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DOCTOR OF CLINICAL PSYCHOLOGY (DClinPsy)

VOLUME I

Research Component

Toward a Behavioural Phenotype for Sotos Syndrome

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Overview

This thesis comprises of two volumes, representing the research and clinical elements submitted to the University of Birmingham in partial fulfilment of the degree of Doctor of Clinical Psychology (DClinPsy).

Volume I of the thesis is made up of the research component which includes three papers; a review paper, an empirical paper and a public domain briefing paper.

The first paper is a critical review of the literature from 1980 to the present day, which has examined intellectual, behavioural and psychological characteristics in participants with Sotos syndrome. The predominant behaviours reported include; communication and language difficulties, atypical social behaviour and ADHD and hyperactivity. Methodological limitations of the studies were discussed including the use of non standardised measures and single case methodology. Overall no clear behavioural phenotype has emerged from the literature. Suggestions for future research are made.

The second paper is an empirical study which examines the behavioural phenotype of participants with Sotos syndrome in comparison to 3 other genetic syndromes; Down syndrome, Prader-Willi syndrome and Autism Spectrum Disorder. Well validated, standardised questionnaires were used across the four groups. Challenging behaviour was seen in the Sotos group, in which self-in injurious behaviour was displayed in 40% of participants. This has not previously been reported in the literature. Levels of Autism Spectrum Disorder (ASD) were high in Sotos participants with over 70% reaching clinical cut off levels for ASD. Patterns of repetitive behaviour in participants with Sotos syndrome were most similar to that seen in Prader-Willi, although there was also some overlap with the ASD

group. Both of these papers were written with the aim of publication in the Journal of Intellectual Disability Research.

The third paper is a Public Domain Briefing Paper which is written in a more accessible style for the general public and gives details of the literature review and empirical study. The aim is for the Child Growth Foundation (CGF), who supported the research, to disseminate it to parents, carers and individuals with Sotos syndrome in their newsletter and future publications.

Volume II of the thesis is the clinical component. It comprises of four Clinical Practise Reports and the abstract of a fifth which was presented orally. Each report was completed over the duration of the course and reflects some of the work carried out on clinical placements. These reports include; The case of a 52 year old man, presenting with obsessive compulsive symptoms and social anxiety, formulated from a psychoanalytic and cognitive perspective; a service evaluation examining staff needs in working with clients with a personality disorder in secondary care services; a single case experimental design assessing the effectiveness of an experimental behavioural intervention for self injurious behaviour in a 9 year old girl with Cornelia de Lange syndrome; the case of a 70 year old woman with dementia and challenging behaviour; the case of a 41 year old woman with depression formulated from a psychoanalytic perspective.

Dedication

I would like to dedicate this work to my parents Pauline and Liam Hyland. Without their love, support and encouragement over the years, I wouldn't be where I am today.

Acknowledgements

Volume I: Research Component

Table of Contents

Volume II: Clinical Component

Table of Contents

The Behavioural Phenotype of
Sotos Syndrome; A Critical Review

Abstract

Sotos syndrome is a genetic disorder associated with accelerated growth, an advanced bone age, facial characteristics, large hands and feet, poor co-ordination and developmental delay. To date the majority of research around Sotos syndrome has focused on physical and genetic factors. However, some studies have investigated the behavioural, psychological and cognitive characteristics of Sotos syndrome (n=20), which are reviewed in this paper. There are behaviours which are reported more commonly throughout the literature, including communication difficulties, atypical social behaviour and ADHD. Unfortunately though, comparisons between findings are difficult due to a number of methodological limitations which are discussed. Overall, no clear behavioural phenotype of Sotos syndrome has yet emerged.

Introduction

Sotos syndrome was first described by Sotos, Dodge, Muirhead, Crawford and Talbot (1964) and initially named 'cerebral gigantism'. Early descriptions noted excessive growth, increased birth length, advanced bone age, macrocephaly (a disproportionately large and long head) and a 'non-progressive cerebral disorder' with 'mental retardation'. A number of subsequent studies have documented a similar clinical presentation including overgrowth, characteristic facial gestalt, specific physical health problems (Cole & Hughes, 1994; Melo et al., 2002; Sotos, 1997) and a variable degree of intellectual disability, ranging from mild to severe (e.g., Baujat & Cormier-Daire, 2004).

Research into Sotos syndrome has focused predominantly on observable clinical characteristics and genetic cause. However, there are a small number of case studies and cohort studies that have described a variety of behavioural characteristics observed within the syndrome including: Autism Spectrum Disorder (e.g., Zappella, 1990), aggression (e.g., Compton, Celetana, Price & Furman, 2004), ADHD (e.g., Bale, Drum, Parry & Mulvihill, 1985), compromised sociability (e.g., Mauceri et al., 2000), psychosis (e.g., Kessler & Kraft, 2008; Leventopoulos et al., 2009), communication and language difficulties (e.g., Ball, Sullivan, Dulany, Stading & Schaefer, 1985) and anxiety (Sarimski, 2003). As yet however, no clear behavioural phenotype of Sotos syndrome has emerged.

The clinical diagnosis of Sotos syndrome is based on a clinical examination first proposed by Cole and Hughes (1994). An individual must evidence overgrowth, characteristic facial gestalt, and intellectual disability (Cecconi et al., 2005; Faravelli, 2005; Rio et al., 2003; Turkmen et al., 2003). Tatton-Brown et al. (2005) found that these principal features occurred in at least 90% of affected individuals, however a wide spectrum of other associated clinical features were also present which were largely independent of genotype. With the development

of genetic testing, diagnosis can now be confirmed using FISH and DNA analysis (Baujat & Cormier-Daire, 2004).

Prevalence and Genetic Cause

The birth prevalence rate for Sotos is estimated to be between 1 in 10,000 and 1 in 50,000 (Sotos, 1997). Baujat and Cormier-Daire (2004), suggest that the development of genetic screening will help to define prevalence more accurately. Maroun, Schmerler, and Hutcheon (1994), initially suggested that the site of a dominant gene determining Sotos was either 5q35 or 15qss. Imaizumi et al. (2002) later proposed that the gene responsible for Sotos was located on the long arm of chromosome 5. This was confirmed by Kurotaki et al. (2002) who isolated the NSD1 gene from the 5q35 breakpoint. Kurotaki et al. (2002), further discovered that haploinsufficiency of the NSD1 gene was the major cause of Sotos syndrome. It is now widely accepted that mutations and deletions on the NSD1 gene are responsible for Sotos syndrome in approximately 75-90% of cases (Baujat & Cormier-Daire, 2007; Tatton-Brown et al., 2004).

Behavioural Phenotypes

The concept of a behavioural phenotype was first introduced by Nyhan (1972) (cited in O'Brien & Yule 1995; p.1) who emphasised the role of genetic abnormality in the development of self injurious behaviour in Lesch-Nyhan syndrome. Dykens (1995) conceptualisation is now the most widely used definition which describes behavioural phenotypes as:

"...the heightened probability or likelihood that people with a given Syndrome will exhibit certain behavioural or developmental sequelae relative to those without the Syndrome"

(Dykens, 1995; p. 523)

Emerging research identifies a role for the environment in shaping genetic expression. Oliver, Woodcock & Adams, (2010) argue that "observable characteristics [behaviours] often occur as a result of an ongoing interaction between genes and the environment" (p. 139).

Behavioural Phenotype of Sotos syndrome

The aim of this review is to critically evaluate the literature relevant to a possible behavioural phenotype for Sotos syndrome. Studies which have described level of intellectual disability and psychological, behavioural and cognitive characteristics will be reviewed.

A search of PsycINFO and Web of Science (1980 to the present day) was carried out using the key words 'Sotos syndrome', '5q35', 'Cerebral Gigantism' and 'NSD1'. A total of 516 articles were identified. 377 were papers which reported on physical or genetic features, 20 were reviews or book chapters and 102 were letters or meeting abstracts. Accordingly, 15 were appropriate to include, as they described either level of intellectual disability or behavioural, psychological and cognitive characteristics. A further search of the reference section of the remaining 15 articles revealed an additional five studies, which were deemed appropriate to include.

In total 523 cases[1] of Sotos syndrome, with ages ranging from 2 years to 45 years, were reported in the studies. Of the 20 studies, nine were case reports and eleven were cohort studies. Eighteen studies reported on the level of intellectual disability in participants and 15 reported on behavioural, psychological and cognitive characteristics. Tables 1 and 2 show the level of intellectual disability and behaviours that were reported in the studies identified from the search.

[1] The author is not aware of cases being reported twice

The following behavioural and psychological difficulties were most commonly reported in the studies: communication difficulties (57%), ADHD and hyperactivity (52%), atypical social behaviour including: 'seclusiveness', a preference for adult company and being withdrawn (57%), aggression (42%), atypical motor development, including psychomotor retardation and clumsiness (42%), stereotyped, ritualistic and repetitive behaviours (26%), anxiety/depression (17%), autism spectrum disorder (15%), psychosis (15%) and fears and phobias(10%).

Table 1 Reported behaviours and IQ in cohort studies of Sotos syndrome

Authors (years)	Diagnosis	No. of cases & age in years	IQ scores range (Measures)	Behaviours	Number of people
Ball et al. (2005)	Clinical	16, age 1-12	N/A	Communication difficulties	16/16
Bloom et al. (1983)	Clinical	10, age 1-13	62-123 (WISC-R) 59-89 (Stanford-Binet) 61-109 (Leiter)	Communication difficulties Motor skills (psychomotor delay)	3/10 4/10
de Boer, Roder & Wit (2006)	Genetic	27, age 1-45	NSD1=70[1] non NSD1=79 (WPPSI-R) (WISC-R) (WAIS)	ADHD Aggression Anxiety Communication difficulties Motor skills Social difficulty	11/27 19/19 19/19 21/21 26/26 19/19
Finegan et al. (1994)	Clinical	27, age 5-16	21-103 (WISC-R)[2]	ADHD Aggression (temper tantrums) Social difficulty	N/A 11/26 27/27
Rutter & Cole (1991)	Clinical	16, age 5-14	54-96 (WISC-R) (WIPPSI)	Aggression (temper tantrums) Hyperactive Ritualistic behaviours Social difficulty	13/16 6/16 8/16 8/16
Saugier-Veber et al. (2007)	Genetic	116, age 0.1-40	Normal intelligence-Severe 'mental retardation'[3] (N/A)	None reported	-
Sarimski (2003)	Clinical & Genetic	27, age 6-15	Mild-Severe[3] intellectual disability (parent/school report)	Anxiety Ritualistic behaviour Social difficulty Stereotypic behaviour	11/27 5/27 25/25 4/27
Tatton-Brown et al. (2005)	Genetic	266, age not given	Mild-Severe[3] intellectual disability (N/A)	None reported	-
Varley (1984)	Clinical & Genetic	11, age 5-13	40-85 (WISC-R) (Stanford-Binet) (Bayley Mental Scale)	ADHD Hyperactive Social difficulty	3/11 7/11 11/11
Wit et al. (1985)	Clinical	22, age 1-22	Mild-Borderline[3] 'mental retardation' (WHO classification)	Motor skills (clumsiness)	12/22
Zappella (1990)	Clinical	12, age 3-12	'mentally retarded' (N/A)	Autistic features Communication problems Hyperactive Social difficulty Stereotypic behaviour	5/12 11/12 4/12 5/12 6/12

[1] Mean IQ score (range not available)
[2] WISC-R short form (Kaufman, 1976)
[3] Only descriptive IQ levels given

Table 2: Reported behaviours and IQ in case studies of Sotos syndrome

Authors (years)	Diagnosis	No. of cases & age in years	IQ scores range & individual scores[1] (Measures)	Behaviours	Number of people
Bale et al. (1985)	Clinical	3, age 3,7 & 35	79-110 (WISC-R) (WAIS)	ADHD Communication difficulties Motor skills (clumsiness)	1/3 1/3 2/3
Compton et al. (2004)	Clinical	1, age 20	94[1] (WASI)	Aggression Psychosis Social difficulty	1/1 1/1 1/1
Kessler & Kraft (2008)	Clinical	1, age 29	64[1] (WAIS)	Psychosis Social difficulty	1/1 1/1
Leventopolous et al. (2009)	Clinical & Genetic	4, age 0.5-11	N/A	ADHD Aggression Autistic behaviours Motor skills (psychomotor delay) Psychosis	1/4 1/4 1/4 4/4 1/4
Mauceri et al. (2000)	Clinical	6, age 2-12	40-70 (WISC-R) (Brunet-Lezine test)	ADHD Aggression (temper tantrums) Communication difficulties Motor skills (clumsiness & psychomotor delay) Social difficulty	3/6 3/6 4/6 6/6 4/6
Morrow, Whitman & Accardo (1990)	Clinical	1, age 4 yr 11 mth	Normal intelligence	Autistic features Communication difficulties Motor skills Repetitive/stereotyped behaviour Social difficulty	1/1 1/1 1/1 1/1 1/1
Mourisden & Hansen (2002)	Clinical	2, age 3 &13	N/A	Aggression Autism Communication difficulties Hyperactive Motor skills (psychomotor delay) Repetitive/stereotyped behaviour Social difficulty	1/2 1/2 2/2 1/2 2/2 1/2 2/2
Okamoto et al. (2010)	Genetic & Clinical	1, age 14	'Severe mental retardation' (Kyoto scale of Psychological development)	Communication difficulties	1/1
Trad, Schlefer, Hertzig & Kernberg (1991)	Clinical	1, age 4	88[1] (Stanford-Binet)	ADHD Aggression Communication difficulties Motor Skills (clumsiness) Social difficulty	1/1 1/1 1/1 1/1 1/1

Level of Intellectual disability

Of the studies reported in tables 1 and 2, eighteen describe levels of intellectual disability in participants; however only ten studies have used standardised assessments.

The combined mean IQ reported in five case studies, after using either the Wechsler Intelligence Scale for Children, the Wechsler Intelligence Scale for Children-Revised or the Wechsler Adult Intelligence Scale (Wechsler, 1955, 1976, 1999), was 70, with a range of 46-110. Three studies also report higher levels of Verbal IQ (range 88-122) compared to Performance IQ (range 70-93). The largest difference reported in a participant is 29 points (122-93) (Bale, 1985). However, this difference has not been reported as significant. Five cohort studies have used the Wechsler Scale of Intelligence or age appropriate adaptations and versions to report IQ (Wechsler, 1955, 1967, 1986, 1990, 1995). A combined mean IQ of 75 for all participants within the five studies is evident, with scores ranging from 72-81. A higher mean range of scores for Verbal IQ (74-85) compared to Performance IQ (72-80) was also found, although the large differences seen in the case studies are not replicated. A limitation of reporting the mean IQ scores from different Wechsler versions however, is that each IQ scale is based on different norms. Thus when each version is republished it is restructured and norms are re-calculated. Therefore it is difficult to draw firm conclusions from this data.

Bloom et al. (1983) assessed four participants aged between 3.3 to 7.3 years on the Stanford Binet Intelligence Scale and the Leiter International Performance Scale, Arthur Adaptation (Arthur, 1949). Scores were higher on the Leiter scale ranging from 61-109, compared to the Stanford-Binet, where scores ranged from 59-89. The higher scores on the non-verbal Leiter test compared to the verbal Binet tests are in contrast to the findings of studies described above, where participants Verbal IQ was higher than their Performance IQ (i.e. non-verbal skills).

A comparison of levels of intellectual disability between participants with specific Sotos gene alterations has been reported in three studies. de Boer et al. (2006) found higher Verbal, Performance and Full scale IQ scores for participants with non NSD1 mutations, compared to those with NSD1 mutations. Saugier-Veber et al. (2007) and Tatton Brown et al. (2005) found higher numbers of participants with severe intellectual disability with 5q35 deletion; 33% (n=3) and 60% (n=20) respectively, and lower levels in participants with NSD1 mutations, 3% (n=2/69) and 12% (n= 28/233). Tatton-Brown et al. (2005) also report higher levels of moderate/mild intellectual disability within the NSD1 mutation group (41%/30%) compared to the 5q35 deletion group (30%/10%). Unfortunately, these studies do not describe the measures used to determine level of intellectual disability.

Both Sarimski (2003) and Zappella (1990) did not use standardised assessments to record level of intellectual disability. However, Sarimski reports higher levels of mild intellectual disability (59%) compared to moderate (40%) intellectual disability in participants through parental measures and school achievement.

In summary, the studies show that level of intellectual disability in participants with Sotos syndrome is variable. A difference in scores between the Wechsler Performance (non-verbal) and Verbal tests is evident, with non verbal abilities in participants being poorer than verbal abilities. However, the opposite is evident when the Leiter and Binet scores of participants are compared. Furthermore, a difference in levels of intellectual disability between different genetic mutation groups is evident. The NSD1 mutation group show lower Performance and Full scale IQ levels compared to Sotos participants without the NDS1 mutation. However, participants with Sotos syndrome who have an NSD1 mutation are reported to have lower levels of intellectual disability when compared to Sotos participants with a 5q35 deletion.

Communication and Language

Fourteen studies that have investigated language and communication in Sotos syndrome are summarised in Table 3. A variety of different measures have been utilised in four studies which demonstrate poorer expressive compared to receptive language in participants with Sotos syndrome. Deficits in speech and language, including compromised language acquisition and delay are prominent in ten studies, with problems described as: no speech, the use of single words only, inability to sustain conversations and more advanced non verbal skills compared to verbal skills. Five studies reported coarse vocal qualities and monotonous tone in participants with Sotos syndrome.

de Boer et al. (2006) found a difference between mean chronological age of participants (9yrs 6mth) and mean developmental age for communication (7yrs 8mth), which was more noticeable in the NSD1 group. Moreover, older children showed larger discrepancies than younger children. Ball et al. (2005) found a greater severity of fluency impairment (stuttering) in older participants during conversational speech. In contrast two studies (Finnegan, 1994; Sarimski, 2003) describe higher levels of expressive language competence in Sotos participants, compared to a matched comparison group.

To summarise, the majority of studies of communication identify a discrepancy between expressive language (being able to produce speech and communicate a message) and receptive language skills (listening and understanding what is communicated), with participants exhibiting greater difficulty in expressive language.

Table 3: Communication and Language difficulties

Reference	SS, n	SS mean age ± SD (range)	Intellectual disability (range)	Comparison groups (n)	Comparison group age range	Focus of investigation	Communication & Language Measures	Findings relevant to Communication & Language
Ball et al. (2005)	16	6.3mth (1-12)	Not reported	None, compared to normative data	N/A	Speech, language and overall communication skills	Buffalo III voice screening Profile (Wilson, 1987) Clinical evaluation of language fundamentals three screening test (Semel et al., 1996) Goldman-Fristoe test of articulation 2 (Goldman and Fristoe, 2000) Kahn-Lewis phonological analysis 2 (Kahn and Lewis 2002) Mean length of utterance in Morphemes (miller, 1981) Peabody picture vocabulary test (III) (Dunn and Dunn,1997) Preschool language scale 3 (Zimmerman et al., 1992) Social skills rating system (Gresham and Elliott, 1990) Type-Token Ratio (Miller, 1981) Index of augmented speech comprehensibility in children (Dowden, 1997) Systematic analysis of language transcripts (Miller and Chapman, 1991)	Participants produced less diverse vocabulary and used simplified grammar in conversational speech compared to normative data. They also exhibited severe receptive vocabulary impairment. Greater difficulty with expressive vs receptive language was noted which was significantly different compared to the normative sample. The vocal quality of participants was assessed and the largest number of participants (88%) were judged to have a hoarse vocal quality whilst 75% had monotonous or reduced variability. Stuttering was observed in participants during conversational speech, with severity being observed to increase with age, which the authors note is long past the time when stuttering usually emerges (between 2 and 5 years). In comparison to other children of the same chronological age, the amount of sound production errors made by Sotos children was low.

Table 3 continued: Communication and Language difficulties

Reference	SS, n	SS age range	Intellectual disability (range)	Comparison groups (n)	Comparison group age range	Focus of investigation	Communication & Language Measures	Findings relevant to Communication & Language
Bloom (1983)	10	1-13.6 yrs	62-123	None	N/A	Cognition in cerebral gigantism	Bayley Scale of Infant Development (Bayley, 1969) Cattell Infant Intelligent Scale (Cattell, 1960) Leiter International Performance Scale, Arthur Adaptation (Arthur, 1949)	Delayed speech milestones were reported by parents in all children. The verbal skills of 3 children (3-5yr range) were below average and significantly less advanced than their non verbal abilities. Moreover, all school aged children had auditory processing problems – manifested as word finding difficulties and very long latency responding to verbally presented stimuli.
Bale (1985)	3	3-35	90-110	None	N/A	Psychological characteristics	Zimmerman pre-school language scale (Zimmerman, 1979) Bayley Scale of Infant Development (Bayley, 1969)	One child showed particular early difficulties in speech on the Bayley Scale. The scores on the Zimmerman pre-school language scale for 2 children were lower on expressive language compared to receptive language. One participant also had a hoarse vocal quality to her voice.
Compton et al. (2004)	1	20	94	None	N/A	Psychosis	Clinical assessment	Speech articulation problems
de Boer et al. (2006)	27	1-45	70 –NSD1* 79-non NSD1*	None, compared to normal controls on test	N/A	Psychosocial functioning	Vineland screener (Sparrow et al., 1994)	In the NSD1 mutation group a negative correlation was found between chronological age and developmental age for communication. There was also a mean age difference of 1 year and 8 months between chronological age (9.6) and developmental age for communication (7.8) as calculated on the Vineland screener.

Table 3 continued: Communication and Language difficulties

Reference	SS, n	SS age range	Intellectual disability (range)	Comparison groups (n)	Comparison group age range	Focus of investigation	Communication & Language Measures	Findings relevant to Communication & Language
Mauceri et al. (2000)	6	2-12	40-70	None	N/A	Aggressive behaviour	The Denver Developmental Screening Test (Frankenburg & Dobbs, 1967) Brunet-Lezine test (Brunet-Lezine, 1966)	Language and communication deficits including; poor and repetitive expressive language and delayed language acquisition were seen in 4 children. One child also presented with an unusually coarse voice.
Morrow, Whitman & Accardo (1990)	1	4yr 11 mth	Normal intelligence	None	N/A	Autistic behaviour	Clinical observation	Participant displayed immediate and delayed echolalia and was unable to sustain short conversations and answer questions appropriately. He also spoke in a telegraphic manner without inflection.
Mouridsen & Hansen (2002)	2	3 & 13	Not reported	None	N/A	Neuropsychiatric aspects of Sotos	Bayley Scale of Infant Development Reynell Developmental Language Scale Snijders-Oomen Nonverbal Intelligence Scale for Young Children (1976)	Atypical development of communication, abnormal non verbal language and limited expressive language were observed in one child. The second child showed a severe deficit in language areas at an early age, although this improved with language training.
Okamoto (2010)	1	14 yrs	'Severe mental retardation'	None	N/A	Co occurrence of Prader-Willi and Sotos Syndrome	Clinical observation	Showed no vocalised words

Table 3 continued: Communication and Language difficulties

Reference	SS, n	SS age range	Intellectual disability (range)	Comparison groups (n)	Comparison group age range	Focus of investigation	Communication & Language Measures	Findings relevant to Communication & Language
Trad et al. (1991)	1	4 yrs	88 (Stanford-Binet)	None	N/A	Treatment strategies for Sotos and PDD	Clinical observation	A sing song speech melody was present with hollow, atonal repetition of phrases. Pronominal reversals were also present and frequent.
Finegan et al. (1994)	27	5-16	21-103	20 (overgrowth & ID)	5-16	Language and Behaviour	British Picture Vocabulary Scale, Long Form (Dunn et al., 1982) Expressive One-Word Picture Vocabulary Test-Revised (Gardner, 1990) Expressive One-Word Picture Vocabulary Test, Upper Extension (Gardner, 1983) Test for the Reception of Grammar (Bishop, 1989) Word Structure subtest of the Clinical Evaluation of Language Fundamentals-Revised (Semel et al., 1987) Vocabulary subtest of the age appropriate Wechsler scales (Wechsler, 1976, 1990)	No language deficits found in language comprehension or expression.
Sarimski (2003)	27	6-15 Mean age = 10 yrs 7 mnt	Mild-Severe	29 (mixed aetiology	Mean age = 10 years		Heidelberger-Kompetenz-Inventar (HKI; Holtz et al. 1998)	Higher language scores in expressive language and competence compared to the comparison group.

Social Behaviour

Atypical social behaviour is frequently described in Sotos syndrome as evidenced by poor social interaction skills, 'seclusiveness', 'having no friends' and being withdrawn. Eleven studies profiling these difficulties are described in Table 4.

Observational and parental measures in the studies by Kessler & Kraft (2008), Mauceri et al., (2000), Mourisden and Hansen (2002), Morrow et al. (1990), Varley & Crnic (1984), and Zappella (1991), revealed social difficulties including lonely/solitary behaviour, few friends and impaired social interaction. Moreover, a marked preference for adult company was seen in two studies (Rutter & Cole, 1991; Trad et al., 1991) which suggest that children with Sotos might be more attached to parental/adult figures compared to children in a comparison group. This is further supported by Sarimski (2003) who describes significantly high levels of separation anxiety in Sotos participants. The Child Behaviour Checklist (CBCL; Achenbach; 1983) uses three scales including; activities, social and school to discriminate between children who are adapting successfully and those who are not. Two studies (de Boer et al., 2006; Finegan et al., 1994) report CBCL scores in the clinical range for Sotos participants when compared to Achenbach's (1991a, b) sample of children referred for mental health services (i.e. clinically referred).

Overall these studies suggest social difficulties for participants with Sotos syndrome in contrast to comparison groups although the nature of these difficulties is unclear. The main reported problems include: social withdrawal, lack of friendships and poor social interaction skills. Three studies also report a preference for adult attachment figures, with social anxiety and distress seen in participants if separated.

Table 4: Social Behaviour in Sotos syndrome

Reference	SS, n	SS, age range	Comparison groups (n)	Comparison group age range	Focus of investigation	Measures relevant to social behaviour	Findings relevant to social behaviour
Compton et al. (2004)	1	20	None	N/A	Psychosis	Medical notes	History of seclusiveness, no close friendships during adolescence and poor social skills
de Boer et al. (2006)	27	1-45	None, compared to test normal controls (with ID)	N/A	Psychosocial and cognitive functioning	Child Behavior Checklist (CBCL) (Verhulst et al. 1990) Young Adult Behavior Checklist (YABCL)(Achenbach et al. 1983, 1987) Dutch version of the CBCL for children aged 2 to 3 years (99 items) (Achenbach et al. 1987) Dutch version of the CBCL for children aged 18 to 30 years (118 items) Vineland screener (Sparrow et al., 1994)	Both NSD1 and non NSD1 mutation groups (n=19) showed significantly higher scores on the 'Social' subscale of the CBCL in comparison to the reference score. A mean age difference of 2 years 7 months was found between chronological age (9yr 6mth) and developmental age for social competence (6yr 10mth) on the Vineland Screener. This was slightly higher in comparison to a control group of children with ID.
Finegan et al. (1994)	27	5-16	20. Also compared to normative data.	5-16	Language and Behaviour	Child Behavior Checklist (CBCL, Achenbach, 1991a) Teacher Report Form (Achenbach, 1991b)	Children with Sotos showed higher scores on the Social Problems subscale of the CBCL, when compared to Achenbach's "normal" and clinically referred sample.
Kessler & Kraft (2008)	1	29	None	N/A	Psychosis	Clinical Observation	Reported as socially reserved and a shy loner. During examination the participant hardly spoke and remained shy and reserved.
Mauceri et al. (2000)	6	2-12	None	N/A	Aggressive behaviour	Parental reports	Describes the onset of poor social behaviour in one child at the age of 3 and in contrast described sociability in another child (aged 4) stating that 'he liked to be in touch with other people.

Table 4 continued: Social behaviour in Sotos syndrome

Reference	SS, n	SS age range	Comparison groups (n)	Comparison group age range	Focus of investigation	Measures relevant to social behaviour	Findings relevant to social behaviour
Mourisden & Hansen (2002)	2	2 & 13	N/A	N/A	Neuropsychiatric aspects	Clinical Observation	Description of severe difficulties in reciprocal social interaction, withdrawn and solitary play in one child.
Morrow, Whitman & Accardo (1990)	1	4yr 11mth	N/A	N/A	Autistic features	Clinical Observation	Participant showed impairment in his ability to interact socially and would inconsistently seek consolation when hurt or tired.
Rutter & Cole (1991)	16	5-14	None	N/A	Psychological charactersitics	Semi-structured parental interview	Areas of social behaviour described as a concern were; a marked preference for adult company with few close friends among peers (8 children) and a preference for being solitary and playing apart from the rest of the family for much of the time (8 children)
Sarimski (2003)	27	6-15	29	Mean age = 10 years	Behavioural and emotional characteristics	The Children's Social Behaviour Questionnaire (CBSQ; Lutejin et al., 1998; 2000a,b)	Children with Sotos showed more social contact problems, separation anxiety and tended to be more anxious in new situations. Fourteen parents reported that they were not satisfied with their children's social relationships. Fifteen children were reported to have no friend at all in their neighbourhood and ten children were reported to have no or only 1 friend amongst their classmates.
Trad et al. (1991)	1	4	None	N/A	Cerebral Gigantism	Clinical Investigation	The participant showed strong attachment to her mother and up until the age of 3 would refuse to be left in the care of anybody else.
Varley (1984)	11	5-13 Mean=9.5	None	N/A	Emotional, behavioural and cognitive status	Clinical Observation	The major adaptive problem seen was in the area of social functioning. All had socialization deficits ranging from being withdrawn to limited opportunities for peer relationships.
Zappella (1990)	12	3-12	None	N/A	Autistic features	Clinical Observation	Five children were described as lonely and unsociable as well as a gross inability to relate.

Motor skills

Eight studies have profiled motor skill difficulties including psychomotor retardation, delay, poor co-ordination and clumsiness, these are detailed in table 5. Of these eight studies five describe early psychomotor retardation and motor skill deficits in participants during early infancy with a combined average age range of 6 months and 5 years.

Two studies (Bale et al., 1985; Mauceri et al., 2000) describe the development of early psychomotor delay and motor skill deficits as they evolve into clumsiness and poor co-ordination in older participants. A study by Wit et al. (1985) supports the observations that clumsiness is observed in older children with 45% of participants, with an average age of 7.6 years, displaying clumsy behaviour. In addition, Mauceri et al. (2000) describes a vast improvement in motor skills as participants reached adolescence.

In contrast, de Boer et al. (2006) found that gross motor functioning was higher in the Sotos group for individuals aged between 3-7yrs compared to the control group with the motor skills instrument (Schaal voor Motorieck bij Zwakzinnigen), which consisted of 4538 participants with a cognitive disability. However, between the ages of 7-18 only females within the Sotos group showed better gross motor skills when compared to the control group mentioned previously.

The somewhat limited data suggest that psychomotor retardation is seen in younger participants whilst clumsiness and poor co-ordination is found in slightly older participants. There also seems to be an improvement in motor skills as children reach adolescence.

Table 5: Motor development in Sotos syndrome

Reference	SS, n	SS age range	Comparison groups (n)	Comparison group age range	Focus of investigation	Measures relevant to Motor skills	Findings relevant to Motor Skills
Bale (1985)	3	3-35	None	N/A	Psychological characteristics	Clinical assessment	One patient described as 'clumsy' at age 7. Second patient noted to have a significant deficit in her motor skills ages 2.5yrs, however these improved and was later described as poorly co-ordinated at 3.5 years.
Bloom (1983)	10	1-13.6 yrs	None	N/A	Cognition in cerebral giantism	Parental report	Children in the 0-2 range revealed a consistent pattern of psychomotor delay. All also manifested delayed motor milestones based on parental report.
de Boer et al. (2006)	27	1-45	None, compared to test normal controls (with ID)	N/A	Psychosocial and cognitive functioning	Dutch 22 item list (Kraijer, et al. 1994)	Gross motor functioning was significantly higher in Sotos participants aged between 3-7years than controls with intellectual disability. Only females showed better gross motor skills between 7-18years old.
Leventopolous et al. (2009)	4	0.5-11	None	N/A	Rare clinical manifestations	Clinical assessment	Reported mild to severe psychomotor retardation in all participants aged between 6 months and 5 years.
Mauceri et al. (2000)	6	2-12	None	N/A	Aggressive behaviour	The Denver Developmental Screening Test (Frankenburg & Dobbs, 1967)	Reported early psychomotor retardation and clumsiness and poor co-ordination in all patients aged between 2-12. Improvement in motor skills described in all participants during adolescence..
Mourisden & Hansen (2002)	2	2 & 13	N/A	N/A	Neuropsychiatric aspects	Clinical assessment	Described early infancy psychomotor developmental delay in both participants.
Trad et al. (1991)	1	4 yrs	None	N/A	Treatment strategies for Sotos and PDD	Clinical observation	Described 'clumsy movements' in participant during first assessment.
Wit et al. (1985)	22	1-22	None	N/A	Clinical aspects	Clinical assessment	Clumsiness was reported in 12 participants, with a mean age of 7.6 years.

Psychological disorders

Attention Deficit Hyperactivity Disorder (ADHD) and Hyperactivity

The term "Attention Deficit Disorder" was first introduced to the DSM 3rd edition in 1980 and included two forms of the condition (with or without hyperactivity). The term was revised in 1987 to "Attention Deficit/Hyperactivity Disorder" and was applied in the DSM-III-R. Diagnosis was based on the total number of symptoms falling within the areas of hyperactivity, inattention and/or impulsivity. Eleven studies have reported findings on ADHD, ADD, inattentiveness and hyperactivity in Sotos participants. Table 6 summarises these studies. Seven studies assessed ADHD/ADD in participants and six confirmed the presence of ADHD/ADD in 19 participants either via clinical assessment, parental report or standardized measures. No descriptions of the clinical features of the ADHD/ADD diagnosis are described in any of the studies. de Boer et al. (2006) was the only study that found no significant difference in mean scores for ADHD between the Sotos group and control group (children with behaviour problems).

Rutter and Cole (1991), Sarimski (2003) and Varley and Crnic (1984) have all used standardised measures to report levels of hyperactivity in participants with Sotos syndrome. The total number of participants with elevated hyperactivity scores across all three studies was 38% (n=21). Observational reports have also been used by Mourisden and Hansen (2002) and Zappella (1990) to describe hyperactivity in one and four participants respectively.

de Boer et al. (2006) found a difference in hyperactivity levels between NSD1 mutation and non mutation groups, with lower levels seen in the NSD1 mutation group for participants aged 4 to 12 years compared to the non NSD1 mutation group. However, when the mean scores of both NSD1 mutation and non mutation groups were compared to a contrast group

(children with behaviour problems), they were not significantly different. Sarimski (2003) also reported no significant difference in hyperactivity scores between participants with Sotos syndrome and the comparison group, although scores for five Sotos individuals were elevated.

Overall the majority of studies suggest the presence of ADHD and/or hyperactivity in Sotos participants with higher levels being seen in participants with NSD1 mutations compared to non NSD1 mutations. No significant difference has been established between participants with Sotos syndrome and control groups of children with behaviour problems, for the presence of hyperactivity and ADHD.

Table 6 ADHD and Hyperactivity in Sotos syndrome

Reference	SS, n	SS age range	Comparison groups (n)	Comparison group age range	Focus of investigation	Measures relevant to ADHD and/or Attention and Hyperactivity	Findings relevant to ADHD and/or Attention and Hyperactivity
Bale (1985)	3	3-35	None	N/A	Psychological characteristics	Neurological examination	Attention Defecit Disorder without hyperactivity suggested after examination in one participant.
de Boer et al. (2006)	27	1-45	None, compared to test normal controls (with ID)	N/A	Psychosocial and cognitive functioning	18 item Dutch list (Scholte et al., 1998)	No significant difference found between the Sotos and control group mean scores for ADHD. 'Hyperactivity' in patients aged between 4-12 was significantly lower in the NSD1 mutation group compared to the non NSD1 mutation group.
Finegan et al. (1994)	27	5-16	20. Also compared to normative data.	5-16	Language and Behaviour	ADHD Rating Scale (DuPaul, 1991)	Parent's rated 38% of participants as having ADHD compared to only 14% by teachers.
Leventopolous et al. (2009)	4	0.5-11	None	N/A	Rare clinical manifestations	Clinical assessment	Reported one participant with ADHD
Mauceri et al. (2000)	6	2-12	None	N/A	Aggressive behaviour	Clinical assessment	Reported 3 patients with ADHD
Mourisden & Hansen (2002)	2	2 & 13	None	N/A	Neuropsychiatric aspects	Clinical observation	Described one participant as 'inattentive, hyperactive and difficult to manage'.
Rutter & Cole (1991)	16	5-14	None	N/A	Psychological characteristics	Rutter Questionnaires (Rutter, 1967, Rutter et al. 1970)	Found that 3 participants were 'pervasively hyperactive' (e.g. identified by both teachers and parents on the questionnaire) whilst 6 participants were 'situationally hyperactive'.
Sarimski (2003)	27	6-15	29	Mean age 10 years	Behavioural and emotional characteristics	The Nisonger Child Behavior Rating Form (NCBRF; Aman et al., 1996, Tasse et al., 1996)	5 children had elevated hyperactivity scores however this figure did not differ from the comparison group.
Trad et al. (1991)	1	4 yrs	None	N/A	Treatment strategies for Sotos and PDD	Clinical observation	A diagnosis of ADHD was reported in participant.

Table 6 continued ADHD and Hyperactivity in Sotos syndrome

Reference	SS, n	SS age range	Comparison groups (n)	Comparison group age range	Focus of investigation	Measures relevant to ADHD and/or Attention and Hyperactivity	Findings relevant to ADHD and/or Attention and Hyperactivity
Varley & Crnic (1984)	11	5-13	None	N/A	Emotional, behavioural and cognitive status	Achenbach Revised Child Behavior Profile (Edelbrock et al. 1980; Achenbach et al., 1983)	Reported ADHD in 3 participants and levels of hyperactivity were elevated for 7 participants on the Achenbach scale.
Zappella (1990)	12	3-12	None	N/A	Autistic features	Clinical observation	4 participants were described as hyperactive.

Anxiety/Depression

Anxiety and depression have been recorded in five studies as detailed in table 7.

Most studies have used a standardised measure to assess anxiety and depression, except Compton (2004) who describes depressive symptoms and Kessler and Kraft (2008) who describe insecure and anxious behaviour, via a clinical assessment.

The Child Behaviour Checklist (CBCL) has been used to record anxiety/depression in participants with Sotos syndrome in two studies. Finegan et al. (1994) found lower levels of anxiety/depression in participants with Sotos syndrome compared to Achenbach's (1991a,b) sample of children referred for mental health services (i.e. clinically referred). de Boer et al. (2006) found higher scores in participants with Sotos syndrome compared to a typically developing contrast group.

The final study which has reported anxiety is Sarimski (2003). However, the measures used appear to focus on social anxiety and anxious behaviour only, which makes comparisons to the previous studies difficult. The findings on the Nisonger Child Behaviour Rating Form (NCBRF) suggest that children with Sotos syndrome are more insecure/anxious than a comparison group with mixed 'learning disability' aetiology. In contrast, no difference in anxious/rigid behaviour as measured on the Children's Social Behaviour Questionnaire (CSBQ) was found between children with Sotos syndrome and children in the comparison group.

In summary, the findings of anxious/depressed behaviour in Sotos syndrome are mixed and limited.

Psychosis

Three case studies report the development of psychosis in participants with Sotos syndrome, these are detailed in table 8. Symptoms reported by Compton et al. (2004) include auditory hallucinations, delusions of reference and delusions of grandeur. An underlying thought disorder was also found to be present in the participant. Kessler and Kraft (2008) report auditory hallucinations and obsessive and compulsive thoughts related to self blaming in one participant. Although not specifically detailed as studies which mention psychosis, Finegan et al. (1994) and de Boer et al. (2006) report significantly higher levels of 'thought disorder' in Sotos participants compared to a non referred "normal" sample. Although the scores, as measured on the CBCL thought disorder subscale, did not fall within the clinical range it is interesting that characteristics such as seeing or hearing things, repeating acts and strange ideas and behaviour are seen to a greater degree in Sotos compared to "typically developing" controls.

Although only three studies have reported the development of psychosis, there is some evidence for thought disorder in participants with Sotos syndrome as measured on the CBCL thought disorder scale.

Table 7 Anxiety and Depression in Sotos syndrome

Reference	SS, n	SS age range	Comparison groups (n)	Comparison group age range	Focus of investigation	Measures relevant to Anxiety & Depression	Findings relevant to Anxiety & Depression
Compton et al. (2004)	1	20	None	N/A	Psychosis	Clinical assessment	Depressive symptoms described in participant at age 20 after an assessment of personality and social-emotional functioning.
de Boer et al. (2006)	27	1-45	None, compared to test normal controls (with ID)	N/A	Psychosocial and cognitive functioning	Child behaviour checklist (CBCL) (Verhulst et al. 1990) Young adult behaviour checklist (YABCL)(Achenbach et al. 1983, 1987) Dutch version of the CBCL for children aged 2 to 3 years (99 items) (Achenbach et al. 1987) Dutch version of the CBCL for children aged 18 to 30 years (118 items)	The NSD1 mutation and non mutation groups together (n=19) showed significantly higher scores on the anxiety/depression Syndrome scales compared with the reference score.
Finegan et al. (1994)	27	5-16	20. Also compared to normative data.	5-16	Language and Behaviour	Child Behavior Checklist (CBCL, Achenbach, 1991a) Teacher Report Form (Achenbach, 1991b)	Sotos participants had lower scores than clinically referred children on the anxious/depressed Syndrome scale. They did however show higher scores in comparison to Achenbach's "normal" non referred sample.
Kessler & Kraft (2008)	1	29	None	N/A	Psychosis	Clinical assesment	Participant was described as 'insecure and anxious'.
Sarimski (2003)	27	6-15	29	Mean age = 10 years	Behavioural and emotional characteristics	The Children's Social Behaviour Questionnaire (CBSQ; Lutejin et al., 1998; 2000a,b) The Nisonger Child Behavior Rating Form (NCBRF; Aman et al., 1996, Tasse et al., 1996)	On the NCBRF 11 children had scores in social anxiety above those of the reference group of children with intellectual disabilities. 4 were described as 'extreme' (above the 85th centile) and 7 were described as high (above the 50th centile). When the Sotos group scores were further compared to the comparison group, Sotos children had higher insecure/anxious scores.

Table 8 Psychosis in Sotos syndrome

Reference	SS, n	SS age range	Comparison groups (n)	Comparison group age range	Focus of investigation	Measures relevant to Psychosis	Findings relevant to Psychosis
Compton et al. (2004)	1	20	None	N/A	Psychosis	Medical notes	Participant was admitted to a psychiatric inpatient unit at the age of 20 due to the onset of psychiatric symptoms. On further examination the participant showed delusions of reference (belief that the tv/radio addressed him by name) and delusions of grandiosity (he had special telepathic powers). An assessment of personality and social-emotional functioning found the participant to have an underlying thought disorder.
de Boer et al. (2006)	27	1-45	None, compared to test normal controls (with ID)	N/A	Psychosocial and cognitive functioning	Child behaviour checklist (CBCL) (Verhulst et al. 1990) Dutch version of the CBCL for children aged 2 to 3 years (99 items) (Achenbach et al. 1987) Dutch version of the CBCL for children aged 18 to 30 years (118 items)	Significantly higher scores (e.g. 62-65) were seen for 19 Sotos participants on the Thought problems subscale of the CBCL in comparison to Acehnbach's mean score for normative data (50).
Finegan et al. (1994)	27	5-16	20. Also compared to normative data.	5-16	Language and Behaviour	Child Behavior Checklist (CBCL, Achenbach, 1991a) Teacher Report Form (Achenbach, 1991b)	Higher scores seen on the CBCL subscale for Thought problems in Sotos participants compared to Achenbach's clinically referred and non referred 'normal' sample.
Kessler & Kraft (2008)	1	29	None	N/A	Psychosis	Clinical assessment	Participant during assessment reported acoustic hallucinations (thoughts becoming louder in her head) in the form of imperative voices. The participant also reported obsessive and compulsive thoughts, circular thoughts and ruminating on alleged/assumed personal failures linked with self blaming thoughts.
Leventopolous et al. (2009)	4	0.5-11	None	N/A	Rare clinical manifestations	Clinical assessment	One participant is reported to have developed psychosis at the age of 11.

Behaviour Problems

Aggression/Temper Tantrums

Nine studies have investigated aggressive behaviour in Sotos syndrome. The results are summarised in table 9. A number of studies have recruited younger participants, which has led to aggressive behaviour and temper tantrums being jointly described. Due to the different nature of both behaviours and to provide further clarity they will be reviewed separately.

Aggression

de Boer et al., (2006) used the CBCL to report high levels of aggressiveness in 55% (n=19) of Sotos participants when compared to Achenbach's (1991a,b) mean score for normative data. In contrast Finegan et al. (1994), found no difference between scores on the CBCL, for participants with Sotos syndrome and a matched comparison group with delayed motor and language milestones and two overgrowth features.   Five studies describe aggression in participants through either clinical observation/assessment or parental/teacher reports. Two of these studies (Mourisden & Hansen, 2002; Trad et al., 1991) report aggressiveness in two participants in school and with other children, compared to three participants described as aggressive with family (Mauceri et al., 2000). Leventopolous et al. (2009) reports aggressiveness in one participant, whilst Compton et al. (2004) describes the development of temper tantrums into aggressive behaviour in one participant.

Temper Tantrums

Finegan et al. (1994) reports 42% (n=11) of participants with Sotos syndrome experienced temper tantrums as reported on the CBCL. Four studies (Compton et al., 2004; Mauceri et al., 2000; Rutter & Cole, 1991; Trad et al., 1991) all describe temper tantrums in participants with Sotos syndrome as either occurring at home or with a family member. A further two studies

(Mourisden & Hansen, 2002; Varley & Crnic, 1984) describe temper tantrums in four participants, although no description of where these occur is given.

In summary, four studies (Compton et al., 2004; Mauceri et al., 2000; Mourisden & Hansen, 2002; Trad et al., 1991) have described aggression and temper tantrums conjointly in participants, making it difficult to fully separate these two behaviours. The results suggest temper tantrums occur more often at home or with family members in comparison to aggressive behaviour which has been observed in schools or with other children. As only one matched comparison group has been used, it is difficult to determine whether the incidence of aggressive behaviour and temper tantrums in participants with Sotos syndrome is higher or lower than one would expect.

Table 9 Aggression (including Temper Tantrums) in Sotos syndrome

Reference	SS, n	SS age range	Comparison groups (n)	Comparison group age range	Focus of investigation	Measures relevant to Aggression	Findings relevant to Aggression
Compton et al. (2004)	1	20	None	N/A	Psychosis	Clinical assessment and parental report	Early history of angry outbursts and tantrums within the family since the age of 4 years. Aggression also seen at ages 15 and 17, with a brief period of time spent in an psychiatric unit to stabilise his aggression.
de Boer et al. (2006)	27	1-45	None, compared to test normal controls (with ID)	N/A	Psychosocial and cognitive functioning	Child behaviour checklist (CBCL) (Verhulst et al. 1990)	Both NSD1 mutation and non mutation groups(n=19) compared with the reference score showed significantly higher scores on all the aggressive Syndrome scale.
Finegan et al. (1994)	27	5-16	20 (overgrowth & ID)	5-16	Language and Behaviour	Child Behavior Checklist (CBCL, Achenbach, 1991a)	11 participants were reported to have temper tantrums on the CBCL (item 95).
Leventopolous et al. (2009)	4	0.5-11	None	N/A	Rare clinical manifestations	Clinical assessment	Report aggressiveness in one participant.
Mauceri et al. (2000)	6	2-12	None	N/A	Aggressive behaviour	Teacher/Parent report on aggressiveness	3 patients showed aggressiveness/tantrums at home with their family. Two patient's aggressiveness was usually triggered when contradicted.
Mourisden & Hansen (2002)	2	2 & 13	None	N/A	Neuropsychiatric aspects	Clinical observation	Participant was short tempered and aggressive with tantrums, which led to special class placement no longer being possible.
Rutter & Cole (1991)	16	5-14	None	N/A	Psychological characteristics	Semi-structured interviews with parents	13 participants were reported to have tantrums at home.
Trad et al. (1991)	1	4 yrs	None	N/A	Treatment strategies for Sotos and PDD	Clinical observation	Aggressive with other children and temper tantrums observed if separated from her mother.
Varley & Crnic (1984)	11	5-13	None	N/A	Emotional, behavioural and cognitive status	Clinical assessment	"Organic personality Syndrome" with explosiveness, severe tantrums, emotional lability, and impulse control impairment reported in 2 participants.

Stereotyped, ritualistic and repetitive behaviours

Five studies report a variety of stereotyped, ritualistic and repetitive behaviours in participants. These are detailed in table 10. Two studies (Finegan et al., 1994; Sarimski, 2003) report higher scores for stereotypic behaviour on two standardised measures (see Table 3.7) in participants with Sotos syndrome compared to norms and children with typical development. However, there were no significant differences, in either Finnegan's or Sarimski's studies, between participants in the Sotos groups and the matched comparison groups (one with mixed 'learning disability' aetiology and one with delayed motor and language milestones and two overgrowth features).

Ritualistic behaviour was reported in two studies, with 50% of participants in Rutter and Cole's study (1991) and 18% of participants in Sarimski's (2003) study displaying the behaviour. Finally, repetitive behaviour was observed in two participants during play activities. This included 'impoverished play' and turning pages in a book.

In summary, although this is limited, four studies have reported ritualistic and repetitive behaviour in participants with Sotos syndrome. Two studies have reported higher levels of stereotypic behaviour in participants with Sotos syndrome in comparison to normal controls. However, this is not the case when compared to matched controls with mixed learning disability aetiology and overgrowth features and delayed language and motor milestones.

Table 10 Stereotyped. Ritualistic and Repetitive behaviour in Sotos syndrome

Reference	SS, n	SS age range	Comparison groups (n)	Comparison group age range	Focus of investigation	Measures relevant to Stereotyped/ritualistic behaviours	Findings relevant to Stereotyped/ritualistic behaviours
Finegan et al. (1994)	27	5-16	20 (overgrowth & ID)	5-16	Language and Behaviour	Abberant Behaviour Checklist (Aman & Singh, 1986)	Children were found to have significantly higher scores for stereotypic behaviour compared with norms from the standardization sample. Higher scores were also seen against the comparison group although these did not reach the prescribed significance level.
Mourisden & Hansen (2002)	2	2 & 13	None	N/A	Neuropsychiatric aspects	Clinical observation	One participant showed repetitive behaviours (i.e. turning pages in a book).
Rutter & Cole (1991)	16	5-14	None	N/A	Psychological characteristics	Semi-structured interviews with parents	Ritualistic behaviours were displayed in 8 participants.
Sarimski (2003)	27	6-15	29	Mean age 10 years	Behavioural and emotional characteristics	The Children's Social Behaviour Questionnaire (CBSQ; Lutejin et al., 1998; 2000a,b) The Nisonger Child Behavior Rating Form (NCBRF; Aman et al., 1996, Tasse et al., 1996)	Children with Sotos had higher stereotypical behaviour than children with typical development on the CBSQ. There was no difference between the Sotos and control group. 5 children had elevated scores in self isolated/ritualistic behaviour and 4 children showed stereotypic behaviour with a higher frequency than children with an intellectual disability as recorded on the NCBRF.
Trad et al. (1991)	1	4 yrs	None	N/A	Treatment strategies for Sotos and PDD	Clinical observation	Described play activity as impoverished and repetitive.

Autism Spectrum Disorder

Five studies describe autistic features and autistic behaviours in participants with Sotos syndrome, although no standardised assessment measures have been used. Table 11 provides the relevant details. Two studies (Morrow et al., 1990; Zappella, 1990) which have specifically focused on autism spectrum disorder have reported a number of autistic features in 46% of all participants. The features include: lonely and unsociable behaviour, avoidance of eye contact, stereotypic activity, insistence on sameness, repetitive behaviour and difficulties with social interaction. A further two case studies (Leventopolous et al., 2009; Mourisden & Hansen, 2002) describe participants who display 'autistic behaviours', although these are not described in detail. The final study by Finegan et al. (1994) suggests that a few children within the study were similar to children with Asperger's Syndrome. However, this was based on the author's clinical impression and no measures or observations were applied to provide further evidence for this.

Overall, although 'autistic behaviours' have been reported in a small number of studies, there have been no standardised assessments used and no diagnostic criteria explicitly applied. This makes assessing the prevalence of Autism Spectrum Disorder in individuals with Sotos syndrome difficult.

Fears and Phobias

Fears and Phobias have been described in two studies and are summarised in Table 12. Finegan et al. (1994) reports 34% (n=9) of Sotos participants as having fears, as measured on item 29 of the CBCL. After interviewing parents, Rutter and Cole (1991) describe various phobias in 62% (n=10) of Sotos participants including eggs, insects, dogs, washing machines and green objects.

In summary, more than one third of participants with Sotos syndrome in the above studies have fears and phobias, however more data are needed to assess the prevalence of this behaviour in the Sotos population.

Table 11 Autism Spectrum Disorder (ASD) in Sotos syndrome

Reference	SS, n	SS age range	Comparison groups (n)	Comparison group age range	Focus of investigation	Measures relevant to ASD	Findings relevant to ASD
Finegan et al. (1994)	27	5-16	20 (overgrowth & ID)	5-16	Language and Behaviour	Abberant Behaviour Checklist (Aman & Singh, 1986)	The clinical impressions of the authors were that none of the children with Sotos had classical autism; however they state a few were similar to children with Asperger's Syndrome.
Leventopolous et al. (2009)	4	0.5-11	None	N/A	Rare clinical manifestations	Clinical assessment	Describes one participants with 'autistic behaviour'.
Mourisden & Hansen (2002)	2	2 & 13	None	N/A	Neuropsychiatric aspects	Clinical observation	Observations showed one participant met the ICD-10 diagnosis criteria for childhood autism.
Morrow, Whitman & Accardo (1990)	1	4yr 11mth	N/A	N/A	Autistic features	Clinical observation	The participant is described as displaying a collection of 'autistic features' including: fixated eye contact, repetitive stereotypic head banging and hair pulling, twirling himself around, spinning objects, repetitively stroking objects, and an inability to interact socially.
Zappella (1990)	12	3-12	None	N/A	Autistic features	Clinical Observation	5 children showed autistic features according to DSM III-R criteria which could be defined as autistic disorders. The following features were recorded in all 5 children; lonely and unsociable, avoidant eye contact, a gross inability to relate and stereotypic/sameness behaviour.

Table 12 Fears and Phobias in Sotos syndrome

Reference	SS, n	SS age range	Comparison groups (n)	Comparison group age range	Focus of investigation	Measures relevant to Fears & Phobias	Findings relevant to Fears & Phobias
Finegan et al. (1994)	27	5-16	20 (overgrowth & ID)	5-16	Language and Behaviour	Child Behavior Checklist (CBCL, Achenbach, 1991a) Teacher Report Form (Achenbach, 1991b)	9/26 children had fears as scored on item 29 of the CBCL.
Rutter & Cole (1991)	16	5-14	None	N/A	Psychological characteristics	Semi-structured interviews with parents	10/16 children were reported by parents to have some form of phobia including: eggs, insects, dogs, washing machines and gree objects).

Methodological Limitations

The studies selected in this review demonstrate how research into the psychological, behavioural and cognitive characteristics of individuals with Sotos syndrome has developed and consequently how different methodological difficulties seen in earlier studies have been addressed. A number of different methodologies have been utilised by the papers in the current review, these consist of: case studies (e.g. Bale et al., 1985), cohort studies (e.g. Rutter & Cole, 1991), cohort studies with comparison groups of mixed aetiology (e.g. Sarimski, 2003) and cohort studies with within Sotos syndrome comparison groups (e.g. de Boer et al., 2006). Each of these approaches to understanding the behavioural phenotype of Sotos syndrome has advantages and limitations.

The case studies give a very detailed picture of specific behavioural and psychological characteristics of individual participants, often reporting the age of participants. However, case reports do not employ comparison strategies (for example comparison with normative data) and frequently focus either on diagnostic and medical issues or unusual case presentations (e.g., psychosis, autistic behaviours) which are evaluated by clinical observation rather than standardised assessments. This makes replicating these studies difficult and generalisation to the wider population of people with Sotos syndrome problematic. The small numbers and the lack of comparisons with normative data make it unclear if the behaviours reported in Sotos individuals would be seen in others individuals with the same degree of intellectual disability.

The first cohort studies were published between 1983 and1985 (Bloom et al, 1983; Varley, 1984; Wit et al, 1985). Two major strengths of these studies are larger participant groups and the use of standardised assessments for level of intellectual disability. However, there are still

limitations to these cohort studies as no standardised assessments are used for reported behaviours and no comparison groups are utilised. This limits any replication of the studies and hinders the identification of a behavioural phenotype Later cohort studies (Zappella, 1990; Rutter & Cole, 1991; Ball et al., 2005) attempt to address the problem of replication by employing standardised measures for behavioural and psychological characteristics. Two cohort studies make use of comparison groups (Finegan et al., 1994; Sarimski, 2003) and one (de Boer et al., 2006) utilises a within syndrome comparison group to assess differences between Sotos participants with and without NSD1 mutations. The two largest cohort studies (Tatton-Brown et al., 2005; Saugier-Veber et al., 2007) make use of very large participant numbers and compare within Sotos syndrome. However, the predominant focus of the research is genetic so the data reported on level of intellectual disability are limited as standardised IQ measures were not used. Moreover, no explanation was given as to how participants were categorised into different levels of intellectual disability and data for less than half of all participants were reported.

Conclusion

To summarise, the studies reviewed in this paper have highlighted several behavioural and psychological characteristics of participants with Sotos syndrome. The studies which have recorded level of intellectual disability have highlighted a possible discrepancy between verbal and non-verbal IQ, e.g., Verbal verses Performance IQ scores on the Wechsler scales, however others have found the opposite to be true e.g., Leiter verses Stanford-Binet scores. This discrepancy warrants further investigation to identify more precisely the difference between verbal and non verbal IQ.

Reports of social impairments were evident throughout the studies. However the descriptions of such impairments were not precise and several measures were used, making it difficult to compare results. This difficulty is well documented in a review by Cook & Oliver (2011) who highlight a lack of cohesion in this research area, due to the vast range of definitions used for aspects of sociability. Future research should better quantify the social impairments seen in participants with Sotos syndrome in order for comparisons with other Syndromes to be made (e.g. social anxiety in Fragile X Syndrome; social cognition problems as seen in ASD). An initial broad brush methodology, combined with more specific observational studies and a bottom up descriptive approach, would better enable a behavioural phenotype to be established.

The data on motor problems in studies suggests a progression from psychomotor retardation in younger participants to clumsiness and poor co-ordination in older participants, however this is not clear. The precise nature of the developmental trajectory of motor problems and its relationship to other behaviours is important to establish in future research. The presence of ADHD and/or hyperactivity in Sotos participants is suggested in the majority of studies, however more precise descriptions are needed using established measures and\or diagnostic

criteria. Contrasts need to be made with other Syndrome groups for which ADHD characteristics are evident (e.g. Cri du Chat, Fragile X and Smith-Magenis Syndromes).

Studies that have described aggression and temper tantrums in participants with Sotos have used the terms both separately and conjointly. This poses problems as these behaviours could be very different. A good example of this is a recent study by Arron et al. (2010) who have demonstrated a link between physical aggression and impulsivity and overactivity. Thus future research would benefit from providing a detailed description of environmental determinants and examining the relationship to cognitive function.

The prevalence of behaviours characteristic of Autism Spectrum Disorder has been described in a small number of studies, although no explicit diagnostic criteria have been applied and no standardised assessments have been used (such as the ADOS and ADI). Moss & Howlin, (2009) highlight the importance of conducting a fine-grained assessment of ASD in genetic Syndromes. They state that "subtle differences in the quality and nature of specific ASD-like impairments may only be revealed when conducting detailed analyses of behavioural characteristics, and may be masked at the broader level of clinical or algorithm-based diagnoses" (p. 868). Future research needs to examine ASD phenomenology as well as using well recognised assessments tools such as the ADOS in assessing prevalence of ASD in Sotos syndrome.

Ritualistic and repetitive behaviours were reported in a small number of participants with Sotos syndrome in four studies. Only one study used formal measures to record these behaviours. The remaining studies relied on semi-structured interviews with parents and clinical observations providing only limited descriptive detail of the behaviours. Two studies reported stereotypic behaviours; however no significant difference was found between

participants with Sotos syndrome and participants in matched control groups with mixed aetiology of intellectual disability. The use of better measures in future studies would be of benefit, as would investigation into the executive functioning of individuals with Sotos syndrome, given, as previously stated, the limited presence of repetitive behaviours and ADHD phenomenology.

Difficulties with communication and language were most commonly reported in participants with Sotos syndrome. A discrepancy was identified in four studies between expressive language and receptive language skills of participants with Sotos syndrome, with greater difficulty being exhibited in expressive language skills. However, two studies found higher levels of expressive language in participants with Sotos in comparison to control groups. These conflicting findings suggest that further investigation is required.

With regard to what are traditionally considered psychiatric disorders, it is notable that three studies have reported psychosis in participants with Sotos syndrome and there are reports of thought disorder in some participants. Standardised assessment measures are needed to enable comparison and replication. Fears and Phobias are reported in a small number of cohort studies as is anxious/depressed behaviour, however both of these provide very limited definitions and limited data, thus it is difficult to draw any clear conclusions. Specific measurement tools for these behaviours would be beneficial in future studies.

To conclude, there are a number of interesting features such as thought disorder, Autism Spectrum Disorder, repetitive behaviours and a discrepancy in Performance and Verbal IQ that warrant further attention. All of these areas are of theoretical and clinical importance and further research using case control designs with measures that are appropriate for the population would be most appropriate.

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The Behavioural Phenotype of
Sotos Syndrome

Abstract

Background: Case and cohort studies of individuals with Sotos syndrome have reported several behaviours of interest including: atypical social interaction, impaired communication, ADHD, aggression, autistic behaviours, psychosis, stereotyped and ritualistic behaviours and delayed development of motor skills. However, a precise description of the behavioural phenotype has not emerged. The aim of this study is to describe the levels of clinically significant behaviour in participants with Sotos Syndrome and to compare the behavioural phenotype of Sotos syndrome with three contrast groups for which the behavioural phenotype is well documented (Prader Willi, Autism Spectrum Disorder, Down Syndrome).

Method: Thirty eight individuals with Sotos syndrome, aged between 6 and 43 years, participated in the study. Behaviours assessed using a survey design included: repetitive behaviour, autism spectrum phenomenology, activity, sociability, and mood, interest and pleasure.

Results: Self injury and aggression were reported in over one third of participants with Sotos syndrome and were more prevalent than those reported for the Down syndrome group. There is some evidence for higher levels of impulsivity and activity, with scores comparable to those seen in participants with Autism Spectrum Disorder. A large proportion of participants scored at the clinical cut off level for Autism Spectrum Disorder (70.3%) and Autism (32.4%), with over half showing a preference for routine and engaging in repetitive questioning. The profile of Autism Spectrum Disorder differed from that seen in idiopathic ASD.

Conclusions: Aggressive and self-injurious behaviour and impairments similar to those seen in Autism Spectrum Disorder are of clinical concern in Sotos syndrome. The profile of repetitive behaviour in Sotos syndrome is similar to that seen in Prader-Willi syndrome, with differences in stereotyped behaviours to those seen in Autism Spectrum Disorder.

Introduction

The identification and assessment of genetically determined neurodevelopmental disorders associated with intellectual disability has become increasingly refined in recent years with a focus on the profile of resultant behavioural phenotypes. Within this literature there has been a growth in the number studies on the prevalence and profile of Autism Spectrum Disorders with implications for the conceptualisation and possible genetic cause. Syndromes in which an unusually high prevalence of Autism Spectrum Disorder is observed include Tuberous Sclerosis Complex, Fragile X syndrome and Cornelia de Lange syndrome (Moss and Howlin, 2009; Oliver et al., 2010). Sotos syndrome has also attracted attention following reports of the presence of characteristics of Autism Spectrum Disorder.

Sotos syndrome was first described in 1964 as an overgrowth disorder with a variable level of intellectual disability. Kurotaki et al (2002) (cited by Baujat & Cormier-Daire, 2007) reported that both deletions and mutations of the NSD1 gene at the 5q35 breakpoint are the primary cause of Sotos syndrome. The characteristics which typify individuals with Sotos syndrome include; advanced skeletal maturation, as a consequence of accelerated overgrowth particularly in earl infancy (Wit et al., 1985); a distinctive facial appearance consisting of a long narrow face, high forehead, frontal bossing, high arched palates, prominent jaws and an unusually large head (Cole & Hughes, 1991; 1994); large hands and feet from birth (Hook and Reynolds, 1967) and intellectual disability of varying degrees (Tatton-Brown, Cole & Rahman, 2004) Interest in describing the phenotype of Sotos syndrome has increased recently, particularly as comparisons within the syndrome group of participants with and without the NSD1 mutations and deletions are now possible (de Boer et al., 2006).

The literature on the phenotype of Sotos syndrome includes a small number of studies that have investigated the cognitive and behavioural characteristics of participants using both case

study and cohort methodologies[2].   Of the behaviours which are recorded the most widely reported include communication impairments (e.g. Ball et al., 2005), atypical social behaviour (e.g., Rutter & Cole, 1991; Sarimski, 2003) and ADHD and hyperactivity (e.g., Finegan et al., 1994; Varley & Crnic, 1984), with over half of all studies reporting these behaviours.

The studies investigating communication and language skills include findings of speech articulation problems comprising of delayed speech and no speech (Compton et al, 2004; Morrow et al., 1990; Okamoto, 2010); and limited expressive language (Bale et al., 1985; Mauceri et al., 2000; Mourisden & Hansen, 2002). The most extensive cohort study (Ball et al. 2005) reported greater expressive verses receptive language difficulties in individuals with Sotos syndrome compared to the normative sample. In contrast, two cohort studies (Finegan et al., 1994; Sarimski, 2003) found no language deficits.

Atypical social behaviour has been investigated with a variety of methods including, observation (e.g., Mourisden & Hansen, 2002), parental report (e.g., Mauceri et al., 2000; Rutter & Cole, 1991) and standardised measures, (e.g., de Boer et al., 2006; Finegan et al., 1994; Sarimksi, 2003). Two cohort studies (de Boer et al., 2006; Finegan et al., 1994;) report higher scores for Sotos participants on the 'social scale' of the Child Behaviour Checklist (CBCL, Achenbach, 1991a,b) compared to the CBCL's normative data. A number of other studies provide more illustrative descriptions of observed social difficulties, for example; being withdrawn (e.g. Varley & Crnic, 1984; Mourisden & Hansen, 2002) and having no close friends (e.g., Rutter & Cole, 1991; Sarimski, 2003; Compton et al., 2004).

Of the eleven studies reviewed that report ADHD and/or hyperactivity, only five used rating scales or questionnaires (e.g., Finegan et al., 1994; ADHD rating scale, DuPaul, 1991).

[2] For a fuller review of the behavioural research see Hyland (this volume).

Overall, all of the studies report the presence of ADHD and/or hyperactivity in participants, with higher levels seen in individuals with NSD1 mutations compared to non mutations (de Boer et al., 2006)

Other difficulties reported in the literature include aggressive behaviour (e.g. de Boer et al., 2006) and delayed motor skill development (e.g., Mauceri et al., 2000). 55% of individuals across two studies (de Boer et al., 2006; Finegan et al., 1994) showed more aggressiveness than 'normal' controls as measured on the CBCL. Observations of temper tantrums indicate a higher prevalence in family and school environments (e.g. Compton et al., 2004; Rutter & Cole, 1991). Motor skill development has been reported as 'delayed' with the majority of studies reporting early psychomotor retardation in younger children (e.g. Bloom, 1983; Leventopolous et al., 2009) and clumsiness in older children (e.g., Bale et al., 1985; Trad et al., 1991). An improvement is seen during adolescence (Mauceri et al., 2000).

Behaviours which have been observed in some participants, but have been less well reported, include stereotypic, ritualistic and repetitive behaviour, psychosis (e.g. Kessler & Kraft, 2008) and Autism Spectrum Disorder (e.g. Zappella, 1990).

Stereotypic behaviour has been reported in two studies (Finegan et al., 1994; Sarimski, 2003), with Sotos individuals displaying higher levels of stereotypic behaviour in comparison to normative data, whilst ritualistic and repetitive behaviours have been observed in three studies (e.g., Trad et al., 1991). Psychosis and Autism Spectrum Disorder have both been reported using observational methodology. Studies which have investigated ASD describe 'autistic behaviours' (e.g. Leventopolus et al., 2009) and 'autistic features' (Morrow et al., 1990; Zapella, 1990) in a very small number of participants. Psychosis has only been reported in 3 individuals.

The level of cognitive ability varies in reports with IQ scores ranging from 40 to 110. Taken together, this literature does indicate that a behavioural phenotype for Sotos syndrome might be delineated but at present it does not provide a clear profile of the behavioural characteristics associated with the disorder, primarily because the methodology employed militates against clear conclusions being drawn.

Over half of the studies investigating behaviour in Sotos syndrome use case study methodology. These have provided some initial information about the behaviours of interest and the participants. However, limitations of this approach make it difficult to generalise the findings because small numbers of participants and assessments using clinical judgement or observation make replication difficult. The use of cohort methodology addresses some of these difficulties by using standardised measures and larger number of participants (e.g., Finegan et al., 1994; Sarimski, 2003). However, there are limitations to these studies. Many of the behaviours described are not well defined (e.g., social impairment, aggression) and some measures used are not designed for use with the intellectual disability population, again making comparisons and generalisations difficult. Finally, only three studies have employed matched comparison groups (e.g., de Boer et al., 2006; Finegan et al., 1994; Sarimski, 2003). The use of comparison groups is now common in behavioural phenotype research designs. The conceptualisation of behavioural phenotypes typically incorporates the notion of difference between people with a given syndrome, and those without the syndrome, who are comparable with regard to characteristics associated with difference within the population of people with intellectual disability (Dykens, 1995).

Comparison groups are usually matched for mental and chronological age and composed of participants with heterogeneous aetiology. However, an alternative approach, which is

broadly consistent with the perspective adopted by Dykens, is the use of contrast groups of different genetic disorders (Oliver et al., 2010). For the purpose of the present study, Down syndrome, Prader Willi syndrome and Autism Spectrum Disorder are used as contrast groups because they can cover the same range of level of ability as Sotos syndrome and the behavioural phenotype of each disorder has been well documented in the literature. This methodology allows the positioning of Sotos syndrome relative to other genetic syndromes on given constructs.

Prader Willi syndrome is associated with mild to moderate intellectual disability and the main cause is a deletion of genetic information on chromosome 15 in the q11–q13 region (e.g. Whittington et al. 2004). The behavioural phenotype of Prader Willi includes temper outbursts, repetitive questioning, excessive eating, specific repetitive and self-injurious behaviours, mood disturbance, 'stubbornness', 'disobedience', excessive daytime sleepiness and under activity (Oliver, Woodcock & Humphreys, 2009). Autism Spectrum Disorder is a pervasive developmental disorder with a broad array of behavioural difference. These include; impairments of social interaction and communication and restricted, stereotypical, and ritualized patterns of behaviour (Bailey et al., 1996). Intellectual disability is also associated with Autism Spectrum Disorder with approximately two-thirds of individuals being recognised as having an intellectual disability (Smalley, 1997). Down syndrome is the most common genetic syndrome caused by an extra chromosome 21 (trisomy 21) in 95% of individuals (Fidler, 2005) and is associated with characteristic facies (e.g. short stature, flat facial profile, small ears, protruding tongue) and intellectual disability. Distinct behaviours reported in individuals with Down Syndrome include; high sociability (e.g., Jahromi, Gulsrud & Kasari, 2008), high rates of self-talk (e.g., Glenn & Cunningham, 2000), noncompliance,

attention problems, and compulsions (e.g., Coe et al., 1999; Evans & Gray, 2000). Various behaviours have also been noted to increase with age include anxiety, depression and withdrawal (Feeley & Jones, 2006).

The first aim of this study is to describe the levels of clinically significant behavioural disorders in participants with Sotos syndrome. The second aim is to compare the behavioural phenotype of Sotos syndrome with those of the contrast groups of Autism Spectrum Disorder, Down and Prader-Willi syndromes for which the behavioural phenotype is already well described.

Methods

Ethical approval

Ethical review for the present study was provided by the Coventry Research Ethics Committee (See Appendix 1 for the ethics confirmation letter)

Recruitment

Participants were recruited though three different sources: the Child Growth Foundation (CGF; an independent charity supporting children, families of children and adults with growth related problems), the Clinical Genetics Department at Birmingham Women's Hospital and the Clinical Genetics Department at Liverpool Alder Hey hospital. All participants were either registered with the CGF or were known to Clinical Geneticists working within the two departments. In total 152 questionnaire packs were sent out, of which 57% (n=87) were for participants identified as 16 or over and 46% (n=70) for participants under 16. Overall, 42 questionnaire packs were returned (27.63% return rate) and all individuals had a diagnosis of Sotos Syndrome confirmed by a clinical geneticist or paediatrician.

Participants with three other genetic syndromes (Prader-Willi (PW), Autism Spectrum Disorder (ASD) and Down Syndrome (DS)) had given consent for their information and data to be included in the study, after taking part in previous research investigating behavioural phenotypes (e.g., Oliver, Berg, Moss, Arron & Burbidge, 2010).

Procedure

In order to protect confidentiality, questionnaire packs which included a covering letter, consent forms, information sheets and a prepaid return envelope were sent out by each of the three sources (see appendices 2, 3, & 5 for information sheets, consent forms and

questionnaire pack). Parents and Carers of individuals were asked to complete and return the questionnaire pack and consent form to the University of Birmingham. A follow up letter was sent out to participants one month after the questionnaire packs to improve the return rate of questionnaires (see appendix 4 for the follow up letter).

Participants

Descriptive data including; mean age and range, gender, level of self-help ability, mobility, vision, hearing and speech are shown in Table 1. Participants in the Sotos syndrome group were individually matched to participants with other genetic syndromes. Individuals with Prader-Willi, Down syndrome and Autism Spectrum Disorder were matched to participants with Sotos syndrome on age, gender and level of ability.

The mean age of the 150 participants was 17.04 years (standard deviation, 9.30 years) with 66% of the sample being male. The Wessex Scale (Kushlick, Blunden & Cox, 1973) was used to describe speech, vision, hearing impairments and level of ability (self help skills). In total 88% of all participants were able or partly able, 96% were verbal (i.e. used more than 30 signs or words), 89% were mobile (i.e. they did not require assistance), 71% had normal vision and 82% had normal hearing.

Table 1 Demographic characteristics, mean age (and standard deviation), statistical analyses and post hoc analyses for participant groups: Sotos Syndrome (SS), Prader-Willi (PW), Down Syndrome (DS) and Autism Spectrum Disorder (ASD)

		Sotos Syndrome	Prader Willi	Down Syndrome	Autism Spectrum Disorder	F/X^2	df	*p* value	Post hoc analyses
N*		38	38	38	36				
Age**	Mean	16.84	16.86	17.78	16.63	.112	3	ns	N/A
	(SD)	(9.33)	(9.39)	(8.89)	(9.94)				
	Range	6-43	5-44	6-43	6-49				
Gender	% Male	65.8	65.8	65.8	69.4	.164	3	ns	N/A
Self Help[a]	% Partly able/able[b]	84.2	89.5	89.5	86.1	1.32	3	ns	N/A
Mobility[a]	% Mobile[c]	94.7	67.6	94.7	97.2	105.15	3	<.001	ASD > PWS
Vision[a]	% Normal	73.7	68.4	57.9	86.1	7.46	3	ns	N/A
Hearing[a]	% Normal	73.7	92.1	63.2	100	23.64	3	<.001	ASD > DS
Speech[a]	% Verbal	97.3	97.4	97.4	97.1	.005	3	ns	N/A

*N may vary across analysis due to missing data
** In years
[a] Data derived from the Wessex Scale (Kushlick et al. 1973)
[b] Those scoring six or above on the total score of the self help subscale (items g-i).
[c] Those scoring six on the total score of the mobility subscale (items e & f).

Measures

Fifteen questionnaires were sent out to all Sotos participants as part of the standard questionnaire pack. However, only seven questionnaires are reported in the present study due to the availability of corresponding data in the other syndrome groups.

The Demographic Questionnaire

Participants report basic details such as date of birth, gender, mobility, verbal ability (more than 30 signs/words) and diagnostic status (whether given, by whom and when).

The Wessex Scale (Kushlick et al., 1973)

The Wessex scale is designed for completion by parents and carers to assess the level of adaptive behaviour in participants. This is achieved by evaluating the physical and social abilities of individuals on subscales which comprise; self help skills, continence, mobility, speech and literacy. The measure has good inter-rater reliability with children and adults at both the item and subscale level (Kushlick et al. 1973; Palmer and Jenkins 1982).

Activity Questionnaire (TAQ; Burbidge & Oliver, 2008; Burbidge et al., 2010)

The Activity questionnaire is designed to be completed by parents and carers of individuals with intellectual disability and is suitable for use with both non-verbal and verbal individuals. The questionnaire is designed to evaluate hyperactivity and impulsivity and contains 18 items which are assembled into three subscales; impulsivity, overactivity and impulsive speech. Robust internal consistency and reliability has also been established (Burbidge & Oliver, 2008)

The Repetitive Behaviour Questionnaire (RBQ; Moss and Oliver, 2008; Moss et al., 2009)

An informant based questionnaire used with both children and adults with intellectual disabilities to identify specific types of repetitive behaviour. The questionnaire is made up of nineteen operationally defined and observable behaviours across five subscales: restricted preferences, repetitive speech, insistence on sameness, stereotyped behaviour and compulsive behaviour. A five point Likert rating scale is used to record responses which range from 'never' to 'more than once a day'. Other studies have also shown the questionnaire to have good reliability and validity (Moss et al., 2009).

The Challenging Behaviour Questionnaire (CBQ; Hyman, Oliver and Hall, 2002)

The challenging behaviour questionnaire is a brief measure designed to assess the presence or absence of different behaviours over the past month. Behaviours include; physical and verbal aggression, self-injury, destruction of property and inappropriate vocalisations. Good inter-rater reliability has been established (Hyman, Oliver and Hall, 2002).

Mood, Interest and Pleasure Questionnaire Short Version (MIPQ-S; Ross & Oliver, 2003; Ross, Arron & Oliver, 2008)

The Mood, Interest and Pleasure Questionnaire (MIPQ-S) evaluates two constructs associated with depression in adults and children with intellectual disabilities. Informants are required to rate 12 items based on retrospective observations over a two week period. The questionnaire shows good internal consistency and reliability (Ross and Oliver, 2003) and cut-off points for abnormally high (23 interest and pleasure; 24 mood) and low (6-interest and pleasure; 15-mood) scoring individuals under 18 have been identified (Ross et al., 2008). Cut-off scores for individuals over 18 have also been identified as 6-13 and 21–24 respectively.

Social Communication Questionnaire (SCQ; Rutter, Bailey & Lord, 2003)

The Social Communication Questionnaire (SCQ) is a screening tool designed to measure communication and social skills in participants who are suspected of having an Autism spectrum disorder. The questionnaire is comprised of three subscales: communication, social interaction and repetitive and stereotyped behaviours. Higher scores signify the presence of abnormal behaviours, with scores of 15 and above discerning individuals with an Autism Spectrum Disorder and 22 and above indicating Autism. The SCQ was shown to have good concurrent validity with the Autism Diagnostic Observation Schedule and Autism Diagnostic Interview (Berument, Rutter, Lord, Pickles, & Bailey, 1999; Howlin & Karpf, 2004).

The Sociability Questionnaire for Intellectual Disabilities (SQID; Collis & Oliver, unpublished)

The Sociability Questionnaire for People with Intellectual Disabilities (SQID) is designed to measure behaviours indicative of social anxiety and sociability in participants with a range of intellectual disabilities. The SQID is an informant based questionnaire consisting of 24 items across two subscales; social interaction and social performance. Informants are required to complete the questionnaire on the basis of the participant's behaviour in specific social settings over the past two months. Psychometric analysis of the SQID is ongoing, however preliminary findings indicate good inter-rater reliability for both subscales (Collis et al., unpublished).

Data Analysis

All data were tested for normality using Kolmogorov-Smirnov tests. Where data were not normally distributed (<.05), non parametric tests were employed. The percentages of individuals showing self-injurious behaviour, physical aggression, stereotyped behaviour and property destruction in each of the individual groups were derived from the Challenging Behaviour Questionnaire. Kruskal-Wallis tests were carried out at subscale level on the SCQ, TAQ, MIPQ-S and SQID, in order to identify areas of difference in affect, impulsivity, overactivity, autism spectrum characteristics and levels of sociability across the groups. Where significant group differences were identified, post hoc contrasts using pairwise Mann-Whitney U tests were conducted. Scores on the Repetitive Behaviour Questionnaire were compared at full scale, subscale and item levels across all groups using Kruskal-Wallis tests. Post hoc contrasts using pairwise Mann-Whitney U tests were conducted where significant differences were revealed and an alpha level of $p<.01$ was used. Further item level analysis was conducted using the clinical cut off scores. The percentages of participants in each group scoring above the clinical cut off were compared using a series of Chi square tests. Where significant differences were revealed, post hoc contrasts using pairwise Chi square tests were conducted in order to identify the source of difference and an alpha level of $p<.01$ was used.

Results

Demographic Characteristics

Descriptive data for the groups are presented in Table 1. A one-way ANOVA of the mean ages revealed no significant difference across the four participant groups. Chi-square tests revealed no significant differences between the groups regarding gender, level of ability, vision and speech, although significant differences were observed for mobility and hearing. Post hoc contrasts determined significantly higher levels of mobility and hearing in the ASD group compared to the PWS and DS group respectively.

Prevalence of challenging behaviour

As can be seen in Table 2 approximately 40% of participants with Sotos syndrome display self injurious behaviour, physical aggression, stereotyped behaviour and destruction of property in contrast to approximately 17% of participants with Down syndrome. Odds ratio's and 99% confidence intervals calculating the likelihood of individuals showing stereotyped behaviours, self injury, aggression and destruction of property compared with participants in the Down syndrome group are shown in Table 2. Participants with Sotos syndrome were approximately 13.09 times more likely to show each form of challenging behaviour than the Down syndrome group. These levels of challenging behaviour were similar to those reported for participants with Autism Spectrum Disorder and Prader-Willi syndrome.

Table 2 Percentage of individuals showing self-injury, physical aggression, stereotyped behaviours and destruction of property in each group

Group	Self Injurious Behaviour		Stereotyped Behaviour		Physical aggression		Destruction of property	
	Percentage (*n*)	Odds ratio (99% CIs) (*n*)	Percentage (*n*)	Odds ratio (99% CIs) (*n*)	Percentage (*n*)	Odds ratio (99% CIs) (*n*)	Percentage (*n*)	Odds ratio (99% CIs) (*n*)
Down Syndrome	5.3 (2)	-	26.3 (10)	-	26.3 (10)	-	10.5 (4)	-
Prader-Willi Syndrome	**57.9 (22)**	**24.75 (3.17-193.01)**	**42.1 (16)**	**13.09 (1.68-102.09)**	**47.4 (18)**	**16.2 (2.08-125.84)**	**39.5 (15)**	**11.73 (1.5-91.87)**
Sotos Syndrome	**42.1 (16)**	**13.09 (1.68-102.09)**	**43.2* (16)**	**13.71 (1.75-107.32)**	**43.2* (16)**	**13.71 (1.75-107.32)**	**43.2* (16)**	**13.71 (1.75-107.32)**
Autism Spectrum Disorder	**47.2 (17)**	**16.10 (2.05-126.30)**	**77.8 (28)**	**63 (7.43-534.09)**	**55.6 (20)**	**22.5 (2.86-176.75)**	**44.4 (16)**	**14.4 (1.83-113.12)**

* Missing data for one participant

Odds ratios and 99% confidence intervals are shown to demonstrate the likelihood of individuals in each syndrome group showing self-injury, stereotyped behaviour, physical aggression and destruction of property compared with the Down syndrome group. Significant results are indicated in bold type.

Table 3 displays the median and inter quartile range scores for subscales of the TAQ, MIPQ-S, SCQ, and SQUID, with Kruskall Wallis test results and subsequent post hoc analyses.

Impulsivity and Overactivity

As can be seen in Table 3, scores on the TAQ were found to be significantly different between the groups on all three subscales (impulsivity, overactivity and total activity). Post hoc analyses were conducted and the differences between the groups are recorded in Table 3. The participants with Sotos syndrome are scoring at a level which is broadly comparable to the participants with Autism Spectrum Disorder on the TAQ subscales and significantly higher than participants with Down syndrome on the impulsivity and Total activity scores.

Mood, Interest and Pleasure

Table 3 reports scores for each of the MIPQ-S subscales (Mood and Interest and Pleasure) and the total MIPQ-S score. Significant group differences were found on all scales. Post hoc analyses revealed significantly higher levels on both the Mood and Interest and Pleasure subscales for the Sotos group compared with ASD group (indicating a more 'positive' mood for the Sotos group compared to the ASD group).

Autism Spectrum Disorder

Table 3 shows significant group differences on the SCQ total and all SCQ subscales (communication, restricted, repetitive & stereotyped behaviour and reciprocal social interaction). Post hoc analysis revealed the sources of these differences. The participants with Sotos syndrome scored lower than participants with Autism Spectrum Disorder but significantly higher than participants with Prader-Willi and Down syndromes on both the

communication and restricted, repetitive & stereotyped behaviour subscales. On the reciprocal social interaction subscale participants with Sotos syndrome and Autism Spectrum Disorder scored at comparable levels and were both significantly higher than participants with Down syndrome and Prader-Willi syndrome. On the SCQ total scale participants with Autism Spectrum Disorder scored significantly higher than participants with Prader-Willi and Down syndromes but not significantly higher than participants with Sotos syndrome. The participants with Sotos syndrome however did score significantly higher than participants with Down syndrome. The differences between the Sotos and ASD groups on the communication and restricted, repetitive & stereotyped behaviour subscales but not the reciprocal social interaction subscale is notable.

Table 4 reports the cut off levels on the Social Communication Questionnaire (SCQ) for Autism Spectrum Disorder and Autism. A larger proportion of participants with Sotos syndrome scored at the clinical cut off for ASD (68.4%) and Autism (31.5%) in comparison to participants with Down syndrome (25.8% and 9.7% respectively).

Sociability

Table 3 reports the SQID scores for three groups as no data were available for participants with Prader-Willi for this analysis. Scores for participants with Sotos syndrome were below participants with Down syndrome and above participants with Autism Spectrum Disorder on both subscales (sociability with familiar and unfamiliar people). Post hoc analysis revealed that scores for participants with Sotos syndrome were significantly higher than participants with Autism Spectrum Disorder but significantly lower than participants with Down syndrome on both subscales.

Table 3 Median (Inter-quartile range) scores for subscales of the TAQ, MIPQ, SCQ and SQID with results for Kruskal-Wallis and post hoc analyses

	SS	PW	DS	ASD	Kruskal-Wallis			Post hoc Mann-Whitney tests
					df	X^2	p level	**<.05**
TAQ								
Total Impulsivity (All)	15.50 (10.75-21.00)	12.00 (5.50-16.50)	7.00 (3.00-10.00)	16.50 (9.25-22.00)	3	23.03	<0.01	SS,ASD,PWS>DS
Overactivity	12.00 (3.00-18.06)	6.00 (2.00-10.25)	6.00 (2.00-9.50)	14.50 (6.50-23.50)	3	18.77	<0.01	ASD >DS, PWS, SS
Total Activity (All)	27.50 (16.00-44.00)	22.00 (12.75-33.00)	14.50 (7.75-23.75)	35.00 (19.00-50.00)	3	20.52	<0.01	ASD > PWS, DS SS > DS
MIPQ-S								
Total	39.00 (32.50-42.27)	36.50 (31.00-40.25)	41.00 (37.75-44.00)	31.00 (27.00-39.00)	3	24.66	<0.01	DS > PWS>ASD SS >ASD
Mood	22.00 (19.00-23.00)	20.00 (17.75-22.00)	22.00 (20.00-23.00)	18.00 (15.00-21.00)	3	20.93	<0.01	DS > PWS> ASD SS >ASD
Interest and Pleasure	18.00 (15.25-19.50)	16.00 (12.75-19.25)	19.00 (17.00-22.00)	14.00 (11.00-19.00)	3	19.43	<0.01	DS > PWS, ASD SS >ASD
SCQ								
Communication	6.00 (5.00-9.37)	5.14 (1.71-6.85)	3.00 (2.00-7.00)	8.83 (6.00-10.00)	3	24.17	<0.01	ASD > SS> PWS, DS
Restricted, repetitive & stereotypes	4.00 (1.00-6.00)	4.00 (2.00-5.00)	2.00 (1.00-3.75)	5.00 (4.00-7.00)	3	23.52	<0.01	ASD > SS, PWS >DS
Reciprocal social interaction	8.00 (5.00-11.00)	4.29 (1.50-7.50)	3.33 (1.25-7.37)	8.00 (4.00-10.00)	3	14.77	<0.01	ASD,SS>PW,DS
Total	18.00 (12.50-26.00)	8.29 (5.50-15.50)	9.00 (6.00-16.00)	23.00 (15.75-26.25)	3	28.69	<0.01	ASD > PWS> DS SS >DS
SQID								
Familiar	44.00 (37.00-50.25)	n/a	53.00 (48.50-55.50)	37.00 (29.00-47.00)	3	34.07	<0.01	DS > SS>ASD
Unfamiliar	23.00 (15.50-40.50)	n/a	37.50 (27.25-48.00)	15.00 (13.00-26.00)	3	30.68	<0.01	DS > SS,>ASD

Sotos syndrome, Prader-Willi, Down syndrome, Autism Spectrum Disorder

Table 4 Proportions of each group attaining cut-off scores on the Social Communication Questionnaire indicative of Autism Spectrum Disorder (ASD) or Autism

	Sotos Syndrome	Prader-Willi[1]	Down Syndrome[2]	Autism Spectrum Disorder[3]
ASD				
n	26	15	8	27
%	68.4	45.5	25.8	75
Autism				
n	12	8	3	18
%	31.5	24.2	9.7	50

[1] Data missing for 5 participants
[2] Data missing for 7 participants
[3] Data missing for 2 participants

Repetitive Behaviour Questionnaire

Full scale and Subscale Level Analysis

Table 5 reports the mean full scale, subscale and post hoc analyses for scores on the Repetitive Behaviour Questionnaire. Kruskall-Wallis tests and pairwise Mann-Whitney U tests were used to compare the full scale and subscale level scores across the four participant groups using. Significant differences were observed on the verbal and stereotyped behaviour subscales, with post hoc analysis revealing lower levels of stereotyped behaviour in participants with Sotos syndrome and Down syndrome compared to participants with Autism Spectrum Disorder.

Clinical Cut-Off Analysis

Table 6 details the percentage of participants scoring above the clinical cut-off for scroes on the RBQ in each group. Item level Chi square tests and Chi-squared post hoc analysis were used to compare the scores in each group. The participants with Sotos syndrome scored significantly lower than participants with Autism Spectrum Disorder on object and body

stereotypy, with only approximately 10% of participants showing this behaviour. In comparison 40% of participants with Sotos syndrome displayed hand stereotypy compared to around 50% of participants with Autism Spectrum Disorder, although this was not significant. Other behaviours which did not reach significance but occurred in more than a third of participants with Sotos syndrome include attachment to people and restricted conversation. The most common repetitive behaviours seen in participants with Sotos syndrome are; preference for routine and repetitive questioning with over half of all participants displaying these behaviours.

Item Level Analysis

Figure 1 shows the repetitive behaviour profile of each group based on the mean item level scores. As can be seen, the overall profile of participants with Sotos syndrome for repetitive behaviour is more similar to that seen in participants with Prader-Willi Syndrome, for which a small number of specific behaviours are evident, as opposed to participants with Autism Spectrum Disorder, for which a larger number of behaviours feature.

Table 5 Mean scores, standard deviations, statistical analyses and post hoc analyses on full scale and sub scale level scores of the Repetitive Behaviour Questionnaire for all participant groups Sotos Syndrome (SS), Prader Willi (PWS), Down Syndrome (DS) and Autism Spectrum Disorder (ASD)

	Group				df	χ^2	p value	Post hoc analyses
	SS (n=38) Mean (SD)	PW (n=38)	DS (n=38)	ASD (n=36)				
Stereotyped Behaviour	2.68 (2.74)	3.70 (3.99)	2.63 (3.73)	6.41 (3.95)	3	23.44	<0.001	ASD>SS, DS
Compulsive behaviour	5.55 (5.54)	5.62 (5.45)	4.03 (6.20)	8.20 (6.78)	3	11.16	ns	
Insistence on sameness	3.02 (2.69)	3.81 (2.42)	2.00 (2.84)	3.61 (2.90)	3	12.10	ns	
Restricted Preferences**	4.61 (3.89)	3.91 (3.25)	3.29 (3.52)	5.11 (3.84)	3	4.90	ns	
Repetitive speech**	5.21 (4.12)	4.02 (3.08)	2.30 (2.93)	5.71 (4.06)	3	16.51	ns	
Verbal total score**	21.54 (16.02)	27.03 (25.46)	14.09 (15.77)	29.40 (15.81)	3	18.36	<0.001	ASD>DS
Nonverbal total score	15.66 (10.59)	15.08 (10.97)	11.25 (4.34)	27.00 (-)	3	1.59	ns	

** Analysis only includes participants who are verbal
Mean scores reported. Median scores are uninformative with too many zeros

Table 6 Percentage of individuals scoring above the clinical cut-off score on the Repetitive Behaviour Questionnaire: Item level scores and post hoc contrasts for all participant groups Sotos Syndrome (SS), Prader Willi (PWS), Down Syndrome (DS) and Autism Spectrum Disorder (ASD)

	Groups				χ2	*p* value	Post hoc analyses
	SS *(n = 38)*	**PW** *(n=38)*	**DS** *(n= 8)*	**ASD** *(n=36)*			
Stereotyped behaviour							
Q1 Object Stereotypy	10.5	26.3	23.7	44.4	25.40	<0.01	ASD > SS
Q2 Body Stereotypy	10.5	18.4	18.4	44.4	26.10	<0.01	ASD > SS, DS, PWS
Q3 Hand Stereotypy	42.1	42.1	21.1	52.8	29.04	<0.01	ASD > DS
Compulsive behaviour							
Q4 Cleaning	10.5	10.5	7.9	16.7	18.27	ns	
Q5 Tidying	10.5	0	10.5	16.7	17.21	ns	
Q6 Hoarding	18.4	21.1	10.5	11.1	31.93	ns	
Q7 Organising Objects	7.9	10.5	7.9	13.9	10.58	ns	
Q12 Rituals	7.9	5.3	10.5	36.1	21.87	ns	
Q16 Lining up objects	23.7	13.2	10.5	19.4	8.05	ns	
Q18 Completing behaviour	18.4	23.7	13.2	33.3	12.39	ns	
Q19 Spotless behaviour	7.9	7.9	13.2	19.4	14.01	ns	
Restricted preferences							
Q8 Attachment to people**	36.8	21.1	28.9	25.0	8.42	ns	
Q10 Attachment to objects	26.3	23.7	23.7	33.3	6.63	ns	
Q13 Restricted conversation**	36.8	31.6	13.2	50.0	22.16	ns	
Insistence on sameness							
Q15 Preference for routine	50.0	63.2	23.7	52.8	26.68	<0.01	PWS > DS
Q17 Just right behaviour	18.4	18.4	21.1	25.0	10.37	ns	
Repetitive speech							
Q9 Repetitive questions**	50.0	52.6	28.9	41.7	27.66	<0.01	PWS > DS
Q11 Repetitive phrases/signing	31.6	18.4	5.3	50.0	37.64	<0.01	ASD>DS,PWS SS > DS
Q14 Echolalia**	21.1	7.9	10.5	41.7	26.58	ns	

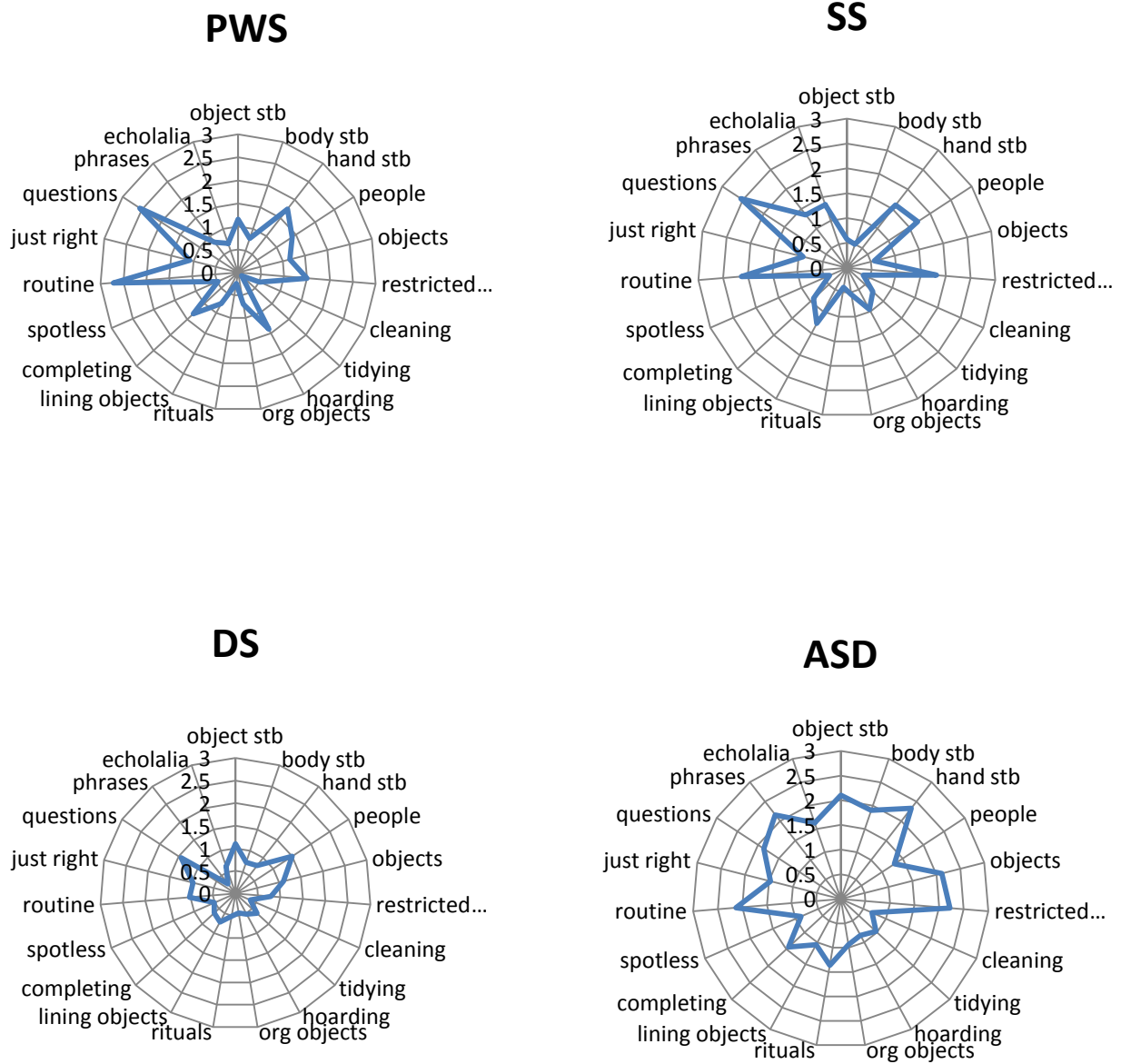** Analysis only includes participants who are verbal

Fig 1 Mean item level scores on the Repetitive Behaviour Questionnaire
*Prader Willi (PWS), Sotos Syndrome (SS), Down Syndrome (DS), Autism Spectrum Disorder (ASD)

Discussion

This is the first study to contrast participants with Sotos syndrome with participants with different genetic syndromes whose behavioural phenotypes are already well documented. All participants were carefully matched on age, gender, level of ability and speech and well validated, standardised questionnaires appropriate for individuals with intellectual disabilities were used. The aims were to describe the levels of clinically significant behavioural difficulties and disorders in participants with Sotos syndrome and to compare the behavioural phenotype of participants with Sotos syndrome with the groups for which the behavioural phenotype has already been well described.

In the current study the prevalence of challenging behaviour was shown to be significantly higher in participants with Sotos syndrome than those with Down syndrome, with the clinically prominent behaviours of self injury and aggression shown by approximately 40% of participants with Sotos syndrome. This is consistent with previous reports of aggression and extends earlier research which had not reported self injury in participants with Sotos syndrome. A strength of the current study is that self injurious behaviour was measured across all groups with the same standardised measure, allowing the prevalence of self-injury for Sotos participants to be shown as broadly comparable to that seen in Autism Spectrum Disorder but much higher than that seen in the Down syndrome group. The latter show challenging behaviour at levels typically reported in the broader intellectual disability population.

There is some evidence for high levels of impulsivity and total activity in participants with Sotos syndrome, with scores comparable to those seen in participants with Autism Spectrum Disorder. High levels of impulsivity have previously been reported in individuals with Autistic Spectrum Disorder (Aman, 2004; Bradley & Isaacs, 2006). In a review of the

literature (Hyland, this volume) the presence of ADHD and/or hyperactivity in Sotos participants was reported in eleven studies (e.g., Finegan et al., 1994; Rutter & Cole, 1991; Varley & Crnic, 1984). The behavioural features of ADHD and hyperactivity have not been clearly described in previous research and these data suggest these areas might warrant further attention.

A large proportion of the participants with Sotos syndrome scored at the clinical cut off level for Autism Spectrum Disorder (68.4%) and Autism (31.5%) on the Social Communication Questionnaire. The proportions of these disorders shown by participants with Down syndrome were similar to those reported by others (e.g. DiGuiseppi et al., 2010; Lowenthal, et al., 2007; Starr et al., 2005), hence the base levels across the syndrome groups, including Sotos syndrome, would appear to be useful estimates. Interestingly, significantly higher scores were seen in comparison to participants with Down syndrome on two of the SCQ subscales (communication, restricted, repetitive & stereotyped behaviour) but scores on these measures for participants with Sotos syndrome were lower than those for participants with Autism Spectrum Disorder. On the reciprocal social interaction scale both participants with Sotos syndrome and Autism Spectrum Disorder scored significantly higher than Prader Willi and Down syndrome participants and at very similar levels. Although a small number of studies have previously reported the presence of Autism behaviours in Sotos participants no standardised assessments have been used and no diagnostic criteria applied explicitly. The present study does indicate a higher prevalence of Autism Spectrum Disorder in participants with Sotos syndrome than might be expected given the level of intellectual disability, but also indicates potential difference in the profile of Autism Spectrum Disorder with evidence of more significant impairment in reciprocal social interaction than repetitive behaviour and communication. This warrants further investigation perhaps using an item level analysis of

the SCQ or measures such as the Autism Diagnostic Interview (Lord et al., 2000) and the Autism Diagnostic Observation Schedule (Lord, Rutter & DiLavore, 1997). This line of enquiry might indicate further differences in the profile of the triad of impairments and the reasons for endorsement of specific items (see Moss and Howlin, 2009).

On the Mood and Interest and Pleasure subscales participants with Sotos syndrome scored significantly higher in comparison to participants with Autism Spectrum Disorder, thus indicating a further dissimilarity between these groups. Significantly higher levels of sociability were found in Sotos participants than participants with Autism Spectrum Disorder, however lower levels were seen in comparison to participants with Down syndrome. These results suggest that participants with Sotos syndrome do have some restriction of social motivation, however this is not at the level seen in participants with Autism Spectrum Disorder. Previous research has reported social impairments in Sotos participants, although these have not been clearly defined (e.g., de Boer et al., 2006; Sarimski, 2003; Varley, 1984). The current finding warrants further research. More specifically, observation of the nature of restricted sociability is warranted and the relationship between this and the profile of the triad of impairments noted previously would be of interest.

Within the ASD phenomenology participants with Sotos syndrome scored significantly lower than participants with Autism Spectrum Disorder on stereotyped behaviour but higher than Down syndrome participants. Only a few studies have reported ritualistic, repetitive and stereotyped behaviours in participants with Sotos syndrome, with the majority of these reliant upon observational data (e.g. Mourisden & Hansen, 2002; Trad et al., 1991) and parental report (e.g. Rutter & Cole, 1991). Other behaviours in the present study which were notable and occurred in over one half of Sotos participants include a preference for routine and repetitive questioning. Interestingly, these are seen in combination in Prader-Willi syndrome,

in the absence of high levels of other repetitive behaviours, and are related to a specific deficit of attention switching (Moss et al., 2009; Woodcock, Oliver & Humphreys, 2009). It is also notable that behaviours seen in over one third of participants include an attachment to people and restricted conversation. The former is reported in Smith-Magenis syndrome, whilst the latter is seen across a number of neurodevelopmental disorders (Moss et al., 2009). The current data on attachment to people, supports findings in three previous studies (Rutter & Cole, 1991; Sarimski, 2003; Trad et al., 1991), which have also reported a preference for adult attachment figures and the presence of anxiety if separated. Finally, it is notable that there is a different profile of stereotyped movements between Sotos syndrome and Autism Spectrum Disorder, comparable levels of body and object stereotyped behaviours but lower levels of hand stereotypies in Sotos. In summary, the overall pattern of repetitive behaviour seen in participants with Sotos syndrome is strikingly similar to that seen in Prader Willi syndrome and overlaps to some extent with that seen in Autism Spectrum Disorder with important differences.

It is important to consider the findings of the current study within the context of a number of methodological limitations. Firstly, the use of survey data is advantageous in that a number of different environments known to the informant across time and larger groups can be sampled. However, it relies upon retrospective reporting, which in itself can be problematic. Furthermore, the use of questionnaire measures does not have the same objectivity as in vivo observational methods. However, these problems are evident across the groups studied and so are unlikely to account for the differences reported. Secondly, as participants were recruited predominately from support groups and clinics, it could be argued that the samples are biased. Indeed, Hyman, Oliver and Hall (2002) hypothesise that individuals caring for a people with challenging behaviour are more likely to become members of support groups. However, if

apparent, this bias is comparable across all groups and thus any comparisons of behaviour between and across the syndrome groups remains valid. Thirdly, a small number of participants within the ASD group did not meet the cut-off scores for Autism Spectrum Disorder, although they had received the diagnosis of autism or autism spectrum disorder. This could have been due to a number of reasons (e.g. misdiagnosis, change between diagnosis and the survey, clinicians using different criteria) and this makes comparisons between the ASD and Sotos groups more problematic. Fourthly, behaviours which seem more frequent in Sotos as compared to Down syndrome, need to be seen in the context that the same behaviours are of low frequency in Down syndrome. Thus, placing behaviours reported in the present study, relative to the Prader-Willi and ASD groups in addition to the Down syndrome group, allows behaviours reported in participants with Sotos syndrome to be compared across groups. Finally, the relatively small sample sizes within the groups make it more difficult to make inferences about the behaviours reported. However, in comparison to the majority of previous studies on Sotos syndrome (e.g. Sarimski, 2003; Finegan et al., 1994), the sample size of participants with Sotos syndrome in the present study is larger.

Future Research

Taken together, the findings in the present study have lent support and expanded previous research on behavioural difficulties in Sotos syndrome such as aggression, hyperactivity and Autism Spectrum Disorder. It has also highlighted a number of areas that would benefit from further investigation and consequently would further our understanding of the behavioural phenotype of Sotos syndrome.

Firstly, further investigation would be justified into Autism Spectrum Disorder within sotos Syndrome because as previously stated, a higher than expected prevalence of Autism Spectrum Disorder was seen in participants in the present study. Furthermore, the possible

difference in the profile of Autism Spectrum Disorder in Sotos syndrome, including more significant impairments in reciprocal social interaction than repetitive behaviour and communication, warrants further in depth investigation so that this profile can be further understood.

Secondly, the results for levels of sociability suggest that participants with Sotos syndrome do have some difficulties in social motivation, although the levels seen fall far below those seen in participants with Autism Spectrum Disorder. The nature of this difference, especially in light of the developing profile around the triad of impairments, would be of interest in future research.

Thirdly, the presence of self-injurious behaviour has not previously been reported in the literature, so the relatively high levels seen in the present study are surprising and concerning given the level of intellectual disability in participants. Research aimed at gaining a greater understanding of what might underpin this behaviour is important.

Fourthly, the current research suggests some evidence for high levels of impulsivity and activity. This area is less well described in the literature, therefore, further research would be of benefit, especially with the use of standardised replicable measures.

One final recommendation for future research would be to investigate behaviours within the Sotos group, (e.g. participants with NSD1 mutations and those with non NSD1 mutations). This would extend Dyken's (1995) definition and provide a microscopic look at any differences within the syndrome.

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Public Domain Briefing Paper

The Behavioural Phenotype of Sotos syndrome

The research detailed below provides a summary of the work submitted as partial fulfilment for the degree of Doctorate in Clinical Psychology at the University of Birmingham. It is comprised of two papers, a literature review and an empirical study

Section One – A review of the literature on behavioural, psychological and cognitive characteristics of individuals with Sotos syndrome.

Research into Sotos syndrome has predominantly focused on the physical and genetic characteristics of the syndrome. However, interest into the cognitive, behavioural and psychological characteristics of individuals with Sotos syndrome and other genetic disorders is increasing. In the current review, a search of the literature from 1980 to the present day identified 20 studies which had reported behaviour difficulties and psychological disorders in participants with Sotos syndrome. Over half of these studies consisted of single case reports where findings were largely based on clinical descriptions and anecdotal evidence. A number of later studies utilised cohort methodology and more robust measures were used to record behaviours. The most commonly reported behaviours across the studies include; communication and language difficulties, atypical social behaviour including; being withdrawn and having no friends, Attention Deficit Hyperactivity Disorder, aggression and motor skill problems, with over 40% of all participants displaying these behaviours. Other behaviours which were less frequently reported include; Autism or Autistic Spectrum Disorder, psychosis and stereotyped and ritualistic behaviour.

A number of methodological limitations with both the case and cohort studies were discussed in the review, for example, only having small participant numbers and not utilising comparison groups. These limitations make it difficult to generalise the findings to the wider Sotos population and it remains unclear if the behaviours reported in Sotos individuals, would be seen in others individuals with the same degree of intellectual disability.

The review concludes that the literature to date highlights the absence of a behavioural phenotype for Sotos syndrome. Recommendations for future studies include the use of comparison groups, standardised measures and larger participant numbers.

Section Two – An empirical study to assess the behavioural phenotype of individuals with Sotos syndrome.

Given the limited amount of literature on the behavioural phenotype of Sotos syndrome, the current research aimed to firstly; describe the levels of clinically significant behaviour in participants with Sotos Syndrome using standardised questionnaires, and secondly; to compare these results with three other genetic groups, for which the behavioural phenotype is already well known (Down syndrome, Prader-Willi syndrome and Autism Spectrum Disorder).

The Study

Thirty eight participants were recruited through the Child Growth Foundation and the Birmingham and Liverpool clinical genetic departments. All participants were sent a questionnaire pack to complete which included measures to look at repetitive behaviour, social communication, mood interest and pleasure, repetitive behaviour, activity levels and

sociability. Questionnaire data for participants in the other genetic syndrome groups (Down syndrome, Prader-Willi syndrome and Autism Spectrum Disorder) was already available, through participation in a previous study. All of the participants were matched to the participants with Sotos syndrome on age, level of ability and gender, providing a total of 150 participants for the current study.

Findings and conclusions

The findings of the current study have provided further evidence for behaviours already seen in the literature and have revealed behaviours that have not been reported before. They are listed below:

The prominent behaviours of self injury and aggression were shown in approximately 40% of Sotos participants, which was similar to the Autism Spectrum Disorder group. This confirms previous reports of aggressive behaviour in individuals with Sotos syndrome, however the presence of self-injurious behaviour is a new finding as it has not been reported before.

Over 70% of participants with Sotos syndrome scored at the clinical cut off level on the Social Communication Questionnaire for Autism Spectrum Disorder and over 30% for Autism. These levels suggest that the presence of Autism Spectrum Disorder may be higher in Sotos syndrome than has been reported in previous studies. Greater difficulty was seen in the area of reciprocal social interaction for participants with Sotos, which is similar to participants with Autism Spectrum Disorder.

Some difficulties were seen in social motivation, as levels of sociability were higher than the ASD group but lower than the Down syndrome group. However clearer definitions of social impairments are needed in order to define what the exact difficulties are.

Specific repetitive behaviours were seen in over one half of participants including; a preference for routine and repetitive questioning. These behaviours are also seen in Prader-Willi syndrome in which they are associated with difficulties switching attention.

Over one third of participants showed a strong attachment to people and restricted conversations.

Further research into the nature of the behaviours described is recommended, using standardised measures and larger participant groups.

Appendices

Appendix 1

Ethics Letter

Appendix 2

Covering letter

Support letters from:

The Child Growth Foundation

Trevor Cole

Dr Alan Fryer

Appendix 3

Information sheet (over 16's)

Information sheet (under 16's)

Consent forms (a-c)

Consultee information sheet

Appendix 4

Follow Up Letter

Appendix 5

Questionnaire Pack