The Cognitive Profile and Autistic Characteristics Associated with Sotos Syndrome

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Abstract

The purpose of this thesis was to advance understanding of the cognitive and behavioural profiles associated with Sotos syndrome. Specifically, the aim of this thesis was to establish the cognitive profile and whether autistic features are associated with Sotos syndrome. Initially, a systematic review of all published literature providing data on cognition and behaviour in Sotos syndrome was conducted. In general, research investigating cognition and behaviour in Sotos syndrome has been sporadic and much of the existing literature is based on small samples. The findings from the systematic review were used to inform the design of the research presented in the subsequent chapters.

The studies reported within this thesis have used the largest samples to date to investigate cognition and behaviour in individuals with Sotos syndrome. Specifically, the findings demonstrate that Sotos syndrome is associated with a high prevalence of autistic features, as well as a clear and consistent cognitive profile. In particular, the Sotos syndrome cognitive profile is characterised by relative strength in verbal ability and visuospatial memory and relative weakness in non-verbal reasoning ability and quantitative reasoning. Furthermore, greater severity of autistic features is associated with lower intellectual ability for individuals with Sotos syndrome. Communicative difficulties are common in both adults and children with Sotos syndrome and individuals display difficulty with both structural and pragmatic aspects of language. Overall, the findings reported within this thesis advance understanding of the cognitive and behavioural phenotype of Sotos syndrome and have important implications for considering the syndrome-specific needs of these individuals.

Chapter 1: Cognition and behaviour in Sotos syndrome: A systematic review

1.1. Introduction

1.1.1. Sotos Syndrome

Sotos syndrome is a congenital overgrowth disorder, initially recognised by Sotos, Dodge, Muirhead, Crawford, and Talbot (1964) who observed five patients with similar clinical features. These included excessively rapid growth, acromegalic features and a non-progressive cerebral disorder with mental retardation. The authors considered this combination of features to be attributable to a specific syndrome, which they termed Sotos syndrome. Excessively rapid growth has been defined as advanced height, weight and bone age; acromegalic features include a prominent forehead, high anterior hairline, prominent chin and downslanting palpebral fissures (Dodge, Holmes, & Sotos, 1983). The syndrome was described as non-progressive, meaning that the symptoms do not significantly worsen throughout development. As macrocephaly is one of the features of the syndrome, initial research often used the terms cerebral gigantism and Sotos syndrome interchangeably to refer to the same condition.

Subsequent research has confirmed these cardinal features in larger samples of individuals with Sotos syndrome. For example, Cole and Hughes (1994) investigated the clinical characteristics of 41 typical cases of Sotos syndrome. The findings confirmed that overgrowth (defined as height and/or head circumference > 97th percentile) with advanced bone age, macrocephaly, characteristic facial appearance and intellectual disability are the cardinal features of the syndrome. Other health problems that are commonly experienced in children with Sotos syndrome are cardiac and genitourinary anomalies, neonatal jaundice, neonatal hypotonia, seizures and scoliosis (Opitz, Weaver, & Reynolds, 1998; Tatton-Brown & Rahman, 2004). Sotos

syndrome has an estimated incidence of approximately 1 in 14,000 (Tatton-Brown & Rahman, 2004).

As well as having macrocephaly, individuals with Sotos syndrome typically display distinctive neurological abnormalities. Schaefer, Bodensteiner, Buehler, Lin, and Cole (1997) investigated structural brain abnormalities in 40 participants with Sotos syndrome, using Magnetic Resonance Imaging (MRI). The findings indicated that participants displayed a characteristic pattern of abnormalities. Specifically, participants displayed abnormality of the corpus callosum, ventricular abnormalities, midline abnormalities and delayed or disturbed maturation of the brain (Schaefer et al., 1997). The focus of this study was to investigate structural brain abnormalities and to date, there are no published studies on functional neural activity in individuals with Sotos syndrome.

The identification of a genetic abnormality responsible for Sotos syndrome was first established in a Japanese sample (Kurotaki et al., 2002). The authors identified that Sotos syndrome is caused by haploinsufficiency of the NSD1 (nuclear receptor binding SET domain protein 1) gene. The NSD1 gene encodes SET domain-containing histone methyltransferases and is located at chromosome 5q35 (Tatton-Brown & Rahman, 2013). Sotos syndrome is caused by intragenic mutations of the NSD1 gene or 5q35 microdeletions encompassing NSD1 and these abnormalities result in loss of function. Subsequent research investigated the prevalence of NSD1 abnormalities in a sample of 266 individuals with a clinical diagnosis of Sotos syndrome (Tatton-Brown, Douglas, Coleman, Baujat, Cole, et al., 2005). The findings from this study identified that abnormalities of the NSD1 gene were present in more than 90% of individuals with a clinical diagnosis of Sotos syndrome (Tatton-Brown, Douglas, Coleman, Baujat, Cole, et al., 2005).

Interestingly, research has identified a distinction in the prevalence of the different types of NSD1 abnormalities present in individuals with Sotos syndrome of different ethnicity. In the Japanese population, a 5q35 microdeletion encompassing the NSD1 gene is the most common cause of Sotos syndrome (Tatton-Brown, Douglas, Coleman, Baujat, Chandler, et al., 2005). However, in individuals of non-Japanese ethnicity, an intragenic mutation of the NSD1 gene is the most common cause of Sotos syndrome, accounting for approximately 83% of cases (Tatton-Brown, Douglas, Coleman, Baujat, Chandler, et al., 2005). As the syndrome is not specifically linked to the X or Y chromosomes, it affects males and females equally. In the majority of cases, the NSD1 abnormalities which cause Sotos syndrome are *de novo*, meaning that they occur spontaneously (Kurotaki et al., 2002). However, the syndrome has an autosomal dominant inheritance pattern, meaning that a child of an individual with Sotos syndrome has a 50% chance of also having the syndrome. A small number of familial cases arising from autosomal dominant transmission have been reported in the literature (Tatton-Brown, Douglas, Coleman, Baujat, Cole, et al., 2005; Tatton-Brown & Rahman, 2007).

Research has investigated potential genotype-phenotype correlations associated with the different NSD1 abnormalities (Novara et al., 2014; Rio et al., 2003; Tatton-Brown, Douglas, Coleman, Baujat, Cole, et al., 2005). Broadly, it has been suggested that individuals with 5q35 microdeletions encompassing the NSD1 gene have less prominent overgrowth and more severe intellectual disability, compared to individuals with an intragenic mutation of the NSD1 gene (Rio et al., 2003; Tatton-Brown, Douglas, Coleman, Baujat, Cole, et al., 2005). These genotype-phenotype relationships have focused on clinical features, as opposed to cognitive and behavioural profiles.

Sotos syndrome is one of several single-gene disorders associated with overgrowth and intellectual disability (OGID) and has recently been identified as the most prevalent OGID (Tatton-Brown et al., 2017). Other examples of OGID include Weaver syndrome (Weaver, Graham, Thomas, & Smith, 1974) and Tatton-Brown Rahman syndrome (TBRS) (Tatton-Brown et al., 2014). Although the cardinal features of Sotos syndrome, Weaver syndrome and Tatton-Brown Rahman syndrome are similar, as all of these syndromes are associated with overgrowth and intellectual disability, the syndromes can be differentiated by subtle differences in the phenotypes. For example, individuals with Weaver syndrome typically have a round face and almond shaped eyes, which are not characteristic facial features associated with Sotos syndrome and less prominent macrocephaly than individuals with Sotos syndrome (Tatton-Brown et al., 2011; Tatton-Brown & Rahman, 2013). In addition, each of these OGID is caused by a distinct genetic abnormality. Specifically, Weaver syndrome is caused by mutation of the EZH2 gene (Tatton-Brown et al., 2011) and TBRS is caused by mutation of the DNMT3A gene (Tatton-Brown et al., 2014).

1.1.2. Motivation for research

Identification of syndrome-specific cognitive and behavioural profiles associated with genetic syndromes can provide insight into interactions between genes, brain and behaviour (Scerif & Karmiloff-Smith, 2005). Single-gene disorders offer a unique opportunity to explore cognition and behaviour within genetically defined populations. This level of description goes beyond that which can be established through the study of behaviourally defined disorders such as autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD), which have been described as heterogeneous disorders with varying causal pathways

(Abrahams & Geschwind, 2008; Thapar, Cooper, Eyre, & Langley, 2013). As Sotos syndrome has an established genetic cause and is associated with intellectual disability and behavioural issues, this is a valuable and homogeneous population in which to investigate cognition and behaviour. Understanding of the cognitive and behavioural profiles associated with Sotos syndrome may provide insight into specific biological mechanisms underlying the phenotype. Furthermore, it is important to establish the syndrome-specific phenotype associated with Sotos syndrome in order to identify the specific needs of these individuals and to provide appropriate support to enable optimal outcomes.

As Sotos syndrome is a relatively rare syndrome, previous research with this population has been fairly limited and in general, there is a lack of awareness of the syndrome. Consequently, on diagnosis, families have limited information about what to expect from their child and often rely on anecdotal evidence to inform their expectations. Similarly, in educational settings, educators are often unaware of Sotos syndrome and syndrome-specific resources for these individuals have not been developed. Therefore, the primary motivation for this thesis was to improve understanding of the cognitive and behavioural phenotype associated with Sotos syndrome and to increase awareness of the syndrome. It was anticipated that the research reported in this thesis would be of direct benefit to families of individuals with Sotos syndrome.

1.1.3. Systematic review

Research investigating cognition and behaviour in Sotos syndrome has been sporadic and to date, there is no published overview of study findings. Therefore, a

systematic review was conducted in order to synthesise and critically evaluate all published literature providing data on cognition and behaviour in individuals with Sotos syndrome. Broadly, the purpose of this review was to establish current understanding of the cognitive and behavioural profiles associated with Sotos syndrome and to identify particular issues which may be common within this population. An additional aim of this review was to identify current gaps in knowledge and to establish potential areas of interest for future research. Specifically, the findings from the systematic review were used to inform the design of the empirical work reported within this thesis.

As the overall aim of this review was fairly broad, three specific research questions were devised in order to ensure that the focus of the review was clear. The research questions were to establish: 1) the degree of intellectual disability in individuals with Sotos syndrome; 2) whether there is evidence for a profile of verbal and non-verbal cognitive abilities; 3) whether there are common behavioural problems associated with Sotos syndrome. Behavioural problems included psychiatric and psychological issues, as well as problems with temperament.

The quality of the published research in these areas was assessed using an objective assessment tool (Kmet, Lee, & Cook, 2004). This was important for evaluating the reliability and validity of findings within the literature. As no systematic review or meta-analysis has been published within the Sotos syndrome literature to date, this review provides a novel and comprehensive overview of the current knowledge base of the syndrome.

1.2. Method

The review was written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRSIMA) Checklist (Moher, Liberati, Tetzlaff, Altman, & Grp, 2009).

1.2.1. Search strategy

Four electronic databases were systematically searched for relevant studies: Web of Science (1964 – 2015), Scopus (1964 – 2015), PsycINFO (1964 – 2015) and PubMed (1964 – 2015). The first paper to recognise Sotos syndrome as a specific syndrome was published in 1964, so the searches were started from this date. The databases were searched using the terms "Sotos" AND "syndrome", OR "cerebral" AND "gigantism". The terms 'Sotos syndrome' and 'cerebral gigantism' have been used interchangeably within the literature so both were included in the database search.

In Scopus and Web of Science, the title/abstract/keywords of the journal articles were searched using the key search terms. In PsycINFO, the abstract/title/key concepts were searched and in PubMed, the title/abstract were searched. Differences in the search strategies implemented were due to the unique search system of each database. The search was conducted in August 2015. In addition to the database search, bibliographies and citations of all papers included in the review were hand-searched to ensure that all relevant papers had been identified.

1.2.2. Study selection

Predetermined inclusion criteria were used to assess whether the articles identified in the initial search were relevant. As an aim of this review was to provide

an overview of findings from published research, only articles published in peer reviewed journals and written in English language were included in the review. In addition, only primary research was included in order to ensure that the same methodology and findings were not reviewed multiple times. Finally, the study was required to provide data relating to cognitive ability and/or behaviour in an individual or individuals with a diagnosis of Sotos syndrome.

When screening the abstracts, papers were considered relevant if they included the term 'intelligence' or if they included terms relating to specific aspects of cognition, such as 'language', 'memory', 'attention', 'executive function' or 'logic/problem-solving'. Abstracts were also considered relevant if they mentioned any behavioural or psychiatric problems, such as 'autism', 'ADHD', 'psychosis', 'anxiety' or 'aggression/tantrums'. Full text articles that met all inclusion criteria were then selected for the review.

1.2.3. Data extraction

Data were extracted from articles that met inclusion criteria. This information included sample size (number of participants with Sotos syndrome), demographic information (age and gender), cognitive or behavioural assessments used and key findings from these measures. In order to satisfy the key aims of this review, studies that reported IQ scores of individuals with Sotos syndrome are summarised in Table 1.1; studies that reported findings related to language abilities and other specific cognitive abilities of individuals with Sotos syndrome are summarised in Table 1.2; studies providing data on aggression and/or tantrums in individuals with Sotos syndrome are summarised in Table 1.3; studies reporting findings related to ASD are

summarised in Table 1.4; studies measuring ADHD are summarised in Table 1.5 and studies providing data on anxiety are summarised in Table 1.6.

1.2.4. Quality assessment

A quality checklist (Kmet et al., 2004) was used to assess the quality of the studies included in this review. This checklist was chosen as it was designed specifically for use with quantitative studies, of various methodological designs and has been used to assess the quality of papers included in a number of systematic reviews (e.g. (Flynn, Hulbert-Williams, Hulbert-Williams, & Bramwell, 2015; Goldsmith, Jackson, O'connor, & Skirton, 2012)). A scoring manual provides detailed guidelines for assessing the quality of the research. The checklist was used in its original form, though questions 5 -7 (from the original checklist) were removed as they related to intervention studies, so were not relevant for this review. In total, the checklist included 11 questions. The quality of all of the papers included in this review was assessed in relation to the topic of interest (cognition or behaviour), as opposed to the quality of the paper in general. Each question was rated as 'yes' (2 points), 'partial' (1 point), 'no' (0 points) or N/A, in accordance with the guidance included within the scoring manual. For each study, the possible total sum was determined (questions rated as N/A were not included in the total possible sum), as well as the actual total sum. The quality score was then calculated as the actual total sum divided by the possible total sum and then multiplied by 10. Scores were rated out of 10, with higher scores corresponding to better quality.

1.3. Results

The literature search yielded 1,304 results. Once duplicate results had been removed, a total of 917 articles were screened for inclusion in the review. The abstracts of these papers were read and papers were considered to be relevant if the abstract met all inclusion criteria. After the abstracts had been screened, fifty five full articles were read to assess eligibility for the review. Eighteen articles were excluded on the basis that the means of assessment for cognitive or behavioural data were not reported, two were excluded because no primary research was reported and one was excluded due to not being published in English. As a result, a total of thirty-four articles met inclusion criteria (see Figure 1.1. for search strategy and study selection). Crucially, the search revealed that no systematic reviews or meta-analyses have been published in the Sotos syndrome literature.

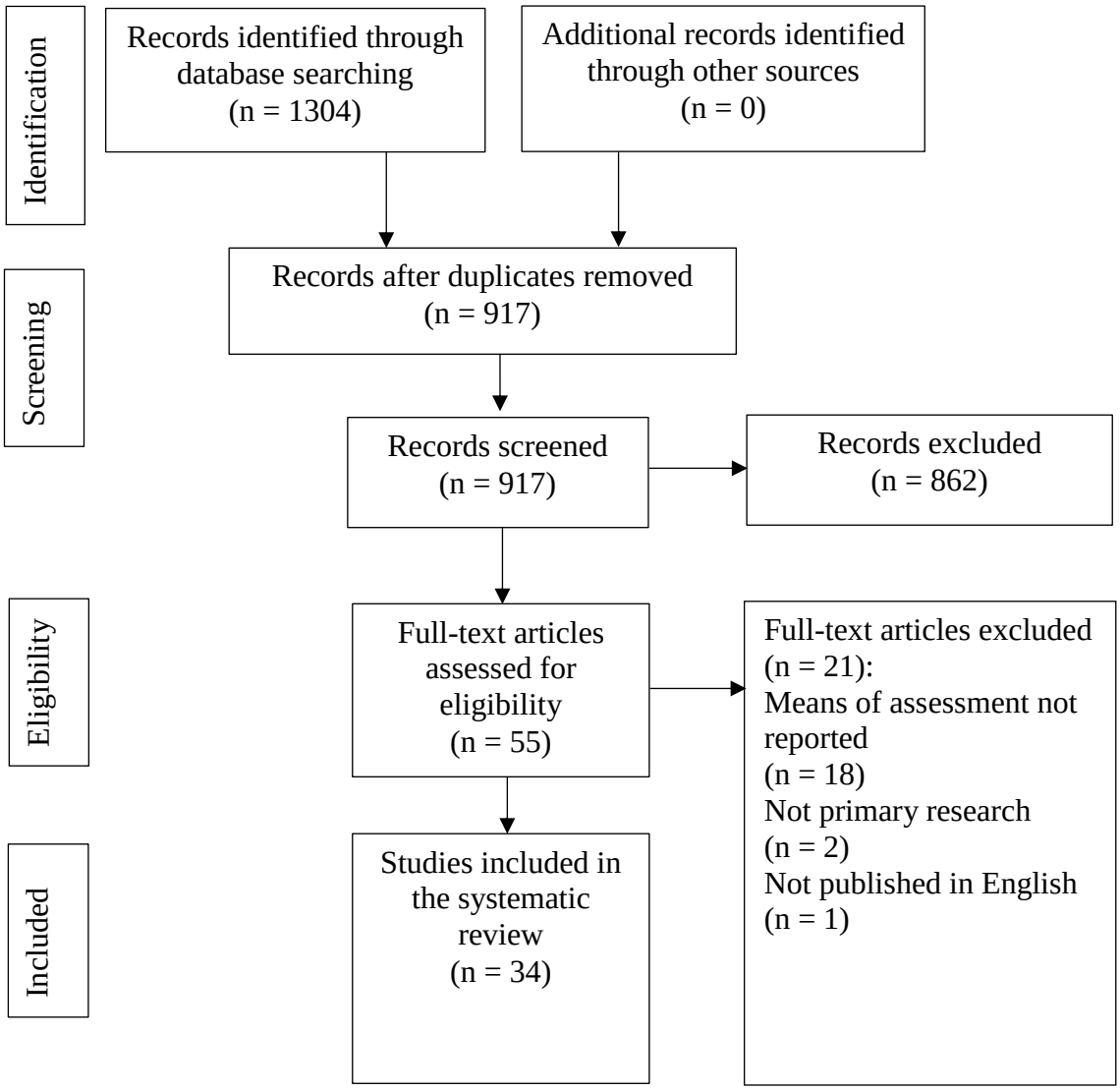


Figure 1.1. Search strategy and study inclusion (August 2015).

1.3.1. Quality of included studies

Each article was assessed in order to establish the quality of the research. The articles were assessed in relation to specific criteria based on objectives, methodology, results and conclusions. When interpreting the findings from the studies, greater weighting was given to findings from studies that received better quality scores. The score for each article is provided in tables 1.1 – 1.6. A second reviewer independently assessed the quality of 20% of the studies in order to ensure that the assessment was

reliable. Intraclass correlation coefficient for the two reviewers was .86, indicating excellent inter-rater reliability (Fleiss, 1986). Both of the reviewers ranked the papers in the same order (lowest-highest). The mean score was 6.8 (*SD* = 1.69) and scores ranged from 1.7 – 9.5. This highlights that there is considerable variation within the quality of the published literature providing data on cognition and/or behaviour in Sotos syndrome.

1.3.2. Common themes emerging from study findings

A small number of studies (*n* = 10) have used a group study design to assess cognitive and/or behavioural features of individuals with Sotos syndrome. The use of cohorts of individuals has allowed comparisons to be made between participants, providing insight into common cognitive and behavioural phenotypes. A case study design was implemented in more than half of the studies (*n* = 24). This means that a significant proportion of the data reported in relation to cognition and behaviour in individuals with Sotos syndrome were based on very small samples. The use of a case study design makes it difficult to establish whether there is a consistent cognitive or behavioural profile associated with the syndrome as the findings often lack generalisability. However, data from case studies are useful in providing a detailed analysis of cognition and behaviour in individuals with Sotos syndrome.

1.3.3. Intelligence quotient (IQ)

Cognitive abilities were assessed, using standardised measures of IQ, in a total of 172 participants, across twenty-five studies (see Table 1.1). Of these, six were group studies and nineteen were case studies. The most common measures of IQ were versions of the Wechsler Intelligence Scale for Children (WISC) (used in eleven

studies) and the Stanford Binet Intelligence Scale (used in eight studies). In three group studies, the mean full scale IQ (FSIQ) of all of the Sotos syndrome participants included in the study was reported. These were 76 (De Boer, Roder, & Wit, 2006), 73.8 (Rutter & Cole, 1991) and 73.67 (Finegan et al., 1994). The number of participants in each of these studies was 21, 15 and 27, respectively. Varley and Crnic (1984) reported a median FSIQ of 62 for the eleven participants included in this study. A limitation of the remaining two group studies is that the mean or median FSIQ was not reported (Leventopoulos et al., 2009; Sarimski, 2003). In one study, cognitive abilities were assessed in terms of cognitive competence (Sarimski, 2003), so the findings from this study are not comparable with the other group studies that measured FSIQ.

Of the six group studies that reported FSIQ scores, four reported the range of these scores. These were 47 – 105 (De Boer et al., 2006), 21 – 103 (Finegan et al., 1994), 54 – 96 (Rutter & Cole, 1991) and 40 – 85 (Varley & Crnic, 1984). This shows that there is a consistent range of ability reported in all of the studies that provided the range of FSIQ scores, suggesting that individuals with Sotos syndrome can be higher functioning, though most are not. In general, the literature suggests that the majority of individuals with Sotos syndrome have mild intellectual disability (IQ = 50 – 69) or are in the borderline range (IQ = 70 – 84). However, level of intellectual functioning is variable and a few cases of severe intellectual disability or intellectual ability within the normal range have been reported.

In addition to FSIQ scores, seven studies (Bale, Drum, Parry, & Mulvihill, 1985; Compton, Celentana, Price, & Furman, 2004; De Boer et al., 2006; Ginter & Scott, 1975; Mouridsen & Hansen, 2002; Patterson, Bloom, Reese, & Weisskopf, 1978; Rutter & Cole, 1991) also reported performance IQ and verbal IQ scores. This

information provides insight into ability in the two separate domains that comprise FSIQ. Verbal IQ scores were reported to be higher than performance IQ scores in all studies, except one case study (Patterson et al., 1978). However, in this study, the participant was reported to have a performance IQ of 101 and a verbal IQ of 100. Overall, the evidence suggests that individuals with Sotos syndrome have better verbal IQ, compared to performance IQ scores.

Other than reporting performance IQ and verbal IQ scores, only one study (Morrow, Whitman, & Accardo, 1990) reported quantitative scores in four specific cognitive domains (verbal reasoning, abstract/visual, quantitative reasoning and short-term memory). This was a case study, reporting findings relating to a 4y 11m old male. As data were based on one young child, it provides only a limited insight into the cognitive profile of individuals with Sotos syndrome. Specific areas of cognitive ability and/or disability were reported in three other studies (Cole & Hughes, 1994; Fickie et al., 2011; Varley & Crnic, 1984). All of the studies reported non-verbal reasoning as a particular area of weakness. However, the degree of ability in the specific areas that were mentioned in each of the studies was not reported in a quantitative format. As a result it is difficult to compare whether participants from each of these studies were performing at a similar ability level and the extent to which the abilities in specific cognitive domains deviated from the general ability of each participant.

In summary, the primary focus of previous research reporting data relating to cognition in Sotos syndrome has been to investigate level of intellectual functioning. This has identified that the majority of individuals with Sotos syndrome have intellectual disability (IQ < 70) or are in the borderline range (IQ = 70 – 84). In addition, the profile of intellectual functioning suggests that individuals achieve higher

verbal IQ scores, compared to performance IQ scores. At present, only one case study (Morrow et al., 1990) has reported quantitative scores for specific cognitive subscales.

1.3.4. Language

Language abilities were reported in thirteen studies (see Table 1.2). Finegan et al. (1994) used the largest sample (N = 27) to assess language abilities using various standardised language assessments, including the British Picture Vocabulary Scale (BPVS) (Dunn, Dunn, Whetton, & Pintilie, 1982) and the Test for the Reception of Grammar (TROG) (Bishop, 1989). Language abilities were examined in relation to general intellectual ability in order to determine whether language development was consistent with general level of intellectual ability within the Sotos syndrome population. The findings from this study indicated that language abilities were consistent with FSIQ scores and that participants exhibited no relative deficits in language comprehension or language expression. In this study, language abilities were compared to a control group matched for IQ and no significant difference between language impairment in the two groups was identified. Therefore, it is important to consider the language development of individuals with Sotos syndrome in the context of general intellectual development in order to establish whether language impairments are syndrome-specific. This study scored 9.5 on the quality checklist and the research is therefore of a high standard.

Delays in speech and communication were reported in four studies (Cole & Hughes, 1994; Livingood & Borengasser, 1981; Mauceri et al., 2000; Sotos et al., 1964), indicating that speech and communication is delayed, when compared to language development in typically developing children. However, as level of

intellectual functioning was not reported, it is difficult to establish whether delays were relative or absolute. Ball, Sullivan, Dulany, Stading, and Schaefer (2005) found that participants had both expressive and receptive language impairments. However, Mouridsen and Hansen (2002), Scarpa, Faggioli, and Voghenzi (1994) and Zechner et al. (2009) reported delays in expressive but not receptive language. Park, Lee, Sohn, and Ko (2014), reported cases of a mother and her 9 month old daughter with Sotos syndrome. The daughter was reported as having both receptive and expressive language difficulties whereas the mother only showed difficulty with expressive language. In all of these studies, language abilities were not compared to a control group matched for intellectual functioning and were often based on clinical observation. It is therefore difficult to establish whether language difficulties are specific to the Sotos syndrome population or whether these difficulties are a consequence of the associated intellectual disability and developmental delay.

Although speech and language delays have been reported in eleven of the thirteen studies that assessed language abilities, Finegan et al. (1994) assessed language abilities using a comprehensive battery of language assessments and the findings from this study suggest that individuals with Sotos syndrome display language abilities that are consistent with their general level of intellectual functioning. Furthermore, one case study reported verbal comprehension as a relative strength (Fickie et al., 2011). Findings from the studies that reported speech and language delays indicate that individuals with Sotos syndrome may display speech and language delays, when compared to typically developing individuals. Specifically, individuals with Sotos syndrome appear to experience greater difficulty with expressive, compared to receptive language.

1.3.5. Aggression and tantrums

Aggressive behaviour and/or tantrums were reported in six studies (Compton et al., 2004; Gajre, Mhatre, & Vijaykumar, 2015; Gomes-Silva, Ruviére, Segatto, De Queiroz, & De Freitas, 2006; Mauceri et al., 2000; Rutter & Cole, 1991; Trad, Schlefer, Hertzig, & Kernberg, 1991) and were assessed through parental report or psychiatric assessment (see Table 1.3). Of these studies, five employed a case study design and only one of the case studies used a female participant (Trad et al., 1991), despite the syndrome affecting males and females equally. In the group study (Rutter & Cole, 1991), parents were asked to describe the behavioural and emotional problems experienced by their child. Thirteen of the sixteen participants were described as having tantrums in the home environment. However, participants may have come to medical attention as a result of behavioural issues so this sample may not be representative of the Sotos syndrome population.

It is important to note that all of the participants reported to have these behavioural issues were children. Consequently, no research has investigated whether these behavioural issues persist during adulthood. As children with Sotos syndrome are often large for their age, behavioural issues may be considered more problematic by others when the child is compared to another child of similar age and/or size. None of the studies used a control group or standardised assessments so it is difficult to establish whether children with Sotos syndrome display significantly more aggressive behaviour and/or tantrums than other children of similar intellectual ability.

1.3.6. Autistic features

Autistic features were reported in four studies (see Table 1.4). One study investigated behaviour in a case series of twelve individuals with Sotos syndrome and reported autistic features in five of these participants (Zappella, 1990). Autistic features were assessed based on clinical observation. A clinical diagnosis of autism spectrum disorder (ASD) was reported in two case studies (Morrow et al., 1990; Mouridsen & Hansen, 2002) of young male participants (4y 11m and 3y 4m, respectively). In addition, pervasive developmental disorder (PDD) was reported in a case study (Trad et al., 1991) of a young female participant (3y 11m). This suggests that ASD may be prevalent in individuals with Sotos syndrome. However, this has not been compared with prevalence of ASD within the intellectual disabilities population and no systematic study in this area has yet been conducted.

1.3.7. Attention deficit hyperactivity disorder (ADHD)

Of the group studies that assessed behaviour, two reported a high prevalence of ADHD (see Table 1.5). Finegan et al. (1994) found that ten of the total twenty-seven participants had ADHD (as measured by parental report) and Varley and Crnic (1984) found that three of the total eleven participants met diagnostic criteria for ADHD. However, De Boer et al. (2006) found no significant difference between mean scores of the Sotos group (n = 20) and the control group, on the 18-item Dutch ADHD list. In addition, only four participants scored in the clinical range for ADHD. Within the case studies that measured behavioural features of individuals with Sotos syndrome, a total of five participants were reported to have a clinical diagnosis of ADHD (Gajre et al., 2015; Gosalakkal, 2004; Mauceri et al., 2000; Mouridsen &

Hansen, 2002). In addition, two cases were reported of individuals who were inattentive, hyperactive and demonstrated a lack of inhibition (Mouridsen & Hansen, 2002; Trad et al., 1991). Findings from these studies suggest that ADHD may be a common behavioural problem associated with Sotos syndrome, though no systematic study in this area has yet been conducted.

1.3.8. Anxiety

Anxiety has been reported in two studies (see Table 1.6). Sarimski (2003) measured anxiety using The Children's Social Behaviour Questionnaire (CBSQ) and found that children with Sotos syndrome displayed significantly more separation anxiety and had a tendency to be more anxious in new situations when compared to a control group matched for age and cognitive ability. Furthermore, the Sotos syndrome group had higher scores in insecure/anxious behaviour (as measured by the Nisonger Child Behaviour Rating Form (NCBRF)), when compared to the matched control group. In addition, Rutter and Cole (1991) found that ten of the total sixteen participants had some form of phobia, as described through parental report. This suggests that anxious behaviour may be more prevalent within the Sotos syndrome population, compared to children of similar intellectual ability. There may also be a specific profile of anxious behaviour in individuals with Sotos syndrome but this needs to be explored in further research.

1.3.9. Longitudinal studies

One of the cardinal features of Sotos syndrome is intellectual disability and this is often associated with developmental delay. Therefore, children with the

syndrome may follow a distinct developmental trajectory. In order to identify the progression of cognitive development in individuals with Sotos syndrome, it is important to investigate developmental changes, over time. One study (Bloom et al., 1983) provided longitudinal data for a small number of participants (N = 10). Cognitive tests were administered to all participants and eight of these were also assessed in at least one-follow up session. The age at which participants were assessed ranged from 1y – 13y 6m. Broadly, the study found that intellectual abilities improved with age and that IQ scores were in the range of 56 – 113. Each participant was administered different cognitive assessments at various ages so it is difficult to establish whether a consistent pattern of cognitive abilities exists in this population. To date, this is the only published longitudinal study that has reported data relating to cognitive abilities in individuals with Sotos syndrome.

1.3.10. Participants

Within the thirty-four studies that were included in this review, cognitive abilities and/or behavioural features were reported for a total of 247 participants. The largest group study included a total of forty-one participants (Cole & Hughes, 1994). Of the studies that reported group data, none of the participants were adults. Cognitive and/or behavioural data were presented in seven case reports of adults with Sotos syndrome (Bale et al., 1985; Compton et al., 2004; Fickie et al., 2011; Ginter & Scott, 1975; Park et al., 2014; Tei, Tsuneishi, & Matsuo, 2006; Zechner et al., 2009). The fact that there is such a small amount of data relating to cognition in adults with Sotos syndrome means that it is difficult to establish whether there is a specific profile or trajectory of cognitive ability associated with the syndrome.

Less than half of the studies (n = 14) were published after identification of the genetic abnormality associated with Sotos syndrome. Of these studies, eight (Ball et al., 2005; De Boer et al., 2006; Fickie et al., 2011; Horikoshi et al., 2006; Okamoto et al., 2010; Park et al., 2014; Tei et al., 2006; Zechner et al., 2009) reported the number of participants with a confirmed genetic diagnosis of Sotos syndrome.

Table 1.1. Summary of studies measuring IQ in Sotos syndrome (*n* = 25)

Author, country of study, year of publication	Sample size (n)	Gender	Mean age in years, months (range)	Cognitive assessment	Findings	Quality score (0 – 10)
Bale et al., USA, (1985)	3	3 (F)	(7y – 35y)	Wechsler Intelligence Scale for Children-Revised (WISC-R); Bayley Scales of Infant Development; Wechsler Adult Intelligence Scale (WAIS).	Case 1: WISC-R full scale IQ = 91, verbal IQ = 103, performance IQ = 87. Case 2: at 15 months, functional age on the Bayley cognitive scale was on the 9 month level. Developmental quotient = 61. Case 3: no developmental delay noted as a child. At age 30, WAIS full scale IQ score = 110, verbal IQ = 122, performance IQ = 93.	7.5
Bloom et al., USA, (1983)	10	7 (M) 3 (F)	Not recorded* (1y – 13y 6m)	Bayley Scales of Infant Development; Cattell Infant Intelligence Scale; Stanford Binet Intelligence Scale, Form L-M; Leiter International Performance Scale, Arthur Adaptation; Wechsler Intelligence Scale for Children-Revised (WISC-R).	Longitudinal study reporting findings from different assessments administered between the ages of 1:11 and 13:6. Six participants had one follow-up assessment and two had two follow-up assessments. Full scale IQ scores ranged from 59 – 113.	7.5

Compton et al., USA, (2004)	1	1 (M)	20y	Wechsler Abbreviated Scale of Intelligence (WASI).	Full scale IQ = 94, verbal IQ = 100, performance IQ = 88.	7.5
de Boer et al., Netherlands, (2006)	21**	Not recorded*	Not recorded*	Dutch adaptations of Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R); Wechsler Intelligence Scale for Children-Revised (WISC-R); Wechsler Adult Intelligence Scale (WAIS).	Mean full scale IQ of 76 (*SD* = 16), mean verbal IQ of 79 (*SD* = 14) and mean performance IQ of 77 (*SD* = 18). No significant difference between IQ scores of NSD1 mutation and NSD1 non-mutation patients.	8.6
Fickie et al., USA, (2011)	1***	1 (F)	63y	Wechsler Adult Intelligence Scale (WAIS-III).	Full scale IQ = 78.	8.3
Finegan et al., UK, (1994)	27	14 (M) 13 (F)	9y 3m (5y – 16y)	Age-appropriate versions of the UK adaptations of the Wechsler scales; Full Scale IQ (FSIQ) estimated from a short form.	Mean full scale IQ = 73.67 (*SD* = 20.62). Scores ranged from 21 – 103. Six participants had an IQ < 70.	9.5
Ginter & Scott, (1975)	2	1 (M) 1 (F)	(13y 9m – 27y)	Wechsler Adult Intelligence Scale (WAIS); Wechsler	Case 1: WAIS full scale IQ = 85, verbal IQ = 96, performance IQ = 72. Wechsler memory quotient = 79. Bender-Gestalt standard error	4.2

				Memory Scale; Bender-Gestalt Test.	score = 79. Case 2: Psychometric testing indicated an IQ of 81.	
Horikoshi et al., Japan, (2006)	3***	3 (M)	(2y – 3y 6m)	Enjouji Developmental Scale for Japanese Children.	Case 1: developmental quotient = 34. Case 2: developmental quotient = 66. Case 3: developmental quotient = 48.	5.1
Jung & Martin, US Virgin Islands, (1969)	1	1 (F)	8y	Wechsler Intelligence Scale for Children (WISC); Draw a Person Test; Bender-Gestalt Test; Grey-Standardised Oral Reading Paragraph Test.	WISC full scale IQ = 69. Draw a person IQ score = 64. Bender-Gestalt score corresponded with her IQ. Reading and arithmetic tests revealed functioning at the beginning first-grader level.	6.7
Leventopoulos et al., Greece, (2009)	19	9 (M) 10 (F)	2y 7m (2m – 12y)	Developmental assessment.	Developmental delay present in 16 participants. Severe mental retardation (IQ < 50) present in 13 participants.	6.8
Mauceri et al., Italy, (2000)	6	5 (M) 1 (F)	(2y – 12y)	Wechsler Intelligence Scale for Children-Revised (WISC-R); Brunet-Lezine Test.	Case 1: WISC-R IQ = 68. Case 2: WISC-R IQ = 40. Case 3: Brunet-Lezine IQ = 46. Case 4: WISC-R verbal IQ = 44. Difficulty with maths. Case 5: WISC-R IQ = 70. Case 6: IQ = 48.	6.7

Mouridsen & Hansen, Denmark, (2002)	2	2 (M)	(3y 4m – 13y)	Bayley Scales of Infant Development; Subtests from Snijders-Oomen Non-Verbal Intelligence Scale for Young Children; Wechsler Intelligence Scale for Children (WISC).	Case 1: moderate mental retardation. Case 2: WISC verbal IQ = 88, performance IQ = 78.	5.8
Okamoto et al., Japan, (2010)	1***	1 (M)	14y	Kyoto Scale of Psychological Development.	Severe mental retardation. Kyoto scale IQ score below 10.	7.5
Patterson et al., USA, (1978)	3	2 (M) 1 (F)	(6y – 10y 8m)	Stanford Binet Intelligence Scale, Form L-M; Leiter International Performance Scale; Wechsler Intelligence Scale for Children-Revised (WISC-R).	Case 1: Stanford Binet IQ = 76. Leiter IQ = 108. Case 2: WISC-R full scale IQ = 75, verbal IQ = 73, performance IQ = 72. Stanford Binet IQ = 90. Case 3: WISC-R full scale IQ = 100, verbal IQ = 100, performance IQ = 101. Stanford Binet IQ = 99.	7.5
Poznanski & Stephenson, USA, (1967)	1	1 (M)	5y 10m	Cattell Intelligence Scale; Stanford Binet Intelligence Scale.	At age 2:6 years, Cattell IQ = 60. At 5:10 years, Stanford Binet IQ = 44.	4.4

Rutter & Cole, UK, (1991)	15	Not recorded*	Not recorded*	Wechsler Intelligence Scale for Children-Revised (WISC-R); Wechsler Preschool and Primary Scale of Intelligence (WPPSI).	87% of participants completed the WISC-R and 13% completed the WPPSI. Full scale IQs ranged from 54 – 96 (*M* = 73.8). Verbal IQs ranged from 47 – 102 (*M* = 76.93) and performance IQs ranged from 51 – 101 (*M* = 74.6).	6.8
Sarimski, Germany, (2003)	27	17 (M) 10 (F)	10y 7m (6y – 15y)	Parental Report; Heidelerger-Kompetenz-Inventar (HKI).	In the mild impairment group (*n* = 16), mean cognitive competence = 185. In the moderate impairment group (*n* = 11), mean cognitive competence = 153.6.	9.5
Scarpa et al., Italy, (1994)	2	1 (M) 1 (F)	(5y – 7y)	Wechsler Preschool and Primary Scale of Intelligence (WPPSI); Brunet-Lezine Test.	Case 1: WPPSI IQ = 58. Case 2: Brunet-Lezine IQ = 45.	5.8
Sobel, USA, (1995)	1	1 (F)	8y	Cattell Intelligence Scale; Vineland Social Maturity Scale.	At 22 months of age, she was delayed by approximately 4 months in mental and social age. On examination at 8 years of age, she was of normal intelligence.	5

Sotos et al., USA, (1964)	5	3 (M) 2 (F)	(2y – 11y 6m)	Stanford Binet Intelligence Scale; Clinical Observation.	Case 1: Stanford Binet IQ = 70. Case 2: Stanford Binet IQ = 70. Case 3: Stanford Binet IQ = 72. Case 4: intelligence judged to be borderline. Case 5: several months retarded in mental development.	7.5
Tei et al., Japan, (2006)	3***	2 (M) 1 (F)	(3y 4m – 37y)	Wechsler Intelligence Scale for Children (WISC-III); Development Test (New-K Style for the Japanese).	Case 1: WISC full scale IQ = 70. Case 2: development test was in the normal limit. DQ = 85. Case 3: no intelligence test performed. Had graduated from a regular senior high school with lower achievement.	7.5
Trad et al., USA, (1991)	1	1 (F)	3y 11m	Stanford Binet Intelligence Scale.	Stanford Binet IQ = 88.	6.7
Varley & Crnic, USA, (1984)	11	6 (M) 5 (F)	9y 5m (5y 11m – 13y 11m)	Wechsler Intelligence Scale for Children-Revised (WISC-R); Stanford Binet Intelligence Scale; Bayley Mental Scale.	Each participant was administered one of the cognitive assessments. 54% completed the WISC-R, 28% the Stanford Binet Intelligence Scale and 18% the Bayley Mental Scale. IQ scores ranged from 40 – 85 with a median of 62.	8.1

Villaverde et al., USA, (1971)	2	2 (M)	(9y – 13y 7m)	Stanford Binet Intelligence Scale; Columbia Mental Maturity Scale; Vineland Social Maturity Scale.	Case 1: at 3 years of age, Stanford Binet IQ = 56. At 9 years of age, Stanford Binet IQ = 56. Mental age measured by the Columbia Mental Maturity Scale = 3:8. On the Vineland Social Maturity Scale, SQ = 49. Case 2: Stanford Binet IQ = 48. Vineland Social Maturity SQ = 67.	8.3
Zechner et al., Germany, (2009)	3***	1 (M) 2 (F)	(8y 6m – 36y)	Wechsler Intelligence Scale for Children (WISC), German Adaptation.	Case 1: at 6 years, WISC IQ = 100 on verbal subtests and WISC IQ = 85 on non-verbal subtests. Case 2: making good-average progress in a normal primary school. Case 3: received special support and had been “slow” in elementary school. Graduated basic secondary school.	7.5

*Demographic data were only presented for all participants within the study. Not all participants completed the cognitive assessments but the study does not report which of the participants took part.

**7 participants had a confirmed genetic diagnosis of Sotos syndrome.

***All participants had a confirmed genetic diagnosis of Sotos syndrome.

Table 1.2. Summary of studies measuring language abilities and/or specific cognitive abilities in Sotos syndrome (*n* = 13)

Author, country of study, year of publication	Sample size (n)	Gender	Mean age in years, months (range)	Cognitive assessment	Findings	Quality score (0 – 10)
Ball et al., USA, (2005)	16**	Not recorded*	6y 3m (1y 5m – 12y 3m)	Buffalo III Voice Screening Profile; Clinical Evaluation of Language Fundamentals Three Screening Test; Goldman-Fristoe Test of Articulation 2; Kahn-Lewis Phonological Analysis 2; Mean Length of Utterance in Morphemes; Peabody Picture Vocabulary Test (III); Preschool Language Scale 3; Social Skills Rating System; Type-token Ration; Index of Augmented Speech Comprehensibility in Children.	Participants exhibited expressive and receptive language impairments, articulation impairments, voice impairments and stuttering.	8.2
Cole & Hughes, UK, (1994)	41	Not recorded*	Not recorded*	Parental recall.	Early delays in speech and performance skills. Older children had particular difficulties with short term memory, abstract	5.6

					ideas and practical reasoning. Numeracy was reported as the weakest area in older children, regardless of IQ.	
Fickie et al., USA, (2011)	1***	1 (F)	63y	Wechsler Adult Intelligence Scale (WAIS-III).	The patient's strengths were in verbal comprehension and behavioural regulation. Areas of weakness included working memory, interpretation of nonverbal information and processing speed.	8.3
Finegan et al., UK, (1994)	27	14 (M) 13 (F)	9y 3m (5y – 16y)	British Picture Vocabulary Scale Long Form; Expressive One-Word Picture Vocabulary Test, Upper Extension; Test for the Reception of Grammar; Word Structure Subtest of Clinical Evaluation of Language Fundamentals-Revised.	Language abilities were consistent with FSIQ scores. No relative deficits observed in language expression or comprehension. No significant difference in language abilities of Sotos group and comparison group when IQ was controlled for.	9.5
Livingood & Borengasser, (1981)	1	1 (F)	1y 11m	Bayley Scales of Infant Development; Alpern-Boll Developmental Profile.	Bayley scales reflected mental functioning at the 15 month level and motor development at the 18 month level. Mother reported: physical	8.3

					age, self-help age and social age = 18 month level, academic age = 15 month level and communication age = 10 month level.	
Mauceri et al., Italy, (2000)	4	3 (M) 1 (F)	(2y – 12y)	Brunet-Lezine Test; Clinical Observation.	Case 1: poor repetitive and expressive language. Case 3: delayed language acquisition. Case 4: mild delay in language. Case 6: severe deficit in language.	6.7
Morrow et al., USA, (1990)	1	1 (M)	4y 11m	Stanford Binet Intelligence Scale.	Stanford Binet scores: verbal reasoning = 96, abstract/visual = 94; quantitative reasoning = 98, short-term memory = 88. Exhibited both immediate and delayed echolalia.	7.5
Mouridsen & Hansen, Denmark, (2002)	1	1 (M)	3y 4m	Bayley Scales of Infant Development; Reynell Developmental Language Scales.	Expressive language was at 12 – 18 months level.	5.8
Park et al., Korea, (2014)	2***	2 (F)	(9m – 32y)	Bayley Scales of Infant and Toddler Development.	Case 1: 2 month delay in receptive language, 6 month delay in expressive language. Cognitive development delayed by 2 months.	7.5

					Case 2: normal intelligence but difficulty with expressive language.	
Scarpa et al., Italy, (1994)	2	1 (M) 1 (F)	(5y – 7y)	Brunet-Lezine Test.	Case 1: delayed expressive language. Case 2: persistent language deficit.	5.8
Sotos et al., USA, (1964)	3	2 (M) 1 (F)	(7y – 11y 6m)	Clinical Observation.	Case 1: failed to speak until 3 years of age. Case 2: did not speak until 3 years of age. Case 3: immature speech.	7.5
Varley & Crnic, USA, (1984)	11	6 (M) 5 (F)	9y 5m (5y 11m – 13y 11m)	Wechsler Intelligence Scale for Children-Revised (WISC-R); Stanford Binet Intelligence Scale; Bayley Mental Scale.	Specific cognitive difficulties observed in language processing, attention span, concentration and visual-perceptual skills.	8.1
Zechner et al., Germany, (2009)	1***	1 (M)	10y 8m	Clinical Observation.	Expressive language delay.	7.5

*Demographic data were only presented for all participants within the study. Not all participants completed the cognitive assessments but the study does not report which of the participants took part.

**3 participants had a confirmed genetic diagnosis of Sotos syndrome.

***All participants had a confirmed genetic diagnosis of Sotos syndrome.

Table 1.3. Summary of studies measuring aggression and tantrums in Sotos syndrome (*n* = 6)

Author, country of study, year of publication	Sample size (n)	Gender	Mean age in years, months (range)	Assessment	Findings	Quality score (0 – 10)
Compton et al., USA, (2004)	1	1 (M)	20y	Psychiatric Assessment.	Admitted to an inpatient psychiatric facility due to the onset of psychotic symptoms (delusions and hallucinations). Parents reported a long history of angry outbursts and tantrums. Had received counselling for angry outbursts since 4 years of age. Quality of thinking was consistent with an underlying thought disorder.	7.5
Gajre et al., India, (2015)	1	1 (M)	11y	Parental and Teacher Rating NICHQ Vanderbilt Assessment Scales.	Behavioural problems included temper tantrums.	4.2
Gomes-Silva et al., Brazil, (2006)	1	1 (M)	3y 7m	Parental Report.	The mother reported that the patient had behaviour problems and was aggressive.	5
Mauceri et al., Italy, (2000)	3	3 (M)	(2y – 8y)	Parental Report; Teacher Report.	Case 1: parents observed behavioural problems. Poor social behaviour and aggressiveness was triggered	6.7

					when he was contradicted. Demonstrated pyromania. Case 2: teachers reported that he was aggressive towards the other children. Case 3: demonstrated aggressiveness.	
Rutter & Cole, UK, (1991)	16	9 (M) 7 (F)	9y 4m (5y 11m – 14y 9m)	Rutter Questionnaires; Semi-Structured Interview with Parent.	On the Parent Questionnaire, scores ranged from 2 – 42 with a mean of 20.4. A Teacher Questionnaire was completed for 14 of the children. Scores ranged from 2 – 23 with a mean of 8.7. Parents reported that 13 of the children had problems with tantrums, 11 had sleep problems, 5 displayed precocious sexual behaviour, 10 had some form of phobia, 8 displayed ritualistic behaviour and 8 were obsessive about routines.	6.8
Trad et al., USA, (1991)	1	1 (F)	3y 11m	Psychiatric Assessment; Social Worker Report; DSM-III-R.	Her social worker noted that she displayed emotional impairment and either played alone or was aggressive with other children.	6.7

Table 1.4. Summary of studies measuring autistic features in Sotos syndrome (*n* = 4)

Author, country of study, year of publication	Sample size (n)	Gender	Mean age in years, months (range)	Assessment	Findings	Quality score (0 – 10)
Morrow et al., USA, (1990)	1	1 (M)	4y 11m	Clinical Observation.	Behaviour was characterised by repetitive and stereotypic head-banging and hair-pulling. Had previously demonstrated repetitive stroking of objects. Impairment in ability to interact socially. Authors report that the patient meets criteria for ASD.	7.5
Mouridsen & Hansen, Denmark, (2002)	1	1 (M)	3y 4m	ICD-10; Clinical Observation.	Case 1: met the ICD-10 diagnostic criteria for childhood autism. Showed repetitive and stereotypic behaviours as well as severe difficulties with reciprocal social interaction.	5.8
Trad et al., USA, (1991)	1	1 (F)	3y 11m	Psychiatric Assessment; Social Worker Report; DSM-III-R.	Met DSM-III-R criteria for Pervasive Developmental Disorder (PDD).	6.7
Zappella, Italy, (1990)	12	11 (M) 1 (F)	6y 9m (3y – 12y)	Behavioural Observation.	Five participants showed marked autistic behaviour.	7.5

Table 1.5. Summary of studies measuring attention deficit hyperactivity disorder (ADHD) in Sotos syndrome (*n* = 8)

Author, country of study, year of publication	Sample size (n)	Gender	Mean age in years, months (range)	Assessment	Findings	Quality score (0 – 10)
de Boer et al., Netherlands, (2006)	28**	Not recorded*	Not recorded*	Child Behaviour Checklist (CBCL); Young Adult Behaviour Checklist (YABCL); 18-item Dutch ADHD list; Dutch Questionnaire Derived from the American Parent and Teacher Questionnaire; Vineland Screener.	Four participants completed the CBCL (2 – 3 years). Of these, one scored in the clinical range for internalising behaviour problems. Nineteen participants completed the CBCL (4 – 18 years). Mean scores for total problems, internalising and externalising scales were significantly higher than the mean score for normative data. Five participants completed the YABCL. Of these, two scored in the clinical range for total problems. Twenty participants completed the ADHD-list. Mean scores of the whole group were not significantly different from the scores of the control group. Twenty-one participants completed the Vineland Screener. Mean developmental ages were 1y 7m, 1y 7m and 2y 7m lower than the mean chronological ages for communication, daily living skills and social competence, respectively.	9.6

Finegan et al., UK, (1994)	27	14 (M) 13 (F)	9y 3m (5y – 16y)	Child Behaviour Checklist (CBCL); Teacher Report Form; Aberrant Behaviour Checklist; ADHD Rating Scale.	CBCL total scores were in the clinical range for 18 of the children by parent report and 17 by teacher report. Parents reported 10 participants as having ADHD.	9.5
Gajre et al., India, (2015)	1	1 (M)	11y	DSM-5; Parental and Teacher Rating NICHQ Vanderbilt Assessment Scales.	Behavioural problems included inattention, hyperactivity and impulsiveness. Behavioural assessment led to a diagnosis of ADHD. Received behaviour modification therapy.	4.2
Gosalakkal, UK, (2004)	1	1 (M)	8y	Neuropsychological Evaluation.	Previously been diagnosed with ADHD. Current evaluation suggests possible ADHD and difficulty with impulse control.	1.7
Mauceri et al., Italy, (2000)	3	3 (M)	(2y – 12y)	Parental Report; Teacher Report.	Case 2: teachers reported that he was inattentive and hyperactive. Case 3: had a diagnosis of ADHD. Case 4: had a diagnosis of ADHD.	6.7

Mouridsen & Hansen, Denmark, (2002)	1	1 (M)	13y	ICD-10; Clinical Observation.	Case 2: attended a special education program for children with ADHD and later attended a class for children with autistic features. He was inattentive, hyperactive and difficult to manage.	5.8
Trad et al., USA, (1991)	1	1 (F)	3y 11m	Psychiatric Assessment; Social Worker Report; DSM-III-R.	Demonstrated lack of inhibition and impulsive behaviour.	6.7
Varley & Crnic, USA, (1984)	11	6 (M) 5 (F)	9y 5m (5y 11m – 13y 11m)	Psychiatric Evaluation; Achenbach Revised Child Behaviour Profile.	All participants had socialisation deficits. Nine met criteria for a psychiatric disorder. Of these, three had ADHD and two had organic personality syndrome. The scales most frequently elevated on the Achenbach Child Behaviour Profile were hyperactivity (*n* = 7), withdrawn/schizoid (*n* = 6), somatic complaints (*n* = 3) and obsessive (*n* = 3).	8.1

*Demographic data were only presented for all participants within the study. Not all participants completed the behavioural assessments but the study does not report which of the participants took part.

**11 participants had a confirmed genetic diagnosis of Sotos syndrome.

Table 1.6. Summary of studies measuring anxiety in Sotos syndrome (*n* = 2)

Author, country of study, year of publication	Sample size (n)	Gender	Mean age in years, months (range)	Assessment	Findings	Quality score (0 – 10)
Rutter & Cole, UK, (1991)	16	9 (M) 7 (F)	9y 4m (5y 11m – 14y 9m)	Rutter Questionnaires; Semi-Structured Interview with Parent.	Parents reported that 10 of the children had some form of phobia, 8 displayed ritualistic behaviour and 8 were obsessive about routines.	6.8
Sarimski, Germany, (2003)	27	17 (M) 10 (F)	10y 7m (6y – 15y)	Parental Report; Heidelerger-Kompetenz-Inventar (HKI); Children's Social Behaviour Questionnaire (CSBQ); Nisonger Child Behaviour Rating Form (NCBRF).	According to the CSBQ, participants showed significantly more separation anxiety (p = .005) and tended to be more anxious (p = .08), compared to a control group of children with intellectual disabilities matched for age and cognitive ability. Participants with Sotos syndrome had higher scores in insecure/anxious behaviour (p < .05) compared to the control group.	9.5

1.4. Discussion

The primary aim of this review was to synthesise and critically evaluate all published literature providing data on cognition and behaviour in individuals with Sotos syndrome in order to establish current understanding of these facets of the syndrome. The specific research questions were to establish: 1) the degree of intellectual disability in individuals with Sotos syndrome; 2) whether there is evidence for a profile of verbal and non-verbal cognitive abilities; 3) whether there are common behavioural problems associated with Sotos syndrome, such as psychiatric problems and issues with temperament. The quality of the identified research was assessed using a standardised checklist and scores were rated out of 10. The mean score was 6.8 (*SD* = 1.69) and scores ranged from 1.7 – 9.5. The findings from the published literature were extracted and summarised in order to provide a comprehensive overview of current understanding of cognition and behaviour in Sotos syndrome.

Broadly, the literature suggests that the majority of individuals with Sotos syndrome have mild intellectual disability (IQ = 50 – 69) or are in the borderline range (IQ = 70 – 84) and this evidence supports the inclusion of intellectual disability as one of the main diagnostic criteria of the syndrome. In addition, findings from research using standardised intelligence tests indicate that verbal IQ scores are consistently higher than performance IQ scores. Language abilities are comparable with general level of intellectual functioning (Finegan et al., 1994). Language delays are more commonly reported in expressive, compared to receptive language (Mouridsen & Hansen, 2002; Park et al., 2014; Scarpa et al., 1994). Behavioural problems that may be common in Sotos syndrome are ASD (Morrow et al., 1990; Zappella, 1990), ADHD (Finegan et al., 1994; Varley & Crnic, 1984), anxiety (Sarimski, 2003) and aggression/tantrums (Compton et al., 2004; Rutter & Cole, 1991). However, no

systematic study has been conducted in relation to these behavioural issues so it is difficult to establish whether there is a specific behavioural profile associated with Sotos syndrome. In addition, prevalence of behavioural problems has not been compared to prevalence within a sample of individuals of similar intellectual ability so it is not clear whether these behavioural issues are syndrome-specific.

This review only included published studies as an aim of the review was to establish current understanding of the literature reporting data on cognition and behaviour in Sotos syndrome. It is important to note that a limitation of this approach is that the review is subject to publication bias. In addition, only papers published in English language were reviewed which means that findings from data published in other languages were automatically excluded from the review.

1.4.1. Cognition in Sotos syndrome

The cognitive literature identified that almost all of the reported cases of Sotos syndrome have intellectual disability. This ranged from mild to severe. The International Statistical Classification of Diseases and Related Health Problems (ICD-10) (World Health Organization, 2004) suggests the following guidelines for classification of the degree of intellectual impairment: borderline intellectual functioning (70 – 84), mild intellectual disability (IQ = 50 – 69), moderate intellectual disability (IQ = 35 and 49) and severe intellectual disability (IQ = 20 – 34). Most of the cognitive data were presented in the form of an IQ score and the research to date has focused on the use of intelligence tests to measure overall level of intellectual functioning. The informative value of a full scale IQ score alone is limited in terms of its contribution to identifying ability in specific cognitive domains. Although this can provide a general indication of intellectual ability, it does not provide any information

relating to strengths or weaknesses in different aspects of cognition. Thus, in order to establish whether individuals with Sotos syndrome have a clear and consistent cognitive profile, it will be necessary to investigate patterns of ability and disability in specific cognitive domains using a standardised battery of cognitive tests. The cognitive profile associated with Sotos syndrome will be investigated in Chapter 3.

1.4.2. Behaviour in Sotos syndrome

Behavioural problems such as aggression/tantrums, ASD, ADHD and anxiety have been reported in fourteen studies of individuals with Sotos syndrome. More than half of these were case studies and as a result, the findings within the behavioural literature are based on a limited sample size. It has been suggested that children with Sotos syndrome may display more behavioural problems, compared to typically developing children (Cole & Hughes, 1994; Sarimski, 2003). This could be due to the fact that children with Sotos syndrome are usually large for their age and are therefore often mistaken as older and more able than their actual developmental level. This assumption can lead to frustration for the child which then manifests itself in behavioural problems. In order to determine whether behavioural problems are syndrome-specific, it is essential for behavioural features to be assessed in a representative sample, using standardised measures.

1.4.3. Limitations of reviewed studies

More than half of the studies included in this review were published prior to identification of the NSD1 genetic abnormality which was identified in 2002 (Kurotaki et al., 2002). It is therefore not possible to ascertain how many of the

participants were NSD1-positive. Tatton-Brown, Douglas, Coleman, Baujat, Cole, et al. (2005) investigated 239 cases of Sotos syndrome with NSD1 mutations. This study provided a detailed understanding of the clinical phenotype of individuals with Sotos syndrome who were identified as having the NSD1 abnormality. However, the main aim of this research was to investigate the whole clinical phenotype (facial dysmorphism, childhood overgrowth, scoliosis etc.) so cognition and behaviour were not explored in detail. As genetic testing is now more widely available, Sotos syndrome is only diagnosed if an individual has an NSD1 abnormality and meets the clinical criteria for the syndrome. This means that Sotos syndrome can be diagnosed objectively and future research can investigate the cognitive and behavioural profiles of individuals who have the NSD1 abnormality associated with Sotos syndrome.

As stated by Cole and Hughes (1994), a number of patients reported within the literature have come to medical attention due to developmental delay. Consequently, this may have resulted in a bias for recruitment of participants with more severe intellectual disability and/or behavioural problems. As awareness of Sotos syndrome is fairly limited, this is a difficult issue to overcome. Any individuals who do not present with significant symptoms or who are not assessed by a clinician who is aware of the syndrome, are less likely to be given a diagnosis of Sotos syndrome. Thus, until there is greater awareness of the syndrome, it will be difficult to assess cognitive and behavioural facets in a large and fully representative sample.

A fundamental methodological issue present in most of the studies included in this review is the limited sample size. As Sotos syndrome has a relatively low incidence, there is a limited population from which to recruit participants. It is therefore important for future research to utilise all available recruitment strategies in order to collect a large and representative dataset. A further methodological problem,

identified in more than half of the studies, was a failure to use standardised measures to assess cognition and/or behaviour or, in some cases, a failure to report which measures were used. Findings from these studies lack validity as it is not clear whether the results were obtained using standardised measures. As a result, these studies tended to score lower on the quality assessment checklist.

1.4.4. Areas of interest for future research

The overall aim of the experimental work presented in this thesis is to advance understanding of the cognitive and behavioural phenotype of Sotos syndrome. A number of cognitive and behavioural features have been identified in individuals with Sotos syndrome such as language difficulties (Ball et al., 2005), ADHD (Varley & Crnic, 1984) and ASD (Zappella, 1990). However, these are based on limited samples. It is therefore essential for future research to explore these facets in a representative sample, using the same standardised measures for all participants. In particular, research with adults would inform understanding of the trajectory of cognitive development in Sotos syndrome, an area in which there is currently very little published research.

The suggestion that verbal IQ scores are higher than performance IQ scores in Sotos syndrome is particularly interesting as the opposite is often reported in individuals with ASD (Happe, 1994; Shah & Frith, 1993). As ASD has been reported in some individuals with Sotos syndrome, future research could investigate the direction of the discrepancy between verbal IQ and performance IQ in individuals with a diagnosis of Sotos syndrome who have high levels of autistic traits, or even a comorbid diagnosis of ASD. In addition, the suggestion that ASD may be linked to Sotos syndrome is based on limited data and therefore, future research should

investigate co-morbidity in a larger sample. The prevalence and profile of autistic features in Sotos syndrome will be investigated in Chapters 2 and 5.

Much of the literature included in this review has investigated intellectual functioning in Sotos syndrome, as opposed to focusing on specific cognitive abilities. In Chapter 3, the individual components, or subscales, that comprise general intelligence scores will be assessed within this population in order to establish whether individuals with Sotos syndrome display a consistent pattern of ability and/or disability in distinct cognitive domains. Furthermore, memory will be explored in Chapter 4. Specifically, a cognitive profile can inform education and allow appropriate teaching techniques to be implemented, in order to enhance learning and development. In addition, awareness of associated behavioural, social and emotional problems can lead to quicker identification and the implementation of effective management strategies.

Cognitive and behavioural phenotyping of genetic syndromes associated with intellectual disability can be extremely beneficial for individuals affected by these syndromes as it enables families to be aware of the likely strengths and difficulties that an individual with a diagnosis of a genetic syndrome may experience. For example, the cognitive and behavioural phenotype of Williams syndrome has been well-researched and broadly, the phenotype is characterised by hypersociability, relative strength in language abilities and relative weakness in visuospatial skills (Bellugi, Lichtenberger, Jones, Lai, & George, 2000; Martens, Wilson, & Reutens, 2008). Sotos syndrome has a similar prevalence to that of Williams syndrome yet the phenotype of Sotos syndrome is considerably under-researched in comparison to Williams syndrome.

1.4.5. Conclusion

In summary, during the fifty-one years since the initial recognition of Sotos syndrome, a total of thirty-four papers reporting data on cognition and/or behaviour in Sotos syndrome have been published in peer-reviewed journals. The current literature supports the view that a significant number of individuals with Sotos syndrome have intellectual disability (IQ < 70) and nearly all participants had an FSIQ score < 100. The highest reported FSIQ score was 113 (Bloom et al., 1983) and the lowest was 21 (Finegan et al., 1994), indicating significant variability in level of intellectual functioning within the Sotos syndrome population. Few studies have explored specific cognitive abilities but there is evidence to suggest that verbal IQ scores may be higher than performance IQ scores. Language abilities seem to be consistent with general level of intellectual functioning. Fourteen studies have provided data on behavioural features in Sotos syndrome and the findings suggest that there may be a high prevalence of ADHD, anxiety, aggression/tantrums and ASD within this population. Although a range of studies have provided insight into cognition and behaviour in individuals with Sotos syndrome, syndrome-specific cognitive and behavioural profiles have not yet been fully specified. Overall, the findings from this review demonstrate the need for further research in this considerably under-researched population.

Chapter 2: Characteristics of autism spectrum disorder in Sotos syndrome

2.1. Introduction

The findings from the systematic review presented in Chapter 1 indicate a potential association between Sotos syndrome and ASD, as evidenced by case reports of individuals with diagnoses of Sotos syndrome and ASD (see section 1.3.6). In order to further understanding of the relationship between Sotos syndrome and ASD, this chapter aims to investigate the prevalence and profile of ASD symptomatology within a large and representative sample of adults and children with Sotos syndrome.

2.1.1. Autism spectrum disorder (ASD)

ASD is a behaviourally defined developmental disorder associated with social communication impairment and restricted interests and repetitive behaviours (DSM-5) (American Psychiatric Association, 2013). ASD is a spectrum disorder and consequently, there is significant heterogeneity and variability between individuals with ASD. It is estimated that ASD occurs in approximately 1% of the population (Baird et al., 2006; Baron-Cohen et al., 2009). Idiopathic ASD refers to individuals who have a primary diagnosis of ASD and for which the underlying cause is unknown. In contrast, syndromic ASD refers to individuals who have a diagnosis of a specific syndrome and also have a co-morbid diagnosis of ASD. Neurodevelopmental disorders associated with a high prevalence of ASD can be considered as syndromic causes of ASD (Abrahams & Geschwind, 2008; Betancur, 2011).

2.1.2. ASD in genetic syndromes

ASD symptomatology has been reported in a number of congenital syndromes, including Fragile X (Kaufmann et al., 2004), Cornelia de Lange (Moss, Howlin,

Magiati, & Oliver, 2012) and Angelman syndrome (Peters, Beaudet, Madduri, & Bacino, 2004). It has been suggested that approximately 10 – 20% of cases of ASD are caused by genetic syndromes, cytogenetics lesions and rare *de novo* mutations (Abrahams & Geschwind, 2008). Consequently, a number of aetiological genetic pathways may be implicated in ASD (Abrahams & Geschwind, 2008; Zhao et al., 2007). Thus, investigation of the association between ASD and genetic syndromes is particularly valuable in identifying genetic mechanisms associated with ASD. Furthermore, distinct ASD phenotypes may be associated with each genetic syndrome (Moss & Howlin, 2009). It is therefore important to establish the profile of autistic symptomatology within a syndrome as this will facilitate understanding of both autism and genetic syndromes.

A recent systematic review and meta-analysis investigated the prevalence of reported ASD symptomatology in a range of genetic syndromes (Richards, Jones, Groves, Moss, & Oliver, 2015). Twelve syndromes were included in this review and a quality-weighted effect prevalence was generated for each of the syndromes. This was based on the reported prevalence of ASD in the relevant studies for each of the syndromes and adjusted, based on the quality ratings of the studies. A quality checklist was generated by the authors using existing standardised quality criteria for intervention and prevalence studies. Higher quality studies received greater weighting in the prevalence estimates. The prevalence estimates of the number of individuals who met clinical cut-off for ASD ranged from 11% in 22q11.2 deletion syndrome to 61% in Rett syndrome and all twelve syndromes had a prevalence estimate significantly above that of the general population. Thus, this review provides evidence for increased prevalence of ASD symptomatology in genetic syndromes and suggests significant variability in prevalence between syndromes. Sotos syndrome was not

included in this review due to a lack of previous research investigating the prevalence of ASD in Sotos syndrome. However, as Sotos syndrome has a genetic cause, it is important to establish the prevalence of ASD within this population in order to determine whether the NSD1 gene could be implicated in ASD.

Comparison of the profiles of ASD symptomatology in distinct syndromes is beneficial in advancing understanding of the specific behavioural profile associated with a particular syndrome. This is useful for identifying areas in which to target interventions. Van Eeghen et al. (2013) used a cross-disorder approach to investigate relationships between ASD and several biologically related disorders: tuberous sclerosis complex (TSC), neurofibromatosis type 1 (NF1) and childhood-onset epilepsy of unknown cause (EUC). Sotos syndrome was not included in this study as it is not associated with mutations in a tumour-suppressor gene and is therefore not biologically related to TSC, NF1 or EUC. Autistic features were assessed using The Social Responsiveness Scale (SRS) (Constantino & Gruber, 2005) which provides a quantitative measure of ASD symptomatology. The findings from this study suggest that each of the disorder groups displayed a trait profile similar to that of ASD, specifically in relation to difficulties in social cognition and repetitive mannerisms, but at a lower severity level. Although some disorders display similar trait profiles to that of ASD, some congenital syndromes are associated with subtly different profiles of ASD symptomatology. For example, although a high proportion of individuals with Cornelia de Lange syndrome (CdLS) meet clinical cut-off for ASD, analysis of scores on specific subdomains indicates that individuals with CdLS are less likely to show repetitive and stereotyped behaviours and tend to demonstrate less impaired eye contact and gestures compared to individuals with idiopathic ASD (Moss et al., 2012). It is therefore important to explore the trait profile of ASD symptomatology within the

Sotos syndrome population in order to establish whether the behavioural profile is similar or distinct to that of idiopathic ASD.

2.1.3. Sotos syndrome and ASD

The systematic search presented in Chapter 1 (Lane, Milne, & Freeth, 2016) identified four studies which have provided data relating to Sotos syndrome and ASD. Of these, three were case studies of individuals who had co-morbid diagnoses of Sotos syndrome and ASD. Mouridsen and Hansen (2002) reported a case of a young child with Sotos syndrome who met the ICD-10 diagnostic criteria for childhood autism. Morrow et al. (1990) reported a child with Sotos syndrome who, following clinical observation, was reported to meet diagnostic criteria for ASD. Additionally, Trad et al. (1991) reported a case of a child with Sotos syndrome who met DSM-III-R criteria for Pervasive Developmental Disorder. In addition to these case studies, Zappella (1990) reported a case series of 12 children with Sotos syndrome. The aim of this study was to investigate the prevalence of autistic features in each of these 12 children, using behavioural observation. Within this sample, the authors noted that five children (42%) displayed autistic features consistent with the DSM-III-R criteria for autistic disorders. While this study suggests that the incidence of ASD in Sotos syndrome is greater than in the general population, the small sample size means that it is not possible to establish the prevalence of ASD within the Sotos population as a whole.

Since the systematic search presented in Chapter 1 was conducted, two published studies have investigated the relationship between Sotos syndrome and ASD. Timonen-Soivio et al. (2016) explored the relationship between ASD and Sotos syndrome in a cohort of Finnish children. Population registers were searched in order to identify the number of individuals with co-morbid diagnoses of distinct congenital

syndromes and ASD. The study identified a significant association between ASD and Sotos syndrome. Of the 13 children identified with Sotos syndrome, 7 (54%) had a co-morbid diagnosis of ASD. Therefore, this study provides further evidence for an increased prevalence of ASD within the Sotos population but again, the sample size is small. In addition, this study assessed the relationship between ASD and Sotos syndrome in terms of co-morbid diagnoses and therefore autistic symptomatology was not explicitly measured within this study. It is possible that further individuals with Sotos syndrome may display behaviour that would meet diagnostic criteria for ASD but had not received a formal diagnosis.

In another study, Sheth et al. (2015) reported characteristics of ASD in a sample of 38 individuals with Sotos syndrome, as assessed by the Social Communication Questionnaire (SCQ) (Rutter, Bailey, & Lord, 2003) and the Repetitive Behaviour Questionnaire (RBQ) (Moss & Oliver, 2008). Mean age of the participants was 17.3 years, with an age range of 6 – 43 years. The SCQ is a standardised 40-item questionnaire, designed to assess symptomatology associated with ASD. There are three SCQ subscales (reciprocal social interaction; communication; restricted, repetitive and stereotyped patterns of behaviour) which are based on the DSM-IV criteria for ASD. There are two versions of the SCQ: a Current form and a Lifetime form. Sheth et al., (2015) used the Lifetime form which is concerned with both behaviours that have been present at any point in the individual's life, as well as behaviours that occurred during a 12 month period (4 – 5 years of age). Consequently, the Lifetime form has a significant focus on the period of development during the ages of 4 and 5 years and is therefore not an appropriate measure to compare changes in symptomatology over time.

Sheth et al., (2015) found that 26 of 38 participants with Sotos syndrome (68%) met clinical cut-off for ASD, as measured by total score on the Lifetime version of the SCQ (clinical cut-off was considered as a total score ≥15). Data from the Sotos syndrome group were compared with data from three distinct, matched control groups: ASD, Prader-Willi syndrome and Down syndrome. Participants with Sotos syndrome scored significantly lower than the ASD group on the repetitive behaviour subscale of the SCQ but there were no significant differences between the Sotos and ASD groups on the social communication and social interaction subscales. Subsequent analyses using only the Sotos syndrome participants who scored above clinical cut-off, identified no significant differences between the Sotos and ASD groups for the three SCQ subscales. The RBQ is a 19-item questionnaire, designed to assess behaviours across five subscales: restricted preferences, repetitive speech, insistence on sameness, stereotyped behaviour and compulsive behaviour. No standardised norms or clinical cut-off are available for this measure. However, when compared to an ASD group, the Sotos syndrome group scored significantly lower than the ASD group on the stereotyped behaviour subscale but there were no significant differences between scores on the remaining subscales between the Sotos syndrome and ASD participants. Overall, the findings from this study suggest that a high proportion of individuals with Sotos syndrome display autistic characteristics of a clinical nature. Difficulties associated with repetitive behaviour are less severe than observed in ASD for individuals with Sotos syndrome who do not score above clinical cut-off, despite significant impairment in social communication and social interaction. As this study used the Lifetime version of the SCQ, some of the questions focus on the developmental period of 4 – 5 years of age so it is therefore not currently known whether these reported difficulties also apply to later childhood and adulthood.

The current study complements and extends the findings from Sheth et al. (2015) in a number of important ways. Based on previous literature, the variability of ASD symptom severity within the Sotos population is not clear and a detailed profile analysis of ASD symptomatology has not been established. In addition, the effects of age and gender on symptom severity have not been explored. Here, the prevalence of symptoms associated with ASD is investigated in a larger sample (N = 78), using a measure of ASD symptomatology that is consistent with the DSM-5 criteria for ASD diagnosis – the Social Responsiveness Scale, second edition (SRS-2) (Constantino & Gruber, 2012). The SRS-2 provides a quantitative measure of autistic symptomatology and is designed to measure severity of deficit in reciprocal social interaction, as well as deficit in restricted interests and repetitive behaviours. Scores are categorised as non-clinical, or as indicative of mild, moderate or severe issues with reciprocal social interaction. To date, this measure has not been used to investigate quantitative, intragroup autistic features in Sotos syndrome. An additional benefit of the SRS-2 is that, by providing T-scores, it is possible to compare data from males and females and from different age groups. Furthermore, a recent factor analysis (Frazier et al., 2014) identified five empirically derived factors that can be assessed using the SRS-2: emotion recognition, social avoidance, interpersonal relatedness, insistence on sameness and repetitive mannerisms. These additional factors can be used to explore the profile of ASD symptomatology. The SRS-2 can also be used to investigate effects of age and gender (Frazier et al., 2014) on ASD symptomatology and these factors have not yet been explored within the Sotos syndrome population.

The primary aims of this study were to identify the prevalence of autistic features within a large cohort of individuals with Sotos syndrome and to explore the profile of autistic features within this population. It was hypothesised that a significant

proportion of individuals with Sotos syndrome would score above clinical cut-off for ASD symptomatology. Secondary aims of this study were to investigate differences in symptom severity in relation to age and gender.

2.2. Method

2.2.1. Participants

The SRS-2 was completed by a family member for 78 individuals with a diagnosis of Sotos syndrome (see Table 2.1 for participant characteristics). Families were recruited via the Child Growth Foundation (CGF; a UK charity that supports families of individuals affected by growth disorders) and advertisements on Sotos syndrome support groups on social media. Specifically, the research was advertised on two Facebook groups: 'Sotos Syndrome – UK' and 'Sotos Syndrome/Cerebral Gigantism' as a 'personality and behaviour study'. ASD was not mentioned in the study information, in order to avoid biasing the sample. All respondents were asked to complete a screening form, in order to establish eligibility for the study. Families were asked to state whether their child or partner had been diagnosed with any developmental disorders and if so, to list these. Any families who did not list Sotos syndrome were excluded. One family was excluded as they reported that their child had 'reverse Sotos syndrome' and one family was excluded on the basis that their child had 'suspected Sotos syndrome' but a diagnosis of Sotos syndrome had not yet been confirmed by a clinician. As well as reporting a diagnosis of Sotos syndrome, some respondents reported that their child or partner also had a comorbid diagnosis of ASD (n = 16), an anxiety disorder (n = 10) or ADHD (n = 4).

Table 2.1. Participant characteristics

Characteristics	Participants (*N* = 78)
Age (in years)	
Mean	12.13
SD	8.99
Range	2.5 – 50
Gender (*n*)	
Males	43
Females	35
Nationality (*n*)	
British	40
American	18
Other	20

2.2.2. Measures

The SRS-2 is a 65-item questionnaire with each item being coded on a Likert scale (0 = not true to 3 = almost always true), designed to assess symptoms associated with ASD. A total score indicates severity of ASD symptomatology, with a higher score indicating greater severity. The SRS-2 has a conceptually derived two-factor structure that is consistent with the DSM-5 criteria for ASD. The factors are social communication impairment and restricted interests and repetitive behaviours. The SRS-2 has been found to be a valid measure of autistic symptomatology across cultures (Bölte, Poustka, & Constantino, 2008; Wigham, Mcconachie, Tandos, Le Couteur, & Team, 2012). Previous research has identified that scores on the SRS-2 are not related to intelligence (Charman et al., 2007) or age (Bölte et al., 2008). A recent

confirmatory factor analysis (Frazier et al., 2014) identified an additional five SRS-2 specific factors: emotion recognition, social avoidance, interpersonal relatedness, insistence on sameness and repetitive mannerisms.

Age appropriate versions of the SRS-2 were used; pre-school (2.5 – 4 years; *n* = 15), school age (4 – 18 years; *n* = 46) and adult (19 years and older; *n* = 17) and the questionnaire was completed by either the parent/caregiver (*n* = 76), other specialist (*n* = 1) or spouse (*n* = 1) of each participant. All questionnaires were completed in English. Licensing was received by the publishers of the SRS-2 to allow online administration of the questionnaire. The study received ethical approval from the university Departmental Ethics Committee.

2.3. Results

2.3.1. Clinical cut-off

Clinical cut-off was considered as a total T-score ≥60 (Constantino & Gruber, 2012). The mean T-score of this group of 78 individuals was 77.13 (*SD* = 15.91) and 65 participants (83.33%) met clinical cut-off for behavioural symptomatology associated with ASD (see Figure 2.1). All participants with diagnoses of both Sotos syndrome and ASD (*n* = 16) scored above clinical cut-off (*M* = 87.50, *SD* = 13.54). Within the total sample, 55.13% (*n* = 43) were in the severe clinical range (T-score ≥76), 19.23% (*n* = 15) were in the moderate clinical range (T-score of 66 – 75) and 8.97% (*n* = 7) of scores were in the mild clinical range (T-score of 60 – 65). Total T-scores ranged from 44 – 109. Data were normally distributed.

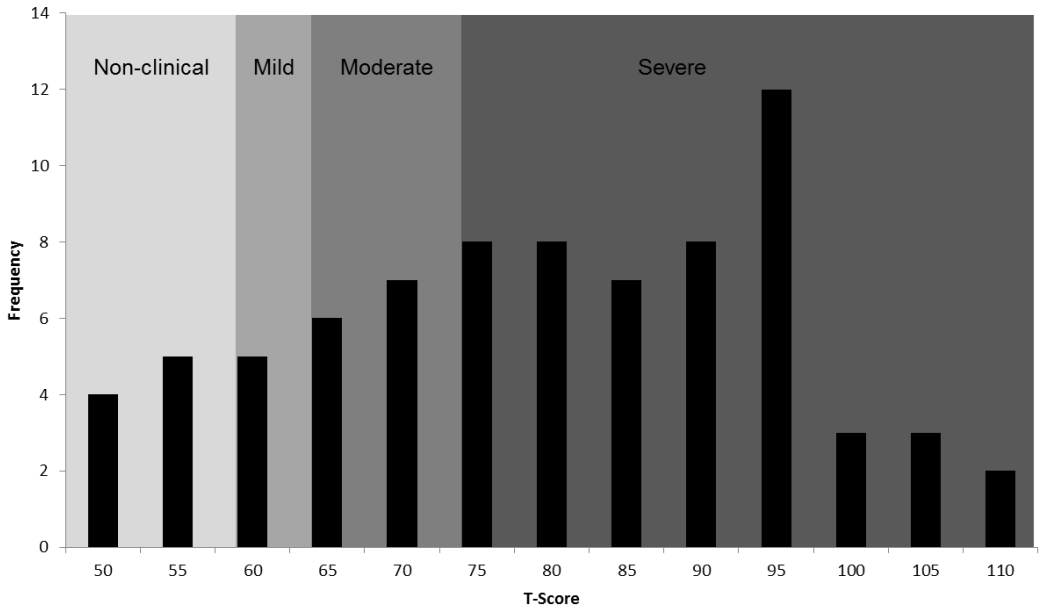


Figure 2.1. Distribution of SRS-2 total T-scores.

2.3.2. Gender differences

In order to establish whether gender affects ASD symptom severity within the Sotos syndrome population, an independent samples *t*-test was used to compare total T-scores for male and female participants. The analysis identified no significant difference ($t(77) = 0.93$, $p = .926$) in total T-scores for male ($M = 76.98$, $SD = 14.61$) and female ($M = 77.31$, $SD = 17.59$) participants. This suggests that within the Sotos population, there are no gender differences in ASD symptom severity.

2.3.3. Age differences

In order to investigate the severity of symptoms across development, participants were categorised into five age groups: 2 years 6 months – 4 years 11 months ($n = 16$); 5 years – 9 years 11 months ($n = 24$); 10 years – 14 years 11 months ($n = 15$); 15 years – 19 years 11 months ($n = 10$) and 20 years and older ($n = 13$). A one-way ANOVA found a significant main effect of age category on total T-scores

($F(4,77) = 4.88$, $p = .002$). Specifically, this analysis identified that the model of best fit was quadratic ($F(4,77) = 15.98$, $p < .001$), indicating an inverted U-shaped pattern of total T-scores. Figure 2.2 shows that individuals with Sotos syndrome display ASD symptomatology which is less severe in early childhood (up to the age of 5 years) and adulthood, compared with childhood.

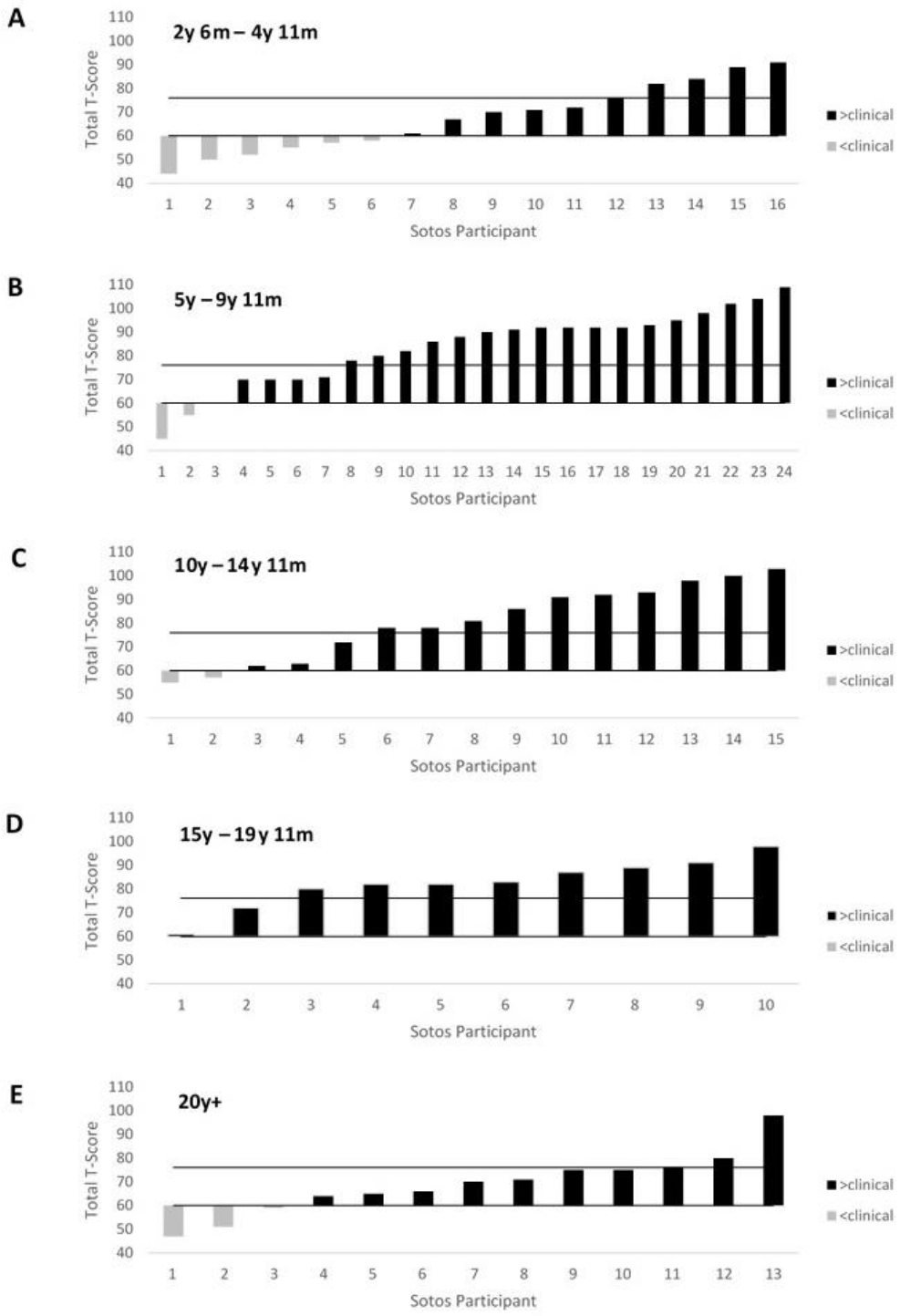
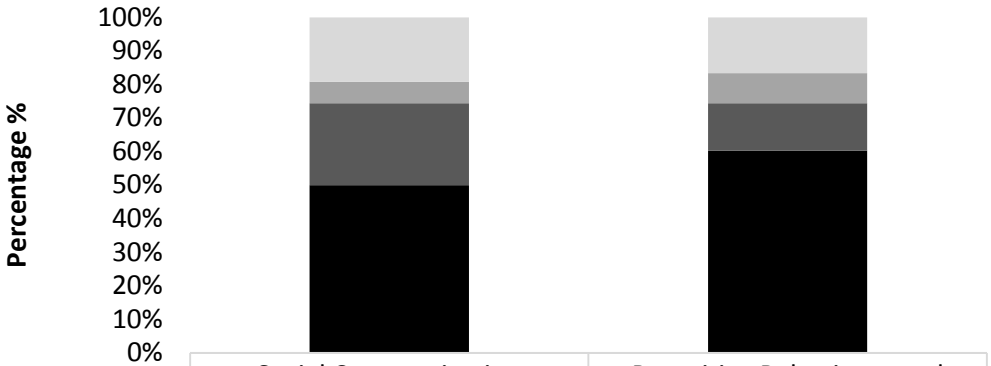


Figure 2.2. Waterfall plots of SRS-2 total T-scores by age category. In **A, B, C, D** and **E**, total T-scores are shown for Sotos individuals in distinct age categories: 2y 6m - 4y 11m, 5 – 9y 11m, 10 – 14y 11m, 15 – 19y 11m and 20y+, respectively. In each, the *lower line* depicts a T-score of 60. Scores *below this line* are non-clinical and scores on or above this line are in the mild and moderate symptom severity range. The *upper*

line depicts a T-score of 76 and *scores on or above this line* are in the severe symptom severity range. In **A**, scores in the severe range were reported in 5 children (31.25%). In **B**, scores in the severe range were reported in 17 children (70.83%). In **C**, scores in the severe range were reported in 10 children (66.67%). In **D**, scores in the severe range were reported in 8 individuals (80%). In **E**, scores in the severe range were reported in 3 individuals (23.08%)

2.3.4. DSM-5 compatible subscales

In order to investigate whether there were particular difficulties observed in either of the two DSM-5 domains, a paired-samples *t*-test was used to compare scores on each of these subscales. The analysis identified a significant difference between T-scores on the social communication impairment ($M = 75.57$, $SD = 15.43$) and restricted interests and repetitive behaviours ($M = 79.45$, $SD = 16.44$) subscales, indicating that individuals with Sotos syndrome display greater difficulty with restricted interests and repetitive behaviours, compared with social communication impairment ($t(77) = 4.37$, $p < .001$). This was a large effect ($d = 0.99$). This is consistent with the profile of SRS-2 scores that is found in individuals with ASD and other clinical groups (Van Eeghen et al., 2013). Figure 2.3 shows the distribution of scores for the restricted interests and repetitive behaviours subscale and the distribution of scores for the social communication impairment subscale. The same categorisation of severity that was used for total T-scores was used for the subscales: non-clinical (T-score < 60), mild (T-score of 60 – 65), moderate (T-score of 66 – 75) and severe (T-score ≥76).



	Social Communication Impairment	Repetitive Behaviours and Restricted Interests
Non-clinical	15	13
Mild	5	7
Moderate	19	11
Severe	39	47

Figure 2.3. Distribution of severity of scores on each of the DSM-5 compatible subscales: social communication impairment and restricted interests and repetitive behaviours. The numbers represent total number of participants in each category.

2.3.5. Subscale analysis of factors identified from Frazier et al. (2014)

A recent factor analysis derived five empirical factors from the SRS-2: emotion recognition, social avoidance, interpersonal relatedness, insistence on sameness and repetitive mannerisms. The first three factors relate to social communication impairment and the remaining two factors relate to restricted interests and repetitive mannerisms (Frazier et al., 2014). The mean item scores and variance for each of the five factors from children with ASD (N = 271) and their unaffected siblings (N = 119), were taken from the Frazier et al. (2014) paper. In both the ASD and unaffected siblings groups, participants ranged in age from 4 – 18 years. These data were compared to the Sotos syndrome data. In order to provide a comparable sample, only the data from participants between 4 – 18 years of age were used for the Sotos syndrome group (n = 46). Average item scores of the Sotos syndrome children

for each of the five factors were: emotion recognition (*M* = 1.90, *SD* = 0.58), social avoidance (*M* = 1.09, *SD* = 0.76), interpersonal relatedness (*M* = 1.88, *SD* = 0.66), insistence on sameness (*M* = 1.76, *SD* = 0.61) and repetitive mannerisms (*M* = 1.52, *SD* = 0.72). A 2 x 5 (Sotos/ASD x SRS subscale) mixed measures ANOVA found no main effect of diagnosis, ($F(1,315) = 0.62$, $p = .43$). There was also no significant group x subscale interaction, ($F(4,1137) = 1.40$, $p = .23$), demonstrating that children with Sotos syndrome appear to display a very similar symptom severity and profile of behaviour to that of children with ASD (see Figure 2.4). By contrast, a 2 x 5 (Sotos/Sibs x SRS subscale) mixed measures ANOVA found a highly significant main effect of group, ($F(1,163) = 474.88$, $p < .001$) as scores for the children with Sotos syndrome were considerably higher than for the unaffected siblings. A significant group x subscale interaction, ($F(4,606) = 18.37$, $p < .001$), indicated that the behavioural profile was also different (see Figure 2.4).

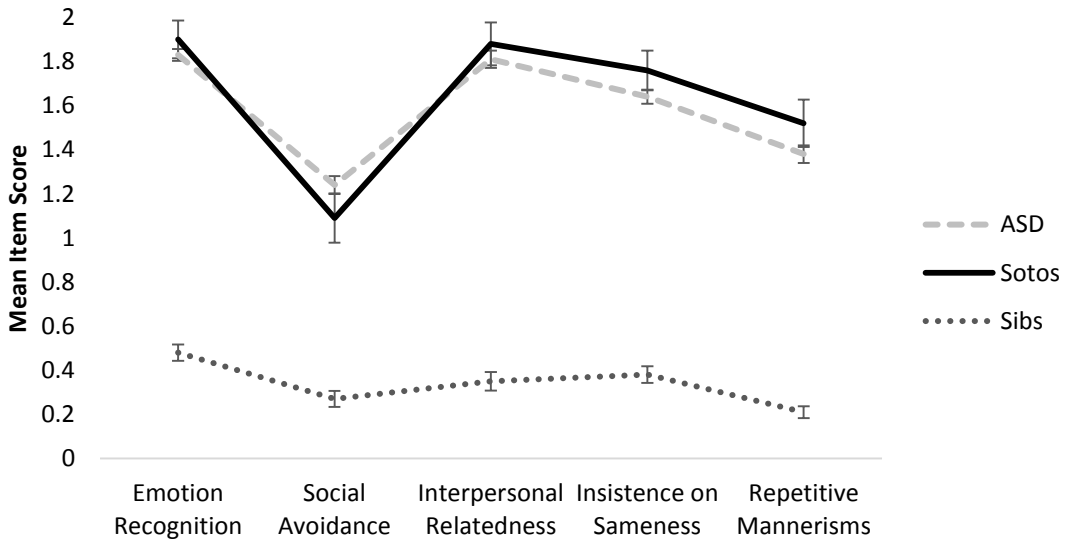


Figure 2.4. Mean item scores for the five subscales identified in the Frazier et al. (2014) factor analysis of the SRS-2. Data taken from (Frazier et al. 2014). Error bars show +/- standard error.

2.4. Discussion

The primary aim of the present study was to investigate the prevalence and profile of autistic features in a large and representative sample of individuals with Sotos syndrome. Secondary aims of the study were to investigate the effects of age and gender on ASD symptom severity within the Sotos syndrome population. Within this study, 83% of participants met clinical cut-off for ASD, as measured by the SRS-2. This finding suggests that the majority of individuals with Sotos syndrome display a current behavioural profile associated with the DSM-5 criteria for ASD (social communication impairment and restricted interests and repetitive behaviours). This indicates an important relationship between the behavioural phenotypes of Sotos syndrome and ASD.

Previous research has suggested relationships between other congenital syndromes and ASD. A recent systematic review and meta-analysis reported prevalence of ASD in a number of genetic syndromes with the highest estimate of 61% identified in Rett syndrome (Richards et al., 2015). This particular review did not include Sotos syndrome, due to the fact that there is a lack of previous research investigating ASD within this population. However, it is clear from the findings in the present study that autistic symptomatology may be more prevalent in Sotos syndrome than many other genetic syndromes.

The reported prevalence of ASD symptomatology in Sotos syndrome in the present study is consistent with previous literature suggesting an association between Sotos syndrome and ASD (Lane et al., 2016; Sheth et al., 2015; Timonen-Soivio et al., 2016). Sheth et al., (2015) found that 26 of 38 participants (68%) met clinical cut-off for ASD symptomatology, as assessed by the Lifetime form of the SCQ. However, as the present study found a significant effect of age and Sheth et al., (2015) used the

Lifetime form to assess ASD symptomatology, which has a significant focus on the 4 – 5 years age range, this could account for the slightly higher prevalence identified in the present study. In addition, the profile of ASD symptomatology may be affected by age which could explain differences in the relative severity of impairment in social communication impairment and restricted interests and repetitive behaviours in the present study and the findings from Sheth et al., (2015).

In the present study, there was no effect of gender on symptom severity, indicating that there is no significant difference between the prevalence of behavioural characteristics associated with ASD in males and females with Sotos syndrome. This is an important finding as there is a significant gender difference in diagnosis of ASD, with males more likely to receive a diagnosis than females (Fombonne, 2009). However, our findings indicate that severity of ASD symptomatology is comparable in both males and females with Sotos syndrome. It is important to note that within our sample, 16 participants had diagnoses of both Sotos syndrome and ASD, yet only two of these participants were female. This suggests that although males and females with Sotos syndrome appear to display a very similar behavioural phenotype, there is a clear disparity between diagnosis of ASD in males and females with Sotos syndrome.

The findings from the present study suggest that within the Sotos syndrome population, age affects severity of ASD symptomatology. Specifically, ASD symptomatology was less severe in young children (2.5 – 5 years) and in adults (20+ years) when compared to children over the age of 5 years through to adolescence, in the current sample. This is an important finding as it suggests that severity of ASD symptomatology may decrease as an individual transitions into adulthood. Research investigating age-related effects of ASD symptomatology in individuals with idiopathic ASD indicates that the symptoms of ASD tend to abate, to some extent, in

adolescence and young adulthood (Seltzer, Shattuck, Abbeduto, & Greenberg, 2004). Thus, findings from the present study are consistent with previous research investigating age-related effects in individuals with idiopathic ASD, indicating a similar trend within the Sotos population towards improvement in ASD symptomatology across the lifespan. However, as the present study used a cross-sectional design, an important future direction will be to examine the effect of age using a longitudinal design, so that developmental trajectories can be effectively tracked. It is important to note that participants were recruited via syndrome support groups so this may have resulted in a bias towards recruitment of participants with more severe difficulties. It will therefore be useful for future research to utilise alternative recruitment strategies in order to determine whether these age-related effects are observed in a different cohort of individuals with Sotos syndrome.

It has been suggested that distinct profiles of ASD symptomatology may be associated with different genetic syndromes (Moss & Howlin, 2009). The findings from the present study suggest that individuals with Sotos syndrome display trait profiles that are similar to those present in idiopathic ASD. This is supported by the comparison of the Sotos syndrome and ASD data on the five empirically derived subscales identified by the recent factor analysis of the SRS-2 (Frazier et al., 2014). Children with Sotos syndrome appear to display behavioural characteristics of a similar profile and severity to that identified in idiopathic ASD and were distinct from scores identified in the unaffected siblings of the ASD children. Although individuals with Sotos syndrome would be considered as having syndromic ASD, the findings from the present study suggest that the syndromic ASD observed in Sotos syndrome is very similar to idiopathic ASD. However, as this study measured autistic features using a parental questionnaire, it will be important for future research to explore the

profile of ASD symptomatology in Sotos syndrome in more detail, using clinical evaluations, such as the Autism Diagnostic Observation Schedule (Lord et al., 2000) and a matched control group of individuals with ASD. Furthermore, it will be useful for future research to investigate factors which may affect severity of ASD symptomatology within this population, such as cognitive ability and verbal ability in order to enhance understanding of the behavioural phenotype of Sotos syndrome. The relationship between intellectual ability, verbal ability and communication skills will be explored in Chapter 5.

2.4.1. Conclusion

In summary, this is the largest study to date to investigate symptomatology associated with ASD in individuals with Sotos syndrome. The findings reported in this chapter demonstrate a high prevalence of autistic symptomatology within the Sotos syndrome population and suggest that the majority of individuals with Sotos syndrome display clinically significant behavioural symptomatology associated with ASD. Symptom severity does not appear to be affected by gender but does seem to differ in relation to age, with more prominent behavioural characteristics in childhood (5 – 19 years), compared with early childhood (2.5 – 5 years) and adulthood (20 years and older). As the majority of cases of Sotos syndrome are caused by abnormality of the NSD1 gene, the findings provide further evidence to suggest a possible genetic mechanism associated with ASD. An important clinical implication of the findings is that clinicians should screen for ASD in individuals with Sotos syndrome as there may be a number of unidentified cases of comorbidity.

Chapter 3: The cognitive profile of Sotos syndrome

3.1. Introduction

As discussed in Chapter 1, cognitive abilities have not been explored in detail within the Sotos syndrome population (see section 1.4.1). The aim of this chapter is to advance understanding of cognition in Sotos syndrome by using a standardised, quantitative measure to assess ability in distinct areas of cognition. Specifically, the aim of this approach is to identify whether Sotos syndrome is associated with a syndrome-specific cognitive profile.

3.1.1. Cognition in genetic syndromes

A cognitive profile characterises the relative cognitive strengths and weaknesses of an individual and in some cases, can be generalised to individuals within a specific population. Distinct cognitive profiles have been identified in a number of congenital syndromes such as Williams syndrome (Mervis et al., 2000; Udwin & Yule, 1991), Fragile X syndrome (Borghgraef, Fryns, Dlelkens, Pyck, & Berghe, 1987; Van Der Molen et al., 2010) and Down syndrome (Silverman, 2007; Wang, 1996). Each of these syndromes has an identifiable genetic cause. Williams syndrome is associated with a deletion at chromosome 7 (Ewart et al., 1993); Fragile X syndrome is associated with silencing of the FMR-1 gene, which is located on the X chromosome (Verkerk et al., 1991); Down syndrome is caused by trisomy of chromosome 21 (Lejeune, 1959). In addition, these syndromes are typically associated with intellectual disability, as well as distinct and varied cognitive profiles. The presence of such variability has important implications when considering the most effective educational strategies for individuals with neurodevelopmental disorders and for designing interventions and support to improve the outcomes of these populations.

Sotos syndrome is associated with intellectual disability but the cognitive profile is unknown. It is therefore an important population in which to investigate cognition.

Broadly, cognitive assessments can be used to determine whether individuals have an uneven cognitive profile by examining whether there is a significant difference between performance on tasks which assess verbal ability and tasks which assess non-verbal reasoning ability. Previous research with other neurodevelopmental disorders has explored discrepancies between these aspects of cognition. In Williams syndrome, this is a striking component of the cognitive profile, with individuals typically displaying relative strength in verbal ability and relative weakness in non-verbal reasoning ability (Udwin & Yule, 1991). In contrast, Down syndrome is typically associated with relative weakness in verbal ability, compared with non-verbal reasoning ability (Wang, 1996). Both of these syndromes are associated with intellectual disability, yet the cognitive profiles are distinct (Klein & Mervis, 1999).

In addition, previous studies involving individuals with Williams syndrome have identified an association between verbal ability and the relative discrepancy between verbal ability and non-verbal reasoning ability, indicating that higher verbal ability is associated with a greater discrepancy (Jarrold, Baddeley, & Hewes, 1998). This study used a cross-sectional design and the findings suggest that the rate of development of these abilities is distinct within the Williams syndrome population. In particular, the findings indicate that the discrepancy between verbal ability and non-verbal reasoning ability becomes more apparent later in development. In a longitudinal assessment of the development of verbal ability and non-verbal reasoning ability in individuals with Williams syndrome, Jarrold, Baddeley, Hewes, and Phillips (2001) identified that participants displayed diverging developmental trajectories in relation to verbal ability, as assessed by the British Picture Vocabulary Scale (BPVS) and non-

verbal reasoning ability, as assessed by the pattern construction subscale of the Differential Ability Scales (DAS). As this was assessed using a longitudinal design, as opposed to a cross-sectional design, this provides additional support for the finding that verbal ability develops to a greater extent than non-verbal reasoning ability within the Williams syndrome population. As Sotos syndrome may also be characterised by relative strength in verbal ability, compared with non-verbal reasoning ability (Lane et al., 2016), it is therefore important to assess the relationship between these abilities within the Sotos syndrome population.

The identification of syndrome-specific cognitive profiles enables differentiation between individuals with distinct congenital syndromes. Specific criteria extend the broad phenotype established by research investigating discrepancies in verbal ability and non-verbal reasoning ability by examining differences in performance between the specific tasks that comprise verbal ability and non-verbal reasoning ability. For Williams syndrome, the cognitive profile is characterised by relative strength in verbal ability and auditory memory but relative weakness in visuospatial construction (Mervis et al., 2000; Udwin & Yule, 1991). Mervis et al. (2000) operationalised the cognitive profile of Williams syndrome with four specific criteria: (1) 'digit recall, naming/definitions or similarities > 1st percentile'; (2) 'pattern construction T-score < 20th percentile'; (3) 'pattern construction < mean T-score' (4) 'pattern construction T-score < digit recall T-score' (Mervis et al., 2000). This provides a specific quantitative measure of the cognitive profile associated with Williams syndrome. As there is currently very limited knowledge available in relation to the cognitive profile associated with Sotos syndrome, it is important to establish the relative cognitive strengths and weaknesses

of individuals within this population in order to ensure that appropriate educational strategies are utilised.

3.1.2. Cognitive abilities in Sotos syndrome

As noted in the systematic review presented in Chapter 1, the majority of the existing literature reporting data on cognition in Sotos syndrome has focused on level of intellectual ability, indicating that most individuals with Sotos syndrome have intellectual disability or borderline intellectual functioning. In the largest study to date to investigate the clinical features of Sotos syndrome, Tatton-Brown et al., (2005) found that intellectual disability was present in 97% of 266 individuals with Sotos syndrome. However, intellectual ability was determined via clinical assessment in this study in which individuals were classified as having normal intellectual ability or mild, moderate or severe intellectual disability based on clinical observation. Therefore, intellectual ability was classified using descriptive labels as opposed to quantitative scores derived from a standardised cognitive assessment, so it is not possible to identify the associated cognitive profile from this study.

To date, very little is known about specific cognitive abilities, such as memory, numeracy and reasoning skills, within the Sotos syndrome population and only one case study has reported quantitative scores for specific cognitive subscales (Morrow et al., 1990). An additional finding from the systematic review presented in Chapter 1 was that individuals with Sotos syndrome appear to display relative strength in verbal IQ, compared with performance IQ (Lane et al., 2016). However, the discrepancy between verbal IQ and performance IQ was not explicitly assessed in any of the studies that reported these scores.

The primary aim of the present study was to investigate the prevalence of intellectual disability within the Sotos syndrome population, using a standardised cognitive assessment and to identify the associated cognitive profile. Cognitive abilities were assessed using the British Ability Scales, third edition (BAS3) (Elliott & Smith, 2011) in a large and representative sample of adults and children with Sotos syndrome. The BAS3 is a standardised battery of cognitive tasks, appropriate for use with individuals of a wide age range, as well as individuals of varying intellectual ability. The American equivalent of the BAS3 (The Differential Ability Scales; DAS) (Elliott, Murray, & Pearson, 1990) has been used to quantify the cognitive profile associated with Williams syndrome and is therefore an appropriate and established methodology for identifying cognitive profiles associated with neurodevelopmental disorders.

3.2. Method

3.2.1. Participants

The sample comprised 52 participants (31 males) with a diagnosis of Sotos syndrome, ranging in age from 3 years 8 months to 50 years 3 months (M = 14.62 years, SD = 9.61 years). Families were recruited via the Child Growth Foundation (CGF; a UK charity that supports families of individuals affected by growth disorders) and advertisements on a Sotos syndrome support group on social media (the 'Sotos Syndrome – UK' group on Facebook). In order to assess eligibility for the study, families were asked to complete a screening form and to indicate whether their child or partner had been diagnosed with any developmental disorders. If Sotos syndrome was stated on the screening form, families were invited to participate and were sent further information about the study.

3.2.2. Procedure

The majority of participants were visited at their home (n = 24) or their school (n = 23). One participant took part in the study at the Department of Psychology, University of Sheffield and a small number of participants completed the study at the annual CGF Conventions, in either 2015 or 2016 (n = 4). Participants were administered the BAS3; a standardised battery of cognitive tasks, designed to assess a range of cognitive abilities. The BAS3 consists of two batteries: an early years (EY) battery, which has norms for children aged 3:0 – 7:11 years and a school age (SA) battery, which has norms for children aged 5:0 – 17:11 years of age. Each battery comprises six core scales which are used to determine a General Conceptual Ability (GCA) score (equivalent to an IQ score). GCA scores are calculated as standard scores (M = 100, SD = 15) on the basis of the distribution of T-scores (M = 50, SD = 10) for the six core scales.

The BAS3 core scales form three distinct clusters: verbal (V) ability, non-verbal reasoning (NVR) ability and spatial (S) ability. The cluster scores are also calculated as standard scores (M = 100, SD = 15). Completion of all core scales is required for profile analysis. A description of the abilities measured by each task and the corresponding clusters, as stated in the BAS3 administration and scoring manual (Elliott, 2011), is presented in Tables 3.1 (EY battery) and 3.2 (SA battery).

Table 3.1. Early years battery core scales

Core scales	Abilities measured
Verbal cluster	
Verbal comprehension	Receptive language: understanding of oral instructions involving basic language concepts
Naming vocabulary	Expressive language; knowledge of names
Non-verbal reasoning cluster	
Picture similarities	Non-verbal reasoning shown by matching pictures that have a common element or concept
Matrices*	Inductive reasoning: identification and application of rules governing relationships among pictures and abstract figures
Spatial cluster	
Pattern construction*	Non-verbal reasoning and spatial visualisation in reproducing designs
Copying	Visual-perceptual matching and fine-motor co-ordination in copying line drawings

*task included in both the EY and SA batteries.

Table 3.2. School age battery core scales

Core scales	Abilities measured
Verbal cluster	
Word definitions	Expressive language; explanation of word meanings
Verbal similarities	Verbal reasoning and verbal knowledge
Non-verbal reasoning cluster	
Matrices*	Inductive reasoning: identification and application of rules governing relationships among pictures and abstract figures
Quantitative reasoning	Inductive reasoning: detection and application of rules concerning sequential patterns in dominoes and relationships between pairs of numbers
Spatial cluster	
Recognition of designs	Short term memory for geometric forms
Pattern construction*	Non-verbal reasoning and spatial visualisation in reproducing designs

*task included in both the EY and SA batteries.

Although both the EY and SA batteries have norms for children 5:0 – 7:11 years of age, the EY battery was used with participants from the ages of 3:8 – 7:11 years, as it was anticipated that the majority of participants would have intellectual disability and therefore use of the EY battery would reduce the likelihood of floor

effects. All participants who were 8 years or older were administered the SA battery. Of the 52 participants, 15 were tested on the EY battery and 37 were tested on the SA battery. The BAS3 was administered in accordance with the administration manual.

All families provided informed consent. Participants aged 18 years and over provided informed consent and for children under the age of 18 years, the parent/caregiver of the participant was required to give informed consent. The study received ethical approval from the departmental ethics committee.

3.3. Results

3.3.1. General conceptual ability

The mean GCA of the 52 participants was 60.75 (*SD* = 16.68) and GCA scores ranged from 37 – 101. Intellectual disability was considered as GCA < 70, borderline intellectual ability was considered as GCA of 70 – 89 and average intellectual ability was considered as GCA of 90 – 109. See Figure 3.1 for percentage of participants in each of these categories. A Pearson's bivariate correlation did not find a significant increase or decrease in GCA with age (r = .036, N = 52, p = .802).

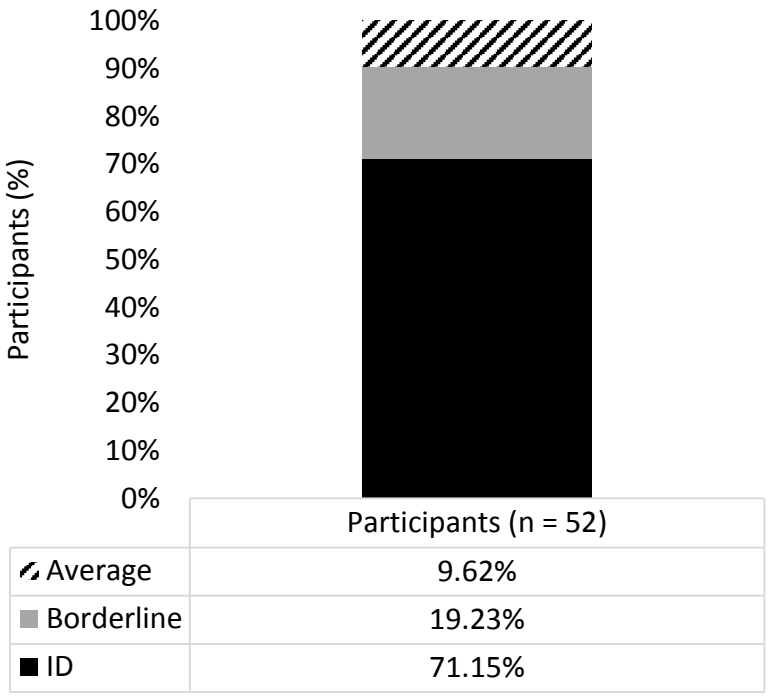


Figure 3.1. Percentage of participants with ID (GCA < 70), borderline intellectual functioning (GCA 70 – 89) and average intellectual functioning (GCA 90 – 109).

3.3.2. Cluster score profile

In order to establish whether participants displayed a distinct profile of performance on the clusters, a repeated measures ANOVA was used to compare scores for the verbal (V) ability, non-verbal reasoning (NVR) ability and spatial (S) ability clusters. As these clusters are calculated on the basis of performance on the core scales of either the EY battery or SA battery and most of the core scales tasks are unique to each of the batteries, separate analyses were conducted for participants in the EY battery and participants in the SA battery. Six of the participants (all male) found the tasks too challenging so were unable to complete all or some of the core scales and were therefore removed from the subsequent analyses regarding the cognitive profile of Sotos syndrome (4 from the EY battery and 2 from the SA battery).

School age cluster score profile. A repeated measures ANOVA identified a significant difference in performance on the three clusters for participants (n = 35) in the SA battery ($F(2, 68) = 35.91$, $p < .001$). After correcting for multiple comparisons (using a Bonferroni correction, $p < .017$ required for significance), paired samples t-tests revealed that performance on the V ability (M = 74.91, SD = 15.25) cluster was significantly better than performance on the NVR ability (M = 61.29, SD = 12.58) cluster ($t(34) = 8.62$, $p < .001$). This was a large effect (d = 1.46). In addition, scores on the S ability (M = 70.63, SD = 15.89) cluster were significantly higher than scores on the NVR ability cluster ($t(34) = 6.22$, $p < .001$). This was a large effect (d = 1.05). There was no significant difference between performance on the V ability cluster and S ability cluster, though there was a trend for V ability scores to be higher than S ability scores which approached significance ($t(34) = 2.34$, $p = .025$). The findings indicate that participants displayed relative strength in V and S abilities and relative weakness in NVR ability (see Table 3.3).

Early years cluster score profile. A repeated measures ANOVA identified a significant difference in performance on the three clusters for participants (n = 11) in the EY battery ($F(2, 20) = 13.22$, $p < .001$). After correcting for multiple comparisons (using a Bonferroni correction, $p < .017$ required for significance), paired samples t-tests revealed that performance on the V ability (M = 82.82, SD = 14.68) cluster was significantly better than performance on the S ability (M = 65.82, SD = 12.63) cluster ($t(10) = 6.4$, $p < .001$). This was a large effect (d = 1.93). There was no significant difference between scores on the V ability cluster and NVR ability (M = 71.82, SD = 11.17) cluster ($t(10) = 2.64$, $p = .025$) or between scores on the NVR ability cluster and S ability cluster ($t(10) = 1.97$, $p = .078$). This suggests that participants in the EY

battery displayed relative strength in V ability and relative weakness in S ability (see Table 3.3).

Table 3.3. Cluster scores for the school age battery and early years battery

Cluster	M	SD
SA Battery		
Verbal ability	74.91	15.25
Non-verbal reasoning ability	61.29	12.58
Spatial ability	70.63	15.89
EY Battery		
Verbal ability	82.82	14.68
Non-verbal reasoning ability	71.82	11.17
Spatial ability	65.82	12.63

3.3.3. Verbal – non-verbal reasoning discrepancies

As the cluster score analyses revealed relative strength in V ability for participants in both batteries and relative weakness in NVR ability for participants in the SA battery, the consistency of discrepancies between V ability and NVR ability within the sample was explored. Of the 46 participants who completed all of the core scales of either the EY battery or the SA battery, 43 exhibited a V > NVR profile of performance on the cluster scores, demonstrating a consistent relative strength in V

ability and relative weakness in NVR ability within the Sotos syndrome population. For each participant, a discrepancy score was calculated by subtracting the NVR ability score from the V ability score. V – NVR discrepancies ranged from -7 to 46 (M = 13, SD = 10.48). A one sample t-test was used to determine whether V – NVR discrepancies were significantly greater than 0. The analysis revealed a significant difference ($t(45) = 8.41$, $p < .001$), indicating that the discrepancy between V ability and NVR ability was significantly greater than 0. This was a large effect (d = 1.24). This demonstrates that participants displayed a consistent V > NVR profile, indicating that relative strength in V ability is a defining characteristic of the cognitive profile of Sotos syndrome.

In order to investigate whether V ability was associated with V – NVR discrepancy, Pearson's correlation was used to determine the relationship between these variables. The analysis identified a strong positive correlation between V ability and V – NVR discrepancy ($r = .551$, $N = 46$, $p < .001$), indicating that the discrepancy was greater for individuals with higher overall V ability scores (see Figure 3.2). This suggests that V ability may develop to a greater extent, compared to NVR ability for individuals with Sotos syndrome as the discrepancy between these abilities was more pronounced in participants with higher V ability. This indicates that NVR ability is a consistent relative weakness in individuals with Sotos syndrome, regardless of V ability.

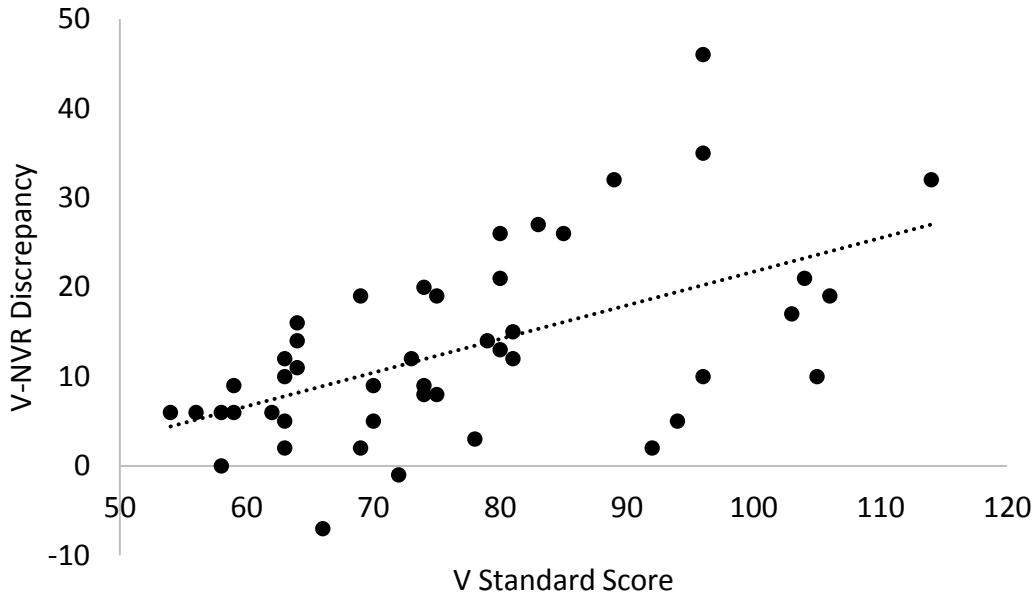


Figure 3.2. Relationship between verbal ability and verbal – non-verbal reasoning discrepancy scores.

3.3.4. Early years core scales profile

A repeated measures ANOVA was used to compare performance on the six core scales of the EY battery (see Figure 3.3 for means and standard error of the EY core scales). Eleven participants (4 males) completed all six of the EY core scales and were included in the analyses. Participants ranged in age from 3 years 8 months to 7 years 10 months (M = 6.53, SD = 1.39). All analyses were conducted using T-scores (M = 50, SD = 10). Mean T-score was calculated on the basis of scores on the six core scales of the EY battery. The analysis identified a significant difference between scores on the core scales of the EY battery ($F(5,50) = 6.53$, $p < .001$), indicating that young children with Sotos syndrome display an uneven cognitive profile of relative cognitive strengths and weaknesses. Pairwise comparisons using a Bonferroni correction ($p < .003$ required for statistical significance) were used to compare performance on all of the core scales of the EY battery. The comparisons revealed a

trend for the naming vocabulary mean T-score to be higher than the pattern construction mean T-score (p = .004) and the copying mean T-score (p = .021). This suggests that young children with Sotos syndrome tend to display relative strength in expressive language and relative weakness in tasks designed to assess spatial abilities.

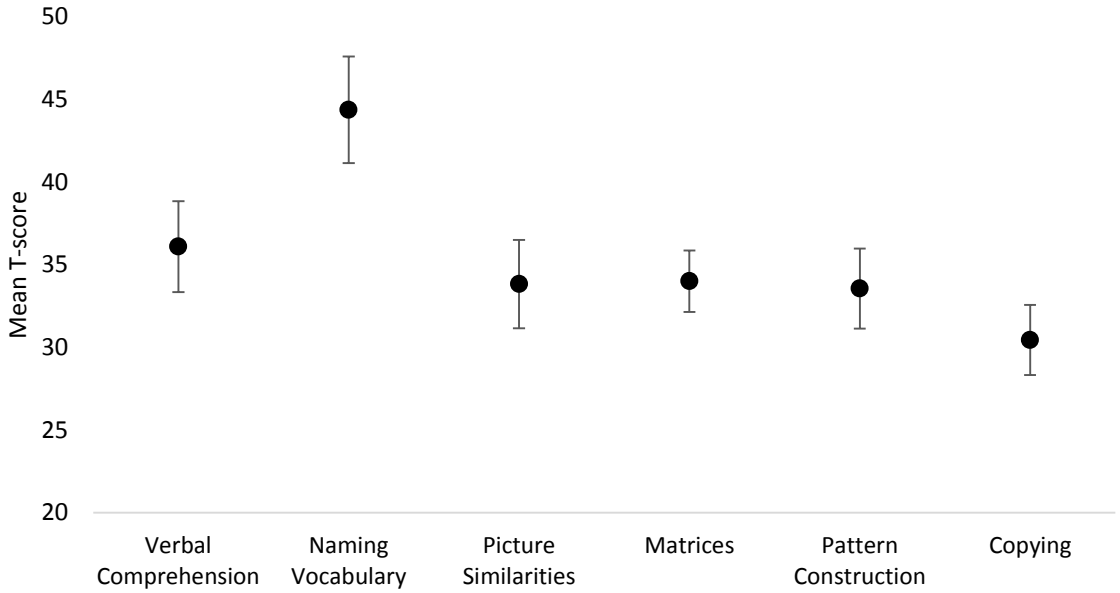


Figure 3.3. Mean T-scores for the core scales of the EY battery. Error bars show +/- standard error.

3.3.5. Sotos syndrome cognitive profile (SSCP)

In order to investigate the specific cognitive profile in more detail, a repeated measures ANOVA was used to compare performance on the six core scales of the SA battery (see Figure 3.4 for means and standard error of the SA core scales). Participants were only included in the analyses if they completed all six core scales of the SA battery. In total, thirty-five participants were included in the profile analyses (21 males) and participants ranged in age from 8 years 3 months to 50 years 3 months (M = 18.17, SD = 9.69).

All analyses were conducted using T-scores (M = 50, SD = 10). Mean T-score was calculated on the basis of scores on the six core scales of the SA battery. The analysis identified a significant difference between scores on the core scales of the SA battery ($F(5,170) = 23.63$, $p < .001$), indicating that individuals with Sotos syndrome display specific strengths and weaknesses, as evidenced by relative differences in performance on the core scales of the SA battery. Pairwise comparisons using a Bonferroni correction ($p < .003$ required for statistical significance) were used to compare performance on all of the core scales of the SA battery. The comparisons revealed that recognition of designs mean T-score was significantly higher than quantitative reasoning mean T-score ($p < .001$), matrices mean T-score ($p < .001$) and pattern construction mean T-score ($p < .001$); verbal similarities mean T-score was significantly higher than quantitative reasoning mean T-score ($p < .001$) and matrices mean T-score ($p < .001$); word definitions mean T-score was significantly higher than quantitative reasoning mean T-score ($p < .001$) and matrices mean T-score ($p = .001$). Therefore, the findings from these analyses provide insight into the cognitive profile of Sotos syndrome. Overall, participants displayed enhanced performance on a task assessing visuospatial memory (recognition of designs), as well as tasks assessing verbal ability (e.g. verbal similarities and word definitions) but relative weakness in performance on tasks designed to assess non-verbal reasoning ability (e.g. quantitative reasoning and matrices).

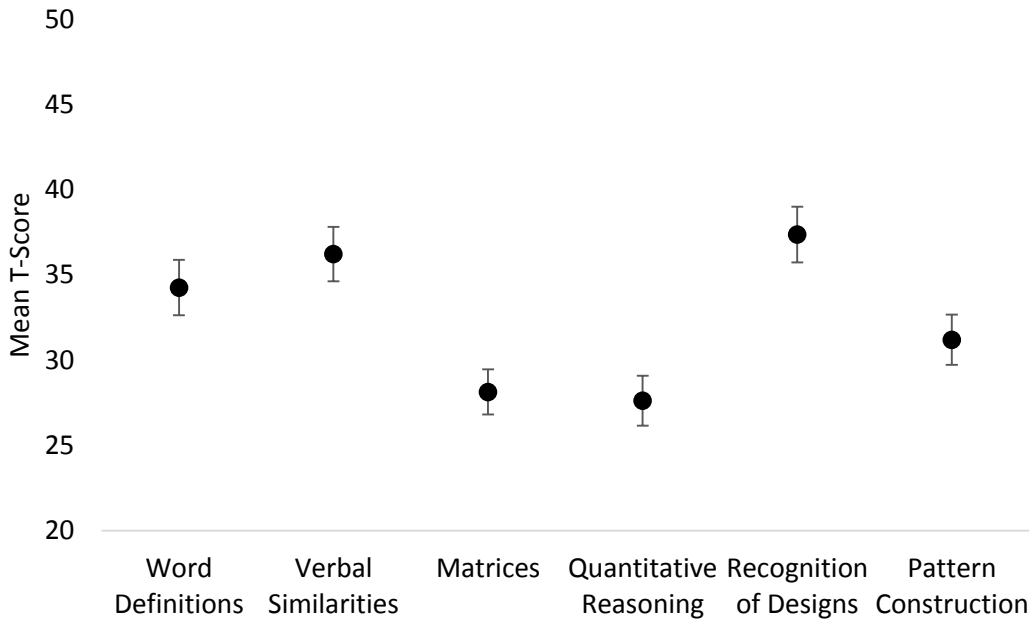


Figure 3.4. Mean T-scores for the core scales of the SA battery. Error bars show +/- standard error.

In order to operationalise the cognitive profile of individuals with Sotos syndrome, the following criteria were proposed as the Sotos Syndrome Cognitive Profile (SSCP):

SSCP1: Verbal ability > Non-verbal reasoning ability

SSCP2: Quantitative reasoning T-score or Matrices T-score < 20th percentile

SSCP3: Quantitative reasoning T-score < Mean T-score

SSCP4: Recognition of designs T-score or Recognition of pictures T-score > Mean T-score

These criteria were chosen due to the significant V-NVR discrepancy identified in the previous analyses, as well as the relative strengths and weaknesses that were identified in the analysis of performance on the core scales of the SA battery (see Figure 3.4). A visualisation of SSCP criteria 3 and 4 is presented in Figure 3.5. This presents the 'quantitative reasoning' task T-score, 'recognition of designs' task T-score and mean T-score of each participant and demonstrates the consistency of relative strength in visuospatial memory and relative weakness in quantitative reasoning between participants.

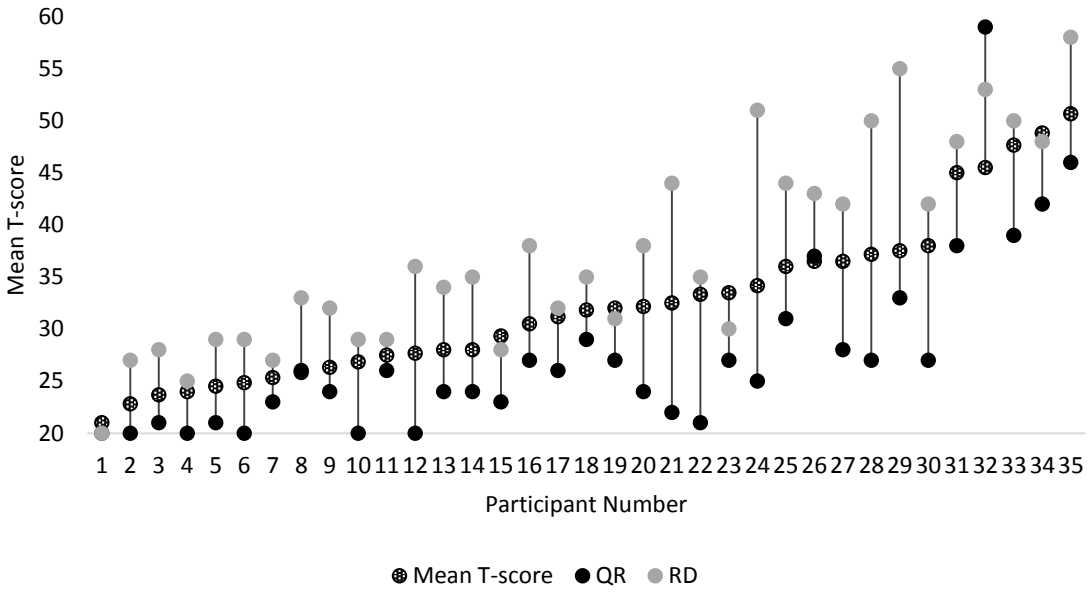


Figure 3.5. Mean T-score, quantitative reasoning (QR) T-score and recognition of designs (RD) T-score for each participant. Participants ordered by mean T-score.

SSCP sensitivity. In order to establish the sensitivity of each of the SSCP criteria, the proportion of individuals meeting each criteria was calculated (see Table 3.4). The SSCP criteria were applied to all participants who completed all six core scales of the SA battery in order to determine the sensitivity of the SSCP. Of the 35 participants who completed the SA battery, 28 (80%) met all four criteria of the SSCP,

yielding a sensitivity (*Se*) of 0.8. In total, 34 (97.14%) of the participants met at least three of the SSCP criteria and all participants met at least two of the SSCP criteria.

Table 3.4. Proportion of participants meeting SSCP criteria and sensitivity of each SSCP criteria

Criteria	N	*Se*
SSCP1: Verbal ability > Non-verbal reasoning ability	33	0.94
SSCP2: Quantitative reasoning T-score or Matrices T-score < 20th percentile	34	0.97
SSCP3: Quantitative reasoning T-score < Mean T-score	32	0.91
SSCP4: Recognition of designs T-score or Recognition of pictures T-score > Mean T-score	33	0.94

3.3.6. Gender differences

Gender differences in relation to intellectual disability and the associated cognitive profile of Sotos syndrome were explored. GCA scores for male participants were not normally distributed so non-parametric analyses were carried out. A Mann-Whitney U analysis identified a significant difference in GCA between genders (U = 218.5, p = .046), indicating that female participants (M = 66.52, SD = 17.35) typically achieved higher GCA scores than male participants (M = 56.84, SD = 15.27). In total, 14.29% (n = 3) of female participants had average intellectual ability, 28.57% (n = 6) had borderline intellectual ability and 57.14% (n = 12) had intellectual disability. For

male participants, 6.45% (n = 2) had average intellectual ability, 12.9% (n = 4) had borderline intellectual ability and 80.65% (n = 25) had intellectual disability. This suggests that males with Sotos syndrome may be more severely affected by intellectual disability than females. No significant differences in relation to gender were observed in any of the other analyses.

3.4. Discussion

The aim of the present study was to investigate the prevalence of intellectual disability within the Sotos syndrome population and to identify the associated cognitive profile. This was assessed using a standardised battery of cognitive tasks, in a large and representative sample of adults and children with Sotos syndrome.

Results indicate that the majority of participants either had intellectual disability (GCA < 70) or fell in the borderline intellectual ability range (GCA 70 – 89). This finding supports previous research (Lane et al., 2016; Tatton-Brown et al., 2005), indicating that the majority of individuals with Sotos syndrome have impaired intellectual ability. However, in the present study, nearly 10% of participants had average intellectual ability (GCA 90 – 109). This highlights the variability of intellectual ability within this population and demonstrates that some individuals with Sotos syndrome do not have intellectual disability.

The systematic review presented in Chapter 1 identified that individuals with Sotos syndrome may have higher verbal IQ compared to performance IQ scores (Lane et al., 2016). However, this finding was based on just seven studies, the majority of which were case studies and none of which explicitly assessed the discrepancy between verbal IQ and performance IQ. Thus, the finding of a V > NVR profile in

individuals with Sotos syndrome is consistent with the suggestion from the systematic review. As the present study included a large cohort of individuals with Sotos syndrome, this is a robust finding which has now been established in a large and representative sample.

Previous studies investigating cognition in Williams syndrome have identified an association between verbal ability and the relative discrepancy between verbal ability and non-verbal reasoning ability, indicating that higher verbal ability is associated with a greater discrepancy (Jarrold et al., 1998; Jarrold et al., 2001). This suggests that the rate of development of these abilities is distinct within the Williams syndrome population. The findings from the present study indicate that this association is also observed in individuals with Sotos syndrome. This suggests that the rate of development of verbal ability and non-verbal reasoning ability is distinct within the Sotos syndrome population. It will be important for future research to use a longitudinal design to assess the relationship between these abilities in more detail in order to establish the trajectory of these abilities.

In order to identify the cognitive profile associated with Sotos syndrome, performance on the core scales of the SA battery of the BAS3 was compared. This approach has not previously been used within the Sotos syndrome population. It is important to note that the focus of this approach was to establish relative, as opposed to absolute, cognitive strengths and weaknesses. The profile analysis revealed that participants displayed relative strength in visuospatial memory and relative weakness in quantitative reasoning. The finding of relative strength in visuospatial memory is a novel finding which has important implications for understanding how individuals with Sotos syndrome process and learn information. Furthermore, the finding of a relative weakness in quantitative reasoning supports a suggestion reported by Cole and

Hughes, (1994) that individuals with Sotos syndrome display particular difficulty with numeracy. This finding indicates that individuals with Sotos syndrome may require additional support with numeracy.

In order to operationalise the cognitive profile, four specific criteria were proposed as the Sotos syndrome cognitive profile (SSCP): 'Verbal ability > Non-verbal reasoning ability' (SSCP1), 'Quantitative reasoning T-score or Matrices T-score < 20th percentile' (SSCP2), 'Quantitative reasoning T-score < Mean T-score' (SSCP3), 'Recognition of designs T-score or Recognition of pictures T-score > Mean T-score' (SSCP4). In total, 80% (n = 28) of participants met all four criteria of the SSCP and 97.14% (n = 34) met at least three of the criteria. This suggests that the SSCP has a good degree of sensitivity. In addition, each of the SSCP criteria had a sensitivity greater than 0.9 (M = 0.94), indicating that reasons for not meeting all criteria for the SSCP were varied. The SSCP sensitivity were comparable to the sensitivity of the Williams syndrome cognitive profile (WSCP) criteria, reported by Mervis et al., (2000) in which the sensitivity of the four WSCP ranged from 0.91 – 1.00 (M = 0.95). Although the WSCP reported by Mervis et al., (2000) and the SSCP reported in the present study were devised on the basis of performance on the same cognitive assessment, different cognitive abilities were identified as relative strengths and weaknesses for individuals within these populations. This demonstrates that the WCSP and the SSCP are syndrome-specific and can be used to differentiate between individuals with Williams syndrome and individuals with Sotos syndrome. Overall, the SSCP criteria provide a quantifiable and replicable characterisation of the cognitive profile associated with Sotos syndrome which can be used to differentiate between individuals with and without a diagnosis of Sotos syndrome.

Performance on the core scales of the EY battery of the BAS3 was also compared in order to establish whether young children with Sotos syndrome displayed a consistent cognitive profile. However, only 11 participants completed the EY battery. The analyses did not reveal significant differences in performance on the EY core scales, although there was a trend for participants to display relative strength in expressive language and relative weakness in spatial tasks. The fact that there were no significant differences in performance on the EY core scales is likely due to the small sample size. Furthermore, the EY core scales are not designed to assess visuospatial memory or quantitative reasoning so the findings from the EY battery cannot be used to determine whether the SSCP can be generalised to young children with Sotos syndrome.

Differences in intellectual ability in relation to gender have not previously been explored within the Sotos syndrome population. The findings from the present study indicated that females with Sotos syndrome had significantly higher GCA scores, compared to males with Sotos syndrome. This suggests that, on average, males with Sotos syndrome may be more likely to have a greater degree of intellectual disability than females with Sotos syndrome. No significant relationship was identified between age and GCA scores, indicating that increase or decrease in intellectual ability is not associated with age within the Sotos syndrome population. However, as the present study used a cross-sectional design, it will be important for future research to utilise a longitudinal design to establish the rate and trajectory of cognitive development within this population.

Establishing the cognitive profiles associated with congenital syndromes is valuable in discriminating between individuals with distinct syndromes (Mervis et al., 2000). Previous research has identified that individuals with Williams syndrome

typically display relative strength in verbal ability but relative weakness in non-verbal reasoning ability (Udwin & Yule, 1991) and the findings from the present study indicate that this is also characteristic of individuals with Sotos syndrome. However, by investigating differences in the abilities underlying these domains, these populations can be distinguished. For example, individuals with Williams syndrome typically display relative strength in auditory memory and relative weakness in pattern construction (Mervis et al., 2000) but individuals with Sotos syndrome display relative strength in visuospatial memory and relative weakness in quantitative reasoning. Although the focus of the present study was to conduct within-group comparisons, it will be important for future research to build on this initial work, using cross-syndrome comparisons. For example, this approach has been used to compare specific cognitive skills, such as face recognition, in individuals with autism, Williams syndrome and Down syndrome (Annaz, Karmiloff-Smith, Johnson, & Thomas, 2009) and to explore the dissociation between verbal and visuospatial short-term memory in individuals with Williams syndrome and Down syndrome (Jarrold, Baddeley, & Hewes, 1999; Wang & Bellugi, 1994). Thus, cross-syndrome comparisons will enable the specificity of the SSCP to be established and will contribute to understanding of the cognitive profiles associated with distinct congenital syndromes. In addition, this approach could inform understanding of the potential genetic and biological mechanisms underlying performance in specific cognitive domains.

The development of cognition is a complex process and there is considerable value in establishing cognitive profiles in infancy (Paterson, Brown, Gsödl, Johnson, & Karmiloff-Smith, 1999). In the present study, as the SSCP was established in relation to the core scales of the SA battery, children with Sotos syndrome under the age of 8 years were not included in the profile analysis. It will therefore be valuable

for future research to use tasks to assess skills such as visuospatial memory and quantitative reasoning in infants and young children with Sotos syndrome in order to determine whether the SSCP is consistent across age groups. This will inform understanding of the development of cognitive abilities within the Sotos syndrome population.

As identified in Chapter 2, previous research has established that the majority of individuals with Sotos syndrome display clinically significant behavioural symptomatology associated with ASD (Lane, Milne, & Freeth, 2017; Sheth et al., 2015). Therefore, it will be valuable for future research to further understanding of the relationship between Sotos syndrome and ASD by investigating the association between cognition and autistic features within this population and whether the cognitive profiles are similar or distinct. This will be explored in Chapter 5.

3.4.1. Conclusion

In summary, this is the first study to identify the cognitive profile associated with Sotos syndrome. The findings from the present study indicate that the Sotos syndrome population is relatively homogeneous, with participants displaying a clear and consistent profile of distinct cognitive strengths and weaknesses. The Sotos syndrome cognitive profile is characterised by relative strength in verbal ability and visuospatial memory but relative weakness in non-verbal reasoning ability and quantitative reasoning. Thus, the findings reported in this chapter provide important implications in relation to educational considerations for individuals with Sotos syndrome.

Chapter 4: Memory in Sotos syndrome

4.1. Introduction

As the findings from Chapter 3 identified that individuals with Sotos syndrome display relative strength in visuospatial memory, the aim of this chapter is to explore memory in more detail within the Sotos syndrome population. This was investigated using tasks from the diagnostic scales of the BAS3.

4.1.1. Memory

Memory is fundamental for learning as it enables individuals to process and store perceptual information. Short-term memory is the temporary storage of information for a brief period of time. Short-term memory can be differentiated from working memory, which is the temporary storage and maintenance of information, in the face of potential distraction, in order to guide behaviour and inhibit irrelevant information (Kane, Bleckley, Conway, & Engle, 2001). Thus, working memory involves the manipulation of information, as well as attentional control, in order to process and store information, so involves more complex processes than short-term memory (Cowan et al., 2005; Engle, Tuholski, Laughlin, & Conway, 1999).

In the Baddeley & Hitch model of the working memory system, working memory is comprised of three distinct subcomponents: the central executive, the phonological loop and the visuospatial sketchpad (Baddeley, 1986; Baddeley & Hitch, 1974). The central executive is the co-ordinating system which is responsible for high-level processing and two further domain-specific systems (the phonological loop and the visuospatial sketchpad) permit the short-term maintenance and temporary storage of verbal and visuospatial information. The phonological loop corresponds to a verbal

system and enables verbal information to be processed and maintained, so facilitates the acquisition of language (Baddeley, Gathercole, & Papagno, 1998). The visuospatial sketchpad corresponds to a visuospatial system, enabling visuospatial information to be processed and maintained. Research with typically developing children has identified that the capacity of verbal short-term memory and visuospatial short-term memory is subject to individual differences and that to some extent, the distinct memory stores are dissociable (Alloway, Gathercole, & Pickering, 2006; Pickering, Gathercole, & Peaker, 1998). In order to establish how individuals with Sotos syndrome process and store information, it is important to investigate whether there are differences in the capacity of verbal memory and visuospatial memory storage systems.

4.1.2. Memory in genetic syndromes

Memory impairments have been reported in individuals with intellectual disability (Van Der Molen, Van Luit, Jongmans, & Van Der Molen, 2007), as well as in individuals with genetically identified neurodevelopmental disorders such as Down syndrome, Williams syndrome and Fragile X syndrome. The impairments observed within these populations provide evidence to support the dissociation of verbal and visuospatial memory storage systems. For example, Down syndrome is associated with a selective impairment in verbal short-term memory and individuals with Down syndrome typically perform poorly on tasks which assess verbal serial order memory, such as digit span tasks (Brock & Jarrold, 2005; Jarrold & Baddeley, 1997; Lanfranchi, Cornoldi, & Vianello, 2004). This suggests that individuals with Down syndrome have a selective deficit in verbal short-term memory. In contrast, individuals with Williams

syndrome typically display a selective deficit in visuospatial short-term memory (Vicari, Brizzolara, Carlesimo, Pezzini, & Volterra, 1996). Further evidence for dissociation of verbal memory storage and visuospatial memory storage has been established in cross-syndrome comparisons of individuals with Williams syndrome and individuals with Down syndrome (Jarrold et al., 1999; Wang & Bellugi, 1994). These studies indicate that these genetically identified syndromes are associated with contrasting performance on tasks of verbal short-term memory and tasks of visuospatial short-term memory. This suggests a dissociation between the two storage systems and provides evidence for syndrome-specific memory profiles.

Long-term memory has been assessed using tasks such as the Doors and People test (Baddeley, Emslie, & Nimmo-Smith, 2006). This assessment involves tasks of both verbal and visuospatial recall, as well as verbal and visuospatial recognition and the delayed recall trials provide a measure of long-term memory. Jarrold, Baddeley, and Phillips (2007) used the Doors and People test with individuals with Down syndrome and individuals with Williams syndrome in order to determine whether individuals displayed general processing difficulties or whether the difficulties were specific to short-term memory. The findings demonstrated that participants with Williams syndrome displayed difficulties in both the short-term and long-term visuospatial memory tasks, suggesting that individuals with Williams syndrome have difficulty with visuospatial processing, as opposed to a specific deficit in short-term memory. For individuals with Down syndrome, deficit in verbal memory was specific to short-term memory and participants did not display relative deficit in performance on the verbal long-term memory task. This indicates that individuals with Down syndrome have a specific deficit in verbal short-term memory.

Individual differences in working memory performance have been associated with general intelligence, in that greater working memory capacity is associated with higher general intelligence (Conway, Cowan, Bunting, Therriault, & Minkoff, 2002). In addition, working memory impairments have been reported in individuals with intellectual disability (Bayliss, Jarrold, Baddeley, & Leigh, 2005). As individuals with neurodevelopmental disorders typically have intellectual disability, working memory impairments are common in individuals with neurodevelopmental disorders. For example, research with individuals with Fragile X syndrome has investigated the core components of the Baddeley & Hitch model of memory and identified a general impairment in working memory (Munir, Cornish, & Wilding, 2000). As working memory requires attentional control, working memory impairment in individuals with Fragile X syndrome may be associated with the attentional difficulties that are often prevalent within this population (Lanfranchi, Cornoldi, Drigo, & Vianello, 2009).

4.1.3. Memory in Sotos syndrome

As identified in the systematic review presented in Chapter 1, quantitative scores for specific cognitive domains have only been reported in one case study of a four year old child with Sotos syndrome (see section 1.3.3). Consequently, there is no published research reporting quantitative data on memory in a cohort of individuals with Sotos syndrome. However, the findings presented in Chapter 3 identified that individuals with Sotos syndrome display relative strength in visuospatial short-term memory (as measured by a recognition of designs task). The study presented in Chapter 3 investigated a range of different cognitive abilities but the only form of memory that was assessed in this study was visuospatial short-term memory. Specifically, the

recognition of designs task provides a measure of visuospatial recognition. Therefore, it is not clear whether individuals with Sotos syndrome have a relative selective strength in visuospatial memory or whether individuals also display relative strength in other memory domains. Furthermore, research has not investigated whether individuals with Sotos syndrome display a dissociation between verbal memory storage and visuospatial memory storage. In order to support learning in individuals with Sotos syndrome, it is important to explore memory within this population in order to establish whether individuals have relative selective strengths or deficits.

The primary aim of the present study was to investigate memory within the Sotos syndrome population and to establish whether individuals with Sotos syndrome have a relative selective strength in visuospatial memory or whether individuals perform comparably on tasks assessing other memory domains. Specifically, performance on three tasks assessing the core components of the Baddeley & Hitch model of memory were assessed: recall of digits forward (phonological loop), recognition of pictures (visuospatial sketchpad) and recall of digits backward (central executive). In addition, performance on recall of objects tasks (immediate and delayed trials) was compared in order to establish whether participants displayed differences in the capacity of short-term memory, long-term memory, verbal memory storage and visuospatial memory storage.

4.2. Method

4.2.1. Participants

Participants were a subset of individuals from the study presented in Chapter 3. Participants were included in this study if they completed all of the memory tasks

within the BAS3 diagnostic scales: the four recall of objects tasks, as well as the recall of digits forward, recognition of pictures and recall of digits backward tasks. As these tasks are used in both the EY and SA batteries, the analyses included participants from both batteries. Analyses were conducted using T-scores so that performance on the tasks was comparable. The sample comprised 38 participants (22 males) with a diagnosis of Sotos syndrome, ranging in age from 6 years 5 months to 50 years 3 months (*M* = 16.94 years, *SD* = 9.97 years). In total, 32 participants completed the SA battery and the remaining 6 participants completed the EY battery.

4.2.2. Measures

The BAS3 includes seven diagnostic scales which assess components of memory. These tasks are used in both the EY and SA batteries. Participants completed the BAS3 diagnostic scales in the same testing session as the BAS3 core scales, reported in the previous chapter. A brief description of the seven BAS3 diagnostic scales which assess memory and the specific abilities measured by each task is presented in table 4.1. The exact procedure for each of the memory tasks is explained below.

Table 4.1. Diagnostic scales

Diagnostic scales	Abilities measured
Recall of digits forward (RODF)	Short-term auditory memory (phonological loop)
Recognition of pictures (RP)	Short-term visuospatial memory (visuospatial sketchpad)
Recall of digits backward (RODB)	Working memory (central executive)
Recall of objects: immediate verbal (ROIV)	Short-term verbal memory
Recall of objects: immediate spatial (ROIS)	Short-term visuospatial memory
Recall of objects: delayed verbal (RODV)	Long-term verbal memory
Recall of objects: delayed spatial (RODS)	Long-term visuospatial memory

Recall of digits forward. The recall of digits forward task is essentially a digit span task. The experimenter says a sequence of numbers and participants are required to repeat the sequence. The sequences start with two numbers and participants complete five trials of each sequence length in each block, before progressing to a longer sequence. The task finishes if the participant fails two or more of the sequences within a block. This task provides a measure of verbal serial order recall, as well as an index of the phonological loop.

Recognition of pictures. In the recognition of pictures task, participants are shown a picture or pictures for 5 seconds. Participants are then presented with a set of pictures, including distractor pictures as well as the picture or pictures they were initially shown and are required to identify the correct picture or pictures. The task becomes progressively more difficult with participants required to remember up to four pictures. This task assesses visuospatial short-term recognition and provides an index of the visuospatial sketchpad.

Recall of digits backward. In the recall of digits backward task, the experimenter says a sequence of numbers and the participants are required to repeat the sequence in reverse order. Once again, there are five trials in each block and the trials start with two numbers, with the sequences become progressively longer (an extra number in each block). The task finishes if the participant fails two or more of the sequences within a block. This task provides a measure of working memory, as participants are required to hold the sequence in mind, whilst manipulating the information in order to repeat the sequence in reverse order. This ability is associated with the functioning of the central executive.

Recall of objects. The recall of objects task has four separate tasks which assess verbal short-term memory (ROIV), visuospatial short-term memory (ROIS), verbal long-term memory (RODV) and visuospatial long-term memory (RODS) for visually presented information. The task involves showing participants an A4 card with 20 small pictures of objects (e.g. tree, fire, ball). Participants have 40 seconds to memorise the objects and are then required to verbally recall as many of the objects as possible. For the next two trials, participants have a further 20 seconds to memorise the objects before verbally recalling the objects. After the three verbal recall trials, participants are then presented with a blank grid and picture cards of the objects. In

the spatial recall trial, participants are required to recreate the original object display by putting the picture cards in the correct spatial location. These tasks provide a measure of short-term memory in both verbal and visuospatial domains. Approximately 15 minutes after completing these trials, participants are required to repeat the tasks, starting with verbal recall and then spatial recall. Participants are not told that the tasks will be repeated. These delayed trials provide a measure of long-term memory in both verbal and visuospatial domains.

4.3. Results

The mean GCA of the 38 participants was 63.97 (*SD* = 16.14) and GCA scores ranged from 39 – 101. The participants were representative of the larger cohort reported in Chapter 3 (see section 3.3.1). Figure 4.1 displays mean T-scores for the seven BAS3 diagnostics scales which assess memory. In order to investigate different components of memory, the BAS3 diagnostic scales were analysed in two distinct analyses. The first set of analyses involved the three diagnostic scales which assess the core components of the Baddeley & Hitch model of memory: recall of digits forward (RODF), recognition of pictures (RP) and recall of digits backward (RODB). The RODF task was used as an index of the phonological loop, the RP task was used as an index of the visuospatial sketchpad and the RODB task was used as an index of the central executive. Performance on these tasks was compared in order to determine whether participants displayed relative selective strength or deficit in these aspects of memory. The second set of analyses relates to the four recall of objects tasks: immediate verbal (ROIV), immediate spatial (ROIS), delayed verbal (RODS) and delayed spatial (RODS). Performance on these tasks was compared in order to

investigate short-term memory, long-term memory, verbal storage and visuospatial storage in Sotos syndrome.

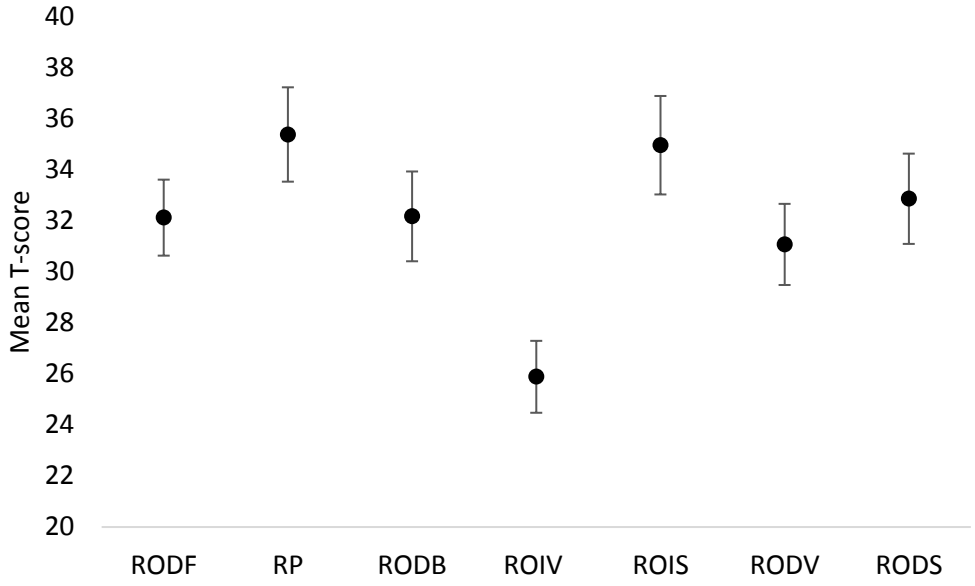


Figure 4.1. Mean T-scores for the BAS3 diagnostic scales. Error bars show +/- standard error.

4.3.1. Central executive, visuospatial sketchpad and phonological loop

Performance on three different memory tasks from the BAS3 diagnostic scales was compared in order to assess the core components of the Baddeley & Hitch model of memory: 'recall of digits forward' task (phonological loop), 'recognition of pictures' task (visuospatial sketchpad) and 'recall of digits backward' task (central executive).

Data were not normally distributed so non-parametric analyses were carried out. A Friedman test identified a significant difference between performance on the recall of digits forward (M = 32.13, SD = 9.17), recognition of pictures (M = 35.39, SD = 11.39) and recall of digits backward (M = 32.18, SD = 10.86) tasks ($x^2(2) = 7.41$,

p = .025). Post-hoc analyses using Wilcoxon signed-rank tests were used to determine whether there were significant differences in performance on the three tasks (p < .017 was required for statistical significance). The analyses revealed a significant difference between performance on the RP task and the RODF task (Z = -2.43, p = .016) and a significant difference between performance on the RP task and the RODB task (Z = -2.53, p = .012). There was no significant difference in performance on the RODF task and the RODB task (Z = -0.13, p = .900). This indicates that participants displayed relative strength in performance on a task associated with the functioning of visuospatial sketchpad, compared with performance on tasks associated with the functioning of the phonological loop and the central executive (see Figure 4.2).

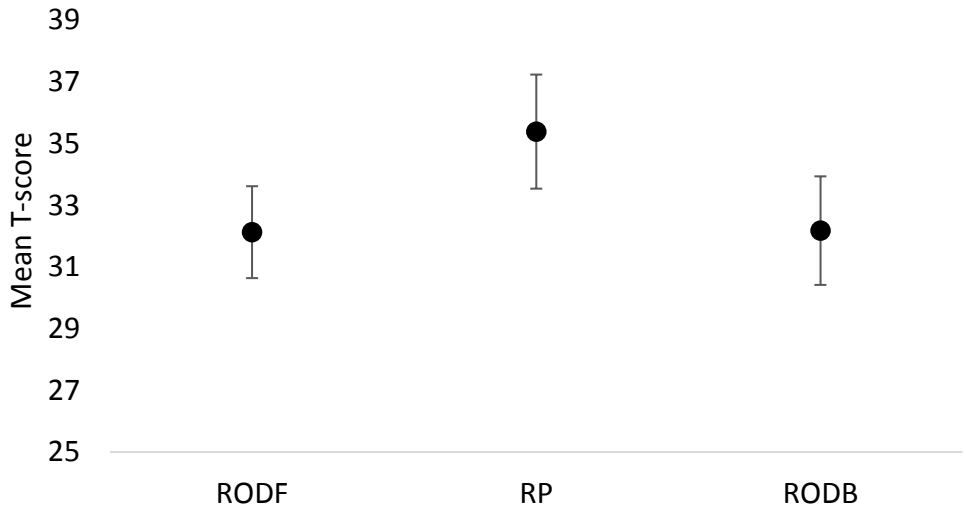


Figure 4.2. Mean T-scores for the recall of digits forward (RODF), recognition of pictures (RP) and recall of digits backward (RODB) tasks. Error bars show +/- standard error.

4.3.2. Recall of objects

Short-term memory. In order to determine whether participants displayed relative differences in verbal short-term memory and visuospatial short-term memory, performance on the recall of objects: immediate verbal (ROIV) and immediate spatial (ROIS) tasks were compared. For the purpose of analysis, T-scores were used. Data were not normally distributed so non-parametric analyses were carried out. A Wilcoxon signed-rank test revealed that performance on the ROIS task (M = 34.97, SD = 11.92) was significantly better than performance on the ROIV task (M = 25.89, SD = 8.66) (Z = -4.19, $p < .001$). This indicates that participants displayed relative strength in visuospatial short-term memory, compared with verbal short-term memory as evidenced by better performance on the visuospatial short-term memory task (ROIS). This supports the finding of a relative strength in visuospatial short-term memory, reported in the previous analyses.

The T-scores that are generated for these two tasks are based on slightly different scoring procedures as the ROIV task has three trials whereas the ROIS task has just one trial. The following analyses were carried out to check that the significant difference identified in relation to the T-scores was not simply the result of methodological factors. In order to check that scores were not affected by the number of trials, raw scores for each of the three trials of the ROIV task were compared to determine whether participants recalled significantly more objects on any of the three ROIV trials. The maximum raw score is 20 and the average raw score of the sample was calculated for each ROIV trial. A repeated measures ANOVA revealed no significant difference between the raw scores for trial 1 (M = 7.18, SD = 3.38), trial 2 (M = 6.18, SD = 3.34) or trial 3 (M = 7.03, SD = 3.60) ($F(2, 74) = 1.97$, $p = .147$). As there was no significant difference in performance between the three trials, an average

raw score was calculated for each participant on the basis of performance on all three trials. Table 4.2 shows the raw scores for all of the recall of objects tasks.

The average raw score for the ROIV task was then compared with the raw score for the ROIS task in order to determine whether there was a significant difference between the actual number of objects recalled in these two tasks. A Wilcoxon signed-rank test revealed a significant difference between raw scores for the ROIV task (M = 6.80, SD = 2.85) and ROIS task (M = 10.34, SD = 6.67) (Z = -3.44, p = .001), indicating that participants recalled significantly more objects on the visuospatial short-term memory task compared with the verbal short-term memory task. On average, participants recalled 34.00% of objects in the ROIV task, compared with 51.70% in the ROIS task. This supports the finding from the analysis using the T-scores for these two tasks and indicates that participants performed significantly better on the task requiring visuospatial short-term memory (ROIS), compared with verbal short-term memory (ROIV).

Long-term memory. As the previous analyses identified that participants displayed relative strength in visuospatial short-term memory compared with verbal short-term memory, performance on tasks of long-term memory were compared in order to establish whether there was also a significant difference in visuospatial long-term memory and verbal long-term memory. For this analysis, performance on the recall of objects: delayed tasks (RODV and RODS) were compared. The RODV and RODS tasks are exactly the same as the ROIV and ROIS tasks and were completed approximately 15 minutes after the ROIV and ROIS tasks. For the delayed STM tasks, only one trial was completed for the RODV and RODS tasks. Data were not normally

distributed so non-parametric analyses were carried out. A Wilcoxon signed-rank test revealed no significant difference between mean T-scores for the RODV task (M = 31.08, SD = 9.78) and RODS task (M = 32.87, SD = 10.94) (Z = -1.04, p = .300), indicating that there was no difference in performance between the verbal long-term memory and visuospatial long-term memory tasks. Furthermore, a Wilcoxon-signed rank test identified no significant difference between raw scores for the RODV and RODS tasks (Z = -1.14, p = .251), indicating that participants recalled a similar number of objects in both tasks. This is in contrast with the findings from the previous analysis of performance on the short-term memory tasks in which participants recalled significantly more objects in the visuospatial short-term memory task (ROIS), compared with the verbal short-term memory task (ROIV).

Table 4.2. Raw scores for each of the recall of objects tasks

Task	**M**	**SD**	**Range**
ROIV trial 1	7.18	3.38	2 – 15
ROIV trial 2	6.18	3.34	1 – 15
ROIV trial 3	7.03	3.60	1 – 18
ROIV average	6.80	2.85	2 – 14
ROIS	10.34	6.67	0 – 20
RODV	7.55	4.60	0 – 15
RODS	8.55	6.61	0 – 20

Verbal storage. The previous analyses revealed a significant difference in performance on the verbal and visuospatial short-term memory tasks but no significant difference in performance on the verbal and visuospatial long-term memory tasks. In order to examine verbal storage in more detail, performance on the verbal short-term memory and verbal long-term memory tasks was compared. Data were not normally distributed so non-parametric analyses were carried out. A Wilcoxon signed-rank test revealed a significant difference between mean T-scores for the ROIV task (M = 25.89, SD = 8.66) and RODV task (M = 31.08, SD = 9.78) (Z = -3.30, p = .001), indicating that participants had significantly better recall on the verbal long-term memory task compared with the verbal short-term memory task. Once again, raw scores for the ROIV task and RODV task were compared in order to determine whether there was a significant difference in the actual number of objects recalled. The average raw score for the ROIV task was used for the purpose of analysis and the raw scores for the ROIV and RODV tasks were normally distributed. A paired samples t-test revealed no significant difference in raw scores for the ROIV and RODV tasks (t(37) = -1.69, p = .100) indicating that participants recalled a similar number of objects in both of the tasks. This suggests that participants were able to effectively retain the objects in the verbal storage system and did not forget the objects between the immediate and delayed trials.

Visuospatial storage. In order to see whether there was a difference in performance on the visuospatial memory tasks, mean T-scores for the visuospatial short-term memory task (ROIS) and visuospatial long-term memory task (RODS) were compared. Data were not normally distributed so non-parametric analyses were carried out. A Wilcoxon signed-rank test revealed no significant difference between

mean T-scores for the ROIS task (*M* = 34.97, *SD* = 11.92) and RODS task (*M* = 32.87, *SD* = 10.94) (*Z* = 1.69, *p* = .089), indicating that participants displayed similar performance on both the short-term memory and long-term memory tasks. However, when comparing raw scores for the two tasks, a Wilcoxon signed-rank test revealed a significant difference in performance (*Z* = -3.07, *p* =.002), indicating that participants recalled significantly fewer objects on the visuospatial long-term memory task (RODS). Figure 4.3 displays the mean T-scores for all of the recall of objects tasks.

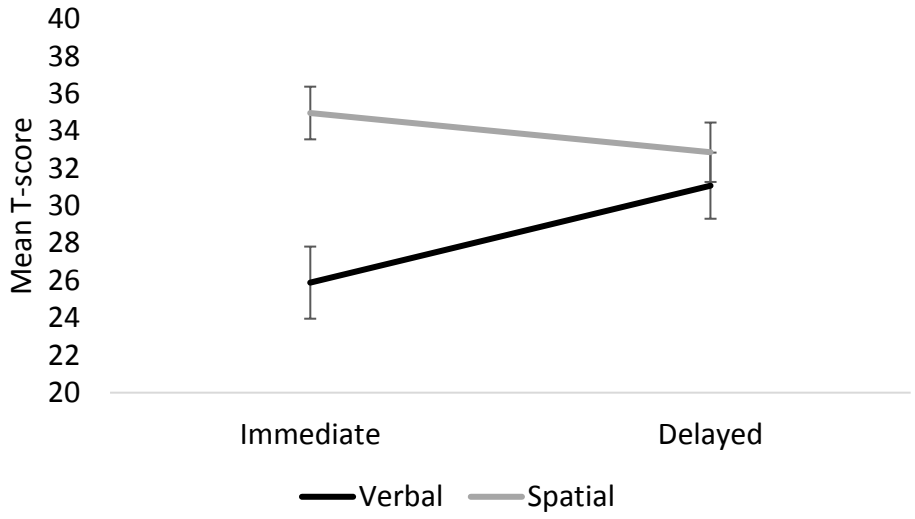


Figure 4.3. Mean T-scores of the four recall of objects tasks (immediate verbal, immediate spatial, delayed verbal and delayed spatial). Error bars show +/- standard error.

4.4. Discussion

The primary aim of the present study was to explore memory within the Sotos syndrome population and to establish whether individuals with Sotos syndrome display a relative selective strength in visuospatial memory or a general relative strength in memory. Initially, performance on three tasks assessing the core

components of the Baddeley & Hitch model of memory were compared. In addition, the capacity of short-term memory, long-term memory, verbal memory and visuospatial memory was assessed.

The Baddeley & Hitch model of memory (Baddeley, 1986; Baddeley & Hitch, 1974) was used as a theoretical basis for comparing performance on three tasks which assess the core components of the model. The analyses demonstrated no significant difference in performance between tasks assessing verbal short-term memory (RODF) and working memory (RODB), indicating that verbal short-term memory was comparative to working memory. However, performance on the task assessing visuospatial short-term memory (RP) was significantly better than performance on the RODF and RODB tasks. These findings suggest that individuals with Sotos syndrome display a relative selective strength in visuospatial short-term memory, as opposed to a selective deficit in verbal short-term memory, when compared with working memory ability.

In general, the findings presented in this study provide further evidence to support the dissociation of verbal short-term memory and visuospatial short-term memory which has been reported in previous research (Alloway et al., 2006; Pickering et al., 1998). In the comparison of verbal short-term memory and visuospatial short-term memory, as assessed by the ROIV and ROIS tasks, participants displayed a relative weakness in verbal short-term memory. This indicates that individuals with Sotos syndrome have a selective deficit in verbal short-term memory. This is consistent with the profile of performance that is typically observed in individuals with Down syndrome (Brock & Jarrold, 2005; Jarrold & Baddeley, 1997; Lanfranchi et al., 2004). Furthermore, this finding was observed when both T-scores and raw scores were used. This demonstrates that the difference in T-scores between the ROIV and

ROIS tasks was not simply a result of the scoring procedure as individuals recalled significantly less objects in the verbal short-term memory task. As participants performed better on the visuospatial recall task, as opposed to the verbal recall task, individuals with Sotos syndrome may find it easier to process and store information when using visuospatial strategies.

Comparison of performance on the same recall of objects task, assessing long-term memory as opposed to short-term memory, revealed no significant difference in performance on the verbal long-term memory (RODV) and visuospatial long-term memory (RODS) tasks. This was a consistent finding which was observed when both T-scores and raw scores were used. This suggests that participants used efficient encoding strategies as performance was comparable on both the verbal long-term memory and visuospatial long-term memory tasks, indicating that encoding strategies resulted in similar long-term recall for both verbal and visuospatial domains. Before completing the verbal long-term memory task, participants completed the visuospatial short-term memory task (ROIS). Therefore, it is important to consider that administration of the ROIS task provided participants with an additional opportunity to learn the objects and this could have supported performance in the verbal long-term memory task.

In terms of verbal memory storage, participants performed significantly worse on the verbal short-term memory (ROIV) task compared with the verbal long-term memory (RODV) task. This indicates that individuals with Sotos syndrome have a selective deficit in verbal short-term memory. Once again, this is consistent with the profile of performance that is typically observed in individuals with Down syndrome as research has established that individuals with Down syndrome have a selective deficit in verbal short-term memory but this deficit is not observed in tasks of verbal

long-term memory (Jarrold et al., 2007). It is important to note that a significant difference between the verbal short-term memory and verbal long-term memory tasks was only observed when T-scores were used. In contrast, the analysis of raw scores did not identify a significant difference in the actual number of objects that participants recalled. This finding suggests that individuals with Sotos syndrome were able to retain the information in the verbal storage system. As the previous analyses have demonstrated a relative selective strength in visuospatial memory, it is possible that completion of the ROIS task supported learning of the objects, resulting in better performance in the RODV task. Therefore, when compared with the typically developing normative sample, individuals with Sotos syndrome had particularly poor verbal short-term memory. However, analysis of the raw scores indicated no significant difference in the capacity of verbal short-term memory and verbal long-term memory for individuals with Sotos syndrome.

In relation to visuospatial memory storage, there was no significant difference between performance on the visuospatial short-term memory (ROIS) and visuospatial long-term memory (RODS) tasks when comparing the mean T-scores for these tasks. This suggests that, compared with the typically developing normative sample, participants performed similarly on both tasks. However, when comparing the raw scores on the ROIS and RODS tasks, participants recalled significantly fewer objects on the visuospatial long-term memory task compared with the visuospatial short-term memory task. As there was a significant difference between the mean T-scores for these two tasks, the findings indicate that individuals with Sotos syndrome displayed a similar profile of performance compared with the typically developing normative sample.

The mean T-score for the recall of digits backward task indicates that, in general, participants performed worse than the typically developing normative sample. This is consistent with previous literature, indicating that individuals with intellectual disability typically have difficulty with working memory (Bayliss et al., 2005). However, performance was not indicative of a selective deficit in working memory so a general difficulty with working memory could be attributable to intellectual disability, rather than being syndrome-specific. It has been suggested that the working memory deficits observed in individuals with Fragile X syndrome are associated with attentional difficulties (Munir et al., 2000). It will therefore be important for future research to explore attention within the Sotos syndrome population as to date, it is not clear whether individuals display significant attentional difficulties (Lane et al., 2016). However, if attentional control is an issue for individuals with Sotos syndrome, attention could be associated with working memory performance within this population.

Serial order recall was assessed using a verbal short-term memory task within the present study but a measure of serial order recall using a visuospatial short-term memory task was not included. This was due to the fact that the BAS3 diagnostic scales do not assess visuospatial serial order recall. Thus, it will be important for future research to assess serial order recall for both verbal short-term memory and visuospatial short-term memory in order to establish whether individuals with Sotos syndrome also display a relative strength in visuospatial serial order recall.

Performance on the recall of objects task indicated that participants displayed a selective deficit in verbal short-term memory, compared with visuospatial short-term memory. This task assessed verbal short-term memory using a verbal recall task. In addition, performance on the recall of digits forward task was significantly worse than

performance on the recognition of pictures task. However, in this analysis, verbal short-term memory was assessed using a serial order recall task whilst visuospatial short-term memory was assessed using a recognition task. This suggests that verbal short-term memory is selectively impaired, when compared with visuospatial short-term memory. In contrast, performance on the recall of digits forward task was comparable with performance on the recall of digits backward task, indicating that participants did not display a selective deficit in verbal short-term memory when compared with working memory. It will therefore be important for future research to use a broad range of tasks to assess different components of memory in order to establish the extent to which individuals with Sotos syndrome have a selective deficit in short-term memory. For example, the Doors and People test would be an appropriate measure to use as it can be used to assess both short-term and long-term memory for verbal and visuospatial information and has been used with individuals with Down syndrome and Williams syndrome (Jarrold et al., 2007).

The focus of the present study was to explore within-group differences but it will be important for future research to use a cross syndrome-approach in order to establish whether the memory profile is syndrome-specific. In addition, a cross-syndrome approach could provide insight into the extent to which differences in the syndrome-specific cognitive profiles may be associated with selective deficits in distinct memory domains. For example, the broad cognitive profiles of Down syndrome and Sotos syndrome appear to be distinct as individuals with Down syndrome display relative weakness in verbal ability (Wang, 1996) whereas for individuals with Sotos syndrome, verbal ability is a relative strength (see Chapter 3). However, the findings from the present study suggest that individuals with Sotos syndrome have a selective deficit in verbal short-term memory and this deficit has also

been reported in individuals with Down syndrome (Jarrold & Baddeley, 1997). It has been proposed that the phonological loop may be related to language learning (Baddeley et al., 1998). Therefore, a direct comparison of individuals within these two populations may provide insight into the extent to which verbal short-term memory is associated with language development.

In general, the central executive does not appear to be selectively impaired within the Sotos syndrome population, as evidenced by performance on the working memory task (RODB). It will be important for future research to investigate other executive functions, such as inhibitory control and cognitive flexibility, within the Sotos syndrome population in order to determine whether individuals have selective deficits in distinct executive functions.

4.4.1. Conclusion

In summary, the findings presented in this chapter demonstrate that individuals with Sotos syndrome display selective relative strength in visuospatial memory, as evidenced by superior performance on several tasks assessing visuospatial memory. However, it is important to note that participants displayed impairment in all memory domains, compared with typically developing individuals, as the mean T-scores were below the standardisation sample average. Therefore, the selective strength in visuospatial memory observed in individuals with Sotos syndrome should be interpreted as a relative strength. In general, the findings have important implications for considering how individuals with Sotos syndrome process information and the types of strategies which may support effective learning within this population, such as the use of pictures and physical representations when presenting information.

Overall, this study has provided an initial exploration of memory within the Sotos syndrome population but it will be important for future research to investigate memory in more detail, using alternative measures and a cross-syndrome approach.

Chapter 5: Communication skills and verbal ability explain variation in autistic behaviour traits in Sotos syndrome

5.1. Introduction

So far, the findings presented within this thesis have demonstrated that Sotos syndrome is associated with clinically significant ASD symptomatology, as well as a clear and consistent profile of relative cognitive strengths and weaknesses. The findings from Chapter 2 identified inter-individual variation in relation to severity of ASD symptomatology within the Sotos syndrome population. In addition, the findings from Chapter 3 established considerable variability in level of intellectual ability for individuals with Sotos syndrome. Therefore, the focus of the present study is to explore the cognitive and behavioural phenotype associated with Sotos syndrome in more detail and to establish whether certain factors explain individual differences in the severity of the phenotype. Specifically, the aims of this study are to establish whether cognitive factors such as intellectual ability and verbal ability explain inter-individual variation in severity of autistic behaviour traits within the Sotos syndrome population and to explore the language profile associated with Sotos syndrome.

5.1.1. Sotos syndrome and ASD – recap

Until recently, the cognitive and behavioural phenotype of Sotos syndrome was considerably under-researched. The systematic review of all published research articles reporting data on cognition and behaviour in Sotos syndrome (N = 34), presented in Chapter 1, identified a potential association between Sotos syndrome and autism spectrum disorder (ASD) (Lane et al., 2016). Since this systematic search was conducted, two studies have investigated the relationship between Sotos syndrome and ASD using larger samples (Lane et al., 2017; Sheth et al., 2015). As well as

investigating the prevalence of autistic behaviour traits in Sotos syndrome, the effects of age and gender on severity of autistic behaviour traits were explored in Chapter 2. The findings identified a significant effect of age but no effect of gender on severity of SRS-2 total T-scores (Lane et al., 2017). Although the prevalence of autistic behaviour traits in Sotos syndrome has been established, it is not clear whether other specific factors, such as intellectual ability and language ability, are associated with variation in severity of autistic behaviour traits within this population. The current study will improve understanding of the facets of cognition associated with behaviour within this population. In addition, identification of relationships between factors may provide evidence to suggest potential mechanisms underlying these relationships.

5.1.2. Factors associated with severity of autistic behaviours

Intellectual disability (IQ < 70) is often co-morbid with ASD and has been reported to occur in approximately 50% of individuals with ASD (Baird et al., 2006; Lai, Lombardo, & Baron-Cohen, 2014). Similarly, intellectual disability is one of the cardinal features of Sotos syndrome and the majority of individuals with Sotos syndrome have intellectual disability or borderline intellectual functioning (IQ 70 – 84). However, a significant range in intellectual ability has been reported within this population (see Chapter 3) and this indicates that, for individuals with Sotos syndrome, there may be predictors of intellectual ability but these are yet to be identified.

The Social Responsiveness Scale (SRS) is a 65-item questionnaire designed to provide a quantitative measure of severity of autistic behaviour traits. This measure and the more recent second edition (SRS-2) are commonly used in research to assess autistic behaviour traits. Some studies have found that factors such as age (Bölte et al.,

2008) and intelligence (Charman et al., 2007) are not associated with severity of scores on the SRS/SRS-2. In contrast, other research has identified several factors which affect scores on the SRS/SRS-2, including behavioural problems, expressive language ability and non-verbal IQ (Havdahl et al., 2016; Hus, Bishop, Gotham, Huerta, & Lord, 2013). This indicates that, for individuals with idiopathic ASD, there may be specific predictors of severity of autistic behaviours. However, the findings are inconsistent and this could be due to the heterogeneity of ASD (Geschwind & Levitt, 2007).

Research focusing on genetic syndromes in which autistic behaviour traits are heightened enables relationships between cognitive factors and autistic behaviour traits to be investigated within a homogeneous population. For example, a significant association between autistic behaviour traits and intellectual ability has been identified in syndromes of known genetic cause, such as Fragile X syndrome (FXS) (Loesch et al., 2007) and Tuberous Sclerosis Complex (TSC) (Granader et al., 2010; Jeste, Sahin, Bolton, Ploubidis, & Humphrey, 2008). Specifically, lower intellectual ability is associated with greater severity of autistic behaviour traits within these populations. This indicates that a specific mechanism may be associated with both autistic behaviour traits and intellectual ability within these populations. As Sotos syndrome has a known genetic cause and is associated with heightened autistic behaviour traits, it is therefore important to explore whether autistic behaviour traits are associated with cognitive factors within the Sotos syndrome population. This may provide further insight into the potential mechanisms underlying autistic behaviour traits and intellectual ability.

5.1.3. Cognitive profiles of Sotos syndrome and ASD

The findings from the study presented in Chapter 3 established the cognitive profile associated with Sotos syndrome and identified that verbal (V) ability is a relative strength within this population, compared with non-verbal reasoning (NVR) ability and spatial (S) ability. Broadly, this indicates that the cognitive profiles associated with Sotos syndrome and ASD may be distinct as, historically, the cognitive profile associated with ASD has been characterised by relative strength in performance IQ and relative weakness in verbal IQ, as well as relative strength in block design tasks (Happe, 1994). However, research has identified significant heterogeneity in relation to the cognitive profile of ASD (Charman et al., 2011; Joseph, Tager-Flusberg, & Lord, 2002). For example, Joseph et al. (2002) investigated the cognitive profiles of children with ASD using the Differential Ability Scales (DAS). The findings from this study identified significant variability in the cognitive profiles; some participants displayed relative strength in non-verbal reasoning ability and others displayed relative strength in verbal ability. Thus, the suggested profile of relative strength in performance IQ and relative weakness in verbal IQ (Happe, 1994) is not universally observed within the ASD population. The present study aimed to investigate whether specific aspects of cognition, such as V ability, NVR ability and S ability explain variance in severity of autistic behaviour traits for individuals with Sotos syndrome. This will provide insight into the relationship between the Sotos syndrome cognitive profile and severity of autistic behaviour traits within the Sotos syndrome population.

5.1.4. Language and communication in Sotos syndrome

Several studies have reported communication impairment and language delays in Sotos syndrome. Finegan et al., (1994) conducted the most comprehensive study of language skills in individuals with Sotos syndrome to date and found that language ability was consistent with overall intellectual ability. However, this study focused on the discrepancy between verbal comprehension and expressive language and therefore did not investigate specific communication skills, such as pragmatic ability and language structure. In relation to language ability in Sotos syndrome, the majority of studies have used small samples and the prevalence and nature of the communicative impairments has not been explored (see section 1.3.4). It is therefore important to establish whether individuals with Sotos syndrome display a consistent and characteristic profile of communication impairment and the extent to which individuals experience difficulty with pragmatic and structural aspects of language. This will enable a more comprehensive overview of language and communication within the Sotos syndrome population.

The Children's Communication Checklist, second edition (CCC-2) is a valid measure for differentiating between individuals with distinct communicative impairments (Norbury, Nash, Baird, & Bishop, 2004) and has also been found to correlate with the SRS (Charman et al., 2007). However, the SRS is designed to focus on behavioural symptomatology whilst the CCC-2 has a greater focus on communicative difficulties. In particular, the CCC-2 is effective in distinguishing between individuals with a language profile consistent with developmental language disorder (DLD) and individuals with a language profile consistent with ASD (Geurts & Embrechts, 2008; Norbury et al., 2004). Broadly, individuals with DLD typically display greater difficulty with structural aspects of language whilst individuals with

ASD typically display greater difficulty with pragmatic aspects of language. Investigation of the pragmatic language skills and structural language skills of individuals with Sotos syndrome will determine whether these individuals display linguistic profiles that are similar or distinct to the established profiles associated with other developmental disorders, such as DLD and ASD.

In summary, there is a clear link between Sotos syndrome and ASD, as evidenced by a high prevalence of autistic behaviour traits within this population. However, there is considerable inter-individual variation in severity of autistic behaviour traits within this population and to date, cognitive factors which could explain this variance have not been identified. The study presented within this chapter had two aims. The first of these was to investigate whether intellectual ability accounts for variation in severity of autistic behaviour traits for individuals with Sotos syndrome and if so, whether particular aspects of cognition, such as V ability, NVR ability and S ability, explain variance in autistic behaviour traits. An additional aim of this study was to explore the language profile associated with Sotos syndrome and to establish whether the pragmatic language deficit typically observed in ASD is present in individuals with Sotos syndrome.

5.2. Method

5.2.1. Participants

The sample comprised 42 participants (21 females) with a diagnosis of Sotos syndrome. Mean age of the sample was 15.6 years (*SD* = 10.07 years), participants ranged in age from 3 years 8 months to 50 years 3 months. Participants were a subset of participants reported in the previous chapters. Families were recruited via the Child

Growth Foundation (CGF; a UK charity that supports families of individuals affected by growth disorders) and advertisements on a Sotos syndrome support group on social media (the 'Sotos Syndrome – UK' group on Facebook). In order to assess eligibility for the study, families were required to complete a screening form. If their child or partner had received a diagnosis of Sotos syndrome, they were invited to participate in the study.

5.2.2. Measures

The British Ability Scales, third edition (BAS3). The BAS3 is a standardised cognitive assessment designed to assess a range of cognitive abilities (see section 3.2.2 for a detailed description of this measure).

The Social Responsiveness Scale, second edition (SRS-2). The SRS-2 is a 65-item questionnaire designed to assess severity of autistic behaviour traits (see section 2.2.2 for a detailed description of this measure).

The Children's Communication Checklist, second edition (CCC-2). The CCC-2 is a 70-item questionnaire which can be used to identify children with significant communicative problems. Items are coded on a Likert scale to determine the frequency of communicative difficulties (0 = less than once a week or never to 3 = several times a day or always). The questionnaire can also be used to assess deficit in language structure skills and pragmatic/social communication skills. The CCC-2 has 10 subscales which assess: (A) speech; (B) syntax; (C) semantics; (D) coherence; (E) inappropriate initiation; (F) stereotyped language; (G) use of context; (H) nonverbal communication; (I) social relations; (J) interests. Each of the subscales has 7 items; 5 relate to communicative difficulties and 2 relate to communicative strengths.

Two composite scores are derived from the CCC-2: the General Communication Composite (GCC) and the Social Interaction Deviance Composite (SIDC). The GCC provides a general indication of the communicative ability of a child and is calculated as the sum of scores on the 10 subscales. The SIDC provides an indication of the discrepancy between language structure skills and pragmatic/social communication skills. The SIDC is calculated as the difference between the sum of scales (E, H, I and J) and the sum of scales (A, B, C and D). In addition, a language structure score (sum of scales A, B, C and D) and a pragmatic language score (sum of scales E, F, G and H) can be calculated in order to directly compare language structure skills and pragmatic language skills.

The Communication Checklist – Adult (CC-A) (Whitehouse & Bishop, 2009). The CC-A has the same format as the CCC-2 but the item content is modified in order to be appropriate for use with adults. As with the CCC-2, the CC-A has 70 items which are coded on a Likert scale to determine the frequency of communicative difficulties (0 = less than once a week or never to 3 = several times a day or always). A total score provides an indication of the general communicative ability of an adult.

5.2.3. Procedure

Participants were included in the study if they completed all six core scales of the BAS3 and their parent/caregiver or spouse completed the SRS-2. In addition, the parent/caregiver completed the CCC-2 for 23 participants (11 females) ranging in age from 4 years 3 months to 16 years 5 months (M = 9.89 years, SD = 3.29 years). The CC-A was completed by the parent/caregiver or spouse for 13 participants (7 females), ranging in age from 17 years, 3 months – 50 years, 3 months (M = 26.83 years, SD =

9.41 years). Licensing was received by the publishers of the SRS-2, CCC-2 and CC-A to allow online administration of the questionnaires.

All families provided informed consent. The parent/caregiver of each participant provided consent for each of the questionnaire measures. For completion of the BAS3, the parent/caregiver provided consent for children under the age of 18 years and participants aged 18 years and over provided their own consent. The study received ethical approval from the university departmental ethics committee.

5.3. Results

5.3.1. Relationship between intellectual ability and autistic behaviour traits

In order to investigate whether there was a significant relationship between intellectual ability and autistic behaviour traits within the Sotos syndrome population, a Pearson's bivariate correlation was used to determine the relationship between GCA scores and SRS-2 total T-scores. The analysis identified a moderate negative correlation (r = -.334, N = 42, p = .03) between GCA scores (M = 63.71, SD = 16.34) and SRS-2 total T-scores (M = 78.64, SD = 15.52). This suggests that, within the Sotos syndrome population, greater severity of autistic behaviour traits is associated with lower overall cognitive ability level (see Figure 5.1).

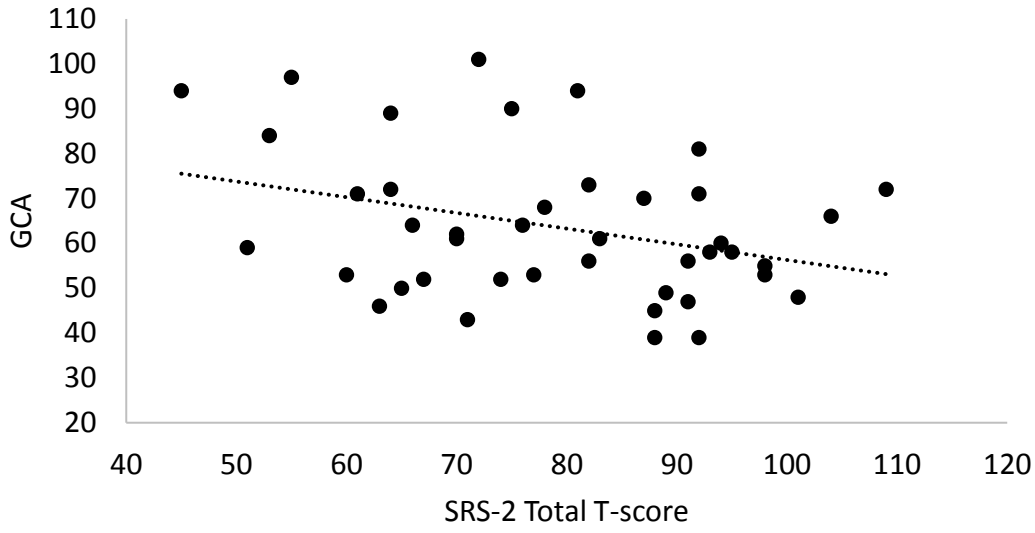


Figure 5.1. Relationship between GCA scores and SRS-2 total T-scores.

5.3.2. Predictive value of BAS3 cluster scores on autistic behaviour traits

As a significant relationship was identified between intellectual ability and autistic behaviour traits, a multiple regression analysis was used to determine whether specific aspects of cognition, as assessed by the BAS3 cluster scores (V ability, NVR ability and S ability), were significant predictors of SRS-2 total T-scores. The regression equation was significant ($F(3, 38) = 3.30$, $p = .031$, $R^2 = .21$). Inspection of the beta weights revealed that V ability was a significant predictor of SRS-2 total T-scores but that NVR ability and S ability did not significantly predict SRS-2 total T-scores (see Table 5.1).

Table 5.1. Multiple regression analysis of BAS3 cluster scores and SRS-2 total T-scores

Variable	B	SE B	Sig.
Verbal ability	-.624	.238	.013
Non-verbal reasoning ability	.233	.267	.388
Spatial ability	0.78	.232	.740

R^2= .21

5.3.3. Functional language profile

Within the CCC-2, the social interaction deviance composite (SIDC) score can be used to discriminate between different types of communicative problems. Specifically, the SIDC score provides an indication of the extent to which an individual has relative difficulty with either language structure or pragmatic aspects of language. The SIDC is interpreted when an individual has a GCC score ≤ 55. A negative SIDC score indicates that an individual has greater difficulty with pragmatic aspects of language, relative to language structure and this profile is characteristic of ASD (Bishop, 2003). In contrast, an SIDC score ≥ 9 suggests that an individual has particular difficulty with language structure, relative to pragmatic language and this profile is characteristic of developmental language disorder (DLD) (Bishop, 2003).

Within the sample (n = 23), SIDC scores ranged from -12 – 23 (M = 2.43, SD = 8.35). Eight participants (35%) met criteria for an ASD language profile and three participants (13%) met criteria for a DLD language profile. The remaining eleven participants (48%) with GCC ≤ 55 had communicative impairment but did not meet criteria for either an ASD or DLD language profile. This suggests that children with Sotos syndrome do not display a consistent profile of relative difficulty with either

language structure or pragmatic language. Figure 5.2 shows the GCC and SIDC scores for each participant and demonstrates the variability in SIDC scores within the sample.

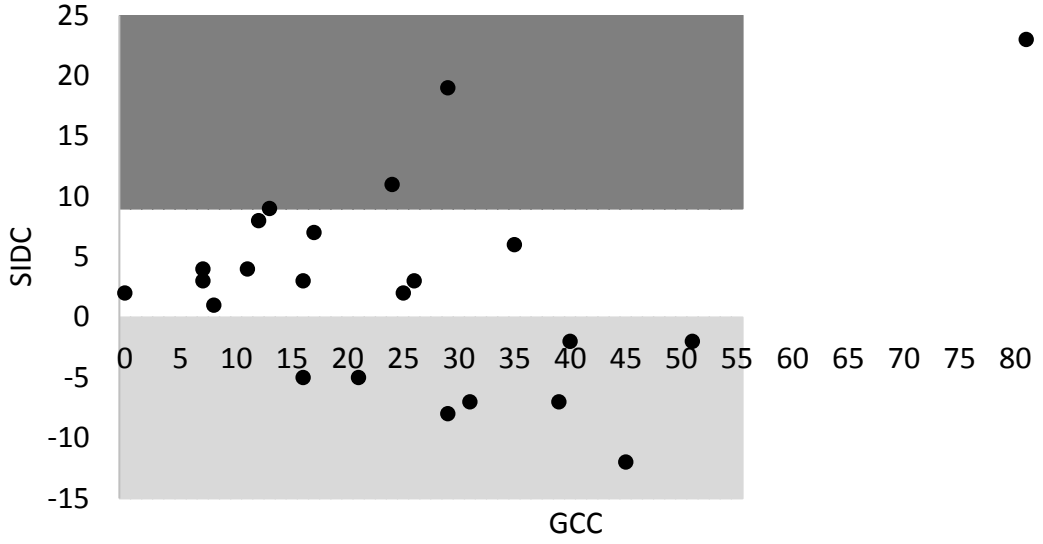


Figure 5.2. GCC scores and SIDC scores for each participant. Participants in the dark grey band had language profiles characteristic of DLD and participants in the light grey band had language profiles characteristic of ASD.

In order to explore the language profile in more detail, language structure scores were directly compared with pragmatic language scores. Data were not normally distributed so non-parametric analyses were carried out. A Wilcoxon signed-rank test revealed no significant difference between mean language structure scores (M = 12.17, SD = 9.18) and mean pragmatic language scores (M = 14.17, SD = 10.36) (Z = -1.09, p = .276). This demonstrates that children with Sotos syndrome display similar difficulty with both language structure and pragmatic language skills.

The SIDC is not available for the CC-A. However, the CC-A has three composite scales which can be used to investigate the functional language profile: structural language, pragmatic skills and social engagement. The composite scales are measured as scaled scores and a scaled score of 6 or less indicates that an individual

has communicative impairment. Relative deficit in the structural language composite scale (scaled score of 5 or less) with a normal scaled score (7 or more) for the pragmatic skills composite is suggestive of a DLD language profile. In contrast, relative deficit in the pragmatic skills composite scale (scaled score of 5 or less) with a normal scaled score (7 or more) for the language structure composite is suggestive of an ASD language profile.

Within the sample (n = 13), one participant (8%) had scaled scores suggestive of an ASD language profile. The remaining 12 participants (92%) had communicative impairment but did not have scaled scores suggestive of either a DLD or ASD language profile. This suggests that adults with Sotos syndrome do not display a consistent profile of relative deficit in either structural language or pragmatic skills.

5.3.4. *Relationship between functional language ability and autistic behaviour traits*

In order to explore the relationship between language and autistic behaviour traits within the Sotos syndrome population, functional language ability was investigated. Functional language was assessed on the basis of GCC scores for children (n = 23) with Sotos syndrome (4 – 16:11 years) and CC-A total Z-scores for adults (n = 13) with Sotos syndrome (17 years and older).

Functional language ability and autistic behaviour traits in children. GCC scores ranged from 1 – 82 (M = 26.35, SD = 18.00). GCC scores ≤ 55 indicate that an individual has significant communicative problems. In total, 22 participants (96%) had GCC scores within this range. This suggests that the majority of children with Sotos syndrome have significant communication impairment. GCC scores were not normally distributed so non-parametric analyses were carried out.

In order to determine whether functional language ability was related to severity of autistic behaviour traits in children with Sotos syndrome, Spearman's rank was used to investigate the relationship between GCC scores and SRS-2 total T-scores. The analysis revealed a strong negative correlation between these variables (r_s = -.712, N = 23, p < .001), indicating that weaker communication skills are associated with greater severity of autistic behaviour traits for children with Sotos syndrome (see Figure 5.3).

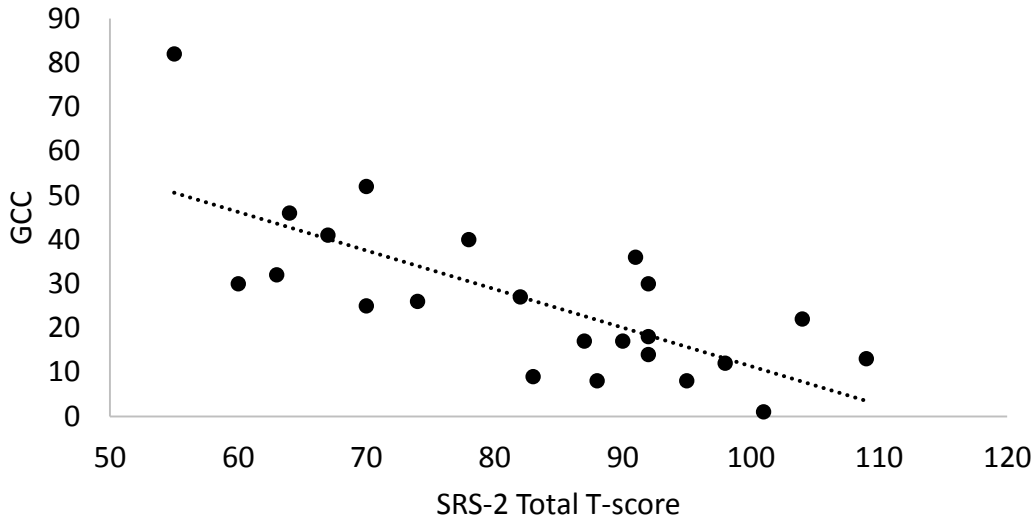


Figure 5.3. Relationship between GCC scores and SRS-2 total T-scores.

Functional language ability and autistic behaviour traits in adults. CC-A total Z-scores ranged from -4 to -1.8 (M = -3.02, SD = 1.16). A total Z-score < -1 suggests that an individual has communicative difficulties. All participants had total Z-scores < -1, indicating that all of the adults within our sample displayed communicative impairment. Six of the participants (46%) scored at floor and all participants scored below the 4th percentile. CC-A Z-scores were not normally distributed so non-parametric analyses were carried out.

In order to establish whether functional language ability was related to severity of autistic behaviour traits in adults with Sotos syndrome, Spearman's rank was used to investigate the relationship between CC-A total Z-scores and SRS-2 total T-scores. The analysis revealed a strong negative correlation between these variables (r_s = -.605, N = 13, p = .029), indicating that weaker communication skills are associated with greater severity of autistic behaviour traits for adults with Sotos syndrome (see Figure 5.4).

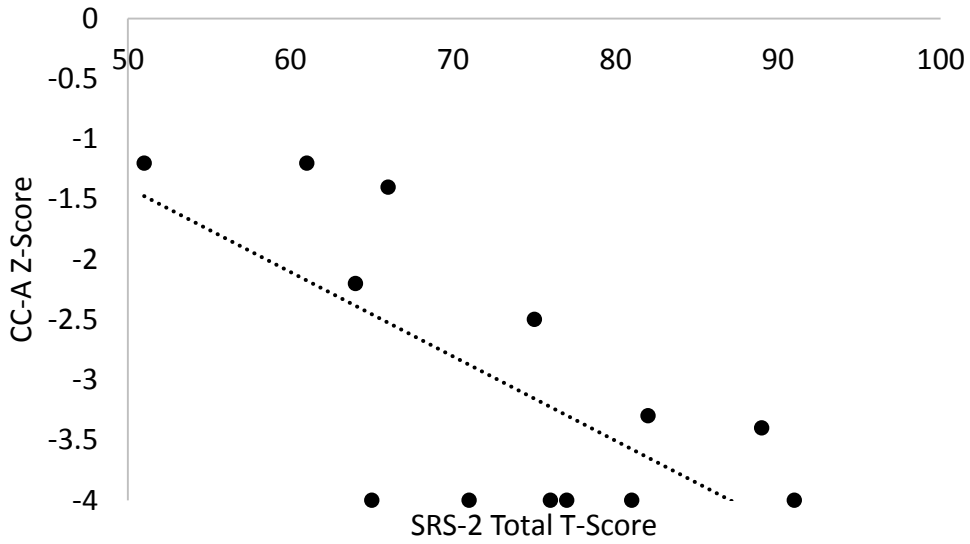


Figure 5.4. Relationship between CC-A total Z-scores and SRS-2 total T-scores.

5.4. Discussion

The present study aimed to investigate whether intellectual ability accounts for variance in severity of autistic behaviour traits within the Sotos syndrome population and if so, whether specific aspects of cognition (V ability, NVR ability and S ability) explain variance in severity of autistic behaviour traits. A further aim of the study was to explore the language profile of individuals with Sotos syndrome and to establish

whether individuals with Sotos syndrome display a language profile consistent with that observed in ASD.

Within the sample of 42 individuals with Sotos syndrome, lower intellectual ability was associated with greater severity of autistic behaviour traits, indicating that higher intellectual ability could be a protective factor for autistic behaviour traits within the Sotos syndrome population. This is in contrast with previous research of individuals with ASD or other special educational needs (Charman et al., 2007) in which intellectual ability was not related to severity of autistic behaviour traits, as assessed by the SRS. However, our findings are consistent with findings from research with other genetic syndromes, such as FXS (Loesch et al., 2007) and TSC (Granader et al., 2010; Jeste et al., 2008), in which intellectual ability has been associated with severity of autistic behaviour traits. It is possible that, within these syndromes of known genetic cause, a shared mechanism may account for variation in the severity of the cognitive and behavioural phenotype.

In order to further understanding of the relationship between cognition and autistic behaviour traits within the Sotos syndrome population, the extent to which specific aspects of cognition were significant predictors of autistic behaviour traits was explored. Verbal ability, as assessed by the V ability cluster of the BAS3, accounted for a significant proportion of variance in autistic behaviour traits within the sample. This suggests that poor verbal ability is a significant predictor of severity of autistic behaviour traits for individuals with Sotos syndrome. Interestingly, NVR ability was not a significant predictor of autistic behaviour traits within our sample. This is in contrast with research involving individuals with idiopathic ASD and individuals with other neurodevelopmental disorders (not associated with genetic syndromes) in which severity of autistic behaviour traits is associated with NVR ability (Havdahl et al.,

2016). This finding advances understanding of the relationship between Sotos syndrome and ASD and the potential differences in relation to the cognitive profiles of these disorders, as distinct aspects of cognition predict severity of autistic behaviour traits within these populations.

In terms of language, the majority of participants had significant global communicative impairment, as assessed by the CCC-2, with only one participant scoring in the normal range. Children with Sotos syndrome displayed varying functional language profiles and there was no difference between language structure skills and pragmatic language skills. In addition, all of the adults included in the present study displayed communicative impairment, as assessed by the CC-A, demonstrating that communication difficulties persist into adulthood within the Sotos syndrome population. Overall, the findings support previous research demonstrating that individuals with Sotos syndrome typically display communication impairment (Finegan et al., 1994; Lane et al., 2016). Furthermore, the findings from the present study extend previous research by identifying that individuals with Sotos syndrome can have difficulty with both pragmatic and structural aspects of language.

As well as investigating the functional language profile of individuals with Sotos syndrome, an association between functional language ability and autistic behaviour traits was observed. Specifically, poor functional language ability, as assessed by the CCC-2, was associated with greater severity of autistic behaviour traits, as assessed by the SRS-2. It is important to note that scores on the SRS and the CCC-2 have been found to correlate (Charman et al., 2007), indicating that there may be some overlap between the behaviours assessed by these measures. Therefore, it will be important for future research to use alternative measures of functional language ability and autistic behaviour traits in order to establish whether this is a consistently

observed relationship within the Sotos syndrome population, regardless of the measures used.

As identified in the systematic review presented in Chapter 1, previous research has suggested that behaviours such as anxiety, ADHD and aggression/tantrums are common in Sotos syndrome (Lane et al., 2016). Future research should investigate the extent to which emotional/behavioural problems are associated with severity of autistic behaviour traits as previous research has identified that emotional/behavioural problems may be associated with elevated scores on the SRS-2 (Havdahl et al., 2016; Hus et al., 2013). Therefore, it will be important for future research to assess the behavioural phenotype of Sotos syndrome in more detail and to explore the relationship between emotional/behavioural problems and autistic behaviour traits within this population.

5.4.1. Clinical Implications

An important clinical implication of the findings from the present study is that individuals with Sotos syndrome who have moderate/severe intellectual disability are more likely to display increased severity of autistic behaviour traits. It is therefore important for clinicians to screen for ASD within this population and, in particular, to screen for ASD in individuals with moderate/severe intellectual disability. Furthermore, the findings from the present study demonstrate that most individuals with Sotos syndrome display significant communicative difficulties. However, a consistent functional language profile was not observed within the sample. Therefore, it is important to support language development within this population and to provide general support in relation to communication skills. Interventions should focus on both

pragmatic and structural aspects of language and individual assessments of children with Sotos syndrome will enable support to be targeted to the specific needs of the child.

5.4.2. Conclusion

In summary, the findings reported in this chapter facilitate understanding of the extent to which cognitive factors explain variance in autistic behaviour traits within this syndromic cause of autism. Specifically, intellectual ability is associated with severity of autistic behaviour traits so higher intellectual ability may be a protective factor for ASD for individuals with Sotos syndrome. Furthermore, verbal ability explains variance in severity of autistic behaviour traits within this population, indicating that poor verbal ability is associated with increased severity of autistic behaviour traits for individuals with Sotos syndrome. The findings have implications for considering the language development of children with Sotos syndrome and for identifying individuals within this population who may have co-morbid ASD. Overall, the findings from the present study advance understanding of the cognitive and behavioural phenotype of Sotos syndrome.

Chapter 6: Discussion

The aim of this thesis was to advance understanding of the cognitive and behavioural profiles associated with Sotos syndrome, specifically in relation to autistic features and the cognitive profile. The systematic search presented in Chapter 1 revealed relatively limited published research in relation to the cognitive and behavioural phenotypes associated with Sotos syndrome and identified gaps in knowledge which could be addressed in future research. In terms of cognition, previous research has investigated level of intellectual ability within the Sotos syndrome population and found that, in general, intellectual ability is reduced in Sotos syndrome. However, performance in specific cognitive domains has not been reported in a group of individuals with Sotos syndrome, using a standardised assessment, so understanding of cognition in Sotos syndrome is limited (Lane et al., 2016). Furthermore, a number of behavioural issues have been reported within the Sotos syndrome population, such as ADHD, anxiety, ASD and aggression/tantrums. However, once again, the majority of the published literature is based on relatively small samples so the prevalence and nature of these behavioural problems has not been established (Lane et al., 2016).

Based on the findings from the systematic review reported in Chapter 1, the subsequent chapters presented within this thesis aimed to further understanding of the cognitive and behavioural profiles associated with Sotos syndrome. In particular, the studies reported within this thesis investigated the prevalence and profile of autistic features in Sotos syndrome, the cognitive profile associated with Sotos syndrome, memory in Sotos syndrome, communication skills and language in Sotos syndrome and the extent to which cognitive factors are associated with severity of autistic features within this population. ASD was chosen as an area of focus as it was

anticipated that this research would provide a valuable contribution to the field due to recent interest and progress in identifying a genetic basis for ASD. This Chapter will provide a summary of the findings reported within this thesis and the implications of these findings in context. In addition, suggestions for future research involving individuals with Sotos syndrome will be discussed.

6.1. Summary of findings

The first study (Chapter 2) investigated the prevalence and profile of ASD symptomatology in Sotos syndrome. In total, 78 participants with Sotos syndrome were included in the study and ASD symptomatology was assessed via completion of the SRS-2. This study complements and extends previous research investigating the prevalence of ASD in Sotos syndrome conducted by Sheth et al., (2015), by exploring the effects of age and gender on symptom severity and exploring the profile of ASD symptomatology within this population. The findings reported in Chapter 2 identified a high prevalence of ASD symptomatology within the Sotos syndrome population. In total, 83% of the sample scored above clinical cut-off for ASD, as assessed by the SRS-2. This is the largest study to date to explore ASD in Sotos syndrome and the findings indicate a significant association between Sotos syndrome and ASD. Furthermore, this is the first study to investigate the effects of age and gender on ASD symptom severity within the Sotos syndrome population. The study found no effect of gender on ASD symptom severity but a significant effect of age, indicating that individuals with Sotos syndrome display greater severity of ASD symptomatology in childhood (5 – 19 years) compared with early childhood (2.5 – 5 years) and adulthood (20+ years). In addition, when compared with data from a recent factor analysis (Frazier et al., 2014) participants displayed a subscale profile consistent with that

observed in idiopathic ASD, demonstrating overlap between the behavioural profiles of Sotos syndrome and ASD.

The next study (Chapter 3) aimed to identify the cognitive profile associated with Sotos syndrome. This was assessed using the BAS3 in a large sample of adults and children with Sotos syndrome (N = 52). This is the largest study to date to investigate cognitive abilities in Sotos syndrome. Overall, participants displayed a consistent relative strength in verbal ability and relative weakness in non-verbal reasoning ability. This finding supports the suggestion that verbal IQ scores are consistently higher than performance IQ scores within the Sotos syndrome population which was identified in the systematic review presented in Chapter 1 (Lane et al., 2016). Furthermore, comparison of performance on the core scales of the BAS3 identified that Sotos syndrome is associated with a clear and consistent profile of relative cognitive strengths and weaknesses. Specifically, participants displayed relative strength in visuospatial memory and relative weakness in quantitative reasoning. In summary, the findings from this study further understanding of cognitive abilities within the Sotos syndrome population and provide insight into how individuals with Sotos syndrome think and learn.

As the findings from the study presented in Chapter 3 demonstrated that individuals with Sotos syndrome display relative strength in visuospatial memory, the aim of Chapter 4 was to explore memory in more detail within the Sotos syndrome population, using the diagnostic scales from the BAS3. Within this study, the Baddeley & Hitch model of memory (Baddeley, 1986; Baddeley & Hitch, 1974) was used as a theoretical basis for comparing performance on tasks from the BAS3 diagnostic scales. This analysis identified that participants displayed a selective relative strength in visuospatial short-term memory, when compared with verbal short-

term memory and working memory. In addition, verbal memory storage and visuospatial memory storage were assessed and compared. Verbal short-term memory storage was identified as a selective deficit for individuals with Sotos syndrome whilst visuospatial memory storage was a selective relative strength. Overall, the findings from this study demonstrate that although individuals with Sotos syndrome generally performed below average in comparison with the typically developing standardisation sample, participants displayed a selective relative strength in tasks assessing visuospatial memory.

As the findings reported in Chapter 2 identified considerable variability in relation to severity of ASD symptomatology, the final study (Chapter 5) aimed to explore whether specific aspects of cognition could account for this variability. Specifically, the study presented in Chapter 5 aimed to establish whether cognitive factors such as intellectual ability explained inter-individual variation in severity of autistic behaviour traits within the Sotos syndrome population. A further aim of this study was to explore the language profile associated with Sotos syndrome, using the CCC-2 and CC-A. In general, the findings from this study indicate that lower intellectual ability and verbal ability are associated with greater severity of ASD symptomatology. In addition, although participants had significant communicative difficulties, a consistent functional language profile was not identified, indicating that individuals with Sotos syndrome display difficulty with both structural and pragmatic aspects of language. Overall, the findings from this study highlight the importance of exploring relationships between different aspects of the phenotype in order to establish whether specific factors explain individual differences in the severity of the phenotype.

6.2. Implications

6.2.1. Syndromic ASD

The study of cognitive and behavioural profiles associated with neurodevelopmental disorders provides an opportunity to establish syndrome-specific phenotypes within genetically defined populations. A recent systematic review investigating the prevalence of ASD in genetic syndromes demonstrated that neurodevelopmental disorders, such as Rett syndrome, Angelman syndrome and Cornelia de Lange syndrome, are associated with increased prevalence of ASD (Richards et al., 2015). One of the findings from this systematic review was that the prevalence of ASD within each disorder included in the review was variable, indicating that some disorders are associated with greater prevalence of ASD. Genetic syndromes associated with a high prevalence of ASD can be considered as syndromic causes of ASD (Abrahams & Geschwind, 2008; Betancur, 2011). The findings presented in Chapter 2 indicate that Sotos syndrome is associated with a high level of clinically significant ASD symptomatology and therefore, Sotos syndrome could be considered as a syndromic cause of ASD.

ASD is a behaviourally defined disorder associated with a spectrum of symptoms and severity (DSM-5, APA, 2013). As there is considerable heterogeneity associated with ASD, research has investigated whether there are specific biological causes of ASD. For example, whether individuals with ASD have identifiable genetic abnormalities (Zhao et al., 2007). This can be investigated by screening for genetic abnormalities within a large sample of individuals with a clinical diagnosis of ASD. To date, this approach has led to the identification of several hundred genes which have been implicated as causes of ASD, demonstrating significant variability in the aetiology of ASD (Betancur, 2011; Devlin & Scherer, 2012). A limitation of this

approach is that it requires very large samples. However, a recent systematic review identified over thirty big open data resources for ASD (e.g. Simons Foundation Autism Research Initiative and Autism Genetic Resource Exchange), indicating that it is possible to ascertain and utilise big datasets for ASD research (Al-Jawahiri & Milne, 2017). An alternative approach is to establish whether individuals within a genetically defined population display behavioural symptomatology associated with ASD (Moss et al., 2012; Richards et al., 2015). This is the method that was used within this thesis and the findings from Chapter 2 therefore indicate that the NSD1 gene may be implicated in ASD. The NSD1 gene is involved in transcriptional regulation which means that it controls the expression of many genes. As abnormality of the NSD1 gene affects both growth and intellectual ability, it is likely that the gene has a role in these processes but the exact function of the gene is currently unknown (Tatton-Brown, Douglas, Coleman, Baujat, Cole, et al., 2005).

Research has established that up to 20% of children with ASD have early brain overgrowth and macrocephaly (Fombonne, Rogé, Claverie, Courty, & Frémolle, 1999; Lainhart et al., 1997). This suggests a potential link between overgrowth and ASD. Increased prevalence of ASD has been associated with abnormality of genes such as PTEN (Butler et al., 2005; Zhou & Parada, 2012) which results in both overgrowth and macrocephaly. As Sotos syndrome is an overgrowth disorder associated with macrocephaly, this population provides a further opportunity to explore the relationship between overgrowth and ASD. Therefore, the findings presented in Chapter 2 (Lane et al., 2017) provide further evidence to support an association between overgrowth and ASD and indicate that overgrowth disorders could be important syndromic causes of ASD.

6.2.2. Syndrome-specific cognitive profiles

The aim of Chapter 3 was to investigate a range of cognitive abilities within the Sotos syndrome population in order to establish the cognitive profile associated with Sotos syndrome. This approach enabled relative cognitive strengths and weaknesses to be identified. In most cases, individuals with Sotos syndrome performed worse than the BAS3 normative sample as the majority of individuals with Sotos syndrome have intellectual disability. This demonstrates the importance of interpreting performance in specific cognitive domains in relation to overall level of intellectual ability in order to establish relative strengths, as opposed to absolute strengths. A within-group comparison of performance on specific cognitive tasks revealed an uneven cognitive profile of relative cognitive strengths and weaknesses within the Sotos syndrome population. This provides additional evidence to indicate that individuals with intellectual disability display significant variability in terms of cognitive abilities. Therefore, it is important to establish syndrome-specific cognitive profiles for syndromes associated with intellectual disability. This approach enables the specific needs of individuals within a particular population to be identified and appropriate and optimal support to be provided.

Single-gene neurodevelopmental disorders provide a unique model for investigating the relationship between genes and cognitive outcomes (Scerif & Karmiloff-Smith, 2005). Neurodevelopmental disorders are often associated with a syndrome-specific profile of relative cognitive strengths and weaknesses, indicating that the phenotype is attributable to the genetic abnormality. The findings reported in Chapter 3 identified that individuals with Sotos syndrome display a clear and consistent cognitive profile, characterised by relative strength in verbal ability and visuospatial memory and relative weakness in non-verbal reasoning ability and

quantitative reasoning. As Sotos syndrome is caused by abnormality of a single gene (NSD1) (Kurotaki et al., 2002), this suggests that there is a biological mechanism which is underlying the cognitive phenotype. However, it is also important to consider the interaction between different genes and how abnormality of a single gene may affect the function and expression of other genes. In particular, the NSD1 gene is involved in transcriptional regulation so it is likely that abnormality of the NSD1 gene affects the expression of other genes. It is therefore necessary to investigate the network of genes in order to establish how abnormality of a single gene results in a specific phenotype.

Research has also investigated the relationship between neurological abnormalities and cognitive deficits for individuals with neurodevelopmental disorders. For example, individuals with Williams syndrome have difficulty with visuospatial skills and a particular weakness in visuoconstructive ability (Mervis et al., 2000). Research investigating the relationship between neurology and performance on visuospatial tasks has identified that individuals with Williams syndrome typically display functional deficits in the dorsal visual stream and that these deficits could account for difficulty with visuospatial skills within this population (Atkinson et al., 2006; Meyer-Lindenberg et al., 2004; Meyer-Lindenberg, Mervis, & Berman, 2006). This highlights the importance of exploring the relationship between neurology and cognitive abilities in order to establish whether neurological abnormalities underlie performance in specific cognitive domains for individuals with neurodevelopmental disorders. As Sotos syndrome is associated with distinctive neurological abnormalities, such as abnormality of the corpus callosum, ventricular abnormalities, midline abnormalities and delayed or disturbed maturation of the brain (Melo et al., 2000; Schaefer et al., 1997), as well as relative weakness in quantitative reasoning, it

is possible that the deficit in quantitative reasoning may be associated with specific neurological abnormalities within this population.

6.2.3. Profile inconsistencies

The findings from Chapter 2 demonstrated that the majority of individuals with Sotos syndrome display behavioural symptomatology associated with ASD (Lane et al., 2017). However, in Chapter 3, verbal ability was identified as a relative strength for individuals with Sotos syndrome, compared with non-verbal reasoning ability. For individuals with ASD, the cognitive profile is characterised by relative strength in non-verbal reasoning ability, compared with verbal ability (Happe, 1994; Shah & Frith, 1993). This indicates that although individuals with Sotos syndrome display a similar behavioural profile to that observed in ASD, the cognitive profiles appear to be distinct. Furthermore, the findings from Chapter 5 identified that individuals with Sotos syndrome display similar difficulty with both language structure and pragmatic language skills. Once again, this is in contrast with the communicative profile typically observed in ASD, which is characterised by relative difficulty with pragmatic language, compared with language structure skills (Geurts & Embrechts, 2008; Norbury et al., 2004). Thus, these findings highlight the importance of assessing several different aspects of the phenotype in order to establish similarities and differences between the profiles associated with neurodevelopmental disorders.

In Chapter 3, verbal ability was identified as a relative strength compared with non-verbal reasoning ability for individuals with Sotos syndrome. Previous research has established that verbal short-term memory is associated with language ability (Baddeley et al., 1998). However, in Chapter 4, participants displayed a relative weakness in verbal short-term memory, as evidenced by performance on the recall of

objects task. It is important to note that although the cognitive profile associated with Sotos syndrome is characterised by relative strength in verbal ability, this is relative to other cognitive abilities and is not an absolute strength. This means that, for a number of participants, verbal ability scores were below the population average and this may account for the difficulty with verbal short-term memory observed in Chapter 4. An alternative explanation is that the design of the recall of objects task may have affected performance on the immediate verbal short-term memory task. Specifically, scores on this task were calculated on the basis of performance across three trials. However, during the testing sessions, it was noted that some participants did not appreciate the need to try to recall all of the objects in each trial and instead, attempted to recall all of the objects across the trials. This may account for the poor performance on this task, compared with the other recall of objects tasks in which participants only completed one trial. The use of alternative measures to assess verbal short-term memory will further understanding of the relationship between language ability and verbal short-term memory within the Sotos syndrome population.

6.2.4. Sample size for neurodevelopmental disorders research

In order to establish a syndrome-specific cognitive profile, it is important to have an appropriate sample size. This will ensure that the cognitive profile has a good degree of sensitivity. However, research with rare populations can be challenging as there is a limited population from which to recruit and this means that studies often use fairly small samples. For example, a review of 178 published studies reporting data on the cognitive, behavioural or neuroanatomical features of Williams syndrome identified that the median sample size ranged from 6 – 17 participants in studies assessing these domains, using an experimental design (Martens et al., 2008).

Consequently, findings based on small samples often lack generalisability and it is therefore difficult to establish whether the findings are representative of the syndrome population. In total, 94 individuals with Sotos syndrome participated in the studies reported within this thesis. This included 52 individuals who completed the cognitive assessment in a face-to-face testing session and a further 42 individuals for whom their parent/caregiver completed the SRS-2. Overall, it was possible to recruit a large and representative sample of individuals with Sotos syndrome and therefore, the research reported in this thesis demonstrates the feasibility of research with the Sotos syndrome population.

6.2.5. Phenotype across the lifespan and research approaches

A neuroconstructivist perspective can be applied to the study and understanding of neurodevelopmental disorders. This perspective assumes that neurodevelopmental disorders are associated with a developing system which is distinct from a typically developing system and that syndrome-specific phenotypes arise from an interaction between genetic, neural and environmental factors (Karmiloff-Smith, 1998; Karmiloff-Smith, 2009). Consequently, the phenotype is considered to be attributable to dynamic developmental processes. It is therefore important to investigate the process of development for individuals with neurodevelopmental disorders and to explore the phenotype across the lifespan. This can inform understanding of the development of cognitive process and the extent to which factors in early development may impact the resulting phenotype.

A longitudinal design can be used to assess the development of the phenotype of over time. This approach has been used to assess the relationship between cognitive

abilities and behaviour in individuals with Fragile X syndrome. Specifically, research has identified that visual attention predicts ADHD symptoms longitudinally for boys with Fragile X syndrome, with greater visual attention accuracy predicting lower severity of ADHD symptoms over time (Scerif, Longhi, Cole, Karmiloff-Smith, & Cornish, 2012). In contrast, auditory attention predicts ASD symptoms longitudinally for these individuals, with poorer auditory attention predicting greater severity of ASD symptoms (Cornish, Cole, Longhi, Karmiloff-Smith, & Scerif, 2012). This demonstrates the differential effects of specific attentional abilities on behavioural symptoms over time for individuals with Fragile X syndrome. In addition, these findings highlight the importance of investigating the relationship between cognitive abilities and behaviour in infancy and across the lifespan for individuals with neurodevelopmental disorders. Thus, future research providing a thorough examination of cognitive abilities in infancy for individuals with Sotos syndrome could enable early predictors of behavioural symptomatology to be identified.

In order to establish whether difficulties persist during adulthood, it is important to assess the phenotype across the lifespan. In the studies reported in this thesis, the findings from Chapter 2 indicate that severity of ASD symptomatology in individuals with Sotos syndrome decreases in adulthood, when compared with childhood. A possible explanation for this finding could be that adults with Sotos syndrome develop strategies to manage their symptoms. Chapter 3 used a cross-sectional design and the findings identified no relationship between intellectual ability and age. This could be due to the variability in intellectual ability within the Sotos syndrome population. However, an additional finding from Chapter 3 was that verbal ability may develop to a greater extent for individuals with Sotos syndrome compared with non-verbal reasoning ability. This suggests that verbal ability may continue to

develop during adulthood for individuals with Sotos syndrome. However, it will be important to assess this using a longitudinal design in order to establish the rate of development. Furthermore, the findings from Chapter 5 indicate that communicative difficulties persist during adulthood for individuals with Sotos syndrome. Overall, the findings reported within this thesis have provided some insight into the phenotype associated with Sotos syndrome in adulthood, using a cross-sectional approach. Although intellectual disability and communicative difficulties persist throughout adulthood, ASD symptomology seems to become less severe in adulthood for individuals with Sotos syndrome.

6.2.6. Clinical Implications

The findings from Chapter 2 demonstrate that, in general, individuals with Sotos syndrome have difficulty with social skills. In addition, the findings from Chapter 5 indicate that individuals with Sotos syndrome have poor communication skills, relative to typically developing peers of a similar age. The findings from these chapters therefore suggest that it is important to support social skills and communication skills in children with Sotos syndrome. The findings from Chapter 5 demonstrate that parents reported their children as having very poor communication skills and difficulty with both structural and pragmatic aspects of language. These difficulties were reported for both adults and children with Sotos syndrome. However, in Chapter 3, verbal ability was identified as a relative strength for individuals with Sotos syndrome. This suggests that although individuals with Sotos syndrome have a good understanding of language, their ability to communicate appropriately with others and to structure their language is relatively poor. This could be associated with increased prevalence of ASD symptomatology and a general difficulty with social

interaction within the Sotos syndrome population, which was reported in Chapter 2. Overall, the findings reported within this thesis demonstrate the need to support social skills and communication skills for individuals with Sotos syndrome.

The findings from Chapter 3 demonstrate that approximately 10% of the participants included in this study did not have intellectual disability. At present, intellectual disability is considered to be one of the cardinal features of Sotos syndrome (Tatton-Brown et al., 2005). However, it is important for clinicians to be aware that some individuals with Sotos syndrome have intellectual ability in the range 90 – 109 which is considered to be the average range for the general population. Families are more likely to be referred to services if the child has significant difficulties and there may therefore be a number of unidentified cases of Sotos syndrome in which individuals have mild difficulties which have not required significant support (Tatton-Brown, Douglas, Coleman, Baujat, Cole, et al., 2005). If the child is clinically suspected as having Sotos syndrome, the parents will also be screened to determine whether the NSD1 abnormality is *de novo* or the result of familial transmission. Therefore, in some cases, a parent of a child with Sotos syndrome has also been identified as having the NSD1 abnormality. This provides evidence that some milder cases of Sotos syndrome have not been identified until adulthood. In summary, it is important for clinicians to be aware that increased prevalence of ASD symptomatology, as well as difficulty with social skills and communication skills are common within the Sotos syndrome population. In addition, there is significant variability in intellectual ability for individuals with Sotos syndrome and milder cases of Sotos syndrome may be harder to identify and diagnose if the clinical features are less severe.

6.3. Future research

6.3.1. Cross-syndrome comparisons

Cross-syndrome comparisons are valuable in identifying differences between disorders in relation to specific cognitive functions and behavioural profiles. It will therefore be important for future research to utilise a cross-syndrome approach to explore the extent to which the phenotype associated with Sotos syndrome is similar or distinct to that associated with other congenital syndromes in which the cognitive and behavioural phenotypes are well established, such as Williams syndrome and Fragile X syndrome. For example, this approach has been used to assess differences in the attentional profiles of toddlers and children with Williams syndrome, Down syndrome and Fragile X syndrome (Cornish, Scerif, & Karmiloff-Smith, 2007). The authors note the importance of utilising a cross-syndrome design and the need to identify subtle differences in the component parts of cognitive abilities in order to differentiate between distinct genetic syndromes. This approach can provide insight into the processes underlying task performance and relationships between different cognitive abilities. In addition, it will be important to compare the phenotype of Sotos syndrome with the phenotype of other overgrowth disorders, such as Weaver syndrome and Tatton-Brown Rahman syndrome. This will provide further insight into the relationship between overgrowth, ASD, cognition and the syndrome-specific genetic abnormalities associated with each of these overgrowth syndromes.

As the findings presented in Chapter 4 demonstrate that individuals with Sotos syndrome display a selective relative strength in visuospatial memory, it will be important for future research to use a cross-syndrome approach to compare memory performance in individuals with Sotos syndrome with individuals with other neurodevelopmental disorders. This will provide insight into the extent to which

memory performance is syndrome-specific and whether distinct processes underlie memory performance in different neurodevelopmental disorders. Furthermore, this approach could inform understanding of whether task performance is associated with domain general or domain specific abilities for individuals with Sotos syndrome.

6.3.2. Infancy and early development

An advantage of studying neurodevelopmental disorders is that individuals with a genetic abnormality can be diagnosed very early in life. This means that a genetic syndrome can typically be diagnosed much earlier than behaviourally defined disorders, such as ADHD and non-syndromic ASD. Therefore, neurodevelopmental disorders provide a valuable opportunity to assess the development of the phenotype from early infancy and to identify factors which may account for individual differences in the severity of the phenotype within a specific syndrome. This highlights the importance of exploring the phenotype associated with Sotos syndrome in early infancy and the benefit of using a longitudinal design to provide insight into risk factors or protective factors which may account for individual differences in the severity of the phenotype.

Cognitive development is a dynamic process and early performance in a cognitive domain does not necessarily predict later performance (Karmiloff-Smith, 1998). It is therefore important to examine cognitive abilities in infancy in order to determine whether the profile is consistent across the lifespan. For example, in Williams syndrome and Down syndrome the infant phenotype is quite different to the adult phenotype, particularly in terms of numeracy and language development (Paterson et al., 1999). Assessment of the phenotype from infancy through to

adulthood can inform understanding of the development of cognitive abilities and the role of gene expression and neurological abnormalities early in development. It will be important for future research to investigate cognitive abilities in infancy within the Sotos syndrome population and to establish whether the adult phenotype can be predicted from abilities in infancy.

6.3.3. Genotype-phenotype relationships

Genotype-phenotype relationships have been explored in neurodevelopmental disorders. For example, severity of working memory impairments in Fragile X syndrome have been found to correlate with FMRP levels, demonstrating a clear association between the degree of expression of FMRP and the severity of the phenotype in Fragile X syndrome (Menon, Kwon, Eliez, Taylor, & Reiss, 2000). Sotos syndrome is associated with abnormality of the NSD1 gene (Kurotaki et al., 2002), as well as distinctive neurological abnormalities (Melo et al., 2000; Schaefer et al., 1997). To date, there is no published research using EEG or fMRI to explore the relationship between brain function and behaviour or cognition within the Sotos syndrome population. Further research explicitly investigating the relationship between genotype, neurology and cognitive and behavioural phenotype within this population will advance understanding of the mechanisms underlying this syndrome. The findings presented in this thesis provide evidence to demonstrate the need for further research into Sotos syndrome, using a collaborative and integrative approach. This is essential for establishing a comprehensive understanding of neurodevelopmental disorders. As there is a consistent phenotype within the Sotos syndrome population, particularly in terms of cognition, it will be important for future research to explore genotype-phenotype relationships.

6.3.4. Attention

A finding from the systematic review reported in Chapter 1 was that individuals with Sotos syndrome display an increased prevalence of ADHD. However, the nature of these attentional difficulties and the prevalence of ADHD is unclear as the published literature is based on relatively small samples (Lane, Milne & Freeth, 2016). Previous research involving individuals with Sotos syndrome has focused on prevalence of ADHD, as opposed to investigating specific aspects of attention such as attentional control and social attention. In addition, attention has only been assessed in group studies of individuals with Sotos syndrome using parental questionnaires (De Boer et al., 2006; Finegan et al., 1994; Varley & Crnic, 1984). It will therefore be important for future research to use experimental paradigms to assess aspects of attention such as selective attention, social attention and sustained attention in order to determine whether there is a specific attentional profile associated with Sotos syndrome. Furthermore, previous research has identified that ADHD and ASD are often comorbid (Simonoff et al., 2008). As Sotos syndrome is associated with a high prevalence of ASD symptomatology, it will be important to establish whether individuals with Sotos syndrome also display clinically significant symptoms associated with ADHD.

The findings reported in this thesis inform educational considerations for the Sotos syndrome population and have important implications for designing appropriate interventions for individuals with Sotos syndrome. However, it will be important for future research with the Sotos syndrome population to explore other factors such as attention and executive functions which have been found to affect educational outcomes and the development of cognitive skills (Posner & Rothbart, 2007; Steele, Karmiloff-Smith, Cornish, & Scerif, 2012). For example, research involving

individuals with Fragile X syndrome has identified attention as an important predictor of educational outcomes (Scerif et al., 2012). Attention is critical for learning new information and therefore has a significant impact on learning as a child needs to be able to attend to relevant aspects of the environment in order to acquire information. It will therefore be important for future research to investigate attention within the Sotos syndrome population.

In addition, executive functions are associated with academic and educational outcomes (Blair & Razza, 2007; St Clair-Thompson & Gathercole, 2006). For example, executive functions have been found to predict maths ability in typically developing children (Bull & Scerif, 2001). As the findings from Chapter 3 identified that individuals with Sotos syndrome display relative weakness in quantitative reasoning, it will be important for future research to assess executive functions within the Sotos syndrome population and the extent to which executive functions are associated with numeracy skills for these individuals. To date, executive functions have not been investigated within the Sotos syndrome population. However, the findings presented in Chapter 4 provide some insight into working memory ability for individuals with Sotos syndrome and indicate that although participants generally scored below the typically developing normative sample, working memory was not an area of relative weakness for individuals with Sotos syndrome. Other executive functions such as inhibitory control and cognitive flexibility have not yet been explored within the Sotos syndrome population.

6.4. General conclusion

In summary, the findings reported in this thesis have significantly advanced understanding of the cognitive and behavioural phenotype of Sotos syndrome in

several important ways. Specifically, the studies within this thesis have demonstrated that Sotos syndrome is associated with a high prevalence of ASD, that individuals with Sotos syndrome have a clear and consistent cognitive profile, as well as a selective relative strength in visuospatial memory, and that the severity of the phenotype may be associated with specific risk factors and protective factors. Ultimately, understanding of the cognitive and behavioural phenotypes associated with Sotos syndrome will enable syndrome-specific interventions to be devised. Although Sotos syndrome is considered to be a rare syndrome, the incidence is not insignificant and based on the estimated incidence, there are several thousand individuals in the UK with Sotos syndrome. Therefore, research with this population is warranted. It is crucial for families, educators and clinicians to be aware of the phenotype associated with Sotos syndrome in order to understand the needs of these individuals and to ensure that appropriate and effective support is provided to enable optimal outcomes for these individuals.

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