all groups initiated more interactions during the voluntary social interaction condition compared to other conditions. However, individuals with CdLS showed less initiations of interaction compared to individuals with DS during the voluntary interaction condition.

These findings led to hypotheses about the potential underlying cognitive mechanisms influencing social anxiety in those with CdLS. Despite showing motivation to interact, these individuals may become more anxious during voluntary interaction as it is less structured and more unpredictable than other conditions. As adults and adolescents with CdLS show executive function (EF) deficits relative to their overall cognitive ability (Reid, Moss, Nelson, Groves, & Oliver, 2017), unpredictable environments may be more difficult as they place greater demand upon executive function. The lack of social initiations in individuals with CdLS during the voluntary interaction condition (Crawford et al., in prep) may reflect an attempt to escape or avoid interaction. In contrast, social anxiety in those with FXS and RTS is generalised across social situations. These findings demonstrated how detailed descriptions of the environments in which distinct behaviours occur can elucidate potential causal mechanisms underpinning behavioural difficulties in specific syndromes.

Recent literature suggests that the time spent interacting with another person may influence components of sociability in some genetic syndromes. Hall and colleagues (2009) found that children with FXS showed less gaze avoidance over a twenty-five-minute interaction with an unfamiliar examiner where participants were repeatedly prompted to look at the examiner's face. Roberts and colleagues (2007) found that children with FXS showed

more social approach behaviours towards the examiner (including eye contact) over the course of an assessment day. Overall, results suggest that although individuals with FXS may initially struggle with social interaction, they are motivated to interact (Crawford et al., in prep) and will "warm-up". Social anxiety could potentially be reduced through exposure to social interaction and repeated prompts in individuals with FXS (Hall et al., 2009).

Although the influence of time spent interacting with another person upon social behaviour has not been directly assessed in individuals with CdLS or RTS, their social behaviour is differentially influenced by level of familiarity of whom they interact with. Adults and adolescents with CdLS are less likely to initiate speech (Nelson et al., 2017), social interactions and show more social anxiety when interacting with an unfamiliar than a familiar adult, whereas individuals with RTS did not show any differences in behaviours indicative of social anxiety or social motivation (Crawford et al., in prep). Similar findings have been reported in day-to-day contexts using the SQID. Individuals with CdLS show more sociability when initiating and receiving social interaction with familiar adults compared to individuals iASD and FXS, but show similar levels to these groups when interacting with unfamiliar adults. In contrast, individuals with RTS showed similar levels of sociability with both familiar and unfamiliar adults (Moss et al., 2016). These findings suggest that like individuals with FXS, quality of social interaction skills and behaviours in individuals with CdLS may improve the more time they spend (and thus the more familiar they become) with someone, whereas individuals with RTS are not influenced by level of familiarity of who they are interacting with. Similarities and differences in "warm-up" effects may be driven by similarities (between individuals with CdLS and FXS) and differences (RTS) in their behavioural phenotypes, such as prevalence of ASD (Oliver et al., 2011; Powis, 2014) or sociability (Moss et al., 2016).

3.2.3 Changes in sociability with age

Behavioural phenotypes in some genetic syndromes change with age. For example, individuals with Angelman syndrome show a decline in sociability across childhood (Adams et al., 2011; 2015) and adults with Down syndrome show cognitive and behavioural deterioration related to early onset of Alzheimer's disease (Hithersay et al., 2017; Ball et al., 2006). Investigating these changes is important as cross-syndrome comparisons at group level in cohorts that include a wide range of ages may mask important clinical changes within a group (Oliver et al., 2013). Identifying when and what causes these changes helps target the neurobiological pathways that underpin these changes within specific syndromes at the critical time point.

Previous literature indicates a range of changes in behaviour with age specific to individuals with CdLS. Cross-syndrome comparisons indicate a decline in parent rated sociability when interacting with an unfamiliar adult from childhood into adolescence on a group level in individuals with CdLS but not in those with FXS or RTS (Moss et al., 2016). Similarly, Moss and colleagues (2017) found that older individuals with CdLS who were NIPBL positive were reported to show lower mood and greater insistence in sameness. Other difficulties found more prevalent in adults with CdLS when compared to children include heightened levels of impulsivity and negative affect (Oliver et al., 2011), communication difficulties (Wulffaert et al., 2009), anecdotal reports of the onset of aggression and destruction of property in adolescence in those who are mildly affected (Oliver et al., 2013).

Whilst many individuals with CdLS reach cut-off scores on clinical assessments of ASD (Moss et al., 2013), changes with age in individuals with CdLS appear to be unrelated to ASD symptomatology. Basile, Villa, Selicorni and Molterni (2007) found increases in disruptive behaviour and behavioural difficulties with age but no association between

chronological age and prevalence of ASD. Similarly, Nakanishi and colleagues (2009) found no differences in ASD symptomatology across individuals with the mild to moderate CdLS phenotype across age groups. Cochran and colleagues (2015) found that parent reported ASD severity did not change over a 2.5-year period in individuals with CdLS, although this contrasts with the finding that significantly more individuals with CdLS over the age of fifteen years met the cut-off criteria for ASD compared to those under the age of fifteen.

These findings suggest that aetiological mechanism associated with these changes are not the same as those underpinning ASD symptomatology in individuals with CdLS. Increases in social difficulties with age may reflect deterioration in executive function skills observed in adolescents and adults with CdLS (Reid et al., 2017; Johnson, 2015). This deterioration would make daily tasks and social interaction more unpredictable and difficult, leading to lower mood and social withdrawal (Oliver et al., 2013). Deterioration in executive function skills may be underpinned by genetic mutations that lead to dysregulated protein expression on the cohesion pathway that cause CdLS, which cause increased oxidative stress and reduced DNA repair (Gimigliano et al., 2012) and have been implicated in cognitive and behavioural changes in individuals with CdLS (Oliver et al., 2013; Kline et al., 2007). These neurobiological changes may similarly influence sociability more broadly in individuals with CdLS.

Studies investigating changes with age in individuals with FXS have focused on ASD symptomatology using parent report measures. Cochran and colleagues (2015) found that individuals with FXS of a wide range of ages showed less severe ASD-related social impairments over time and there were no differences in age bands in the number of participants reaching cut-off scores of ASD. However, the overall literature investigating ASD symptomatology across age in individuals with FXS is variable (O'Brien & Bevan,

2011), with other longitudinal studies showing that whilst ASD classification remained stable, ASD symptomatology significantly increased over several time points within two years in infants with FXS (Hatton et al., 2006).

Studies investigating other aspects of the behavioural phenotype in FXS indicate the developmental profile of social behaviours is mixed. Oliver and colleagues (2010) found that positive affect was prominent in adults, but not children, with FXS when compared to a range of individuals with different genetic syndromes. In contrast, in a cross-sectional study, Hartly and colleagues (2015) found that whilst ASD classification did not differ across age groups in adults with FXS ranging from 18 to 40 years, these individuals showed a trend towards decreased disruptive behaviour with age. Roberts and colleagues (2007) found that older males with FXS showed less physical approach behaviours and poorer eye contact than younger individuals. However, the lack of a comparison group makes it difficult to discern whether this change is specific to individuals with FXS, or whether the reduction of physical contact may be developmentally appropriate as individuals age.

The few studies that have assessed age-related changes in social behaviour in individuals with RTS have relied on carer reports. Moss and colleagues (2016) did not find any age differences in sociability between age bands of individuals with RTS. In contrast, Stevens and colleagues (2010) found that caregivers reported a decrease in social interaction and more limited speech in a survey of adults with RTS and anecdotal reports indicate sudden mood changes, anxiety and aggressiveness as individuals reach adolescence (Hennekam, 2006; Milani et al., 2015). In addition, Yagihashi and colleagues (2012) found that a group of older individuals aged fourteen years or above with RTS showed significantly higher rates of carer reported anxiety, depression and aggressive behaviour in comparison to a younger group. However, as these studies often include adolescents or younger adults with RTS with

no comparison groups, these changes may be developmentally appropriate for individuals entering puberty.

Overall, findings indicate that individuals with CdLS, FXS and RTS show different patterns of associations between different social behaviours and ASD symptomatology and age, even in syndromes that demonstrate similar risk for ASD i.e. CdLS and FXS (Oliver et al., 2010; Cochran et al., 2015; Moss et al., 2016). These differences in behavioural phenotypes within syndromes would have been masked by total group comparisons (Oliver et al., 2013). Problematic changes with age have also been reported in individuals with RTS, a syndrome not typically associated with difficulties in social interaction skills and behaviours (Galéra et al., 2009). However, previous literature has produced mixed findings, which may reflect the heavy reliance upon carer-report questionnaires to assess social behaviour (Moss et al., 2016; 2017; Wulffaert et al., 2009; Basile et al., 2007; Nakanishi et al., 2012; Cochran et al., 2015; Hatton et al., 2006; Hartley et al., 2015; Hennekam, 2006; Yagihasi et al., 2012), which are subject to bias and retrospective recall. Many studies lacked a comparison group (Wulffaert et al., 2009; Basile et al., 2007; Nakanishi et al., 2012; Hartley et al., 2015; Roberts et al., 2007; Hennekam, 2006; Yagihasi et al., 2012), making it difficult to determine what changes are phenotypic to a syndrome and which are developmentally appropriate. In this study, I will investigate the association between observable social interaction skills and behaviours and age across individuals with CdLS, FXS and RTS who are comparable on age and ability.

3.2.4. The association between ASD symptomatology and sociability

Individuals with CdLS and FXS have a heightened likelihood of reaching clinical cut-off scores on assessments of ASD (Moss et al., 2013; Davenport et al., 2016; Oliver et al., 2011), whereas individuals with RTS have a lower risk of ASD compared to individuals with CdLS and FXS (Powis, 2014). As ASD is a neurodevelopmental disorder (DiCicco-Bloom et al., 2006), subtle differences in ASD profiles in genetic syndromes may reflect neurobiological processes that underpin specific ASD-related presentations or difficulties, from genetic abnormality to behaviour (Oliver et al., 2010).

However, genetic syndromes associated with high scores on measures of ASD have shown that social interaction and communication skills differ to those with iASD. High scores on measures of ASD are driven more by communication difficulties in CdLS than those with iASD (Moss et al., 2008) and changes with age in individuals with CdLS do not correspond with the trajectory of ASD symptomatology in this group (Basile et al., 2007). Fine-grained phenomenological differences may indicate that whilst behaviours in individuals with CdLS and FXS may be broadly ASD-*like,* subtle differences in distinct behaviours between these syndromes and iASD may indicate their underlying aetiology may be different from one another. Whilst boys with FXS+ASD show similarities in showing, giving, and initiating joint attention, they show less impairments in social smiling, facial expression, response to joint attention, gaze integration and quality of social interactions (McDuffie et al., 2015; Wollf et al., 2012) and greater impairments in pragmatic language skills (Martin et al., 2017) compared to boys with iASD. These phenomenological similarities and differences may highlight which behaviours may share similar aetiological pathways between certain genetic syndromes and iASD and which behaviours do not.

Associations between ASD symptomatology and broader components of sociability within syndromes may suggest the aetiological mechanisms that lead to that social interaction skill or behaviour is associated with ASD. These findings help refine hypotheses of the aetiological mechanisms that may influence profiles of sociability in a specific genetic syndrome for future investigation. Such investigation is vital when deciding whether ASD related interventions that may target specific behaviours are appropriate for individuals with these syndromes, as well as evaluating the validity and appropriateness of diagnostic tools on these populations (Oliver et al., 2010). Therefore, in the current study I will investigate the association between severity of ASD symptomatology and components of sociability in individuals with CdLS, FXS and RTS.

3.2.5. Aims

The broad aim of this chapter is to further characterise the profiles of sociability of individuals with CdLS, FXS and RTS beyond diagnostic criteria of ASD and specific social behaviours. The nature and quality of a range of social interaction skills and social behaviours are assessed using the *CSRS* in these syndromes during a standardised semi-structured social interaction with an examiner (ADOS-II). The ADOS-II enabled flexible administration in which the examiner adjusts their social interactions in response to the participant's behaviours, providing a sample of natural social interaction amongst the social presses and is a robust standardised observational assessment. In this study, I aim to:

1) Compare the quality of social interaction skills, social motivation, social enjoyment and social discomfort in individuals with CdLS, FXS and RTS.

2) Examine whether the quality of these social skills and social behaviours changes according to the amount of time spent interacting with the examiner in individuals with CdLS, FXS and RTS.
3) Investigate whether the quality of these social interaction skills and behaviours changes with age in CdLS, FXS and RTS.
4) Explore whether severity of ASD symptomatology is associated with behaviours indicative of social interaction skills, social motivation, social enjoyment and social discomfort in individuals with CdLS, FXS and RTS.

I hypothesise that:

1) The quality of social interaction skills and behaviour will be higher in individuals with RTS compared to individuals with CdLS and RTS.
2) The quality of social behaviours shown by individuals with FXS and CdLS will improve over the duration of the assessment but not in individuals with RTS.
3) As age increases in individuals with CdLS, the quality of some social interaction skills and behaviours will not increase, but instead will decrease. No hypotheses can be stated for those with FXS or RTS due to either mixed or a lack of literature for these groups respectively.
4) Individuals with CdLS and FXS will show different profiles of associations between components of sociability and severity of ASD symptomatology. Due to the low risk of ASD reported in individuals with RTS (Powis, 2014), I predict that sociability in RTS will not be associated with severity of ASD symptomatology.

3.3. Results

3.3.1. Participant characteristics

From the original sample (table 2.2), thirty-six individuals with CdLS (19 female, M_{age}=12.42, SD=10.27), thirty-six individuals with FXS (0 female, M_{age}=15.24, SD=12.59) and twenty-five individuals with RTS (13 female, M_{age}=15.22, SD=13.78) whose ADOS footage was available were included in the following analyses. Table 3.1 reveals that these groups did not significantly differ in chronological age or non-verbal mental age. There was a significant difference in gender across the groups, due to girls with FXS being excluded from the following analyses for reasons previously outlined in section 2.2.1. Appendix G shows the frequencies of participants who took part in each ADOS-II module per syndrome. Visual inspection of the data suggests that the percentage of participants in each module do not greatly differ across syndromes.

Table 3.1.
Participant characteristics for individuals with CdLS, FXS and RTS assessed by the CSRS

	CdLS (*n* = 36)	FXS (*n* = 36)	RTS (*n* = 25)	*p*	Post-hoc tests (p<0.05)
Mean chronological age in years (SD)	12.42 (10.27)	15.24 (12.59)	15.22 (13.78)	0.57	
Gender % female	53%	0%	52%	**<.01**	CdLS, RTS < FXS
Mean non-verbal Mental Age in years (SD)	3.82 (2.15)*	3.45 (1.11)**	3.35 (1.35)*	0.79	

* Information not available for one participant due to non-completion of the relevant measure

** Information not available for two participants due to floor/ceiling effects

3.3.2. Data analysis

When data were not normally distributed, non-parametric tests were used. One-way ANOVAs or Kruskal-Wallis tests were used to compare participant's chronological age, non-verbal mental age and ADOS-II classification severity score across syndrome groups. Any significant differences were investigated in more detail using post-hoc t-tests or Mann Whitney U tests. Chi square tests were used to investigate differences in proportions of male and female participants in each group, as well as the proportion of participants who reached the cut-off scores for ASD and autism on the ADOS-II. If a significant difference was found across all groups, these were followed up with 2 x 2 chi-square to determine which specific groups significantly differ from each other. A $p<.05$ cut-off was used to detect differences across groups.

Due to low variability in the data, the following *CSRS* items were removed from subsequent analyses: *Negative Emotional Affect, Frequency of Spontaneous Physical Contact,* and *Nature of Physical Contact Initiated.* In addition, the item *Motivation for Adult Engagement* was not included in analyses as the item was originally designed to be coded during a specific social condition in which the examiner purposefully does not interact with the participant to observe how often the participant attempts to gain the examiner's attention (Moss et al., 2013). Scores for the items *Social Anxiety* and *Avoidance of Social Interaction* were reversed so that higher scores indicated that participants showed more anxiety and avoidance respectively.

Mean scores for each item per participant were calculated from the scores across the first three ten minute segments of their ADOS-II assessment. To account for multiple comparisons, an adjusted p value of $\leq .01$ was used to detect differences across groups in the

main analysis, and a *p* value of .05 was used for post-hoc analyses to determine where group differences lied.

3.3.3. The broad profile of social interaction skills, social motivation, social enjoyment and social discomfort in individuals with CdLS, FXS and RTS.

The first aim of the study was to broadly compare profiles of social interaction skills, social motivation, social enjoyment and social discomfort across groups. Figure 3.1 shows the median *CSRS* item scores across all domains in each syndrome. Kruskal-Wallis tests were conducted to compare mean item scores in each *CSRS* item across syndromes. There were no significant differences between syndromes on any items in the *Social Enjoyment* or *Social Discomfort* domains. However, differences were found between syndromes on an item in the *Social Interaction Skills* domain (*Eye Contact*) ($\chi(2)=16.83$, $p<.01$). Mann Whitney U tests revealed that eye contact was overall significantly better in those with CdLS compared to both FXS ($U(70)=317.50$, $z=-3.96$, $p<.01$, $r=-.47$) and RTS ($U(59)=267.00$, $z=-2.96$, $p<.01$, $r=-.35$). In addition, differences were found across syndromes in an item in the *Social Motivation* domain (*Focus of Attention*) ($\chi(2)=9.22$, $p=.01$). Mann Whitney U tests revealed that individuals with CdLS focused their attention more on others, as opposed to objects, in comparison to participants with FXS ($U=386.00$, $z=-2.98$, $p<.01$, $r=-.35$).

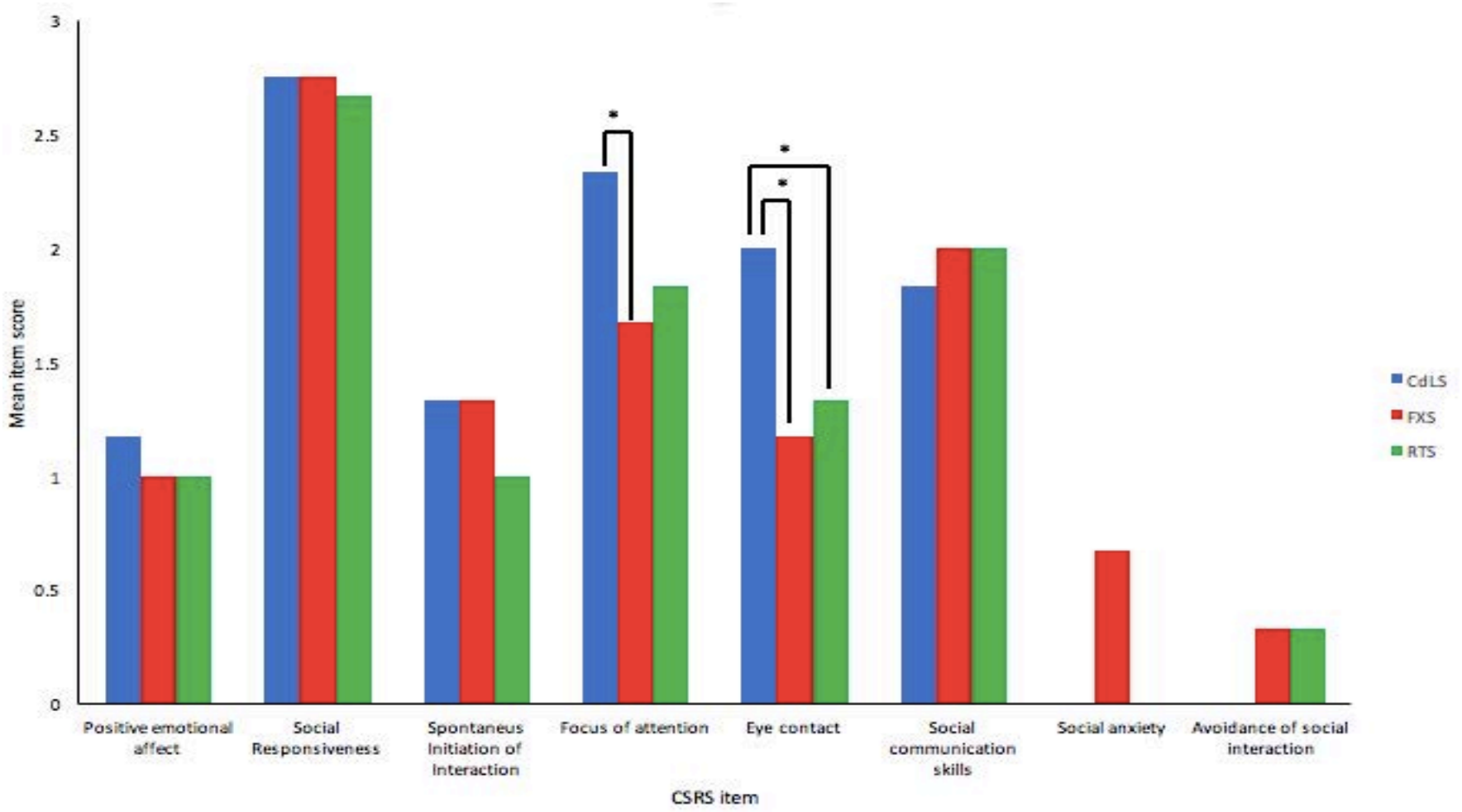
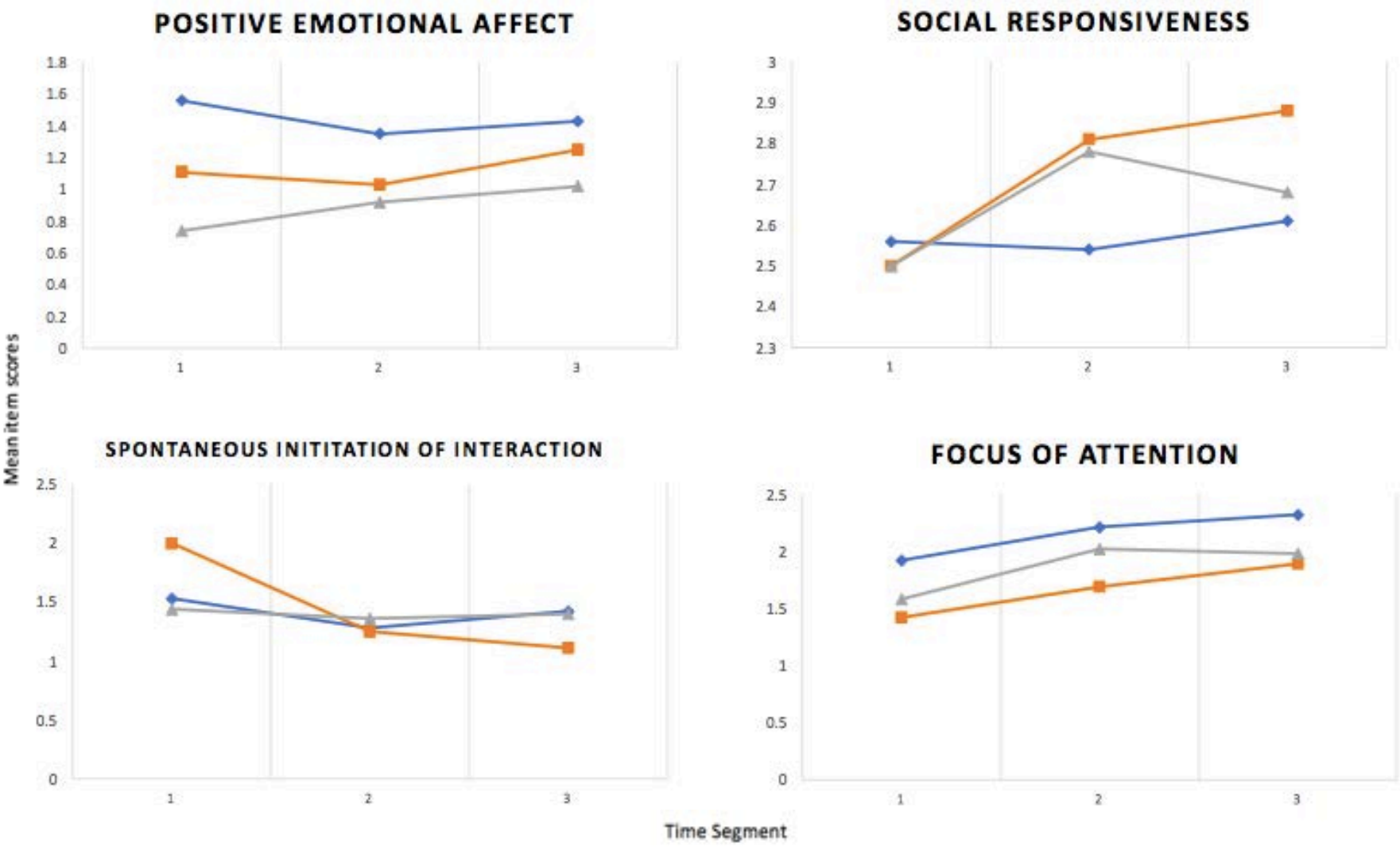


Figure 3.1. *Median item scores on each CSRS item per syndrome.*

3.3.4 The effect of time spent with the examiner on social interaction skills, social motivation, social enjoyment and social discomfort in individuals with CdLS, FXS and RTS.

The second aim of the study was to investigate whether social behaviour changed over time during the ADOS-II assessment. Within group comparisons using Friedman tests were conducted comparing participant's scores across the first three ten minute segments (TS1, TS2 and TS3) of the ADOS-II assessment for each syndrome group. Significant effects were followed-up using post-hoc pairwise Wilcoxon sign rank tests to investigate which time points the quality of behaviour differed between. Figure 3.2 shows syndromes mean scores across each time segment as in some items the medians do not adequately show where the differences lie between time segments.


POSITIVE EMOTIONAL AFFECT
SOCIAL RESPONSIVENESS
SPONTANEOUS INITITATION OF INTERACTION
FOCUS OF ATTENTION
Mean item scores
Time Segment

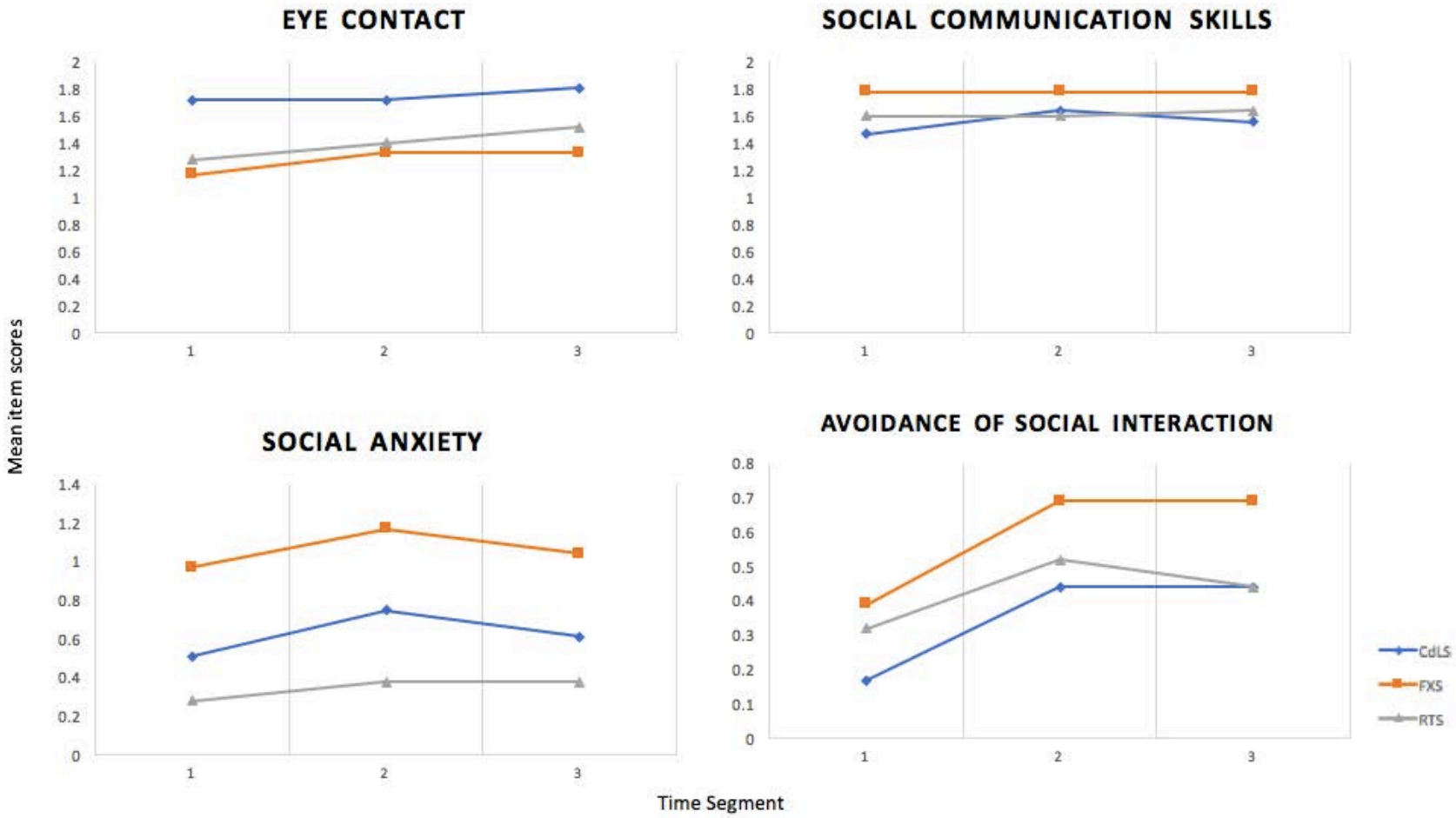


Figure 3.2. *Mean scores for each CSRS item per syndrome across time segments (TS1, TS2 and TS3)*

3.3.4.1 CdLS.

For participants with CdLS, significant differences were found across time for *Focus of Attention* ($\chi(2)=12.76$, $p<.01$), in which individuals with CdLS showed less person oriented attention and more object oriented attention in TS1 than in TS2 ($Z= -2.41$, $p<.01$, $r=-.40$) and TS3 ($Z= -3.84$, $p<.01$, $r=-.71$). Significant differences were also found for *Avoidance of Social Interaction* ($\chi(2)=9.85$, $p<.01$), in which individuals with CdLS show less avoidance at TS1 than at TS2 ($Z= -2.71$, $p<.01$, $r=-.45$) and TS3 ($Z= -2.50$, $p=.01$, $r=-.42$). No significant differences were found for *Positive Emotional Affect*, *Social Responsiveness*, *Spontaneous Initiation of Interaction*, *Eye Contact*, *Social Communication Skills* or *Social Anxiety*.

3.3.4.2 FXS.

For participants with FXS, significant differences across time were found for *Spontaneous Initiation of Interaction* ($\chi(2)=9.96$, $p<.01$) in which the quality and frequency of social initiations were higher in TS1 than in TS2 ($Z= -2.79$, $p<.01$, $r=-.47$) and TS3 ($Z= -2.81$, $p<.01$, $r=-.47$). As with participants with CdLS, a significant effect was found in *Focus of Attention* ($\chi(2)=14.10$, $p<.01$), in which individuals with FXS showed less person oriented attention and more object oriented attention in TS1 than in TS2 ($Z= -2.50$, $p=.013$, $r=-.42$) and TS3 ($Z= -3.56$, $p<.01$, $r=-.59$). Finally, a significant effect was found for *Avoidance of Social Interaction* ($\chi(2)=9.35$, $p<.01$), in which participants with FXS overall showed less aversion to the examiner's approaches at TS1 than in TS2 ($Z= -2.40$, $p=.02$, $r=-.40$). and TS3 ($Z= -2.67$, $p<.01$, $r=-.45$). No significant differences were found for *Positive Emotional Affect*, *Social Responsiveness*, *Eye contact*, *Social Communication Skills* or *Social Anxiety*.

3.3.4.3 RTS.

For participants with RTS, as with participants with CdLS and FXS, significant differences were found across time segments for *Focus of Attention* ($\chi(2)=10.98$, $p<.01$), in which participants showed less person oriented attention and more object oriented attention in TS1 than in TS2 ($Z= -3.28$, $p<.01$, $r=-.66$) and TS3 ($Z= -2.23$, $p=.03$, $r=-.45$). No significant differences were found for *Positive Emotional Affect*, *Social Responsiveness*, *Spontaneous Initiation of Interaction*, *Eye Contact*, *Social Communication Skills*, *Social Anxiety* or *Avoidance of Social Interaction.*

3.3.5 The association between components of sociability and chronological age in CdLS, FXS and RTS

The third aim was to investigate the association between the quality of social behaviour and chronological age within each syndrome group. Table 3.2 displays the Kendall Tau correlations that were run between participant's chronological age in years and their mean scores on each *CSRS* item per syndrome. Results reveal that chronological age was associated with different items in different syndromes.

Individuals with CdLS showed moderate positive associations between age and *Positive Emotional Affect* ($\tau_b(34)= .35$, $p<.01$), *Focus of Attention* ($\tau_b(34)=.34$, $p<.01$), *Social Communication Skills* ($\tau_b(34)= .38$, $p<.01$) and *Social Anxiety* ($\tau_b(34)=.40$, $p<.01$). A moderate negative association between chronological age and *Avoidance of Social Interaction* ($\tau_b(34)=-.34$, $p=.01$) was also found. These findings indicate that older participants show more positive emotional affect, more person focused attention, greater quality social communication skills, more social anxiety and less social avoidance.

Table 3.2
Kendall Tau correlations for mean CSRS item scores, and chronological age and ADOS-II CSS for each syndrome. Significant correlations are highlighted in bold

CSRS item	CdLS		FXS (*p*)		RTS (*p*)	
	Chronological age (*p*)	ADOS-II SA CSS (*p*)	Chronological age (*p*)	ADOS-II SA CSS (*p*)	Chronological age (*p*)	ADOS-II SA CSS (*p*)
Positive emotional affect	**.35 (<.01)**	.24 (.06)	-.05 (.70)	-.08 (.56)	-.34 (.02)	**-.60 (<.01)**
Social responsiveness	.28 (.02)	-.31 (.02)	**.32 (<.01)**	**.**04 (.76)	.05 (.76)	-.29 (.06)
Spontaneous initiation of interaction	.07 (.55)	.30 (.02)	.03 (.84)	.04 (.76)	.04 (.81)	-.11 (.48)
Focus of attention	**.34 (<.01)**	-.14 (.26)	.04 (.75)	-.09 (.50)	.06 (.69)	-.35 (.03)
Eye contact	.30 (.03)	-.24 (.09)	-0.26 (.04)	-.21 (.12)	-.21 (.12)	**-.45 (<.01)**
Social communication skills	**.38 (<.01)**	-.33 (.02)	**.43 (<.01)**	.16 (.30)	.03 (.87)	-.22 (.21)
Social anxiety	**.40 (<.01)**	.28 (.04)	**.56 (<.01)**	**.40 (<.01)**	.12 (.49)	.21 (.21)
Avoidance of social interaction	**-.34 (.01)**	.15 (.28)	.03 (.81)	.01 (.93)	.13 (.40)	.17 (.31)

In participants with FXS, results showed moderate positive associations between chronological age and *Social Responsiveness* (τ_b (34)=.32, p<.01) and *Social Communication Skills* (τ_b (34)=.43, p<.01). Similar to those with CdLS, participants with FXS also showed a moderate positive association between chronological age and *Social Anxiety* (τ_b (34)=.56, p<.01). These findings indicate older participants with FXS are more socially responsive, show greater social communication skills and more social anxiety.

In contrast to individuals with CdLS and FXS, individuals with RTS chronological age was not associated with any of the CSRS items.

As chronological age and non-verbal mental age are associated with one another in participants with CdLS (τ_b (33)=.60, p<.01) and FXS (τ_b (32)=.54, p<.01), items that were found to significantly correlate with chronological age were then correlated with participants non-verbal mental age in participants for which these data were available (table 3.1). In participants with CdLS, significant moderate positive associations were found for *positive emotional affect* (τ_b (33)=.42, p<.01) , *Social Communication Skills* (τ_b (33)=.55, p<.01), a strong association for *Social Anxiety* (τ_b (33)=.60, p<.01) and a moderate negative association was found for *Avoidance of Social Interaction* (τ_b (33)= -.36, p<.01). No association was found between non-verbal mental age and *Focus of Attention* in those with CdLS. In individuals with FXS, moderate positive associations were found between non-verbal mental age and *Social Communication* (τ_b (32)=.53, p < .01),and *Social Anxiety* (τ_b (32)=.48, p<.01). Pearson's correlations revealed a positive moderate correlation between participant with FXS's non-verbal mental age and *Social Responsiveness* (r (32)=.57, p<.01).

Overall, findings suggest that different components of sociability changes with chronological age in individuals with CdLS and FXS. However, these changes with age may be due to increases in non-verbal age as individuals age in all items, except for *Focus of*

Attention in individuals with CdLS. In contrast, social interaction skills and behaviours in individuals with RTS do not change with chronological age.

3.3.6 The association between components of sociability and severity of ASD symptomatology in CdLS, FXS and RTS

The final aim was to investigate the association between the quality of social behaviours and the overall severity of ASD symptomatology in participants within each syndrome group. Table 3.3 shows the percentage of participants per syndrome group who reached cut-off scores on the ADOS-II for an ASD classification and an autism classification, as well as each syndrome's mean scores of ADOS-II total and social affect subscale classification severity scores (CSS). Chi-square tests revealed that fewer participants with CdLS and RTS reached cut-off scores for autism compared to participants with FXS. In addition, more individuals with FXS reached cut-off scores for ASD compared to those with CdLS and RTS and more participants with RTS reached cut-off scores for ASD compared to those with CdLS. Kruskall-Wallis tests revealed that syndrome groups significantly differed in level of overall ASD symptomatology (including both social affect and restricted and repetitive behavioural difficulties) and in level of ASD-related social difficulties (i.e. *Social Affect CSS*).

Table 3.3.
The percentage of participants who reached clinical cut-off scores on the ADOS-II, and ADOS-II Total and Social Affect Classification Severity Scores (CSS) means per syndrome group

	CdLS (n = 36)	FXS (n = 36)	RTS (n = 25)	p	Post-hoc tests (p<0.05)
% reach ADOS-II ASD clinical cut-off score	47%	94%	73%	**<.01**	CdLS < RTS < FXS
% reach ADOS-II ASD clinical cut-off score	44%	83%	57%	**<.01**	CdLS, RTS < FXS
ADOS-II Total CSS (SD)	4.58 (3.01)	6.89 (2.00)	5.23 (2.35)	**<.01**	CdLS, RTS < FXS
ADOS-II Social Affect CSS (SD)	4.94 (2.93)	6.69 (2.12)	5.53 (2.12)	**.02**	CdLS, RTS < FXS

Table 3.2 displays the Kendall Tau correlations run between participant's SA CSS and mean scores on each CSRS item per syndrome. Syndromes showed differences in the profile of items that were associated with ASD symptomatology (specifically, ASD-related social difficulties). Individuals with FXS showed a moderate positive association between ADOS-II social affect CSS and *Social Anxiety* (τ_b (34)=.40, p<.01). Individuals with RTS showed a moderate negative association and *Eye Contact* (τ_b (23) = -.45, p<.01), and a strong negative association with *positive emotional affect* (τ_b (23)=-.60, p<.01). No significant associations were observed in CdLS. These findings suggest that ASD symptomatology is associated with different components of sociability in individuals with FXS and RTS, but not individuals with CdLS.

3.4 Discussion

In this study, operationalised social behaviours indicative of social enjoyment, social motivation, social interaction skills and social discomfort were investigated in children and adults with CdLS, FXS and RTS. These behaviours were evaluated in ten minute segments during the first thirty minutes of an ADOS-II assessment. This is the first study to directly compare the quality of components of sociability across these syndromes in groups of participants who are comparable on chronological age and non-verbal mental age. It is also the first study to explore the associations of these components with time spent interacting with an examiner, participant's chronological age and ASD symptomatology.

3.4.1 Cross-syndrome comparisons of social enjoyment, social motivation, social interaction skills and social discomfort

The first aim was to investigate the profiles and the quality of behaviours indicative of social enjoyment, social interaction skills, social motivation, and social discomfort in individuals with CdLS, FXS and RTS. Broad comparisons across groups mean item scores showed differences in *Eye Contact* (an item in the *Social Interaction Skills* domain) and *Focus of Attention* (*Social Motivation* domain). These findings suggest that on a group level, individuals with CdLS showed more frequent and appropriate eye contact than individuals with FXS and RTS.

Whilst the finding that the FXS group had one of the lowest scores on *Eye Contact* corresponds to the phenotypic gaze aversion observed in these individuals (Cohen et al., 1989; Crawford et al., in prep; Hall et al., 2009), the finding that individuals with RTS did not significantly differ in quality of eye contact from FXS is novel. Previous investigations of eye contact in those with RTS have revealed mixed findings. These studies were restricted to case

studies or have evaluated the frequency but not the quality of eye contact within social interaction. Whereas a recent case study reported the eye contact of a young girl with RTS to be "poor/inconsistent" (Monica, 2016), another reported that along with vocalisations, eye contact was one of the main modes of communication in a young boy with RTS (Carvey & Bernhardt, 2009). Powis (2014), found that on a battery of tasks assessing early social cognition and intentionality understanding, individuals with RTS showed the most difficulty in understanding the communicative intent of another person's gaze to direct their attention to a hidden object relative to other social cognitive abilities. This is the first study that has compared observational social skills of individuals with RTS with other genetic syndromes during social interaction with an examiner. Overall, findings suggest that individuals with RTS show impairments in using their own and understanding other's eye contact in social communication and the quality of eye contact warrants more detailed investigation in these individuals.

Without a comparison group of TD individuals, it is difficult to discern whether eye contact in CdLS is intact or just less impaired compared to those with FXS and RTS. Previous literature investigating eye contact in CdLS has yielded mixed findings, which may be indicative of the range of genetic causes that lead to the syndrome (Sarimski, 2007; Deardorf et al., 2012; Moss et al., 2017; Gillis et al., 2004; Nakanishi et al., 2012). Whereas Moss, Howlin, Magiati and Oliver (2012) found that children with CdLS have better quality of eye contact than those with iASD, Sarimski (2007) found that, alongside other socially related behaviours, the amount of eye contact within the group varied greatly from individual to individual during an intensive interaction with an examiner, highlighting the heterogeneity of behavioural outcomes often observed in cohorts of individuals with CdLS (Moss et al., 2017). Quality of eye contact may differ depending on the environmental context in individuals with

CdLS but not in other syndromes. Individuals with CdLS showed more eye contact than those with Down syndrome when interacting with a familiar adult during a social performance task requiring participants to tell the examiner a story based on picture cards. No differences were seen between these groups in any other conditions that varied in their level of social demand (Nelson et al., 2017). Richards and colleagues (2009) found verbally fluent participants with CdLS demonstrated more fleeting eye contact during situations with high social demands in comparison to individuals with Cri du Chat syndrome who demonstrated similar levels of social anxiety. Future work should investigate the quality of eye contact across individuals with CdLS with different genotypes against a group of TD individuals, across different social contexts.

Individuals with CdLS showed more person focused attention than individuals with FXS. These findings may be associated with the better quality and thus most likely more frequent eye contact with the examiner in individuals with CdLS, in addition to the extreme gaze aversion demonstrated in those with FXS. However, no differences were found in focus of attention between individuals with RTS and FXS, or between those with RTS and CdLS. Although individuals with RTS show impairments in some social interactions skills, such as eye contact, which are likely to impact upon evaluations of their focus of attention, their relatively intact social interest (Galéra et al., 2009; Moss et al., 2016; Verhoeven, Tuinier, Kujipers, Egger & Brunner, 2010) may have compensated for the effect of poor eye contact and led to more person focused attention compared to individuals with FXS. Both frequency and quality are evaluated in the *Eye Contact* item, so whilst the quality of eye contact may have been poor, it may have been more frequent compared to those with FXS.

In contrast to previously reported heightened social motivation in RTS (Hennekam, 2006; Galéra et al., 2009; Moss et al., 2016), individuals with RTS did not score higher on the

item *Spontaneous Initiation of Interaction* than those with CdLS or FXS. This item also evaluates both frequency and quality of participant's social initiations. To obtain a score higher than two, a participant must show an example of initiating interaction with the examiner that is socially motivated and not related to personal demands at least once. If individuals with RTS did initiate interaction with the examiner more often than those with CdLS and FXS, this would not have been captured within this item if these initiations were not socially motivated. This finding highlights the importance of considering the level of quality and appropriateness of social behaviours beyond simply the frequency when describing sociability in these syndromes.

The hypothesis that individuals with RTS would show more strengths was not confirmed by the current findings. There is a paucity of research investigating the social behavioural phenotype in those with RTS in comparison to other genetic syndromes such as FXS. This is one of the first studies that has assessed individuals with RTS beyond parent report (e.g. Powis, 2014; Moss et al., 2016) through detailed and direct observational assessment and direct comparisons with other genetic syndromes comparable on age and ability. These findings indicate that the sociable nature reported in global assessments or caregiver reports may mask social difficulties or impairments in this syndrome. This hypothesis is supported by the few studies that have directly investigated social behaviours and skills and have found difficulties understanding other's gaze cues (Powis, 2014) and social anxiety, despite showing social motivation to interact (Crawford et al., in prep).

3.4.2 Changes in sociability over time during social interaction

The second aim was to explore whether quality of social behaviour may change over the duration of social interaction with the examiner. Findings indicate that the quality of some

social behaviours changed between the first two 10 minute time segments (TS1 and TS2). All groups showed an increase in person-focused attention. Both individuals with CdLS and FXS showed an increase in avoidance of social interaction, and only individuals with FXS showed a decrease in the frequency of social initiations made.

The current findings do not confirm the hypothesis that quality of social interaction skills and behaviours would improve over interaction time in individuals with FXS and CdLS, but instead showed the opposite pattern. These findings contradict previously reported warm-up effects seen in individuals with FXS (Hall et al., 2009; Roberts et al., 2007). Thirty-minutes of social interaction may not provide enough time for warm-up effects to emerge. Whilst Hall and colleagues (2009) found that children with FXS showed less eye-gaze avoidance over just a 25-minute session of social interaction, the decrease in eye contact reported was slight. As the *CSRS Eye Contact* item broadly evaluates the frequency and nature of eye contact, the item may not have been sensitive enough to pick up these subtle changes. In addition, whilst Hall and colleagues carried out the social interaction session upon arrival at participant's home, the ADOS-II assessment was the last assessment to be carried out in this study to ensure that participants with social difficulties did not become too overwhelmed or anxious by the social demands to participate in the remaining assessments.

Changes in sociability in CdLS and FXS may reflect the increased social demands placed by the examiner upon the participant as per the standardised ADOS-II procedure that were not initially considered. During the first ten minutes, all participants are given time to play or perform a task independently. The remaining assessment consists of the examiner placing social demands on participants through the form of social presses. These changes in social demands may be reflected in the increase in person centred attention that occurs in all three groups, as increased social demands elicited by the examiner is likely to demand an

increase in an individual's attention across syndromes. Avoidance during environments with high levels of social demands has been demonstrated in previous studies in both CdLS and FXS (e.g. Hall, DeBernardis & Reiss, 2006; Arron et al., 2006; Crawford et al., in prep). Increases in social interaction demands would elicit social avoidance more often.

The findings that individuals with RTS did not show any unique changes in sociability over time corresponds to previous findings that social anxiety, social motivation and sociability in these individuals are consistent across conditions varying in level social demand, and when interacting with a familiar compared to an unfamiliar adult (Crawford et al., in prep; Moss et al., 2016). Overall, these findings suggest that the profile of sociability in individuals with RTS is more consistent and not influenced by environmental factors as for individuals with CdLS and FXS. However, the range of environments and direct assessment of their effect on sociability in individuals with RTS has been limited and warrants further research.

The interpretation that these findings are due to changes in social demand are speculative, as level of social demand was not systematically controlled for within time segments. Nevertheless, these findings highlight the importance of investigating sociability in finer-grained detail beyond what is captured by broad cut-off scores obtained at total and/or subscale level (Moss et al., 2013), as these differences across syndromes profiles were missed when scores were averaged across all three time segments. Future research should systematically vary the level of social demands to explicitly identify the environments that lead to changes in sociability.

3.4.3 Associations between age and sociability

The third aim was to explore whether the quality of social behaviours changes with age in CdLS, FXS and RTS. Findings provide exploratory evidence of differences across ages in different components of sociability between syndromes. Older individuals with CdLS showed more frequent and better quality social communication skills, more positive emotional affect, social anxiety and less avoidance of social interaction. Older participants with FXS showed more frequent and better social responses, social communication skills, and more social anxiety. Individuals with RTS did not show any associations between components of sociability and chronological age.

Except for *Focus of Attention* in individuals with CdLS, all *CSRS* items that correlated with chronological age also correlated with participant's non-verbal mental age in the same direction as chronological age. As chronological age was associated with non-verbal mental in all syndrome groups, it is difficult to disentangle whether changes occur with time as opposed to with cognitive development. Non-verbal mental age was likely to be associated with *Social Responsiveness* and *Social Communication Skills*, as higher scores of these items require a greater verbal ability to express complex ideas and thoughts and working memory (Daneman, 1991; Shao, Janse, Visser & Meyer, 2014) to remember several steps to build upon interactions with the examiner.

Whilst the associations between social anxiety with chronological and non-verbal mental age in individuals with CdLS and FXS concurs with previous literature (Basile et al., 2007; Hessl et al., 2006), the cause of these association is not as clear cut as for the *Social Responsiveness* and *Social Communication Skills* items. A key diagnostic feature of social anxiety disorder is extreme self-consciousness in social or performance situations (American Psychological Association, 2013). Individuals with syndromes associated with social anxiety

and who are more cognitively able may be more self-aware of their social difficulties, leading to greater self-consciousness and social anxiety than less able individuals (Sterling, Dawson, Estes & Greenson, 2008). Alternatively, individuals may be exposed to more social or performance situations as they enter adolescence and adulthood.

Chronological age and cognitive ability may have a combined influence on sociability in genetic syndromes. Oliver and colleagues (2013) hypothesised that deterioration in executive function skills with age in individuals with CdLS, potentially due to a cumulative effect of impaired neural repair and oxidative stress as individual's age resultant from genetic abnormalities that lead to the syndrome, may lead to environments becoming more demanding. As individuals transition into adolescence and adulthood, more social demands are placed upon them and the importance of social relationships increase (Caputi, Lecce, Pagnin & Banerjee, 2012). In addition, there are changes in the environment, such as transitions from school to college or work (Blakemore & Mills, 2014), as well as moving from home to residential care or independent living. Anxiety may emerge with age due to the increased levels of unpredictability and the lack of executive function skills to allow flexible responses (Blakemore & Mills, 2014).

Older individuals with CdLS showed more positive emotional affect and person focused attention and a decrease in social avoidance, despite also showing more social anxiety with age. As with warm-up effects observed in FXS (Hall et al., 2009), these findings may represent a motivation and willingness to interact despite finding these situations anxiety provoking. These findings suggest that individuals with CdLS may be motivated to engage in interventions to improve symptoms of social anxiety.

Individuals with RTS did not show any age-related changes, even on items where it would be expected due to their relationship with cognitive ability (i.e. *Social Communication*

Skills and *Social Responsiveness*). These findings may indicate that individuals with RTS show a "zero trajectory" (Thomas et al., 2009) in these skills, in which the frequency and quality of their social communication skills and social responses shown by younger individuals with RTS may be intact relative to their mental age but due to biological or cognitive constraints during development, these skills do not improve with other cognitive abilities. Previous reports suggest that adults with RTS show decreased social interaction and more limited speech over time (Stevens et al., 2011). However, whilst this interpretation may be true for *Social Responsiveness*, visual inspection of boxplots (Appendix H) revealed that the lack of association between chronological and *Social Communication Skills* may be due to the lack of variability of lower scores compared to CdLS and FXS. This may instead reflect ceiling effects on this item in RTS.

Future studies should investigate the relationship between chronological age and components of sociability in more detail and investigate the influence of these factors longitudinally to better establish the degree of causality that these factors have on sociability. Although the specific influence of these factors cannot be delineated, these findings nevertheless identified phenotypic differences across syndromes and identified components of sociability that may have deviating developmental trajectories influenced by chronological age and/or ability.

3.4.4 Associations between sociability and ASD symptomatology

The final aim sought to explore the association between ASD symptomatology and components of sociability assessed by the *CSRS*. Overall, findings suggest that the profile of components of sociability that are associated with ASD symptomatology differ across groups. Individuals with FXS who showed greater ASD symptomatology showed greater levels of

social anxiety. Individuals with RTS who showed greater ASD symptomatology showed less positive emotional affect and lower quality of eye contact. Individuals with CdLS did not show any associations between ASD-related social difficulties and components of sociability

These findings may have implications for understanding the aetiology of sociability in these syndromes. Whereas sociability in individuals with CdLS is not associated with ASD-symptomatology, social anxiety in FXS and positive emotional affect and eye contact in individuals with RTS may be associated with similar aetiological mechanisms that lead to these behaviours in those with iASD. Like individuals with FXS (Hall & Venema, 2017), children and adults with iASD have a heightened chance of reaching cut-off scores for social anxiety disorder compared to the TD population (Maddox & White, 2015). However, direct comparisons reveal differences in the profile of behaviours indicative of social anxiety between pre-schooler's with FXS and boys with iASD, suggesting differences in the aetiology underpinning social anxiety between these groups (Scher, Hogan, Hatton & Roberts, 2017). Therefore, the association between social anxiety and ASD symptomatology may reflect a unique relationship between these variables in individuals with FXS. In contrast, there has been no direct observational comparison of social interaction skills and behaviours between individuals with RTS and iASD. However, the association between ASD symptomatology, and positive emotional affect and eye contact highlights the need for detailed direct comparisons into the phenomenological similarities and differences between these groups to undercover similarities and differences in aetiological mechanisms that drive these behaviours in individuals with RTS.

The association between ASD symptomatology and quality of eye contact observed in individuals with RTS, suggests that the poor eye contact observed in the cohort included in this study may be related to percentage of participants with RTS who reached clinical cut-off

scores for autism. 57% of individuals with RTS in the current cohort reached cut-off scores for Autism on the ADOS-II, which is higher than those with an ID (ranging between 8-28%; Bryson, Bradley, Thompson & Wainwright, 2008; Bhaumik et al., 2010; Kiani, Tyrer, Hodgson, Berkin & Bhaumik, 2013; Tonnsen et al., 2016) and previous investigations using the *Social Communication Questionnaire* (Rutter et al., 2003), a caregiver report that previously found a 29% prevalence in a different cohort of individuals with RTS (Powis, 2014). In the current study, the severity of ASD-related social difficulties of individuals with RTS (previously characterised by intact social skills; Galéra et al., 2009) was comparable to those with CdLS and FXS, syndromes associated with a range of social difficulties (Hall & Venema, 2017; Hogen et al., 2017; Moss et al., 2013; Richards et al., 2009). These findings may suggest that the cohort of individuals with RTS were not representative and the broad difficulties with eye contact observed in the current cohort may differ in individuals with RTS who do not reach clinical cut-off scores for autism. However, except for Powis (2014), the presentation of ASD symptomatology has not been studied in individuals with RTS. This is the first study to directly assess ASD symptomatology in individuals with RTS using a gold standard observational assessment of ASD (ADOS-II). Examiners who administered the ADOS-II were at a research reliable standard, and so are likely to be less biased and more accurate at evaluating ASD-related social interaction skills and behaviours than caregivers. However, future research sythesising both carer-reports and observational assessments with bigger sample sizes of individuals with RTS is required to obtain a more accurate estimate of ASD prevalence in this group.

3.4.5 Limitations

Investigation into the relationship between social interaction skills and behaviours, and chronological age and ASD-related social difficulties was correlational. Whilst the differences in associations across groups are interesting, these findings cannot determine the direction of the relationship or establish causality between these variables. However, these findings have provided a rationale for future study into the nature of these relationships.

In line with the study's ethical review, individuals over the age of 16 were only included if they could consent to participating. This may have led to a sampling bias in which older individuals with CdLS were more likely to have the SMC1a mutation, leading to the 'milder' presentation of CdLS (Deardorff et al., 2012) compared to the NIPBL mutation, which is associated with more severe disability (Gillis et al., 2004; Nakanishi et al., 2012). Whilst no differences have been found in levels of ASD symptomatology in those with and without NIPBL (Nakanishi et al., 2012), previous research has shown that changes with age in mood, pleasure and interest were associated with those with NIPBL mutation and not in those without that mutation (Moss et al., 2017). Future studies should investigate the genotype-phenotype associations to investigate whether the current results are influenced by different patterns of genetic causes across ages in this data set. A similar concern for sampling bias for older individuals more broadly may mean that those with more social impairments may not have wished to take part in the study, making it difficult to generalise the findings and may mask the effect of social interaction difficulties in these populations. However, the pattern of results suggests this factor did not impact as increases in social anxiety with age were found in both individuals with CdLS and FXS despite this potential bias to avoid new social situations by taking part in this research.

3.4.6 Summary

In summary, this chapter demonstrates that the profiles of sociability in individuals with CdLS, FXS and RTS show some broad differences across groups and are influenced by different factors in different ways across syndromes. Individuals with FXS and RTS show significantly lower quality eye contact in comparison to those with CdLS and those with FXS show significantly less person-centred focus of attention in comparison to those with CdLS. These results revealed a novel finding of social interaction difficulties (i.e. eye contact) not previously reported in individuals with RTS and highlights the need for detailed investigation into social difficulties in RTS through direct observation. More detailed investigation of the influence of assessment duration on quality of behaviours again revealed different components of sociability changed between TS1 and TS2 in different syndromes. Whilst these findings may be due to increased level of social demand in TS2 compared to TS1, this interpretation should be taken with caution as this factor was not experimentally and systematically varied between these time segments. Associations between chronological age and different components of sociability were identified in individuals with CdLS and FXS but not in individuals with RTS. These behaviours were correlated with non-verbal mental age, highlighting the importance of distinguishing between the independent associations between chronological age and development, and the related social interaction skills and behaviours to further understanding of the aetiological mechanisms that may drive these changes. Finally, the pattern of associations between ASD symptomatology and components of sociability differed between syndromes. Whilst sociability in individuals with CdLS appears unrelated to characteristics associated with iASD, some components of sociability appear to be associated with ASD symptomatology in those with FXS and RTS. Further work is needed to distinguish whether these associations illustrate similarities in underlying aetiology in FXS,

RTS and iASD, or whether these associations show a unique relationship between ASD-like characteristics and broader behaviours.

CHAPTER FOUR

THE DEVELOPMENTAL TRAJECTORY OF SOCIAL COGNITIVE ABILITIES IN CORNELIA DE LANGE, FRAGILE X AND RUBINSTEIN-TAYBI SYNDROMES

4.1. Preface

In Chapter One, models of behavioural phenotypes observed in genetic syndromes and the importance of understanding the causal mechanisms associated with behavioural phenotypes within syndromes was discussed. Social cognition was described and research highlighting the influence of social cognition on social behaviour was outlined. Chapter Three demonstrated that individuals with different genetic syndromes(i.e. CdLS, FXS and RTS) have different profiles of sociability that are influenced differently during social interactions and are differentially associated with chronological age and ASD symptomatology. Differences in the development of social cognition potentially arising from each syndromes genetic causes may lead to these differences in behaviour. Therefore, this chapter aims to investigate the development of social cognitive abilities as a potential mechanism that leads to the differentiation observed in resultant profiles of sociability in individuals with CdLS, FXS and RTS.

4.2. Introduction

As outlined in Chapter One, social cognition is an umbrella term referring to a range of cognitive abilities that allow an individual to understand other's intentions, thoughts, beliefs and behaviours within social contexts (Frith, 2008; Frith & Frith, 2012; Tomasello et al., 2005; Schaller & Rauh, 2017). Social cognition can be broken down into abilities that help individuals to interpret and predict other's behaviours based on understanding an individual's intentionality (Tomasello et al., 2005) and the ability to explicitly reason and attribute other's mental states (ToM) (Frith & Frith, 2012). Previous literature demonstrated that individual differences in social cognitive ability predict individual differences in social outcomes in TD populations, including prosocial behaviour (Imuta et al., 2016), the likelihood of developing friendships in childhood (Fink et al., 2014) and aggression (Hudley & Novac, 2007). In addition, it has been proposed that the social communication and interaction difficulties observed in ASD are due to social cognitive deficits (Varga, 2011; Baron-Cohen, 1994). Finally, differences in social cognition may contribute to the diverse profiles of sociability in genetic syndromes such as Williams and Down syndrome (Karmiloff-Smith et al., 1995; Hahn et al., 2013).

Previous literature (see section 1.4 for an overview) and Chapter Three's findings indicate that individuals with CdLS, FXS and RTS have unique profiles of sociability. Despite research demonstrating the link between social cognitive ability and social outcomes, there has been limited investigation of social cognitive abilities in these syndromes, which may underpin their profiles of sociability. Like individuals with iASD (Baron-Cohen et al.,1985), individuals with FXS (Grant et al., 2007; Cornish et al., 2005; Losh et al., 2012) and CdLS (Collis et al., 2008) demonstrate delays during false belief tasks relative to their mental age. Whilst difficulties understanding false belief may elucidate why individuals with CdLS and FXS demonstrate social difficulties broadly, they do not explain the subtle differences observed

between these groups, e.g. profiles of social anxiety (Crawford et al., in prep). In addition, similar difficulties on false belief tasks have been observed in individuals with syndromes associated with contrasting profiles. Boys with FXS show similar performance on false belief tasks to boys with Down syndrome (Cornish et al., 2005), a syndrome with a behavioural phenotype characterised by high levels of sociability (Moss et al., 2016), but whom show more subtle difficulties in social interaction and developing friendships (Guralnick, Connor & Johnson 2011). These findings suggest that a single cognitive approach cannot elucidate the detailed mechanistic social cognitive differences that may drive the refined differences in sociability across genetic syndromes.

As discussed in Chapter One, recent work has progressed from a single cognitive approach, in which the false belief task was once the "litmus" test for social cognition and ToM (Corbett et al., 2013) to conceptualising social cognition as a range of abilities that encompass understanding of different types of understanding of other's intentions and mental states, which emerge at different ages. This has led to the development of scales that demonstrated that social cognitive abilities develop in a stringent and cumulative sequence in TD children (Wellman & Liu, 2004; Peterson et al., 2005; 2012; Powis 2014; Powis et al., in revision). These developmental scales provide a robust normative benchmark to compare the development of social cognitive abilities in groups associated with differences in profiles of sociability across development.

Developmental trajectory approaches aim to distinguish whether abilities in genetic syndromes are: 1) delayed relative to an individual's mental age (i.e. is there delay) and 2) whether the pattern of development of these abilities are the same or different from developmental patterns observed in typical development (is there a difference). Both have implications for theorising and refining hypotheses regarding the underlying mechanisms that

drive the development of these abilities in genetic syndromes (Thomas et al., 2009). This information helps develop complete models of sociability and better stratified interventions that target specific social cognitive abilities that certain syndromes show poorer performance on.

Developmental delay and difference can be investigated using developmental scales. Both late-signing deaf children and children with iASD demonstrate delayed scale progression on the *Theory-of-Mind Scale (ToMS).* Interestingly, individuals with iASD, but not late-signing deaf children, passed tasks in an alternative order from TD children, in which they passed *"Hidden Emotion"*, which assesses a participant's ability to distinguish between the emotion another person is experiencing (real) and the emotion which that person is outwardly expressing (apparent) even when those emotions contrast to one another, before passing *Contents False Belief* (Peterson et al., 2005; 2012). These findings show how developmental scales can help identify and justify biological and environmental variables that may influence individual's social cognitive development and social behaviour in future work. The authors hypothesised that whereas similarities in overall delay may reflect broad similarities in atypical social experiences that do not offer as many opportunities to learn about other's mental states, the divergent developmental sequence in iASD may reflect group specific neurobiological or environmental (e.g. teasing) influences that make processing hidden emotion easier or more relevant to their day-to-day life than other's false beliefs.

The development of the *Early Social Cognition Scale (ESCS)* enabled investigation of social cognitive abilities in genetic syndromes associated with ID (Powis, 2014; Powis et al., in revision), who may be non-verbal and/or do not have the cognitive ability to take part in traditional social cognitive tasks assessing mentalising skills. As social difficulties in genetic syndromes emerge from as young as one year (e.g. Hogan et al., 2017), the *ESCS* provides a tool to assess important social cognitive abilities that may underpin these difficulties even in

individuals who are very cognitively delayed, as well abilities that can be targeted in early intervention.

Combining the *ESCS* and *ToMS* enables investigation of social cognitive abilities across development across individuals with a range of abilities and ages. Using both task batteries, Powis (2014) found that individuals with RTS showed profiles of spared and impaired abilities. Whereas at a broad level early intentionality understanding was relatively 'spared', later ToM abilities are delayed in these individuals. However, whereas individuals with RTS showed the same developmental sequence as TD children for ToM, children with RTS did not conform to the normative sequence in the *ESCS*, showing a pronounced difficulty with understanding the communicative intention of another person's use of gaze to direct their attention to where an object was hidden (Powis, 2014).

These findings led to the generation of hypotheses of what may drive the behavioural phenotype in RTS. A lack of understanding of others' minds may lead to an inability to recognise when individuals may be duplicitous. Individuals with RTS have anecdotally been reported to be socially vulnerable. Powis, Waite, Beck and Oliver (2009) suggested this may be due to a profile of heightened social motivation with impaired social cognition, lending these individuals to be more vulnerable to social exploitation.

When comparing the sequence of social cognitive abilities in genetic syndromes to TD individuals, there are three possible outcomes (Powis, 2014). The first is that syndromes pass tasks in the same stringent cumulative sequence as TD children, suggesting that social cognitive abilities develop in the same way between these groups. The second possibility is that individuals with a syndrome pass tasks in an alternative sequence to TD children. These results would suggest that whilst individual's in that syndrome group may develop these abilities differently from TD individuals, the underlying mechanism driving social cognitive

development is the same across individuals within that syndrome. The third possibility is that a coherent sequence does not emerge, as individuals within a syndrome show diverse patterns of pass and fails that may be due to characteristics that vary within that group. As demonstrated by previous studies (Powis, 2014), divergences in the developmental sequence may identify variables that influence social cognitive development in different syndromes.

The aim of the current study is to explore the potential casual social cognitive mechanisms that may underpin different profiles of sociability by extending research that assesses the trajectory of social cognitive development in CdLS, FXS and RTS. In this study, I aim to investigate:

1) the developmental trajectory of social cognitive skills in individuals with CdLS, FXS and RTS relative to participant's non-verbal mental age, to establish whether these abilities are advanced, preserved or delayed within each syndrome group.
2) whether individuals with CdLS, FXS and RTS develop social cognitive abilities in the same order as observed in TD children and/or one another or in a different and idiosyncratic orders.

It was hypothesised that:

1) individuals with CdLS and FXS will show a delay in acquiring these abilities. Based on Powis' (2014) previous findings, individuals with RTS are hypothesised to show an advantage in tasks assessing intentionality abilities and a delay in tasks assessing ToM abilities
2) Individuals with CdLS and FXS will not develop these skills in the same order as observed in TD. Individuals with RTS will show a unique developmental sequence in intentionality but not ToM abilities.

4.3. Data analysis.

As the two social cognitive batteries (i.e. the *ESCS* and *ToMS*) were appropriate for different ages and abilities, most individuals only participated in one battery except for three participants who participated in both. Therefore, these batteries are analysed separately. The data analysis protocols follow the same procedure and use a similar approach to Powis, Wellman and colleagues (Powis, 2014; Powis et al. in revision; Wellman & Liu, 2004; Peterson et al., 2005; 2012). The same approach used in Chapter Three was used to investigate participant characteristics in both cohorts.

4.4. Results

4.4.1. Early Social Cognition Scale

4.4.1.1. Demographic characteristics.

Twenty-two children with CdLS (M_{age}=77.98 months, SD=39.46), nineteen with FXS (M_{age}=71.70 months, SD=30.40) and eighteen with RTS (M_{age}=110.61 months, SD=45.95) took part in the *ESCS*. Table 4.1 shows that children were not comparable on chronological age, as those in the RTS group are significantly older that in the CdLS and FXS groups. This is most likely due to this syndrome being the rarest (Park et al., 2014) and less likely to be diagnosed as young as the other syndromes. However, these groups are comparable on non-verbal mental age and the focus of this chapter is upon the emergence of social cognitive abilities relative to individual's ability rather than chronological age. In addition, to investigate the *developmental sequence* of social cognitive abilities scale *within* syndromes, scaling analysis only requires that participants in a cohort have a wide range of ages and abilities that span the ages that TD children passed tasks within each battery. Based on these aims, and due to the rarity of these syndromes, it was considered keeping as many participants

in the sample as possible was appropriate for the purposes of this study. As in the previous chapter, the groups are not matched on gender due to the large number of males in the FXS group.

Table 4.1.
Participant characteristics of children with CdLS, FXS and RTS who took part in the ESCS

	CdLS (n = 22)	FXS (n = 19)	RTS (n = 18)	p	Post-hoc tests (p<0.05)
Mean chronological age in months (SD)	77.98 (39.46)	71.70 (30.40)	110.61 (45.95)	**.02**	CdLS, FXS<RTS
Gender % female	59	0	50	**<.01**	FXS<CdLS, RTS
Mean non-verbal mental age in months (SD)	29.62* (13.67)	33.01 (10.42)	30.32** (9.52)	.63	

* Information not available for one participant due to non-completion of the relevant measure

** Information not available for two participants due to non-completion of the relevant measure

4.4.1.2. Control trials.

Three tasks, *Helping*, *Gestures-Point* and *Gestures-Gaze*, included control trials to review whether children passed these tasks because they understood the experimenter's intention or due to other low level cues (Powis, 2014; Powis et al., in revision). Performance on these control trials was investigated at a group level for all children who took part in the battery.

4.4.1.2.1. Helping.

Table 4.2 shows the number of children who passed the *Helping* experimental trials who: 1) passed the target item during control conditions to the examiner and 2) took

possession of items in the experimental trials before handing it over to the examiner. Out of forty-six children who passed back an item during the *Helping* experimental conditions, only eight handed over the target item during one of the control conditions. Out of these children, seven passed back the pen, whereas only one child passed the cones to the examiner during each respective control condition. Only five participants took possession of target items during the experimental trials before handing over. As the number of children who either passed the item back during control conditions, or took possession of the item before handing it to the experimenter in the experimental trials was low, children who passed were overall considered to have been helping the adult as opposed to reinstating the original situation or taking the object primarily for themselves in all syndromes.

Table 4.2.
Number of children who passed each respective experimental helping trial in the total sample and within each syndrome group, who passed back the target item during control conditions and took possession of the target items during each experimental trial before handing it over to the examiner

	All participants (*N*=46)	CdLS (*N* = 14)	FXS (*N* = 16)	RTS (*N* = 16)
Total *N* passed item back during control conditions	8	1	5	2
N passed target item during pen control condition	7	1	5	1
N passed target item during cones control condition	1	0	0	1
Total *N* took possession of target item in experimental trials	6	3	2	1
N took possession of item in experimental pen trial	3	1	1	1
N took possession of target item in experimental cones trial	2	2	0	0

4.4.1.2.2. Gestures.

Mann-Whitney U tests were run to compare participant's performance in control trials compared to the scores that would be expected by chance in each respective *Gestures* task. Results indicated participant's choices between containers did not significantly differ from chance in either the *Gestures-Point* (U(df) = 1339.50, $p = .08$) or *Gestures-Gaze* trials (U(df) = 1548.50, $p = .64$). These results suggest that children who passed each *gestures* task only followed intentional cues.

4.4.1.3. Developmental trajectory of intentionality abilities in children with CdLS, FXS and RTS

Table 4.3 shows the number of children who passed each task within each syndrome. To explore whether social cognitive ability was overall delayed or preserved in CdLS, FXS and RTS, participant's non-verbal mental age (where these data were available; see table 4.1) was plotted against the number of *ESCS* tasks they passed, with a line of best fit included per syndrome group (Figure 4.1). The mean age TD infants who originally participated in the validation study of the *ESCS* achieved the number of tasks were also plotted (Powis, 2014; Powis et al., in revision). Visual inspection of figure 4.1 reveals that all groups show an overall delay in acquiring social cognitive abilities in comparison to the ages TD infants pass these tasks. Many children in all syndrome groups had a non-verbal mental age beyond that expected to be able to pass these tasks.

Table 4.3
The number and percentage of TD children and children with CdLS, FXS and RTS that passed each task

	TD (*N* = 86)*	CdLS (*N* = 22)	FXS (N = 19)	RTS (N = 18)
Helping	76 (88%)	14 (64%)	16 (84%)	16 (89%)
Gestures-Pointing	58 (67%)	6 (27%)	6 (32%)	8 (44%)
Re-enactment of Intended Acts	54 (63%)	14 (64%)	16 (84%)	15 (83%)
Gestures-Gaze	37 (43%)	2 (9%)	3 (16%)	1 (6%)
Cooperation-Tubes	32 (37%)	3 (14%)	7 (37%)	6 (33%)
Cooperation-Trampoline	19 (22%)	2 (9%)	3 (16%)	7 (39%)

* Percentages for TD group taken from Powis (2014) and colleagues (in review)

Correlations were run to determine whether, despite delay, overall social cognitive ability increased with ability. Kendall Tau correlations revealed moderate positive correlations in the CdLS (τ_b (20)=.45, p=.01) and FXS groups (τ_b (20)=.49, p<.01). A Pearson correlation revealed a strong positive correlation in the RTS groups (r(14)=.69, p<.01). These findings show that the higher an individual's non-verbal ability, the more social cognitive tasks they passed.

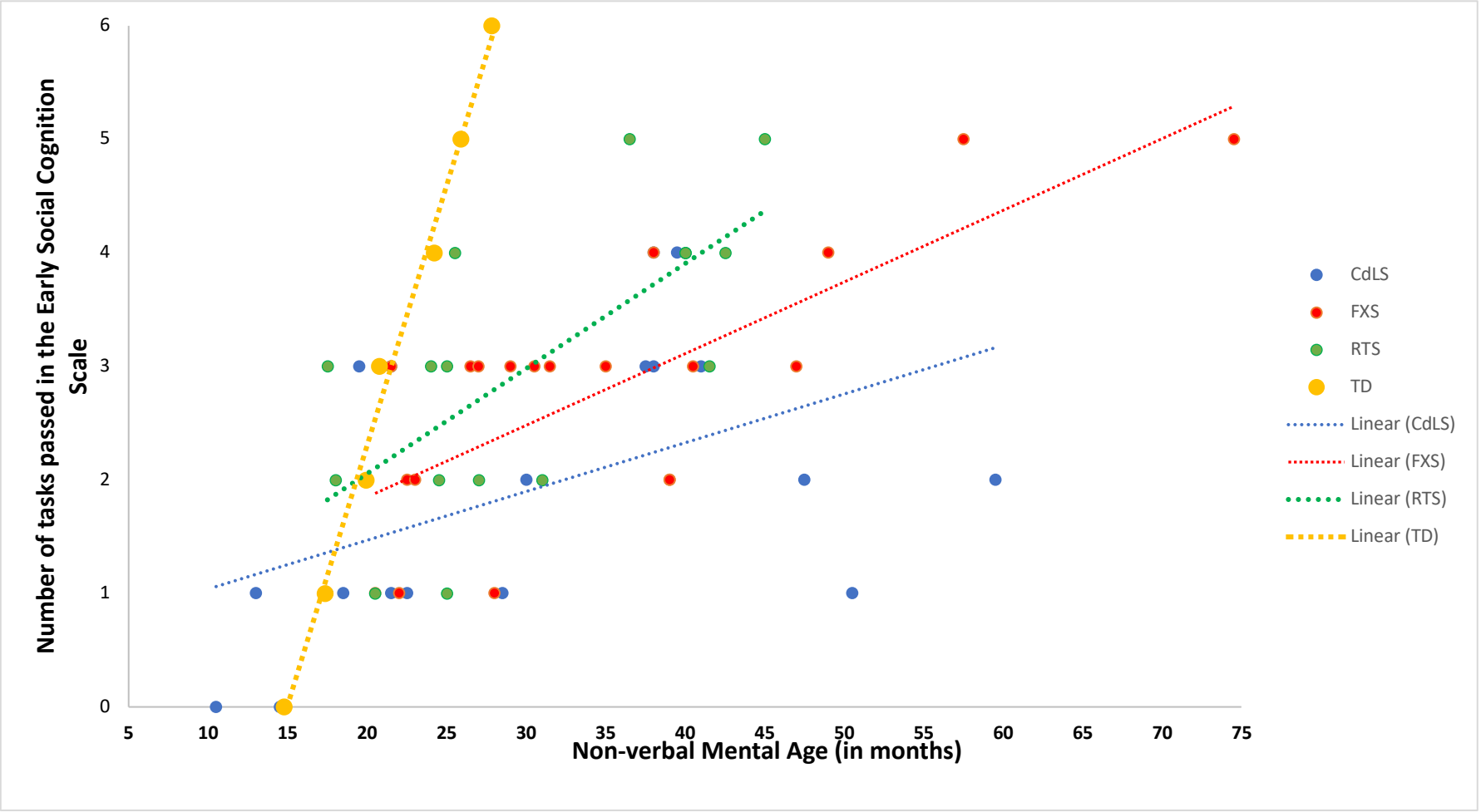


***Figure* 4.1.** *Number of tasks each participant passed in the* ESCS *plotted against their non-verbal mental age for each syndrome and mean age that TD infants pass each number of tasks, derived from previous literature (Powis, 2014; Powis et al., in revision).*

To explore whether one group may be more delayed than another overall, a Kruskal-Wallis test was conducted to investigate whether syndrome groups differed in the number of tasks they passed. Significant differences were found in the number of tasks passed between syndromes ($\chi(2)=7.08$, $p=.03$). Post-hoc Mann Whitney U tests revealed that both individuals with FXS ($U(39)=131.50$, $z=-2.11$, $p=.04$, $r=0.33$) and RTS ($U(38)=113.50$, $z=-2.37$, $p=.02$, $r=-.36$) passed significant more tasks than the CdLS group. There were no significant differences found between individuals with FXS and RTS, despite differences in chronological age between these groups (Table 4.1). These findings suggest that overall individuals with CdLS show a greater delay in acquiring intentionality abilities than individuals with FXS and RTS.

4.4.1.4. The developmental sequence of intentionality abilities in children with CdLS, FXS and RTS: Comparisons to TD children.

Guttman scaling analysis was conducted to explore whether those within each syndrome developed social cognitive abilities in the stringent and cumulative order observed in TD infants (Powis et al., in revision, Powis, 2014). Scaling establishes whether a very specific sequence (i.e. one in which children will pass all tasks in order of difficulty up to a certain task dependent on their developmental stage and subsequently fail any task that is more difficult past that point) emerges reliably *within* children. The technique "constrains theorising" surrounding whether and how these abilities are developmentally related (Wellman & Liu, 2004) by capturing the *progression* that these tasks develop as opposed to simply what ages they are observed. As such, scaling analysis goes beyond replicating statistical differences found between groups of ages outlined in previous studies and establishes a conceptual framework by identifying whether a set of varied abilities considered

related to one another theoretically form a consistent and stringent developmental sequence. The developmental progression outlined by Powis, Wellman and colleagues indicates that the abilities assessed are distinct stepping stones of the same developmental sequence (as opposed to occurring at these ages coincidentally) in either the *ESCS* or the *ToMS* respectively.

Each group was assessed for the degree the cohort's responses conformed to the original four-item Guttman scale observed in TD infants. Because the tasks *Re-enactment of Intended Acts* and *Gestures-Point* are both attained at a similar age in TD infants (around 18 months; Bellagamba and Tomasello, 1999; Behne et al., 2005; Powis, 2014), as are *Gestures-Gaze* and *Cooperation-Tubes* tasks (around 24 months; Powis, 2014; Behne et al., 2005; Warneken, Chen & Tomsello, 2006), these tasks were placed on a step of equal difficulty. Children were coded as having passed that step if they had passed either of the tasks of equal difficulty (e.g. *Re-enactment of Intended Acts* OR *Gestures-Point*).

Three summary statistics were calculated: 1) the percentage of children who fit the proposed order exactly, 2) the co-efficient of reproducibility (*Rep*) and 3) the index of consistency (*IoC*). The *Rep* indicates how much the pattern of passes and fails fit into a perfect Guttman scale by measuring how many responses deviate from this ideal scale. As it is unlikely to attain a perfect scale across all participants, an approximation of the perfect scale is 0.9 or above – i.e. the data are at least 90% reproducible (Guttman, 1947). The *IoC* estimates whether the observed co-efficient of reproducibility is significantly greater than that achieved by chance. An *IoC* of 0.5 or more is considered scalable.

Green's (1956) technique was used to calculate an estimation of the *Rep* and *IoC*. Green provides two techniques of estimating *Rep*, both identifying the number of "errors" that deviate from an expected pattern. For example, a participant may demonstrate the following response pattern: (--, --, +, +, --), in which items are ranked easiest to most difficult, and ranked from one

to five. 'First-order errors', i.e. items that show errors adjacent to one another (--, +), are removed and counted. In the current example-, items two and three are removed leaving the following pattern: (--, +, --). Following the same procedure, second-order errors are then removed and counted (now between items originally labelled one and four), leading to a total error count of two and the following pattern: (--). Depending on the number of items, further higher-order errors can also be removed and counted. The equation is as follows:

$$\textbf{Rep} = \mathbf{1}\frac{\mathbf{1}}{\boldsymbol{Nk}}\sum\textbf{(+ -)} - \frac{\mathbf{1}}{\boldsymbol{Nk}}\sum\textbf{(+ + - -)} - \textbf{terms of higher order}$$

The simplified formula to calculate the *Rep* is as follows, in which *E* is the total number of errors/deviations from the expected pattern, *N* is the number of participants, and *k* is the number of tasks (Green, 1956):

$$\textbf{Rep} = \mathbf{1} - \frac{\mathbf{E}}{\boldsymbol{Nk}}$$

The techniques by Green (1956) provides an estimate of *Rep* as it considers only first and second order errors, based on the reasoning that higher order errors are unlikely to occur. The two techniques differ in that whereas *RepA* calculates second-order errors by tabulating the raw data, *RepB* provides a formula that is only an estimate for these errors (further information on how these are calculated is outlined in Green, 1956). Both the average discrepancy between the two *Rep* estimates and the *'true Rep'* are negligible (0.002 and 0.003 for *RepA* and *RepB* respectively). However, the following analysis reports *RepA* calculations as overall it provides a slightly more accurate estimate to the *'true Rep'* than *'RepB'*.

Table 4.4 shows the scalogram patterns previously observed in TD infants, and the percentage of children in each syndrome group whose responses fitted each pattern perfectly. Although many individuals fitted one of the expected patterns (73% of children with CdLS, 74% with FXS and 78% with RTS), results indicate that none of the syndrome groups passed the tasks in the same scalable fashion as TD infants. For the CdLS group, although the co-

efficient of reproducibility was .93, the index of consistency was .32. For the FXS group, whereas the co-efficient of reproducibility was .93, the index of consistency was .11. Finally, for the RTS group the co-efficient of reproducibility was .94, but the index of consistency was .41. These findings suggest that individuals with CdLS, FXS and RTS do not develop early social cognition skills in the same order as TD infants. This is supported by visual inspection of the pass and fails for each step as per the original scale (Appendix I) which reveals many errors in all syndromes where participants fail supposedly easier tasks, but pass more difficult tasks.

Table 4.4
Guttman scalogram of patterns of performance for the four item ESCS observed in children with CdLS, FXS and RTS

Pattern	0	1	2	3	4	Other patterns	*N*	*N* fit scale exactly
Helping	-	+	+	+	+			
REI or Point	-	-	+	+	+			
Gaze or Tubes	-	-	-	+	+			
Trampoline	-	-	-	-	+			
Syndrome								
CdLS	2	3	7	2	2	6	22	16 (73%)
FXS	0	0	7	5	2	5	19	14 (74%)
RTS	0	2	5	2	5	4	18	14 (78%)

A plus sign indicates that a child passed a task, whereas a minus sign indicates that a child failed a task.

4.4.1.4.1 Exploring alternative developmental sequences of early social cognitive abilities: Pairwise comparisons.

To explore whether individuals with CdLS, FXS and RTS develop social cognitive abilities in a reliable but alternative progression to TD infants, McNemar's tests with Yate's corrections were conducted between tasks increasing in difficulty for each syndrome group. Bonferonni corrections were used to control for family wise errors. However, there is an

argument that Bonferonni corrections may be too conservative (Pallant, 2007), especially in smaller sample sizes. Therefore, results are presented first without corrections (figure 4.2), and then with corrections (figure 4.3).

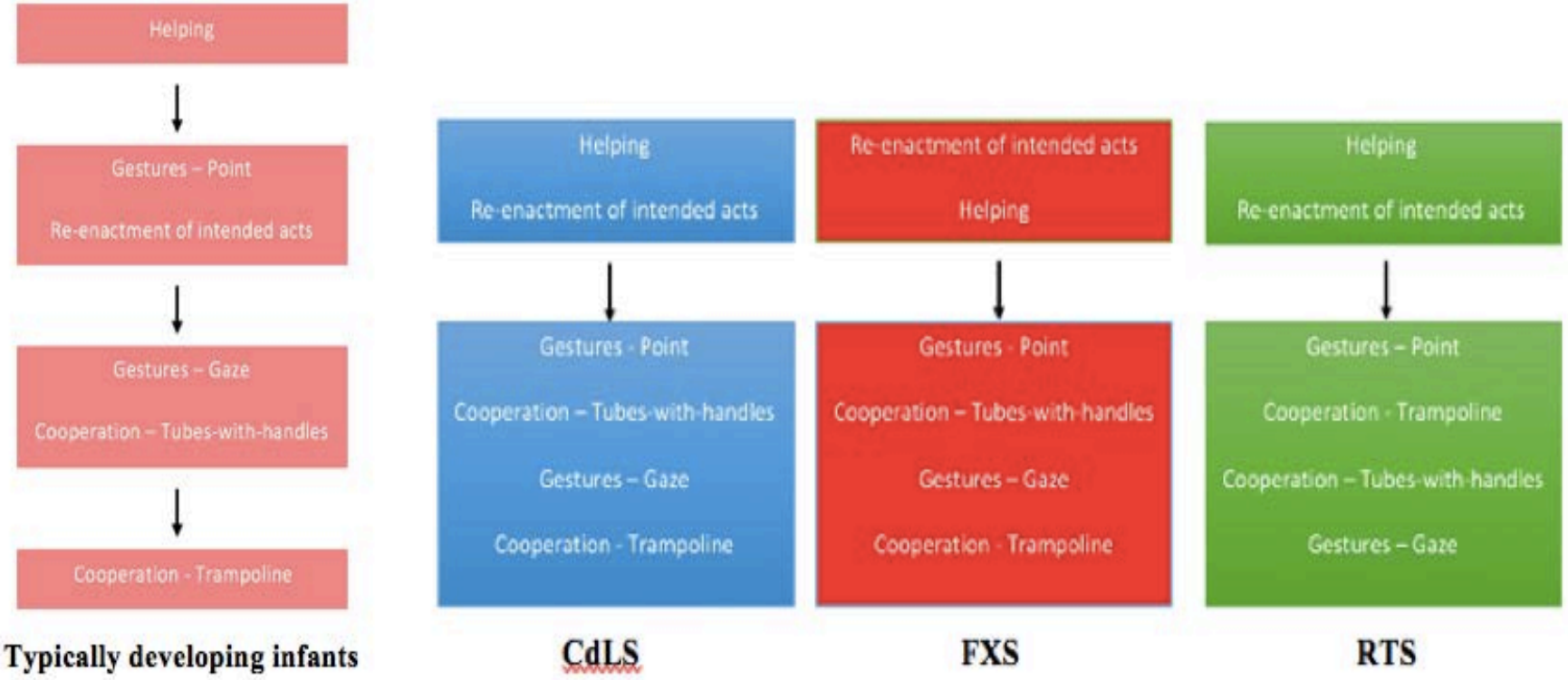


Figure 4.2. *Developmental progression children with CdLS, FXS and RTS passed ESCS tasks before correcting for multiple comparisons compared with the developmental sequence observed in TD infants (Powis, 2014; Powis et al., in revision**).***

4.4.1.4.1.1 CdLS.

Uncorrected pairwise comparisons revealed that the *Gestures-Point* task was significantly harder than *Re-enactment of Intended Ccts* (p=.04) but no significant differences were found between *Helping* and *Re-enactment of Intended Acts*, *Gestures-Point* and *Cooperation-Tubes*, *Cooperation-Tubes* and *Gestures-Gaze*, or the *Gestures-Gaze* and *Cooperation-Trampoline* task pairs. When corrected, no significant differences were found between any task pairs.

4.1.1.4.1.2. FXS.

Uncorrected comparisons revealed that the *Cooperation-Tubes* task was significantly harder than the *Helping* task (p<.01). No differences were found between *Re-enactment of Intended Acts* and *Helping*, the *Gestures-Point* and *Cooperation-Tubes*, the *Cooperation-Tubes* & *Gestures-Gaze* and the *Gestures-Gaze* and *Cooperation-Trampoline* task pairs. When corrected, the *Cooperation-Tubes* task remained significantly more difficult than the *Helping* task (p<.01).

4.1.1.4.1.3. RTS.

Uncorrected comparisons revealed that the *Gestures-Point* task was significantly more difficult that the *Re-enactment of Intended Acts* task (p=.04). No differences were found between *Helping* and *Re-enactment of Intended acts*, the *Gestures-Point* and the *Cooperation-Trampoline*, the *Cooperation-Trampoline* and *Cooperation-Tubes* or the *Cooperation-Tubes* and *Gestures-Gaze* task pairs. When corrected, no significant differences were found between any task pairs.

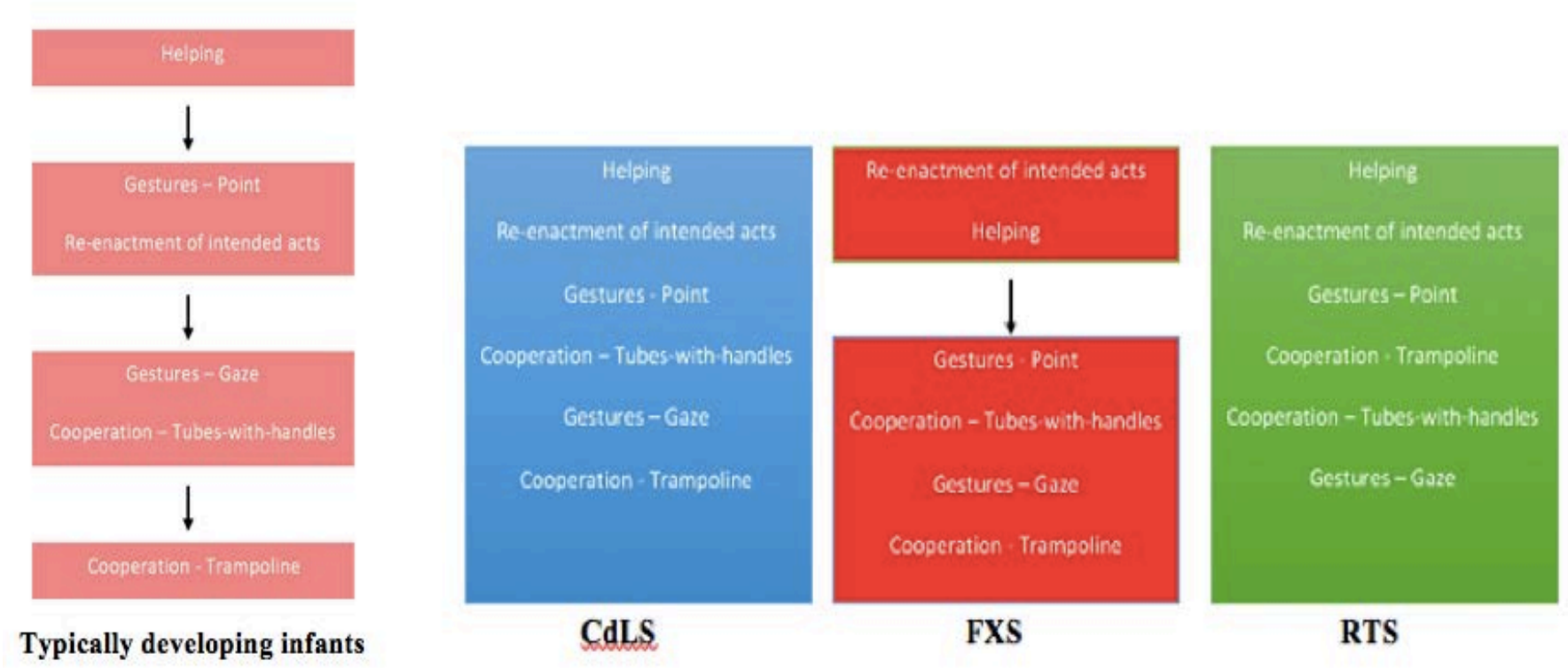


Figure 4.3. *Developmental progression children with CdLS, FXS and RTS passed ESCS tasks after Bonferonni corrections compared with the developmental sequence observed in TD infants (Powis, 2014; Powis et al., in revision)*

4.4.1.5. Summary of ESCS results

Although the number *ESCS* tasks that participants passed increased with non-verbal mental age, individuals with CdLS, FXS and RTS show a delay in developing intentionality abilities given their non-verbal mental age. In addition, at a group level individuals with CdLS seem to show a greater delay in acquiring these abilities relative to those with FXS and RTS.

As well as showing delay, all three syndromes show a difference in early social cognitive development compared to TD infants. Guttman scaling analysis revealed that none of the groups passed *ESCS* tasks in the same cumulative sequence as TD infants. Prior to Bonferroni corrections, pairwise comparisons between tasks of increasing difficulty for each syndrome revealed a similar pattern in which the two of the easiest tasks (*Helping* and *Re-enactment of Intended Acts)* are significantly easier than the last four (both *Gestures* and both *Cooperation* tasks). However, this difference remained significant only in the FXS group following corrections.

4.4.2. Theory of Mind Scale

This section describes investigation of the development of ToM abilities in individuals who participated in the *ToMS*.

4.4.2.1. Demographic Characteristics.

Eighteen children and adults with CdLS (M_{age}=21.43 years, SD=11.15), sixteen with FXS (M_{age}=23.98, SD=10.45) and fifteen with RTS (M_{age}=22.35, SD=15.50) took part in the *ToMS*. Table 4.5 shows that the groups did not differ significantly on chronological age or non-verbal mental age. The groups were again not comparable on gender due to FXS disproportionately affecting males.

Table 4.5
Participant characteristics for children and adults who participated in the ToMS

	CdLS (*n*=18)	FXS (*n*=16)	RTS (*n*=15)	*p*	Post-hoc tests (*p*<.05)
Mean chronological age in years (SD)	21.43 (11.15)	23.98 (10.45)	22.35 (15.50)	0.52	
Gender % female	67%	0%	53%	**<.01**	CdLS, RTS < FXS
Mean non-verbal mental age in years (SD)	5.37 (1.89)*	4.33 (.66)**	4.44 (.86)***	0.16	

* Information not available for one participant due to non-completion of the relevant measure

** Information not available for one participant due to floor/ceiling performance

*** Information not available for three participants due either to 1) floor/ceiling performance (one participant) or 2) non-completion of non-verbal scales of a cognitive assessment.

4.4.2.2. Control conditions.

To pass the four most difficult tasks of the *ToMS*, individuals were required to also pass control questions that assessed their comprehension and memory of the stories they were told. *Knowledge Access*, *Contents False Belief*, *Hidden Emotion* and *Sarcasm* tasks had additional control questions to assess whether participants who failed these tasks could comprehend or remember the story. Out of 21 participants from the entire sample who failed the *Knowledge Access* task, six participants (26%) passed the associated control question. Out of forty participants who failed the *Contents False Belief* task, twenty (50%) passed the control question. Out of fifty-six participants who failed the *Hidden Emotion* task, eighteen (32%) passed the first control question, and only two passed the second (4%). Finally, out of fifty-nine participants who failed the *'Sarcasm'* task, thirty-nine (66%) passed the preliminary question and thirty-one (53%) passed the control question. In previous studies, TD children who failed the target questions had passed these control questions, suggesting that these

children failed tasks due to a lack of that social cognitive ability. (Wellman & Liu, 2004). However, it is unclear whether participants in the current study failed tasks due difficulty with ToM or memory difficulties (Powis, 2014).

Table 4.6 shows the breakdown of the numbers of participants who failed tasks with control questions and, of these participants, the number that also failed the respective control tasks. To investigate whether one syndrome failed the control questions more often than others, Kruskall-Wallis tests were run to compare the number of control questions that participants got correct overall between syndromes. Results showed that the groups significantly differed ($\chi(2)=14.33$, $p<.01$). Mann-Whitney U tests revealed that individuals with RTS passed significantly less control questions in comparison to individuals with both CdLS ($U(2)=47.00$, $z=-3.05$, $p<.01$, $r=-.54$) and FXS ($U(2)=20.50$, $z=-3.35$, $p<.01$, $r=-.61$). Overall, these findings suggest that individuals with RTS may have had greater memory problems than those with CdLS and FXS in these tasks, which may have led many of these individuals to fail tasks in the *ToMS*.

Table 4.6.
Number and percentage of participants who failed each ToMS task with control tasks out of the total cohort and the number of participants within that sample who also failed the relevant control tasks per syndrome

	Total sample (*N*=49)	CdLS (*N*=18)	FXS (*N*=16)	RTS (*N*=15)
Knowledge Access	22 44%	6 33%	5 31%	11 73%
Knowledge Access control question	15 68%	4 67%	2 40%	9 82%
Control False Belief	40 81%	12 67%	14 88%	14 93%
Contents False Belief control question	19 48%	5 42%	4 29%	10 71%
Hidden Emotion	46 94%	16 89%	16 100%	14 93%
Hidden Emotion control question 1	27 59%	11 69%	5 31%	11 79%
Hidden Emotion control question 2	41 89%	14 88%	16 100%	11 79%
Sarcasm	49 100%	18 100%	16 100%	15 100%
Sarcasm preliminary question	17 49%	5 28%	2 13%	10 67%
Sarcasm control question	16 33%	5 28%	3 19%	8 53%

4.4.2.3. Developmental trajectory of ToM abilities in children and adults with CdLS, FXS and RTS

Table 4.7 shows the number of participants who passed each task within each syndrome group. Figure 4.4 shows participants' non-verbal mental age plotted by the number of tasks passed in the *ToMS* for participants for whom this information was available (table 4.5), alongside the mean age TD children who originally participated in the validation study of the *ToMS* typically achieved the number of tasks (Wellman & Liu, 2004). Kendall Tau correlations were run to determine if there was an association between participants' non-verbal mental age and the number of tasks they passed in the *ToMS* in each syndrome. Individuals with CdLS ($\tau_b(15)=.50$, $p=.01$) and RTS ($\tau_b(10)=.53$, $p=.04$). showed moderate positive associations. No association was found in individuals with FXS.

Table 4.7.
Percentage of individuals passing each ToMS item per syndrome group compared to TD children (Wellman & Liu, 2004)

	TD (n = 75*	CdLS (n = 18)	FXS (n = 16)	RTS (n = 15)
Diverse Desires	71 (95%)	17 (94%)	14 (88%)	15 (100%)
Diverse Beliefs	63 (84%)	14 (78%)	15 (94%)	14 (93%)
Knowledge Access	55 (73%)	11 (61%)	11 (69%)	4 (27%)
Contents False Belief	44 (59%)	6 (33%)	2 (13%)	1 (7%)
Hidden Emotion	39 (52%)	2 (11%)	0 (0%)	1 (7%)
Sarcasm	N/A	0 (0%)	0 (0%)	0 (0%)

*Percentages for TD sample taken from Wellman & Lui (2004)

Visual inspection of figure 4.4 indicates large variation in participants' performance relative to their ability and differences in advanced and delay skills between earlier and later developing ToM abilities. Some individuals in all groups show advanced ToM abilities relative to their non-verbal mental age, whereas others show a delay. The lines of best fit suggest that, at a group level, most participants showed advanced abilities assessed by the first two easiest tasks of the *ToMS*, as several participants passed these tasks with a lower non-verbal mental age that TD children typically pass these tasks (Wellman & Liu, 2004). However, the point at which the lines of best fit for each syndrome intersect with the line of best fit for TD children indicate that these groups show a delay in passing the final four tasks.

To investigate whether any of the groups show overall better or worse performance from one another, Kruskall-Wallis tests were run to evaluate whether groups differed overall in the number of tasks they passed. Results showed that there were no significant differences across groups ($\chi(2)=2.33$, $p = .31$). These findings suggest that social cognitive ability does not broadly differ across groups.

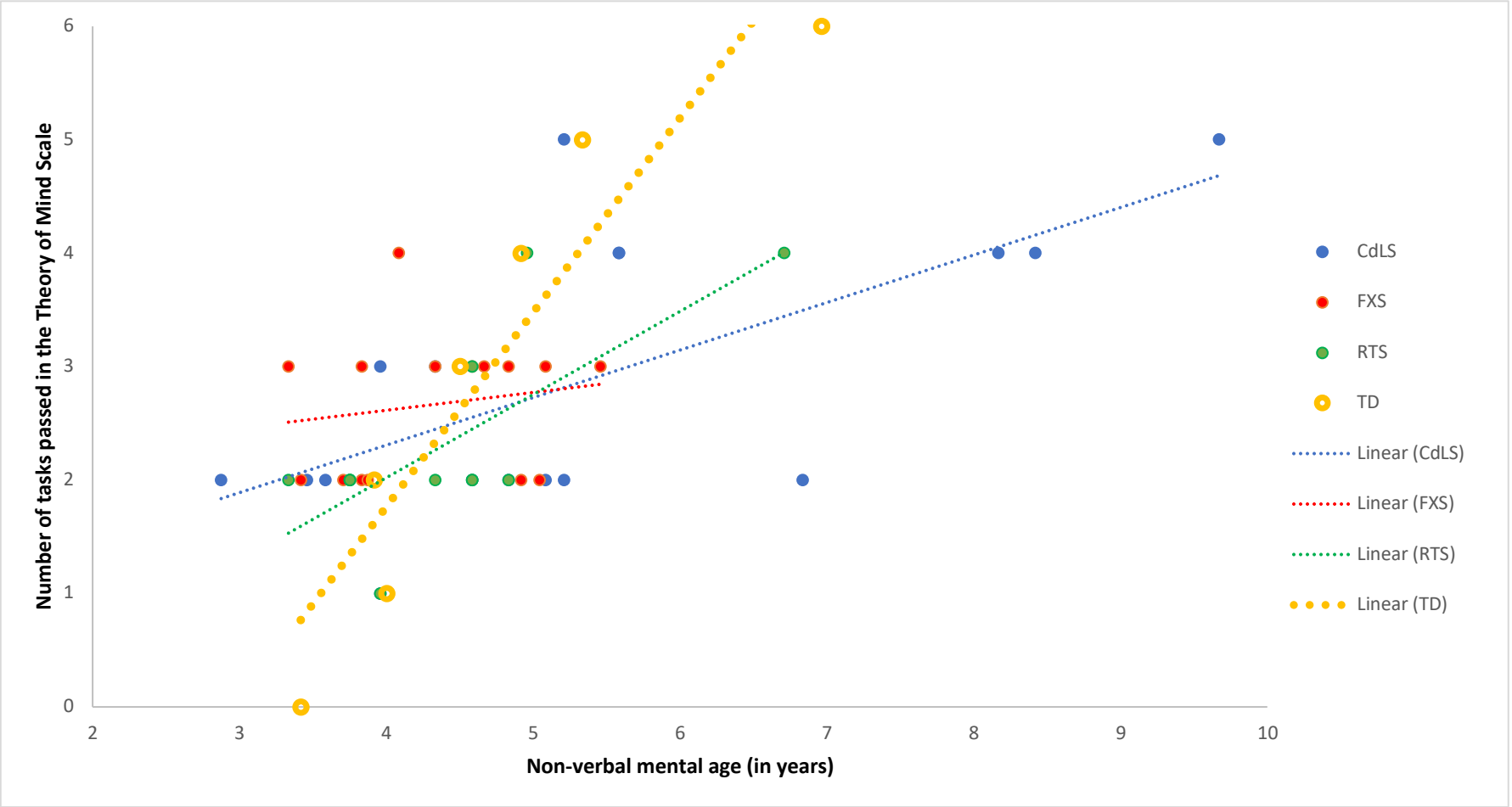


Figure 4.4. *Number of tasks each participant passed in the* ToMS *plotted against their non-verbal mental age for each syndrome and mean age that typically developing (TD) pass each number of tasks, derived from previous literature (Wellman & Lui, 2004).*

4.4.2.4. The developmental sequence of ToM abilities in children with CdLS, FXS and RTS: Comparisons to TD.

Table 4.8 shows the scalogram patterns previously observed in TD and the percentage of participants in each syndrome group whose responses fitted each pattern perfectly. Although many individuals fitted one of the expected patterns (83% of individuals with CdLS, 82% with FXS and 93% with RTS), results indicate that none of the syndrome groups passed the tasks in the same scalable fashion as TD children. For the CdLS group, although the co-efficient of reproducibility was .96, the index of consistency was .43. For the FXS group, whereas the co-efficient of reproducibility was .97, but the index of consistency was .06. Finally, for the RTS group the co-efficient of reproducibility was .99, and the index of consistency approached the cut-off point at .48.

Table 4.8
Guttman scalogram of patterns of performance for the six item ToMS observed in children with CdLS, FXS and RTS

Pattern	0	1	2	3	4	5	6	Other patterns	*N*	*N* fit scale exactly
Diverse Desires	-	+	+	+	+	+	+			
Diverse Beliefs	-	-	+	+	+	+	+			
Knowledge Access	-	-	-	+	+	+	+			
Contents False Belief	-	-	-	-	+	+	+			
Hidden Emotion	-	-	-	-	-	+	+			
Sarcasm	-	-	-	-	-	-	+			
CdLS	0	1	6	3	3	2	0	3	18	15 (83%)
FXS	0	0	5	7	1	0	0	3	16	13 (82%)
RTS	0	1	10	2	1	0	0	1	15	14 (93%)

A plus sign indicates that an individual passed a task, whereas a minus sign indicates that an individual failed a task.

Visual inspection of pass and fails per participant (appendix J) shows that whereas deviations from the scale seen in participants with CdLS and FXS consist of failures in easier tasks and success in more difficult tasks, only one error that does not conform to a cumulative pattern was seen by one individual with RTS in a later task (*Contents False Belief*). Unlike in individuals with CdLS and FXS, the pattern of pass and fails for the first tasks were consistent with the pattern observed in TD children. This is further confirmed when the *Rep* and *IoC* were calculated in each syndrome for only the first four tasks. For individuals with CdLS the *Rep* was .93, but the IoC was .1. For individuals with FXS, the *Rep* was .95 but the IoC was .06. Finally, for individuals with RTS, the *Rep* was 1 and the *IoC* was 1, indicating a perfect scale. These findings suggest that individuals with CdLS and FXS do not develop ToM abilities in the same order as TD children. In comparison, individuals with RTS show the same scale progression as TD children in at least the first three tasks.

4.4.2.4.1. Exploring alternative development progressions of ToM abilities: Pairwise comparisons.

To explore whether individuals with CdLS and FXS develop these abilities in a reliable but alternative progression to TD children, McNemar's tests with Yate's corrections were conducted between tasks increasing in difficulty for each syndrome group. The same procedure was applied to RTS to investigate whether there were any strengths and weaknesses between early and later developing ToM tasks. Both uncorrected and Bonferroni corrected results used to control for family wise errors are presented. Figure 4.5 summarises the developmental sequence per syndrome compared against the sequence observed in TD.

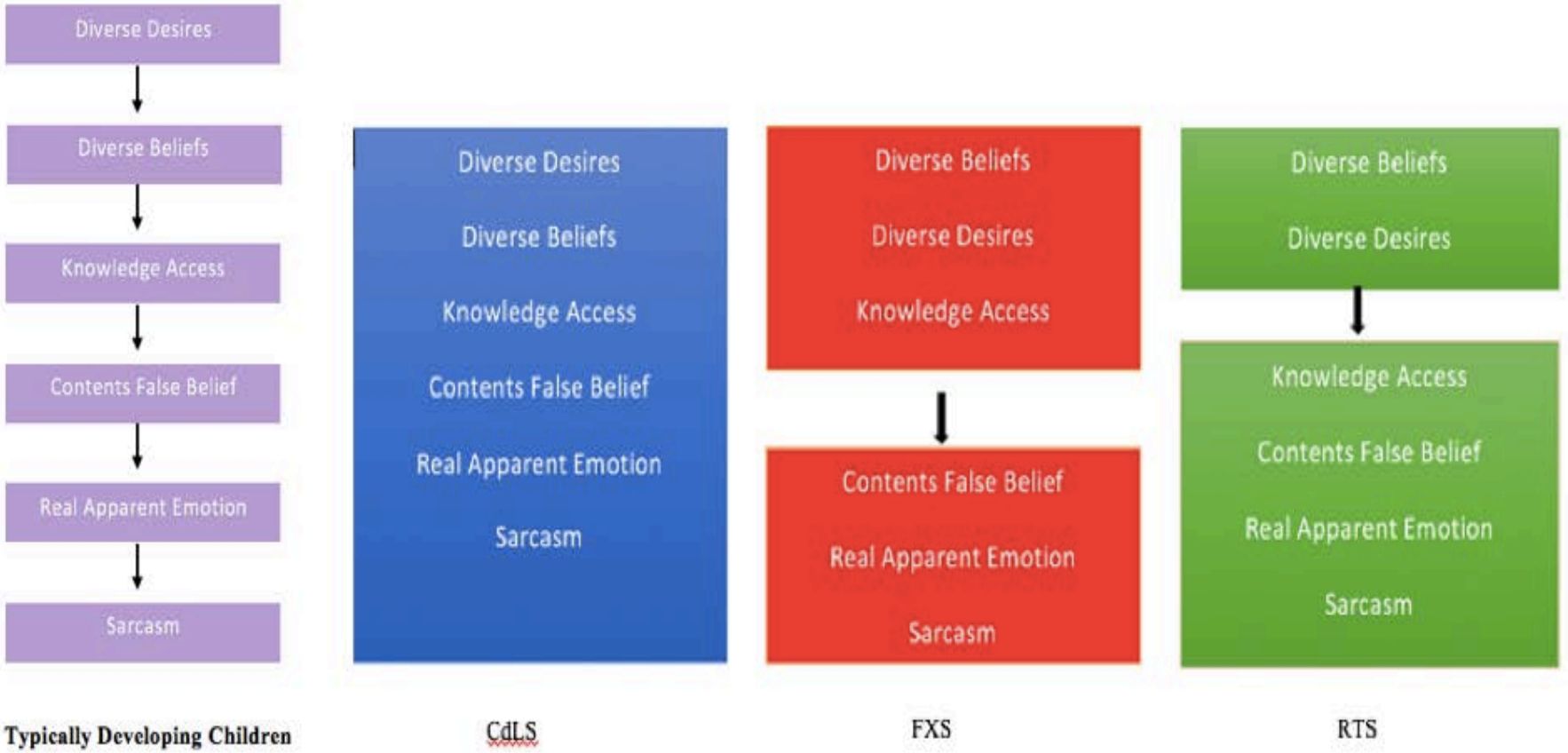


Figure 4.5. *The developmental sequence that individuals with CdLS, FXS and RTS pass tasks in the ToMS compared with the developmental sequence observed in TD children after corrections (Wellman & Liu, 2004; Peterson et al., 2005; 2012)*

4.4.2.4.1.1. CdLS.

No task was found to be significantly more difficult in any of the task pairs.

4.4.2.4.1.2. FXS.

When uncorrected, the *Contents False Belief* was significantly harder than the *Knowledge Access* task ($p<.01$). No differences were found between *Diverse Beliefs* and *Diverse Desires*, *Diverse Beliefs* and *Knowledge Access*, *Contents False Belief* and *Hidden Emotion*, or *Hidden Emotion* and *Sarcasm* task pairs. When corrected, *Contents False Belief* remained significantly harder than *Knowledge Access* (p=.02).

4.4.2.4.1.3. RTS.

When uncorrected, pairwise comparisons revealed that the *Knowledge Access* task was significantly harder than *Diverse Beliefs* task ($p<.01$), but no significant differences were found between the *Diverse Desires* and *Diverse Belief*, *Knowledge Access* and *Contents False Belief*, *Contents False Belief* and *Hidden Emotion*, or the *Hidden Emotion* and *Sarcasm* task pairs. When corrected, *Knowledge Access* remained significantly more difficult than *Diverse Beliefs* ($p=.01$).

4.4.2.5 Summary of ToMS results

Overall ToM ability increased with non-verbal mental age in individuals with CdLS and RTS, but not FXS. All groups show variability in overall ToM ability, with some participants showing a delay and others shows advanced social cognitive abilities. Whilst there is a lot of variability across participant's performance, at a group level the lines of best

fit indicate an overall pattern of advanced abilities for the first two easiest tasks, and delay in the final four most difficult tasks.

Guttman scaling analysis revealed that none of the groups passed *ToMS* tasks in the same cumulative sequence as TD children. Both before and after Bonferroni corrections, pairwise comparisons between tasks of increasing difficulty for each syndrome revealed different patterns of strengths and weaknesses. Individuals with FXS found the three easiest tasks (*Diverse Desires, Diverse Beliefs,* and *Knowledge Access*) significantly easier than the three most difficult tasks (*Contents False Belief, Hidden Emotion*, and *Sarcasm*). Individuals with RTS found the two easiest tasks (*Diverse Desires* and *Diverse Beliefs*) significantly easier than the four most difficult tasks (*Knowledge Access, Contents False Belief, Hidden Emotion* and *Sarcasm*). In contrast, individuals with CdLS did not show any differences in performance between tasks. However, these results must be interpreted with caution in reflection of analysis of control trials, which indicate that many individuals who failed tasks, particularly those with RTS, also failed their corresponding control trials. These findings make it difficult to discern whether these participants failed due to a lack of understanding of these later ToM concepts, or whether other factors such as memory difficulties may have contributed to performance.

4.5. Discussion

This study employed novel experimental instruments to explore both the presence of delay and difference of social cognitive development in children and adults with CdLS, FXS and RTS. Social cognitive ability was assessed using robust behavioural tasks that are well established within the literature, with success on these tasks indicative of a participant's

understanding of other's intentionality and mental states. This is the first study to characterise the development of a broad range of social cognitive abilities across genetic syndromes that have been shown to have subtle but unique profiles of sociability, across a range of social cognitive abilities that develop from infancy to adolescence.

The first aim was to investigate whether overall social cognitive ability in individuals with CdLS, FXS and RTS was advanced, preserved or delayed relative to non-verbal mental age. The second aim was to investigate whether participants in each syndrome group passed social cognitive tasks in the same stringent and cumulative order as TD infants and children or whether they passed tasks in an order unique to their syndrome. Therefore, these findings are discussed in three sections: the first summarising findings from the *ESCS*, the second summarising findings from the *ToMS*. Findings are then discussed more broadly in terms of themes that are related to both scales and social cognitive development.

4.5.1. Early Social Cognition Scale

In the *ESCS,* the higher a child's non-verbal mental age, the greater numbers of social cognitive tasks they passed. However, visual inspection of the number of tasks that each participant passed plotted against participant's non-verbal mental age per syndrome suggested that overall, participants in all groups were delayed in passing many of these tasks, despite most individuals reaching the non-verbal mental age that would be expected to pass them. In addition, despite the groups not differing on non-verbal mental age, children with CdLS passed significantly less tasks than children with FXS or RTS. This finding suggests that individuals with CdLS show a greater delay in developing intentionality abilities.

Guttman scaling analyses revealed that individuals with CdLS, FXS or RTS did not develop intentionality abilities in the same developmental order as TD infants. These

findings indicate that early social cognitive development is disrupted in children with CdLS, FXS and RTS.

Prior to corrections for multiple comparisons, all groups showed a pattern in which the first two easiest tasks were spared (*Helping* and *Re-enactment of Intended Acts*) relative to the last four more difficult tasks (*Gestures-Point*, *Gestures-Gaze*, *Cooperation-Tubes*, and *Cooperation-Trampoline)*. However, when corrected, this pattern of strengths and weaknesses is lost in the CdLS and RTS groups but remains for the FXS group. These findings indicate that children with FXS show more pronounced strengths and weaknesses, whereas individuals with CdLS and RTS show a more heterogeneous profile across tasks. Although individuals with CdLS and RTS did not show the same extreme drop-off point as individuals with FXS, it is interesting that a similar drop-off point was observed before corrections for multiple comparisons. Specifically, the difference in performance between the *Re-enactment of Intended acts* and *Gestures-Point* tasks, which typically emerge around the same developmental point in TD infants (Powis, 2014; Powis et al., in revision), is particularly interesting and may have theoretical implications for how these abilities develop.

Tomasello and colleagues (2005) propose that two developmental streams that emerge in infancy contribute to an individual developing a shared intentionality with another person. These are: 1) a basic understanding of other's intentional actions, shared at least with some other great ape species and 2) a species unique motivation to share their psychological states with others, to represent shared states cognitively and to communicate to direct another's attention to a shared object of interest (Moll & Tomasello, 2007; Frith, 2008). Despite the abilities that are required to pass the *Helping* and *Re-enactment of Intended Acts* tasks typically emerge at different developmental steps, they may contribute to the same

developmental stream. Passing the first two easiest abilities may reflect that an individual has developed the first stream but shows a significant delay in the latter.

The profile of strengths and weaknesses may also reflect the importance of joint attention. Joint attention is a social referencing skill that enables an individual to respond to and direct another person's attention to environmental stimuli (Mosconi, Reznick, Mesibov, & Piven, 2009), enabling two individuals to share attention on stimuli of interest within the environment (Tomasello & Carpenter, 2007). Previous literature indicates that JA is an important precursor to language development, ToM and socialisation skills in Down syndrome, FXS and TD children (Charman et al., 2000; Mundy, Sigman, & Kasari, 1990; Hahn et al., 2013; Hahn, Brady, Fleming & Warren, 2016). Joint attention is hypothesised to be a crucial component of shared intentionality by sharing common ground to enable cooperative activities (Tomasello & Carpenter, 2007) and impairments in social orienting, including joint attention, are early core impairments in individuals with iASD (Adamson, Bakeman, Deckner & Nelson, 2012; Mosconi et al., 2009; Lord et al., 2012).

Joint attention may be a key skill required to pass the more difficult tasks in the *ESCS*. During the *Helping* and *Re-enactment of Intended Acts* tasks, the participant can pass the task by inferring the examiner's intention by their actions. In comparison, the latter four tasks of the scale require the ability to respond and use triadic engagement. Whereas in both *Gestures* tasks, participants must respond to the examiners use of joint attention to choose the correct box that a toy is hidden, in the *Cooperation* tasks, participants must respond to the examiner's use of joint attention inviting participate in the cooperative activities and use joint attention to reengage the examiner during an interruption period when the examiner discontinues their role.

The distinct pattern of strengths and weaknesses observed in children with FXS may indicate greater difficulties with initiating and/or responding to joint attention. Wollf and

colleagues (2012) found that although individuals with FXS were more able to respond to others' joint attention compared to individuals with iASD, they demonstrated a comparable level of difficulty with initiating joint attention. In addition, relative to TD children, individuals with FXS may still be impaired (albeit less so than children with iASD). Difficulties in joint attention is likely in these individuals when considering the extreme gaze aversion observed in those with FXS (Wolff, Gardner, Paccia & Lappen, 1989; Crawford et al., in prep). Gaze aversion would make it difficult to track and respond to another person's use of gaze to direct their attention and for the person with FXS to direct another person's attention whilst avoiding looking at the eye area. Cross-syndrome comparisons comparing the profiles of joint attention skills may better elucidate the degree to which joint attention influences differences in social cognition between these syndromes.

The current study's findings differ from previous research investigating social cognitive development in individuals with RTS. In the current sample, children with RTS show an overall delay in passing early social cognitive tasks, whereas Powis (2014) concluded that these abilities are spared. When investigating overall social cognitive development, Powis assigned participants a 'scale point position' determined by the last task on the original order observed in TD before accruing two consecutive fails. However, the current study utilised total number of tasks passed, as using scale point positions based on the original order was deemed inappropriate as participants did not pass tasks in the same cumulative order as TD. Arguably, Powis' approach over-inflated overall social cognitive ability as participants who passed one later tasks but not earlier tasks would have been given a high scale point position.

Differences in findings are influenced by individual differences in the cohort's characteristics. All participant's in Powis' cohort passed both *Cooperation* tasks, whereas

only around one third of participants with RTS passed these in the current study. However, participants included in Powis' (2014) analysis were overall more able (mean mental age 46 months, compared to the current cohort's mean being 30 months) and included a greater range of abilities (range of mental age of participants who took part in the *ESCS* in the Powis (2014) study was between 15-89 months compared to 11-58 months in the current study). As the most difficult task in the *ESCS* emerges in TD children just after twenty-four months, the lack of difference in performance in the original cohort may reflect ceiling effects in Powis (2014) study, that are not reflected in the current cohort due to a lack of individuals included who we may expect to pass these tasks after accounting for general delay.

In addition, Powis concluded that children with RTS found all tasks were a similar level of difficulty except for the *Gestures-Gaze* task, which individuals in this previous cohort found particularly challenging in comparison to all other tasks. However, this pronounced difficulty in *Gestures-Gaze* was not found in the current study. Differences in findings likely reflect differences in data analyses procedures. Powis found that all participants passed the *Helping* and both *Cooperation* tasks, 81% passed the *Re-enactment of Intended acts* and *Gestures-Point* tasks, and 57% passed the *Gestures-Gaze* task, and ran comparisons between all tasks. Whereas the *Gestures-Gaze* task was significantly harder than the *Helping* and both *Cooperation* tasks, no other differences were found. The lack of differences between tasks is likely due to having to correct for multiple comparisons, meaning that differences were found between only the easiest and hardest tasks. Although gaze had the lowest number of participants who passed, the procedure used in this study would not have picked up differences between very easy and very difficult tasks, as comparisons were only made between tasks increasing in difficulty. This procedure was deemed more appropriate to

investigate the developmental progression of these tasks without having to run as many multiple comparisons.

4.5.2 Theory of Mind Scale

In the *ToMS*, whereas individuals with CdLS and RTS showed an increase in the number of tasks that they passed with age, the FXS group did not show this association. These findings suggest that whilst individuals with FXS acquire earlier ToM abilities, they either: 1) show an increased delay in acquiring later ToM abilities or 2) may be unable to learn these abilities at all due to cognitive restraints that appear to not be directly associated with general cognitive ability.

Visual inspection of figure 4.4 indicates that some participants showed advanced ToM abilities in the first two tasks (*Diverse Desires* and *Diverse Beliefs*) relative to their non-verbal mental age. These findings may highlight the role of environmental experience that may scaffold these abilities within these groups. Although participant's non-verbal mental age may be comparable to the original validated sample of TD children, the current study's cohort included adults, whom over time will have had more exposure to social situations. Alternatively, individuals with CdLS, FXS and RTS may develop these abilities differently from TD children, perhaps dependent on their endophenotype. Individuals with iASD who pass false-belief tasks use different neurocognitive systems from TD individuals, representing mental states based on content of speech rather than social intuition per se. Instead, these individuals learn about others minds through listening and speaking with others to learn about other's mental states (Tager-Flusberg, 2007). These findings highlight the potential interacting roles of neurocognition and the environment upon the diverging development of social cognitive abilities in these genetic syndromes.

As in the *ESCS*, individuals with CdLS and FXS' task performance did not conform to the pattern observed in TD (Wellman & Liu, 2004; Peterson et al., 2005; 2012), with many individual's showing failures in typically easier ToMS tasks and success in more difficult tasks. In contrast, although individuals with RTS did not scale across the entire scale, their performance did show scaling within the first three tasks. Powis (2014) found that the performance on the original 5-item ToMS of a more able sample of children and adults with RTS followed the same order as TD children. These findings together suggest that the earlier developing ToM abilities required to pass the first three tasks in the *ToMS* may develop typically in individuals with RTS. Further work is needed to distinguish whether later tasks show a different pattern or not.

A relatively high proportion of individuals in all syndrome groups who failed tasks in the *ToMS* also failed their relevant control tasks. In contrast, very few TD children failed the control questions in the original studies (Wellman & Liu, 2004; Peterson et al., 2005; 2012). These findings suggest that whereas TD children failed tasks due to a lack of understanding of the relevant social cognitive concept that a task assessed, many participants in the current cohort may have failed tasks because of memory difficulties. Although tasks were intended to have been designed to be comparable in format and materials, they differ in critical aspects including the length of the vignette read to participants (ranging between 60 to 236 words), and the number of control questions that participants were required to answer correctly to pass the task (between 0 to 2), both of which tended to increase with more difficult tasks.

Individuals with RTS showed the most difficulty in passing these control questions. These difficulties may be due to attention (Galéra et al., 2009) and memory problems observed in individuals with RTS relative to their overall ability. Both verbal and visuo-spatial working memory has been shown to be impaired in individuals with RTS relative to

their mental age, with some participants struggling to retain as little as two items in memory despite demonstrating understanding of the task (Waite et al., 2016). These issues may reflect a syndrome specific deficit in RTS related to mutations that lead to reduced CREBBP, which has been linked to difficulties in mouse models for both long-term and short-term memory by activating genes important for learning and memory (Chen et al., 2010). Alternatively, poor performance on these tasks may reflect attention difficulties observed in those with RTS (Stephens et al., 1990; Galéra et al., 2009).

In contrast, individuals with FXS showed a 'drop-off' point between the *Knowledge Access* and *Contents False Belief* tasks. These findings correspond with Grant and colleagues' (2007) study, who found that boys with FXS show greater difficulties in false belief tasks compared to a group of boys with ID of mixed aetiology matched on ability. Out of those who failed, boys with FXS also failed the control trials significantly more than the comparison group. Like individuals with RTS, failures in some boys with FXS may be due to working memory difficulties, but less severely as individuals with RTS.

Individuals with CdLS and FXS whom failed tasks but passed control questions may have failed due to difficulties with executive function associated with these syndromes (Johnson, 2014). Executive function places top-down control over several processes competing for control of behaviour (Frith & Frith, 2012). These processes are required to be able to reflect, capitalise and learn from our experiences (Benson, Sabbagh, Carlson & Zelazo, 2013), inhibit initial responses to many tasks in the *ToMS* based on our own beliefs and knowledge of reality (e.g. as in the *contents false belief* task) and update our responses following reasoning about new information about the character's belief (Tager-Flusberg, 2007). It has been proposed that executive function is a prerequisite and determines the developmental trajectory of ToM development, although many of these assumptions have

been based on correlations between executive function and ToM abilities making it difficult to determine the direction of the relationship (Brunsdon & Happé, 2014). Further research is need to disentangle the association between executive function and ToM abilities in individuals with CdLS, FXS and RTS.

4.5.3 General discussion

Overall, syndromes did not conform to a cumulative pattern in either the *ESCS* or the *ToMS*. Visual inspection of the raw data indicates that there is a lot of heterogeneity in the patterns of pass and fails in individuals across all syndromes in both scales, with perhaps the exception of those with RTS who participated in the *ToMS*. These individual differences within syndromes development indicate the numerous interplaying genetic, motivational, cognitive and environmental factors that contribute to social cognitive development. Whereas the previous sections have discussed factors specific to abilities assessed by each battery, factors that may be related to social cognition broadly are discussed here.

These findings may be driven by the genetic heterogeneity in these syndromes. CdLS (Yuan et al., 2013; Whitehead et al., 2015) can be caused by abnormalities by several different genes and been shown to lead to within-syndrome differences (Sarimski, 2007; Deardorf et al., 2012; Moss et al., 2017; Gillis et al., 2004; Nakanishi et al., 2012). Similarly, RTS can be caused by a range of different genetic mechanisms, in which those with genes that lead to the most histone acetylase disruption occurred in the most developmentally delayed, suggesting a level of variability across those with the disorder (Lopez-Atalaya et al., 2011; Park et al., 2014). In contrast, FXS can only be caused on a mutation on the FMR1 gene on the X chromosome (Davenport et al., 2016). These differences in genetic heterogeneity across syndromes may explain why the FXS conform to a more uniform pattern than those

with CdLS and RTS. However, there is some genetic variability across individuals with FXS. The number of CGG repeats an individual has may have differentiating effects upon the nervous system. Previous research showed that the number of CGG repeats an individual had correlated with the number of tasks they passed on the *ToMS* (Losh et al., 2012). In addition, some individuals with FXS show genetic mosacism, in which the number of cells affected by transcriptional silencing by the production of FMRP may differ person to person due to differences in the number of CGG repeats they may have in the FMR1 gene on the X chromosome (Pretto et al., 2014).

Broadly, cognitive tests are rarely 'process pure' and often to a small degree require other domains that are not intended to be directly assessed (Brunsdon & Happé, 2014). Passing early tasks requires children to be motivated to engage in the tasks and to interact with the examiner. Rather than lacking the social cognitive abilities to pass these tasks, children may have not been motivated by the task. However, by the nature of social cognitive abilities to develop these children are required to have at least some social motivation. Social motivation is a fundamental feature of Tomasello's cultural hypothesis, which suggests that shared intentionality is a species unique motivation that leads to the development of social cognitive skills (Tomasello & Herrman, 2010). There has been some conceptualisation that ToM tasks may be indicative of an individual's level of social motivation which consequently influence social outcomes throughout development (Apperly, 2012).

Although it is not possible to disentangle whether and which of these variables contributes to the disruption of social cognitive development in these syndromes within this dataset, this study has demonstrated how identifying patterns of spared and impaired abilities in these syndromes has helped generate hypotheses of the factors that contribute and interact to disrupt social cognitive development within each syndrome.

These findings therefore have potential clinical implications. Although various interventions aiming to improve ToM have been developed, overall there has been mixed success in individuals with iASD (e.g. Loukas, Raymond, Perron, McHarg & LaCroix Doe, 2009; Begeer et al., 2011). These findings have identified factors that may influence social cognitive development in these syndromes, such as joint attention in understanding other's intentions, and executive function upon ToM skills. These factors, if targeted through intervention, may improve social cognition in those with CdLS, FXS and RTS. Further work is needed to explicitly delineate the relationship between joint attention and executive functioning upon social cognition throughout development to ensure the abilities that will have the most influence is targeted at the most critical developmental point.

However, there are several limitations to the current study. Non-verbal mental age was used to characterise participant's ability as this was available for the most participant's and thus best characterised the groups. As discussed in section 2.2.2.3, although participant's verbal ability was assessed, many children and adults assessed with the BAS-III showed ceiling and floor performance. Conclusions on the trajectory of social cognitive skills can only be made in relation to individuals non-verbal mental age and not their verbal ability or their overall broad level of ability in general. Whilst verbal ability has been implicated in a range of ToM tasks (Lorusso et al., 2007), the relationship between verbal ability and ToM is not clear cut. Individuals with Down syndrome have relatively intact ToM abilities (Baron-Cohen, 1989) but impaired receptive and expressive language deficits relative to their overall ability (Chapman, Schwartz & Bird, 1991; Roisin, Swift, Bless & Vetter, 1988; Cleland, Wood, Hardcastle, Wishart & Timmins, 2010). Further research needs to delineate the influence of language on social cognitive abilities within these syndrome groups.

In this chapter, I aimed to examine social cognitive development in individuals with CdLS, FXS and RTS. Findings indicate similarities and differences across groups in both intentionality and ToM abilities. In the *ESCS*, all groups showed an overall delay in acquiring intentionality abilities relative to their non-verbal mental age. In the *ToMS*, individuals from all groups show advanced ToM skills for the first two easiest tasks but an overall delay for the most difficult four. Scaling analyses revealed that these syndromes do not develop these abilities in the same cumulative sequence as TD children. Differences in strengths and weaknesses in these groups have highlighted potential factors that may lead to disruption in social cognitive development within each syndrome. Following the review of literature highlighting the relationship between social cognition and social outcomes and the evidence from this chapter that social cognition is disrupted in these syndromes, in the following chapter, I aim to investigate the degree that social cognitive ability predicts social outcomes in these syndromes.

CHAPTER FIVE

THE LINK BETWEEN SOCIAL COGNITIVE ABILITIES AND SOCIABILITY IN CORNELIA DE LANGE, FRAGILE X AND RUBINSTEIN-TAYBI SYNDROMES

5.1. Preface

Chapters Three demonstrated that individuals with CdLS, FXS and RTS show different profiles of sociability that show differential associations with chronological age and ASD symptomatology. Chapter Four demonstrated that individuals with these syndromes show similarities and differences in the development of social cognitive abilities. Social cognition is considered vital for successful social communication and social interaction and individual differences in social cognition lead to individual differences in social interaction skills and behaviours (Caputi et al., 2012; Henry et al., 2016). In Chapter One the wealth of literature demonstrating an influence of social cognitive ability on social behaviour in typically developing (e.g. Imuta et al., 2016; Fink et al., 2014; Jevis & Baker, 2004; Korucu et al., 2017) and ASD populations (e.g. Sasson et al., 2012; Frith et al., 1994; Jervis & Baker, 2003) was outlined. However, the potential relationship between social cognition and sociability in genetic syndromes such as CdLS, FXS and RTS has yet to be investigated and established. The following study is a 'proof of principle' investigation to assess the

association between overall social cognitive ability and different domains of sociability in CdLS, FXS and RTS, i.e. social enjoyment, social interaction skills, social motivation and social discomfort, and the severity of ASD symptomatology. Components of sociability and ASD symptomatology will be collectively referred to as 'social outcomes' throughout this chapter.

5.2.1. Introduction

Findings from Chapter Four demonstrate that individuals with CdLS, FXS and RTS have profiles of strengths and weaknesses across the development of social cognitive abilities, which may contribute to their distinct profiles of sociability[1]. The association between social cognition and sociability in CdLS, FXS and RTS has yet to be directly investigated. Whilst this association is likely to be bidirectional and transactional (Brink, Lane & Wellman, 2015), the focus of this thesis is to create models that explain profiles of sociability in individuals with CdLS, FXS and RTS. Therefore, in this study I aim to investigate the factors that influence social outcomes and establish: 1) whether and which social outcomes are predicted by overall early (intentionality abilities) or later (ToM abilities) developing social cognitive abilities across all groups, 2) whether syndrome predicts social outcomes independently from social cognition and, if so 3) whether social cognition is differentially associated with social outcomes between syndromes.

5.2.2 The influence of social cognition on social outcomes in typical and atypical populations

There has been very little research directly investigating the association between social cognition and social outcomes observed in genetic syndromes. Previous research in typical and atypical populations suggests that social cognition is associated with some social outcomes and not others. For example, in typical development, there have been mixed findings showing an association between poor ToM and greater antisocial behaviours (Hudley

[1] Sociability is an umbrella term that encompasses a broad range of social skills and behaviours that contribute to an individual's social competence (Cook & Oliver, 2011). Social interaction skills and behaviours considered to contribute to profiles of sociability will be investigated in individuals with CdLS, FXS and RTS.

& Novac, 2007; Korucu et al., 2017). Findings indicate that poor ToM may be associated only with specific forms of aggression (Korucu et al., 2017). Whilst ToM deficits have accounted for some social and communication deficits in ASD, it has not been able to explain all characteristics of these difficulties or the variation that is observed across individuals with the disorder (Tager-Flusberg, 2007). These studies highlight the importance of investigating the relationship between social cognition and social outcomes beyond global measures of overall 'social competence'. Identifying which specific social outcomes are associated with social cognition is vital for evaluating the success of interventions aiming to improve individual's social interaction skills and behaviours through social cognition training, by identifying the exact outcomes that can be expected to improve with greater social cognitive ability (Wang & Spillane, 2009).

Whilst most studies have investigated sociability using global assessments of 'social competence' (e.g. Etel & Yagmurlu, 2015; Watson, Linkie, Wilson & Capage, 1999), there has been some investigation into which components of social competence are specifically associated with social cognition in typical and atypical populations. Out of the social domains included in this study, the association between social cognition and social interaction skills has received the most investigation. For example, higher scores on a parent report measure of ToM abilities in daily life was associated with greater parent reported social skills in children with iASD (Lerner, Hutchins & Prelock, 2011). In addition, an intervention shown to improve social cognitive abilities in high functioning children with iASD also led to improvements in naturalistic observations of social skills, including eye contact during peer interaction, both immediately and four-months post-intervention (Bauminger, 2002; 2007). Within the general population, the influence of characteristics associated with a 'broad autism phenotype' on 'social abnormalities' and reduced social skills including difficulties with speech,

conversation skills and using facial expressions and eye contact appropriately when interacting with an experimenter was mediated by performance on a range of ToM tasks (Sasson et al., 2012). Social cognition has been considered one of the main components that contribute specifically to social communication development by enabling understanding behind the goals and intentions of others verbal and nonverbal communication (Adams, 2005). For example, pre-schoolers with higher levels of social cognitive ability made clearer requests when making an initial communicative request to a peer during free-play (Lefebvre-Pinard, Bouffard-Bouchard & Feider, 1982). These findings suggest that social cognition is likely to predict a broad range of social interaction skills in both typical and atypical populations.

Social discomfort can be characterised by social anxiety and social avoidance (Moss et al., 2013) and has been theorised to be driven in part by a lack of social cognitive abilities (Sutterby, Bedwell, Passler and Deputla, 2012). Social cognitive abilities enable individuals to make predictions about other agents and interpret other's behaviours based on hypotheses about the mental states that drive them. These abilities are vital in predicting another's response to behaviour and lead to successful social interactions (Frith & Frith, 2012). An inability to predict what will happen during social interactions may lead to social anxiety in social environments (Herry et al., 2007). Alternatively, in more able individuals, a lack of social cognitive understanding and a negative cognitive bias that has been commonly reported in those with social anxiety is likely to lead to mistaken cognitions about others' behaviour (e.g. they are laughing at me) leading to social anxiety (Happe & Frith, 2014; Ritter, Brück, Jacob, Wildgruber & Kreifelts, 2015). In both scenarios, social anxiety becomes a motivating factor for avoiding social interaction (Frith & Frith, 2012; Langthorne & McGill, 2009). However, the empirical investigation into the association between social cognition and social

anxiety has been limited and mixed. Banerjee and Henderson (2001) found that children rated as more anxious by teachers performed poorer on tasks assessing the link between emotions, intentions and beliefs in social situations. In contrast, Sutterby and colleagues (2012) found that female undergraduate students with high levels of self-reported social anxiety performed better on a social inference test, whereas performance did not differ between males with high or low social anxiety. Differences in findings may reflect developmental differences and ages of participants included in these studies. These findings suggest that the association between social cognition on social discomfort, as well as the role of age and development, warrants further investigation.

Research investigating the influence of social cognitive ability on social motivation has also been limited. Hong, Dunkin and Reiss (2011) found that although girls with Turner syndrome performed poorly on ToM tasks, parent reported social motivation was comparable to TD peers. In contrast, increased social motivation was reported 3-months post-intervention in high functioning children with iASD who took part in an intervention aiming to improve their ToM skills, but not in those who took part in an alternative intervention targeting friendship-making skills or a non-treatment group (Waugh & Peskin, 2015). Both studies have relied on the 'social motivation' subscale of the Social Responsiveness Scale (Constantino & Gruno, 2012), a parent report measure that primarily assesses social impairments associated with ASD. Whilst these findings may indicate that the influence of social cognition on social motivation may differ across groups, they are limited by a lack of direct observational outcomes and assessment of a narrow range of behaviours specific to ASD. These findings indicate that whilst social cognition may predict social motivation, this association requires further investigation with better measures of social motivation.

There appears to be no direct investigation of the association between social cognition and social enjoyment in the typical and atypically developing literature. As such, investigation into the degree that social cognition predicts social enjoyment in individuals with CdLS, FXS and RTS in this study will be exploratory.

To the author's knowledge there has been no investigation into the influence of intentionality abilities upon social outcomes, despite its hypothesised importance in the development of children's successful cooperative and communicative abilities (Tomasello & Carpenter, 2007). This study will be a proof of principle to evaluate the extent to which social cognitive ability predicts social interaction skills and behaviours in CdLS, FXS and RTS, but also the first study to empirically test the assumption that an individual's level of intentionality predicts social outcomes in any population.

Overall, whilst there has been some investigation into the association between social cognition and social enjoyment, social motivation, social interaction skills and social discomfort literature, except for social interaction skills, findings have been mixed across typical and atypical populations (Hong et al., 2011; Waugh & Peskin, 2015; Banerjee & Henderson, 2001; Sutterby et al., 2012). These findings may reflect the complexity of the associations between social cognition and social behaviour, which may not be direct. Previous studies in typical and atypical literature have demonstrated social outcomes are driven by an interaction between social cognition and other variables, such as autism symptomatology (Sasson et al., 2012), prosocial behaviour (Caputi et al., 2012) and aggression (Song et al., 2016). Similarly, distinct characteristics associated with syndrome may interact with social cognition to influence social interactions skills and behaviours.

Except for a handful of studies (e.g. Sasson et al., 2012, Lefebvre-Pinard et al., 1982) there has been a lack of investigation of the association between social cognition and direct

observational assessment of behaviours. Previous studies have relied on indirect assessments of social interaction skills and behaviours such as self or carer report measures of behaviours (e.g. Jervis & Baker, 2004; Korucu et al., 2017; Song et al., 2016; Frith et al., 1994; Peterson et al., 2009; Hughes et al., 1997; Hong et al.,2011), which are subject to bias and retrospective recall. Different informants (e.g. parents vs. professionals) have been shown to rate the same child's behaviour differently on carer-report measures of children's social behaviour (Hughes et al, 1995). It is not clear whether these findings reflect differences in behaviour or differences in respondent's perceptions of the quality of behaviour. In contrast, Chapter Three utilised experimental measures that directly assessed operationalised behaviours indicative of social enjoyment, social motivation, social interaction skills, social discomfort and social difficulties associated with ASD. In addition, many studies have used a narrow range of social cognitive tasks, which fails to capture the dynamic range of social cognitive abilities and is an inadequate measure to assess individual differences in social cognitive ability. The current study accounts for the spectrum of these abilities with the range of tasks included in the *ESCS* and *ToMS* that capture social cognitive ability across development in individuals with CdLS, FXS and RTS.

5.2.3 The influence of syndrome on social outcomes

As discussed in Chapter One, whilst there has been a range of studies describing the profiles of sociability and endophenotypes in genetic syndromes, there has been relatively little research attempting to explicitly delineate the causal pathways between aetiological mechanisms and behaviours within syndromes and how these pathways differ across syndromes (Oliver & Woodcock, 2008). Woodcock and colleagues (2009a) found that greater attention switching difficulties were associated with increased temper outbursts in those with

Prader-Willi syndrome but were associated with heightened levels of social anxiety in boys with FXS. Similarly, differences in how social cognitive abilities develop in syndromes may lead to differences upon the influence that these abilities have on social outcomes. Individuals with iASD who pass false-belief tasks have been shown to do so by recruiting different neurocognitive mechanisms from TD children (Tager-Flusberg, 2007). Similarly, individuals with CdLS, FXS and RTS may develop different compensatory styles either in place of absent social cognitive skills by recruiting alternative cognitive mechanisms or due to an atypical way of developing these abilities. If these individuals with these syndromes develop different ways of passing social cognitive tasks from one another, they may show different associations between social cognitive abilities and social outcomes. Therefore, I will investigate whether syndrome predicts social outcomes over and above social cognition, and explore the nature of these associations across individuals with CdLS, FXS and RTS.

The influence of syndrome on the associations between social cognition and social outcomes will be exploratory due to a lack of literature investigating these associations within individuals with CdLS, FXS and RTS. However, the influence of syndrome on the associations between social cognition and ASD symptomatology is likely to differ between these groups. Section 3.2.4 outlined literature showing similarities and differences between individuals with CdLS, FXS and iASD (Moss et al., 2008; Basile et al., 2007; McDuffie et al., 2014; Wollf et al., 2012; Martin et al., 2016). Findings from Chapter Three indicated that whilst sociability in individuals with CdLS appears unrelated to characteristics associated with iASD, some components of sociability was associated with ASD symptomatology in those with FXS and RTS. These findings highlighted behaviours that may or may not share similar aetiological mechanisms with individuals with iASD within each syndrome. Social cognitive impairments are considered to lead to the social and communication difficulties

observed in individuals with iASD (Varga, 2011; Baron-Cohen, 1994) and may be a shared aetiological mechanism associated with social outcomes in individuals with RTS and FXS, and iASD. Therefore, similar to associations identified between ASD symptomatology and components of sociability, the association between social cognition and ASD symptomatology is likely to differ across groups.

5.2.4. Aims and hypotheses

In this study, I will investigate the association between social cognition and syndrome on social outcomes in individuals with CdLS, FXS and RTS. Specifically, I aim to investigate:

1) Whether intentionality and ToM abilities independently predict components of sociability (i.e. social enjoyment, social interaction skills, social motivation and social discomfort) and severity of ASD symptomatology, in children and adults with CdLS, FXS and RTS after accounting for chronological and non-verbal mental age.
2) The association between syndrome, and components of sociability and severity of ASD symptomatology in CdLS, FXS and RTS by:
    a. Investigating the degree to which syndrome influences social outcomes independent of social cognitive ability, chronological and non-verbal mental age
    b. Investigate the degree to which the presence of a syndrome has a differential influence on the association between social cognitive ability and domains of sociability.

I hypothesise that:

1) Social cognitive abilities will predict social outcomes independent of other factors that are likely to influence social outcomes (i.e. chronological age and non-verbal ability). Based on previous literature, I hypothesise that social interaction skills will be predicted by later developing ToM abilities. Due to the mixed and/or lack of literature investigating the association between ToM and other social outcomes will be exploratory. Due to the paucity of literature investigating the association between intentionality and social outcomes, investigation of influence of intentionality will also be exploratory

2.a. Syndrome will predict social outcomes independent of other factors.

2.b. Different syndromes will show differences in the patterns of associations between social cognition and components of sociability.

5.3 Data analysis

Social cognitive ability was operationalised as a composite score of the number of tasks participants passed within the social cognitive battery that they participated in (i.e. the *ESCS* or the *ToMS*). The *ESCS* and *ToMS* batteries were analysed separately. Four domain scores were calculated from *CSRS* items that were investigated in Chapter Three (Moss et al., 2013). *Social Enjoyment* domain scores were derived from the sum of participant's *Positive Emotional Affect* and *Social Responsiveness* item scores. *Social Motivation* domain scores were derived from the sum of *Spontaneous Initiation of Interaction* and *Focus of Attention* item scores. *Social Interaction Skills* domain scores were derived from the sum of *Eye Contact* and *Social Communication* item scores. Finally, *Social Discomfort* domain scores were derived from the sum of *Social Anxiety* and *Avoidance of Social Interaction* item scores.

Participant's scores on each subdomain ranged from 0 (indicating low levels of e.g. social enjoyment) to 8 (indicating high levels). The same approach used in Chapter Three and Four was used to investigate participant characteristics.

Kendall-Tau correlations were run to determine which characteristics (i.e. overall social cognitive ability, chronological and non-verbal mental age) were associated with *CSRS* domain scores and ADOS-II social affect classification severity scores. Separate hierarchical linear regression models were run for each domain that was significantly associated with social cognitive ability. As data were non-normally distributed, hierarchical linear regressions were run employing a resampling bootstrap estimation approach with 1000 samples and a 95% confidence interval was constructed (Field, 2013). The same procedure was run for items within domains that were significantly predicted by social cognitive ability to investigate the influence of social cognition on social outcomes at a fine-grained level. Finally, for domains and items in which syndrome was found to have a significant influence on social outcomes, Kendall-Tau correlations were run between social cognition and the relevant social outcome for each syndrome group to investigate whether the effect of syndrome was driven by differences in these associations between groups. As this study is exploratory and given the small number of comparisons, effects were considered significant at $p<.05$.

5.4 Results

5.4.1 Intentionality abilities

5.4.1.1. Participant characteristics.

From the original sample, twenty-one children with CdLS (10 female, M_{age}=77.65 years, SD=40.40), nineteen children with FXS (0 female, M_{age}=71.70, SD=30.40) and sixteen individuals with RTS (8 female, M_{age}=107.37, SD=45.29) whose *CSRS* and *ESCS* data were

available were included in the following analyses. Table 5.1 reveals that these groups did not significantly differ in non-verbal mental age. However, a significant difference was found for chronological age, in which post-hoc analyses revealed that the RTS group was significantly older than the FXS group. As in the previous chapter, the groups were not matched on gender due to the large number of males in the FXS group.

Table 5.1.
Participant characteristics for participants with both ESCS and CSRS data available

	CdLS (n = 21)	FXS (n = 19)	RTS (n = 16)	*P*	Post-hoc tests (p<0.05)
Mean chronological age in months (SD)	77.65 (40.40)	71.70 (30.40)	107.37 (45.29)	**.04**	FXS < RTS
Gender % female	48%	0%	50%	**<.01**	FXS < CdLS, RTS
Mean non-verbal mental age in months (SD)	29.62 (13.67)*	33.01 (10.42)	29.50 (9.25)*	.58	

* Information not available for one participant due to non-completion of the relevant measure

5.4.1.2 Associations between predictor and criterion variables at a domain level.

Table 5.2 displays the means, standard deviations and correlations between the three predictor variables (*ESCS* score, chronological and non-verbal mental age) and the five criterion variables (each *CSRS* domain and ADOS-II social affect calibrated severity scores). Results reveal different predictor variables were associated with different social outcomes. Participant's *ESCS* scores showed significant positive associations with *Social Enjoyment* (τ_b (54)=.22, p=.03)*, Social Motivation* (τ_b (54)=.23, p=.03), and *Social Interaction Skills* (τ_b (54)=.21, p=.04). No associations were found between *ESCS* score and *Social Discomfort,* nor ADOS-II social affect calibrated severity scores. Non-verbal mental age was significantly

positively associated with *Social Interaction Skills* (τ_b (52)=.25, p=.01), but not with *Social Enjoyment, Social Motivation, Social Discomfort* or ADOS-II social affect severity scores. Finally, chronological age was not associated with any of the social outcomes.

Table 5.2
Means, standard deviations and correlations of predictor and criterion variables for participants who took part in both the ESCS and CSRS

Variable	M	SD	1	2	3	4	5	6	7	8
1. *ESCS* score	2.46	1.25	-	.22*	.44**	.22*	.23*	.21*	-.14	-.01
2. Chronological age (in months)	83.43	41.61		-	.37**	-.18	-.09	-.03	.18	.23*
3. Non-verbal mental age (in months)	30.77	11.37			-	.15	.12	.25*	.11	.05
4. *Social Enjoyment CSRS* domain	3.35	1.33				-	.59**	.58**	-.31**	-.43**
5. *Social Motivation CSRS* domain	3.05	1.47					-	.57**	-.26**	-.39**
6. *Social Interaction Skills CSRS* domain	2.93	.97						-	-.17	-.34**
7. *Social Discomfort CSRS* domain	.81	.97							-	.30**
8. ADOS-II SA CSS	5.2	2.41								-

* p<..05 **p<.01

5.4.1.3 Hierarchical linear regressions – domain level.

Hierarchical linear regressions were only run in relation to social outcomes that were significantly predicted by intentionality abilities. The first aim was to investigate whether social cognitive ability predicted social outcomes independent of chronological and non-verbal mental age. Correlations revealed that only *Social Interaction Skills* were significantly associated with non-verbal mental age, whereas no other domains showed an association between chronological or non-verbal mental age. Therefore, *ESCS* score was entered into the first step for all domains except for *Social Interaction Skills*, in which *ESCS* score was entered into the second step following non-verbal mental age at the first. As the second aim was to investigate the degree that syndrome differentially influenced social outcomes, syndrome group was entered at the step after *ESCS* score for each domain. All models had a high tolerance (ranging between.64-.83) and low variance inflation factor (VIF) (ranging between 1.20-1.78) suggesting a low level of multicollinearity between predictors. The Durbin-Watson values for each model were in an acceptable range (between 2.05-2.58), suggesting the assumption of independent errors is tenable.

5.4.1.3.1 Social Enjoyment domain.

At step one, *ESCS* score contributed significantly to the regression model (F (1, 54)=8.43, p <.01) and accounted for 14% of the variance. The higher an individual scored on the *ESCS*, the higher they scored on the *Social Enjoyment* domain. At step two, syndrome accounted for an additional 1%, but this change was not significant (F(2. 52)=.37, p=.70). Regression statistics are presented in table 5.3.

Table 5.3.
Linear model of predictors of Social Enjoyment domain scores of participants who took part in the ESCS, with 95% bias corrected and accelerated confidence intervals reported in parentheses. Confidence intervals and standard errors based on 1000 bootstrapped samples. Significant changes to the model are highlighted in bold.

	b	SE B	β	*p*	*R*	*R2*	ΔR2
Step 1					.37	.14	**.14**
Constant	2.43 (1.68, 3.20)	.36		<.01			
ESCS	.39 (.09, .67)	.13	.34	.01			
Step 2					.38	.15	.01
Constant	2.48 (1.69, 3.29)	.4		<.01			
ESCS	.43 (.09, .76)	.17	.41	.02			
CdLS vs FXS	-.16 (-.95, .74)	.42	-.06	.73			
CdLS vs RTS	-.38 (-1.36, .67)	.50	-.13	.45			

5.4.1.3.2 Social Motivation domain.

At step one, *ESCS* score contributed significantly to the regression model (F (1, 54)=5.05, p=.03) and accounted for 9% of the variance. The higher an individual scored on the *ESCS*, the higher they scored on the *Social Motivation* domain. At step two, syndrome accounted for an additional 4%, but this change was not significant (F(2. 52)=1.23, p=.30). Regression statistics are presented in table 5.4.

Table 5.4.
Linear model of predictors of Social Motivation domain scores of participants who took part in the ESCS, with 95% bias corrected and accelerated confidence intervals reported in parentheses. Confidence intervals and standard errors based on 1000 bootstrapped samples. Significant changes to the model are highlighted in bold.

	b	SE B	β	*p*	*R*	*R2*	ΔR2
Step 1	2.18	.43			.29	.09	**.09**
Constant	(1.39, 3.07)			<.01			
	.34	.17	.29				
ESCS	(.03, .68)			.06			
		.47					
Step 2					.36	.13	.04
Constant	2.34	.47		<.01			
	(1.50, 3.28)						
ESCS	.45	.17	.38	.02			
	(.11, .78)						
CdLS vs FXS	-.67	.43	-.22	.13			
	(-1.47, .24)						
CdLS vs RTS	-.65	.54	-.20	.24			
	(-1.68, .46)						

5.4.1.3.3 Social Interaction Skills domain.

At step one, non-verbal mental age score contributed significantly to the regression model (F (1, 52)=6.05, p = .02) and accounted for 10% of the variance. The higher an individual's non-verbal mental age, the higher they scored on the social motivation subscale. At step two, *ESCS* score accounted for an addition 1% of the variance, but this change was not significant (F(1, 51)=.40, p=.53). At step three, syndrome accounted for an additional 2% of the variance, but this change was not significant (F(2, 49)=.46, p= .64. Regression statistics are presented in table 5.5.

Table 5.5.
Linear model of predictors of Social Interaction Skills domain score of participants who took part in the ESCS, with 95% bias corrected and accelerated confidence intervals reported in parentheses. Confidence intervals and standard errors based on 1000 bootstrapped samples. Significant changes to the model are highlighted in bold.

	b	SE B	β	*p*	*R*	*R2*	ΔR2
Step 1					.32	.10	**.10**
Constant	2.08 (1.29, 2.81)	.39		<.01			
Non-verbal mental age	.03 (.01, .05)	.01	.32	.02			
Step 2					.33	.11	.01
Constant	2.04 (1.28, 2.79)	.39		<.01			
Non-verbal mental age	.02 (.00, .05)	.01	.27	.10			
ESCS	.08 (-.14, .31)	.12	.10	.54			
Step 3					.36	.13	.02
Constant	2.12 (1.30, 2.98)	.43		<.01			
Non-verbal mental age	.02 (-.01, .05)	.01	.23	.17			
ESCS	.13 (-.14, .39)	.13	.16	.34			
CdLS vs FXS	-.02 (-.63, .61)	.33	-.01	.97			
CdLS vs RTS	.30 (-1.11, .45)	.38	-.14	.41			

Overall, these findings suggest that early social cognitive abilities significantly predict social enjoyment and social motivation over and above chronological age and non-verbal mental age, but not social interaction skills, social discomfort or ASD symptomatology in individuals with CdLS, FXS and RTS. Syndrome group membership did not have an

influence on any social domain independent of social cognition, chronological or non-verbal mental age.

5.4.1.4 Associations between predictor and criterion variables at an item level.

Table 5.6 displays the Kendall Tau correlations run between predictor variables (*ESCS* score, chronological and non-verbal mental age) and scores on *CSRS* items within domains that were significantly predicted by *ESCS* score. Results reveal different predictor variables were associated with different social outcomes at an item level.

Table 5.6
Means, standard deviations and correlations of predictor and criterion (items from Social Enjoyment and Social Motivation domains) variables for participants who took part in the ESCS

Variable	M	SD	1	2	3	4	5	6	7
1. *ESCS* score	2.46	1.25	-	.22*	.44**	.27*	.06	.29**	.10
2. Chronological age (in months)	83.43	41.61		-	.37**	-.13	-.15	-.07	-.14
3. Non-verbal mental age (in months)	30.77	11.37			-	.20*	.06	.14	.09
4. *Social Responsiveness (Social Enjoyment)*	2.31	.87				-	.34	.51**	.59**
5. *Positive Emotional Affect (Social Enjoyment)*	1.07	.68					-	.28**	.40**
6. *Spontaneous Initiation of Interaction (Social Motivation)*	1.29	1.01						-	.44**
7. *Focus of attention (Social Motivation)*	1.73	.62							-

* significant at $p < .05$, ** significant at $p < .01$

In the *Social Enjoyment* domain, *Social Responsiveness* scores were significantly associated with *ESCS* scores (τ_b (54)=.27, p=.01) and non-verbal mental age (τ_b (52)=.20, p=.04), but not chronological age. No associations were found between *Positive Emotional Affect* and *ESCS* scores, chronological or non-verbal mental age.

In the *Social Motivation* domain, *Spontaneous Initiation of Interaction* was significantly positively associated with *ESCS* scores (τ_b (54)=.29, p<.01) but not with chronological or non-verbal mental age. *Focus of Attention* was not associated with *ESCS* scores, chronological or non-verbal mental age.

5.4.1.5 Hierarchical linear regressions – item level.

All models had a high tolerance (ranging between .56-.83) and low VIF (ranging between 1.2-1.78), and the Durbin-Watson values for each model were in an acceptable range (between 2.15-2.49).

5.4.1.5.1 Social Responsiveness.

At step one, non-verbal mental age contributed significantly to the regression model (ΔF (1, 52)=6.41, p=.01) and accounted for 11% of the variance. The higher an individual's non-verbal mental age, the higher their score on the *Social Responsiveness* item. At step two, *ESCS* scores accounted for an additional 8% of the variance, and this change was significant (ΔF (1, 51)=4.95, p=.03). The higher an individual's score on the *ESCS*, the higher their score on the *Social Responsiveness* item. At step three, syndrome did not account for any additional variance (ΔF (2, 49)=.07, p=.94). Regression statistics are presented in table 5.7.

Table 5.7.
Linear model of predictors of Social Responsiveness item scores of participants who took part in the ESCS, with 95% bias corrected and accelerated confidence intervals reported in parentheses. Confidence intervals and standard errors based on 1000 bootstrapped samples

	b	SE B	β	*p*	*R*	*R2*	ΔR2
Step 1					.33	.11	**0.11**
Constant	1.51 (.69, 2.35)	.43		<.01			
Non-verbal mental age	.03 (.00, .05)	.01	.33	.04			
Step 2					.43	.19	**0.08**
Constant	1.37 (.62, 2.20)	.40		<.01			
Non-verbal mental age	.01 (-.01, .04)	.01	.15	.37			
ESCS	.24 (.03, .46)	.12	.34	.03			
Step 3					.44	.19	0.00
Constant	1.38 (.56, 2.26)	.44		<.01			
Non-verbal mental age	.01 (-.02, .04)	.01	.13	.44			
ESCS	.25 (.04, .48)	.11	.35	.03			
CdLS vs FXS	.03 (-.45, .56)	.26	.02	.91			
CdLS vs RTS	-.08 (-.72, .56)	.32	-.04	.79			

5.4.1.5.2 Spontaneous Initiation of Interaction.

At step one, *ESCS* scores contributed significantly to the regression model (ΔF (1, 54)=6.63, p=.01) and accounted for 11% of the variance. The higher an individual's score on the *ESCS*, the higher the score on the *Spontaneous Initiation of Interaction* item. At step two, syndrome contributed an additional 2% to the variance, but this contribution was not significant (ΔF (2, 52)=.53, p=.59). Regression statistics are presented in table 5.8.

Table 5.8.
Linear model of predictors of Spontaneous Initiation of Interaction scores of participants who took part in the ESCS, with 95% bias corrected and accelerated confidence intervals reported in parentheses. Confidence intervals and standard errors based on 1000 bootstrapped samples

	b	SE B	β	*p*	*R*	*R2*	ΔR2
Step 1					.33	.11	**.11**
Constant	0.63 (.08, 1.27)	.29		.04			
ESCS	0.27 (.04, .50)	.11	.33	.03			
Step 2					.36	.13	.02
Constant	.70 (.11, 1.44)	.32		.04			
ESCS	.31 (.10, .53)	.11	.39	<.01			
CdLS vs FXS	-0.26 (-.78, .29)	.27	-.13	.34			
CdLS vs RTS	-.33 (-.95, .37)	.34	-.15	.34			

5.4.1.6 Summary of results from the ESCS.

At a domain level, greater intentionality abilities significantly predicted social enjoyment and social motivation but not social discomfort. Although an association was found between intentionality abilities and participant's level of social interaction skills, intentionality abilities did not significantly predict these skills after accounting for participant's non-verbal ability.

Within the *Social Enjoyment* domain, the amount of positive emotional affect individuals showed during social interaction was not associated with their intentionality abilities. However, greater intentionality abilities predicted more frequent and better social responsiveness independent of non-verbal mental age. Within the *Social Motivation* domain at an item level intentionality abilities were not associated with the amount of attention

participants gave to people vs. objects. However, the greater a participant's intentionality abilities, the greater the amount and quality of social initiations of interactions they showed.

At both a domain and item level, syndrome did not have an effect independent of the other predictor variables included in each model.

5.4.2 Theory of Mind Scale

5.4.2.1 Participant characteristics.

From the original sample, sixteen participants with CdLS (11 female, M_{age}=20.07, SD=10.93), fifteen participants with FXS (0 female, M_{age}=24.04, SD=9.86) and 10 individuals with RTS (5 female, M_{age}=22.12, SD=16.85) for whom both *CSRS* and *ESCS* data were available were included in the following analyses. Table 5.9 reveals that these groups did not differ significantly in chronological age or non-verbal mental age. The groups are not matched on gender due to the large number of males in the FXS group.

Table 5.9
Participant characteristics for participants with both ToMS and CSRS data available

	CdLS (*n*=16)	FXS (*n*=15)	RTS (*n*=10)	*p*	Post-hoc tests (p<.05)
Mean chronological age in years (SD)	20.07 (10.93)	24.04 (9.86)	22.12 (16.85)	0.21	
Gender % female	69%	0%	50%	<.01	FXS<CdLS, RTS
Mean non-verbal mental age in years (SD)	5.53 (1.83)	4.35 (.68)*	4.58 (.87)	0.1	

* Information not available for one participant due to ceiling and floor effects on the relevant measure

5.4.2.2 Associations between predictor and criterion variables at a domain level.

Table 5.10 displays the means, standard deviations and correlations between the three predictor variables (*ToMS* score, chronological and non-verbal mental age) and the five criterion variables (each *CSRS* domain and ADOS-II social affect calibrated severity scores). Results reveal different predictor variables were associated with different social outcomes. *ToMS* scores showed significant positive associations with *Social Enjoyment* (τ_b (39)=.44, p<.01) and a negative association with ADOS-II social affect calibrated severity scores (τ_b (39)=.28, p=.03). No associations were found between *ToMS* score and *Social Motivation*, *Social Interaction Skills* or *Social Discomfort*. Chronological age was significantly positively associated with *Social Discomfort* (τ_b (39)=.24, p=.04), but not with *Social Enjoyment, Social Motivation, Social Interaction Skills* or ADOS-II social affect severity scores. Finally, non-verbal mental age was not associated with any of the social outcomes.

Table 5.10
Means, standard deviations and correlations of predictor and criterion variables for participants who took part in the ToMS

Variable	M	SD	1	2	3	4	5	6	7	8
1. *ToMS* score	2.65	.92	-	.15	.40**	.44**	.23	.26	-.07	-.28**
2. Chronological age (in years)	21.97	12.12		-	.01	.10	.04	-.12	.24*	.16
3. Non-verbal mental age (in years)	4.88	1.38			-	.17	.13	.18	-.07	-.20
4. *Social Enjoyment CSRS* domain	4.47	1.12				-	.36**	.39**	-.27*	-.43**
5. *Social Motivation CSRS* domain	3.79	1.4					-	.28*	-.30**	-.33**
6. *Social Interaction Skills CSRS* domain	3.48	.57						-	-.41**	-.33**
7. *Social Discomfort CSRS* domain	1.57	1.52							-	.47**
8. ADOS-II SA CSS	6.45	2.56								-

* significant at $p < .05$, ** significant at $p < .01$

5.4.2.3 Hierarchical linear regressions – domain level.

All models had a high tolerance (between .62-.97) and low VIF (between 1.03-1.63), and the Durbin-Watson values for each model were in an acceptable range (between 1.56-2.01).

5.4.2.3.1 Social Enjoyment subscale.

At step one, *ToMS* scores contributed significantly to the regression model (ΔF (1, 39)=23.55, p<.01) and accounted for 37% of the variance. The higher an individual's score on the *ToMS*, the higher their score on the social enjoyment subscale. At step two, syndrome accounted for an additional 7%, but this change was not significant (ΔF(2. 52)=.37, p=.70). Regression statistics are presented in table 5.11.

Table 5.11.
Linear model of predictors of Social Enjoyment total scores of participants who took part in the ToMS, with 95% bias corrected and accelerated confidence intervals reported in parentheses. Confidence intervals and standard errors based on 1000 bootstrapped samples

	b	SE B	β	*p*	*R*	*R2*	ΔR2
Step 1					.61	.38	**.37**
Constant	2.40 (1.40, 3.39)	.50		<.01			
ToMS	.80 (.42, 1.17)	.19	.61	<.01			
Step 2					.67	.44	.07
Constant	2.84 (1.75, 3.98)	.54		<.01			
ToMS	.75 (.35, 1.11)	.19	.57	<.01			
CdLS vs FXS	-.28 (-1.00, .43)	.37	-.11	.46			
CdLS vs RTS	-.81 (-1.43, -.21)	.31	-.29	.01			

5.4.2.3.2 ADOS-II Social Affect Severity Scores.

At step one, *ToMS* scores contributed significantly to the regression model (ΔF (1, 39)=9.07, p<.01) and accounted for 19 % of the variance. The higher an individual scored on the *ToMS*, the lower their ADOS-II SA severity scores were. At step two, syndrome accounted for an additional 13% of the variance, and this change was significant (ΔF (2, 37) = 3.43, p<.01). Regression statistics are presented in table 5.1.

Table 5.12.
Linear model of predictors of ADOS-II Social Affect total classification severity scores of participants who took part in the ToMS, with 95% bias corrected and accelerated confidence intervals reported in parentheses. Confidence intervals and standard errors based on 1000 bootstrapped samples

	b	SE B	β	*p*	*R*	*R2*	ΔR2
Step 1					.43	.19	**.19**
Constant	9.62 (7.34, 11.79)	1.1		<.01			
ToMS	-1.22 (-2.00, -.39)	.41	-.43	<.01			
Step 2					.57	.32	**0.13**
Constant	8.86 (5.89, 11.41)	1.39		<.01			
ToMS	-1.17 (-1.98, -.31)	.42	-.42	<.01			
CdLS vs FXS	1.85 (.23, 3.50)	.82	.34	.04			
CdLS vs RTS	-.24 (-1.98, 1.56)	.91	-.04	.80			

5.4.2.3.2.1 The association between social cognition and ADOS-II CSS within each syndrome.

To investigate whether the additional influence of syndrome was driven by mediating effect upon the relationship between *ToMS* scores and autism symptomatology, Kendall Tau correlations were run between *ToMS* scores, and *ADOS-II* social affect severity scores per

syndrome. Results reveal there were no significant associations between these variables in any of the syndrome groups.

5.4.2.4 Associations between predictor and criterion variables at an item level.

Table 5.13 displays the means, standard deviations and correlations between potential predictor variables (*ToMS* score, chronological and non-verbal mental age) and scores on *ToMS* items within the *Social Enjoyment* domain. Both *Positive Emotional Affect* (τ_b (39)=-.34, p<.01) and *Social Responsiveness* (τ_b (39)=-.32, p=.01) scores were significantly associated with *ToMS* scores, but not chronological or non-verbal mental age.

Table 5.13
Means, standard deviations and inter-correlations of predictor and criterion (items from the social enjoyment domain) variables for participants who took part in the ToMS

Variable	M	SD	1	2	3	4	5
1. ToMS score	2.65	.92	-	.15	.40**	.34**	.32*
2. Chronological age (in years)	21.97	12.12		-	.01	.07	.17
3. Non-verbal mental age (in months)	4.88	1.38			-	.12	.17
4. Positive Emotional Affect	1.34	.90				-	.07
5. Social Responsiveness	3.13	.59					-

* significant at p < .05, ** significant at p <.01

5.4.2.5 Hierarchical linear regressions – item level.

All models had a high tolerance (between .79-.97) and low VIF (between 1.03-1.26), and the Durbin-Watson values for each model were in an acceptable range (between 1.80-2.18).

5.4.2.5.1 Positive Emotional Affect.

At step one, *ToMS* scores contributed significantly to the regression model (ΔF (1, 39)=15.72, $p < .01$) and accounted for 29% of the variance. As participant's *ToMS* scores increased, so did their scores on the *Positive Emotional Affect* item. At step two, syndrome contributed an additional 13% to the variance, which was significant (ΔF (2, 37)=4.15, p=.02). Regression statistics are presented in table 5.14

Table 5.14.
Linear model of predictors of Positive Emotional Affect item scores of participants who took part in the ToMS, with 95% bias corrected and accelerated confidence intervals reported in parentheses. Confidence intervals and standard errors based on 1000 bootstrapped samples

	b	SE B	β	*p*	*R*	*R2*	ΔR2
Step 1					.54	.29	**.29**
Constant	-.08 (-.79, .72)	.38		.82			
ToMS	.55 (.20, .83)	.16	.54	<.01			
Step 2					.65	.37	**.13**
Constant	.44 (-.29, 1.20)	.38		.25			
ToMS	0.49 (.166, .737)	.14	.48	<.01			
CdLS vs FXS	-.37 (-.92, .27)	.30	-.19	.27			
CdLS vs RTS	-.89 (-1.38, -.39)	.25	-.41	<.01			

5.4.2.5.1.1 The association between social cognition and Positive Emotional Affect within each syndrome.

Kendall Tau correlations were run between *ToMS* scores, and *Positive Emotional Affect* scores per syndrome. Results revealed a significant positive association between these variables in participants with CdLS (τ_b (14)=.54, p=.03), but not in FXS or RTS.

5.4.2.5.2 Social Responsiveness.

At step one, *ToMS* scores contributed significantly to the regression model (ΔF (1, 39)=7.12, p=.01) and accounted for 15% of the variance. The higher an individual's score on the *ToMS*, the higher their score on the *Social Responsiveness* item. At step two, syndrome did not account for any additional variance (ΔF (2, 37)=.10, p=.91). Regression statistics are presented in table 5.15.

Table 5.15.
Linear model of predictors of Social Responsiveness items scores of participants who took part in the ToMS, with 95% bias corrected and accelerated confidence intervals reported in parentheses. Confidence intervals and standard errors based on 1000 bootstrapped samples

	b	SE B	β	*p*	*R*	*R2*	ΔR2
Step 1					.39	.13	**.15**
Constant	2.47 (1.953, 2.94)	.26		<.01			
ToMS	.25 (.09, .43)	.09	.39	<.01			
Step 2					.40	.16	.00
Constant	2.41 (1.81, 3.05)	.31		<.01			
ToMS	.26 (.08, .45)	.09	.40	<.01			
CdLS vs FXS	.08 (-.31, .48)	.20	.07	.68			
CdLS vs RTS	.08 (-.37, .51)	.23	.06	.72			

5.4.2.6 Summary of results from the ToMS.

At a domain level, greater ToM ability significantly predicted a greater level of social enjoyment and less ASD symptomatology during interaction with the examiner. No association was found between ToM abilities and how much social motivation, social discomfort and the level of social interaction skills a participant showed. Syndrome influenced some but not all social outcomes. At a domain level, syndrome significantly predicted the level of ASD symptomatology. The lack of association between ASD symptomatology and social cognitive ability within each syndrome suggests that the influence of syndrome membership is independent and does not have an interacting effect with social cognitive ability. Although no effect of syndrome was found in *Social Enjoyment* domain, one of its items, *Positive Emotional Affect*, was significantly predicted by syndrome. An

association between *ToMS* score and *Positive Emotional Affect* was found in individuals with CdLS, but not FXS or RTS, suggesting that syndrome has a mediating effect on the association between ToM abilities and the amount of positive emotional affect shown by participants with CdLS, FXS and RTS.

5.5 Discussion

This 'proof of principle' study evaluated the degree to which social cognitive abilities predicts social outcomes in CdLS, FXS and RTS. It is the first study to explore the association between social cognition and social outcomes in these syndromes, as well as the potential role of intentionality abilities upon social outcomes. In both the typically and atypically developing literature, previous studies mostly utilised indirect measures of behaviour, such as carer-reports or interviews which may be subject to inaccuracies such as reporter or retrospective recall bias. In contrast, the current study utilised robust observational assessments to capture a range of social cognitive abilities and social outcomes. Table 5.16 summarises the main findings of this study.

Table 5.16
Summary of the influence of non-verbal mental age, intentionality and ToM abilities on social outcomes in CdLS, FXS and RTS

Relationship between intentionality abilities and social outcomes

	Social outcomes - domain level				
Predictor variables	*Social enjoyment*	*Social motivation*	*Social interaction skills*	*Social discomfort*	*ASD symptomatology*
Non-verbal mental age	-	-	+	-	-
Intentionality abilities	+	+	-	-	-
Syndrome	-	-	-	-	-

	Social outcomes - item level			
	Items from social enjoyment domain		Items from the social motivation domain	
Predictor variables	*Social responsiveness*	*Positive Emotional affect*	*Spontaneous initiation of interaction*	*Focus of attention*
Non-verbal mental age	+	-	-	-
Intentionality abilities	+	-	+	-
Syndrome	-	-	-	-

Relationship between ToM abilities and social outcomes

	Social outcomes - domain level				
Predictor variables	*Social enjoyment*	*Social motivation*	*Social interaction skills*	*Social discomfort*	*ASD symptomatology*
Intentionality abilities	+	-	-	-	+
Syndrome	-	-	-	-	+

No associations found between ToM abilities and ASD symptomatology in CdLS, FXS or RTS

	Social outcomes - item level		
	Items from social enjoyment domain		
Predictor variables	*Social responsiveness*	*Positive Emotional affect*	
Intentionality abilities	+	+	
Syndrome	-	+	**Significant associations between ToM abilities and *positive emotional affect* in individuals with CdLS, but not FXS or RTS.**

5.5.1 The influence of intentionality and ToM abilities on sociability in CdLS, FXS and RTS

The first aim was to investigate which social outcomes were influenced by earlier (i.e. intentionality abilities) and later (ToM abilities) developing social cognitive abilities. Findings indicate that different social cognitive abilities predict different social outcomes in individuals with CdLS, FXS and RTS. At a domain level, greater intentionality abilities predicted greater social enjoyment and social motivation. Although intentionality abilities correlated with social interaction skills, this relationship was not significant over and above non-verbal mental age. Preliminary correlations revealed there was no association between intentionality abilities and the amount of social discomfort or ASD symptomatology shown by participants during social interaction. In contrast, although greater ToM ability also predicted greater social enjoyment, unlike intentionality abilities, ToM abilities also predicted greater ASD symptomatology. No association was found between ToM abilities and *Social Motivation, Social Interaction Skills,* and *Social Discomfort* domains. Overall, findings indicate that different social cognitive abilities (i.e. intentionality vs. ToM abilities) influence different social outcomes in individuals with CdLS, FXS and RTS.

More detailed investigation into social outcomes that were significantly predicted by social cognitive ability revealed fine-grained differences at an item level. Within the *Social Enjoyment* domain, both non-verbal mental age and intentionality abilities significantly and independently predicted greater frequency and quality of participant's social responses. However, no association was found between intentionality abilities and *Positive Emotional Affect* item scores, also an item within the *Social Enjoyment* domain. Within the *Social Motivation* domain, intentionality abilities significantly predicted greater frequency and quality of *Spontaneous Initiation of Interactions,* whereas no association was found between intentionality abilities and *Focus of Attention*. These findings highlight the importance of elucidating associations between social cognition and social outcomes at a more detailed level, as domain general scores may mask these relationships. In contrast, ToM abilities significantly predicted both items in the *Social Enjoyment* domain, i.e. *Positive Emotional Affect* and *Social Responsiveness*.

Both greater intentionality and ToM abilities significantly predicted greater social enjoyment in CdLS, FXS and RTS. These findings correspond with social cognition accounts, which predict that individuals with compromised abilities to understand other's intentions and minds may lose interest (Chevallier, Kohls, Troiani, Brodkin, & Schultz, 2012) and subsequently would not find social interaction enjoyable. Both intentionality and ToM abilities were found to predict the amount and quality of participant's social responsiveness. When considering the social cognitive account of social enjoyment, social cognition may encourage and enhance reciprocal interaction, which is captured by the *Social Responsiveness CSRS* item. An individual is more likely to show a social response that will lead to an enjoyable outcome if they have the social cognitive abilities to respond to their partner's intentions or mental states that underlie their partner's initial action. However, with

compromised social cognitive abilities, an individual's bid may not be appropriate, which may eventually lead to reduced social responsiveness as responses do not lead to enjoyable outcomes and are subsequently not rewarding.

In contrast, *Positive Emotional Affect* was significantly predicted by ToM but not intentionality abilities. These differences may reflect the different purposes that smiling may have across development. In early development, smiling appears to be, at first, an automatic and unconscious behaviour that emerges in response to interaction with a caregiver, and later develops to communicate to others a single dimension of positive emotion (Messinger & Fogel, 2007). However, as individuals develop and engage in more sophisticated social interaction, participants may smile for a range of reasons other than to communicate simple positive affect, such as to be polite (Riediger, Studtmann, Westphal, Rauers, & Weber, 2014) and smiling may therefore play a more regulatory role during social interaction. Social cognitive abilities may have a greater influential role in the use of smiling in later development, as a sophisticated understanding of the intentions and mental states behind a partner's actions is vital in ensuring that showing positive emotional affect is appropriate to the current context. Whilst these findings are preliminary, this study has provided the first empirical evidence for the hypothesised association.

The findings that social interaction skills were not significantly and independently predicted by social cognitive ability contrasts with the first hypothesis of this study and findings from previous literature. These differences may be due to the current study accounting for the influence of cognitive ability on social outcomes, whereas previous literature did not directly assess or include cognitive ability in analyses as a co-variate (Lerner et al., 2011; Sasson et al., 2012; Lefebvre-Pinard et al., 1982; Bauminger, 2002; 2007). In addition, interventions improving social cognitive abilities and social interaction skills in

children with iASD did not include a control group, making it difficult to determine whether these changes are due to developmental maturation across time (Bauminger, 2002; 2007). These caveats suggest that the original association between social cognitive and social interaction skills may have been a by-product of overall development rather than social cognitive ability influencing these social outcomes directly.

Social motivation was significantly predicted by intentionality, but not ToM abilities. These findings suggest that different types of social cognitive abilities contribute to social motivation and are consistent with Tomasello's hypothesis that intentionality abilities are associated with a species unique motivation to share psychological states with others (Tomasello & Herman, 2010). The current study provides evidence that intentionality abilities contribute to the development of social motivation.

However, recent competing views suggest that social motivation may instead influence the development of social cognition (Apperly, 2012). The social motivation hypothesis of ASD suggests that social cognitive deficits are caused by a downstream influence of disrupted social motivation in these individuals. Early impairments in motivation for social affiliation prevent children from actively engaging in social learning and opportunities to scaffold relevant social skills and development (Chevallier et al., 2012). Many tasks within the *ESCS* assess a component of motivation, and the development of shared intentionality is considered to require a species unique motivation to share psychological states with others (Tomasello et al., 2005). However, the association between social motivation and social cognition may be a more complex transaction rather than a simple unidirectional cause and effect relationship.

Studies showing a deficit in social orienting, particularly joint attention, have been claimed to be indicative of a lack of social motivation in iASD (Chevallier et al., 2012).

However, it could be argued that social orienting difficulties reflect a deficit in cognitive attentional systems (Mundy & Newell, 2007), indicating a discrete social skill difficulty rather than reflecting an individual's motivational state. Many individuals with iASD show motivation to form and maintain friendships, but lack the social skills required to maintain their quality, such as ToM abilities and coordinated play, even though many are actively involved in social interactions with friends during play (Mendelson, Gates, & Lemer, 2016; Bauminger et al., 2008). Similarly, girls with Turner syndrome show deficits in numerous social domains including ASD symptomatology, social competence and social cognition, but spared social motivation (Hong et al., 2011). Although this proof of principle study cannot distinguish between these possibilities, it has demonstrated that social cognition is worthy of further investigation for future work to delineate the concepts and the relationship between social motivation and social cognition in further detail in CdLS, FXS and RTS.

Neither early nor later developing social cognition was associated with social discomfort. These findings correspond to previous investigations in other genetic syndromes. Wingbermuhle, Egger, Verhoeven, van der Burg and Kessels (2012) found that despite performing comparably on a battery of tasks assessing mentalising skills to a group of neurotypical adults matched on gender, IQ and age, adults with Noonan syndrome demonstrated heightened levels of social distress. In addition, girls with Turner syndrome show poor ToM performance, but do not show significant levels of social anxiety (Hong et al., 2011). These previous and the current study's findings suggest that social cognition may not have a direct influence on social discomfort.

Different types of social cognitive abilities had different influences on ASD symptomatology in individuals with CdLS, FXS and RTS. Whereas ToM abilities significantly predicted lower ASD symptomatology, intentionality abilities did not. These

findings may suggest that intentionality and ToM abilities are distinct social cognitive abilities and whereas ToM abilities may underpin ASD symptomatology, intentionality abilities do not. However, these associations need to be established in individuals with iASD before conclusions can be made regarding the aetiology of ASD symptomatology more broadly.

The proportion of variance for which social cognition accounted for social outcomes that had significant models was much greater for models including ToM abilities (ranging between 15-48%) compared to intentionality abilities (8-14%). This is interesting considering the lower sample size (and subsequently lower statistical power) of participants who took part in the *ToMS* compared to the *ESCS.* These findings suggest that later developing ToM abilities better predict social outcomes than early intentionality skills. However, it is not clear why this may be the case within the current data set. These findings may highlight that social cognition may have different roles at different points in development. As individuals develop and engage in more sophisticated social interactions, they may require more flexible and sophisticated social cognitive abilities. In addition, social interactions are likely to be less scaffolded in later compared to early development, requiring individuals to use their own abilities rather than relying on others to support the ongoing interaction (Moretti & Peled, 2004). Alternatively, findings may again reflect that intentionality and ToM abilities are distinct from another and have unique influences upon sociability.

5.5.2 The influence of syndrome on the relationship between intentionality and ToM abilities, and sociability in CdLS, FXS and RTS

The second aim was to investigate whether syndrome had an influence on sociability independent of social cognition. Findings indicate that syndrome did not have an additional influence on social outcomes independent of intentionality in individuals with CdLS, FXS and RTS. These findings suggest that the causal pathways from early social cognition to behaviours in these social outcomes do not differ between syndrome groups. This may indicate that cognitive abilities recruit other more general mechanisms that are also used in non-social problem solving, such as associative learning or executive function (Frith & Frith, 2012).

In contrast, in more able and older individuals and at a domain level, syndrome predicted ASD symptomatology independent of ToM abilities. In addition, although at a domain level for these participants scores on the *Social Enjoyment* were not influenced by syndrome, syndrome influenced scores on the items *Positive Emotional Affect* but not *Social Responsiveness* within this domain. To further investigate the nature of the associations between syndrome, ToM abilities and social outcomes, in domains and items that syndrome was found to have a significant independent influence, correlations were run between ToM abilities and these social outcomes within each syndrome to determine whether syndrome exerted its influence through interaction with ToM abilities. This would suggest that the aetiological pathways from social cognition to social behaviours differ between syndromes. Whilst no differences in these patterns were found between syndrome groups for ASD symptomatology, a positive association between the number of *ToMS* tasks passed and the amount of positive emotional affect participants showed was found in individuals with CdLS, but not those with FXS or RTS.

The former findings suggest that syndrome exerts its influence upon ASD symptomatology independently from social cognition. Further work is needed to establish how syndrome exerts this influence i.e. what neurobiological or endophenotypic factors may influence ASD symptomatology.

The association between social cognition and positive emotional affect in CdLS is difficult to interpret due to the lack of previous literature investigating the association between these variables. Chapter Three indicated a syndrome specific association between chronological age and positive emotional affect only in individuals with CdLS. However, neither chronological or non-verbal mental age were associated with *Positive Emotional Affect*, suggesting that the influence of social cognition on the amount of positive affect participants with CdLS show is independent from these variables. However, collectively these findings suggest that the association between ToM abilities and the amount of positive emotional affect shown by participants during social interaction is unique to individuals with CdLS.

These findings have clinical implications. Whereas social cognition predicted social outcomes in *CSRS* domains and items, syndrome did not have an effect independent of the influence of social cognition for all items except for *ASD symptomatology* and *Positive Emotional Affect* in later development. These findings suggest that the expected influence of interventions targeting social cognitive abilities should be expected to have the same influence upon social outcomes across all syndrome groups. However, further work is needed to identify whether specific social cognitive abilities influence social outcomes differently across syndromes.

5.5.3 Limitations

Due to the rarity of these syndrome, a limitation of this study is its inevitably small sample sizes. This may have contributed to the relatively small effect sizes of the correlations and models. However, this study is strengthened by its use of direct observational assessments to better and more accurately characterise the social outcomes under investigation. In addition, previous studies have also reported that social cognition accounted for a small amount of variability in social outcomes (e.g. Lefebvre-Pinard et al., 1982) and social cognition may have a mediation rather than a direct influence upon social outcomes (Lefebrve-Pinard et al., 1982; Imuta et al., 2016). The current study provides proof of principle support for the suggestion that social cognition may be an influencing factor on social outcomes within a multifaceted account. Future work should elucidate the interactive relationship between social cognitive abilities and other influencing factors on social outcomes in CdLS, FXS and RTS.

Another limitation of this study is its cross-sectional design. Caputi, Lecce, Pagnin and Banerjee (2012) found that whilst no association was found between children's performance on ToM tasks, and their prosocial behaviour and level of acceptance from peers within time points, ToM performance at age five predicted both these outcomes two years later. As such, the dynamic influence of ToM may not fully have been observed in the current study. Nevertheless, this is the first study to have attempted to show an association between overall social cognitive performance and social interaction skills and behaviours within these groups in a relatively large sample comparative to the rarity of these groups.

5.5.4 Conclusions

This is the first study to empirically establish an association between social cognition and social outcomes in individuals with CdLS, FXS and RTS. Findings indicate similarities and differences in the domains of sociability that early and later developing social cognitive abilities influence in these syndromes. These differences may indicate: 1) developmental differences in the role of social cognition upon social outcomes, or 2) that these early and later developing social cognitive abilities (intentionality and ToM abilities respectively) are distinct constructs that influence sociability differently from one another. Syndrome did not influence sociability independently from social cognitive ability, with two exceptions. In more able individuals who participated in the *ToMS*, syndrome had an additional influence upon ASD symptomatology and the amount of positive emotional affect participants showed during social interaction. Correlations between ToM abilities and severity of ADOS symptomatology within each syndrome revealed no associations between these variables in CdLS, FXS or RTS. These findings suggest that the influence of syndrome upon ADOS symptomatology in these syndromes is completely independent from social cognition. In contrast, a unique positive association between ToM abilities and the amount of positive emotional affect participants showed during social interaction was found in individuals with CdLS, but not FXS or RTS. These findings suggest that syndrome may have a unique influence upon the association between ToM abilities and the amount of positive emotional affect participants show during social interaction. Overall, these findings demonstrate that further investigation into this association is worthy and that social cognitive ability may be a significant contributor to explanatory models of social outcomes observed in these syndromes.

CHAPTER SIX

DISCUSSION

6.1. Preface

This chapter will discuss the results from Chapters Three, Four and Five and synthesise these findings with existing literature. From this discussion, a preliminary model outlining associations between social cognition and sociability investigated in this thesis and hypothesised associations between genetic abnormality, neurobiology, cognition, sociability and the environment in individuals with CdLS, FXS and RTS is described.

6.2. Introduction

In this thesis, I aimed to describe behavioural and social cognitive aspects of sociability in three genetic syndromes (CdLS, FXS and RTS) with purportedly distinct behavioural phenotypes. Sociability is an umbrella term that encompasses a range of social skills and behaviours that contribute to an individual's social competence (Cook & Oliver, 2011). Previous literature utilising carer reports has demonstrated that different genetic syndromes can be placed on a continuum of sociability. Whereas individuals with CdLS, FXS and iASD are characterised by low levels of sociability, those with RTS, Angelman and Down syndrome were described as "hypersociable" (Moss et al., 2016). Syndromes at both ends of the continuum show atypical social interactions and are socially vulnerable, which have negative consequences on these individual's wellbeing (Karmiloff-Smith, 2012; Jawaid et al., 2012).

Developing explanatory models of profiles of sociability, including multiple levels of explanation, can help streamline interventions by identifying aetiological mechanisms or environmental variables that influence specific components of sociability. This thesis utilised cross-syndrome comparisons across syndromes comparable on non-verbal mental age to investigate: 1) the similarities and differences in the phenomenology of behaviour (e.g. sociability) and 2) the relevant aetiological mechanisms (e.g. social cognition) (Hodapp & Dykens, 2001) that may be phenotypic to a syndrome. Comparisons between syndromes with broad differences in sociability, such as syndromes characterised by social anxiety and withdrawal (e.g. CdLS and FXS; Nelson, 2010; Richards et al., 2009; Hall & Venema, 2017) against syndromes characterised by heightened motivation for social interaction and greater social competence (RTS; Galéra et al., 2009; Hennekam, 2006) can help identify differences

in the aetiological mechanisms that may be associated with profiles of sociability in genetic syndromes. A nuanced 'same-but different' investigation between two groups (i.e. CdLS and FXS) characterised by social anxiety (Richards et al., 2009; Hall & Venama, 2017) and social and communication impairments (Hogan et al., 2017; Moss et al., 2013) was utilised to identify subtle differences between these groups and potentially elucidate refined differences in aetiology leading to these behaviours (Hodapp & Dykens, 2001).

Differences in social cognitive abilities and their development may underpin differences in sociability in TD children (Imuta et al., 2016; Fink et al., 2014; Jervis & Baker, 2004; Kirschner & Tomasello, 2010; Hudley & Novac, 2007; Song et al., 2016; Kinderman et al., 1998), individuals with iASD (Sasson et al., 2012; Frith et al., 1994; Jervis & Baker, 2003; Peterson et al., 2005; 2009; Hughes et al., 1997) and genetic syndromes (Powis, 2014; Powis et al., in review; Hahn et al., 2013). However, there has been little investigation of how social cognitive abilities develop and how these abilities may be associated with sociability in individuals with CdLS, FXS and RTS. Previous research shows that individuals with CdLS and FXS show delays in understanding other's false beliefs relative to TD children (Grant et al., 2007; Cornish et al., 2005; Losh et al., 2012; Collis et al., 2008). However, groups with similar delays on false belief tasks, i.e. children with iASD and late-signing deaf children, show differences in social cognitive development on a developmental scale assessing a range of ToM abilities (Peterson et al., 2005; 2012). These differences may underpin differences in sociability between these groups and helped generate hypotheses regarding potential aetiological mechanisms leading to disrupted social cognition within each group. This thesis utilised the same novel scaling approach to investigate social cognitive abilities in individuals with CdLS, FXS and RTS across development.

Three empirical studies that utilised direct assessments of sociability and social cognitive ability in individuals with CdLS, FXS and RTS across development were conducted. The results of these studies contributed to the development of a preliminary model of sociability in CdLS, FXS and RTS. This model highlights associations investigated within this thesis and hypothesised associations for future investigation. The following sections will outline the main findings of this thesis and how these findings relate to other variables investigated in previous literature.

6.3. Summary of findings

6.3.1. The profile of sociability in CdLS, FXS and RTS

In Chapter Three, the profiles of sociability in individuals with CdLS, FXS and RTS was investigated. The frequency and quality of a range of behavioural responses indicative of broad social interaction skills (i.e. eye contact and social communication skills) and social behaviours (social enjoyment, social motivation and social discomfort) were assessed in these groups during semi-structured social interaction with an examiner. Previous literature suggests that social interaction skills and behaviours in CdLS, FXS and RTS may change across time spent interacting with another person and change across chronological age. In addition, components of sociability may be associated with ASD symptomatology differentially between syndrome groups.

The first aim was to compare the quality of components of sociability (social interaction skills, social motivation, social enjoyment and social discomfort) between individuals with CdLS, FXS and RTS. Based on previous reports, it was predicted that individuals with RTS would show a better quality of social interaction skills and behaviours compared to those with CdLS or FXS. Out of the eight social behaviours investigated,

significant differences were found in relation to quality of eye contact and the amount of person vs object focused attention. Eye contact was significantly better in individuals with CdLS compared to those with FXS and RTS and individuals with CdLS showed more person focused attention in comparison to individuals with FXS. No differences between syndromes were found for the quality of participant's positive emotional affect, social responsiveness, spontaneous initiation of interaction, social communication skills or the amount of social anxiety and avoidance of social interaction they showed during social interaction.

The finding that the FXS group was one of the groups with the worst eye contact is likely to be caused by the phenotypic gaze aversion that is well documented in FXS (Cohen et al., 1989; Crawford et al., in prep; Hall et al., 2009). The finding that the quality of eye contact in RTS was comparable with FXS and lower quality compared to individuals with CdLS contrasts with my hypothesis that those with RTS would show overall better quality social interaction skills and behaviours than individuals with CdLS and FXS. However, a case study indicated difficulties in using eye contact communicatively in those with RTS (Monica, 2016) and an experimental social cognitive task revealed that children with RTS show poor abilities in understanding and responding to another person's use of eye gaze to direct their attention to where a toy is hidden (Powis, 2014). In contrast, studies reporting greater sociability in individuals with RTS have relied on parent report measures (e.g. Galéra et al., 2009; Hennekam, 2006; Moss et al., 2016) and have not assessed social skills per se. This is the first study to directly assess eye contact in individuals with RTS during social interaction, and supports the need for detailed investigation into the strengths and weaknesses of specific social interaction skills and behaviours in individuals with RTS.

Without a TD comparison group, it is difficult to determine whether eye contact in CdLS is spared or just less impaired than individuals with FXS and RTS. Previous literature

investigating eye contact in individuals with CdLS has revealed mixed findings (Moss et al., 2012; Sarimski, 2007). The mixed literature potentially reflects the genetic heterogeneity and subsequently the variability in the quality of socially related behaviour previously reported in this syndrome (Sarimski, 2007; Deardorf et al., 2012; Moss et al., 2017; Gillis et al., 2004; Nakanishi et al., 2012), highlighting a potential pathway from gene disorder to behaviour (i.e. sociability) in CdLS. Eye contact has been shown to be influenced by different environments specifically in individuals with CdLS. Whereas individuals with CdLS show more eye contact than those with Down syndrome during a social performance task (Nelson, 2010), they also show more fleeting eye contact in comparison to individuals with Cri du Chat syndrome during conditions when the examiner maintained high levels of verbal attention and kept within close proximity to the participant (Richards et al., 2009).

The second aim was to examine the quality of components of sociability according to the amount of time spent interacting with the examiner in individuals with CdLS, FXS and RTS. Previous research has shown that individuals with a certain syndrome will show higher levels of a behaviour within a specific context (McGill & Langthorne, 2011; Oliver et al., 2013). Individuals with FXS show 'warm-up' effects over the course of an interaction, suggesting that despite being motivated to interact, these individuals show initial social difficulties upon initial social interaction. Therefore, it may be possible to reduce social anxiety in these individuals by exposing them to social interaction and prompts (Hall et al., 2009). Whilst warm-up effects have not been assessed directly in individuals with CdLS or RTS, previous research indicates that individuals with CdLS show more speech and greater sociability when interacting with familiar than unfamiliar adults (Nelson, 2010; Crawford, 2015; Moss et al., 2016), whereas those with RTS do not show differences in social behaviour when interacting with a familiar or unfamiliar adult (Crawford, 2015). Therefore, it was

hypothesised that the quality of social interaction skills and behaviours would increase over time in individuals with CdLS and FXS but not in individuals with RTS.

All groups showed an increase in person focused attention between the first ten-minute segment (TS1) and the second ten-minute segment (TS2). Individuals with CdLS and FXS showed more aversion to examiner's approaches in the second than the first ten-minute segment of the ADOS-II assessment. Finally, individuals with FXS additionally showed lower quality and less frequent spontaneous initiations of interaction during TS2 than during TS1.

These findings conflict with my hypothesis and may reflect increased social demands between TS1 and TS2 rather than the influence of duration of social interaction with the examiner. However, this conclusion is speculative as level of social demand was not controlled systematically. Nevertheless, these findings are novel in that they indicate that, compared to individuals with CdLS and FXS and in concordance with previous literature (Crawford et al., in prep), social interaction skills and behaviours observed in individuals with RTS may be more consistent and less influenced by environmental context. These findings support the need for further work to delineate whether and which environments this pattern is true for in those with RTS.

The third aim was to investigate whether the frequency and quality of components of sociability change with age in individuals with CdLS, FXS and RTS. Previous literature has identified a deterioration in abilities, such as poorer eye contact in FXS (Roberts et al., 2007) and social withdrawal in CdLS (Moss et al., 2016), or increases in challenging behaviours, such as aggressive behaviours in RTS (Hennekam, 2006; Milani et al., 2015). Understanding when these changes occur can help families and practitioners anticipate and plan for difficulties that may emerge. Based on previous literature (Moss et al., 2016; 2017; Oliver et

al., 2010; Wulffaert et al., 2009; Basile et al., 2007), changes with age were predicted to occur within individuals with CdLS. However, investigation into changes with age was exploratory in individuals with FXS and RTS, as the available literature investigating these syndromes has been somewhat inconclusive to date.

Correlations between participant's scores on *CSRS* items and chronological age within each syndrome revealed different patterns of associations between CdLS, FXS and RTS. Older participants with CdLS showed more positive emotional affect, better quality social communication skills, more social anxiety and less avoidance of social interaction with age. They also focused their attention more on people than objects. Older participants with FXS showed more frequent and better quality social responses, social communication skills and more social anxiety with age. Finally, the frequency and quality of components of sociability in participants with RTS was not associated with their chronological age.

Except for *Focus of Attention* in those with CdLS, these items also correlated with participant's non-verbal mental age, making it difficult to disentangle the degree to which findings reflect changes with time versus changes with development. Whereas quality of social interaction skills and social responsiveness are likely to improve with development and ability, the potential association between ability and social anxiety and social discomfort is not as clear. One hypothesis is that as individuals with CdLS and FXS develop, they may become more self-aware and self-conscious in social situations, leading to social anxiety, implicating an association between development and sociability. Alternatively, changes with time may reflect changes with age rather than development. A syndrome specific deterioration in executive function with age in CdLS, due to cumulative effects of impaired repair and oxidative stress over time resultant from the syndrome related genetic abnormality (Gimigliasno et al., 2012), may lead to environments requiring flexible cognitive and

behavioural, such as to-and-fro social interaction, to become more difficult with age (Reid et al., 2017). This would delineate an aetiological route from gene (i.e. an abnormality on chromosome, to neurobiology (oxidative stress), to endophenotype (executive function), that changes over age, and subsequently interacts with the environment (social situations) and determines behaviour (social anxiety) differently with age.

Despite an increase in social anxiety with chronological and non-verbal mental age, older individuals with CdLS showed less avoidance of social interaction, and more positive emotional affect and person focused attention. These results may suggest that, whilst these individuals experience social anxiety during social interaction, they are still motivated to interact. Previous warm-up effects in those with FXS has led to similar hypotheses (Hall et al., 2009). These hypotheses suggest that individuals with CdLS and FXS may be willing to engage in interventions to help improve their social interaction skills and behaviours and reduce their anxiety.

The final aim of this study was to explore the extent to which the severity of ASD symptomatology is associated with components of sociability in CdLS, FXS and RTS. Whilst many individuals with CdLS and FXS reach clinical cut-off scores on assessments of ASD (Oliver et al., 2011; Moss et al., 2013), fine-grained investigation indicate similarities and differences in the profile of ASD-related behaviours between individuals with CdLS and FXS, and those with iASD (Moss et al., 2008; Basile et al., 2007; McDuffie et al., 2014; Wollf et al., 2012; Martin et al., 2016). These findings highlight aetiological pathways that lead to behaviours in these groups that may or may not be shared between different genetic syndromes and iASD. Similarly, associations between ASD symptomatology and broader aspects of sociability within syndromes may highlight similarities in the underlying mechanisms that drive these behaviours, that can be investigated in future work. I predicted

that some components of sociability would be associated with ASD symptomatology severity in individuals with CdLS and FXS but not in individuals with RTS due to the low level of ASD reported in this group (Powis, 2014).

Correlations between participant's scores on *CSRS* items and their severity scores on the *Social Affect* ADOS-II subscale revealed different profiles of association between ASD symptomatology and components of sociability across syndrome groups. In FXS, those with more severe ASD symptomatology showed more social anxiety, whereas individuals with RTS with greater severity scores showed less positive emotional affect and reduced quality of eye contact. Individuals with CdLS did not show any associations between broader social skills and ASD symptomatology.

Findings suggest that some components of sociability may be associated with ASD symptomatology in individuals with FXS and RTS but not in CdLS. However, the nature and direction of these associations are difficult to interpret. Previous work indicates differences in the profile of social anxiety in those with FXS and iASD, suggesting that the aetiological mechanism driving social anxiety in these groups differ (Scher et al., 2017). Overall, findings suggest that whilst there is an association between ASD symptomatology and social anxiety at a behavioural level, it is likely that the nature of this association is mediated by other variables at the neurobiological or cognitive levels that are yet to be identified and investigated, that may or may not be the same as those with iASD. Despite hypersociability previously reported in carer-reports (Moss et al., 2016; Stephens et al., 1990; Hennekam, 2006), individuals with RTS may show social difficulties that overlap with iASD in some social interaction skills and behaviours. Further work is needed to disentangle the nature of this association and social difficulties in individuals with RTS more broadly.

6.3.2. The development of social cognition in CdLS, FXS and RTS

Findings from Chapter Three further highlight the unique and distinct behavioural phenotypes in CdLS, FXS and RTS. Given the wealth of literature demonstrating the influence of social cognition upon a range of social behaviours, the development of social cognitive abilities was identified as a potential aetiological mechanism that may be associated with the variable profiles of sociability in these groups. To investigate the development of social cognitive abilities in individuals with CdLS, FXS and RTS, participants took part in one of two scaled batteries of behavioural tasks assessing the development of either early intentionality (*ESCS*) or later developing ToM social cognitive abilities (*ToMS*). The development of intentionality and ToM abilities were assessed in two ways: 1) whether overall performance on intentionality and ToM abilities were advanced, preserved or delayed relative to participant's non-verbal mental age and 2) whether the order in which these abilities emerged followed the same developmental order as that observed in TD children.

6.3.2.1 Early social cognition scale

Findings revealed that the development of intentionality abilities was delayed in children with CdLS, FXS and RTS relative to non-verbal ability. Cross-syndrome comparisons of the overall number of tasks passed suggested that individuals with CdLS showed a greater delay in passing these tasks than individuals with FXS and RTS. Findings suggest that a mechanism other than overall general cognitive ability is disrupting social cognitive development in these individuals.

Guttman scaling analyses revealed that none of the syndrome groups developed these abilities in the same cumulative sequence observed in TD infants. Pairwise comparisons between tasks of increasing difficulty within each syndrome group revealed similarities and

differences in spared and impaired abilities across these groups. Prior to corrections for multiple comparisons, all groups showed a pattern in which the first two easiest tasks (i.e. a *Helping* task, requiring participants to understand the examiner's intention when they reached for a dropped object and '*Re-enactment of Intended Acts'*, which required participants to understand the intention behind an examiner's failed action) were significantly easier than the final four tasks (two *Gestures* tasks, requiring participant's to understand the intention of an examiner's point or gaze gesture to direct them to a container where an object of interest is hidden and two *Cooperation* tasks, requiring infants to form a shared intentionality with the examiner in order to cooperate and complete either a problem solving or social game). However, following corrections, this distinction between early and later developing intentionality abilities only remained in individuals with FXS.

Results from scaling analyses helped elucidate variables that may disrupt intentionality abilities in CdLS, FXS and RTS. Whilst differences between performance on earlier versus later developing intentionality abilities may be more pronounced in FXS than in children with CdLS and RTS, the mechanism disrupting the development of intentionality abilities may be similar across these groups. The break in performance between tasks assessing early and later developing intentionality abilities observed in all syndromes prior to corrections for multiple comparisons may reflect two sets of abilities that emerge from two distinct developmental streams hypothesised to lead to shared intentionality (Tomasello and colleagues, 2005). These streams are 1) a basic ability to understand other's intentions and 2) a species unique motivation to share and represent others psychological states and to direct another's attention to shared objects of interest (Moll & Tomasello, 2007; Frith, 2008). Genetic and subsequently neurobiological differences between CdLS, FXS and RTS may lead to differences in how the second developmental stream is disrupted, and subsequently the

degree to which later developing intentionality abilities assessed by the *ESCS* are disrupted between these groups. This hypothesis outlines a pathway from genetic abnormality, to neurobiology, to cognition across development.

In addition, disruption to the development of joint attention, a social referencing skill (Mosconi et al., 2008), considered to be a core precursor to social cognition as well as a range of social interaction and behaviours (Charman et al., 2000; Mundy et al., 1990; Hahn et al., 2013; Hahn et al., 2016), may disrupt social cognitive development similarly between CdLS, FXS and RTS. Whilst participants can pass the two easiest *ESCS* tasks by making inferences based on the examiner's actions, the latter four require participants to either respond to the examiner's use of joint attention indicating which box a toy is hidden in (both *Gestures* tasks) or initiate joint attention to direct the examiner's attention so that they can fulfil their role to complete a joint goal (both *Cooperation* tasks). Whilst this hypothesis suggests joint attention has a direct influence on social cognition, it may also have an indirect influence via a mediating or moderating association with Tomasello's (2005) hypothesised later developmental stream. The development of cognitive architecture to be able to represent the intentions and roles of others may also be associated with an individual's ability to share common ground with a partner to cooperate via joint attention abilities, to achieve a joint goal together (Tomasello & Carpenter 2007; Tomasello et al., 2005). As above, genetic and neurobiological differences in CdLS, FXS and RTS may lead to different profiles of joint attention skills, leading to disruptions in later developing intentionality abilities.

Overall, findings suggest that phenotypic differences in the developmental mechanisms at a cognitive level (i.e. the development of the second developmental stream), and/or at a behavioural level (i.e. joint attention) between CdLS, FXS and RTS, may lead to differences in the patterns of intentionality abilities observed in these groups. These potential

cognitive and behavioural differences likely emerge from neurobiological differences between these syndromes.

6.3.2.1 Theory of Mind Scale

Many participants from each syndrome group showed attainment of advanced abilities required to pass the first two easiest *ToMS* tasks i.e. *Diverse Desires* (the ability to understand that others can have desires different from your own) and *Diverse Beliefs* (the understanding that others can have beliefs that are different from your own), relative to non-verbal ability. However, many participants from all syndrome groups showed delayed performance in the final four tasks of the *ToMS,* i.e. *Knowledge Access* (the ability to understand what another person knows based on what you know about their previous experiences), *Contents False Belief* (the ability to understand that someone can have a belief that is different from your own and discrepant with reality), *Hidden Emotion* (understanding that someone can show an emotion that is different to the one they are actually experiencing) and *Sarcasm* (the ability to understand the meaning behind a person's non-literal comment). These findings suggest that whilst ToM development is disrupted in individuals with CdLS, FXS and RTS, as the sample consisted of adults they may have learned alternative coping strategies through exposure to social situations over time, indicating a time x environment interaction.

Guttman scaling analyses revealed that, as with intentionality abilities, children and adults with CdLS and FXS did not pass *ToMS* tasks in the same developmental sequence as TD children. However, visual inspection of pass and fails in the RTS group revealed that these participants largely conformed to the same sequence observed in TD children, except for one participant who passed the *Hidden Emotion* task but not the *Contents False Belief* task that TD children find easier. Guttman scaling analysis on the first four easiest *ToMS* tasks in

participants for RTS revealed that the pattern that they passed these tasks formed a perfect cumulative scale, suggesting that individuals with RTS develop the abilities required to pass the first four tasks in the same developmental sequence as TD children.

Whereas the CdLS group showed a heterogeneous profile in which no tasks were significantly more difficult than the other, the FXS and RTS groups showed 'drop-off points' between groups of tasks assessing earlier and later developing ToM abilities, but between different tasks. Whereas individuals with FXS found the first three tasks significantly easier overall than the last three tasks, individuals with RTS found only the first two tasks significantly easier than the four most difficult tasks.

However, whereas most TD children who failed these tasks in previous studies passed these control questions (Wellman, 2004; Peterson et al., 2005; 2011), individuals with CdLS, FXS and RTS who failed also failed the tasks respective control questions. Participants with CdLS, FXS and RTS may have had difficulties in remembering key facts about the story, despite having the non-verbal mental age expected to be able to remember this information. Performance on these control tasks make it difficult to distinguish the degree participants failed tasks due to a lack of the social cognitive ability, versus more global difficulties (i.e. memory, executive function) and how these factors may influence social cognitive understanding and social behaviour more broadly.

Cross-syndrome comparisons comparing the mean number of control questions tasks between participants who failed the experimental trials indicate that individuals with RTS failed the most control questions compared to individuals with FXS and RTS. The genetic cause of RTS leads to abnormalities on the CREBBP locus, leading to deficits in histone acetylation in cell lines (Lopez-Atalaya et al., 2011). These deficits have been implicated in both short (Chen et al., 2010) and long term memory deficits (Park et al., 2014) observed in

those with RTS (Waite et al., 2016). Genetic and neurobiological differences may explain why individuals with RTS showed greater memory difficulties in comparison to individuals with CdLS and FXS. Previous research indicates that children with FXS failed false belief tasks due to working memory difficulties (Grant et al., 2007). However, as individuals with FXS passed more controls trials than those with RTS, those with FXS were likely to be less severely affected by working memory difficulties than those with RTS.

Individuals who failed social cognitive tasks but passed control questions may have failed due to executive function difficulties, considered to be a prerequisite and determines the developmental trajectory of ToM development (Brunsdon & Happé, 2014). Individuals with CdLS, FXS and RTS show profiles of performance on measures of executive function (Johnson, 2015), which may be associated with differences in ToM development. However, the association between executive function and social cognition is yet to be investigated in CdLS, FXS and RTS.

Overall, findings suggest that differences in the genetic cause and subsequent neurobiological consequences (e.g. changes on the CREBBP locus) may lead to differences in cognition (e.g. memory or executive function) in individuals with CdLS, FXS and RTS. These differences at the cognitive level may lead to differences in the development of ToM abilities. Despite difficulties at a cognitive level, an environment x time interaction may lead to older individuals with CdLS, FXS and RTS to develop alternative coping strategies learned from experience that enabled participant's to develop some ToM understanding that leads to an advanced ability to pass the first two easiest tasks on the *ToMS* relative to their non-verbal mental age.

6.3.3 The link between overall social cognitive ability and sociability in CdLS, FXS and RTS

Chapters Three and Four established the similarities and differences in the profiles of sociability and social cognition respectively between individuals with CdLS, FXS and RTS. Chapter Five is the first 'proof of principle' investigation to assess whether and how overall intentionality and ToM abilities influence observable components of sociability and ASD symptomatology in CdLS, FXS and RTS. Hierarchical linear regressions were employed to investigate: 1) whether and which components of sociability (*social enjoyment, social motivation, social interaction skills* and *social discomfort*) and ASD symptomatology were predicted by overall intentionality or ToM abilities (the number of tasks participants passed in the *ESCS* or *ToMS*), over and above participant's chronological age and non-verbal age, 2) whether syndrome had an additional influence upon these social outcomes above overall social cognitive ability and if so 3) whether the associations between social cognitive abilities and social outcomes differed between syndrome groups. The influence of social cognition and syndrome was first investigated broadly at a domain level. Social outcomes significantly predicted by social cognition were followed up for more refined investigation by running hierarchical linear regression on *CSRS* items within those domains. Analyses were run on data from the *ESCS* and the *ToMS* separately.

6.3.3.1 Overall influence of social cognition in individuals with CdLS, FXS and RTS

At a broad level, greater intentionality abilities predicted greater frequency and quality of behaviours indicative of social enjoyment and social motivation but not social interaction skills, social discomfort or ASD symptomatology in children with CdLS, FXS and RTS. In comparison, greater ToM abilities significantly predicted greater quality of behaviours

indicative of social enjoyment and less severe ASD symptomatology in individuals with CdLS, FXS and RTS. These findings may suggest that intentionality and ToM abilities are distinct concepts that fall under the umbrella of social cognition and subsequently influence different social components. Whereas social motivation may be associated with a species unique motivation to share psychological states with others, which is a key component of intentionality (Tomasello & Herman, 2010), social motivation may not be as closely associated with ToM ability.

At a refined level, for items within the social motivation domain, greater intentionality abilities predicted greater frequency and quality of initiations of interactions made but did not influence the amount of person versus object focused attention shown by participants. Findings may reflect a specific influence on specific social interaction skills within this domain (i.e. *Social Responsiveness*) but not others (*Focus of Attention*).

Intentionality and ToM abilities predicted different behaviours within the *Social Enjoyment* domain. Greater intentionality abilities predicted more frequent and better quality social responses but not the amount of positive emotional affect shown by participants. In contrast, greater ToM abilities predicted both greater social responsiveness and positive emotional affect. The differences in positive emotional affect between intentionality and ToM abilities may reflect the different functions of smiling in early and later development. Whereas smiling at an early age simply signals one emotion, i.e. joy (Messinger & Fogel, 2007), smiling in later development may constitute a range of functions such as being polite (Riediger et al., 2014), which relies on social cognitive abilities to ensure that they are relevant to the current context.

Overall, findings indicate that different aspects of social cognition, i.e. intentionality and ToM abilities, differentially predict components of sociability at both a broad and refined

level. These skills may illustrate that intentionality and ToM abilities are distinct from one another and subsequently have differential influences upon social outcomes in individuals with CdLS, FXS and RTS. Alternatively, differences in the social outcomes may reflect developmental differences in how social cognitive abilities are broadly used during social interaction.

6.3.3.2 The influence of syndrome on the association between intentionality and ToM abilities, and sociability in CdLS, FXS and RTS

The nature of associations between an individual's cognitive profile and behavioural phenotype may differ across syndromes (Woodcock et al., 2009a; 2009b). However, findings from Chapter Five indicate that the association between overall social cognitive ability and social outcomes does not differ across syndrome groups, except for ASD symptomatology and the amount of positive emotional affect that participants showed (both predicted by ToM abilities). Correlations revealed no associations between ToM abilities and ASD symptomatology within any syndrome groups. These findings indicate that the additional influence of syndrome is not exerted by an interaction with social cognitive ability, suggesting that the influence of social cognition on these social outcomes is the same across those with CdLS, FXS and RTS. However, individuals with CdLS, but not FXS or RTS, showed a unique positive association between social cognitive abilities and the amount of positive affect they showed.

Overall, findings suggest that the associations between cognitive (intentionality and ToM abilities) and behavioural levels (components of sociability and ASD symptomatology) are mostly the same across individuals with CdLS, FXS and RTS. However, additional genetic and neurobiological factors (syndrome) have an additional influence upon ASD

symptomatology during later development that appears unrelated to social cognition. However, in individuals with CdLS, genetic and neurobiological abnormalities may lead to a unique association between social cognition and the amount of positive emotional affect they show during social interaction in later development.

6.4 Model of the development of social cognition and sociability in CdLS, FXS and RTS.

This thesis includes the first studies to describe the profiles of sociability, the development of social cognition and the association between social cognition and sociability in CdLS, FXS and RTS. These studies can inform a model of social cognition and sociability that represents hypothesised associations and the associations investigated in this thesis between variables across and within levels of explanation. With further research, this model can be adapted to better accommodate new insights from research investigating these hypothesised associations.

As the development and overall influence of 'early' and 'later' developing social cognitive abilities upon components of sociability was investigated separately, separate models have been made for 'early' (figure 6.1) and 'later' (figure 6.2) development. Whilst these two categories of social cognitive abilities have been theorised to be developmentally related (Tomasello et al., 2005), currently there is no empirical evidence or investigation of this link. As the focus of this thesis is concerned with the influence of social cognition upon sociability, only components of sociability shown to be associated with social cognition in Chapter Five are included in these models. Future work establishing these links may lead to the development of more inclusive and dynamic models.

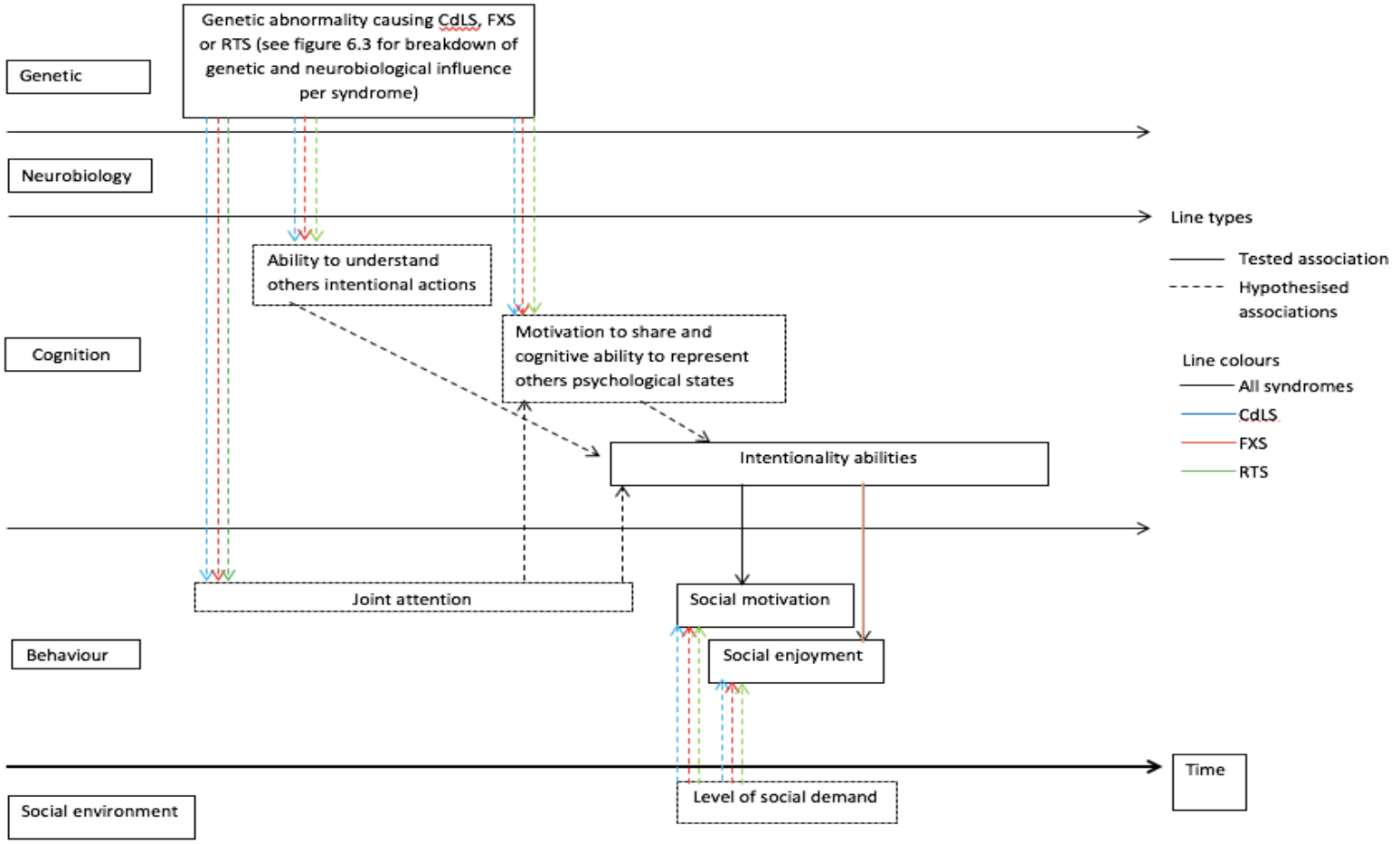


Figure 6.1. *Model of sociability in individuals with CdLS, FXS and RTS during early development, outlining hypothesised and empirically tested associations between genes, cognition, behaviour and the social environment*

The models adopt aspects of the Accessible Cause-Outcome Representation and Notation system (ACORNS; outlined in section 1.3). This approach was chosen over other notation tools such as Morton's (2004) causal modelling approach, due to the dynamic developmental nature of social cognitive abilities (Wellman & Liu, 2004; Peterson et al., 2004; 2009) and sociability across age and development (Moss et al., 2016; Oliver et al., 2010; Basile et a., 2007; Cochran et al., 2015; Stephens et al., 2010; Fisch et al., 2012; Fisher et al., 2016). Whereas the causal modelling approaches represents variables as static, the ACORNS includes a time dimension to account for the dynamic development of behavioural phenotypes and the influencing genetic, neurobiological, cognitive and environmental factors that interact and leads to the development of behavioural phenotypes. Figures 6.1 and 6.2 include a time axis to represent the hypothesised developmental sequence of variables.

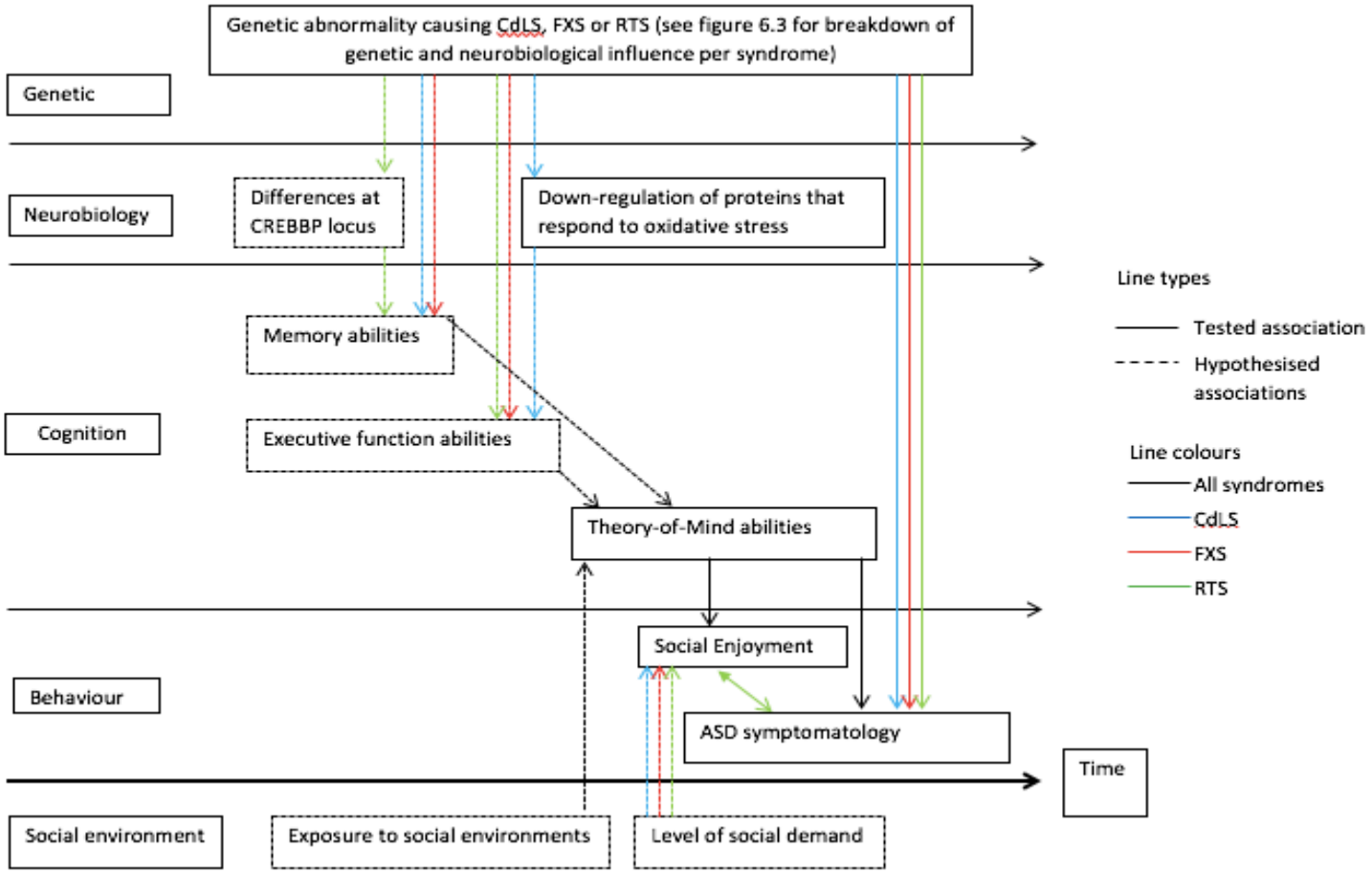


Figure 6.2. *Model of sociability in individuals with CdLS, FXS and RTS during later development, outlining hypothesised and empirically tested associations between genes, cognition, behaviour and the social environment.*

Associations that have been investigated empirically in this thesis and hypothesised associations generated from current findings and previous literature are included in these models. Solid arrows indicate associations that have been investigated and established in this thesis. Dotted arrows indicate hypothesised associations between variables. The colour of arrows highlight similarities and differences of associations between variables between individuals with CdLS, FXS and RTS. Black arrows indicate the influence and nature of aetiological pathways between two variables may be the same across CdLS, FXS and RTS. Arrows of different colours (one colour per syndrome groups) suggest that the nature of the aetiological pathway may differ between syndrome groups.

The proposed model includes variables that transverse between biological and neurological impact of genetic cause and cognitive profiles and represent how these variables influence behaviour. Variables external to the individuals i.e. the environment, that influence behaviour are also included. The model is not intended to be comprehensive, but instead provides a tool to represent the hypothesised associations between these variables for future research.

The following sections will describe each model between genetic abnormality, neurobiology, cognition and behaviour (i.e. aspects of sociability), as well as descriptions of the influence of the environment on behaviour.

6.4.1 Genetic and neurobiological influences

The development of profiles of cognition and behaviour in CdLS, FXS and RTS are likely be caused by the genetic abnormality that cause each syndrome. Figure 6.3 outlines the pathway from gene to neurobiology in CdLS, FXS and RTS. The influence of the distinct genotypes and neurobiological differences within each group is likely to influence cognition

and behaviour differently. These differences are represented in figures 6.1 and 6.2 by multi-coloured arrows. Genetic and neurobiological causes hypothesised to be related specifically to the development of social cognition and/or sociability are outlined in the main models and described below.

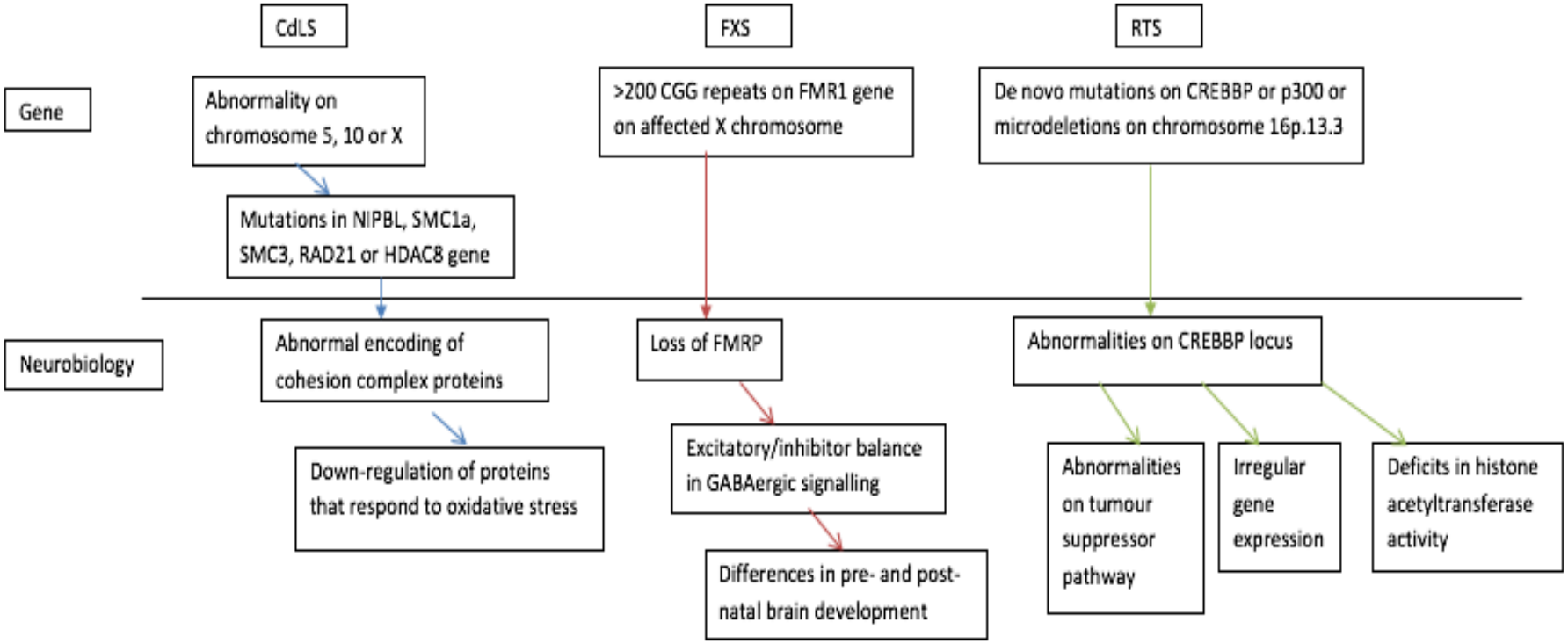


Figure 6.3. *Genetic abnormalities and subsequent influences upon neurobiology in individuals with CdLS, FXS and RTS*

6.4.2 Early Development

In this model (figure 6.1), differences at the genetic and neurobiological level are hypothesised to influence differentially the two developmental streams hypothesised by Tomasello (2005) that lead to an individual to develop a shared intentionality to cooperate and coordinate their own actions with others. These are 1) an ability to understand other's intentional actions, which develops before 2) a motivation to share their own and a cognitive ability to represent other's psychological states. The two developmental streams may contribute to the groupings of tasks in which the first two tasks (i.e. *Helping* and *Re-enactment of Intended Acts*) are easier than the four most difficult tasks (*Gestures-Point, Gestures-Gaze, Cooperation-Tubes, Cooperation-Trampoline)* identified in Chapter Four. These two developmental streams are hypothesised to influence the development of intentionality abilities at the cognitive level.

At the behavioural level, joint attention may contribute to the development of intentionality abilities directly and/or indirectly. Differences in each syndrome's genetic cause and subsequently their neurobiology may lead to differences in their ability to respond and use joint attention. The four most difficult tasks in the *ESCS* require individuals to either respond or use joint attention, suggesting a direct influence of joint attention upon intentionality abilities in CdLS, FXS and RTS. Joint attention may exert an indirect influence on intentionality abilities via a mediating or moderating influence on the development of children's abilities to represent cognitively other's psychological states, by enabling children to share common ground with others (Tomasello & Carpenter 2007; Tomasello et al., 2005).

The similarities of strengths and difficulties in the development of intentionality abilities observed in children with CdLS, FXS and RTS in Chapter Four suggests that the influence of the second developmental stream at the cognitive level and the hypothesised

direct and indirect influences of joint attention on the development of intentionality abilities may be the same across group. These influences are represented with a dotted black arrow.

Chapter Five demonstrated proof of principle that social cognitive abilities predict the quality of social behaviours indicative of social enjoyment and social motivation in children with CdLS, FXS and RTS, but not social interaction skills, social discomfort or severity of ASD symptomatology. Chapter Five indicates that syndrome did not have an additional influence upon social motivation or social enjoyment independent of social cognitive ability, suggesting the associations between social cognition and these components of sociability are the same across syndromes. Therefore, the associations between intentionality abilities (from the cognitive level) and domains of sociability (behavioural level) are represented with a solid black line.

6.4.3 Later development

Findings from Chapter Four indicate that at the cognitive level, many participants who failed tasks in the *ToMS* also failed control items that serve as memory checks. Individuals with RTS failed significantly more control trials compared to those with CdLS and FXS. Individuals with RTS show memory difficulties (Waite et al., 2016) that may be caused by abnormalities on the CREBBP locus that emerge from the mutations on the CREBBP that cause RTS (Park et al., 2014; Chen et al., 2010; Lopez-Atalaya et al., 2011). This association is represented on the model with a green dotted arrow from the neurobiological (CREBBP) to the cognitive level (memory). Blue and red arrows (representing CdLS and FXS respectively) from gene to cognition (memory) are also included, to represent the hypothesised differentiating influence of genetic cause upon the development of memory between syndromes. As all syndromes showed difficulties in control questions, the association

between working memory and ToM abilities is hypothesised to be similar across groups and is represented with a dotted black arrow.

Executive function is hypothesised to be an important precursor to ToM (Brunsdon & Happé, 2014) and individuals with CdLS, FXS and RTS show different difficulties across executive function abilities (Johnson, 2015). The differences in development of executive function between syndromes are represented with multi-coloured arrows from the genetic/neurobiological level to the cognitive level (executive function). A specific pathway from gene, to neurobiology, to cognition is included for individuals with CdLS, as increased oxidative stress and subsequent decreased neural repair over time in individuals with CdLS has been hypothesised to lead to deterioration in executive function (Gimigliasno et al., 2012; Oliver et al., 2013).

Results from Chapter Four indicate that participants with CdLS, FXS and RTS showed advanced abilities in passing the first two easiest tasks relative to their non-verbal age. A hypothesised environment x time interaction, in which participants learn alternative coping strategies through experience with social interactions over time that enable them to pass these first two *ToMS* tasks, has been included in the model.

Chapter Five revealed that ToM abilities influenced different domains of sociability. Greater ToM abilities predicted greater social enjoyment and less ASD symptomatology in CdLS, FXS and RTS. As in early development, syndrome did not have an additional influence upon social enjoyment, suggesting that the aetiological pathway between social cognition and these domains of sociability do not differ between syndromes. Therefore, the influence of social cognition (cognition) upon social enjoyment (behaviour) is represented with a solid black line. In contrast, syndrome did have an additional influence upon ASD symptomatology. However, no differences were found between groups in the patterns of

association between social cognition and ASD symptomatology, suggesting that the influence of syndrome is independent from social cognition. Therefore, the influence of social cognition upon ASD symptomatology is represented with a black arrow. Three coloured arrows, representing each syndrome, is placed from the genetic level to ASD symptomatology. Further work should identify the pathway from genes to cognition to behaviour (ASD symptomatology) within these syndromes.

6.4.4 The role of the environment in both early and later development

Results described in Chapter Three indicated that different components of sociability changed over the duration of the ADOS-II assessment between individuals with CdLS, FXS and RTS. Whereas both individuals with CdLS and FXS showed a range of changes between the first (TS1) and second (TS2) 10-minute segments, individuals with RTS showed a more stable profile. Whilst it is not possible from the current dataset to determine what environmental factor influenced these changes, these findings correspond to previous literature that have found that individuals with CdLS and FXS show more changes in behaviour dependent on level of social demand than individuals with RTS (Crawford et al., in prep). Therefore, the influence of environment upon social domains is represented with a dotted arrow and should be investigated through systematic manipulation to investigate the influence of level of social demand upon observational behaviours indicative of components of sociability.

6.5 Clinical implications

These models identify variables that can be targeted in interventions that aim to improve social cognition and components of sociability in individuals with CdLS, FXS and

RTS. There are currently no social cognitive interventions specifically designed for individuals with CdLS, FXS and RTS. However, a Cochran review evaluating the outcome of ToM interventions for individuals with iASD suggest that improvements in social cognitive ability are not maintained over time (Fletcher-Watson, McConell, Manola & McConachie, 2014). A possible explanation for these findings are that targeting later developing ToM abilities may be more difficult to improve than earlier developing abilities. Participants may not be able to learn ToM abilities before establishing core skills, such as joint attention or executive function abilities that later social cognitive abilities are scaffolded from. Further research should investigate these hypothesised aetiological associations between these variables and social cognition across development to identify the variables and developmental points that intervention would be most successful.

Many social cognitive interventions have failed to show improvements in social behaviour (Fletcher-Watson et al., 2014; Wang & Spillane, 2009; Quinn et al., 1999; Bellini et al., 2007). Findings from Chapter Five indicate that different social cognitive abilities influence different components of sociability. However, previous studies investigating the influence of social cognition training upon social behaviour have used global measures of social competence, which may include behaviours that are not associated with social cognition. Chapter Five's findings support the need for evaluations of social cognitive interventions to choose appropriate measures that assess social behaviour that previous literature has established is associated with social cognition within a specific clinical group.

For many older individuals, early intervention may not be appropriate. However, Chapter Four indicates that many individuals showed advanced development of two of the easiest ToM abilities relative to their non-verbal mental age in later development. Similarly, individuals with high functioning iASD can pass traditional false belief tests by representing

mental states based on the content of speech through listening and speaking with others about other's mental states (Tager-Flusberg, 2007). These findings suggest that these individuals may be able to develop understanding of ToM concepts through alternative cognitive mechanisms. Interventions may benefit from utilising the spared cognitive domains specific to each syndrome, such as verbal domains in William syndrome or non-verbal domains in Down syndrome (Jarrold, Baddeley & Hewes, 1998; Chapman & Hesketh, 2000; Wang & Bellugi, 1994).

6.6 Strengths, limitations and future directions

In this thesis, a main aim was to build upon previous work that mainly utilised indirect assessments of sociability and carer-reports (Moss et al., 2016; Jervis & Baker, 2004; Korucu et al., 2017; Song et al., 2016; Frith et al., 1994; Peterson et al., 2009; Hughes et al., 1997; Hong et al.,2011). A strength of all the studies included in this thesis is the use of direct observational assessments of: 1) a range of observable behaviours that are indicative of both social interaction skills and behaviours that contribute to these profiles of sociability in CdLS, FXS and RTS and 2) profiles of social cognitive abilities across development. In addition, this thesis described the profile of sociability and social cognition in individuals with CdLS, FXS and RTS beyond a basic conceptualisation of sociability and social cognition. Different syndromes have shown different associations between specific cognitive abilities and components of their behavioural phenotypes (Woodcock et al., 2009a; 2009b). Subtle phenomenological differences in behaviours that initially appear broadly similar, e.g. social anxiety in those with CdLS and FXS (Crawford et al., in prep), suggest differences in the underlying aetiology leading to these behaviours within each syndrome. Therefore, it was deemed necessary to investigate sociability and social cognitive abilities at a more fine-

grained level to better elucidate the differences across groups and subsequently refine hypotheses of the underlying mechanisms that lead to the development of these constructs.

This thesis used a novel scaling approach that facilitated assessment of social cognitive abilities by removing barriers to participation in a cohort of participants with syndromes associated with various levels of ID. Many social cognitive assessments place high demands on language domains, including the tasks in the *ToMS* (Powis, 2014), leading to difficulties of assessing social cognition in non-verbal individuals with CdLS, FXS and RTS. The development of the *ESCS* has extended the investigation of social cognitive abilities to children and less able individuals. The *ESCS* and *ToMS* combined enabled investigation of social cognitive abilities across development and the range of abilities associated with these syndromes. The simple materials and quick administration ensured that participants did not become disengaged or lose interest, despite many individuals with a syndrome or ID showing difficulties with attention (Grefer et al., 2016; Galéra et al., 2009; Stevens et al., 2011; Emerson, 2003). The use of simple materials enabled experimenters to visit families at their homes who were not able to visit the University and subsequently would not have been able to participate.

These tools helped gain a large sample of participants within each syndrome group, despite the rarity of these syndromes and the practicalities of researching individuals with ID. In the UK, many studies consist of up to 25 participants per syndrome group (e.g. Crawford, 2015; Moss et al., 2013; Nelson, 2010; Richards et al., 2008; Johnson, 2015). In this thesis, a total of thirty-nine participants with CdLS, thirty-eight participants with FXS and thirty-two participants with RTS were included. As well as increasing the statistical power to investigate sociability broadly across these groups, these larger numbers enabled the investigation of

earlier and later developing social cognitive abilities by splitting these groups and still attaining samples large enough to investigate these abilities.

Whilst the number of participants that were included in each syndrome group was larger than previous studies, the numbers included in analyses were still relatively small. In this thesis, emphasis was placed on investigating sociability and social cognition at a fine-grained level. Chapters Three and Chapter Four investigated the profile of sociability and social cognition at a refined level of detail beyond global measures of these constructs. However, in Chapter Five, the small sample sizes, as well as the extreme strengths and weaknesses shown by participant's performance at a group level on many social cognitive tasks, meant that many social cognitive tasks had only a few participants who passed or failed a particular task. Therefore, it was not possible to investigate the influence of specific intentionality or ToM abilities upon components of sociability. However, Chapter Five is the first proof of principle study investigating the influence of social cognition upon sociability in these groups. In addition, investigating the associations between social cognition and sociability at a domain (rather than an item) level reduced the likelihood of type 1 errors. As this study has provided proof of this concept, future work should aim to refine understanding of these associations at a more detailed level.

Social interaction is a reciprocal and dynamic process between at least two agents with success dependent upon the interplay between each partner's responsiveness to each other's intentions and needs and how the initial request of one person influences their partner's response (Lefebvre-Pinard et al., 1982). Although some *CSRS* items investigated participant's behaviours within a reciprocal context (e.g. *Social Responsiveness*), only the participant's behaviour was evaluated. In addition, whilst this thesis focuses upon the influence of social cognition on social outcomes in CdLS, FXS and RTS, it is important to recognise the likely

transactional nature of the relationship between these variables. However, findings from this thesis provided proof of principle and a rationale to examine the complex nature of social cognition and social outcomes in CdLS, FXS and RTS by providing the first evidence of an association between these variables within these syndromes.

Cognitive tests are never 'process pure' (Brunsdon & Happé, 2014) and to pass many items in a battery of cognitive tasks often requires participants to recruit cognitive processes/domains other those under direct assessment. However, this is an issue common across many developmental assessments including the Mullen Scales of Early Learning (Mullen, 1995) and the Bayley Scale of Infant and Toddler Development (Bayley, 2005). Like these developmental scales, the *ESCS* and the *ToMS* provide a robust normative developmental benchmark to compare the development of social cognitive abilities in individuals with CdLS, FXS and RTS against and findings using these tools helped generate hypotheses of variables that may influence the performance observed in these groups for further research. However, checks on control tasks on items on the *ESCS* suggest that participants who failed relevant experimental tasks did so due to a lack of the social cognitive ability assessed as opposed to other factors.

Data on non-verbal mental age was not available for all participants within this sample, due to ceiling and floor effects on some of the scales of the cognitive assessments. Arguably, these difficulties reflect the uneven profiles of cognitive abilities within these syndromes (Fung et al., 2012; Mulder et al., 2016; Grados et al., 2017; Lorusso et al., 2007; Stephens et al., 1990; Stevens et al., 2010). Non-verbal mental age was chosen as profiles of strengths and weaknesses are not as variable across many genetic syndromes and this was the measure of ability that was available for the most number of participants. Whilst these data were missing for only a few participants, it is important to take these into account when

interpreting the evidence of comparability of level of ability between syndromes included in analyses.

6.7 Closing statement

In this thesis, it has been shown that the profiles of sociability and social cognition evidence similarities and differences across individuals with CdLS, FXS and RTS and provided proof of principle that social cognitive abilities may underpin aspects of the profile of sociability in CdLS, FXS and RTS. These findings have led to the first attempts at modelling the relationships between genes, neurobiology, cognition, behaviour and the environment and emphasise the need for the development of theory driven interventions based on research outlining the complex aetiological relationships that lead to profiles of sociability. However, whilst this thesis has refined understanding of sociability and social cognitive abilities in individuals with CdLS, FXS and RTS, it has also generated a plethora of research questions for future investigation. Future research will undoubtedly transform the current working models outlined in this chapter to incorporate the widening understanding of social cognition and sociability in CdLS, FXS and RTS.

APPENDICES

Appendix A: Summary tables of findings including females with FXS. Table and figure numbers correspond to the table numbers in the main text.

Summary tables from Chapter Two

Table 2.2.
Participant characteristics for all participants included in this thesis including males and females with FXS

	CdLS (n = 39)	FXS (n = 44)	RTS (n = 33)	p	Post-hoc tests (p<.05)
Mean chronological age in years (SD)	13.31 (10.92)	13.96 (11.77)	16.72 (13.54)	.30	
Gender % female	56%	14%	52%	**<.01**	FXS < CdlS, RTS
Mean non-verbal mental age in years (SD)	3.80 (2.13)*	3.61 (1.30)**	3.40 (1.23)***	.85	

* Information not available for three participants due to non-completion of the relevant measure

** Information not available for three participants due either to floor/ceiling performance (one participant)

*** Information not available for four participants due either to 1) floor/ceiling performance (one participant) or 2) non-completion of non-verbal scales of a cognitive assessment.

Summary tables from Chapter Three

Table 3.1.
Participant characteristics for participants who took part in the CSRS including males and females with FXS

	CdLS (n = 36)	FXS (n = 42)	RTS (n = 25)	p	Post-hoc tests ($p<0.05$)
Mean chronological age in years (SD)	12.42 (10.27)	14.22 (11.99)	15.22 (13.78)	.59	
Gender % female	58%	14%	52%	**<.01**	CdLS, RTS < FXS
Mean non-verbal mental age in years (SD)	3.82 (2.15)*	3.58 (1.32)**	3.35 (1.35)*	.74	

* Information not available for one participant due to non-completion of the relevant measure

** Information not available for two participants due to floor/ceiling effects

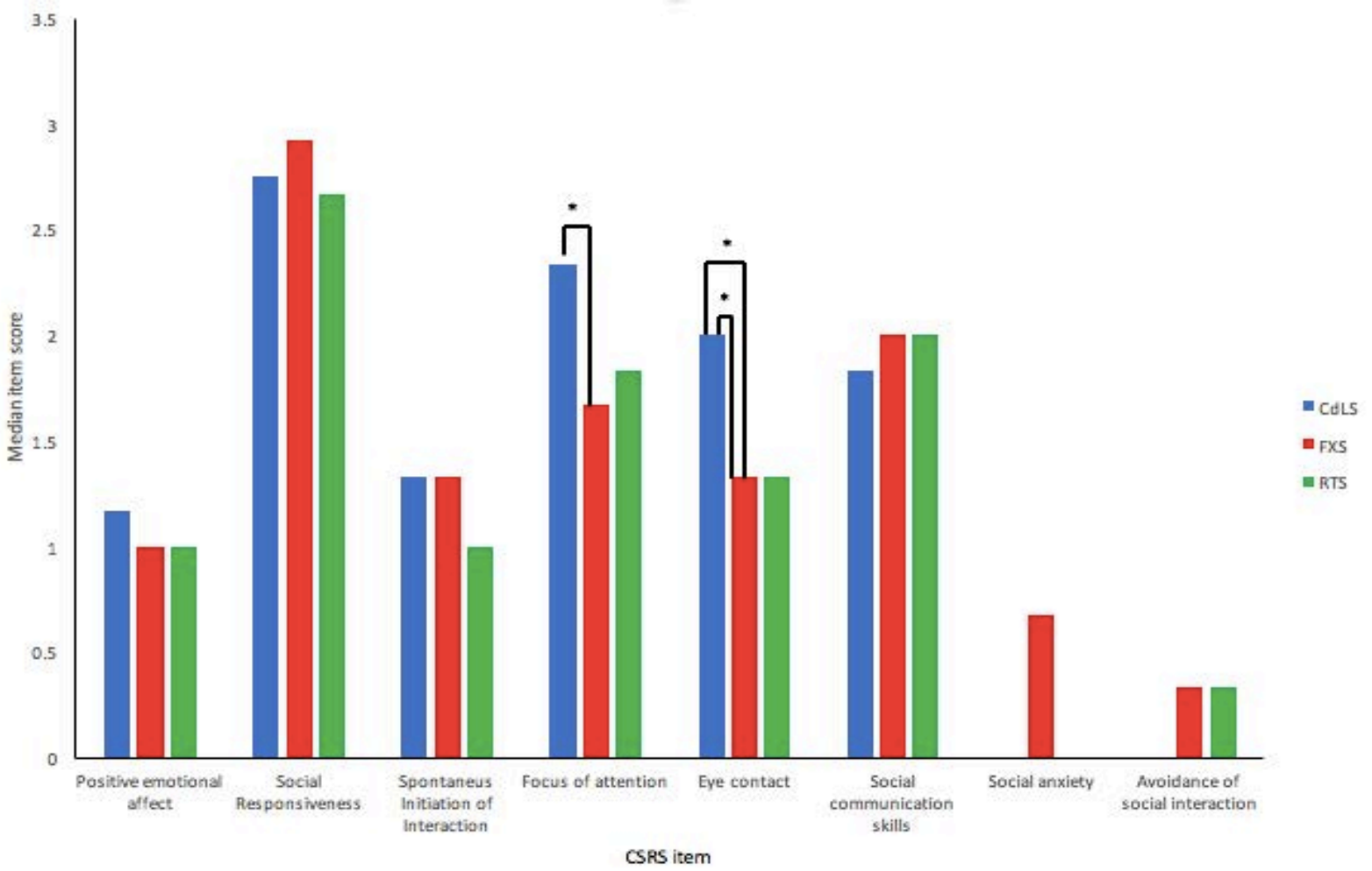
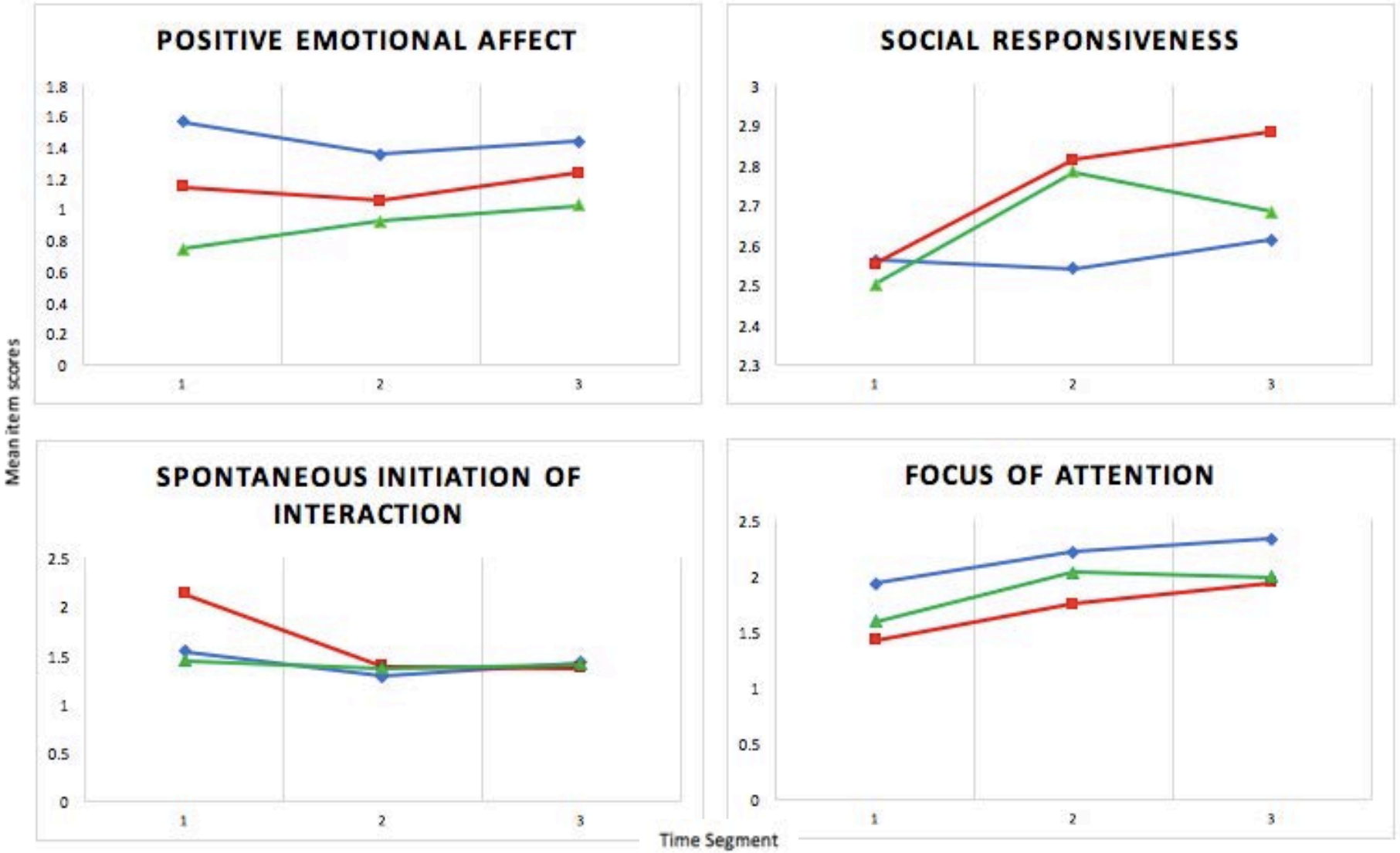


Figure 3.1. Median item scores on each CSRS item for per syndrome including males and females with FXS.


POSITIVE EMOTIONAL AFFECT
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
1
2
3
SOCIAL RESPONSIVENESS
3
2.9
2.8
2.7
2.6
2.5
2.4
2.3
1
2
3
SPONTANEOUS INITIATION OF INTERACTION
2.5
2
1.5
1
0.5
0
1
2
3
FOCUS OF ATTENTION
2.5
2
1.5
1
0.5
0
1
2
3
Mean item scores
Time Segment

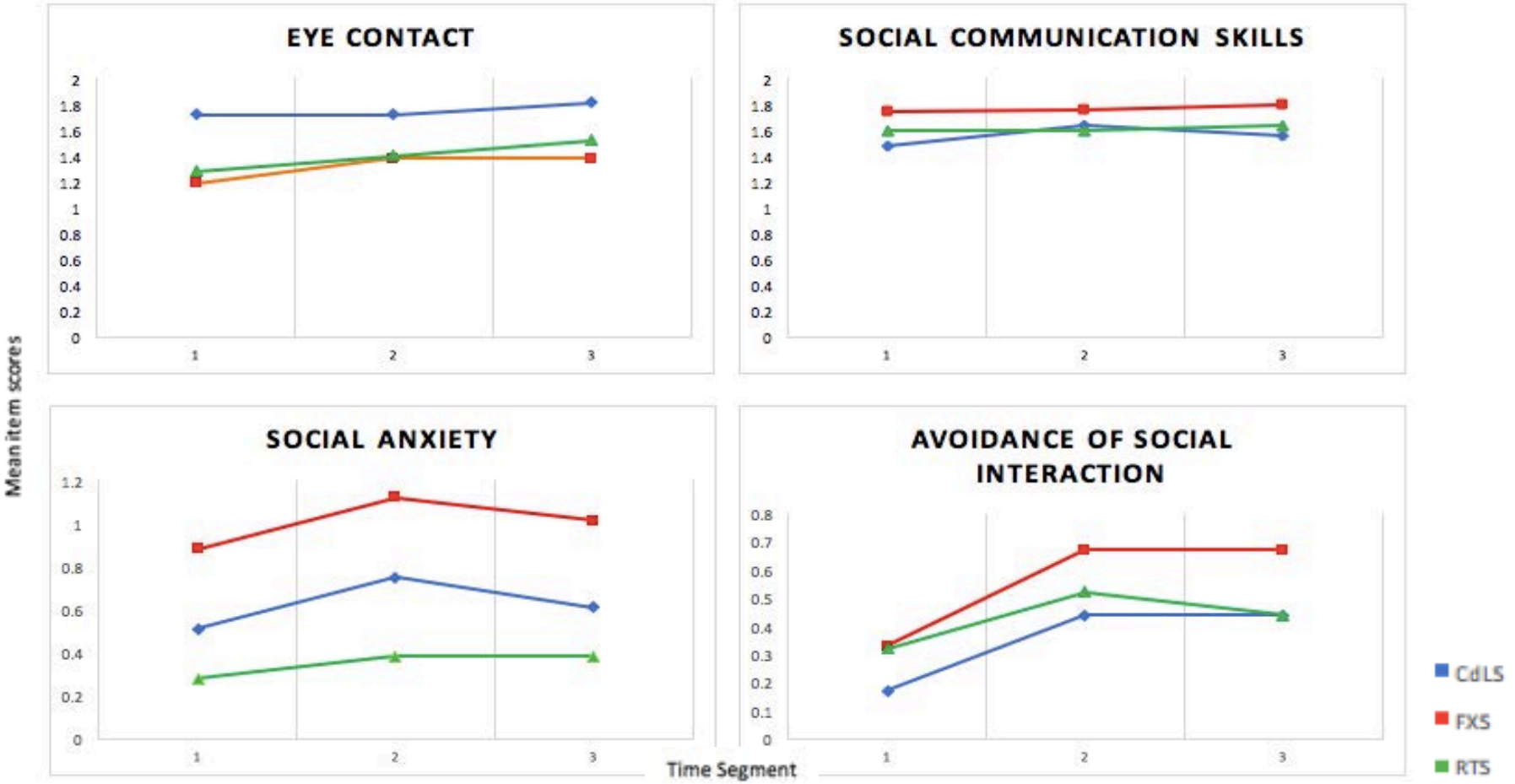


Figure 3.2. Median scores for each CSRS item per syndrome across time segments (TS1, TS2 and TS3) including males and females with FXS.

Table 3.2
Kendall Tau correlations for mean CSRS item scores, and chronological age and ADOS-II CSS for males and females with FXS.. Significant correlations are highlighted in bold

CSRS item	FXS	
	Chronological age (*p*)	ADOS-II SA CSS (*p*)
Positive emotional affect	-.03 (.77)	-.29 (.02)
Social responsiveness	**.32 (<.01)**	-.04 (.82)
Spontaneous initiation of interaction	.03 (.80)	-.12 (.31)
Focus of attention	.01 (.60)	-.28 (.07)
Eye contact	-.24 (.04)	-.29 (.02)
Social communication skills	**.46 (<.01)**	**.34 (<.01)**
Social anxiety	**.58 (<.01)**	**.49 (<.01)**
Avoidance of social interaction	.02 (.82)	.14. (.27)

Table 3.3.
The percentage of participants who reached clinical cut-off scores on the ADOS-II, and ADOS-II Total and Social Affect Classification Severity Scores (CSS) means per syndrome group

	CdLS (*n* = 36)	FXS (*n* = 42)	RTS (*n* = 25)	*p*	Post-hoc tests (p<0.05)
% reach ADOS-II ASD clinical cut-off score	47%	88%	73%	**<.001**	CdLS < FXS, RTS
% reach ADOS-II Autism clinical cut-off score	44%	77%	57%	**.008**	CdLS < FXS
ADOS-II Total CSS (SD)	4.58 (3.01)	6.45 (2.30)	5.23 (2.35)	**.01**	CdLS, RTS < FXS
ADOS-II Social Affect CSS (SD)	4.94 (2.94)	6.33 (2.32)	5.54 (2.12)	.07	

Summary tables from Chapter Four –*Early Social Cognition Scale*

Table 4.1.
Participant characteristics for those who took part in the ESCS including males and females with FXS

	CdLS (*n* = 22)	FXS (*n* = 22)	RTS (*n* = 18)	*p*	Post-hoc tests (p<0.05)
Mean chronological age in months (SD)	77.98 (39.46)	71.01 (30.92)	110.61 (45.95)	**<.01**	CdLS, FXS<RTS
Gender % female	58.82%	10%	50%	**<.01**	FXS<CdLS, RTS
Non-verbal Mental Age in months (SD)	29.62* (13.67)	34.17 (13.42)	30.32** (9.52)	.42	

* Information not available for one participant due to non-completion of the relevant measure

** Information not available for two participants due to non-completion of the relevant measure

Table 4.3
The number and percentage of children that passed each task per syndrome including males and females with FXS

	TD (*N* = 86)*	CdLS (*N* = 22)	FXS (N = 22)	RTS (N = 18)
Helping	76 (88%)	14 (63%)	19 (86%)	16 (89%)
Gestures-Pointing	58 (67%)	6 (27%)	8 (36%)	8 (44%)
REI	54 (63%)	14 (63%)	18 (82%)	15 (83%)
Gestures-Gaze	37 (43%)	2 (9%)	5 (23%)	1 (6%)
Cooperation-Tubes	32 (37%)	3 (13%)	7 (32%)	6 (33%)
Cooperation-Trampoline	34 (22%)	2 (9%)	4 (18%)	7 (39%)

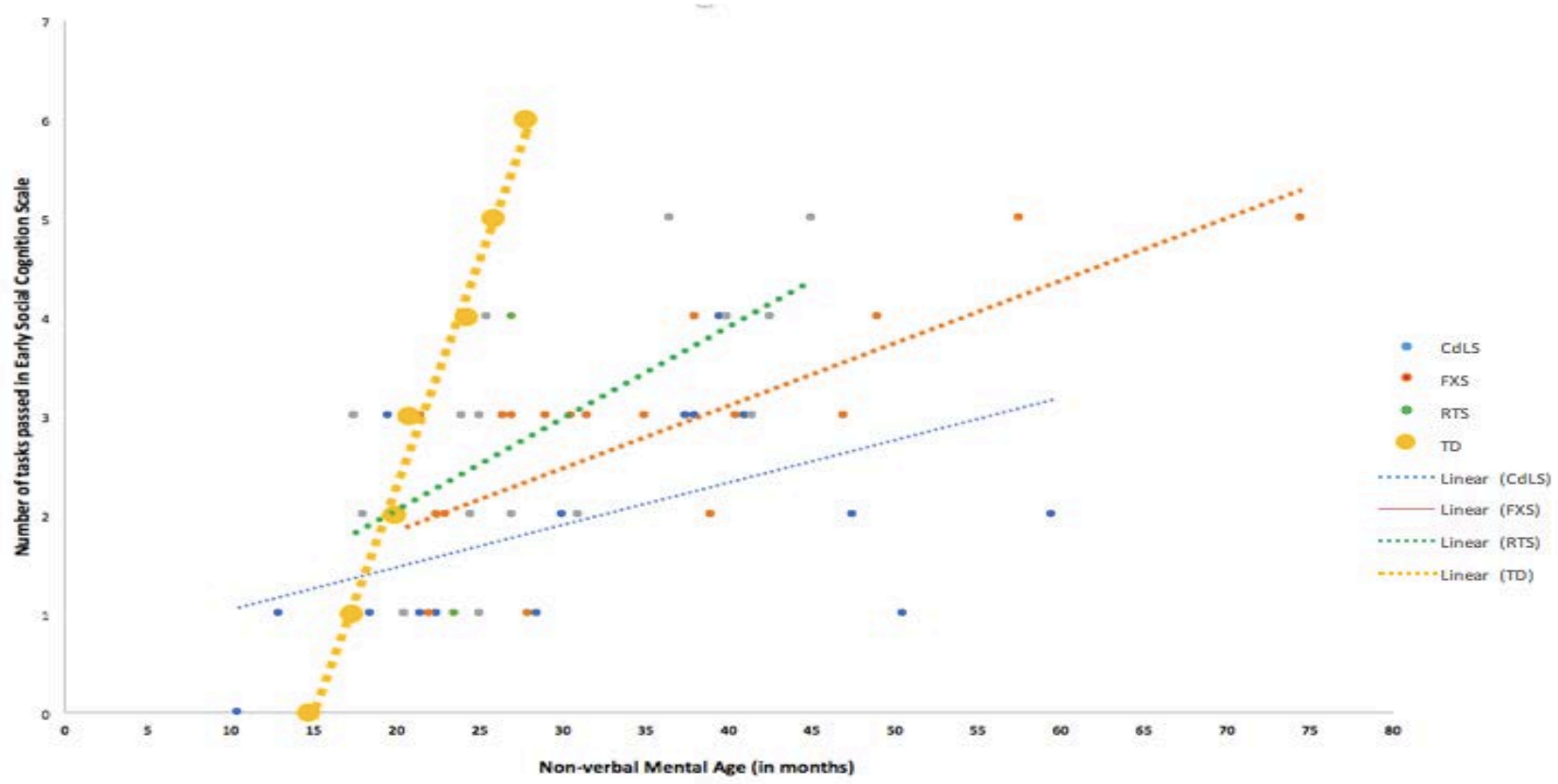


Figure 4.1. Number of tasks each participant passed in the *ESCS* plotted against their non-verbal mental age for each syndrome including males and females with FXS, and mean age that typically developing (TD) pass each number of tasks, derived from previous literature (Powis, 2014; Powis et al., in review).

4.3.2.3. Developmental trajectory of early social cognitive abilities in children with CdLS, FXS and RTS

Correlations were run to determine whether, despite delay, overall social cognitive ability increased with ability. Kendall Tau correlations revealed moderate positive correlations in the CdLS (τ_b (20)=.45, p=.01), FXS (τ_b (20), A Pearson correlation revealed a strong positive correlation in the RTS groups (r(14)=.69, p<.01).

To explore whether one group may be more delayed than another overall, a Kruskal-Wallis test was conducted to investigate whether syndrome groups differed in the number of tasks they passed. Significant differences were found in the number of tasks passed between syndromes (χ(2)=7.40, p = .03). Post-hoc Mann Whitney U tests revealed that both individuals with FXS U(42) = 148.00, z=-2.29, p=.02, r=-.35) and RTS (U(38)=113.50, z=-2.37, p=.02, r=-.36) passed significant more tasks than the CdLS group. There were no significant differences found between individuals FXS and RTS, despite differences in chronological age between these groups (Table 4.1).

4.3.2.4. The developmental sequence of early social cognitive abilities in children with CdLS, FXS and RTS: Comparisons to TD.

Table 4.4
Guttman scalogram for the four item ESCS

Pattern	0	1	2	3	4	Other patterns	*N*	*N* fit scale exactly
Helping	-	+	+	+	+			
REI or Point	-	-	+	+	+			
Gaze or Tubes	-	-	-	+	+			
Trampoline	-	-	-	-	+			
Syndrome								
CdLS	2	3	7	2	2	6	22	16 (73%)
FXS	0	0	7	6	3	6	22	16 (73%)
RTS	0	2	5	2	5	4	18	14 (78%)

For males and females with FXS, whereas the co-efficient of reproducibility was 0.93, the index of consistency was 0.11. Finally, for the RTS group the co-efficient of reproducibility was 0.93, but the index of consistency was 0.15.

4.3.2.4.1. *Exploring alternative developmental sequences of early social cognitive abilities: Pairwise comparisons.*

4.3.2.4.1.2. *FXS.*

Uncorrected comparisons revealed that the *Cooperation-Tubes* task was significantly harder than the *Helping* task ($p<.01$). No differences were found between the *Helping* and *REI* tasks, the *Gestures-Point* and *Cooperation-Tubes* tasks, the *Cooperation-Tubes* & *Gestures-Gaze* tasks and the *Gestures-Gaze* and *Cooperation-Trampoline* tasks. When corrected, the *Cooperation-Tubes* task remained significantly more difficult than the *Helping* task ($p<.01$).

Summary tables from Chapter Four –*Theory of Mind Scale*

Table 4.5.
Participant characteristics for those who took part in the ToMS including males and females with FXS

	CdLS (*n* = 18)	FXS (*n* = 21)	RTS (*n* = 15)	*p*	Post-hoc tests (p<0.05)
Mean chronological age in months (SD)	21.43 (11.15)	20.57 (11.07)	22.35 (15.50)	.99	
Gender % female	58.82	25	50	**<.01**	FXS<CdLS, RTS
Non-verbal Mental Age in years (SD)	5.37* (1.89)	4.57** (0.97)	4.33** (0.66)	.24	

* Information not available for one participant due to non-completion of the relevant measure

** Information not available for one participant due to floor/ceiling performance

*** Information not available for three participants due either to 1) floor/ceiling performance (one participant) or 2) non-completion of non-verbal scales of a cognitive assessment.

Table 4.7.
Percentage of individuals passing each *ToMS* item including males and females with FXS

	TD (n = 75*	CdLS (n = 18)	FXS (n = 21)	RTS (n = 15)
Diverse Desires	71 (95%)	17 (94%)	18 (86%)	15 (100%)
Diverse Beliefs	63 (84%)	14 (78%)	18 (86%)	14 (93%)
Knowledge Access	55 (73%)	11 (61%)	14 (67%)	4 (27%)
Contents False Belief	44 (59%)	6 (33%)	4 (19%)	1 (7%)
Hidden Emotion	39 (52%)	2 (11%)	0 (0%)	1 (7%)
Sarcasm	N/A	0 (0%)	3 (14%)	0 (0%)

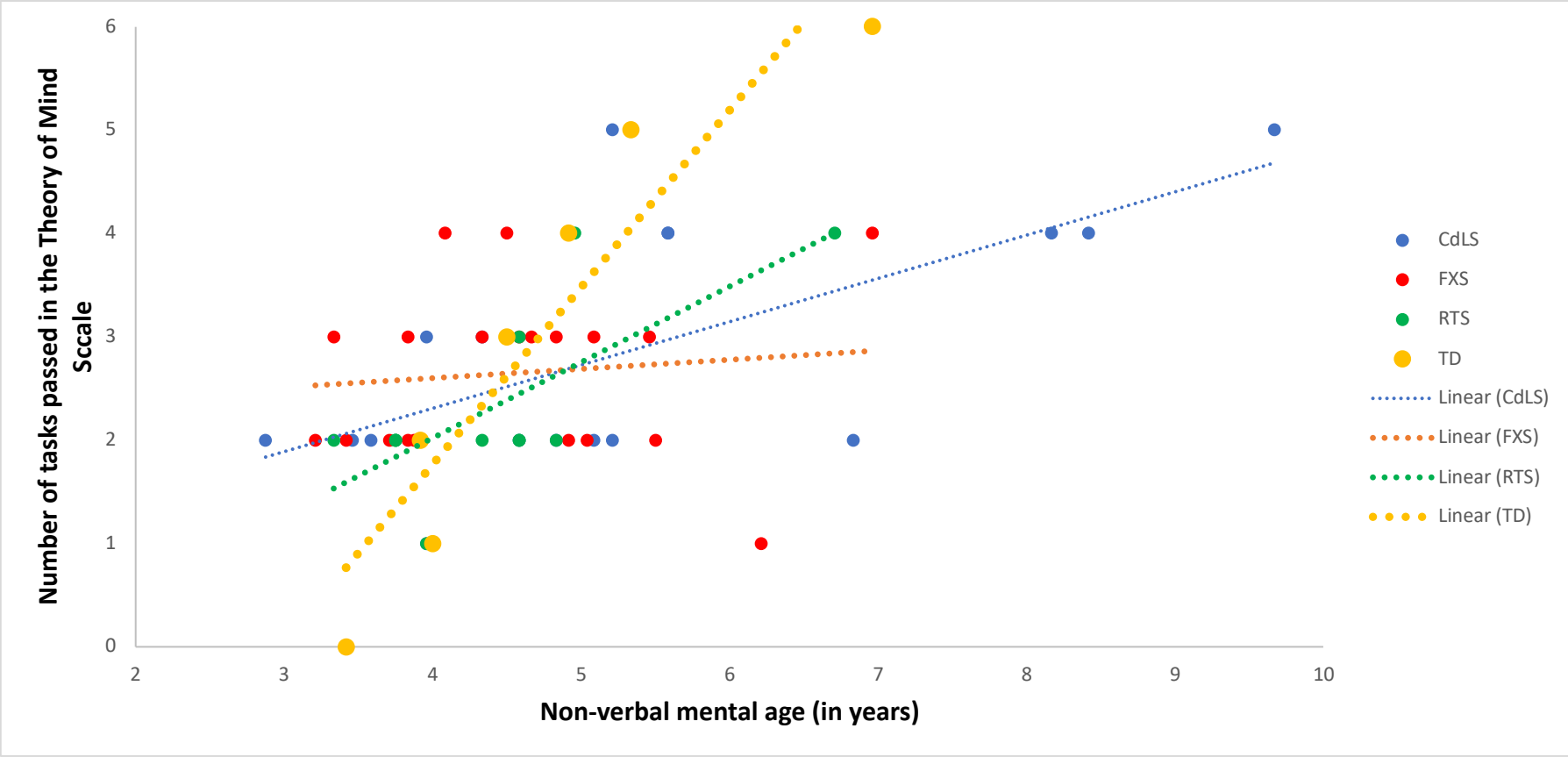


Figure 4.4. Number of tasks each participant passed in the *ToMS* plotted against their non-verbal mental age for each syndrome, including males and females with FSX, and mean age that typically developing (TD) pass each number of tasks, derived from previous literature (Wellman & Lui, 2004; Peterson, Wellman & Slaughter, 2012)

4.3.3.3. Developmental trajectory of later developing social cognitive abilities in children and adults with CdLS, FXS and RTS

Kendall Tau correlations were run to determine if there was a relationship between participant's non-verbal mental age and the number of tasks they passed in the *ToMS* in each syndrome. No association was found in males and females with FXS.

To investigate whether any of the groups are comparatively more delayed, Kruskall-Wallis tests were run to evaluate whether groups differed overall in the number of tasks they passed. Results showed that there were no significant differences across groups ($\chi(2)=1.90$, $p = .39$).

4.3.3.4. The developmental sequence of ToM abilities in children with CdLS, FXS and RTS: Comparisons to TD.

Table 4.8 shows the scalogram patterns previously observed in TD and the percentage of participants in each syndrome group whose responses fitted each pattern perfectly. For males and females with FXS, whereas the co-efficient of reproducibility was .97, but the index of consistency was .32.

Table 4.8
Guttman scalogram for the six item Theory of Mind Scale including males and females with FXS

Pattern	0	1	2	3	4	5	6	Other patterns	*N*	*N* fit scale exactly
Diverse Desires	-	+	+	+	+	+	+			
Diverse Beliefs	-	-	+	+	+	+	+			
Knowledge Access	-	-	-	+	+	+	+			
Contents False Belief	-	-	-	-	+	+	+			
Hidden Emotion	-	-	-	-	-	+	+			
Sarcasm	-	-	-	-	-	-	+			
CdLS	0	1	6	3	3	2	0	3	18	15 (83%)
FXS	0	1	6	7	2	0	0	5	21	16 (76%)
RTS	0	1	10	2	1	0	0	1	15	14 (93%)

4.3.3.4.1. *Exploring alternative development progressions of ToM abilities: Pairwise comparisons.*

4.3.3.4.1.2. FXS.

When uncorrected, the *Contents False Belief* was significantly harder than the *Knowledge Access* task (p<.01). No differences were found between *Diverse Beliefs* and *Diverse Desires*, *Diverse Beliefs* and *Knowledge Access*, *Contents False Belief* and *Sarcasm*, or *Sarcasm* and *Hidden Emotion* task pairs. When corrected, *Contents False Belief* remained significantly harder than *Knowledge Access* (p=.01).

Summary tables from Chapter Five –*Intentionality abilities*

Table 5.1.
Participant characteristics for participants with both ESCS and CSRS data available including girls with FXS

	CdLS (n = 21)	FXS (n = 22)	RTS (n = 16)	p	Post-hoc tests (p<0.05)
Mean chronological age in months (SD)	77.65 (40.40)	71.01 (30.92)	107.37 (45.29)	**.02**	CdLS, FXS < RTS
Gender % female	48%	10%	50%	**<.01**	FXS < CdLS, RTS
Mean non-verbal mental Age in months (SD)	29.62 (13.67)*	34.17 (13.42)	29.50 (9.25)*	.40	

* Information not available for one participant due to non-completion of the relevant measure

Table 5.2
Means, standard deviations and inter-correlations of predictor and criterion variables for participants who took part in both the ESCS and CSRS, including males and females with FXS

Variable	M	SD	1	2	3	4	5	6	7	8
1. ESCS score	2.49	1.29	-	.20*	.45**	.22*	.21*	.21*	-.16	-.05
2. Chronological age (in months)	83.24	40.83		-	.37**	-.14	-.02	.80	.18	.25**
3. Non-verbal mental age (in months)	31.33	12.55			-	.17	.13	.27**	.10	.06
4. Social enjoyment CSRS domain	3.36	1.30				-	.57**	.60**	-.29**	-.43**
5. Social motivation CSRS domain	3.05	1.47					-	.56**	.22*	.42**
6. Social interaction skills CSRS domain	2.92	0.95						-	-.15	-.34**
7. Social discomfort CSRS domain	0.83	0.98							-	.35**
8. ADOS-II SA CSS	5.12	2.47								-

* significant at $p < .05$, ** significant at $p < .01$

Table 5.3.
Linear model of predictors of social enjoyment domain scores, with 95% bias corrected and accelerated confidence intervals reported in parentheses. Confidence intervals and standard errors based on 1000 bootstrapped samples. Significant changes to the model are highlighted in bold. Includes all syndrome, including males and females with FXS.

	b	SE B	β	*p*	*R*	*R2*	ΔR2
Step 1					.36	.13	**.13**
Constant	2.46 (1.76, 3.17)	.36		<.01			
ESCS	.36 (.10, .63)	.13	.36	<.01			
Step 2					.37	.14	.01
Constant	2.53 (1.80, 3.27)	.38		<.01			
ESCS	0.40 (.11, .70)	.15	.40	.01			
CdLS vs FXS	-.23 (-1.06, .54)	.40	-.09	.57			
CdLS vs RTS	-.35 (-1.36, .53)	.47	-.12	.47			

Table 5.4.
Linear model of predictors of social motivation domain scores, with 95% bias corrected and accelerated confidence intervals reported in parentheses. Confidence intervals and standard errors based on 1000 bootstrapped samples. Significant changes to the model are highlighted in bold. Includes all syndrome, including males and females with FXS.

	b	SE B	β	*p*	*R*	*R2*	ΔR2
Step 1	2.25 (1.45, 3.10)	.41		<.01	.29	.08	**.08**
Constant	0.32 (-<.01, .64)	.16	.29	.05			
ESCS							
Step 2					.33	.11	.03
Constant	2.40 (1.56, 3.37)	.45		<.01			
ESCS	.41 (.09, .73)	.16	.36	.02			
CdLS vs FXS	-.55 (-1.35, .27)	.41	-.18	.19			
CdLS vs RTS	-.61 (-1.62, .37)	.50	-.19	.24			

Table 5.5.
Linear model of predictors of social interaction skills domain scores, with 95% bias corrected and accelerated confidence intervals reported in parentheses. Confidence intervals and standard errors based on 1000 bootstrapped samples. Significant changes to the model are highlighted in bold. Includes all syndrome, including males and females with FXS.

	b	SE B	β	*p*	*R*	*R2*	ΔR2
Step 1					0.36	0.13	**0.13**
Constant	2.04 (1.37, 2.70)	.33		<.01			
NVMA	.03 (.01, .05)	.01	.36	<.01			
Step 2					0.36	0.13	0.00
Constant	2.01 (1.36, 2.69)	.33		<.01			
NVMA	.03 (.00, .05)	.01	.32	.03			
ESCS	.05 (-.17, .28)	.11	.6	.68			
Step 3					0.38	0.14	0.01
Constant	2.09 (1.36, 2.84)	.37		<.01			
NVMA	.02 (.00, .05)	.01	.29	.06			
ESCS	.09 (-.15, .33)	.13	.12	.48			
CdLS vs FXS	-.08 (-.70, .61)	.32	-.04	.80			
CdLS vs RTS	-.26 (-.91, .54)	.36	-.12	.46			

Table 5.6
Means, standard deviations and correlations of predictor and criterion (items from social enjoyment and social motivation domains) variables for participants who took part in the ESCS, including males and females with FXS

Variable	M	SD	1	2	3	4	5	6	7
1. ESCS score	2.49	1.29	-	.21*	.45**	.26**	.04	.26*	0.08
2. Chronological age (in months)	83.24	40.83		-	.37**	-.08	-.14	-.03	-.09
3. Non-verbal mental age (in months)	31.33	12.55			-	.23*	.05	.15	.10
4. Social Responsiveness	2.30	0.87				-	.35**	.50**	.59**
5. Positive Emotional Affect	1.06	0.67					-	.30**	.39**
6. Spontaneous Initiation of Interaction	1.33	1.01						-	.46**
7. Focus of attention	1.73	0.62							-

* significant at $p < .05$, ** significant at $p < .01$

Table 5.7.
Linear model of predictors of social responsiveness item scores, with 95% bias corrected and accelerated confidence intervals reported in parentheses. Confidence intervals and standard errors based on 1000 bootstrapped samples. Includes males and females with FXS.

	b	SE B	β	*p*	*R*	*R2*	ΔR2
Step 1					.37	.14	**0.14**
Constant	1.48 (.76, 2.10)	.34		<.01			
Non-verbal mental age	.03 (.00, .05)	.01	.37	<.01			
Step 2					.45	.20	**0.06**
Constant	1.35 (.71, 1.93)	.32		<.01			
Non-verbal mental age	.01 (-.01, .03)	.01	.19	.20			
ESCS	.21 (.00, .43)	.11	.31	.06			
Step 3					.45	.20	0.00
Constant	1.36 (.64, 2.07)	.36		<.01			
Non-verbal mental age	.01 (-.01, .04)	.01	.19	.24			
ESCS	.21 (-.02, .45)	.12	.32	.08			
CdLS vs FXS	-.02 (-.49, .53)	.25	-.01	.93			
CdLS vs RTS	-.04 (-.68, .62)	.33	-.02	.91			

Table 5.8.
Linear model of predictors of spontaneous initiation of interaction scores, with 95% bias corrected and accelerated confidence intervals reported in parentheses. Confidence intervals and standard errors based on 1000 bootstrapped samples. Including males and females with FXS

	b	SE B	β	*p*	*R*	*R2*	ΔR2
Step 1					.33	.11	**.11**
Constant	0.68 (.14, 1.29)	.29		.03			
ESCS	0.26 (.05, .45)	.11	.33	.02			
Step 2					.35	.12	.01
Constant	.73 (.16, 1.42)	.32		.04			
ESCS	.30 (.10, .49)	.10	.38	<.01			
CdLS vs FXS	-0.16 (-.71, .36)	.27	-.08	.55			
CdLS vs RTS	-.31 (-.90, .44)	.35	-.14	.38			

Summary tables from Chapter Five –*ToM abilities*

Table 5.9.
Participant characteristics for participants with both ToMS and CSRS data available, including males and females with FXS

	CdLS (*n* = 16)	FXS (*n* = 19)	RTS (*n* = 10)	*p*	Post-hoc tests (p<0.05)
Mean chronological age in years (SD)	20.07 (10.93)	21.83 (10.87)	22.12 (16.85)	0.72	
Gender % female	69%	16%	50%	**<.01**	FXS < CdLS, RTS
Mean non-verbal Mental Age in years (SD)	5.53 (1.83)	4.60 (1.02)*	4.58 (.87)	0.12	

* Information not available for one participant due to ceiling and floor effects on the relevant measure

Table 5.10
Means, standard deviations and correlations of predictor and criterion variables for participants who took part in both the ToMS and ADOS-II, including males and females with FXS.

Variable	M	SD	1	2	3	4	5	6	7	8
1. *ToMS* score	2.62	.94	-	.20	.34**	.40**	.15	.18	-.06	-.17
2. Chronological age (in years)	21.27	12.16		-	.00	.04	-.05	-.16	.24*	.23*
3. Non-verbal mental age (in years)	4.93	1.40			-	.14	.15	.15	-.07	-.18
4. Social enjoyment CSRS domain	4.57	1.17				-	.37**	.40**	-.28**	-.41**
5. Social motivation CSRS domain	3.91	1.38					-	.29*	-.29**	.42**
6. Social interaction skills CSRS domain	3.51	0.56						-	-.41**	-.37**
7. Social discomfort CSRS domain	1.49	1.46							-	.46**
8. ADOS-II SA CSS	6.16	2.67								-

Table 5.11.
Linear model of predictors of social enjoyment total scores, with 95% bias corrected and accelerated confidence intervals reported in parentheses. Confidence intervals and standard errors based on 1000 bootstrapped samples Includes males and females with FXS

	b	SE B	β	*p*	*R*	*R2*	ΔR2
Step 1					.57	.33	**.33**
Constant	2.69 (1.77, 3.56)	.47		<.01			
ToMS	.72 (.36, 1.06)	.19	.57	<.01			
Step 2					.64	.40	.08
Constant	3.03 (2.02, 4.06)	.52		<.01			
ToMS	.68 (.32, 1.03)	.19	.54	<.01			
CdLS vs FXS	-.15 (-.79, .52)	.33	-.06	.66			
CdLS vs RTS	-.83 (-1.42, -.22)	.29	-.30	.01			

Table 5.13
Means, standard deviations and correlations of predictor and criterion (items from the social enjoyment domain) variables for participants who took part in the ToMS. Includes males and females with FXS

Variable	M	SD	1	2	3	4	5
1. ToMS score	2.62	.94	-	.20	.38**	.31*	.27*
2. Chronological age (in years)	21.27	12.16		-	.00	.05	.10
3. Non-verbal mental age (in months)	4.93	1.40			-	.06	.18
4. Positive Emotional Affect	1.40	.93				-	.06
5. Social Responsiveness	3.17	.58					-

* significant at $p < .05$, ** significant at $p < .01$

Table 5.14.
Linear model of predictors of Positive Emotional Affect item scores, with 95% bias corrected and accelerated confidence intervals reported in parentheses. Confidence intervals and standard errors based on 1000 bootstrapped samples. Includes males and females with FXS.

	b	SE B	β	*p*	*R*	*R2*	ΔR2
Step 1					.50	.25	**.25**
Constant	.09 (-.60, .79)	.35		.78			
ToMS	.50 (.19, .77)	.14	.50	<.01			
Step 2					.62	.38	**.13**
Constant	.60 (-.16, 1.26)	.35		.12			
ToMS	0.45 (.17, .69)	.14	.45	<.01			
CdLS vs FXS	-.31 (-.85, .25)	.27	-.17	.27			
CdLS vs RTS	-.91 (-1.37, -.41)	.25	-.41	<.01			

Table 5.15.
Linear model of predictors of Social Responsiveness items scores, with 95% bias corrected and accelerated confidence intervals reported in parentheses. Confidence intervals and standard errors based on 1000 bootstrapped samples Includes males and females with FXS.

	b	SE B	β	*p*	*R*	*R2*	ΔR2
Step 1					0.36	0.13	**0.13**
Constant	2.60 (2.10, 3.04)	.24		<.01			
ToMS	0.22 (.07, .38)	.08	0.36	.01			
Step 2					0.48	0.14	0.02
Constant	2.47 (1.91, 3.00)	.28		<.01			
ToMS	.23 (.07, .40)	.08	.38	<.01			
CdLS vs FXS	.17 (-.20, .55)	.19	.15	.41			
CdLS vs RTS	.08 (-.36, .52)	.23	.06	.75			

Appendix C: Vineland Behavior Scales-II © Sparrow, Balla, & Cicchetti, 2005

Appendix E: The Early Social Cognition Scale: Assessing understanding of intentionality from 14 to 34 months (Powis, Ellis, Oliver, Waite, Heald & Apperly, in revision)

This paper is currently in revision for future submission to PLoS One.

Abstract

Recent research indicates children develop a range of theory of mind (ToM) abilities which emerge in a strict developmental sequence between three to six years of age. The current study investigated whether this sequence extended to early social cognitive abilities that emerge during infancy. 86 infants from Birmingham aged 14-34 months participated in tasks assessing their understanding of distinct types of intention between February and June 2010. Guttman analyses revealed that six out of seven tasks formed a scalable set that infants passed cumulatively with age. These results extend assessment of social cognitive abilities both in younger individuals and individuals who may show atypical scale progression but are too cognitively delayed to participate in traditional ToM tasks.

Introduction

Social cognition can be defined as the cognitive skills required for individuals to interpret and respond to social information. Amongst the most researched social cognitive abilities are Theory of Mind (ToM) skills, which consists of 'mentalising' or 'mind-reading' skills that enable individuals to understand that other's mental states (belief, desires, intentions etc.) can be different from one's own or discrepant with reality [1, 2]. ToM has been studied most intensively in young children aged 3 to 6 years [3, 4], generating evidence that suggests ToM abilities in this period form a strict developmental scale. The present research sought to extend this powerful scaling approach to a novel set of tasks that assess early understanding of other's goals and intentional actions. These abilities are often claimed to form a developmental

basis for later-developing ToM skills, and the application of a scaling approach would provide a new tool for examining the development of social cognition from infancy into early childhood.

It is well-established that some tests of ToM are easier than others: for example, on average, children successfully judge what others do or don't know before they make successful judgements about others' false beliefs [3]. However, such group-level patterns do not entail that individual children will reliably pass tasks in the same order. Wellman and Liu [5] used statistical scaling to assess whether five ToM tasks were indeed passed in a reliable order within individuals aged two to seven years. The outcome was reliable scaling whereby children tended to pass all tasks up to a certain point, and then failed all subsequent tasks.

When there are good theoretical grounds for supposing that abilities in a particular domain may be developmentally related, scaling analysis makes it possible to test whether tasks in that domain are indeed passed in a cumulative, unidimensional sequence [6-8]. Wellman & Liu concluded that the cumulative structure of their scale indicated that early skills may be required for later skills to develop through a process of modification, in which early understanding broadens throughout development to encompass later understanding, or mediation, in which earlier abilities scaffold the development of later abilities [2, 5, 9-11]. Therefore, this scaling is theoretically informative and practically useful because: 1) compared with group-level analyses it provides stronger evidence that earlier-developing abilities form the foundation of later-developing abilities, 2) such a scale provides a normative benchmark, and subsequently 3) provides a robust tool to assess individual differences in children's progression through the developmental sequence it describes in typical and atypical individuals [12-15].

However, a key limitation of this approach to date is that the earliest mentalising ability that the existing scale can assess typically emerges from around two years [16], yet much

evidence suggests that social cognition and perhaps even the foundations of ToM lie significantly earlier in development [17, 18]. One body of evidence suggests that at least some concepts assessed by the scale (such as knowledge and belief) may be observed in infancy, when researchers examine infants' looking times or predictive gaze, rather than requiring explicit responses [19]. However, it remains controversial whether such results indicate the presence of ToM concepts, or a set of learned behavioural rules (see e.g., Heyes, 2014 for a recent discussion) [20]. Moreover, it is not clear either in theory or in practice (given the current diversity of ages at which infants show these abilities) whether there might be developmental relationships among these concepts or a reliable sequence for their acquisition. Thus, without taking sides in the debate around these findings, our strategy was to focus on a second body of evidence of children's development of a 'shared intentionality'.

We selected a range of tasks from a well-established program of work led by Tomasello, Carpenter and colleagues (see e.g., Tomasello, 2014; Wellman, 2014 for recent overviews) [2, 9] for the following reasons. Success or failure in these tasks represent the presence or absence of a more basic set of social cognitive abilities that develop prior to traditional ToM competencies. Specifically, these tasks aim to assess types of intention understanding, which requires an individual to understand another person's goal and their action plan to achieve that goal [17]. In addition, in common with other such task batteries (e.g. the Mullen Scales of Early Learning) [21] these tasks have the useful property of being based upon simple materials that can be transported, and require no more than two experimenters.

This body of literature indicates that, similar to ToM understanding assessed in Wellman and Liu's scale, distinct types of intention understanding emerge at different ages. For example, from as young as 14-months infants demonstrate understanding and motivation to assist others with their unachieved goals [22-28], by 18-months infants can make inferences

about the communicative intentions behind gestures and distinguish these gestures from unintentional cues [29-31] and by 24-months infants coordinate and cooperate with others in problem-solving activities, and thus are considered to have developed a 'shared intentionality'. Finally, from 24 months' infants further develop their shared intentionality to achieve mutual goals that are inherently social (i.e. to carry out a task for mutual enjoyment), as opposed to a simple mutual desire to obtain a tangible object (as in a problem-solving task) [32-36].

Comparable to the ToM concepts studied by Wellman and Liu, these abilities are not held merely to vary in difficulty for infants, but the abilities assessed by easier tasks (e.g., assessing basic intentions behind other's goal directed actions) are hypothesized to be the foundations for developing a shared intentionality and cooperation skills that emerge later in development. To develop a 'shared intentionality', an individual must first acquire earlier developing understanding of goals behind a range of intentional actions, as well as a species unique motivation to share and represent these psychological states with another, in order to reciprocally and appropriately respond within a given scenario to achieve a joint goal [17, 18, 37]. This theoretical framework suggests that infant's performance on these tasks may be appropriate for assessment with a cumulative scale.

Therefore, we hypothesise that infant's patterns of passes and fails on tasks taken from the current literature that assess different types of intentionality understanding will conform to a cumulative scale in an order of difficulty that corresponds to age approximations previously reported. These findings would provide stronger evidence that the social cognitive abilities assessed by these tasks may be developmentally related to one another, and that skills that develop early may form the foundations for those that develop later [13]. They would also provide a normative benchmark of the typical sequence these very early developing abilities develop.

Materials and Methods

Participants

Nurseries across Birmingham were sent a letter describing the study in January 2010, followed by a phone call asking whether they would participate. The 13 nurseries who agreed distributed opt out consent forms to parents. Between February and June 2010, 98 infants were initially recruited, although 12 infants were not tested due to an inability to settle with the experimenters (mean age = 21 months, range = 14 months – 25 months). Therefore, 86 infants participated (mean age = 22 months, range = 14 months – 34 months). Infants were predominantly from a middle-class population and white British, although approximately 10% were of other ethnicities.

Tasks, materials, and scoring

Tasks were selected according to two principal criteria: 1) they should assess putatively different components of early understanding of intentionality, and 2) they should range in difficulty across ages from one to three years. In addition, for practical reasons we selected tasks that used simple equipment and required no more than two experimenters, so that the tasks could be administered easily in a nursery or (for future work) in participants' homes. Table 1 outlines the tasks and ages of success observed in the original studies. Although these studies did not identify precise ages that abilities appear or whether these ages generalised over different populations, these age approximations indicated which tasks were likely to be passed earlier or later. Task methods were based closely upon the original studies, with minor modifications to fit a within- rather than between-subjects design. While all tasks had either multiple trials or multiple scoring criteria, scaling analysis requires each child to be assigned a

pass or fail for each task. We rejected a liberal passing criterion, in which one instance of the target behaviour was sufficient for passing, because the 50% guessing rate on two tasks (Gaze and Point) greatly inflated the pass rate, so that performance on these tasks appeared much better than in the reported literature. We rejected a stringent passing criterion, in which at least two instances of every target behaviour were necessary for passing, because some behaviours (such as Helping) were unlikely to occur by chance, and the strict criterion risked underestimating performance. Our final scoring criteria, described below, struck a balance between these considerations. Importantly, however, the serial order of task difficulty was the same under all scoring schemes, with the exception of Gaze and Point under the liberal passing criterion, where the inflation due to guessing resulted in these tasks being passed at the same rate as Helping. Table 2 summarises the passing criteria for each task.

Table 1. Predicted age of acquisition for each task

Task name	Age of acquisition (in months)
Helping	14
Seeing-is-knowing	14
Re-enactment of intended acts	18
Gestures - Point	18
Gestures - Gaze	24
Cooperation - Tubes-with-handles	24
Cooperation - Trampoline	>24

Table 2. Passing criteria for each task.

Task	Passing criteria
Helping	The infant picks up an item that the examiner 'accidentally' dropped and returns it to the experimenter, without any explicit prompts, in at least one out of two experimental trials.
Seeing-is-knowing	The infant must 1) pass the correct toy named by the examiner in one out of two pre-tests, and 2) pass the item that the examiner has not previously seen before in both experimental trials.
Re-enactment of intended acts	The infant must carry out the examiner's intended act, rather than imitating the examiner's failed actions, in two out of three trials.
Gestures - Point	The infant must choose the correct box with the toy hidden inside in both experimental trials, in which the second examiner indicates the location of the toy with a communicative and intentional pointing gesture.
Gesture – Gaze	The infant must choose the correct box with the toy hidden inside in both experimental trials in which the experimenter indicates the location of the toy with a communicative and intentional ostensive gaze gesture.
Cooperation – Tubes-with-handles	The infant must 1) show sufficient coordination to open the tubes with the examiner across all four trials, and 2) show at least one attempt to reengage the examiner to complete the task during two interruption periods in which the examiner stops performing their role. More detailed information can be found in tables 3 and 4.
Cooperation - Trampoline	The infant must 1) be sufficiently engaged and successfully bounce the block on the trampoline with the examiner across all four trials, and 2) show at least one attempt to reengage the examiner to complete the task during two interruption periods in which the examiner stops performing their role. More detailed information can be found in tables 3 and 4.

Helping.

The 'out of reach' helping tasks designed by Warneken & Tomasello [22, 23] determined whether infants possessed the social cognitive ability to understand another person's intentions and unachieved goals, and their altruistic motivation to act on behalf of another. Materials included: (1) a pen and (2) six polystyrene cones, a pair of tongs and an empty cardboard box.

During trial one, the infant watched experimenter 2 (E2) draw using the pen, then 'accidentally' drop the pen and unsuccessfully reach for it. During trial two, three cones were placed next to E2 and three were placed by the infant, out of E2's reach. Using the tongs E2 picked up each cone and placed them in the cardboard box, then attempted but failed to reach for the cones on the infant's side.

Two control trials served to check that as a group, participants were not showing 'helping' behaviour indiscriminately. For trial one, E1 intentionally threw the pen on the floor and did not reach for it. For trial two E1 placed the cones on their side in the box but did not reach for those on the infant's side. If infants showed the 'helping' behaviour on these trials it would indicate that it was not based upon an understanding of the adult's intentions in this task situation.

To pass, infants had to either pass the pen or paper balls to the experimenter. One demonstration was considered sufficient as helping behaviour was considered unlikely to occur by chance.

Seeing-is-knowing.

The 'joint attention' condition used by Moll & Tomasello [38] assessed whether an infant could understand that an individual would know about an object that the infant and the individual were previously jointly engaged with. Task materials were modified from a gardening utensil, a birdcage item, and a slide rule to more appealing items. In trial one, toys included a tambourine with a mirror on the back, a maraca, and a yellow block with a button that opened a door when pressed (the target item). In trial 2, toys included a soft snail rattle, a jelly car, and a blue block with a button that made a butterfly and bee spin when pressed (target item).

During a pre-test, whilst sat at a table the infant played with each toy for 30 seconds with two experimenters. E2 placed each toy on a tray in front of the infant, then E1 requested the infant to pass each toy successively by name. To pass, the infant had to pass at least one of the first two toys requested. During experimental trials, E2 handed a toy to E1 whilst saying "Look what I've got here". E1 and the infant played with the toy together for 60 seconds. E2 then took the object, placed it on a tray, brought out a second toy and repeated the procedure. E1 then announced that they were leaving and left the room. E2 said "E1 is outside, they can't see us, but we'll keep playing anyway". E2 brought out a final (target) toy, played with the infant for 60 seconds, and then placed the toy on the tray. E1 returned, exclaiming "Oh look, look at that! Wow! Look at that!" pointing towards the tray. E1 then added "Wow...can you pass it to me?" a maximum of five times with an outstretched hand. The procedure was repeated for a second trial with the different items. To pass**,** infants must have passed the pre-test and passed the target item to the examiner in both trials.

Re-enactment of intended acts (REI).

Bellagamba and Tomasello's [39] 'demonstrate intention' conditions assessed the social cognitive ability to infer other's intentions by interpreting that person's goal-oriented (but unsuccessful) action.

For each trial, E1 presented the infant with an object pair and modelled failing to perform a target act. After three attempts E1 offered the object pair to the infant. E1 did not provide any prompts or cues, but gained the infant's attention by saying "Oh, look what I have here", "what's this?" and "now it's your turn". Object pairs included: a loop that could be hung over a peg, beads that could be lowered into a cup, and a square with a hole in the middle that could be placed over a vertical peg. To pass, infants had to perform two out of three target acts.

Gestures: Point and Gaze.

The Gestures tasks [29] assessed whether an infant could follow communicative gestures to a referent object and understand that the gesture was intentionally directed towards them and relevant to their current social context. There were two trials for each experimental gesture, with corresponding control trials to distinguish whether infants understood that the communicative act was an intentional action by the experimenter, or whether infants were simply following low level attentional cues.

During a warm-up phase, E1 placed a set of opaque containers open in front of the infant and brought out a small toy. Whilst the infant was watching, E1 announced "look, I'll hide it", placing the toy in a container. E1 placed the lids back on at the same time, and then said, "can you get the toy?" The procedure was repeated with two other sets of containers. During the experimental trials, E1 placed a screen in front of the containers, lowered the toy behind the screen and said, 'Now I'll hide it'. E1 pushed the containers together, hid the toy in one, and then moved them far enough apart that the infant could not grab both containers at once. During this hiding procedure E2 alternated their gaze between the containers and the infant, whilst announcing "I can see". E1 removed the screen and turned away from the table, placing the screen behind them. During this, E2 established eye contact with the infant, giving one of two communicative gestures with raised eyebrows to express intent: (1) Point, where E2 extended their index finger and pointed at the container, or (2) ostensive Gaze, where E2 gazed at the target container and back to the infant.

Control trials served to check that performance was not due to low level attentional cueing. These followed the same procedure as the experimental trials, except that E2 did not indicate that they were watching during the hiding procedure. In addition, E1 did not turn away when removing the screen, but instead gave one of two non-communicative control cues: (1) distracted point, where E1 held out their hand, slightly extended their index finger, and looked

down at it with an expression indicating they were preoccupied by something on their hand, and (2) gaze, where E1 gazed at the container with unfocused eyes and a neutral facial expression. For each task, the passing criterion required infants to pick the correct boxes in both experimental trials.

Cooperation – Tubes-with-handles and Trampoline.

A cooperative problem solving task (Tubes-with-handles) and a social game (Trampoline) [32] assessed whether an infant could develop 'shared intentionality' to produce and achieve a joint goal with another individual. These tasks assessed 1) the skill that infants could coordinate with a partner and 2) whether infants communicated to reengage a partner who disrupted achieving a joint goal.

The goal of the Tubes-with-handles task was to recover a toy hidden in the middle of two tubes slotted together by pulling the tubes apart with the handles at each end. The task required two people as the tube was too long to pull apart by oneself. The infant was first familiarised with the tubes and the handles. The experimenters then put a toy inside, pushed the tubes together, and then demonstrated how to retrieve the toy. The experimental trials followed. During trials one and two, E1 and the child carried out the task successfully. During trials three and four, whilst pulling the tubes apart E1 dropped the tube and positioned their hands and face towards the ground for 15 seconds, causing an interruption period. E1 then picked up the tube and continued as before. However, if the infant was unsuccessful (table 3) in cooperating with E1 to achieve the joint goal during trials one or two, then the task ended and trials three and four were not carried out.

The goal of the Trampoline task was to bounce a wooden block on a trampoline that two people had to hold on opposite ends. If one person did not hold their side, the trampoline

would collapse and could no longer bounce the block. Apart from differences in materials, the procedure was parallel to Tubes-with-handles. This task was predicted to be more difficult because its goal is inherently more social compared to the goal of obtaining a tangible object in Tubes-with-handles, and success in this task may be driven more by the species unique motivation considered to develop ontogenetically later [17].

Infants were coded for how coordinated they were at opening the tubes during each Tubes-with-handles trial, and for how engaged they were during each Trampoline trial (Table 3). In both tasks, infant's behaviour during interruption periods were coded (Table 4). To pass either task, infants had to score a median of three for coordination or engagement, and demonstrate at least one re-engagement attempt during the interruption period.

Table 3. Coding schema for level of coordination or engagement for each cooperation task [32]

Category	**Definition**
Tubes-with-handles	
No success (0)	Tubes not opened
Uncoordinated (1)	Success after more than 5 seconds of inappropriate actions such as standing on wrong side, letting tube drop more than once, individual play, or individual attempts
Coordinated (2)	Success, but some inappropriate actions, but not for more than 5 seconds; releasing handle not more than once
Very coordinated (3)	Success after immediate understanding of their role. Infant positions herself in correct location and performs the correct action without mistakes.
Trampoline	
No success (0)	Infant does not hold and lift trampoline
Low engagement (1)	Joint play but lots of stopping and not too excited. Infant needs a lot of persuasion.
Medium engagement (2)	Some stopping or not too excited.
High engagement (3)	Continuous play and rather excited (placing block on trampoline; initiating play; active shaking)

Numbers in brackets represent the score given for each category.

Table 4. Coding schema for behavior during interruption periods [32]

Category	Definition
Disengagement	Infant leaves apparatus or plays without pursuing the goal by banging the apparatus, climbing on it, etc.
Individual attempt	Infant attempts to retrieve the object individually (infant attempts to hold both handles or peel it open on one side) or attempts to continue the game alone.
Waiting	Infant remains on correct side of the apparatus, ready to perform their role
Reengagement	Infant is ready to perform their role and in addition tries to re-enage E1, e.g. pushing the tube, pointing at the object and vocalising whilst looking at the partner.

Procedure

The study was approved by the Science, Technology, Engineering and Mathematics Ethical Review Committee at the University of Birmingham. Infants were tested in a quiet room in their nursery. Experimenters played with each infant for 10-15 minutes to ensure that infants felt comfortable prior assessing them on all tasks in one of four orders (Table 4). Similar to Wellman and Liu [5] each order began with two tasks deemed engaging (i.e. Seeing-is-knowing, and both Cooperation tasks) to encourage the infant and avoid early frustration. Pearson chi square tests were conducted to check that children's performance did not differ as a function of which order they participated in tasks. There was no significant association between task order and whether children passed or failed in any of the tasks (all *p*s> .17). Tasks were administered over two separate test sessions to ensure that infants did not become tired. The helping control and experimental trials, and the two Seeing-is-knowing trials were separated by the session break.

Table 4. Orders for task administration.

Order 1	Order 2	Order 3	Order 4
• Seeing-is- knowing (1) • Cooperation: Tubes-with-handles • Helping – control • REI	• Cooperation: Trampoline • Seeing-is-knowing (1) • Helping – control • Cooperation: Tubes-with-handles	• Seeing-is-knowing • Cooperation: Tubes-with-handles • Gestures • Helping - Control	• Cooperation: Tubes-with-handles • Seeing-is-knowing (1) • REI • Helping - control
SESSION		**BREAK**	
• Seeing-is-knowing (2) • Cooperation: Trampoline • Gestures • Helping - experimental	• Helping – experimental • REI • Gestures • Seeing-is-knowing (2)	• Seeing-is-knowing (2) • Cooperation: Tubes-with-handles • Helping – experimental • REI	• Gestures • Seeing-is-knowing (2) • Trampoline • Helping - experimental

Results

Analysis of control trials

Two tasks had checks to ensure that participants produced target behaviours only in experimental and not in control trials that were superficially similar but lacked social intentions to communicate or to elicit help. We analysed those data separately, to check that the sample as a whole were producing the target behaviours in response to interpretation of the examiner's intentions, and not low level cues.

Helping control trials.

Only three out of the 76 infants that handed over an item during the experimental trials also handed over an item in the control trials and only two infants took possession of the item

before handing it over. These patterns clearly indicated that infants were 'helping' rather than trying to reinstate the original situation, getting the adult to repeat the action, or to collect the object primarily for themselves [23].

Gesture control trials.

Using data from infants who passed experimental trials, Pearson chi square tests were used to compare the likelihood of the overall group's pattern of responses (choosing 0, 1 or 2 correct boxes) compared to the pattern of responses that would be expected based on chance for both control cues. Results indicated that search performance did not differ significantly from chance for either cue type: 'Control Point' X^2 (2) = 4.56, p>0.05; 'Control Gaze' – X^2 (2) = 0.22, p>0.05. Therefore, it was judged that infants who passed the task had treated control cues as meaningless and chose which container to search for the hidden object randomly during control trials.

Task performance

Table 5 displays the percentage of infants who passed each task in ascending order. To ascertain which differences were statistically reliable, McNemar's tests with Yate's correction for continuity were conducted between six task pairs in increasing difficulty. Results showed that the Helping task was easier than the Pointing task, the Pointing and REI tasks were easier than the Gaze task, and the Gaze, Tubes-with-handles and Seeing-is-knowing tasks were easier than the Trampoline task. No differences were found between the Point and REI, between the Gaze and Tubes-with-handles, or between the Tubes-with-handles and Seeing-is-knowing tasks. Overall, results corresponded with previous literature with the exception of Seeing-is-knowing which was expected to be similar in difficulty to Helping but in fact appeared substantially harder. One possibility is that this is a failure to replicate the original findings,

though we note that they have been widely replicated elsewhere [40-44]. Instead we think it is likely that this effect was due to our replacement of unappealing objects used in the original study (e.g., a gardening utensil) with more appealing objects (e.g. a tambourine). Informal observation suggested that infants often had a strong preference for particular toys, which were then selected when the adult experimenter requested an item. Since this would have led to many false negative results, and since the absolute difficulty of the task did not accord with the previous literature, the task was removed from the final scale.

Table 5. The percentage of infants that passed each task in the battery and the pairwise comparison results between tasks in ascending order.

Task	Pass rate	Number of passes	Number of fails	Pairwise comparisons
Helping	88%	76	10	p<.001**
Pointing	67%	58	28	p=.572
REI	63%	54	32	p=.005**
Gaze	43%	37	49	p=.473
Tubes-with-handles	37%	32	54	p=1.000
Seeing-is-knowing	36%	31	55	p=0.036*
Trampoline	28%	19	67	

* indicates significance at or below 0.05, ** indicates significance at or below 0.01.

Guttman Scale

These pairwise comparisons indicate that the tasks form a reliable progression at a group level, but does not capture whether infants pass these tasks in a strict order at an individual level. Guttman [6, 7] proposed a stringent and conservative method of scalogram analysis outlining that for items to constitute a true scale they should be arranged in an order so that if

an individual responded positively to one item they should also have responded positively to all items of lower rank. Wellman and Liu [5] used this conservative method of analysis in the construction of their ToMS, and we applied the same method to the present data. The technique includes the production of two summary statistics: 1) the coefficient of reproducibility (Rep) i.e. how close results fit into the pattern of a 'perfect' cumulative scale and 2) the index of consistency i.e. the likelihood of the observed Rep occurring by chance [45].

Similarity in difficulty between certain tasks was accounted for by allocating infants 'pass' if they had passed *either* one of the tasks of equal difficulty (i.e. passed Pointing or 'REI'; or Gaze or Tubes-with-handles. Table 6 outlines infant's responses based on this four-item order. 88% of the sample fit this four-item scale exactly. The co-efficient of reproducibility was 0.96, which exceeded the required value of 0.9. The index of consistency met the required value of 0.5. These results indicated that the data formed a reliable scale.

Table 6. Guttman scalogram patterns.

Pattern	0	1	2	3	4	Other Patterns
'Helping' task	—	+	+	+	+	
'Point OR REI'	—	—	+	+	+	
'Gaze OR Tubes'	—	—	—	+	+	
'Trampoline' task	—	—	—	—	+	
Total	**4**	**7**	**19**	**29**	**14**	**13**
Average age (m)	**14.8**	**16.9**	**19.7**	**23.6**	**27.1**	**21.5**
Age range	14-17	14-23	14-27	15-33	22-34	14-27

Discussion

The current study used tasks designed to assess children's understanding of intentionality and joint intentionality. These tasks were chosen as they assess skills that have been hypothesized to involve cumulative development, and to provide foundations for later-emerging social abilities [17, 18]. Six out of the seven tasks selected showed levels of performance consistent with previous reports in the literature. Analysis of a four-item sequence accounting for tasks that were similar in difficulty showed that infants passed these tasks in a reliable and scalable fashion. As highlighted by Wellman and Liu [5], successful task scaling goes beyond observed differences in difficulty, providing stronger support for the inference that some abilities develop prior to (and so may form the developmental foundations for) later abilities. Thus, while being correlational in nature, the present findings provide new and stronger evidence that most infants first possess the social cognitive understanding and altruistic motivation to 'help' another; followed by either understanding the communicative intent of a pointing gesture or being able to re-enact the intended (rather than actual) outcome of someone's action, or both; followed by either understanding the communicative intent of a gaze gesture or coordinating intentions and actions with another person to form a joint goal during a problem solving task with a non-social goal, or both; followed by the ability to form joint goals with others during a game with an essentially social goal.

Why might this consistent sequence be observed? The explanation that fits best with Tomasello and colleagues' research programme [9], and with Wellman and Liu's [5] interpretation of their ToM scale for older children, is that the sequence is observed because earlier-developing abilities form the developmental foundations for later-developing abilities.

This pattern is consistent with Tomasello and colleague's hypothesis that infants must first develop a basic understanding of the intention behind another's action (i.e. to achieve a goal), which they can build upon through a developmental process of modification or mediation. Wellman and Liu [5] gloss the relationships they observe in terms of conceptual change, and that is also possible for the present data, though Tomasello and colleagues typically see children as developing "capacities" or "abilities" rather than concepts. Nothing in the present data helps decide between these alternatives.

A less interesting alternative is that the tasks happen to make increasing demands on some other cognitive resource, perhaps memory or attention, that develops independently between 1 and 3 years, giving rise to the developmental sequence for reasons unrelated to infants' understanding of intentionality. Due to the constraints on task selection (i.e. tasks requiring simple equipment and no more than two experimenters), which are common requirements in developmental scales assessing cognitive ability in young children [21], the tasks available from previous literature could not easily be adapted to ensure materials and procedures were the same as one another. Therefore, infant's performance may have been influenced by differences in task demands other than type of intention understanding that it aimed to assess. However, we do not favour this explanation because most of the tasks had control trials (either in the present study or at least in the original studies) that placed many of the same demands on memory or attention as experimental trials. High levels of appropriate behaviours on these control trials indicate that infants typically had the requisite memory and attention resources for successful task performance, and were not subject to task-specific behavioural biases that may have obscured success. A third alternative is that the developmental sequence reflects a timetable of biological maturation for largely independent "modules" subserving the social capacities assessed by each task [46, 47].

The current study provides a tool for distinguishing between these possibilities in future work examining the performance of individuals with neurodevelopmental disorders on our Early Social Cognition Scale. Disorders such as autism spectrum disorders, Fragile X, and Down syndromes show diverse profiles of social and cognitive difficulties [48-51]. For example, individuals with Fragile X syndrome show gaze aversion [52, 53], so might be expected to find the Gaze task in the scale particularly difficult, whereas individuals with Down syndrome gaze appears relatively intact [54]. If specific later abilities in the scale build upon understanding intentions in gaze behaviour, then these later-developing abilities should also be impaired in individuals with Fragile X, but not Down syndrome. However, if abilities assessed in the scale develop rather independently – as might be expected by a more modular account - then it should be possible to observe selective impairment to the Gaze task without specific consequences for later points in the scale. Similarly, in the unlikely case that the position of items in the scale in typically developing children is due to demands made upon memory and attention, rather than social cognition, then we would expect to see different scales in disorders that affect memory and attention more than social abilities (e.g. Down syndrome [55, 56] compared with disorders that are characterised more so by their social difficulties (e.g. autism spectrum disorders) [57]. Of course, work with neurodevelopmental disorders not only provides the opportunity to test between theoretical accounts of the scale, but also the opportunity to better understand the nature of social cognition in these disorders, as has already been demonstrated for the later-developing scale [14, 15].

In summary, the findings of this study support and extend the current literature describing early social cognitive abilities in typically-developing infants and very young children. Whereas previous evidence has suggested the possibility of a developmental progression between assessments of increasingly sophisticated understanding of intentionality,

the present study shows that such abilities indeed form a progression that is reliably consistent within individual participants. The Early Social Cognition Scale maps the progressive development of social cognitive skills during infants' early years that no single cognitive test could capture. Following the ground-breaking approach of Wellman and Liu [5], this work suggests that understanding of intentionality typically develops in a coherent and reliable sequence. It lays the foundations for better assessment of individual differences in these precursor abilities in typically-developing children, and by using early-developing non-verbal tasks it greatly extends the range of atypically-developing children whose social-cognitive abilities can be assessed with a reliable experimental instrument.

Appendix F: Description of Theory-of-Mind Scale tasks (Peterson, Wellman & Slaughter, 2012)

Diverse Desires.

The *'Diverse Desires'* task (originally designed by Repacholi and Gopnik, 1997) assesses whether a participant can predict an individual's actions by inferring that agent's desires based upon their previous knowledge of that individual's preferences, and understand that the agent's desire about an object may differ to their own.

The participant is introduced to a toy man and shown a picture of a carrot and a picture of a cookie side by side. The experimenter says "Here's Mr Jones. Its snack time, so Mr. Jones wants a snack to eat. Here are two different snacks: a carrot and a cookie". The experimenter points to the carrot and the cookie upon their mention. The experimenter then asks the participant about their own desires; "Which would you like best? Would you like the carrot or the cookie best?" Most participants state that they prefer the cookie. After the participant responds, the experimenter continues: "Well, that's a good choice, but Mr Jones likes carrots best" if the participant gives the expected response. If the participant says that they prefer carrots best, then the experimenter says cookies instead. The experimenter asks the participant the target question: "So, now it's time to eat. Mr Jones can only choose one snack, just one. Which snack will Mr Jones choose, a carrot or a cookie?" pointing to the pictures in correspondence to what he/she says. To pass, the participant must identify the snack that Mr Jones would prefer rather than what they would like when asked the target question.

Diverse Beliefs.

The *'Diverse Beliefs'* task (Wellman & Bartsch, 1988) assesses whether a participant can predict an agent's actions by interpreting knowledge of that individual's belief of the location of a desired object, when the participant has no knowledge of the true location of the object themselves, and the agent's belief conflicts with the participant's.

The participant is shown a picture including some bushes and a garage and then introduced to a puppet. The experimenter says "Here's Linda. Linda wants to find her cat. Her cat might be hiding in the bushes, or it might be hiding in the garage", and then asks the participant about their own beliefs: "Where do you think the cat is? In the bushes or in the garage?" After the participant responds, the examiner continues: "Well that's a good idea, but Linda thinks her cat is in the garage. She thinks her cat is in the garage" if the participant previously expressed a belief that the cat was in the bushes. If the participant believed that the cat was in the garage, then the experimenter says "bushes" instead of "garage". The experimenter then asks the participant the target question "So, where will Linda look for her cat? In the bushes or in the garage"? To pass, the participant must identify that Linda will look for her cat in the place that Linda believes it is, as opposed to where they think the cat is.

Knowledge Access.

The *'Knowledge Access'* task (Pratt & Bryant, 1990; Pillow, 1989) assesses whether a participant can assess an agent's knowledge and/or ignorance about an object based on the participant's knowledge of that agent's previous experiences with that object.

The participant is shown a box with a single draw that can be pulled out. The experimenter says "Here's a draw. What do you think is inside the draw?" After the participant responds, the examiner continues: "Let's see" and opens the draw to show a duck is inside. The examiner closes the draw and asks the participant "what is in the drawer?" After the participant responds, the examiner introduces a puppet: "This is Polly. Polly has never seen inside this draw. Now here comes Polly." The participant is then asked the target question ("So, does Polly know what is in the draw?") followed by the memory question ("Did Polly see inside the draw?"). To pass, the participant must answer both the target and the memory questions correctly i.e. identifying that Polly does not know what is in the draw, and that Polly had not seen inside the draw respectively.

Contents False Belief.

The *'Contents False Belief'* task (Perner, Leekham & Wimmer, 1987) assesses a participant's ability to predict an agent's actions by interpreting knowledge of that agentl's belief about the contents of a container even when it conflicts with the participant's knowledge of what is actually inside the container.

The participant was first shown a smarties box. The examiner then said "Here's a smarties box. What do you think is inside the smarties box?" After the participant responds, the examiner opens the box to reveal "It's really pencils inside". The examiner closes the box and asks the control question "Okay, what is in the smartie's box?" After the participant responds, the examiner brings out a soft toy resembling a boy. "This is Peter, Peter has never seen insight the smarties box. Now here comes Peter." The examiner then asks the target question; "so, what does Peter think is in the box? Smarties or pencils?" followed by the

memory question; "did Peter see inside the box?" To pass, the participant must identify both that Peter will think there are smarties in the box, and that Peter had not seen inside the box.

Hidden Emotion.

The *'hidden emotion'* task (Harris, Donelly, Guz & Pitt-Watson, 1986) assesses participant's ability to distinguish between the emotion an agent is experiencing (real) and the emotion which that agent is outwardly expressing (apparent), even when those emotions contrast to one another.

The participant is shown a sheet of paper with a picture of a happy, sad and neutral face and is asked to identify each face: "can you point to the happy face? Can you point to the sad face? Can you point to the face that is just okay?" The examiner places the pictures slightly to the side and then shows the participant a picture of a boy and says: "This story is about a boy. I'm going to ask you about how the boy really feels inside and how he looks on his face. He might really feel one way inside but look a different way on his face. Or, he might really feel the same way inside as he looks on his face. I want you to tell me how he really feels inside and how he looks on his face". After clarifying whether the participant understands, the examiner told the story: "This story is about Matt. Matt's friends were playing together and telling jokes. One of the older children, Rosie, told a mean joke about Matt and everyone laughed. Everyone thought it was very funny, but not Matt. But, Matt didn't want the other children to see how he felt about the joke, because they would call him a baby. So, Matt tried to hide how he felt". The participant is then asked two memory questions: 1) "What did the other children when Rosie told a mean joke about Matt?" and, 2) In the story, what would the other children do if they knew how Matt felt?" Whilst pointing to

the faces, the examiner asks the target feel question ("so how did Matt really feel when everyone laughed? Did he feel happy, sad or just okay?"), followed by the target look question ("how did Matt really feel when everyone laughed? Did he feel happy, sad or just okay?"). To pass, the participant must retain essential facts about the story (i.e. the other children laughed when Rosie told a mean joke about Matt and that the other children would call him a baby if they knew how Matt felt) as assessed by the memory questions, and correctly identify that Matt really felt sad when everyone laughed, but looked happy or just okay on his face when responding to the target questions.

Sarcasm.

The *'sarcasm'* task (Happé, 1994) assesses a participant's ability to understand social inference i.e. the communicative intent behind another individual's non-literal statement (i.e. understanding irony or sarcasm).

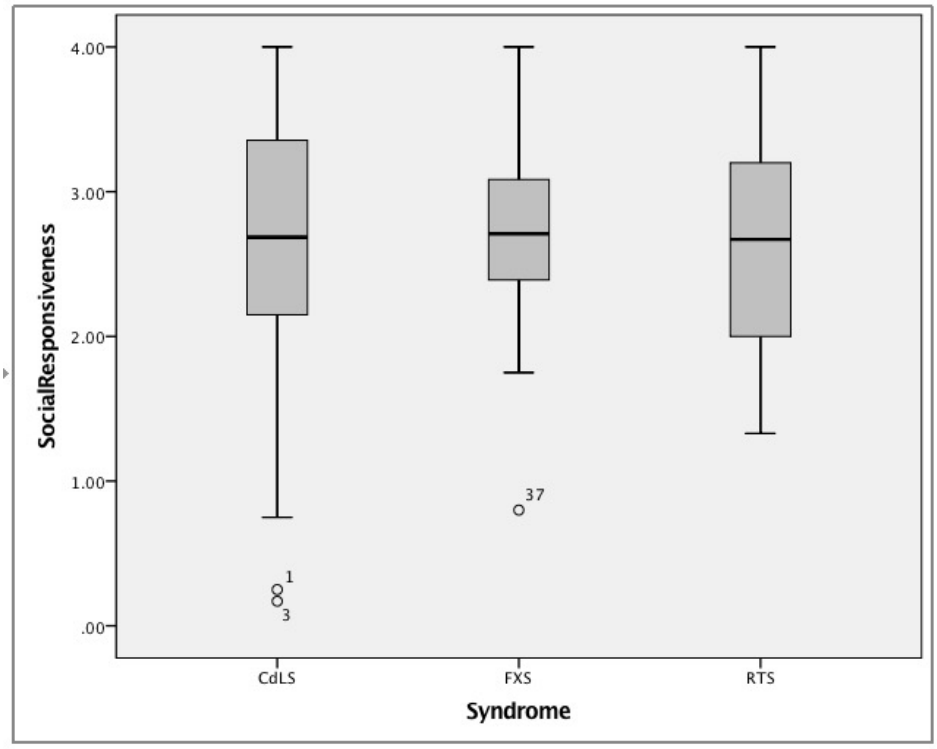
The participant is shown a picture of the back of a boy and a girl's head, raindrops, and a wet cake and other food on a picnic rug. The experimenter says "the boy and a girl are going on a picnic. It is the boy's idea. He says it will be a lovely sunny day. But when they get the food out, big storm clouds come. It rains and the food gets all wet." The examiner continues with no special intonation "the girl says: "It's a lovely day for a picnic." The participant is asked a reality question "is it true, what the girl said?" followed by the target question "why did the girls say it's a lovely day for a picnic?" Finally, the participant is asked the control question "was the girls happy about the rain?" To pass, participants must identify that what the girl said was not true (reality questions) and was not happy about the rain

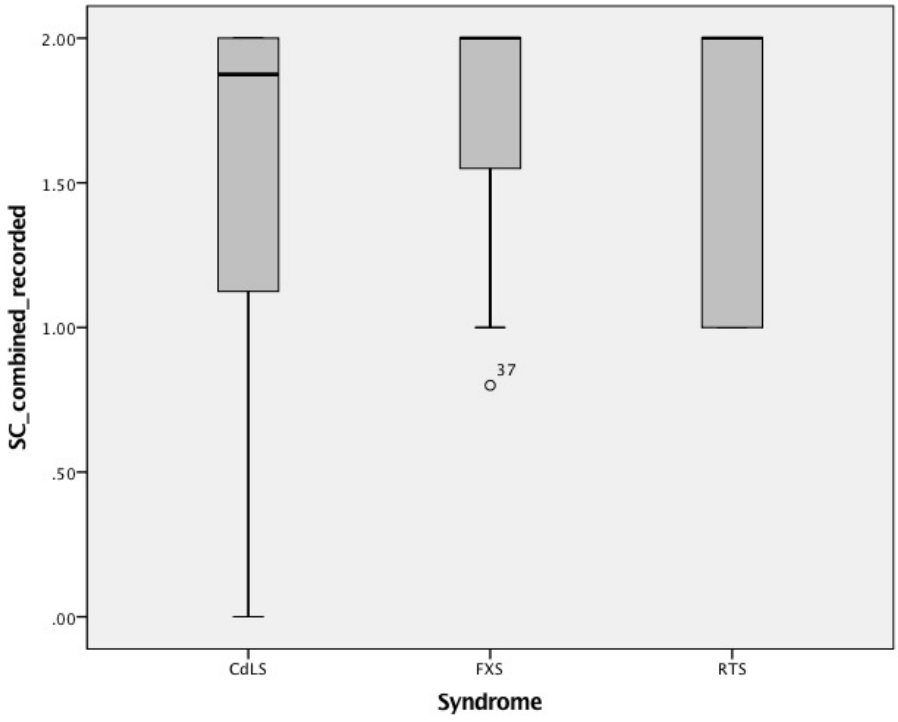
(control question), and finally allude to the fact that the girl was being sarcastic in response to the target question (e.g. “was being sarcastic”, “she didn’t mean it”, “was joking”).

Appendix G: Frequencies, mean chronological age and non-verbal mental age of participants participating in each ADOS-II module per syndrome group

	Syndrome		
Module	CdLS (*n* = 36)	FXS (*n* = 36)	RTS (*n* = 25)
T	3 (8%)	0 (0%)	1 (4%)
Mean CA (SD)	2.31 (0.5)	N/A	2.25 (N/A)
Mean NVMA (SD)	1.36 (.244)	N/A	N/A
1	15 (42%)	12 (33%)	12 (48%)
Mean CA (SD)	6.67 (3.14)	5.01 (1.66)	9.15 (3.44)
Mean NVMA (SD)	2.48 (1.08)	2.23 (.45)	2.19 (0.59)
2	6 (17%)	9 (25%)	6 (24%)
Mean CA (SD)	11.21 (2.07)	10.25 (4.8)	10.56 (4.08)
Mean NVMA (SD)	4.52 (0.55)	3.65 (0.58)	3.76 (0.31)
3	4 (11%)	4 (11%)	2 (8%)
Mean CA (SD)	10.65 (1.48)	11.56 (5.47)	11.17 (2.12)
Mean NVMA (SD)	6.11 (2.09)	4.27 (0.77)	4.77 (0.27)
4	8 (22%)	11 (31%)	4 (16%)
Mean CA (SD)	28.81 (8.87)	31.80 (8.34)	38.31 (15.76)
Mean NVMA (SD)	5.89 (2.2)	4.46 (0.66)	5.12 (1.03)

Appendix H: Box plots of CSRS *social responsiveness* and *social communication* item scores in individuals with CdLS, FXS and RTS





Appendix I: Pattern of pass and fails for each *Early Social Cognition* task per participant in each syndrome group for the original scale.

Syndrome	Helping	REI or Point	Gaze or Tubes	Trampoline
CdLS	0	0	0	0
	1	1	0	0
	1	1	0	0
	1	1	0	0
	1	1	1	1
	1	0	0	0
	1	1	1	0
	1	1	0	0
	0	0	0	0
	0	0	1	0
	1	1	0	0
	0	1	0	0
	0	1	0	0
	1	1	0	0
	1	1	0	0
	1	1	1	1
	1	0	0	0
	1	0	0	0
	0	1	0	0
	0	1	0	0
	0	1	0	0
	1	1	1	0
FXS	0	0	1	0
	1	1	1	0
	0	0	1	0
	1	0	1	0
	1	1	0	0
	1	1	0	0
	1	1	0	0
	1	1	1	0
	1	1	0	0
	0	1	0	0
	1	1	0	0
	1	1	1	0
	1	1	1	0
	1	1	0	1

	1	1	0	0
	1	1	1	1
	1	1	0	0
	1	1	1	0
	1	1	1	1
RTS	1	1	0	1
	0	1	0	0
	1	1	0	0
	1	1	1	1
	1	1	1	1
	1	1	1	1
	1	1	1	1
	1	1	0	0
	1	0	0	0
	1	1	1	0
	1	1	1	1
	1	1	0	1
	0	1	0	0
	1	1	0	0
	1	1	0	0
	1	1	0	0
	1	1	1	0
	1	0	0	0

Appendix J: Pattern of pass and fails for each *ToMS* task per participant in each syndrome group.

Syndrome	Diverse desires	Diverse beliefs	Knowledge Access	Contents False Belief	Real Apparent Emotion	Sarcasm
CdLS	1	0	1	0	0	0
	0	0	1	1	0	0
	1	1	0	0	0	0
	1	1	0	0	0	0
	1	1	0	0	0	0
	1	1	1	1	1	0
	1	1	1	1	0	0
	1	1	0	0	0	0
	1	1	1	0	0	0
	1	0	1	0	0	0
	1	1	1	1	0	0
	1	0	0	0	0	0
	1	1	0	0	0	0
	1	1	1	0	0	0
	1	1	0	0	0	0
	1	1	1	0	0	0
	1	1	1	1	1	0
	1	1	1	1	0	0
FXS	1	1	1	0	0	0
	1	1	1	1	0	0
	1	1	0	0	0	0
	1	1	1	0	0	0
	1	0	1	0	0	0
	1	1	1	0	0	0
	1	1	1	0	0	0
	1	1	0	0	0	0
	1	1	0	0	0	0
	1	1	1	0	0	0
	1	1	1	0	0	0
	1	1	0	0	0	0
	1	1	0	0	0	0
	0	1	1	1	0	0
	1	1	1	0	0	0

	1	1	1	1	0	0
	1	0	0	0	0	0
	0	1	1	0	0	0
RTS	1	1	1	0	1	0
	1	1	0	0	0	0
	1	1	1	0	0	0
	1	1	0	0	0	0
	1	1	0	0	0	0
	1	1	0	0	0	0
	1	1	0	0	0	0
	1	1	0	0	0	0
	1	1	1	1	0	0
	1	1	0	0	0	0
	1	1	1	0	0	0
	1	1	0	0	0	0
	1	0	0	0	0	0
	1	1	0	0	0	0
	1	1	0	0	0	0

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